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第46回 日本神経化学会（新潟）大会抄録集号

平成 15 年 8 月

1日1回、24時間

パーキンソン病に

ドパミン作動薬 創薬 指定医薬品 要指示医薬品*

カバサル錠[®]

(カベルゴリン) 0.25mg 1.0mg

薬価基準収載 *注意一医師等の処方せん・指示により使用すること

禁忌 (次の患者には投与しないこと)

1. 麦角製剤に対し過敏症の既往歴のある患者
2. 妊婦又は妊娠している可能性のある婦人
[「妊婦、産婦、授乳婦等への投与」の項参照]

【効能・効果】 パーキンソン病

【用法・用量】

通常、成人にはカベルゴリンとして1日量 0.25mgから始め、2週目には1日量を0.5mgとし、以後経過を観察しながら、1週間毎に1日量として0.5mgずつ増量し、維持量(標準1日量2~4mg)を定める。いずれの投与量の場合も1日1回朝食後経口投与する。なお、年齢、症状により適宜増減する。

【用法・用量に関連する使用上の注意】

1. 本剤投与は、少量から開始し、消化器症状(悪心、嘔吐等)、血圧等の観察を十分に行い、慎重に維持量まで増量すること。2. 本剤の減量・中止が必要な場合は、漸減すること。[類薬(レボドパ、塩酸アママンタジン、ドロキシドパ、メシル酸ベルゴリド、メシル酸プロモクリプチン)において、急激な減量又は中止により、高熱、意識障害、高度の筋硬直、不随意運動、ショック症状等の悪性症候群(Syndrome malin)があらわれたとの報告がある。]

【使用上の注意】 抜粋

1. 慎重投与(次の患者には慎重に投与すること)

- (1) 高度の肝機能障害又はその既往のある患者 [外国で重度の肝不全患者で本剤の血中AUCが上昇することが明らかにされている。]
- (2) 線維化性肺疾患又はその既往歴のある患者 [胸水、胸膜又は肺の線維症が報告されている(「副作用」の項参照)。]
- (3) 消化性潰瘍や消化管出血又はその既往歴のある患者 [症状を悪化させるおそれがある。]
- (4) レイノー病の患者 [末梢血管障害を悪化させるおそれがある。]
- (5) 精神病又はその既往歴のある患者 [ドパミン受容体作動性のため精神分裂病の症状である幻覚、妄想などを悪化させる可能性がある。]
- (6) 低血圧症患者 [血圧低下がみられることがある。]
- (7) 重篤な心血管障害又はその既往歴のある患者 [外国で狭心症の報告がある。]

(8) 授乳婦 [「妊婦、産婦、授乳婦等への投与」の項参照]

(9) 高齢者 [「高齢者への投与」の項参照]

2. 重要な基本的注意

(1) 間質性肺炎、胸水、胸膜又は肺の線維症があらわれることがあるので、患者の状態を十分に観察するとともに、患者に対し、本剤の投与中に発熱、咳嗽、呼吸困難等があらわれた場合には、本剤の服用を中止し、直ちに連絡するよう指導すること。[「副作用」の項参照]

(2) 起立性低血圧がみられることがあるので、自動車の運転、機械の操作、高所作業等危険を伴う作業には従事させないよう注意すること。

3. 相互作用 本剤の代謝にはCYP3A4が関与している。

併用注意(併用に注意すること)

血圧降下剤/ドパミン拮抗剤：フェノチアジン系薬剤(クロプロマジン等)、ブチロフェノン系薬剤(ハロペリドール等)、メトクロプラミド等/マクロライド系抗生物質

4. 副作用

調査症例数821例中、副作用発現症例は346例であり、副作用発現件数は延べ723件であった。その主なものは、消化器症状で嘔気114件(13.9%)、食欲不振75件(9.1%)、胃部不快感75件(9.1%)、口渇37件(4.5%)、嘔吐21件(2.6%)、便秘20件(2.4%)、精神症状で幻覚45件(5.5%)、妄想15件(1.8%)、興奮11件(1.3%)、眩暈10件(1.2%)、神経症状でふらつき31件(3.8%)、めまい25件(3.0%)、頭重感17件(2.1%)、循環器系で起立性低血圧24件(2.9%)等であった。

臨床検査成績の異常変動は、主に血色素量減少6.4%(48/748件)、ヘマトクリット値減少6.3%(47/748件)、赤血球数減少5.1%(38/748件)、白血球数減少2.5%(19/748件)、CK(CPK)上昇10.2%(65/638件)、LDH上昇7.5%(56/744件)、ALT(GPT)上昇4.8%(36/757件)、AST(GOT)上昇3.7%(28/757件)、総コレステロール上昇1.6%(12/738件)、ALP上昇2.3%(17/742件)であった。(承認時)

(1) 重大な副作用

1) 幻覚(5.5%)、妄想(1.8%)、失神(頻度不明)、せん妄(頻度不明)、錯乱(頻度不明)：幻覚、妄想、失神、せん妄、錯乱があらわれることがあるので、このような場合には、減量、休業又は投与中止等の適切な処置を行うこと。

2) 間質性肺炎(頻度不明)：間質性肺炎があらわれることがあるので、観察を十分に行い、発熱、咳嗽、呼吸困難、肺音の異常(捻髪音)等があらわれた場合には、速やかに胸部X線検査を実施し、異常が認められた場合には投与を中止し、適切な処置を行うこと。

3) 胸水(頻度不明)、胸膜又は肺線維性変化(頻度不明)：胸水があらわれることがある。また、本剤の長期投与及びドパミン受容体刺激作用を有する麦角製剤の治療歴のある患者に本剤を投与した場合、胸膜又は肺の線維症が報告されている。本剤の投与中に、呼吸器症状等があらわれた場合には、速やかに胸部X線検査を実施し、異常が認められた場合には投与を中止し、適切な処置を行うこと。

4) 肝機能障害(頻度不明)、黄疸(頻度不明)：AST(GOT)、ALT(GPT)、γ-GTPの上昇等を伴う肝機能障害、黄疸があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

5) 狭心症(頻度不明)、肢端紅痛症(頻度不明)：狭心症、肢端紅痛症があらわれたとの報告がある。

■その他の使用上の注意等の詳細については、製品添付文書をご参照ください。

販売元

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製造元

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第46回日本神経化学会 抄 録 集

46th JSN



Niigata

- 会 期 平成15年9月24日（水）～26日（金）
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日本神経化学会・日本生物物理学会合同年会 新潟 朱鷺メッセ 9月23日～26日

第46回日本神経化学会大会

9月24日(水)～26日(金)

第41回日本生物物理学会年会

9月23日(火, 祝)～25日(木)

第46回日本神経化学会大会と第41回日本生物物理学会年会は、新潟の朱鷺メッセで合同して行われます。どちらかの年会へ参加登録すると、合同年会のすべての講演を聴くことができます。また、両学会による合同シンポジウムも企画されています。

概 要

合同シンポジウム：マリンホール

9月24日(水) 14:45～18:00

神経化学会特別講演・会長講演：マリンホール

9月25日(木) 14:50～16:55, 17:40～18:30

生物物理学会「市民のための公開シンポジウム」：マリンホール

9月23日(火) 14:00～17:00

ランチョンセミナー：マリンホール, スノーホール, ROOM302, ROOM301, ROOM201

9月23日(火) 12:30～13:45

9月24日(水) 11:45～13:00

9月25日(木) 11:45～13:00

機器展示：ウェーブマーケット A

書籍展示：アトリウム

9月23日(火) 9:00～17:00

9月24日(水) 9:00～17:00

9月25日(木) 9:00～15:00

神経化学会総会：マリンホール

9月25日(木) 16:55～17:40

生物物理学会総会：スノーホール A

9月24日(水) 12:30～

合同懇親会：ウェーブマーケット B

9月24日(水) 18:30～21:00

こ 換 拶

第 46 回日本神経化学学会大会 大会長 辻 省次

第 46 回日本神経化学学会を新潟の地でお世話させていただくことになりました。新潟は、新潟大学脳研究所をはじめとして、脳研究の盛んなところであり、日本の脳研究のメッカであると自負しています。そのような新潟の地で皆様をお迎えすることができることを大変嬉しく思います。新潟で日本神経化学学会が開かれるのは 1976 年の大会以来で、27 年ぶりの開催であります。個人的なことで恐縮ですが、実は、私が初めて学会発表というものを経験したのは 1976 年のこの新潟大会でありました。当時、大学を卒業して間もない時期で、十分な研究実績のないままの発表でした。当時の神経化学学会は口演を重視する方針で、私の発表も 10 分の口演時間に加えて、何と 10 分の討論時間がありました。案の定、口演終了と同時に質問攻めにあい、壇上で立ち往生してしまい大変困ったことを記憶しています。自分にとって、学会発表に対してどのように望むべきかを改めて認識させられた強烈な経験でした。

振り返ってみますと、昨今の学会は、マンモス化し、ポスター発表が中心であります。シンポジウムにしても、いつも同じ顔ぶれの人達をよくお見受けします。神経化学学会は、マンモス学会でないで、比較的小回りの利く学会でもあります。新潟大会をお引き受けするに当たり、初心に返りまして、若い世代の人達の発表をできるだけ多く一般口演に取り込み、討論の時間をできるだけとりたいと考えました。大いに議論をしていただきたいと思っております。

新潟大学脳研究所は、脳腫瘍の研究にそのルーツがありますが、脳疾患の診療、研究を原点に発展してきています。特に、長年にわたる臨床の積み重ねがあり、また、現在では日本のどこもやっていないと思いますが、24 時間常時スタンバイの病理解剖など、膨大な脳疾患のリソースが集積されています。昨今の日本は、アメリカの真似ばかりして、高速道路をいかに速く走るかだけを考えた研究が幅を利かせていますが、じっくりと将来を見据えて、新たな道を開拓するような研究を大切にすることが大切ではないかと、日頃考えております。新潟での神経化学学会がそのようなことに思いを巡らす機会になればと願っています。

神経化学学会は、脳機能の物質的基盤を解明し、正常と病態の理解を推進するというポリシーに立っていると思います。新潟大会が、臨床系研究者、基礎系研究者が幅広く活発に交流し大いに議論をする場となるよう企画をさせていただきました。シンポジウムについては、プログラム委員会で 6 つのシンポジウムを企画させていただき、これに加えて評議員の先生方から公募させていただき、5 つのシンポジウム（「高齢脳と可塑性」、「疲労・疲労感の神経化学」、「神経系における細胞外 ATP 機能の多様性」、「グリアニューロン間クロストークによる神経情報処理機構」、「ニューロトロフィンの合成と分泌のメカニズム」）を採択させていただきました。また、一般演題の中から、プログラム委員会で評価をさせていただき、8 つのミニシンポジウムを構成させていただきました。プログラムの構成にあたっては、できるだけ十分な討議の時間をとれるように配慮させていただきましたが、討議の時間を十分にとることは神経化学学会の伝統でもあり、活発で刺激的な討議が展開されることを期待しています。

神経化学学会のもう一つのポリシーとして、学会の国際化の推進があげられています。新潟大会でも、国際化の推進をさらにいっそう進めるために、抄録、ポスターを英語で表記すること、シンポジウムにおいても積極的に海外からの招待講演者をお招きし、英語のセッションを増やすこと、また、海外、特にアジアから若手研究者の参加を積極的に促すことを目的に、札幌大会に引き続き Young Investigator Award を設けてあります。

今回の神経化学学会の大きなイベントは、日本生物物理学会との合同開催であります。異なる discipline の両学会ですが、物質に基づくという原点を共有しており、今回は、1 分子イメージングを軸に、意欲的な合同シンポジウムを企画してみました。同じ会場で開催され、相互の参加は自由にならなっておりますので、活発な交流をしていただけますようお願いいたします。

今回の会場は、開業したばかりの新潟コンベンションセンター（朱鷺メッセ）です。懇親会は、日本生物物理学会との合同開催を計画しており、そこでは、新潟の「食」を堪能していただきたいと思っています。本学会員だけでなく、日本生物物理学会の方々とも幅広く交流をしていただき、新たな研究の発展の場になればと希望しております。

皆様を新潟でお待ちしています。

生物物理学会からのごあいさつ

第 41 回日本生物物理学会年会
実行委員長 美宅成樹

学会の歴史を超えて、さらにさかのぼると、生物物理という学問は、多分 17 世紀のロバート・フックによる「ミクログラフィア」あたりに源流があると思う。フックは、バネの法則で有名な物理学者であるが、当時の最新技術である光学顕微鏡によって、生物の微小な構造を克明に記述・描写した（細胞内小器官も見られる）。その後、物理の最新観測技術は常に生物（あるいは生体物質）に適用され、生物物理の太い流れとなってきている。今回の年会で行われる神経化学会との合同シンポジウム「分子・細胞イメージングの最前線、神経研究とサイエンスを面白くするために何をどう測るべきか」は、神経という対象とイメージングという観測技術を組み合わせ、それまで見えなかったものを見えるようにするというものである。フック以来の生物物理のテーマ（見えないものを物理的技術で見る）が、現代版として復活していると言える。

生物物理には、もう 1 つの流れがある。生物（あるいは生体物質）を物理的な考え方で理解するという流れである。最近のヒトゲノム計画からタンパク質科学へという科学の発展の中で、物理的な考え方がますます重要になってきていると思う。ゲノム計画からすべてのアミノ酸配列が手に入った現在、物理的な考え方によってタンパク質の構造・機能を知ることができるになれば、すべての生物科学に対するインパクトの大きさは計り知れない。もちろん神経細胞の cDNA から神経細胞のすべての部品が理解できるようになったら、（それはいつのことになるか分からないが）もう一度神経化学会と合同年会を行うことになるのではないだろうか。

生物物理学会は、これまで独自路線を歩み、他の学会と合同年会は行ってこなかった。しかし、学問の世界は大きく動いている。昨年のノーベル賞を持ち出すまでもなく、科学と技術は一体化してきている。また、ゲノム解析をきっかけとした大量データ生産の流れは、多くの学問分野を巻き込んで、その融合を促進している。科学技術の基盤である物理的手法、物理的考え方を基礎とした生物物理学会にとって、合同年会の芽はたくさんある。これまで生物物理学会が合同年会を行ってこなかったのが不思議なくらいである。今回の年会実行委員長として私が考えていることは、唯一つ。両学会の会員の方々にとって、気持ちよく議論できる環境を提供することである。学会には、それぞれ固有の文化がある。文化をあまりに主張すれば、合同年会自体が成立しない。しかし、固有の文化を消しては、研究の特徴も薄まる。そのバランスを見極め、すべての参加者が気持ちよく議論できることを願い、準備を進めている。もちろん合同年会がすぐ直接的な成果につながるかどうかは分からない。しかし、若い人たちの視野が広がり、彼らに境界領域の面白さを感じてもらえれば、この合同年会は成功だと思う。

最後に、会場のある新潟市で、この年会のために大変努力していただいている神経化学会の方々（新潟大学の方々）に深く感謝いたします。また、実行委員長の私が名古屋大学に移ってしまった後、むづかしいこの年会の準備をきっちりと進めていただいている在京の生物物理学会年会実行委員の方々にも、本当に感謝します。これらの方々のために、そして両学会の発展のために、多くの会員が集って、今回の年会に参加していただくことを願っています。

こ 案 内

1. ランチョンセミナー（要整理券）

ランチョンセミナーは、神経化学会主催のものと生物物理学会主催のものがあり、その区別なくどちらにも参加することができます。ふるってご参加下さい。ただし参加人数の調整をするために、事前にそれぞれのセミナーごとの整理券を発行し、整理券をお持ちの方のみが参加できるという形式をとらせていただきます。整理券の配布は、3日間とも午前 8:30 より総合受付で行い、定員に達したところで締め切らせていただきます。

2. 合同懇親会

本年の懇親会は、神経化学会・生物物理学会の合同懇親会です。新潟ならではの郷土料理と、12種の地酒をご堪能下さい。懇親会後には、シャトルバスを運行する予定です。

3. 昼 食

昼食は、ランチョンセミナーでとっていただくか、また、会場付近には食堂がほとんどないため、新潟市街中心部行きのシャトルバスを昼食時に出す予定ですので、ご利用下さい。シャトルバスは、24日・25日の2日間、午前11時から午後2時まで15分間隔で運行する予定です。詳細は当日総合受付でご案内いたします。尚、24日～26日のお弁当販売を希望される方は、特設の予約ブースを設置致しますので、前日内にお申し込み下さい。

4. 展示会

ポスター会場のウェブマーケット A では各社の機器展示を、総合受付付近のアトリウムでは書籍展示を行います。是非お立ち寄り下さい。機器展示コーナーでは、コーヒーサービスを予定しています。

5. 託児所について

対 象：学会参加者の子供（生後6ヶ月以上から就学前の乳幼児とします。）

期 間：年会会期中（9月23～26日）。9時から17時を予定しています。

場 所：朱鷺メッセ 新潟コンベンションセンター 2F ROOM202

利用形態：保母さんによる託児サービス（有料）

保護者同伴による親子休憩室としての利用も可（無料）

保 育 料：一人あたり300円／時間

利用方法：利用者は予約が必要です。9月12日（金）までに下記の連絡先までメール、又は電話で予約をして下さい。メールは利用者名・託児対象者の人数・名前・年齢・性別・利用時間・保護者の連絡先（住所、氏名、メールアドレス）、緊急連絡先（住所、電話など）を記入して下さい。研究発表等を予定している方は、発表者名・演題・発表形式を必ず記入して下さい。

§ 当託児所の開設にあたりましては、株式会社インビトロジェン様よりご支援を賜りました。

連絡先：神経化学会側窓口

新潟大学脳研究所神経内科 小林敦子

TEL : 025-227-0666, E-mail : jsn46@bri.niigata-u.ac.jp

生物物理学会側窓口

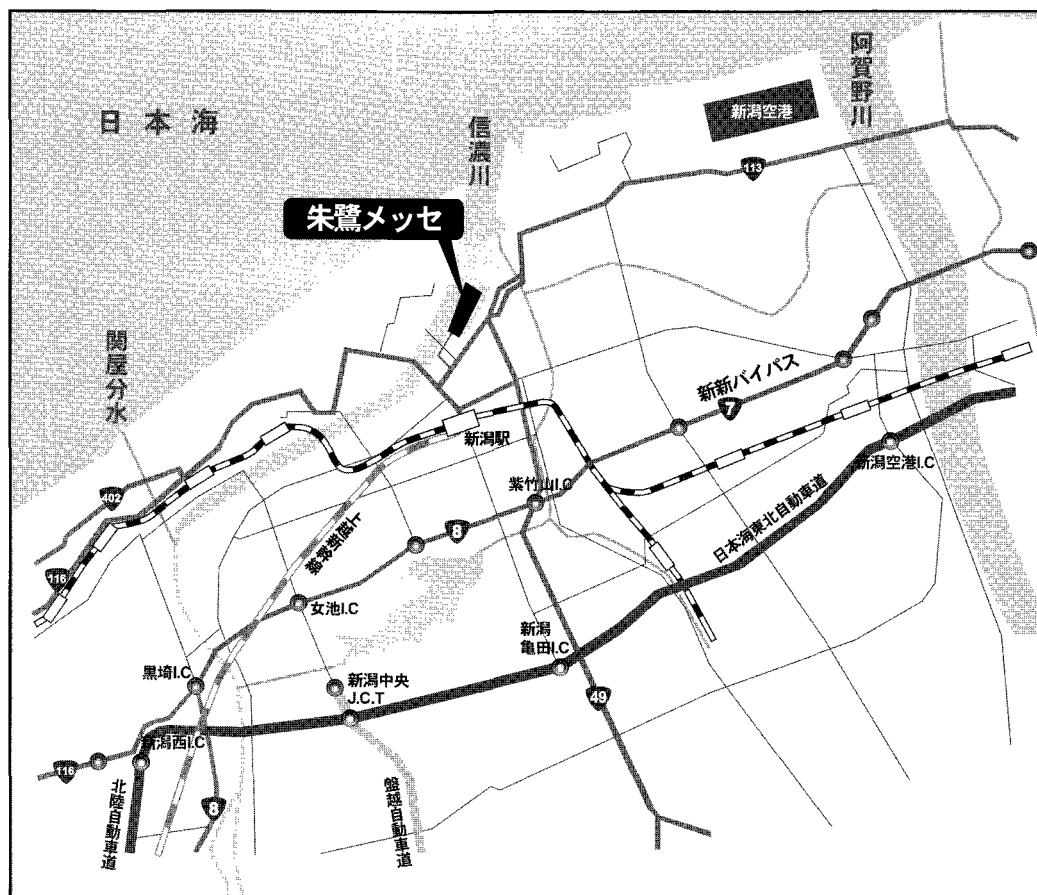
産業技術総合研究所 生命情報科学研究センター 諏訪牧子

TEL : 03-3599-8051, E-mail : m-suwa@aist.go.jp

6. コラボレーションサロン

ROOM305 は、委員会等が開催されていない時間は、両学会員の皆様に会議の場所等として提供いたします。使用をご希望の場合は、予め受付でご予約下さい。

会場への交通案内図



新潟への交通ご案内

JR (新潟駅)

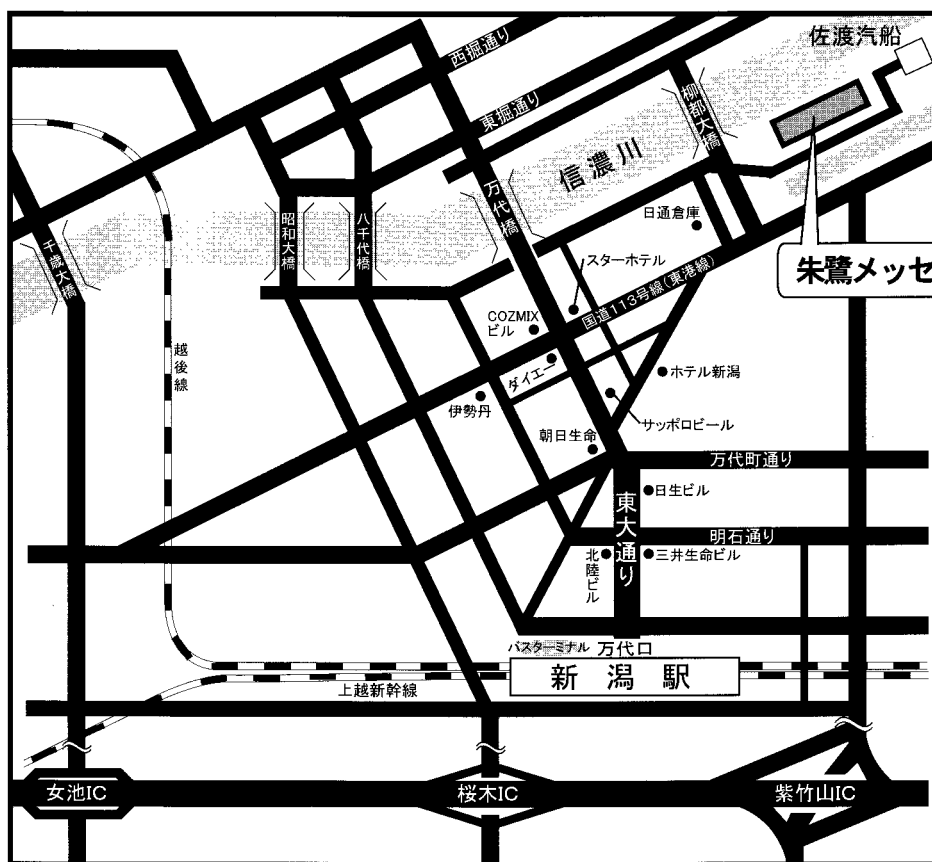
- 東京から上越新幹線 約2時間00分
- 大阪から北陸線経由・特急 約6時間30分
- 名古屋から東海道・上越新幹線 約3時間30分
- 仙台から東北・上越新幹線 約3時間50分

航空機 (新潟空港)

- 大阪から約60分 ● 名古屋から約60分 ● 札幌から約75分
- 福岡から約90分 ● 広島から約105分

自動車

- 関越自動車道・東京練馬ICから 約3時間40分
- 北陸自動車道・金沢東ICから 約3時間
- 米原ICから 約5時間
- 磐越自動車道・福島ICから 約3時間
- 新潟西料金所より 約25分
- 紫竹山インターより 約10分
- 新潟空港より 約20分



■会場 朱鷺メッセ 新潟コンベンションセンター
新潟市万代6-1 TEL/025-246-8400

●朱鷺メッセまで・・・

- ・JR新潟駅万代口より徒歩約20分
- ・JR新潟駅よりバスで約10分
(新潟駅万代口バスターミナル6番線・新潟交通17系統)
(佐渡汽船連絡「朱鷺メッセ」停留所下車)
- ・JR新潟駅よりタクシー約5分

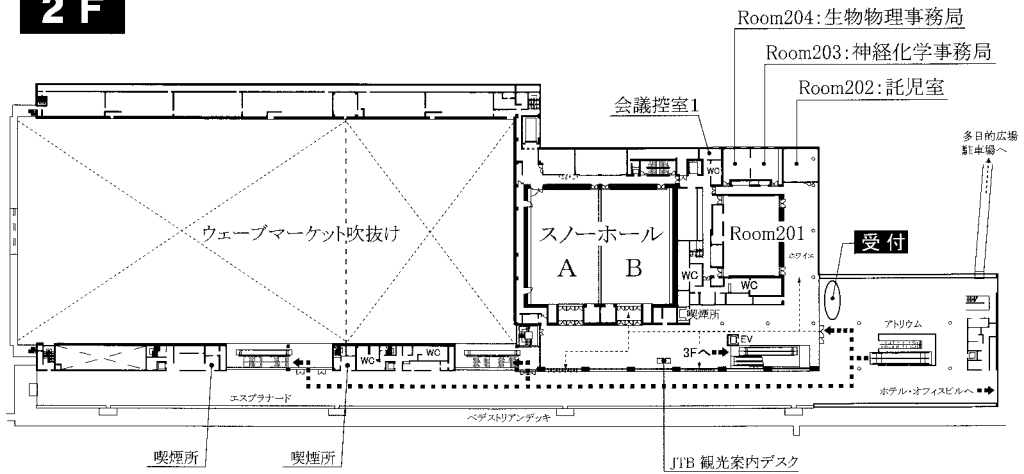
※会場までの詳しい交通案内については、朱鷺メッセのホームページをご覧ください。
<http://www.niigata-bandaijima.com/access/access0f.html>

新潟駅よりの徒歩ルート (JR新潟駅万代口より, 徒歩 約20分)

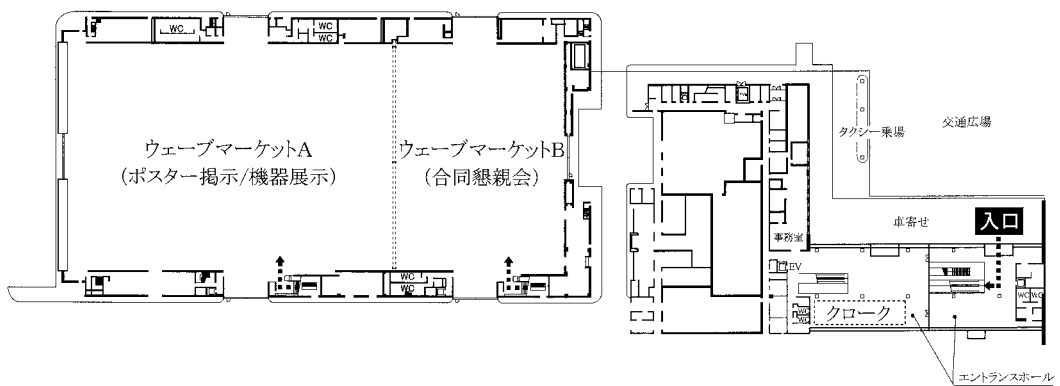


学会場案内図 (朱鷺メッセ：新潟コンベンションセンター)

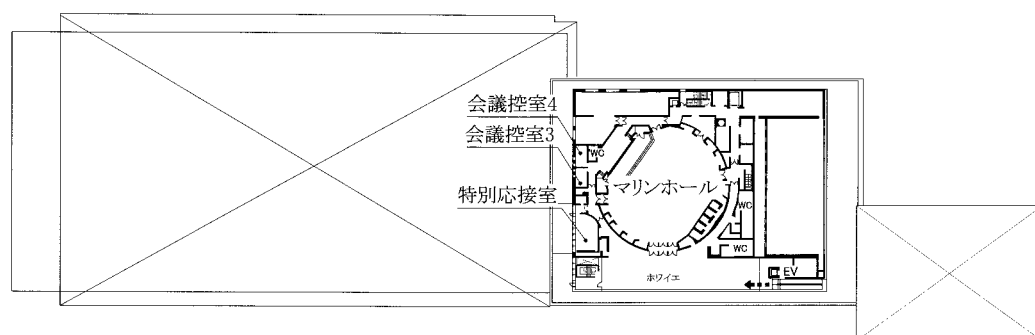
2 F



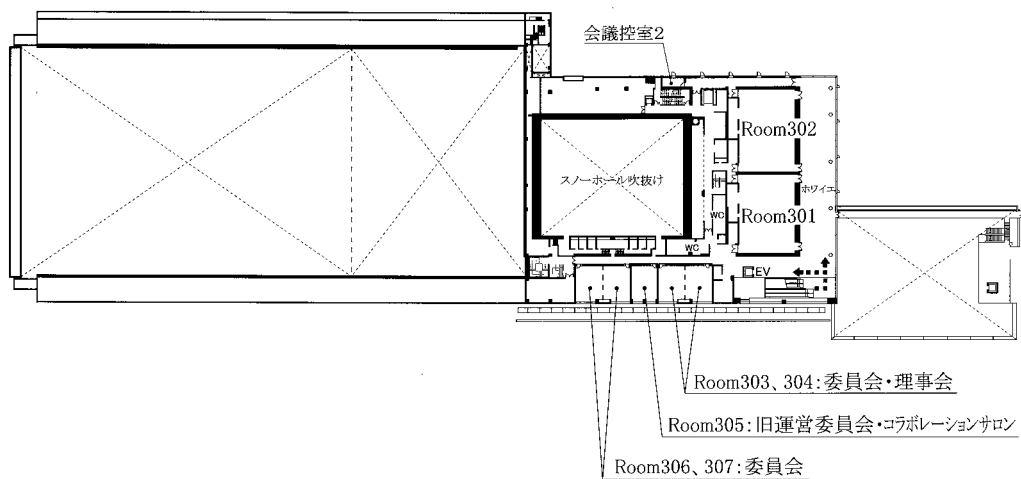
1 F



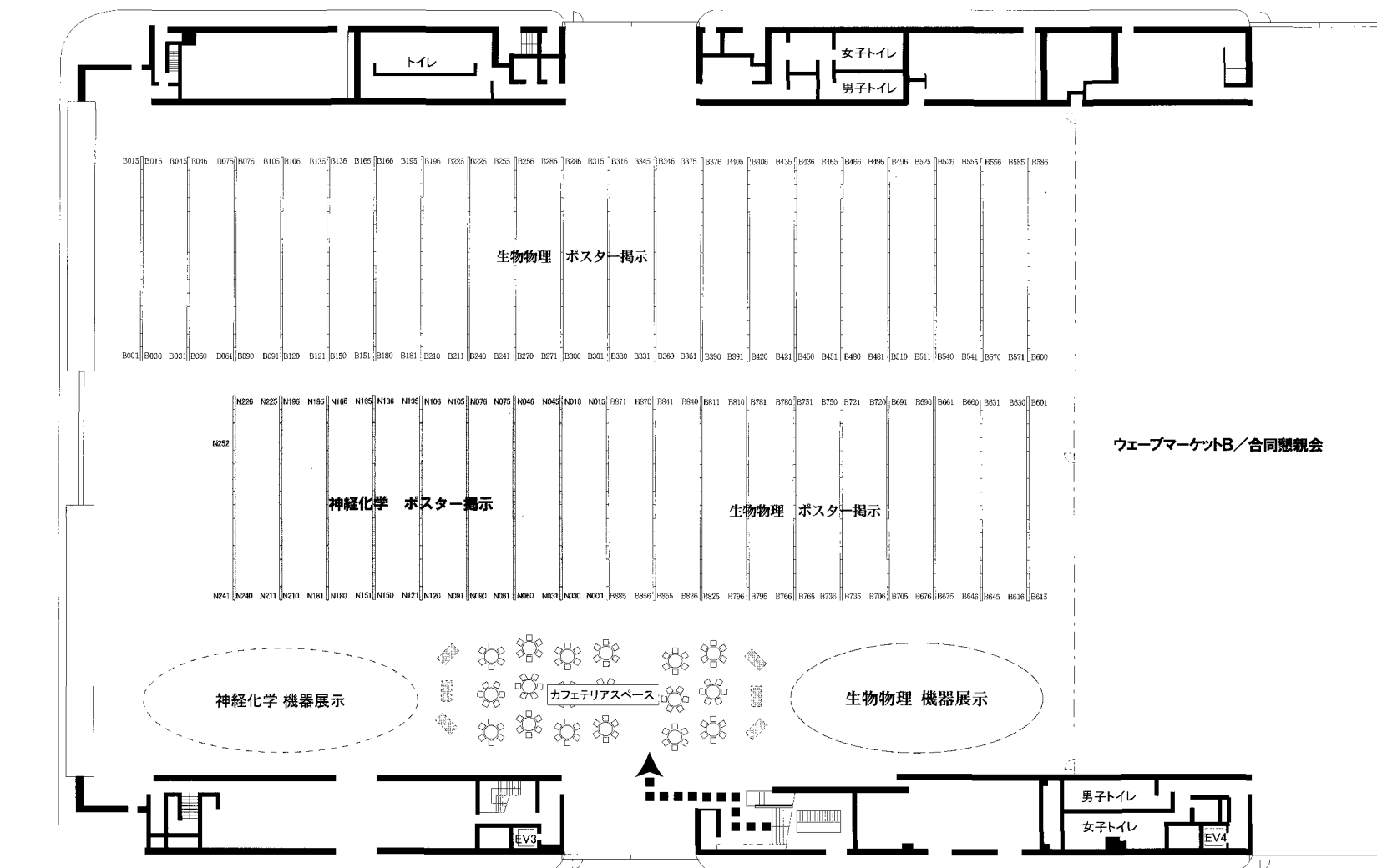
4 F



3 F



ポスターパネル配置図



9月23日 (火)

☒ 神経化学会 ☐ 生物物理学会 ☒ 合同

[illegible]

9月24日（水）

■ 神経化学会 □ 生物物理学会 ■ 合同

会 場 名													
マリンホール	スノーホールA	スノーホールB	ROOM302	ROOM301	ROOM201	ROOM307	ROOM306	ROOM305	ROOM304	ROOM303	ウェーブマーケットA	ウェーブマーケットB	アトリウム
8:15 8:30 9:00					9:00					9:00		9:00	8:30 8:15
LA 奨励賞受賞 シンポジウム		S1 小胞体機能に関連 した細胞死研究の 最先端 一條秀憲（東京大 ・薬）、片山泰一 （大阪大・医）	MS1 神経編成疾患の分 子機構	MS2 神経再生	10:15						ポスター 討論 生物物理		
11:00			MS3 痴呆性疾患の分子 機構	MS4 シナプス機能制御	11:30					11:30			
11:30 11:45	ランチョン （アフィメトリクス ・ジャパン株式会社）	12:00 分野別 専門委員会	ランチョン （三菱ウェルファ ーム株式会社）	ランチョン （横河シナリティカル ・システムズ株式会社）	ランチョン （日本ペーリンガー ・インゲルハイム 株式会社）	12:00 評議員会					ポスター 掲示		
13:00		12:30 総会				13:00					機器 展示		書籍 展示
14:00		14:00				13:15 編集委員会		13:15 コラボ レーション サロン	13:15 科研費の新制度を 考える		13:15 ポスター 討論 神経化学		生物 物理 受付
14:45			14:45			14:00			14:00				神経 化学 受付
17:00 17:15	ポスター セレクション 分子モーター	ポスター セレクション 光生物	S2 疲労・疲労感の神 経化学 尾上浩隆（都神経 研）、倉恒弘彦 （関西福祉科学大）	S3 ニューロトロフィ ンの合成と分泌の メカニズム 古川昭栄（岐阜薬 大）、仙波りつ子 （愛知県コロー ン研）	ポスター セレクション 若手研究者					17:00	ポスター 展示	17:00	
18:00			17:15								18:00		
20:00												18:30 合同懇親会	21:00

☒ 神経化学会
 ☐ 生物物理学会
 ☒ 合同

[illegible]

9月26日 (金)

■ 神経化学会 □ 生物物理学会 ■ 合同

会 場 名														
8:15	マリナーホール	スノーホールA	スノーホールB	ROOM302	ROOM301	ROOM201	ROOM307	ROOM306	ROOM305	ROOM304	ROOM303	ウェーブマーケットA	ウェーブマーケットB	アトリウム
9:00	ISN シンポジウム													
11:30														
														神経化学受付
12:30														
14:00	市民公開講座													
15:00														
15:30														

第 46 回日本神経化学会・第 41 回日本生物物理学会 合同年会 委員一覧

第 46 回日本神経化学会大会

大会長

辻 省次 (東京大学大学院医学系研究科)

組織委員

西澤正豊 (新潟大・脳研)

田中隆一 (新潟大・脳研)

崎村建司 (新潟大・脳研)

武井延之 (新潟大・脳研)

小野寺理 (新潟大・脳研)

染矢俊幸 (新潟大・院医)

馬場 洋 (新潟大・院医)

木村智彦 (日本歯科大・新潟歯学)

長友孝文 (新潟薬科大・薬)

成瀬 聡 (新潟大・脳研)

高橋 均 (新潟大・脳研)

那波宏之 (新潟大・脳研)

阿部輝雄 (新潟大・脳研)

樋口宗史 (新潟大・院医)

五十嵐道弘 (新潟大・院医)

桑野良三 (新潟大・脳研)

宇田 裕 (新潟薬科大・衛生薬学)

渡邊和忠 (長岡技術科学大)

五十嵐修一 (新潟大・脳研)

第 41 回日本生物物理学会年会

実行委員長

美宅成樹 (名古屋大学大学院工学研究科)

実行委員

秋山 泰 (産総研・CBRC)

池口満徳 (横浜市大大・院総理)

太田善浩 (東京農工大・工)

木寺詔紀 (横浜市大・院総理)

木下賢吾 (横浜市立大大・院総理)

後藤 修 (京都大・院情報)

曾田邦嗣 (長岡技科大・生物系)

西垣功一 (埼玉大・工)

広川貴次 (産総研・CBRC)

船津高志 (早稲田大・理工)

養王田正文 (東京農工大・工)

有坂文雄 (東工大・院生命理工)

内古閑伸之 (名古屋大・院工)

岡浩太郎 (慶応大・理工)

城所俊一 (長岡技科大・生物系)

黒田 裕 (理研・GSC)

諏訪牧子 (産総研・CBRC)

園山正史 (名古屋大・院工)

西村善文 (横浜市大・院総理)

伏見 譲 (埼玉大・工)

三宅美博 (東京工大・院総合理工)

神経化学会・生物物理学会合同シンポジウム

9月24日(水) 14:45~18:00 マリンホール

分子・細胞イメージングの最前線

神経研究とサイエンスを面白くするために何をどう測るべきか

オーガナイザー：神経化学会・生物物理学会 合同シンポジウム開催準備委員会

合同シンポジウムでは、分子・細胞イメージングにおける最先端の研究を、第一線の研究者に講演していただきます。1分子から生細胞まで幅広いジャンルのイメージングに関する講演を集めることにより、イメージングが神経研究はもとよりサイエンスの発展にどのように貢献できるか探してみたいと考えています。また、シンポジウムをより双方向的なものとするために会員に対してアンケートを実施し、その結果をシンポジウムに可能な限り反映させます。

コーディネーター：御子柴 克彦（東京大・医科研）、相澤 洋二（早稲田大・理工）

（順未定、順番は決定次第 HP に掲載）

S2M51 Physical mapping and morphological imaging of biomolecular structures by atomic force microscopy

Atsushi Ikai (Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology)

S2M52 Digital signal transduction in the cell membrane as revealed by single molecule bionanotechnology

Akihiro Kusumi (Kusumi Membrane Organizer Project, ERATO, JST, Department of Biological Science and Institute for Advanced Research, Nagoya University)

S2M53 Higher, faster, and smaller

Susumu Terakawa (Photon Medical Research Center, Hamamatsu University School of Medicine)

S2M54 Molecular design of bioimaging probes

Tetsuo Nagano (Graduate School of Pharmaceutical Sciences, University of Tokyo)

S2M55 Molecular imaging of the intracellular signal transduction

Katsuhiko Mikoshiba^{1,2,3}, Kozo Hamada³, Hiroko Bannai², Kazumi Fukatsu¹, Hideaki Ando², Toru Matsu-ura¹, Keiko Uchida¹, Takayuki Michikawa¹, Tomohiro Nakayama¹, Yoko Tateishi¹, Songbai Zhang³, Akihiro Mizutani³, Mitsuharu Hattori¹, Takafumi Inoue¹ (¹Department of Molecular Neurobiology, Institute of Medical Science, the University of Tokyo, ²Laboratory of Developmental Neurobiology, RIKEN Brain Science Institute, ³Calcium Oscillation Project, ICORP, JST)

S2M56 PKC signaling for global enhancement of excitatory synaptogenesis in neurons is triggered by local contact with astrocytes

Atsushi Miyawaki (Laboratory for Cell Function and Dynamics, Advanced Technology Development Center, RIKEN Brain Science Institute)

S2M57 Single molecule imaging of dynamic molecular and cellular systems

Toshio Yanagida (Graduate School of Frontier Bioscience, Osaka University)

神経化学会主催ランチンセミナー

9 月 24 日(水) 11:45～13:00

アフィメトリクス・ジャパン株式会社セミナー

マリンホール

座長：高田耕平（アフィメトリクスジャパン株式会社）

「GeneChip products and technology overview ～GeneChip システムとそのテクノロジー」

演者：藤田祐治（アフィメトリクスジャパン株式会社）

「ポリグルタミン病の病態機序 ～遺伝子発現異常の立場から～」

演者：佐藤俊哉（新潟大学脳研究所生命科学リソース研究センター）

三菱ウェルファーマ株式会社セミナー

スノーホール B

座長：田中隆一（新潟大学脳研究所脳神経外科学分野）

「内在性神経幹細胞の活性化による脳卒中再生治療と展望」

演者：川原信隆（東京大学脳神経外科学）

横河アナリティカルシステムズ株式会社セミナー

ROOM 302

座長：近藤直人（アジレント・テクノロジー）

「遺伝子発現解析はどこまで神経化学を解明出来るか」

演者：登内未緒（横河アナリティカルシステムズ(株)）

ベーリンガーインゲルハイム株式会社セミナー

ROOM 301

座長：中村重信（広島大学名誉教授）

「ドパミンアゴニストの神経保護作用の可能性について」

演者：小川紀雄（岡山大学医学部分子細胞医学研究施設）

9月25日(木) 11:45~13:00

エーザイ株式会社セミナー

マリンホール

座長：武田雅俊（大阪大学精神科）

「アルツハイマー病の分子マーカー」

演者：荒井啓行（東京大学付属病院老人科）

ファイザー製薬株式会社セミナー

スノーホール B

座長：山本紘子（藤田保健衛生大学）

「セロトニンをめぐって-頭痛の理解を深める」

演者：有田秀穂（東邦大学第一生理）

大日本製薬株式会社セミナー

ROOM 302

座長：西澤正豊（新潟大学脳研究所神経内科学分野）

「脳神経疾患とフリーラジカル（転換を中心にして）」

演者：横井 功（大分大学医学部生理学第一）

小野薬品工業株式会社セミナー

ROOM 301

座長：馬場広子（東京薬科大学）

「痛みとプロスタグランジン」

演者：伊藤誠二（関西医科大学医化学）

学会への参加受付

1. 参加者の皆様へ

●参加登録をお済ませの方へ

学会当日は大会事務局からお送り致しました参加登録証（名札）を必ずご持参ください。また会期中は名札をお付けくださいますようお願い申し上げます。万一お忘れになられた場合には総合受付までお申し出ください。

●当日参加登録をされる方へ

受付は朱鷺メッセ・2Fアトリウムに設置されております受付において午前8時15分より開始します。お渡しした名札をお付けのうえご入場ください。参加費は以下の通りです。

学生の方はその旨お申し出ください。お渡しする名札には学生であることを明記させていただきます。

当日受付参加費

会 員	11,000円
非 会 員	12,000円
学 生 会 員	4,000円（学生証をご提示ください）
学 生 非 会 員	4,000円（学生証をご提示ください）
懇 親 会（一般）	6,000円
懇 親 会（学生）	3,500円（学生証をご提示ください）

●非会員の方へ

本学会の筆頭発表者は本学会会員に限らせていただいております。非会員の筆頭発表者（代表発表者）は速やかに正会員としての入会手続きをお取りください。詳細は下記日本学会事務センターにお問い合わせください。合同プログラム号、及び第46回日本神経化学学会大会（新潟）抄録号は正会員の方のみ送付されます。ただし参加登録を既にお済ませの非会員の方へも、合同プログラム号だけは送らせていただきます。第46回日本神経化学学会大会（新潟）抄録号は学会当日、総合受付でも販売いたしますので、ご希望の方は買い求めください。（3,000円）

〒113-8622

東京都文京区本駒込5-16-9

（財）日本学会事務センター

日本神経化学学会事務局

TEL：03-5814-5810 FAX：03-5814-5825

●取得単位について

本学会への参加は、日本神経学会、日本小児神経学会、および日本良導絡自律神経学会の認定医研修単位の対象となります。詳細はそれぞれの学会に直接ご照会ください。

2. お知らせ

●会場の入場について

会場は午前8時にならないと入場できません。ご注意ください。

●クローク

会期中は、朱鷺メッセ、1Fに設ける予定ですが、スペースに限りがございます。出来るだけ宿泊されるホテル等のクロークをご利用いただくようお願い致します。

●呼び出し、伝言

放送での参加者のお呼び出し、お電話等の取り次ぎは一切いたしません。朱鷺メッセ、2Fアトリウムに伝言板を設置する予定ですのでご利用ください。

●宿泊・交通・観光案内

朱鷺メッセ、2FホワイエにJTB新潟支店の案内デスクを設置します。また会期中のお問い合わせは下記までお願いします。

JTB新潟支店

「第46回日本神経化学会大会（新潟）」係

〒951-8063

新潟市古町通6番町976

TEL：025-224-2201 FAX：025-229-5775

E-mail：niigata_ei4a@kit.jtb.co.jp

担当：神田、古田、後藤

●学会本部

会期中は、朱鷺メッセの2FのROOM203を本部に致します。連絡先等の詳細は第46回日本神経化学会大会（新潟）ホームページにてご確認ください。

URL：<http://brain.bri.niigata-u.ac.jp/~jsn46/>

●懇親会

大会1日目（24日）の18：30より朱鷺メッセ・ウェーブマーケットBにて行いますので、是非ご参加ください。

講演発表要領

1. 会場

マリンホール、スノーホール、ROOM201、301、302において同時進行で行われます。

2. 発表・討論、進行

- 1) 各演者の発表・討論の時間はプログラムに記載されていますので、時間厳守をお願い致します。
- 2) 進行は座長の責任において行ってください。シンポジウム終了時間を厳守願います。
- 3) 演者は講演時間10分前までに、次演者席にお着きください。
- 4) 座長はご担当のシンポジウムの開始15分前までに、各シンポジウム会場の受付までお越しください。
- 5) 討論者は、あらかじめ会場内の討論用マイクの前でお待ちください。
- 6) 討論においては、簡潔にご発言ください。
- 7) ミニシンポジウムの講演時間は発表10分、討論5分です。時間の厳守をお願い致します。

3. 発表機材

- 1) シンポジウム・ミニシンポジウムでの発表機材は、すべてPCによる発表となります。ご使用にあたっては4.の各項にある使用上の注意をよくお読みください。
- 2) スクリーンは1面です。複数の機材による並写はできません。

4. 液晶プロジェクター (PC)

- 1) パソコンは演者が持参してください。
- 2) ミニDサブ15pinの出力端子が、本体またはアダプターにあることが必要です。
- 3) ソフトウェアは「PowerPoint」の使用を強く推奨いたします。「PowerPoint」以外のソフトウェアをご使用の方は、予め下記連絡先にご相談ください。

連絡先：株式会社 新潟コンベンションサービス

事業推進室 担当／錦織 均

〒950-0088 新潟市万代2丁目4-15-101

TEL：025-240-5400 FAX：025-240-5432

- 4) パソコンを持参できない方は予め準備事務局にご相談ください。
- 5) パソコンからの映写ができることを、実際にお使いになる会場で、事前にご確認くださるようお願い致します。午前の講演予定の方は講演前あるいは前日等、午後の講演予定の方は当日のポスター発表討論時間等、いずれもスタッフを配置していますので、会場にお越しいただき試写をお願い致します。
- 6) パソコンの操作は演者が演台で行うことになります。

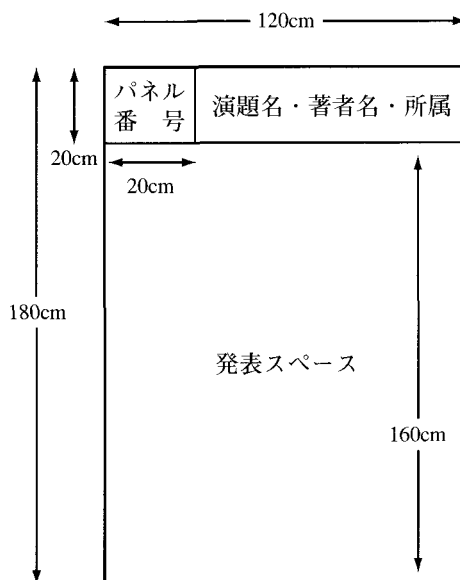
ポスター発表（一般演題）要領

1. 会場

ポスター発表は、ウェーブマーケットAにて行われます。

2. 発表要領

- 1) 本年度のポスターの発表形式は、24日・25日の2日間掲示して頂きます。
- 2) 発表者はできるだけ第1日目の午前10時までにポスターを所定のスペースに展示してください。
- 3) 右図のように、縦20cm×横100cmのサイズに演題、著者名、所属を和英文にて記入したものをご用意ください。
- 4) 発表内容は右図発表スペース（縦160cm×横120cm）に収まるようにしてください。
- 5) パネル番号は大会事務局にて用意します。
- 6) 展示内容についてはすべて英語にて作成をお願い致します。
- 7) 演題番号で示される会場、発表日、パネル番号に従って、下記の掲示時間の間、ポスターを掲示してください。
- 8) プッシュピンはポスター受付でお受け取りください。のり、セロハンテープ等は使用しないでください。
- 9) ポスターは9月25日午後6時以降各自で撤去してください。撤去されなかった掲示物は大会本部にて処分しますのでご了承ください。



3. 掲示時間

9月24日（水） 9：00～18：00

9月25日（木） 9：00～18：00

4. 討論

- 1) 発表者の方には、ポスター受付でリボンをお渡しいたしますので、討論の際には胸につけて、各ポスターパネルの前で参加者の質疑に応じてください。
- 2) 討論は、演題番号の奇数・偶数で2つのグループに分け、2交替制で行います。下記の討論時間には発表者はポスターの前で待機してください。

9月24日（水）	演題番号 奇数	13：15～14：00
	演題番号 偶数	14：00～14：45
9月25日（木）	演題番号 奇数	13：15～14：00
	演題番号 偶数	14：00～14：45

託児室の開設

1. 対 象：

学会参加者の子ども（就学前から乳幼児とする）

2. 期 間：

学会会期中（9月23日～26日）9時から17時を予定しています。

3. 場 所：

朱鷺メッセ 2F・ROOM202

4. 利用状態：

◎保母さんによる託児サービス（有料）

◎保護者同伴による親子休憩室としての利用も可（無料）

5. 保育料

一人あたり300円／時間

6. 利用方法

利用者は予約が必要です。9月12日（金）までに下記の連絡先までメール、又は電話で予約をして下さい。メールは利用者名・託児対象者の人数・名前・年齢・性別・利用時間・保護者の連絡先（住所、氏名、メールアドレス）、緊急連絡先（住所、電話など）を記入して下さい。研究発表等を予定している方は、発表者名・演題・発表形式を必ず記入して下さい。

- ・利用者名、託児対象者の人数・名前・年齢・性別・利用時間
- ・保護者の連絡先（住所・氏名・メールアドレス）
- ・緊急連絡先（住所・電話番号）

連絡先：新潟大学脳研究所神経内科

第46回日本神経化学会大会（新潟）事務局 小林 敦子

E-mail：jsn46@bri.niigata-u.ac.jp

会長講演

9月25日 (木) 14:50~15:25 マリンホール
座長：宮武 正 (昭和薬大)

21世紀の神経疾患研究の展望
辻 省次 (東京大院・医)

特別講演

9月25日 (木) 15:25~16:10 マリンホール
座長：井原康夫 (東京大院・医)

PL-1 Searching for Novel Alzheimer's Disease Genes on Chromosome 10
Steven G. Younkin (Mayo Clinic Jacksonville)

9月25日 (木) 16:10~16:55 マリンホール
座長：辻 省次 (東京大院・医)

PL-2 神経回路の伝達制御機構
中西 重忠 (京都大・生命科学)

9月25日 (木) 17:40~18:30 マリンホール
座長：永津俊治 (藤田保健衛生大)

PL-3 Assembly of a Nervous System — The Initial Strategy
Marshall Nirenberg (NHLBI)

ISNシンポジウム

9月26日 (金) 9:00~11:30 マリンホール

ポリグルタミン病の治療戦略の可能性を探る

オーガナイザー：Kenneth Fischbeck (NIH, NINCDS)
辻 省次 (東京大院・医)

ポリグルタミン鎖をコードするCAGリピートの異常伸長によって生じる遺伝性神経疾患 (ポリグルタミン病) が、現在までにハンチントン病、球脊髄性筋萎縮症、種々の脊髄小脳変性症など少なくとも9疾患で見いだされている。最近のポリグルタミン病の分子病態機序についての進歩によって、これらの疾患の治療についての新しい試みが発展しつつある。このシンポジウムでは、種々の物質を用いた転写の活性化、変異遺伝子によって作られた異常蛋白質の核内輸送の抑制、ポリグルタミン鎖によるコンフォメーション変化により蛋白凝集を抑制する分子をハイスループットでスクリーニングする方法等、新たなポリグルタミン病治療法の開発に焦点を当てる。

- ISN-1 Polyglutamine toxicity in spinal and bulbar muscular atrophy
Kenneth Fischbeck (NIH, NINCDS)
- ISN-2 Intervention of nuclear transport of androgen receptor
Gen Sobue (Nagoya Univ.)
- ISN-3 Exploring RNA interference as a therapeutic strategy in polyglutamine disease
Henry L. Paulson (Univ. of Iowa)
- ISN-4 Inhibition of protein aggregation in Alzheimer's and Huntington's disease:
implications for therapy
Erich E. Wanker (Max Planck Inst.)

オープンシンポジウム

9月25日 (木) 18:00~20:00 スノーホールB

人はなぜ、その行動をとるか

オーガナイザー：武田 雅俊 (大阪大院・医), 三木 直正 (大阪大院・医)

- OS-1 線虫の「好き」と「嫌い」の分子基盤
森 郁恵 (名古屋大・理)
- OS-2 遺伝情報と行動：脳の進化と後発生
八木 健 (大阪大院・生命機能研究科)
- OS-3 脳形成・発達とけいれん
佐藤 真 (福井医大・解)
- OS-4 性行動を制御する遺伝子群
山元 大輔 (早稲田大・理工)
- OS-5 報酬と期待
彦坂 和雄 (都神経研)

市民公開講座

9月26日 (金) 14:00~15:30 マリンホール

座長：西澤 正豊 (新潟大・脳研)

パーキンソン病研究と治療の進歩
水野 美邦 (順天堂大)

奨励賞受賞シンポジウム

9月24日 (水) 9:00~11:00 マリンホール

座長：池中 一裕 (国立生理学研)

- LA-1 アストロサイトによるダイナミックなシナプス伝達制御—細胞外ATPの関与—
小泉 修一 (国立医薬品食品衛生研)
- LA-2 24時間制を生む蛋白質制御メカニズムの研究
田丸 輝也 (東邦大・医)
- LA-3 ポリグルタミン鎖結合ペプチドQBP1によるポリグルタミン病に対する分子療法の確立
永井 義隆 (大阪大院・医)
- LA-4 ムスカリン性アセチルコリン受容体サブタイプの中樞神経における特異的役割
山田 真久 (理化学研)

シンポジウム

9月24日 (水) 9:00~11:30 スノーホールB

S1 小胞体機能に関連した細胞死研究の最先端

オーガナイザー：一條 秀憲 (東京大・薬), 片山 泰一 (大阪大院・医)

- S1-1 Stress-induced Apoptosis by the ASK1-MAP Kinase Signal
一條 秀憲 (東京大・薬)
- S1-2 小胞体ストレス誘導性アポトーシス：分子シャペロンによる制御
後藤 知己 (熊本大)
- S1-3 小胞体ストレス特異的に活性化されるヒトカスパースの探索
人見 淳一 (大阪大)
- S1-4 小胞体膜上で制御される細胞の生と死
今泉 和則 (奈良先端科技大)
- S1-5 ゴルジ体-小胞体間の細胞内小胞輸送による小胞体機能の修飾
青江 知彦 (千葉大)

9月24日 (水) 14:45~17:15 ROOM302

S2 疲労・疲労感の神経化学

オーガナイザー：尾上 浩隆 (都神経研)，倉恒 弘彦 (関西福祉科学大)

このシンポジウムでは、最近鋭意研究が進められている「疲労および疲労感の分子神経メカニズム」についての最新知見、即ち、様々な疲労における脳機能イメージングによる共通項、動物モデルの開発によるサイトカイン-神経伝達物質ネットワークの中での疲労過程の分子ダイナミクスや遺伝子の変化、その回復過程におけるそれぞれの変化、慢性疲労病態の分子神経メカニズムについて講演を行い、疲労に対する有効な回復法・治療法、過労予防に関する提言を行うことを目標に討論を深めたい。

S2-1 疲労の条件づけとセロトニン神経回路

片渕 俊彦 (九州大・医)

S2-2 疲労による遺伝子発現の変化と活性酸素制御

井上 正康 (大阪市立大・医)

S2-3 みどりの香りによる疲労回復

佐々木 和男 (富山大・工)

S2-4 疲労の定量化・評価法の開発

梶本 修身 (大阪外大・保健管理セ)

S2-5 疲労感のイメージングと神経回路

尾上浩隆 (都神経研)

S2-6 慢性疲労症候群の病因と病態

倉恒 弘彦 (関西福祉科学大)

9月24日 (水) 14:45~17:15 ROOM301

S3 ニューロトロフィンの合成と分泌のメカニズム

オーガナイザー：古川 昭栄 (岐阜薬大)，仙波 りつ子 (愛知県コロニー研)

ニューロトロフィンは神経の発達や再生さらに神経の活動に必要な分子であり、その生体における濃度や分泌の調節は重要であるが、これらの研究は意外にも遅れていた。そこで、最近我が国の研究者によって明らかにされつつあるこのテーマをシンポジウムの企画として提案したい。

S3-1 薬物によるBDNF合成の促進機構

仙波 りつ子 (愛知県コロニー研)

S3-2 BDNF発現の転写調節

津田 正明 (富山医薬大)

S3-3 ニューロトロフィンの細胞内プロセッシングと分泌

野元 裕 (岐阜薬大)

S3-4 小脳ニューロンにおけるニューロトロフィン分泌機構と新規制御分子
古市 貞一 (理化学研)

S3-5 BDNFの分泌機能と一塩基多型SNP
小島 正己 (産業技術総合研究所)

9月25日 (木) 9:00~11:30 マリンホール

S4 アルツハイマー病研究の最近の進歩

オーガナイザー：井原 康夫 (東京大院・医)

アミロイド β タンパク ($A\beta$) が蓄積し、神経細胞内にタウが蓄積 (神経原線維変化)、神経細胞が脱落して、痴呆が発症すると考えられている。 $A\beta$ は、その前駆体である膜タンパクが段階的な切断を受けて生じる。最終的な、 $A\beta$ のC末端の切断は膜のちょうど真ん中で起こる (γ cleavage)。本シンポジウムでは、第1に、この膜内切断機構の詳細を検討する。第2に、脳内 $A\beta$ 蓄積におけるneprilysinの役割に焦点をあわせる。第3に、神経原線維変化形成におけるリン酸化の役割に焦点を当てる。全体として、特に創薬のターゲットに関して議論したい。

S4-1 Functional anatomy of the γ -secretase complex
T. Tomita and T. Iwatsubo (Univ. of Tokyo)

S4-2 Relationship between γ and ϵ -cleavage
M. Morishima and Y. Ihara (Univ. of Tokyo)

S4-3 NSAIDs and Alzheimer's disease : An update
Edward H. Koo (Univ. of California, San Diego)

S4-4 Abeta metabolism and Alzheimer's disease
T. Saido (RIKEN)

S4-5 Inhibition of GSK-3— A possible therapeutic target in Alzheimer's disease
A. Takashima (RIKEN)

9月25日 (木) 9:00~11:30 スノーホールB

S5 成長円錐の分子細胞生物学：軸索成長の制御メカニズムへのアプローチ

オーガナイザー：五十嵐 道弘 (新潟大院・医), 辰巳 仁史 (名古屋大院・医)

成長円錐は神経細胞の突起時に形成され、シナプス形成に決定的に重要な役割を果たす。この部位をめぐる、軸索成長とガイダンスを調節する分子群がごく一部ではあるが、明らかになってきた。これらのうち、細胞内情報伝達、特に細胞骨格系と膜融合に関する情報伝達に焦点をあてる。生物物理学会との共催なので、生物物理学会員の方で、成長円錐に関してリアルタイムの観察を通してこれらの問題にアプローチしている方もお呼びして、新たな技術や研究手法も含めて議論を深めたい。

- S5-1 Proteomic approach of the growth cone functions**
五十嵐 道弘 (新潟大院・医)
- S5-2 Dynamics of actin filaments and actin associate proteins revealed by polarized light and fluorescence microscopy**
加藤 薫 (産業技術総合研究所)
- S5-3 Regulation of N-WASP by Src-Family Tyrosine Kinases and Proteasome in Neurite Extension**
末次 志郎 (東京大・医科学研究所)
- S5-4 Plexin mediates bifunctional signals**
稲垣 忍 (大阪大院・医)
- S5-5 The regulation of microtubule dynamics in growth cones by SCG10**
Gabriele Grenningloh (Univ. Lausanne, Switzerland)
- S5-6 神経成長円錐におけるエクソサイトシスと細胞接着形成について**
辰巳 仁史 (名古屋大院・医)

9月26日 (金) 9:00~11:30 スノーホールB

S6 コンディショナル遺伝子発現制御法を用いた脳研究

オーガナイザー：崎村 建司 (新潟大・脳研), 森 寿 (東京大院・医)

特定の脳領域が記憶、学習などの高次機能に果たす役割を分子的に理解するための非常に有効な方法として、脳領域特異的遺伝子発現制御マウスを用いた研究が展開されている。この方法論は、神経回路網の形成や脳病態の分子機構解析にも有力となる。本シンポジウムでは、実際にこのようなマウス系統を作成し、解析を行っている研究者を迎え、遺伝子発現制御の方法論、有効性、新たに明らかにされた脳機能の分子機構について論議する。

- S6-1 脳部位特異的遺伝子改変システムの開発と脳研究への応用**
崎村 建司 (新潟大・脳研)
- S6-2 mGluR1遺伝子操作マウスの作成、解析**
饗場 篤 (神戸大・医)
- S6-3 線条体選択的NMDA受容体欠損マウスの作成と解析**
森 寿 (東京大院・医)
- S6-4 背側終脳特異的遺伝子操作法を用いた体性感覚系回路発達機構の解析**
岩里 琢治 (理化学研)
- S6-5 海馬CA3領域NMDA受容体の記憶学習に果たす役割**
中沢 一俊 (Natl. Inst. of Mental Health, NIH)

9月26日 (金) 9:00~11:30 ROOM302

S7 シナプス機能の分子基盤

オーガナイザー：阿部 輝雄 (新潟大・脳研), 熊倉 鴻之助 (上智大)

最近の研究の進展によって、シナプス伝達を中心とするシナプス機能を支える多くのタンパク質が同定されている。シナプス前部および後部にはこれらのタンパク質間に複雑な相互作用カスケードが存在し、神経活動に応じて可塑的に変化すると考えられる。しかし、カスケード中における個々のタンパク質の生理的役割に関する情報は乏しい。このシンポジウムでは伝達物質放出、受容、シグナル伝達系への連絡等に関与するタンパク質分子の構造、機能、動態について最新の研究成果を発表、議論することにより今後の課題をクロージアアップする。

S7-1 クロム親和細胞における分泌制御

笹川 展幸 (上智大)

S7-2 伝達物質放出におけるシナプトタグミンの役割

Iain Robinson (Case Western Univ.)

S7-3 PSDの分子動態

岡部 繁男 (東京医科歯科大)

S7-4 足場タンパク質の役割

畑 裕 (東京医科歯科大)

S7-5 グルタミン酸受容体の微細マッピング

河西 春郎 (国立生理学研)

9月26日 (金) 9:00~11:30 ROOM301

S8 神経系における細胞外ATP機能の多様性

オーガナイザー：高坂 新一 (国立精神・神経センター), 井上和秀 (国立医薬品食品衛生研)

近年、神経系の様々な細胞種においてATP受容体の発現が確認され、更にはそれらの細胞に対しATPが濃度依存性に、あるいは受容体のタイプ依存性に多岐に渡った生理作用を示すことが明らかにされつつある。このことは、細胞外に放出されたATPが、神経系における細胞間相互作用あるいは神経情報処理に重要な役割を担っていることを示唆している。本シンポジウムでは細胞外ATPの多様な機能に関する最新の話題をとりあげ、その生理的重要性を議論する。

S8-1 神経-グリア-内皮細胞機能連関におけるATPの役割

南 雅文 (京大院・薬)

S8-2 ATPによるニューロン・グリアのアポトーシスと細胞内プロテアーゼ

中西 博 (九州大院・歯)

S8-3 ATPのミクログリアへの多彩な作用

大澤圭子 (国立精神・神経センター)

S8-4 海馬ネットワークのシナプス伝達制御における細胞外ATPの役割は何か?

加藤総夫 (慈恵医大・総合医科研)

S8-5 ATPによるニューロン活動の両方向性制御

井上和秀・小泉修一 (国立医薬品食品衛生研)

9月26日 (金) 12:30~15:00 スノーホールB

S9 ユビキチン・プロテアソーム系と神経疾患

オーガナイザー: 和田 圭司 (国立精神・神経センター)

パーキンソン病, ポリグルタミン病などの神経変性疾患ではその発症において蛋白質の凝集という共通事項が明らかになるとともに蛋白質の品質管理機構の一つとしてのユビキチン・プロテアソーム系の重要性に注目が集まっている。本シンポジウムでは神経疾患とユビキチン・プロテアソーム系に関してこれまで先端的な研究を行っている内外の研究者を招き, 研究の現状を紹介するとともに治療に向けた将来の展望について論議する。

S9-1 Dysfunction of the ubiquitin proteasome system in neurodegenerative disease

Ron Kopito (Stanford Univ.)

S9-2 Parkin and Parkinson's disease

服部 信孝 (順天堂大・医)

S9-3 Parkinson's disease and ER stress -from a study of autosomal recessive juvenile parkinsonism (AR-JP)

今居 譲 (理化学研)

S9-4 Pathophysiological role of ubiquitin C-terminal hydrolase L1 in neurodegeneration

和田 圭司 (国立精神・神経センター)

S9-5 Mechanisms to control degradation of polyglutamine-containing protein

中山 敬一 (九州大・生体防御医学研)

9月26日 (金) 12:30~15:00 ROOM302

S10 老齢脳と可塑性

オーガナイザー: 安藤 進 (都老人総合研)

加齢による脳機能の低下が問題になる中で, 神経細胞あるいはシナプスレベルでの可塑性の発揮が重要視される。そこで老齢脳における遺伝子発現, 神経栄養因子の役割, 活動依存性のシナプス可塑性, ニューロンの再生, などを議論する場としたい。

- S10-1 老齢脳と遺伝子発現**
森 望 (国立長寿研)
- S10-2 老齢脳とヒューマニン**
新倉 貴子 (慶応大・医)
- S10-3 老齢脳における神経栄養因子の役割**
古川 昭栄 (岐阜薬大)
- S10-4 豊富環境によるシナプス強化と学習能向上**
安藤 進 (都老人総合研)
- S10-5 老齢脳ニューロンの再生**
石 龍徳 (順天堂大医)

9月26日 (金) 12:30~15:00 ROOM301

S11 グリアーニューロン間クロストークによる神経情報処理機構

オーガナイザー：工藤 佳久 (東京薬大), 馬場 広子 (東京薬大)

最近, グリアとニューロンの間には直接的な情報伝達機構が存在しており, 脳機能発現に中心的な機能を果たしている可能性が示唆されている。これらの事実を根拠として, グリアーニューロン回路網の機構と意義の解明の重要性を解説する。

- S11-1 グリア細胞の多様性と特異的なグリアーニューロン相互作用**
池中 一裕 (国立生理学研)
- S11-2 グリアによる神経軸索上機能分子の発現および局在化の調節**
馬場 広子 (東京薬大)
- S11-3 グリアーニューロン回路網の存在と機能的意義**
工藤 佳久 (東京薬大)
- S11-4 小脳皮質におけるグリアーシナプス機能連関**
小澤 滯司 (群馬大・医)

ミニシンポジウム (括弧内番号は, 一般演題番号)

9月24日 (水) 9:00~10:15 ROOM302

MS1 神経変性疾患の分子機構

座長：佐野 輝 (鹿児島大院・医), 和田 圭司 (国立精神・神経センター)

- MS1-1 DRPLA蛋白の生理的機能解明に向けて**
(N054) 木村 哲也 (新潟大・脳研)

- MS1-2** 傍腫瘍性神経症候群疑いの患者血清を用いて同定された神経特異的新規ユビキチンリガーゼの機能解析
(N083) 多田 敬典 (慶応大・医/科技団)
- MS1-3** パエル受容体の蓄積および小胞体ストレスに対する4-フェニル酪酸の保護効果
(N056) 窪田 杏子 (北海道大・薬)
- MS1-4** 家族性筋萎縮性側索硬化症2型 (ALS2) の原因遺伝子産物ALS2は, 新規の
(N057) であり, エンドソーム動態調節に関与する
大友 麻子 (科技団/東海大・総合医学研/東海大院・医)
- MS1-5** 低アルブミン血症と眼球運動失行を伴う脊髄小脳変性症 (EAOH) の原因遺伝子
(N058) アプラタキンの一本鎖DNA修復機能における役割に関する検討
伊達 英俊 (新潟大・脳研)

9月24日 (水) 9:00~10:15 ROOM301

MS2 神経再生

座長: 岡野 栄之 (慶応大・医), 木山 博資 (大阪市大・医)

- MS2-1** 胎児由来神経幹細胞におけるG蛋白質共役型受容体の網羅的解析
(N001) 西本 美香 (国立精神・神経センター/東京薬科大・生命科学)
- MS2-2** ラット顔面神経切断により発現上昇する4回膜貫通型蛋白質の解析
(N032) 高坂 新一 (国立精神・神経センター)
- MS2-3** 脱髄モデルマウスへの神経幹細胞の移植とPSA-NCAMの再発現
(N033) 松本 路生 (国立生理学研究所)
- MS2-4** 損傷運動ニューロン生死とDNAメチレーション
(N034) 趙 天成 (大阪市大院・医)
- MS2-5** 損傷部脊髄内Semaphorin 3A阻害剤による損傷軸索の再生
(N035) 金子 慎二郎 (慶応大・医/同・生理)

9月24日 (水) 10:15~11:30 ROOM302

MS3 痴呆性疾患の分子機構

座長: 武田 雅俊 (大阪大院・医), 遠山 正彌 (大阪大院・医)

- MS3-1** マウス・タウ・イントロン10のヘアピン構造によるスプライシング制御
(N103) 山下 雄也 (大阪市大院・医)
- MS3-2** サイクリン依存性キナーゼ5によるFTDP-17型変異タウのリン酸化
(N104) 坂上 史佳 (都立大・理)
- MS3-3** アルツハイマー病セクレターゼはalpha2,6シアル酸転移酵素を生理的基質として
(N105) 切断する
橋本 康弘 (理化学研)

MS3-4 PEN-2によるガンマセクレターゼ活性促進機構の解析

(N106) 白石 博久 (国立長寿研)

MS3-5 セルフリーアッセイ法で β APPの γ セクレターゼによるDUAL切断をみる

(N107) 福森 亮雄 (大阪大院・医)

9月24日 (水) 10:15~11:30 ROOM301

MS4 シナプス機能制御

座長: 熊倉 鴻之助 (上智大), 高橋 正身 (北里大・医)

MS4-1 新規のシナプス後部スカフォードプロテイン, TANC

(N021) 鈴木 龍雄 (信州大院・医)

MS4-2 リガンド結合に依存したPSD-95のクラスターリング機構とPSDのクラスターが神経機能に果たす役割

野中 美応 (京都大・理)

MS4-3 Stargazin ファミリーのNMDA受容体依存的なプロテアーゼによる切断

(N023) 稲村 実穂子 (北里大・医/北里大病院・麻酔)

MS4-4 グルタミン酸刺激によるGFP標識ドレブリンAの樹状突起内局在変化の経時観察

(N024) 水井 利幸 (群馬大院・医)

MS4-5 グルタミン酸繰り返し刺激後の培養海馬切片における週単位の長期的シナプス増強

小倉 明彦 (大阪大院・生命機能研)

9月25日 (木) 8:45~10:00 ROOM302

MS5 神経栄養因子の活性と機能

座長: 古川 昭栄 (岐阜薬大), 那波 宏之 (新潟大・脳研)

MS5-1 ラット線条体初代培養神経細胞におけるEGFファミリー分子の放出調節

(N222) 岩倉 百合子 (新潟大・脳研)

MS5-2 BDNFにより活性化される翻訳伸長過程の解析

(N223) 稲村 直子 (新潟大・脳研)

MS5-3 成体ラット運動ニューロン損傷に対するGIF (MT-III) 組換えアデノウイルスの保護効果

坂本 剛 (都神経科学総合研究所)

MS5-4 bFGFの神経細胞保護作用におけるcalbindin-D28kの役割 -in vitro解析-

(N225) 門嶋 大輔 (第一サントリー生物医学研)

MS5-5 PACAPによる神経幹細胞の分化制御

(N226) 大多 茂樹 (慶応大・医)

9月25日 (木) 8:45~10:00 ROOM301

MS6 プロテインキナーゼ

座長：山内 卓 (徳島大・薬), 山本 秀幸 (熊本大・医)

- MS6-1** 急性けいれんによって引き起こされる自己リン酸化・不活性化・沈降型Ca²⁺/カルモジュリン依存性プロテインキナーゼII
(N146) 山肩 葉子 (国立生理学研)
- MS6-2** Arc による CaM kinase II 依存性神経突起伸展の促進
(N147) 土内 瞳 (徳島大・薬)
- MS6-3** カルモジュリンキナーゼカスケード構成分子の局在と活性制御機構
(N148) 笠原 二郎 (東北大院・薬)
- MS6-4** 視交叉上核における CaM キナーゼ II を介する mPer1 の誘導機構
(N255) 福永 浩司 (東北大院・薬)
- MS6-5** ヒポカルシンとMLK (mixed lineage kinase) 3の相互作用
(N149) 小林 正明 (東邦大・医)

9月25日 (木) 10:00~11:15 ROOM302

MS7 ニューロン・グリア

座長：高坂 新一 (国立精神・神経センター), 馬場 広子 (東京薬大)

- MS7-1** 神経特異的微小管崩壊因子RB3のN末端膜結合ドメインは微小管ダイナミクスを制御する
(N166) 中尾 千登世 (国立長寿研)
- MS7-2** ニューロフィラメント・ゲル形成過程に対する脱リン酸化の影響：マイクロビーズによるリアルタイム観察
(N167) 小野 れい (青学大・理工)
- MS7-3** PCRサブトラクション法を用いたOlig2下流因子の解析
(N174) 政平 訓貴 (国立生理学研/高知医大・医)
- MS7-4** 培養アストロサイトにおける細胞外SODの発現とその活性
(N175) 中村 洋一 (大阪府大院・農)
- MS7-5** 損傷脳における組織幹細胞の動態
(N176) 辰巳 晃子 (奈良県医大・解)
- MS7-6** グリア細胞特異的ERストレスセンサーOASISの機能解析
(N252) 近藤 慎一 (奈良先端科技大院)

9月25日 (木) 10:00~11:15 ROOM301

MS8 細胞分化と細胞系譜の分子機構

座長：池中 一裕 (国立生理研), 松岡 一郎 (北海道大・薬)

MS8-1 アストロサイト由来液性因子によるマウスおよびサルES細胞の神経細胞への分化誘導 (N208)

中山 孝 (横浜市大・医)

MS8-2 NRSF/RESTとDNAメチル化が細胞種特異的なBRINP1 (BMP-2 and Retinoic acid Inducible Neural-specific Protein 1) の発現を調節する (N209)

中谷 俊幸 (北海道大院・薬)

MS8-3 神経幹細胞に発現する転写因子Sox21の解析 (N210)

大場 宏幸 (慶応大・医)

MS8-4 エンドセリン受容体-G蛋白質Gi2による神経前駆細胞の増殖および運動促進 (N150)

浅野 富子 (愛知県コロニー研)

MS8-5 終脳オリゴデンドロサイトの細胞系譜解析 (N211)

竹林 浩秀 (国立生理学研)

MS8-6 Filamin A結合蛋白質FILIPによる大脳皮質脳室帯細胞の形態制御 (N170)

永野 隆 (福井医大・医)

ポスター

受容体, 輸送体

- N001 胎児由来神経幹細胞におけるG蛋白質共役型受容体の網羅的解析 (MS2-1)**
 ○西本 美香^{1,2}, 原 洋子¹, 鮎川 幸一¹, 大橋 洋輝^{1,3}, 工藤 佳久², 阿部 俊昭³, 青木 俊介¹, 和田 圭司¹
 (1国立精神・神経センター神経研究所, 2東京薬科大学 生命科学科, 3慈恵会医科大学 医学部)
- N002 神経型グルタミン酸トランスポーター EAAT3 (EAAC1) を介した特異的なグルタミン酸取り込み機構**
 ○氷見 敏行¹, 池田 正行², 安原 義³, 森田 育男¹, 室田 誠逸¹ (1東京医科歯科大学 大学院医歯学総合研究科 分子細胞機能学, 2国立犀潟病院, 3東京農業大学)
- N003 PC12細胞におけるバニロイドVR1受容体の発現**
 ○染谷 晃好, 国枝 佳奈, 平林 哲也, 堀江 俊治, 村山 俊彦 (千葉大学大学院 薬学研究院 薬効薬理学研究室)
- N004 マウス嗅覚系発生過程におけるTNFレセプタースーパーファミリー, TROY, の発現**
 ○久岡 朋子¹, 森川 吉博¹, 北村 俊雄², 仙波 恵美子¹ (1和歌山県立医科大学 第二解剖, 2東京大学 医科学研究所 先端医療センター 細胞療法分野)
- N005 ラット海馬組織培養におけるbicuculline methiodideの神経毒性作用**
 ○韓 春錫, 河西 奈保子, 鳥光 慶一 (NTT物性科学基礎研究所)
- N006 初代培養神経細胞のインビトロ成熟に伴うNMDA受容体チャネル感受性変化**
 ○中道 範隆, 神戸 悠輝, 及川 弘崇, 米田 幸雄 (金沢大学大学院 自然科学研究科 薬物学研究室)
- N007 精巢内における特定グルタミン酸シグナリング分子の機能的発現**
 ○宝田 剛志, 檜井 栄一, 谷浦 秀夫, 米田 幸雄 (金沢大学 薬学部)
- N008 グループII型mGluRシグナルを介するAP1 DNA結合能の調節**
 ○杉山 千絵, 谷浦 秀夫, 米田 幸雄 (金沢大学大学院 自然科学研究科 薬物学研究室)
- N009 メラニン凝集ホルモン受容体1 (MCHR1) N末端及びC末端の構造機能解析**
 ○斎藤 祐見子, 手塚 満恵, 丸山 敬 (埼玉医科大学 薬理学教室)
- N010 イオントロピック型グルタメイトレセプターの免疫組織化学的検出**
 ○玉置 啓祐¹, 山田 清文¹, 米山 雅紀², 北山 友也³, 米田 幸雄² (1金沢大学 薬学部 病院薬学研究室, 2金沢大学大学院 自然科学研究科 薬物学研究室, 3広島大学大学院 医歯学総合研究科 創生医科学専攻病態探究医科学講座薬理学分野)
- N011 NMDA受容体による成熟脳海馬由来神経系前駆細胞の分化制御**
 ○米山 雅紀¹, 北山 友也², 米田 幸雄¹ (1金沢大学 自然科学研究科 薬物学研究室, 2広島大学大学院 医歯学総合研究科 創生医科学専攻病態探究医科学講座)
- N012 高浸透圧刺激によるp38MAPKを介したアクアポリンの発現調節**
 ○祖父江 和哉¹, 山本 直樹², 有馬 一¹, 伊藤 弘晃¹, 稲垣 雅昭¹, 森島 徹朗¹, 梅西 文範³, 勝屋 弘忠¹, 浅井 清文² (1名古屋大学大学院医学研究科危機管理医学, 2名古屋大学大学院医学研究科分子神経生物学, 3コロラド大学ヘルスサイエンスセンター)
- N013 骨芽細胞におけるGABAトランスポーター**
 ○藤森 さゆ美, 檜井 栄一, 家亦 美佳, 村藤 康裕, 米田 幸雄 (金沢大学大学院 自然科学研究科 薬物学)
- N014 ラット脳膜標品における³⁵S]GTP γ S結合に対する5-HT_{1B/1D}受容体作動薬の影響**
 ○小田垣 雄二, 山内 俊雄 (埼玉医科大学 精神医学)
- N015 エンドフィリン3によるドーパミン D2 受容体エンドサイトーシスの阻害**
 ○杉浦 弘子¹, 岩田 健², 山内 卓³, 芳賀 達也², 山形 要人¹ (1東京都神経科学総合研究所 神経薬理研究部門, 2学習院大学 理学部 生命分子科学研究所, 3徳島大学 薬学部 生化学研究室)
- N016 部位特異的変異体とコンピューター理論計算による嗅覚受容体のリガンド結合部位の解析**
 ○堅田 明子¹, 広川 貴次², 諏訪 牧子², 片岡 宏誌¹, 東原 和成¹ (1東京大学大学院 新領域創成科学研究科 先端生命科学専攻, 2産業技術総合研究所 生命情報科学研究センター)
- N017 味覚受容細胞に発現する苦味受容体とG α サブユニットとの相互作用について**
 ○植田 高史, 鶴川 真也, 山村 寿男, 島田 昌一 (名古屋大学 大学院 医学研究科 分子形態学)

- N018** 初代培養マウス中脳神経細胞細胞内カルシウムシンクロナスオシレーションにおいてドーパミンレセプター2は電位依存性Lタイプカルシウムチャネルを調節する
○安本 史恵¹, 根岸 隆之^{1,3}, 石井 寿幸¹, 久和 茂¹, 黒田 洋一郎^{2,3}, 吉川 泰弘^{1,3} (¹東京大学 大学院 農学生命科学研究科, ²東京都神経科学総合研, ³CREST,JST)
- N019** ラット脳におけるASCT1アミノ酸トランスポーターの分子多様性
山本 敏文¹, ○宅間 仁志¹, 西崎 糸音¹, 額田 敏秀², 古屋 茂樹³, 平林 義雄³, 池田 和隆², 小林 秀昭², 曾良 一郎⁴, 山本 秀子² (¹横浜市立大学 大学院総合理学研究科 分子認識, ²東京都精神医学総合研究所 分子精神医学, ³理化学研究所脳科学総合研究センター, ⁴東北大学大学院医学研究科 精神・神経生物学分野)
- N020** IP3 receptor type 1 mRNA の3'末端非翻訳領域に結合するRNA結合タンパク質Hzfと小脳Purkinje細胞における樹状突起へのmRNA局在化機構
○飯島 崇利^{1,2,3}, 高月 香菜子⁴, 宮崎 太輔⁵, 今井 貴雄^{1,2}, 岡野 ジェームス洋尚^{1,2}, 木村 友喜⁶, 川原 茂敬⁴, Alan Bernstein⁶, 渡辺 雅彦⁵, 桐野 豊⁴, 岡野 栄之^{1,2} (¹慶應義塾大学 医学部 生理学教室, ²科学技術振興事業団, ³大阪大学大学院 医学系研究科 機能形態学講座, ⁴東京大学大学院 薬学研究科 神経生物物理学, ⁵北海道大学大学院 医学研究科 生体構造解析学, ⁶マウントシナイ病院 サミュエルルーネンフェルド研究所)

シナプス

- N021** 新規のシナプス後部スカフホードプロテイン, TANC
(MS4-1) ○鈴木 龍雄, 李 衛陶, 張 静へい (信州大学大学院医学研究科加齢適応医科学系独立専攻神経可塑性学分野)
- N022** リガンド結合に依存したPSD-95のクラスターリング機構とPSDのクラスターが神経機能に果たす役割
(MS4-2) ○野中 美応¹, 田中 彩子¹, 土井 知子¹, 藤吉 好則¹, 竹本-木村 さやか^{2,3}, 尾藤 晴彦³ (¹京都大学 理学研究科 生物科学専攻 生物物理学系, ²京都大学 医学研究科, ³東京大学 医学系研究科)
- N023** Stargazin ファミリーのNMDA受容体依存的なプロテアーゼによる切断
(MS4-3) ○稲村 実穂子^{1,3}, 板倉 誠¹, 辻村 淳², 工藤 佳久², 岡本 浩嗣³, 外 須美夫³, 山森 早織¹, 高橋 正身¹ (¹北里大学医学部, ²東京薬科大学, ³北里大学病院麻酔科)
- N024** グルタミン酸刺激によるGFP標識ドレブリンAの樹状突起内局在変化の経時観察
(MS4-4) ○水井 利幸^{1,2}, 花村 健次¹, 高橋 秀人¹, 白尾 智明¹, 関野 祐子^{1,3} (¹群馬大学 大学院 医学系研究科 高次細胞機能学, ²群馬大学 大学院 医学系研究科 保健学専攻 生体環境情報科学, ³科技団, 戦略基礎)
- N025** グルタミン酸繰り返し刺激後の培養海馬切片における週単位の長期的シナプス増強
(MS4-5) ○小倉 明彦¹, 奥原 啓輔², 富永 (吉野) 恵子¹ (¹大阪大学 大学院生命機能研究科, ²大阪大学 大学院 理学研究科)
- N026** 細胞接着分子L1の海馬における電子顕微鏡解析
○中村 雪子, 山崎 浩誠, 塩坂 貞夫 (奈良先端科学技術大学院大学 バイオサイエンス研究科 細胞構造学講座)
- N027** シナプス前アデノシン受容体による孤束核シナプス伝達短期可塑性の修飾
○津氏 典子¹, 繁富 英治², 加藤 総夫² (¹東京理科大学 薬学研究科 薬理, ²東京慈恵会医科大学 総合医科学研究センター 神経生理)
- N028** I213T PS1ノックインマウスの電気生理学的性状に関する検討
○以倉 康充, 工藤 喬, 金山 大祐, 福森 亮雄, 大河内 正康, 武田 雅俊 (大阪大学大学院 医学系研究科 精神医学教室)

再生, 移植

- N029** 視神経損傷後の金魚とラットにおけるガレクチン1とガレクチン3の発現の違いについて
○金田 学, 田中 聖之, 杉谷 加代, 加藤 聖 (金沢大・院医・脳情報分子学)
- N030** 金魚視神経再生におけるレチノール結合蛋白質ブルブリンの役割
○田中 聖之¹, 松川 通¹, 中川 貴志¹, 馬渡 一浩², 郡山 恵樹¹, 荒井 國三¹, 加藤 聖¹ (¹金沢大・院医・脳情報分子学, ²金沢大・医・保健)

- N031 骨髄移植初期に脳内へ移行する細胞は造血系細胞の性質を維持する**
○小野 健治^{1,2}, 吉原 賢¹, 鈴木 弘美¹, 須原 哲也², 澤田 誠¹ (藤田保健衛生大学 総合医科学研究所 難病治療共同研究部門, ²放射線医学総合研究所 脳機能イメージング研究開発推進室)
- N032 ラット顔面神経切断により発現上昇する4回膜貫通型蛋白質の解析**
(MS2-2) 佐々木 洋, ○星 雅人, 中村 泰子, 都築 早美, 赤澤 智宏, 高坂 新一 (国立精神・神経センター 神経研究所 代謝研究部)
- N033 脱髄モデルマウスへの神経幹細胞の移植とPSA-NCAMの再発現**
(MS2-3) ○松本 路生¹, 竹林 浩秀¹, 鹿川 哲史², François Lachapelle³, Anne Baron-Van Evercooren³, 池田 一裕¹ (1) 岡崎国立共同研究機構 生理学研究所 分子神経生理研究部門, ²熊本大学 発生医学研究センター, ³INSERM U546, France)
- N034 損傷運動ニューロン生死とDNAメチレーション**
(MS2-4) ○趙 天成, 桐生一瀬尾 寿美子, 木山 博資 (大阪市立大学 大学院医学研究科 機能細胞形態学)
- N035 損傷部脊髄内Semaphorin 3A阻害剤による損傷軸索の再生**
(MS2-5) ○金子 慎二郎^{1,2}, 岩波 明生^{1,2}, 中村 雅也¹, 宮尾 幸代^{1,2}, 岸野 晶祥³, 菊地 薫³, 木村 徹³, 熊谷 和夫³, 戸山 芳昭¹, 岡野 栄之² (1) 慶應義塾大学整形外科, ²慶應義塾大学生理学, ³住友製薬研究本部)
- N036 金魚およびラット視神経損傷後網膜における細胞生存・細胞死シグナル**
○本間 啓子, 郡山 恵樹, 菅原 清, 劉 中武, 加藤 聖 (金沢大学 医学部 脳情報分子学)
- N037 ラット顔面神経軸索損傷モデルにおけるSH3 binding domain glutamic acid rich protein like 3 (SH3BGRL3) の発現上昇**
○星 雅人, 佐々木 洋, 赤澤 智宏, 高坂 新一 (国立精神・神経センター 神経研究所 代謝研究部)
- N038 損傷運動ニューロン生死を決定する神経細胞型グルタミン酸トランスポーターEAAC1/EAAT3**
○桐生一瀬尾 寿美子¹, 加藤 隆一^{1,2}, 平山 光久^{1,3}, 木山 博資¹ (1) 大阪市立大学 大学院医学研究科 機能細胞形態学, ²札幌医科大学 泌尿器科, ³旭川医科大学 整形外科)
- N039 パーキンソン病モデルサルにおけるES細胞由来神経幹細胞移植によるドーパミン機能の回復**
○村松 慎一¹, 中山 孝², 永田 三保子¹, 鈴木 豊³, 近藤 靖³, 小野 文子⁴, 池口 邦彦¹, 藤本 健一¹, 寺尾 恵治⁴, 井上 順雄², 塚田 秀夫⁵, 中野 今治¹ (1) 自治医科大学 内科学講座 神経内科, ²横浜市立大学 医学部 生化学第一講座, ³田辺製薬, ⁴国立感染症研究所筑波霊長類センター, ⁵浜松ホトニクス)
- N040 ガレクチン-1に対する2つのモノクローナル抗体Gal3D11とGal5E5の特徴**
○吉村 和法¹, 亀谷 富由樹², 藤牧 香代¹, 門屋 利彦³, 阿相 皓晃⁴, 野村 正彦¹ (1) 埼玉医科大学 医学部 生理学, ²東京都精神医学総合研究所 分子神経生物学, ³キリンビール (株) 医薬カンパニー生産本部 生産技術センター, ⁴東京都老人総合研究所 グリア細胞研究グループ)
- N041 成熟マウス脳由来ニューロソフェアによる脳外傷マウスの行動異常の部分回復**
○水野 勝重, 渡辺 康裕 (防衛医科大学校 薬理学講座)
- N042 冠状切断後のラット脊髄へのFGF-2投与による脊髄内軸索再生および運動機能の改善**
○慈幸 貴洋, 福光 秀文, 古川 昭栄 (岐阜薬科大学 薬学部 分子生物学教室)

老 化

- N043 脳シナプス機能の加齢変化とカルニチン投与効果**
○田中 康一, 岩本 真知子, 脇 初枝, 近 一夫, 安藤 進 (東京都老人総合研究所 脳機能改善研究グループ)
- N044 神経幹細胞に発現するヒストン脱アセチル化酵素Sir2**
○堀尾 嘉幸, 久原 真 (札幌医科大学 医学部 薬理学講座)

疾患モデル

- N045 認知機能における上皮成長因子の関与**
○水野 誠, 橋本 慎也, 丸太 保室, 那波 宏之 (新潟大学 脳研究所 分子神経生物学分野)

- N046 C57BL/6マウスにおけるMPTP誘発ドパミン神経毒性の加齢による影響**
森 厚詞^{1,2}, ○大橋 聡¹, 中井 正三¹, 栗原 直樹¹, 光本 泰秀¹, 森泉 哲次² (1大塚製薬株式会社 探索第二研究所, 2信州大学 医学部 医学科 人体構造学講座)
- N047 全長ハンチンチンを用いたハンチントン病の誘導性トランスジェニックマウスモデル**
○田中 有史¹, 五十嵐 修一², 中村 雅之³, 森田 北斗³, Gabriele Schilling⁴, Tracy Wanner³, Yujin Kim³, Jonathan D. Wood⁵, David R. Borchelt⁴, Christopher A. Ross^{3,6} (1岡山大学大学院 医歯学総合研究科 精神神経病態学教室, 2新潟大学 脳研究所附属 生命科学リソース研究センター, 3ジョンズ・ホプキンス大学 医学部 精神科, 4ジョンズ・ホプキンス大学 医学部 病理学, 5シェフィールド大学 神経内科部門, 6ジョンズ・ホプキンス大学 医学部 神経科学)
- N048 周産期アミオダロン投与がラットの成長後の一般行動に与える影響**
○須崎 真悟¹, 根岸 隆之^{1,4}, 川崎 勝義^{2,4}, 石井 寿幸¹, 久和 茂¹, 吉川 泰弘^{1,4}, 黒田 洋一郎^{3,4} (1東京大学大学院農学生命科学研究科獣医学専攻 実験動物学教室, 2星薬科大学 心理学研究室, 3京都神経科学総合研究所 分子神経生物学研究部門, 4CREST, JST)
- N049 脳内でCre-ERTを発現するトランスジェニックマウスの作成**
○小島 雅代¹, 神谷 鳴美², 一瀬 千穂², 野村 隆英², Daniel Metzger³, Pierre Chambon³, 一瀬 宏¹ (1東京工業大学 大学院 生命理工学研究科, 2藤田保健衛生大学 医学部 薬理学, 3IGBMC, CNRS, INSELM, College de France, Universite Louis Pasteur, Illkirch, France)
- N050 疾患モデルマウスを用いたChorea-acanthocytosis原因遺伝子CHACの機能解析**
○留守 ゆう子¹, 市場 美緒¹, 楠本 朗¹, 森田 恵三子¹, 上野 修一², 佐野 輝¹ (1鹿児島大学大学院 医歯学総合研究科 健康科学専攻 社会・行動医学講座 精神機能病学, 2徳島大学 医学部 情報統合医学 (精神医学))
- N051 Sodium Butyrate Ameliorates Phenotypic Expression in a Transgenic Mouse Model of Spinal and Bulbar Muscular Atrophy**
○南山 誠, 勝野 雅央, 足立 弘明, 小林 靖, 道勇 学, 祖父江 元 (名古屋大学 大学院医学系研究科 神経内科)

発育, 発達障害

- N052 シナプス形成をモニターする定量的オリゴDNAマイクロアレイ「シナプトアレイ」の開発**
○若山 勇太¹, 高橋 理貴¹, 近藤 恭光², 田代 英夫², 田代 朋子^{1,3} (1青山学院大学 理工学部 化学科, 2理化学研究所 工学基盤研究部, 3科学技術振興事業団 戦略的基礎研究推進事業)
- N053 発達期マウス小脳における遺伝子発現とこれに対する実験的甲状腺機能低下の影響**
○高橋 理貴¹, 若山 勇太¹, 近藤 恭光², 田代 英夫², 太田 美佐江^{3,4}, 鯉淵 典之^{3,4}, 田代 朋子^{1,4} (1青山学院大学 理工学部 化学科, 2理化学研究所 工学基盤研究部, 3群馬大学 医学部 生理学第一, 4科学技術振興事業団 戦略的基礎研究推進事業)

変性疾患

- N054 DRPLA蛋白の生理的機能解明に向けて**
(MS1-1) ○木村 哲也¹, 赤岩 靖久¹, 山田 光則², 高野 雅彦¹, 佐藤 俊哉³, 小宅 睦郎¹, 勝木 元也⁴, 西澤 正豊¹, 辻 省次⁵ (1新潟大学 脳研究所 神経内科, 2新潟大学 脳研究所 病理学分野, 3新潟大学 脳研究所 附属生命科学リソース研究センター 動物資源開発支援研究部門, 4基礎生物学研究所, 5東京大学 大学院医学研究科 神経内科)
- N055 蛋白質の構造異常・凝集体形成を標的とするペプチドQBP1によるポリグルタミン病の分子治療**
○永井 義隆¹, ポピエル ヘレナ明子¹, 藤掛 伸宏¹, 乾 隆², 福井 健司¹, 山口 政光³, 裏出 良博⁴, 内木 宏延⁵, 戸田 達史¹ (1大阪大院 医学系 ポストゲノム疾患解析学 ゲノム機能, 2三重短大 生活科学 栄養学, 3京都工繊大 応用生物 染色体工学, 4大阪バイオ研 2部, 5福井医大 2病理)
- N056 バエル受容体の蓄積および小胞体ストレスに対する4-フェニル酪酸の保護効果**
(MS1-3) ○窪田 杏子, 新沼 芳文, 金子 雅幸, 野村 靖幸 (北海道大学 薬学部 薬学研究科)

- N057 家族性筋萎縮性側索硬化症2型 (ALS2) の原因遺伝子産物ALS2は、新規のRab5GEFであり、エンドソーム動態調節に関与する**
 ○大友 麻子^{1,2,3}, 秦野 伸二^{1,2}, 岡田 武也², 水村 光¹, 國田 竜太¹, 西島 ひとし⁴, 将口 淳子², 柳沢 佳子¹, 古曳 英理¹, 須賀 恵津子¹, 安田 まさのり⁵, 大須賀 等^{1,2}, 西本 毅治⁴, 成宮 周⁶, 池田 稜衛^{1,2,3,7}
 (1)科学技術振興事業団 基礎的研究発展推進事, 2)東海大学 総合医学研究所 分子神経科学部門, 3)東海大学 大学院 医学研究科, 4)九州大学 大学院 医学研究科, 5)東海大学 医学部 病理学教室, 6)京都大学 医学部 大学院 医学研究科 神経・細胞薬理, 7)オタワ大学 医学部)
- N058 低アルブミン血症と眼球運動失行を伴う脊髄小脳変性症 (EAOH) の原因遺伝子アブラタキンの一本鎖DNA修復機能における役割に関する検討**
 ○伊達 英俊¹, 五十嵐 修一¹, 高橋 俊昭¹, 高野 弘基¹, 小野寺 理¹, 西澤 正豊¹, 佐野 泰照², 辻 省次³
 (1)新潟大学 脳研究所 神経内科, 2)山口大学 神経内科, 3)東京大学 大学院 医学系研究科 神経内科)
- N059 ALS2 C-terminal like (ALS2CL) : ALS2タンパク質C末領域と高い相同性を示す新規タンパク質をコードする遺伝子の同定とその構造解析**
 ○秦野 伸二^{1,2}, 大友 麻子¹, 柳沢 佳子², 将口 宮田 淳子¹, 鈴木 恭子¹, 國田 竜太², 水村 光², 池田 稜衛^{1,2} (1)東海大学 総合医学研究所 分子神経科学部門, 2)科学技術振興事業団 基礎的研究推進事業)
- N060 全長DRPLA蛋白はCREBおよびp53転写活性化を抑制する**
 ○下畑 享良¹, 小倉 香織¹, 成瀬 聡¹, 五十嵐 修一², 佐藤 俊哉³, 小野寺 理², 西澤 正豊¹, 辻 省次^{1,4}
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- N061 COMPLEX I 阻害剤であるロテノンたんぱく酸化修飾を介するプロテアソーム阻害によりドパミン神経細胞死を惹起する**
 ○丸山 和佳子¹, 直井 信² (1)国立長寿医療研究センター 老化機構研究部 生化学, 代謝研究室, 2)岐阜国際バイオ研究所)
- N062 ラサジリンはNF-kappaBの活性化を介してSH-SY5Y細胞にGDNFおよびBCL-2を誘導する**
 ○直井 信¹, 丸山 和佳子², 新田 淳美³, 平田 洋子⁴ (1)岐阜国際バイオ研究所 脳科学部門, 2)国立長寿医療研究センター, 3)名古屋大学, 4)岐阜大学)
- N063 プロテアソーム阻害剤で誘発されるユビキチン化蛋白質とHsp27の不溶化および細胞死は熱ショック転写因子の活性化が関与している**
 ○加藤 兼房, 伊東 秀紀, 岩本 郁子, 稲熊 裕, 滝澤 剛則 (愛知県心身障害者コロニー 発達障害研究所)
- N064 マウス海馬におけるトリメチルスズによるJNK/SAPK経路の活性化**
 ○西山 徳人¹, 新田 有紀¹, 渡邊 真未¹, 米田 幸雄², 荻田 喜代一¹ (1)摂南大学 薬学部 薬理学研究室, 2)金沢大学大学院 自然科学研究科 薬物学研究室)
- N065 神経芽細胞腫SH-SY5Yにおける小胞体ストレスによる高分子熱ショック蛋白質の発現**
 ○岩本 直子¹, 山室 晶子², 長嶋 玲子¹, 前田 定秋², 伊藤 文昭³, 米田 幸雄⁴, 荻田 喜代一¹ (1)摂南大学 薬学部 薬理学研究室, 2)摂南大学 薬学部 薬物治療学研究室, 3)摂南大学 薬学部 生化学研究室, 4)金沢大学大学院 自然科学研究科 薬物学研究室)
- N066 メタンフェタミンのParkin及びPael-receptor遺伝子発現に対する影響**
 ○山田 英孝¹, 中原 辰雄¹, 黒木 俊秀², 橋本 喜次郎¹, 堤 哲之¹, 梶畑 俊雄², 平野 誠¹ (1)国立肥前療養所 臨床研究部, 2)九州大学 大学院医学研究院 精神病態医学分野)
- N067 神経細胞とグリア細胞で同定された新規Znフィンガー/RINGフィンガー含有分子, MomoとSakura**
 ○荒木 一明¹, 川村 名子¹, 神辺 太樹¹, 石井 京子¹, 市川 富夫², 熊西 敏郎², 田中 啓二³, 武井 延之¹, 那波 宏之¹ (1)新潟大学 脳研究所 分子神経生物学分野, 2)新潟大学 脳研究所 分子病理学分野, 3)東京都臨床医学総合研究所 分子腫瘍学研究部門)
- N068 カイニン酸によるNrf2/Fos-B複合体の形成を介するantioxidant-response element結合の増強**
 ○荻田 喜代一¹, 西山 徳人¹, 渡邊 真未¹, 米田 幸雄² (1)摂南大学 薬学部 薬理学研究室, 2)金沢大学大学院 自然科学研究科 薬物学研究室)
- N069 脳に高発現する膜結合型, 新規ユビキチン・ライゲース (MomoおよびSakura) の生化学的解析**
 ○川村 名子¹, 荒木 一明¹, 鈴木 俊顕², 松田 憲之², 神辺 太樹¹, 千葉 智樹², 田中 啓二², 那波 宏之¹ (1)新潟大学 脳研究所 分子神経生物学分野, 2)東京都臨床医学総合研究所 分子腫瘍学研究部門)

- N070 パーキンソン病モデル線条体へのメラニン合成酵素チロシナーゼ産生細胞の移植**
○浅沼 幹人, 宮崎 育子, 小川 紀雄 (岡山大学 大学院医歯学総合研究科 脳神経制御学講座 神経情報学)
- N071 アミロイドbeta-蛋白 (Abeta) 1-42による神経毒性に対するAbeta1-40の細胞保護作用の検討**
Kun Zou¹, Daesung Kim², 垣尾 敦子³, Kyunghee Byun², キョウ 建生^{1,4}, Myeongju Kim², 澤村 直哉^{1,5}, 西本 清一³, 松崎 勝巳⁶, Bonghee Lee², 柳澤 勝彦¹, ○道川 誠¹ (1国立長寿医療研究センター痴呆疾患研究部, 2チェジュ大学医学部解剖・神経科学, 3京都大学工学研究科 物質エネルギー化学専攻, 4医薬品機構, 5日本学術振興会, 6京都大学大学院薬学研究科)
- N072 伸長ポリグルタミンタンパク質による細胞毒性に対するHsp105の抑制効果**
○石原 慶一¹, 山岸 伸行¹, 斉藤 洋平¹, 足立 弘明², 小林 靖², 祖父江 元², 大塚 健三³, 畑山 巧¹ (1京都薬科大学 薬学部 生化学, 2名古屋大学 神経内科, 3中部大学 環境生物科学)
- N073 西インド諸島グアデロープ島に発生する地域特異的神経変性疾患における原因物質同定へのアプローチ**
○古武 弥一郎¹, 神蘭 真智子¹, 奥田 勝博¹, 松元 直樹¹, 棚橋 孝雄^{1,2}, 原 博³, Dominique Caparros-Lefebvre⁴, 太田 茂¹ (1広島大学 大学院医歯薬学総合研究科, 2神戸薬科大学, 3東京理科大学 薬学部, 4Antilles大学病院 神経科)
- N074 LPS投与神経変性疾患モデルラットにおけるグリア細胞および神経細胞間の相互作用の検討**
○井出 昌利, 田中 佐知子, 沼澤 聡, 吉田 武美 (昭和大学 薬学部 毒物学教室)
- N075 SH-SY5Y細胞におけるパーオキシナイトライトによる小胞体ストレスの誘導**
○森田 恵子, 山室 晶子, 桑田 るみこ, 吉岡 靖啓, 前田 定秋 (摂南大学 薬学部 薬物治療学研究室)
- N076 ポリグルタミンによるin vitro凝集形成**
○豊島 至, 小林 道雄, 小原 講二, 大川 聡, 菅原 正伯 (秋田大学 医学部 第一内科)
- N077 MK-801のプロテアーゼ活性における異なる効果とPTZ誘発離群ラットのグリア細胞発現**
○Md. Mahiuddin Ahmed¹, 知久馬 敏幸², 加藤 武¹ (1横浜市立大学 総合理科学研究科 分子認識部門, 2昭和薬科大学 公衆衛生化学)
- N078 茶葉成分テアニンの神経保護作用分子機構の解明**
藤本 貞毅¹, ○青木 洋満¹, 長井 克仁¹, 左塚 泰之², 下濱 俊³, 長澤 一樹¹ (1京都薬科大学 薬学部, 2静岡県立大学 薬学部, 3京都大学 医学部大学院)
- N079 運動神経変性疾患モデル (Mnd) マウスの中枢神経変性過程におけるリコピンの抗酸化効果**
○芳本 信子¹, 藤田 公和², 村上 洋子¹, 猪飼 弘子¹, 菅沼 大行³, 稲熊 隆博³, 今田 英己², 永田 豊², 宮地 栄一² (1名古屋文理短大, 2藤田保健衛生大学 医学部 生理, 3カゴメ (株) 総合研究所)
- N080 神経変性を伴う無セルロプラスミン血症のin vitroモデル -グリア細胞への鉄の蓄積-**
○大城 聡¹, 中嶋 一行² (1東京医科歯科大学 難治疾患研究所 遺伝生化学, 2創価大学 生命科学研究所 神経化学)
- N081 ポリグルタミン蛋白質の分解におけるオートファジーの関与について**
○岩田 淳¹, Ron Kopito², 辻 省次¹ (1東京大学大学院 医学系研究科 神経内科学教室, 2スタンフォード大学 生物科学科)
- N082 伴性劣性遺伝型副腎白質ジストロフィー症で障害される器官でのアシル CoA 合成酵素 Lipidosin の発現ならびに実験的脱髄・髄鞘再形成過程での発現変化**
○宋 時榮¹, 加藤 千恵子¹, 安達 栄治郎², 稲川-小柏 匡代¹, 橋本 有弘¹ (1三菱化学生命科学研究所, 2北里大学 大学院 医療系研究科 分子形態科学)
- N083 傍腫瘍性神経症候群疑いの患者血清を用いて同定された神経特異的新規ユビキチンリガーゼの機能解析 (MS1-2) 析**
○多田 敬典^{1,2,3}, 岡野 ジェイムス 洋尚^{1,3}, 鹿島 晴雄², 岡野 栄之^{1,3} (1慶応義塾大学 医学部 生理学教室, 2慶応義塾大学 医学部 精神神経学教室, 3科学技術振興事業団 戦略的創造研究)
- N084 DRPLA疾患モデルマウスにおける伸長ポリグルタミンによるCREB依存性転写活性障害の検証**
○高野 政彦¹, 赤岩 靖久¹, 木村 哲也¹, 佐藤 俊哉², 小宅 睦郎¹, 西澤 正豊¹, 辻 省次³ (1新潟大学 脳研究所 神経内科, 2新潟大学 脳研究所 動物資源開発支援研究部門, 3東京大学 神経内科)
- N085 合成polyQ導入大脳皮質培養系における神経及びグリア由来栄養因子とその受容体の発現解析**
○佐竹 輝洋, 小池 達郎 (北海道大学 大学院理学研究科 生物科学専攻)

- N086** ポリグルタミン病における転写障害assay系の確立
○高橋 俊昭¹, 野崎 兼吉¹, 小野寺 理¹, 西澤 正豊¹, 辻 省次² (¹新潟大学脳研究所神経内科, ²東京大学大学院医学系研究科神経内科)
- N087** 1本鎖DNA修復におけるアプラタキシンの生化学的機能の解析
○高橋 哲哉¹, 五十嵐 修一¹, 伊達 英俊¹, 小野寺 理¹, 西澤 正豊¹, 辻 省次² (¹新潟大学 脳研究所神経内科, ²東京大学 神経内科)
- N088** SCA6でのポリグルタミン封入体の形成・分解機序: ユビキチン・プロテアソーム系とライソゾーム系の比較
○石川 欽也¹, 巻淵 隆夫², 木南 英紀³, 水澤 英洋¹ (¹東京医科歯科大学 医学部 附属病院 神経内科, ²国立療養所厚労病院臨床研究部, ³順天堂大学医学部第1生化学)
- N089** synphilin-1の膜脂質結合特性
○高橋 哲也, 永野 義人, 中村 毅, 山下 拓史, 松本 昌泰 (広島大学 医学部 脳神経内科)
- N090** DRPLAノックアウトマウスを用いた遺伝子発現プロファイリング
○赤岩 靖久¹, 高野 政彦¹, 木村 哲也², 佐藤 俊哉³, 小宅 睦郎¹, 辻 省次⁴ (¹新潟大学 脳研究所 神経内科, ²新潟大学医学部保健学科基礎生体情報学講座, ³新潟大学脳研究所附属生命科学リソース研究センター動物資源開発支援研究部門, ⁴東京大学大学院医学系研究科神経内科)

精神疾患

- N091** 不安惹起物質投与により生後発達依存性に発現する脳内遺伝子に関する研究
○車地 暁生, 海野 麻未, 田浪 将和, 伊藤 篤志, 浅川 路子, 伊藤 卓, 石井 澄和, 西川 徹 (東京医科歯科大学大学院 精神行動医科学分野)
- N092** 神経幹細胞の分化誘導能に及ぼす抗うつ薬・気分安定薬の影響
○鶴飼 渉, 小澤 寛樹, 館農 勝, 紺野 雅人, 山本 恵, 酒井 理恵, 池田 官司, 齋藤 利和 (札幌医科大学 医学部 神経精神医学講座)
- N093** 統合失調症の背外側前頭前皮質におけるニューレグリン1の発現解析
○橋本 亮太¹, Richard Straub², Cynthia Weickert², Thomas Hyde², Joel Kleinman², Daniel Weinberger² (¹国立精神・神経センター 神経研究所 疾病研究第三部, ²米国国立衛生研究所 国立精神衛生研究所 臨床脳疾患部門)
- N094** Interleukin-1 α の末梢投与によるラットの音刺激驚愕反応の低下
○任海 学, 那波 宏之 (新潟大学 脳研究所 分子神経生物学分野)

筋疾患

- N095** O-Man型糖鎖不全と神経細胞遊走異常を伴う先天性筋ジストロフィー
○遠藤 玉夫¹, 萬谷 博¹, 小林 千浩², 谷口 紀代美², 戸田 達史² (¹東京都老人総合研究所 糖蛋白質研究グループ, ²大阪大学大学院医学系研究科 ポストゲノム疾患解析学講座 ゲノム機能分野)
- N096** MuSK自己抗体による重症筋無力症の分子機構解析
○重本 和宏¹, 久保 幸穂², 太田 光熙³, 太田 潔江⁴, 丸山 直記² (¹愛媛大学 医学部 衛生学, ²東京都老人総合研究所 加齢臓器障害研究グループ, ³神戸薬科大学 臨床化学, ⁴国立療養所 宇多野病院 臨床研究部)

虚血

- N097** 脳凍結損傷モデルにおけるアクアポリンの発現変化
○山本 直樹¹, 祖父江 和哉², 多田 豊曠³, 浅井 清文⁴ (¹国立長寿医療研究センター 痴呆疾患研究部, ²名古屋市大・院医・危機管理医学, ³名古屋市大・看護, ⁴名古屋市大・院医・分子神経生物学)
- N098** 30分間中大脳動脈一過虚血後のブドウ糖代謝の変化—ex vivo ¹³C-NMRスペクトロスコピーによる研究—
○金松 知幸¹, 高原 ひろみ¹, 五十嵐 博中², 大久保 誠二², 水口 幸代², 片山 泰朗² (¹創価大学 工学部 環境共生工学科, ²日本医科大学 第二内科学教室)

- N099** マイクロスフィア注入脳塞栓モデルラットにおけるカルモデュリン阻害剤DY-9760eの神経保護作用
○白倉 尚¹, 佐藤 俊之², 白崎 康文², 笠原 二郎¹, 竹内 有輔¹, 福永 浩司¹ (1東北大学大学院 薬学研究科 薬理学分野, 2第一製薬創薬第二研究所)
- N100** マウス低酸素-脳虚血時における小胞体関連蛋白質分解関与分子HRD1の誘導
○斉 キン, 大熊 康修, 金子 雅幸, 細井 徹, 野村 靖幸 (北海道大学 薬学研究科 薬理学分野)
- N101** 実験的脳虚血モデルにおけるポリ (ADP-リボース) 合成酵素の活性化とミトコンドリア傷害
○田中 静吾, 竹橋 正則, 飯田 慎也, 上田 國寛 (京都大学 化学研究所 生体反応設計3)

外 傷

- N102** 急性期脊髄損傷に対するIL-6レセプター抗体の効果
○岡田 誠司¹, 中村 雅也², 大杉 義征³, 吉崎 和幸⁴, 戸山 芳昭², 岡野 栄之¹ (1慶応義塾大学 医学部 生理学, 2慶応義塾大学 医学部 整形外科, 3中外製薬株式会社, 4大阪大学 医学部)

痴呆, アルツハイマー病

- N103** マウス・タウ・イントロン10のヘアピン構造によるスプライシング制御
(MS3-1) ○山下 雄也¹, 富山 貴美¹, 沼田 英治², 森 啓¹ (1大阪市立大学大学院 医学研究科 脳神経科学, 2大阪市立大学大学院 理科学研究科 情報生物学)
- N104** サイクリン依存性キナーゼ5によるFTDP-17型変異タウのリン酸化
(MS3-2) ○坂上 史佳¹, 長谷川 成人², 浅田 明子¹, 斉藤 太郎¹, 久永 真市¹ (1東京都立大学 理科学研究科 生物科学専攻, 2東京都精神医学総合研究所 分子神経生物学研究部門)
- N105** アルツハイマー病セクレターゼはalpha2,6シアル酸転移酵素を生理的基質として切断する。
(MS3-3) ○橋本 康弘, 立田 由里子, 岡 律子, 小谷 典弘, 小川 加寿子, 鈴木 実, 堂前 直, 瀧尾 廣士, 西道 隆臣, 北爪 しのぶ (理化学研究所)
- N106** PEN-2によるガンマセクレターゼ活性促進機構の解析
(MS3-4) 蔡 曉蕊^{1,2}, 白石 博久^{1,3}, 王 華芹⁴, 前田 康弘⁵, 西村 正樹⁴, 柳澤 勝彦¹, ○駒野 宏人¹ (1国立長寿医療研究センター痴呆疾患研究部, 2理化学研究所 バイオ・ミメティックコントロール研究センター 生物制御システム研究チーム, 3医薬品機構, 4滋賀医科大学 分子神経科学研究センター, 5名古屋市立大学薬学部)
- N107** セルフフリーアッセイ法でβAPPのγセクレターゼによるDUAL切断をみる。
(MS3-5) ○福森 亮雄¹, 大河内 正康¹, Harald Steiner², 谷井 久志¹, 田上 真次¹, 姜 経緯¹, Nurun Nessa Begum¹, 金山 大祐¹, 工藤 喬¹, Christian Haass², 武田 雅俊¹ (1大阪大学大学院 医学系研究科 未来医療開発専攻 ポストゲノム疾患解析学講座 プロセッシング異常疾患分野, 2ミュンヘン大学医学部 アドルフ・ブーテナント研究所 生化学教室)
- N108** ホロ蛋白PresenilinはSyntaxin 5と結合する
○須賀 圭¹, 富山 貴美², 森 啓², 赤川 公朗¹ (1杏林大学 医学部 第二生理学教室, 2大阪市立大学 医学部 脳神経科学)
- N109** BACE1活性増加によるAPP細胞内ドメイン断片生成への影響
○亀谷 富由樹¹, 久米 秀明^{1,2}, 丸山 敬³ (1東京都精神医学総合研究所 分子神経生物学研究部門, 2東北大学 大学院医学系研究科 医化学分野, 3埼玉医科大学 薬理学教室)
- N110** オートファジーに必須な酵母Apg8の哺乳類ホモログGATE-16の高発現によるAbeta産生の促進
○白石 博久^{1,2}, 鈴木 亮³, 前田 康博³, 蔡 曉蕊⁴, 木南 英紀⁵, 谷田 以誠⁵ (1国立療養所中部病院 長寿医療研究センター 痴呆疾患研究部, 2医薬品副作用被害救済・研究振興調査機構, 3名古屋市立大学 薬学部, 4理化学研究所 バイオ・ミメティックコントロール研究センター, 5順天堂大学 医学部 生化学第一講座)
- N111** β-セクレターゼのプロセッシングとタンパク質相互作用の解析
○村山 紀代子¹, 亀谷 富由樹², 高橋 典子¹, 斉藤 伸哉¹, 荒木 亘¹ (1国立精神・神経センター神経研究所 疾病研究第6部, 2東京都精神医学総合研究所)

- N112** 老齢犬脳におけるアミロイド蛋白 (1-40, 1-42, 1-43) に関する免疫組織化学的検討—年齢, 痴呆評点との相関
○伊藤 龍生, 佐藤 隆夫, 林 義之, 伊藤 浩行 (近畿大学 医学部 病理学教室)
- N113** ラットMK-801投与アルツハイマー病モデルにおけるDNAチップによる遺伝子発現の変化
○隈部 有希子¹, Md. Mahiuddin Ahmed¹, 知久馬 敏幸², 加藤 武¹ (¹横浜市立大学 総合理学研究科 システム機能科学科 分子認識部門, ²昭和薬科大学 衛生化学研究室)
- N114** β アミロイドによって誘導される分子の単離・同定
○内田 洋子, 五味 不二也 (東京都老人総合研究所 老年病ゲノムグループ)
- N115** 複数のタウリン酸化酵素によるアルツハイマー病特異的リン酸化の検討
○橋口 美津子, 橋口 利雄 (東京医科大学 医学部)
- N116** ラット脳内神経ペプチド調節酵素量に対するMK-801の容量依存的影響
○加藤 武¹, Md. Mahiuddin Ahmed¹, 知久馬 敏幸², Md. Khalilur Rahman³ (¹横浜市立大 大学院総合理学 自然情報科学, ²昭和薬科大 衛生化学, ³ダッカ大 分子生物化学)
- N117** ヒト神経芽細胞種糖脂質代謝に及ぼすPS1突然変異の影響の解明
○武藤 多津郎¹, 矢野 成昭¹, 濱野 忠則³, 田平 武², 山本 絃子¹ (¹藤田保健衛生大学 医学部 神経内科学, ²国立長寿医療研究センター, ³福井医科大学第二内科)
- N118** 小胞体ストレスにおけるリン酸化型PKRの役割
○大貫 玲子^{1,2}, 伊藤 元貢¹, 近藤 千尋¹, 板東 良雄^{3,5}, 遠山 正彌^{4,5}, 多比良 和誠^{2,6}, 杉山 雄一¹ (¹東京大学大学院 薬学系研究科, ²産業技術総合研究所 ジーンファンクション研究センター, ³旭川医科大学 第一解剖, ⁴大阪大学大学院 医学系研究科 未来医療開発専攻, ⁵CREST, JST, ⁶東京大学大学院 工学系研究科 化学生命工学専攻)

薬物依存, 精神薬理

- N119** メタンフェタミンの培養アストロサイトに対する影響
○磯部 一郎, 前野 善孝, 小山 宏義, 中村 昌美, 大瀧 純, 長尾 正崇 (名古屋市立大学大学院医学研究科 法医学)
- N120** 日周期リズムのラット前頭葉皮質における抗精神病薬誘導性アセチルコリン放出への影響
○外山 英和¹, James Gitzen³, Yongxin Zhu³, Qin Zhou³, Fuming Xie³, 那波 宏之¹, 染矢 俊幸², Peter Kissinger³ (¹新潟大学 脳研究所 分子神経生物学, ²新潟大学 医学部 精神科, ³バイオアナリティカルシステムズインク)

中毒症

- N121** Effects of neonatal exposure of endocrine disruptors on rat myelin membranes.
○徳山 佳子¹, 小嶋 久子¹, 中村 和生¹, 扇谷 つぐみ¹, 桑田 正広¹, 玉井 洋一² (¹北里大学 医学部 代謝・蛋白学, ²人間総合科学大学)

脳腫瘍

- N122** ヒトグリオーマにおける新規癌抑制遺伝子RFX1はメチル化により不活化されている
○大橋 陽平^{1,2}, 上田 政和³, 河瀬 斌⁴, 河上 裕², 戸田 正博^{1,2,4} (¹慶應義塾大学 医学部 総合医科学研究センター 神経免疫研究グループ, ²慶應義塾大学 医学部 先端医科学研究所 細胞情報研究部門, ³慶應義塾大学 医学部 外科, ⁴慶應義塾大学 医学部 脳神経外科)
- N123** T細胞に認識されるマウスグリオーマ抗原の単離
○飯塚 幸彦^{1,2}, 小嶋 英史⁴, 小端 哲二⁴, 河瀬 斌³, 河上 裕², 戸田 正博^{1,2,3} (¹慶應義塾大学 医学部 神経免疫研究グループ, ²慶應義塾大学 医学部 先端医科学研究所 細胞情報研究部門, ³慶應義塾大学 医学部 脳神経外科, ⁴獨協医科大学 医学総合研究所 免疫学教室)

てんかん

N124 急性キンドリングの発達過程における誘導型COX-2の関与

○山形 要人¹, 竹宮 孝子^{1,2}, 鈴木 香子¹, 川上 順子² (¹(財) 東京都医学研究機構 東京都神経科学総合研究所 神経薬理研究部門, ²東京女子医科大学 医学部 第一生理学教室)

その他

N125 培養神経細胞に対するアセトアルデヒド由来終末糖化産物 (AA-AGE) の細胞毒性

○竹内 正義¹, 岩城 実奈¹, 渡井 孝幸¹, 亀田 幸彦¹, 山岸 昌一², 佐々木 信幸³, 齋藤 利和³ (北陸大学 薬学部 生化学, ²久留米大学 医学部 第三内科, ³札幌医科大学 医学部 神経精神医学)

N126 軸索切断誘発運動神経細胞死におけるFK506の神経保護作用

駒井 清暢¹, ○熊倉 康郎², 山田 正仁¹ (¹金沢大学大学院 脳医科学専攻 脳病態医学講座 脳老化神経病態学 (神経内科), ²金沢大学 薬学部 病院薬学研究室)

N127 Type 1 Collagenを用いたラット胎児由来神経幹細胞3次元培養法の確立

○渡辺 航太¹, 中村 雅也¹, 小川 祐人¹, 千葉 一裕¹, 岡野 栄之², 戸山 芳昭¹ (¹慶應義塾大学 医学部 整形外科教室, ²慶應義塾大学 医学部 生理学教室, 科技団・戦略)

N128 網膜由来神経保護因子の探索

○眞部 孝幸^{1,2,3}, 奥田 洋明^{1,3}, 片山 泰一^{1,2,3}, 遠山 正彌^{1,3} (¹大阪大学大学院 医学系研究科 未来医療開発専攻 ポストゲノム疾患解析学講座 プロセッシング機能形態学分野 (旧第二解剖学教室), ²科学技術振興事業団 研究成果活用プラザ大阪, ³科学技術振興事業団 CREST)

イオンチャンネル, 興奮膜

- N129** sodium-activated K⁺ channelであるSlo2はPSD-95のPDZドメインと結合する
○内野 茂夫, 和田 英則, 本田 静世, 平澤 孝枝, 柳内 茂樹, 中村 泰子, 恩藤 由美子, 高坂 新一 (国立精神神経センター 神経研究所 代謝研究部)
- N130** Naxチャンネルの分布と局在
○渡辺 英治^{1,2,3}, 檜山 武史^{1,4}, 児玉 隆治¹, 野田 昌晴^{1,2,4} (1)岡崎国立共同研究機構 基礎生物学研究所, (2)総合研究大学院大学, (3)さきがけ研究21 科学技術振興事業団, (4)戦略的基礎研究戦略事業 科学技術振興事業団)
- N131** 蛋白リン酸化酵素AによるP/Q型Ca²⁺チャンネル制御に必須の領域がチャンネルα1AサブユニットC末端に存在する
○額田 敏秀¹, 古川 泰司², 並木 芳子¹, 森 泰生³, 吉井 光信⁴ (1)東京都精神医学総合研究所 脳細胞情報伝達研究部門, (2)帝京大学 医学部 内科学部門, (3)岡崎国立共同研究機構 総合バイオサイエンスセンター 分子細胞生理学部門, (4)東京都精神医学総合研究所 神経可塑性研究部門)
- N132** 水素イオンをリガンドに持つアミロライド感受性陽イオンチャンネルASIC とカプサイシンレセプターVR1 のラット後根神経節における共存の組織学的検討
○鶴川 眞也, 植田 高史, 島田 昌一 (名古屋市立大学 医学部 2解剖)

神経伝達物質, 修飾物質

- N133** チロシン水酸化酵素転写における Egr1ならびにAP1 factor
○中島 昭^{1,2}, 太田 明¹, ESTHER SABBAN² (1)藤田保健衛生大学 医学部 第1生理学, (2)Dept. of Biochem. and Mol. Biol., New York Med. Coll.)
- N134** シグマ-1受容体発現増加がドーパミン細胞機能に及ぼす影響
○山本 秀子¹, 額田 敏秀², 亀ヶ谷 悦子¹, 沈 昊偉¹, 山国 徹³, 亀谷 富由樹⁴, 吉井 光信¹, 池田 和隆¹, 曾良 一郎^{1,5}, 山本 敏文^{1,6} (1) (財) 東京都医学研究機構 精神医学総合研究所 分子精神医学, (2) (財) 東京都医学研究機構 精神医学総合研究所 脳細胞情報伝達, (3) 東北大学大学院 薬学研究科 分子生物学, (4) (財) 東京都医学研究機構 精神医学総合研究所 分子神経科学, (5) 東北大学大学院 医学研究科 神経科学, (6) 横浜市立大学大学院 総合理科学研究科 分子認識)
- N135** クロマフィン細胞の細胞内3D構造とクロマフィン顆粒の運動
○熊倉 鴻之助¹, Alessandro Riva², 今泉 美佳³, 村上 正隆⁴ (1)上智大学 生命科学研究科, (2)カリアリ大学 細胞形態学, (3)杏林大学 医学部 生化学第2, (4)生理学研究所 分子生理学)
- N136** ラット内側前頭前野および側坐核におけるアンフェタミン誘発性ドーパミン遊離に対するセロトニン_{2A} 受容体作動薬の効果
○黒木 俊秀¹, 市川 淳二², Meltzer Herbert², 橋本 喜次郎³, 平野 誠³ (1)九州大学 大学院 医学研究科 精神病態医学分野, (2)ヴァンダービルト大学医学部精神科, (3)国立肥前療養所臨床研究部)
- N137** 神経伝達物質放出抑制機構におけるカルパイン特異的なSNAP-25切断
○安藤 公祐^{1,2}, 工藤 佳久¹, 高橋 正身² (1)東京薬科大学 大学院 生命科学研究科, (2)北里大学 医学部 代謝蛋白学)
- N138** 単一PC12h細胞からの開口分泌のアンペロメトリー法による解析
○笹川 展幸, 村山 典恵, 熊倉 鴻之助 (上智大学 生命科学研究科 神経化学)
- N139** Purification of pChAT, a novel splice variant of choline acetyltransferase, from porcine small intestine
○Jean-Pierre Bellier, 相良 良成, 松尾 明典, 安原 治, 遠山 育夫, 木村 宏 (滋賀医科大学 分子神経科学研究センター)
- N140** 牛副腎クロマフィン細胞への高効率遺伝子導入法の検討
○村山 典恵, 笹川 展幸, 吉村 奈津江, 熊倉 鴻之助 (上智大学 生命科学研究科 神経化学)
- N141** PACAP欠損マウスの精神行動異常に対するハロペリドールおよびリスペリドンの作用
○田中 一裕¹, 橋本 均¹, 新谷 紀人¹, 山本 亜希子¹, 川口 ちひろ¹, 馬場 明道^{1,2} (1)大阪大学大学院 薬学研究科 神経薬理学分野, (2)大阪大学大学院 医学研究科 分子医薬)

- N142 セロトニン_{1A}受容体によるマウス大脳皮質セロトニンおよびドーパミン遊離の調節**
○吾郷 由希夫¹, 中村 茂生¹, 小山 豊¹, 馬場 明道², 松田 敏夫¹ (¹大阪大学大学院 薬学研究科 複合薬物動態, ²大阪大学大学院 薬学研究科 神経薬理)
- N143 インターフェロンアルファによるラット海馬BrdU陽性細胞の減少**
○金子 奈穂子, 工藤 耕太郎, 竹本 恵子, 喬 春香, Henny Waty, 井口 博登, 神庭 重信 (山梨大学 医学部 精神神経医学・臨床倫理学講座)
- N144 siRNAを用いたPC12細胞の神経様細胞分化時におけるPRMT機能の解析**
○藤原 達司, 宮田 信吾, 森 泰丈, 遠山 正彌 (大阪大学大学院 医学系研究科 ポストゲノム疾患解析学講座)
- N145 ラット小脳顆粒細胞における開口放出に対するボツリヌス神経毒素と一酸化窒素の作用**
○津々木 博康^{1,3}, 居原 秀^{2,3}, 幸田 知子^{3,4}, 向本 雅郁^{3,4}, 小崎 俊司^{3,4} (¹大阪府立大学 理学系研究科 物質科学専攻, ²大阪府立大学 総合科学部 自然環境科学科, ³大阪府立大学 先端科学研究所, ⁴大阪府立大学 農学生命科学研究科 獣医学専攻)

情報伝達, 変換, 修飾

- N146 急性けいれんによって引き起こされる自己リン酸化・不活性化・沈降型Ca²⁺/カルモジュリン依存性プロテインキナーゼII**
(MS6-1) ○山肩 葉子, 小幡 邦彦 (生理学研究所)
- N147 Arc による CaM kinase II 依存性神経突起伸長の促進**
(MS6-2) ○土内 瞳¹, 杉浦 弘子², 吉村 好之¹, 山形 要人², 山内 卓¹ (¹徳島大学 薬学部 薬学研究科, ²東京都神経研)
- N148 カルモデュリンキナーゼカスケード構成分子の局在と活性制御機構**
(MS6-3) ○笠原 二郎¹, 上江洲 章吉², 福永 浩司¹ (¹東北大学 大学院薬学研究科 薬理学分野, ²熊本大学 大学院医学薬学研究部 細胞情報薬理学)
- N149 ヒポカルシンとMLK (mixed lineage kinase) 3の相互作用**
(MS6-5) ○小林 正明, 高松 研 (東邦大学 医学部 生理学第2講座)
- N150 エンドセリン受容体-G蛋白質Gi2による神経前駆細胞の増殖および運動促進**
(MS8-4) ○浅野 富子¹, 篠原 春夫², 森下 理香¹, 上田 浩¹, 仙波 禮治², 加藤 兼房¹ (¹愛知県心身障害者コロニー 発達障害研究所 神経制御学部, ²三重大学 医学部 解剖学)
- N151 SREBPによるヒト脳アシルCoA水分解素遺伝子発現調節の解析**
○高木 充弘, 須藤 史貴, 渡辺 隆史, 須賀 哲弥, 山田 純司 (東京薬科大学 薬学部 臨床生化学教室)
- N152 急性および慢性拘束ストレスによる延髄腹内側部におけるERKの活性化**
○井辺 弘樹, 村上 修二, 仙波 恵美子 (和歌山県立医科大学 第二解剖学教室)
- N153 海馬由来初代培養神経細胞における反復的磁場曝露の保護効果**
○平居 貴生, 米田 幸雄 (金沢大学大学院 自然科学研究科 薬物学)
- N154 SOCS3によるNPY遺伝子転写活性化の抑制**
○山口 剛, 長谷川 歩未, 大谷 桂, 樋口 宗史 (新潟大学 大学院 医歯学総合研究科 薬理学分野)
- N155 ERAD (小胞体関連分解) に関連する新規ユビキチンリガーゼ (E3) の同定と機能解析**
○上杉 麻依, 金子 雅幸, 野村 靖幸 (北海道大学 大学院薬学研究科)
- N156 ラット脳内におけるビタミンD感受性エレメント結合について**
○伊藤 実¹, 大野 博司¹, 倉本 展行², 杉山 千絵², 谷浦 秀夫², 米田 幸雄² (¹金沢大学 がん研究所 分子薬理学講座, ²金沢大学大学院 自然科学研究科 薬物学)
- N157 培養海馬神経細胞におけるCaM kinase IIに対するホスファターゼの制御**
○上江洲 章吉¹, 笠原 次郎², 田村 眞理³, 山本 秀幸¹, 宮本 英七¹, 福永 浩司² (¹熊本大学大学院医学薬学研究部 細胞情報薬理学分野, ²東北大学大学院薬学研究科 薬理学分野, ³東北大学加齢医学研究所 遺伝子情報研究分野)

- N158 HT22細胞におけるhsp90によるエストロゲン受容体の機能調節**
○鬼頭 昭三, 新郷 S.明子 (兵庫大学 健康科学部)
- N159 6-Hydroxydopamine誘発神経細胞死に対する小胞体ストレスセンサーATF6の活性化**
○山室 晶子¹, 森田 恵子¹, 桑田 るみこ¹, 吉岡 靖啓¹, 伊藤 文昭³, 荻田 喜代一², 前田 定秋¹ (1) 摂南大学 薬学部 薬物治療学研究室, (2) 摂南大学 薬学部 薬理化学研究室, (3) 摂南大学 薬学部 生化学研究室)
- N160 初代培養グリア細胞におけるIL-20誘導機構**
○鈴木 佐和子, 和田 吉世, 細井 徹, 大熊 康修, 野村 靖幸 (北海道大学 大学院薬学研究科)
- N161 不死化海馬ニューロンにおけるエストロゲンによるPKA活性上昇の機構**
○新郷 S.明子, 鬼頭 昭三 (兵庫大学 健康科学部)
- N162 受容体クロストークによるヒスタミン H₁ 受容体 down-regulation と情報伝達の抑制**
○福井 裕行, 三好 勝洋, 河上 希, 横内 初美, 堀尾 修平 (徳島大学 薬学部 薬物学教室)
- N163 カルパインによる限定分解の抑制に関わるCdk5活性化サブユニットp35のリン酸化部位**
○小澤 美来, 斎藤 太郎, 藤田 悠一, 鈴木 久美子, 浅田 明子, 久永 真市 (東京都立大学 理学研究科 生物科学専攻)
- N164 メタアンフェタミンは, ラット線条体及び側坐核でHomer1a遺伝子発現を誘発する**
○橋本 喜次郎¹, 中原 辰雄¹, 黒木 俊秀², 山田 英孝¹, 梶畑 俊雄², 堤 哲之¹, 平野 誠¹ (1) 国立肥前療養所 臨床研究部, (2) 九州大学 大学院 医学研究院 精神病態医学分野)
- N165 5型アデニル酸シクラーゼ欠損マウスにおけるG蛋白サブタイプの役割**
○岩本 彩雄, 岩坪 耕策, 橋本 容子, 泉谷 朱紀, 大津 恒治, 石川 義弘 (横浜市立大学 医学部 循環制御医学)

軸索輸送, 細胞運動, 細胞骨格

- N166 神経特異的微小管崩壊因子RB3のN末端膜結合ドメインは微小管ダイナミクスを制御する (MS7-1)**
○中尾 千登世¹, 伊藤 知彦², 宝谷 紘一², 森 望¹ (1) 国立中部病院長寿医療研究センター 分子遺伝学研究部, (2) 名古屋大学大学院 理学研究科 生命理学専攻)
- N167 ニューロフィラメント・ゲル形成過程に対する脱リン酸化の影響: マイクロビーズによるリアルタイム観察 (MS7-2)**
○小野 れい¹, 中林 和也¹, 森田 泰介¹, 倉知 正², 小宮 義あき², 田代 朋子^{1,3} (1) 青山学院大学 理工学部 化学科, (2) 群馬大学 医学部 分子病態学, (3) 科学技術振興事業団 戦略的基礎研究推進事業)
- N168 神経突起形成時の協調的な細胞骨格相互作用**
○福嶋 伸之 (北海道大学大学院 医学研究科 分子生化学)
- N169 ドレブリン結合タンパク質Drap1のドメイン依存的細胞内局在の解析**
○山崎 博幸, 水井 利幸, 小林 千穂, 白尾 智明 (群馬大学大学院 医学系研究科 高次細胞機能学部門)
- N170 Filamin A結合蛋白質FILIPによる大脳皮質脳室帯細胞の形態制御 (MS8-6)**
○永野 隆¹, 森久保 聡一^{1,2}, 八木 秀司¹, 佐藤 真¹ (1) 福井医科大学 医学部 解剖学 (2), (2) 福井医科大学 医学部 眼科学)
- N171 カルシウム/カルモデュリン依存性蛋白質磷酸化酵素IIにより磷酸化されたタウに対する特異抗体の作製**
○山本 秀幸, 中西 宏之 (熊本大学 医学薬学研究部 細胞情報薬理学)
- N172 神経ステロイド・内分泌かく乱物質によるMAP2を介する微小管重合及び神経突起伸展の変調**
○松永 隼人, 吉田 明, 水野 恭伸, 植田 弘師 (長崎大学 医歯薬学研究科 分子薬理化学研究室)
- N173 成体マウスおよびサル脳室下層における新生ニューロンの移動**
○澤本 和延^{1,5}, 早川 佳芳¹, 岩波 明生^{1,2}, 金子 慎二郎^{1,2}, 川野 仁³, 石井 一⁴, 野村 達次⁴, Hynek Wichterle⁵, Marc Tessier-Lavigne⁶, Arturo Alvarez-Buylla⁵, 岡野 栄之¹ (1) 慶應義塾大学 医学部 生理学教室, (2) 慶應義塾大学 医学部 整形外科, (3) 東京都神経科学総合研究所, (4) 実験動物中央研究所, (5) カリフォルニア大学サンフランシスコ校, (6) スタンフォード大学)

ニューロン, グリア

- N174 PCRサブトラクション法を用いたOlig2下流因子の解析**
(MS7-3) ○政平 訓貴^{1,2}, 竹林 浩秀¹, 清水 恵司², 池田 一裕¹ (岡崎国立共同研究機構 生理学研究所 分子神経生理部門, ²高知医科大学 医学部 脳神経外科)
- N175 培養アストロサイトにおける細胞外SODの発現とその活性**
(MS7-4) ○中村 洋一¹, 北川 貴志¹, 村上 浩司², 米田 幸雄² (大阪府立大学大学院 農学生命科学研究科 獣医学専攻 統合生理学研究室, ²金沢大学大学院 自然科学研究科 生命薬学専攻 分子薬理学研究室)
- N176 損傷脳における組織幹細胞の動態**
(MS7-5) ○辰巳 晃子, 芳賀 敏実, 和中 明生 (奈良県立医科大学 解剖学第2講座)
- N177 CaMキナーゼIIδアイソフォームの細胞内局在の検討**
○竹内 有輔, 福永 浩司 (東北大学 薬学部 薬理学分野)
- N178 神経細胞の成熟においてPKCが果たす役割について**
○濱 裕¹, 原 央子², 小暮 貴子², 宮脇 敦史¹ (理化学研究所 脳科学総合研究センター 先端技術開発グループ 細胞機能探索技術開発チーム CREST JST (Japan Science and Technology), ²理化学研究所 脳科学総合研究センター 先端技術開発グループ 細胞機能探索技術開発チーム)
- N179 ラット顔面神経核由来活性化ミクログリアの細胞特性について**
○中嶋 一行¹, 遠山 陽子¹, 高坂 新一², 栗原 正¹ (創価大学 工学部 生命情報工学科, ²国立精神・神経センター, 神経研究所)
- N180 ラット大脳半球初代培養系におけるグリア細胞の分化・発達に及ぼすdibutyric cyclic AMPの影響**
○足立 達美¹, 高永 博実², 国本 学², 阿相 皓晃³ (国立水俣病総合研究センター 基礎研究部, ²北里大学 薬学部, ³東京都老人総合研究所)
- N181 Apolipoprotein A-I によるアストロサイトの protein kinase C の細胞質への移行**
○伊藤 仁一, 長安 祐子, 横山 信治 (名古屋市立大学大学院 医学研究科 代謝細胞生化学 I)
- N182 過酸化水素による神経細胞死に対するビルビン酸の防御作用**
○神戸 悠輝, 中道 範隆, 井上 真希, 松井 栄一, 高野 桂, 杉山 千絵, 米田 幸雄 (金沢大学大学院 自然科学研究科 薬物学研究室)
- N183 海馬由来培養神経細胞成熟に対する持続的磁場曝露の影響**
○後藤 康彰¹, 山田 清文¹, 平居 貴生², 米田 幸雄² (金沢大学薬学部 医療薬学講座 病院薬学研究室, ²金沢大学大学院 自然科学研究科 薬物学)
- N184 線条体アストロサイトにおけるドパミンレセプターの発現**
○宮崎 育子, 浅沼 幹人, 小川 紀雄 (岡山大学 大学院医歯学総合研究科 脳神経制御学講座 神経情報学)
- N185 脳発達に伴うmouse brain serine proteinaseの発現変化**
○青山 峰芳¹, 横井 誉^{1,2}, 山本 直樹¹, 多田 豊曠⁴, 岡 雄一^{1,3}, 藤田 政隆^{1,3}, 森山 昭彦⁵, 三浦 裕¹, 浅井 清文¹ (1名古屋市立大学大学院医学研究科 分子神経生物学, ²名古屋市立大学大学院医学研究科 先天異常, 新生児, 小児医学, ³名古屋市立大学大学院医学研究科 神経機能回復学, ⁴名古屋市立大学 看護学部, ⁵名古屋市立大学大学院 システム自然科学研究科)
- N186 Pancortinの細胞外分泌に多量体形成は必須である**
○安藤 康一¹, 中村 晃², 永野 隆¹, 佐藤 真¹ (福井医科大 解剖学2, ²奈良先端大学院大学 バイオサイエンス科 細胞構造)
- N187 脊髄におけるドメイン構造に従ったアストロサイト前駆細胞の多様性**
○小川 泰弘¹, Matthew Rasband², 竹林 浩秀¹, 岩崎 靖乃¹, James Trimmer², 池田 一裕¹ (岡崎国立共同研究機構 生理学研究所 分子生理学研究室 分子神経生理研究部門, ²ニューヨーク州立大学ストーニーブルック校)
- N188 PURエレメントによるPurα 蛋白染色とイムノブロットのシグナル増強作用は, PURエレメントとPurαとの結合活性を反映する**
○郭 哲輝, 曾 玲暉, 三木 直正 (大阪大学 医学部 情報薬理)

- N189 運動神経損傷によるグリア細胞応答の研究**
○高原 瑞恵, 倉本 恵梨子, 稲垣 忍 (大阪大学 医学部 保健学科 神経生物学研究室)
- N190 細胞外カリウム濃度の上昇による培養アストロサイトのNO産生増強**
○北川 貴志, 浅井 絵理, 河南 有希子, 森山 光章, 中村 洋一 (大阪府立大学大学院 農学生命科学研究科 獣医学専攻 統合生理学研究室)
- N191 神経系における4回膜貫通蛋白質CD9の役割**
○石橋 智子, 梶ヶ谷 仁志, 馬場 広子 (東京薬科大学 薬学部 機能形態)

ミリエン

- N192 老齢脳におけるミエリン形成不全の新展開**
○酒井 智美^{1,2}, 清和 千佳², 小山内 たか³, 田中 嘉代子⁴, 須川 誠², 山内 豊³, 松本 勲武¹, 阿相 皓晃²
(¹お茶の水女子大学 人間文化研究科 ライフサイエンス専攻, ²東京都老人総合研究所 グリア細胞研究グループ, ³東京都臨床医学総合研究所 生命情報研究部門, ⁴埼玉医科大学 生物化学研究センター)
- N193 内分泌かく乱物質ビスフェノールAがオリゴデンドロサイト前駆細胞に与える影響について**
○清和 千佳¹, 中原 仁¹, 酒井 智美¹, 井口 泰泉^{2,3}, 阿相 皓晃^{1,3} (¹東京都老人総合研究所 グリア細胞研究グループ, ²岡崎国立共同研究機構 総合バイオサイエンスセンター, ³クレスト)
- N194 脱髄におけるセリンプロテアーゼProtease M/neurosin/zymeの発現**
○板東 良雄, 永井 美子, 酒巻 雄二, 只野 雄飛, 吉田 成孝 (旭川医科大学 医学部 医学科)
- N195 末梢神経軸索のチャネル局在化に対するミエリンサルファチドの役割**
○星 登美子^{1,2}, 石橋 智子¹, 鈴木 彩佳¹, 馬場 広子¹ (¹東京薬科大学 薬学部 機能形態学教室, ²東京薬科大学大学院 生命科学研究科 環境動態化学研究室)
- N196 HNK-1糖鎖エピトープを含有する新奇な硫酸含有糖蛋白糖鎖の構造**
○北村 邦男, 関 剣虹, 野村 正彦 (埼玉医大・生理学)
- N197 大脳皮質GABA作動性ニューロンおよび稀突起膠細胞の前駆細胞におけるproteolipid proteinプロモーター活性**
○藤田 裕子¹, Wendy Macklin² (¹慶應義塾大学 医学部 生理学教室, ²クリブランドクリニック 財団 ラーナー研究所)

血液脳関門

- N198 血液-脳関門におけるクエン酸アルミニウムの輸送特性の解析**
○長澤 一樹¹, 伊藤 慎悟¹, 玉井 郁巳², 辻 彰³, 藤本 貞毅¹ (¹京都薬科大学 薬学部 衛生化学教室, ²東京理科大学 薬学部, ³金沢大学 薬学部)

神経免疫

- N199 末梢でのリポポリサッカライド投与は青斑核における炎症性サイトカインの発現に影響を及ぼす**
○金子 葉子¹, 森 啓至¹, 中島 昭¹, 藤原 健太郎², 永津 郁子³, 太田 明¹ (¹藤田保健衛生大学 医学部 生理学I, ²藤田保健衛生大学 医学部 内科学, ³藤田保健衛生大学 医学部 解剖学2)
- N200 LPSの末梢投与によるマウス嗅球への影響**
○森 啓至¹, 金子 葉子¹, 中島 昭¹, 藤原 健太郎², 永津 郁子³, 太田 明¹ (¹藤田保健衛生大学 医学部 生理学I, ²藤田保健衛生大学 内科, ³藤田保健衛生大学 医学部 解剖学)
- N201 PEDFによる炎症関連因子発現調節機構の解析**
○佐柳 友規¹, 西尾 昌子¹, Joan Schwartz³, 矢部 武士^{1,2}, 山田 陽城^{1,2} (¹北里大学北里生命科学研究科, ²北里研究所東洋医学総合研究所, ³米国立衛生研究所)
- N202 脳内IL-1感受性のマウス系統差**
○津田 法子, 那波 宏之 (新潟大学 脳研究所 分子神経生物学分野)

- N203 神経ステロイド・内分泌かく乱物質による細胞膜G蛋白質受容体を介する分泌調節**
○吉田 明, 内田 仁司, 井上 誠, 溝田 香緒里, 植田 弘師 (長崎大学大学院 医歯薬学総合研究科 分子薬理学研究室)
- N204 ヒト炎症性多発性神経障害の自己抗原としての末梢ミエリン蛋白P0**
○林 明子¹, 増尾 直亮¹, 山口 宜秀¹, 大西 雅人¹, 竹田 俊英¹, 薄 敬一郎², 結城 伸泰², 馬場 広子¹
(¹東京薬科大学 薬学部 機能形態, ²獨協医科大学 神経内科)

パターン形成

- N205 大脳皮質形成過程における抑制性神経細胞の配置機構**
○四津 真人^{1,2}, 田畑 秀典^{1,2}, 仲嶋 一範^{1,2} (¹慶應義塾大学 医学部 解剖学教室, ²東京慈恵会医科大学 DNA医学研究所 分子神経生物学研究部門)
- N206 大脳皮質における移動神経細胞の細胞接着性の解析**
○味岡 逸樹^{1,2}, 田畑 秀典^{1,2}, 仲嶋 一範^{1,2} (¹慶應義塾大学 医学部 解剖学教室, ²東京慈恵会医科大学 DNA医学研究所 分子神経生物学部門)
- N207 子宮内エレクトロポレーション法を応用した神経系細胞系譜の解析**
○鹿川 哲史¹, 井上 俊洋¹, 荒木 喜美², 中平 英子³, 池田 一裕³, 田賀 哲也¹ (¹熊本大学 発生医学研究センター 転写制御分野, ²熊本大学 発生医学研究センター 臓器形成分野, ³岡崎国立共同研究機構 生理学研究所 分子神経生理研究部)

細胞分化

- N208 アストロサイト由来液性因子によるマウスおよびサルES細胞の神経細胞への分化誘導 (MS8-1)**
○中山 孝¹, 百木 (曾我) 智子¹, 山口 和彦², 鈴木 豊³, 近藤 靖³, 井上 順雄¹ (¹横浜市立大学 医学部 生化学第一講座, ²理化学研究所 脳科学総合研究センター 記憶学習機構研究チーム, ³田辺製薬株式会社 先端医学研究所)
- N209 NRSF/RESTとDNAメチル化が細胞種特異的なBRINP1 (BMP-2 and Retinoic acid Inducible Neural-specific Protein 1) の発現を調節する (MS8-2)**
○中谷 俊幸, 松岡 一郎 (北海道大学大学院 薬学研究科 神経科学分野)
- N210 神経幹細胞に発現する転写因子Sox21の解析 (MS8-3)**
○大場 宏幸¹, 千代田 達幸¹, 遠藤 恵美¹, 矢野 真人¹, 早川 佳芳¹, 岡野 ジェイムス洋尚^{1,2}, 岡野 栄之^{1,2} (¹慶應義塾大学 医学部 生理学, ²科技団, 戦略)
- N211 終脳オリゴデンドロサイトの細胞系譜解析 (MS8-5)**
○竹林 浩秀¹, 政平 訓貴^{1,2}, 田中 謙二¹, 清水 恵司², 池田 一裕¹ (¹岡崎 生理学研究所 分子神経生理, ²高知医科大学 脳外科)
- N212 脳低温損傷部位に出現する細胞種の検討**
○芳賀 敏実, 辰巳 晃子, 和中 明生 (奈良県立医科大学 第2解剖)
- N213 Ras-MEK細胞内シグナルによるチロシン水酸化酵素遺伝子の転写制御**
○鈴木 崇弘¹, 一瀬 宏^{1,2} (¹藤田保健衛生大学 総合医科学研究所 分子遺伝学, ²東京工業大学大学院 生命理工学研究科 生命科学専攻)
- N214 幹細胞における電気の平衡と細胞運命決定機構**
○山田 真久^{1,2}, 種村 健太郎³, 小澤 美智留³, 水野 秀昭⁴, 宮脇 敦史⁴, 竹内 京子², 河野 真子², 小川 正晴², 近藤 隆³ (¹理研 脳科学 病因遺伝子研究グループ, ²理研 脳科学 細胞培養技術開発, ³理研 脳科学 発生発達研究グループ, ⁴理研 脳科学 細胞機能探索技術開発)
- N215 神経特異的RNA結合蛋白質Huの生化学的・遺伝学的機能解析**
○岡野 ジェイムス洋尚^{1,2}, 赤松 和土^{1,2}, 矢野 真人¹, 岡野 栄之^{1,2} (¹慶應義塾大学 医学部 生理学, ²科技団, 戦略)

突起伸展, 回路網形成

- N216** 培養海馬神経細胞におけるSHPS-1とそのリガンドCD47の局在
○大西 浩史, 坂爪-金子 由夏, 佐藤 竜児, 林 朗子, 富澤 恭子, 小林 久江, 岡澤 秀樹, 的崎 尚 (群馬大学 生体調節研究所 附属生理活性物質センター)
- N217** ラット脳での異なるプロモーターとスプライシングによるNDRG4タンパク質アイソフォームの発現
○本郷 茂樹, 前田 昭彦, 宮崎 章 (昭和大学 医学部 生化学教室)
- N218** Aβ (25-35) により誘発される軸索の萎縮, シナプス減少, 記憶障害がginsenoside Rb₁およびその腸内細菌代謝物M1により回復する
○東田 千尋, 松本 憲昭, 鄧 坤, Meselhy Meselhy, 橋本 斎, 小松 かつ子 (富山医科薬科大学 和漢薬研究所 薬効解析センター)
- N219** Sema4Dの後根神経節ニューロン神経突起伸長作用
○小林 千恵¹, 増田 健太², 古山 達雄³, 古郷 幹彦¹, 稲垣 忍² (¹大阪大学歯学部口腔外科第一, ²大阪大学医学部保健学科・神経生物学研, ³大阪大学医学部解剖学第2)
- N220** Aβ 25-35により障害を与えたラット大脳皮質神経細胞におけるWithanolide AとWithanoside VIのシナプス再形成作用
○久保山 友晴, 東田 千尋, 小松 かつ子 (富山医科薬科大学 和漢薬研究所 薬効解析センター)
- N221** ラット胎生期大脳新皮質における領域特異的発現分子の解析 ―プロテオミクス手法を用いて―
○山口 宜秀, 真柴 友紀, 山田 早織, 馬場 広子 (東京薬科大学 薬学部 機能形態学教室)

栄養因子

- N222** ラット線条体初代培養神経細胞におけるEGFファミリー分子の放出調節 (MS5-1)
○岩倉 百合子, 朴 英善, 武井 延之, 那波 宏之 (新潟大学 脳研究所 分子神経生物学分野)
- N223** BDNFにより活性化される翻訳伸長過程の解析 (MS5-2)
○稲村 直子, 那波 宏之, 武井 延之 (新潟大学 脳研究所 分子神経生物学分野)
- N224** 成体ラット運動ニューロン損傷に対するGIF (MT-III) 組換えアデノウイルスの保護効果 (MS5-3)
○坂本 剛¹, 川添 陽子¹, 内田 洋子², 保住 功³, 犬塚 貴³, 渡部 和彦¹ (¹東京都神経科学総合研究所 分子神経病理, ²東京都老人総合研究所 老人病ゲノムグループ, ³岐阜大学医学部 神経・老年学 分野)
- N225** bFGFの神経細胞保護作用におけるcalbindin-D28kの役割 -in vitro解析- (MS5-4)
○門嶋 大輔, 村山 宣人, 岡 哲志, 杉村 恵二郎, 中村 静雄, 大野 知親 (第一サントリー生物医学研究所)
- N226** PACAPによる神経幹細胞の分化制御 (MS5-5)
○大多 茂樹¹, Weiss Samuel² (¹慶應大学 医学部 神経免疫研究グループ, ²Genes&Development Res. Group, Univ. of Calgary Fac. of Med.)
- N227** リルゾールによるラット海馬のBDNF合成促進を制御する細胞内シグナル伝達経路
○仙波 りつ子, 金子 律子, 北島 哲子, 加藤 兼房 (愛知県心身障害者コロニー 発達障害研究所)
- N228** 疎水性ジペプチドLeu-Ileの神経保護作用
○新田 淳美¹, 西岡 博史², 堀 琢弥², 丸山 慶子², 古川 美子², 鍋島 俊隆¹, 古川 昭栄² (¹名古屋大学 大学院・医学系研究科・医療薬学・医学部附属病院・薬剤部, ²岐阜薬科大学・分子生物学教室)
- N229** ラット脊髄損傷部位のミクログリア/マクロファージにおけるMCP-1とGDNFの共発現
○橋本 学, 西村 祐一郎, 古川 昭栄 (岐阜薬科大学 分子生物学教室)
- N230** 上皮成長因子 (EGF) /ErbBシグナルはラット大脳皮質においてシナプス関連蛋白質群の発現を調節する
○横幕 大作, Hussam Jourdi, 永野 忠聖, 水野 誠, 武井 延之, 那波 宏之 (新潟大学 脳研究所 分子神経生物学分野)
- N231** NG108-15細胞とNeuro2A細胞におけるラディシコールとゲルダナマイシンによる神経突起の誘導作用について
○佐野 護 (京都府立医科大学 医学部 医学科)

- N232 大脳皮質形態形成における髄膜の役割**
○本田 岳夫^{1,2}, 田畑 秀典^{1,2}, 仲嶋 一範^{1,2} (1慶應義塾大学 医学部 解剖学教室, 2東京慈恵会医科大学 DNA医学研究所 分子神経生物学研究部門)
- N233 EGFの慢性投与は大脳皮質GABAergicニューロンのシナプス機能を下方制御する**
○永野 忠聖, 難波 寿明, 武井 延之, 那波 宏之 (新潟大学 脳研究所 分子神経生物学分野)
- N234 bFGFの神経細胞保護作用におけるCalbindinD28kの役割**
○野下 敬史, 村山 宣人, 荻野 涼子, 岡 哲志, 中村 静雄, 大野 知親 (株式会社第一サントリー生物医学研究所)
- N235 色素上皮由来因子PEDFによる細胞生存関連因子の発現制御**
○金光 花月¹, 清水 真弓¹, JOAN P SCHWARTZ³, 矢部 武士^{1,2}, 山田 陽城^{1,2} (1北里大学 北里生命科学研究所, 2北里研究所 東洋医学総合研究所, 3米国国立衛生研究所)
- N236 オンコスタチンM欠損マウスにおける痛覚ニューロンの発生**
○森川 吉博¹, 田村 志宣¹, 宮島 篤², 仙波 恵美子¹ (1和歌山県立医科大学 第二解剖, 2東京大学分子細胞生物学研究所 機能形成研究分野)
- N237 神経細胞細胞死誘導におけるp40BBPの変化**
○濱 登希子¹, 仙波 りつ子² (1三菱化学生命科学研究所 所長フロンティア研究室, 2愛知県コロニー研究所)
- N238 一次知覚神経におけるオンコスタチンMレセプターの発現**
○田村 志宣¹, 森川 吉博¹, 宮島 篤², 仙波 恵美子¹ (1和歌山県立医科大学 第二解剖, 2東京大学分子細胞生物学研究所 機能形成研究分野)
- N239 パーキンソン病モデルにおけるpigment epithelium-derived factor (PEDF) の作用の検討**
○安田 徹¹, 和田 圭一郎¹, 劉 穎¹, 古谷 剛¹, 小野寺 雅史², 望月 秀樹¹, 水野 美邦¹ (1順天堂大学 医学部 老人性疾患病態・治療研究センター, 2筑波大学 臨床医学系 血液内科)
- N240 生薬由来の神経栄養因子作用を有するイリドイド化合物, ゲニピンは一酸化窒素合成酵素に直接結合し活性化する**
○千葉 賢三¹, 大窪 忠利², 山崎 眞津美¹, 毛利 哲郎¹ (1北陸大学 薬学部 生物活性教室, 2救急薬品工業株式会社 研究開発部)
- N241 知覚神経の標的組織である発達期ニワトリ皮膚でのCNTFの二相性発現**
荒川 義弘^{1,2}, ○木元 克輔², 山本 篤², 田澤 直樹², 見目 勝², 西嶋 千晶², 金井 文彦¹, 小俣 政男¹, 渡部 和彦³, 赤澤 智宏⁴, 高坂 新一⁴ (1東京大学 医学部 附属病院 臨床試験部, 2東京大学 医学部 附属病院分院 薬剤部, 3東京都神経科学総合研究所 分子神経病理研究部門, 4国立精神・神経センター 神経研究所 代謝研究部)
- N242 神経活動に依存したEGF family分子のシェディング**
○穴戸 裕二¹, 田中 隆之¹, 岩倉 百合子¹, 東山 繁樹², 武井 延之¹, 那波 宏之¹ (1新潟大学 脳研究所 分子神経生物学分野, 2愛媛大学 医学部 医化学第二講座)

細胞接着因子

- N243 NGFによるギセリン遺伝子の誘導**
○小浜 恵子 (大阪学院大学 医学系研究科 情報薬理学)
- N244 成熟マウス海馬における細胞接着分子群の分布 (光学顕微鏡および電子顕微鏡観察)**
○山崎 浩誠¹, 中村 雪子¹, 渡邊 和忠², 塩坂 貞夫¹ (1奈良先端科学技術大学院大学 バイオサイエンス研究科, 2長岡科学技術大学 生物系)
- N245 FLRT3は損傷神経において発現上昇し軸索伸展を促進する**
○辻 隆治, 山下 俊英, 遠山 正彌 (大阪大学 大学院 医学系研究科 ポストゲノム疾患解析学講座)
- N246 発生過程の小脳における神経認識分子NB-2の短冊状発現**
○藤沢 哲也¹, 笠間 由里¹, 落合 大輔¹, 奥野 聖¹, 霜田 靖¹, 武田 泰生², 渡邊 和忠¹ (1長岡技術科学大学大学院 工学研究科 生物機能工学専攻, 2鹿児島大学大学院 医学研究科 臨床薬理学教室)
- N247 脳に特異的に発現するニューログリンCのコンドロイチン硫酸鎖付加調節機構の解明**
○青野 幸子¹, 時田 義人¹, 周尾 卓也¹, 山内 忍¹, 松井 ふみ子¹, 佐野 護², 大平 敦彦¹ (1愛知県心身障害者コロニー 発達障害研究所 周生期学部, 2京都府立医科大学 生物学教室)

可 塑 性

- N248 ストレス誘発性海馬シナプス可塑的变化におよぼすセロトニン神経系の役割**
 ○松本 真知子, 富樫 広子, 上野 健一, 尾谷 浩, 山口 拓, 吉岡 充弘 (北海道大学 医学部 神経薬理)
- N249 海馬プレシナプスに局在する細胞接着分子L1-camのNMDA依存的なプロテオリシス**
 ○田村 英紀, 松本宮井 和政, 山崎 浩誠, 中村 雪子, 塩坂 貞夫 (奈良先端科学技術大学院大学 バイオサイエンス研究科 細胞構造学講座)
- N250 Arcタンパク質による活動依存的細胞骨格の再構築**
 ○藤本 崇宏, 入江 康至, 三木 直正 (大阪大学 医学系研究科 情報薬理学第一)

プログラム細胞死

- N251 Rho GTPaseシグナル伝達系による標的組織非依存的な運動神経細胞の生存の制御**
 ○小林 憲太¹, 高橋 将文², 松下 夏樹¹, 高橋 一彰¹, 宮崎 純一³, 小池 正人⁴, 八木沼 洋行⁴, 大隅 典子², 貝淵 弘三⁵, 小林 和人¹ (¹福島県立医科大学 医学部附属生体情報伝達研究所 生体機能研究部門, ²東北大学大学院医学研究科 器官構築学分野, ³大阪大学大学院医学系研究科 未来医療開発専攻 幹細胞制御分野, ⁴福島県立医科大学 医学部 解剖学1, ⁵名古屋大学大学院医学研究科 細胞情報薬理学講座)
- N252 グリア細胞特異的ERストレスセンサーOASISの機能解析**
 (MS7-6) ○近藤 慎一¹, 伊関 憲², 和中 明生³, 今泉 和則¹ (¹奈良先端科学技術大学院大学 バイオサイエンス研究科 細胞構造学, ²山形大学 医学部 救急医学講座, ³奈良県立医科大学 第二解剖学)
- N253 Phorbol ester と forskolinによるERK活性化を介した H₂O₂ 誘発細胞死抑制作用**
 ○竹島 直子, 吉岡 靖啓, 今津 邦智, 山室 晶子, 前田 定秋 (摂南大学 薬学部 薬物治療学研究室)
- N254 エストロジェン様化学物質によるStaurosporine誘発神経細胞死の阻害**
 ○根岸 隆之^{1,3}, 石井 寿幸¹, 久和 茂¹, 黒田 洋一郎^{2,3}, 吉川 泰弘^{1,3} (¹東京大学 大学院農学生命科学研究科, ²東京都神経科学総合研究所分子神経生物学研究部門, ³科学技術振興事業団 CREST)

睡眠, 生体リズム

- N255 視交叉上核における CaM キナーゼ II を介する mPer1 の誘導機構**
 (MS6-4) ○福永 浩司¹, 野村 和美², 山口 瞬³, 岡村 均³, 竹内 有輔¹ (¹東北大学大学院 薬学研究科 薬理学分野, ²熊本大学 医学部, ³神戸大学大学院 医学研究科)
- N256 Pituitary adenylate cyclase-activating polypeptide (PACAP) 欠損マウスにおける光刺激による位相変化の異常**
 ○橋本 均¹, 川口 ちひろ¹, 磯島 康史², 永井 克也², 田中 一裕¹, 新谷 紀人¹, 馬場 明道^{1,3} (¹大阪大学大学院 薬学研究科 神経薬理学分野, ²大阪大学蛋白質研究所蛋白質代謝部門, ³大阪大学大学院医学系研究科分子医薬分野)

神経内分泌

- N257 ob/ob マウスの視床下部におけるインスリンを介したグルコース輸送系についての検討**
 ○小森 忠祐¹, 森川 吉博¹, 田村 志宣¹, 南條 輝志男², 仙波 恵美子¹ (¹和歌山県立医科大学 第二解剖, ²和歌山県立医科大学 第一内科)

President's Lecture

September 25 (Thur.) 14:50~15:25 Marine Hall

Chairperson : Tadashi Miyatake (Showa Pharm. Univ.)

Researches on Neurological Diseases in the New Millennium.

Shoji Tsuji (Dept. of Neurol., Grad. Sch. of Med., Univ. of Tokyo)

Plenary Lectures

September 25 (Thur.) 15:25~16:10 Marine Hall

Chairperson : Yasuo Ihara (Univ. Tokyo, Grad. Sch. Med.)

PL-1 Searching for Novel Alzheimer's Disease Genes on Chromosome 10

Steven G. Younkin (Mayo Clinic Jacksonville)

September 25 (Thur.) 16:10~16:55 Marine Hall

Chairperson : Shoji Tsuji (Univ. Tokyo, Grad. Sch. Med.)

PL-2 Regulatory mechanisms of synaptic transmission in the neural circuit

Shigetada Nakanishi (Dept. of Mol. and System Biol., Grad. Sch. of Biostud., Dept. of Biol. Sci., Fac. of Med., Kyoto Univ.)

September 25 (Thur.) 17:40~18:30 Marine Hall

Chairperson : Toshiharu Nagatsu (Fujita Health Univ.)

PL-3 Assembly of a Nervous System — The Initial Strategy

Marshall Nirenberg (NHLBI)

ISN Symposium

September 26 (Fri.) 9:00~11:30 Marine Hall

**Exploring possibilities of therapeutic strategies for
polyglutamine diseases—**

Organizers : Kenneth Fischbeck (NIH, NINCDS)

Shoji Tsuji (Univ. Tokyo, Grad. Sch. Med.)

ISN-1 Polyglutamine toxicity in spinal and bulbar muscular atrophy

Kenneth Fischbeck (NIH, NINCDS)

ISN-2 Intervention of nuclear transport of androgen receptor

Gen Sobue (Nagoya Univ.)

- ISN-3 Exploring RNA interference as a therapeutic strategy in polyglutamine disease**
Henry L. Paulson (Univ. of Iowa)
- ISN-4 Inhibition of protein aggregation in Alzheimer's and Huntington's disease: implications for therapy**
Erich E. Wanker (Max Planck Inst.)

Open Symposium

September 25 (Thur.) 18:00~20:00 Snow Hall B

**Why do we take particular actions?
– Elucidating the Underlying Neural Substrate of Behaviors –**

Organizers : Masatoshi Takeda (Osaka Univ. Grad. Sch. Med.),
Naomasa Miki (Osaka Univ. Grad. Sch. Med.)

- OS-1 Molecular base of "attraction" and "aversion" in the nematode *Caenorhabditis elegans***
Ikue Mori (Grad. Sch. of Sci., Nagoya Univ., Japan)
- OS-2 Diversity of cadherin-related neuronal receptor (*CNR*) genes in the brain**
Takeshi Yagi (Osaka Univ./ Natl. Inst. for Physiol. Sci./ CREST)
- OS-3 Audiogenic seizure and the brain development: lessons from Neurepin-KO mice**
Makoto Sato (Fukui Med. Univ.)
- OS-4 Genes regulating sexual behavior**
Daisuke Yamamoto (Sch. of Sci. and Eng., Waseda Univ. at Higashi-Fushimi, Tokyo, Japan)
- OS-5 Neuronal activities in the primate orbitofrontal cortex in relation to reward expectancy**
Hikosaka Kazuo (Dept. of Psychol., Tokyo Metrop. Inst. for Neurosci.)

Open Lecture

September 26 (Fri.) 14:00~15:30 Marine Hall

Chairperson : Masatoyo Nishizawa (Brain Res. Inst., Niigata Univ.)

Progress in the pathogenesis and treatment of Parkinson's disease
Yoshikuni Mizuno (Dept. of Neurol., Juntendo Univ. Sch. of Med.)

Young Scientists Lectureship Award

September 24 (Wed.) 9:00~11:00 Marine Hall

Chairperson : Kazuhiro Ikenaka (Natl. Inst. Physiol. Sci.)

- LA-1 **Dynamic regulation of synaptic transmission by astrocytic ATP**
 Schuichi Koizumi (Div. Pharmacol., Natl. Inst. Hlth. Sci.)
- LA-2 **Regulation mechanism for 24 hr periodicity in mammalian biological clocks**
 Teruya Tamaru (Dept. of Physiol., Toho Univ. Sch. of Med.)
- LA-3 **A molecular therapy for the polyglutamine diseases by Polyglutamine Binding Peptide 1 (QBP1)**
 Yoshitaka Nagai (Div. of Functional Genomics, Dept. of Post-Genomics & Dis., Osaka Univ. Grad. Sch. Med.)
- LA-4 **Role of specific muscarinic acetylcholine receptor subtypes in CNS**
 Masahisa Yamada (Mol. Neuropathol. Group, RIKEN Brain Sci. Inst.)

Symposium

September 24 (Wed.) 9:00~11:30 Snow Hall B

S1 **Advanced research for cell death relevant to the endoplasmic reticulum function**

Organizers : Hidenori Ichijo (Univ. Tokyo, Grad. Sch. Pharm. Sci.)
 Taiichi Katayama (Osaka Univ. Grad. Sch. Med.)

- S1-1 **Stress-induced Apoptosis by the ASK1-MAP Kinase Signal**
 Hidenori Ichijo (Lab. of Cell Signaling, Grad. Sch. of Pharm. Sci., Univ. of Tokyo)
- S1-2 **Nitric Oxide- and ER stress-mediated Apoptosis and Its Regulation by hsp70/DnaJ Chaperone Pairs**
 Tomomi Gotoh (Dept. of Mol. Genet., Grad. Sch. of Med. Sci., Kumamoto Univ.)
- S1-3 **Caspase induced by endoplasmic reticulum (ER) stress**
 Junichi Hitomi (Dept. of Anat. and Neurosci., Grad. Sch. of Med., Osaka Univ.)
- S1-4 **Cell survival and death regulated on the ER membrane after ER stress**
 K. Imaizumi (Nara Inst. of Sci. and Technol.)
- S1-5 **Impairment of retrieval by the KDEL receptor sensitizes cells to ER stress**
 Tomohiko Aoe (Mol. Embryol., Chiba Univ. Grad. Sch. of Med.)

September 24 (Wed.) 14:45~17:15 ROOM302

S2 Neurochemistry of fatigue and fatigue sensation

Organizers : Hirotaka Onoe (Tokyo Metrop. Inst. Neurosci.)
Hirohiko Kuratsune (Kansai Univ. Welfare Sci.)

- S2-1 Involvement of interferon- α and serotonin system in the immunologically induced fatigue in rats
Toshihiko Katafuchi (Dept. of Integrative Physiol., Grad. Sch. of Med. Sci., Kyushu Univ.)
- S2-2 UV-irradiation Down-regulates Immune Functions and Causes Fatigue by Photo-Optico-Neuronal Network: Lessons From iNOS-knockout Mice
M. Inoue (Dept. Biochem. & Mol. Pathol., Osaka City Univ. Med. Sch.)
- S2-3 Effects of hexenal and hexenol on 5-HT and DA Metabolisms in the Brain and/or on Food Intake under Immobilization Stress and Foot Shock Stress in Rats
K. Sasaki (Div. of Bio-Information Eng., Fac. of Eng., Toyama Univ.)
- S2-4 Development of Advanced Trail Making Test for evaluating mental function -ATMT: a computer-assisted system for assessment of fatigue-
Osami Kajimoto (Sogo-ikagaku-Kenkyusho, Osaka Univ. Foreign Studies)
- S2-5 Neural circuits for fatigue sensation revealed by neuroimaging techniques
Hirotaka Onoe (Dept. Psychol., Tokyo Metrop. Inst. Neurosci., Tokyo)
- S2-6 The pathophysiology of Chronic Fatigue Syndrome (CFS)
Hirohiko Kuratsune (Dept. of Health Sci., Fac. of Health Sci. for Welfare, Kansai Univ. of Welfare Sci.)

September 24 (Wed.) 14:45~17:15 ROOM301

S3 The mechanisms regulating synthesis/secretion of neurotrophins

Organizers : Shoei Furukawa (Gifu Pharm. Univ.)
Ritsuko Katoh-Semba (Aichi Human Service Center)

- S3-1 Mechanisms of drug-induced BDNF synthesis in the rat brain
Ritsuko Katoh-Semba (Inst. for Develop. Res., Aichi Human Service Center, Aichi, Japan)
- S3-2 Transcriptional Regulation of Brain-derived Neurotrophic Factor (BDNF) Gene in Neurons
Masaaki Tsuda (Toyama Med. and Pharm. Univ., Toyama)
- S3-3 Intracellular processing and secretion of neurotrophins
Hiroshi Nomoto (Lab. of Mol. Biol., Gifu Pharm. Univ.)
- S3-4 A novel molecule that mediates neurotrophin release in cerebellar neurons
Teiichi Furuichi (RIKEN)

- S3-5 Functional SNPs in human BDNF gene: roles in BDNF secretion and processing**
Masami Kojima (AIST, Osaka)

September 25 (Thur.) 9:00~11:30 Marine Hall

S4 Recent Advances in Alzheimer's Disease

Organizer : Yasuo Ihara (Univ. Tokyo, Grad. Sch. Med.)

- S4-1 Functional anatomy of the γ -secretase complex**
T. Tomita and T. Iwatsubo (Univ. of Tokyo)
- S4-2 Relationship between γ and ϵ -cleavage**
M. Morishima and Y. Ihara (Univ. of Tokyo)
- S4-3 NSAIDs and Alzheimer's disease**
Edward H. Koo (Univ. of California, San Diego)
- S4-4 Abeta metabolism and Alzheimer's disease**
T. Saido (RIKEN)
- S4-5 Inhibition of GSK-3- A possible therapeutic target in Alzheimer's disease**
A. Takashima (RIKEN)

September 25 (Thur.) 9:00~11:30 Snow Hall B

S5 Molecular signaling for axonal growth in the growth cone

Organizers : Michihiro Igarashi (Niigata Univ., Grad. Sch. Med. Dent. Sci.)
Hitoshi Tatsumi (Nagoya Univ., Grad. Sch. Med.)

- S5-1 Proteomic approach of the growth cone functions**
Michihiro Igarashi (Div. Mol. Cell Biol., Grad. Sch. Med. Dent. Sci., Niigata Univ.)
- S5-2 Dynamics of actin filaments and actin associate proteins revealed by polarized light and fluorescence microscopy**
Kaoru Katoh (Neurosci. Inst., AIST.)
- S5-3 Regulation of N-WASP by Src-Family Tyrosine Kinases and Proteasome in Neurite Extension**
Shiro Suetsugu (Dept. Biochem., Inst. of Med. Sci., Univ. Tokyo)
- S5-4 Plexin mediates bifunctional signals**
Shinobu Inagaki (Group Neurobiol., Sch. Allied Health Sci., Osaka Univ. Fac. Med., Osaka Japan)
- S5-5 The regulation of microtubule dynamics in growth cones by SCG10**
Gabriele Grenningloh (Univ. Lausanne, Switzerland)

- S5-6 Exocytosis and contact formation in neuronal growth cones**
H. Tatsumi (Dept. Physiol. Nagoya Univ. Grad. Sch. of Med.)

September 26 (Fri.) 9:00~11:30 Snow Hall B

S6 Conditional gene manipulation and its application to brain research

Organizers : Kenji Sakimura (Niigata Univ., Brain Res. Inst.)
Hisashi Mori (Univ. Tokyo, Grad. Sch. Med.)

- S6-1 Development of a temporal and cell-specific gene knockout mouse and its application to brain research**
Kenji Sakimura (Dept. of Cellular Neurobiol., Brain Res. Inst., Niigata Univ.)
- S6-2 Role of scaffold proteins interacting with the carboxyl-terminal domain of mGluR1a**
Atsu Aiba (Div. of Cell Biol., Dept. of Cell. & Mol. Biol., Kobe Univ. Grad. Sch. of Med.)
- S6-3 Generation and analysis of striatum-selective NMDA receptor knockout mice**
Hisashi Mori (Dept. Mol. Neurobiol. & Pharmacol., Grad. Sch. Med., Univ. Tokyo and SORST, JST, Tokyo, Japan)
- S6-4 Emx1-Cre Mice Reveal Cortical Mechanisms Involved in the Barrel Formation**
Takuji Iwasato (PRESTO, Japan Sci. and Technol. Corp (JST). / Lab. Behav. Genet., Brain Sci. Inst. (BSI), RIKEN)
- S6-5 Roles of Hippocampal CA3 NMDA Receptors in Learning and Memory**
Kazu Nakazawa (Natl. Inst. of Mental Health, NIH)

September 26 (Fri.) 9:00~11:30 ROOM302

S7 Molecular bases of the synaptic function

Organizers : Teruo Abe (Niigata Univ., Brain Res. Inst.)
Konosuke Kumakura (Sophia Univ., Life Sci. Inst.)

- S7-1 Regulation of exocytotic events in single adrenal chromaffin cells**
N. Sasakawa (Lab. of Neurochem. and Neuropharmacol., Life Sci. Inst., Sophia Univ., Tokyo Japan)
- S7-2 A Genetic Dissection of the Roles of Synaptotagmin and Eps15 in *Drosophila***
Iain Robinson (Case Western Univ.)
- S7-3 Dynamics of postsynaptic density**
Shigeo Okabe (Tokyo Med. and Dent. Univ., Tokyo, Japan, CREST, JST, Kawaguchi, Japan)

S7-4 Potential roles of synaptic scaffolding molecule (S-SCAM) in the molecular organization of synapses

Yutaka Hata (Dept. of Med. Biochem., Grad. Sch. of Med., Tokyo Med. and Dent. Univ.)

S7-5 Structural plasticity of dendritic spines associated with short and long-term potentiation in hippocampal CA1 pyramidal neurons

Haruo Kasai (Dept. Cell Physiol., Natl. Inst. Physiol. Sci., Japan)

September 26 (Fri.) 9:00~11:30 ROOM301

S8 A variety of ATP functions in the nervous system.

Organizers : Shinichi Kohsaka (Natl. Inst. Neurosci.)

Kazuhide Inoue (Natl. Inst. Health. Sci./Kyushu Univ., Grad. Sch. Pharm. Sci.)

S8-1 The role of ATP in neuro-glio-endothelial interaction - ATP-induced chemokine production in astrocytes -

Masabumi Minami (Dept. of Mol. Pharm., Grad. Sch. of Pharm. Sci., Kyoto Univ., Kyoto, Japan)

S8-2 Intracellular Proteases and ATP-induced Apoptosis of Neuronal and Glial Cells

Hiroshi Nakanishi (Lab. of Oral Aging Sci., Fac. of Dent. Sci., Kyushu Univ.)

S8-3 Microglial activation by ATP through Gi/o-coupled purinoceptor, P2Y₁₂

Keiko Ohsawa (Dept. of Neurochem., Natl. Inst. of Neurosci., Tokyo, Japan)

S8-4 Diverse consequences of the ATP application in the hippocampal synaptic transmission

Fusao Kato (Lab. Neurophysiol., Dept. Neurosci., Jikei Univ. Sch. of Med.)

S8-5 Bi-directional regulation of neuronal activities by extracellular ATP

Schuichi Koizumi¹ · Kazuhide Inoue^{2,3}

(Div. ¹Pharmacol, ²Biosignal, Natl. Inst. Hlth. Sci., Tokyo, and ³Grad. Sch. Pharm. Sci., Kyushu Univ.)

September 26 (Fri.) 12:30~15:00 Snow Hall B

S9 The ubiquitin-proteasome system and neurological diseases

Organizer : Keiji Wada (Natl. Inst. Neurosci.)

S9-1 Dysfunction of the ubiquitin proteasome system in neurodegenerative disease

Ron Kopito (Stanford Univ.)

S9-2 Parkin and Parkinson's disease

Nobutaka Hattori (Dept. of Neurol., Juntendo Univ.)

- S9-3 Parkinson's disease and ER stress -from a study of autosomal recessive juvenile parkinsonism (AR-JP)**
Yuzuru Imai (Motor System Neurodegeneration, RIKEN Brain Sci. Inst. (BSI))
- S9-4 Pathophysiological role of ubiquitin C-terminal hydrolase L1 in neurodegeneration**
Keiji Wada (Natl. Inst. of Neurosci., Natl. Center of Neurol. and Psychiatr.)
- S9-5 Mechanisms to control degradation of polyglutamine-containing protein**
Keiichi Nakayama (Dept. of Mol. and Cell. Biol., Kyushu Univ., Fukuoka)

September 26 (Fri.) 12:30~15:00 ROOM302

S10 Aging Brain and Neural Plasticity

Organizer : Susumu Ando (Tokyo Metrop. Inst. of Gerontol.)

- S10-1 Gene Expression Changes and Loss of Neuronal Plasticity in the Aged Brain**
Nozomu Mori (Dept. of Mol. Genet., Natl. Inst. for Longevity Sci.)
- S10-2 Brain aging and Humanin**
Takako Niikura (Keio Univ., Sch. of Med.)
- S10-3 Roles of neurotrophic factors in aged brain**
Shoei Furukawa (Lab. of Mol. Biol., Gifu Pharm. Univ.)
- S10-4 Synaptic Plasticity and Cognitive Enhancement by Enriched Environment**
Susumu Ando (Tokyo Metrop. Inst. of Gerontol.)
- S10-5 Neurogenesis in the hippocampus of aged rats**
Tatsunori Seki (Dept. of Anat., Juntendo Univ. Sch. of Med., Tokyo)

September 26 (Fri.) 12:30~15:00 ROOM301

S11 Neuron - glia Interaction : Its implication in neural information processin

Organizers : Yoshihisa Kudo (Tokyo Univ. Pharm. and Life Sci.)
Hiroko Baba (Tokyo Univ. Pharm. and Life Sci.)

- S11-1 Diversity of astrocytes.**
Kazuhiro Ikenaka (Natl. Inst. for Physiol. Sci., Okazaki Natl. Res. Inst.)
- S11-2 Regulation of axonal functional domain organization by glia**
Hiroko Baba (Dept. of Mol. Neurobiol., Tokyo Univ. of Pharm. and Life Sci.)
- S11-3 Possible roles of glia-neuron networks in brain function**
Yoshihisa Kudo (Sch. of Life Sci., Tokyo Univ. of Pharm. and Life Sci.)
- S11-4 Functions of Ca²⁺-permeable AMPA receptors and glutamate transporters in Bergmann glia**
S. Ozawa (Dept. of Neurophysiol., Gunma Univ. Grad. Sch. of Med.)

Mini Symposium

(The number in a parenthesis is a poster number.)

September 24 (Wed.) 9:00~10:15 ROOM302

MS1 Molecular Mechanism of Neurodegenerative diseases

Chairpersons : Teru Sano (Kagoshima Univ. Grad. Med.)

Keiji Wada (Natl. Inst. of Neurosci., Natl. Ctr. of Neurol. and Psychiatr.)

MS1-1 Targeted Disruption of Mouse DRPLA Gene to Investigate Molecular Pathophysiology of dentatorubral-pallidolusian atrophy (DRPLA)
(N054)

Tetsuya Kimura (Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, Japan)

MS1-2 Functional Analysis of Novel Ubiquitin Ligase, Potential Target Antigen of Paraneoplastic Neurologic Disorder
(N083)

Hirobumi Tada (Dept. of Physiol., Sch. of Med., Keio Univ.)

MS1-3 Inhibitory effects of 4-phenylbutyrate on Pael receptor accumulation and endoplasmic reticulum stress induced cell death
(N056)

Kyoko Kubota (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan)

MS1-4 ALS2, a novel guanine nucleotide exchange factor for the small GTPase Rab5 is implicated in endosomal dynamics
(N057)

Asako Otomo (Dept. of Mol. Neurosci., The Inst. of Med. Sci., Tokai Univ.)

MS1-5 Aprataxin, the causative gene for early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH) as a member of ssDNA repair machinery. -Implication of impaired DNA repair systems in neurodegeneration-
(N058)

Hidetoshi Date (Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, JAPAN)

September 24 (Wed.) 9:00~10:15 ROOM301

MS2 Neuronal regeneration

Chairpersons : Hideyuki Okano (Keio Univ. Sch. Med.)

Hiroshi Kiyama (Osaka City Univ., Grad. Sch. Med.)

MS2-1 ANALYSIS OF EXPRESSION PROFILES OF G-PROTEIN COUPLED RECEPTOR GENES IN EMBRYONIC NEURAL STEM CELLS.
(N001)

Mika Nishimoto (Natl. Inst. of Neurosci. N.C.N.P.)

MS2-2 Molecular Characterization of a Novel Tetraspan Membrane Protein Up-regulated in Neurons of Axotomized Facial Nuclei
(N032)

Shinichi Kohsaka (Dept. of Neurochem., Natl. Inst. of Neurosci.)

- MS2-3 Transplantation of neural stem cells and re-expression of PSA-NCAM in a (N033) mouse model of demyelinating disease**
 Michio Matsumoto (Div. of Mol. Neurobiol., Natl. Inst. for Physiol. Sci., Okazaki, Japan)
- MS2-4 Possible alteration of DNA methylation may affect fate of injured motor neurons (N034)**
 Tian Cheng Zhao (Dept. of Anat. and Neurobiol., Osaka City Univ., Grad. Sch. of Med., Osaka, Japan)
- MS2-5 Axonal Regeneration after Administration of Semaphorin 3A Inhibitor into the (N035) Injured Spinal Cord**
 Shinjiro Kaneko (Dept. of Orthop. Surg., Keio Univ. Sch. of Med.)
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September 24 (Wed.) 10:15~11:30 ROOM302

MS3 Molecular Mechanism of Dementia

Chairpersons : Masatoshi Takeda (Osaka Univ. Grad. Sch. Med.)
 Masaya Tohyama (Osaka Univ. Grad. Sch. Med.)

- MS3-1 Regulation of tau exon 10 splicing by a double stem-loop structure in mouse (N103) intron 10**
 Takenari Yamashita (Dept. of Neurosci., Osaka City Univ. Med. Sch., Osaka, Japan)
- MS3-2 Phosphorylation of FTDP-17 tau mutants by Cyclin-dependent kinase 5 (N104)**
 Fumika Sakaue (Dept. of Biol. Sci., Grad. Sch. of Sci., Tokyo Metrop. Univ., Tokyo, Japan)
- MS3-3 Alzheimer's beta-secretase (BACE1) cleaves alpha2,6sialyltransferase as a (N105) physiological substrate.**
 Yasuhiro Hashimoto (RIKEN Inst.)
- MS3-4 PEN-2 enhances gamma-secretase activity without the stimulation of presenilin (N106) endoproteolysis**
 Hirohisa Shiraishi (Dept. of Dementia Res., Natl. Inst. for Longevity Sci.)
- MS3-5 Dual-cleavage mechanism of betaAPP by Cell Free PS/gamma-secretase assay. (N107)**
 Fukumori Akio (Div. of Psychiatr. and Behav. Proteomics, Dept. of Post-Genomics and Dis., Course of Adv. Med., Osaka Univ. Grad. Sch. of Med. Suita Japan)

September 24 (Wed.) 10:15~11:30 ROOM301

MS4 Regulation of synaptic functions

Chairpersons : Konosuke Kumakura (Life Science Inst., Sophia Univ)
Masami Takahashi (Kitasato Univ. Sch. of Med.)

MS4-1 A novel postsynaptic scaffold protein, TANC, which contains TPR, ankyrin and (N021) coiled-coil domain.

Tatsuo Suzuki (Dept Neuroplasticity, Inst Aging and Adaptation, Shinshu Univ. Grad Sch. Med, Matsumoto, Japan)

MS4-2 The ligand dependent synaptic clustering of PSD-95 and its role in neuronal (N022) function

Mio Nonaka (The Dept. of Biophys., Grad. Sch. of Sci., Kyoto Univ., Kyoto, Japan)

MS4-3 NMDA-dependent proteolytic cleavage of stargazing in cultured neurons (N023)

Mihoko Inamura (Dept. Bioch, Kitasato Univ. Sch. Med.)

MS4-4 Time lapse recording of translocation of GFP-drebrin A, an actin-binding (N024) protein in dendritic spines, induced by activation of glutamate receptors in hippocamal neurons

Toshiyuki Mizui (Dept. of Neurobiol. and Behavior, Gunma Univ Grad. Sch of Med, Maebashi, Japan)

MS4-5 A week-order long-term synaptic enhancement in cultured hippocampal slice (N025) after repeated exposure to glutamate

Akihiko Ogura (Osaka Univ. Grad. Sch. of Frontier Biosci., Osaka, Japan)

September 25 (Thur.) 8:45~10:00 ROOM302

MS5 Neurotrophic factors: their activities and functions

Chairperson : Shoei Furukawa (Gifu Pharm. Univ.)
Hiroyuki Nawa (Niigata Univ., Brain Res. Inst.)

MS5-1 Regulated Release of EGF-like Molecules from Rat Striatum Culture: Their (N222) Trophic Activity on Midbrain Dopaminergic Neurons.

Yuriko Iwakura (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)

MS5-2 BDNF activates translation elongation in cultured cortex neurons.

(N223) Naoko Inamura (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)

MS5-3 Adenoviral gene transfer of growth inhibitory factor (metallothionein-III) (N224) prevents degeneration of injured adult rat motoneurons

Tsuyoshi Sakamoto (Dept. of Mol. Neuropathol., Tokyo Metrop. Inst. for Neurosci.)

- MS5-4 The role of calbindin-D28k in the neuroprotective action of basic fibroblast growth factor -in vitro assay by using neurons derived from calbindin-D28k KO mice-**

Taisuke Kadoshima (Daiichi Suntory Biomedical Reserch Co., Ltd., Osaka, Japan)

- MS5-5 PITUITARY ADENYLATE CYCLACE- ACTIVATING POLYPEPTIDE (PACAP) REGULATES NEURAL STEM CELL FATE IN VITRO AND IN VIVO**

Shigeki Ohta (Neuro-immunol. Res. Group, Keio Univ. Sch. of Med.)

September 25 (Thur.) 8:45~10:00 ROOM301

MS6 Proteinkinase

Chairpersons : Takashi Yamauchi (Tokushima Univ., Grad. Sch. Pharm.)

Hideyuki Yamamoto (Kumamoto Univ. Med. Sch.)

- MS6-1 Autophosphorylated, inactivated and sedimentable Ca^{2+} /calmodulin-dependent protein kinase II during acute brief seizure activity in rats in vivo**

Yoko Yamagata (Natl. Inst. for Physiol. Sci.)

- MS6-2 Stimulation of CaM kinase II-dependent neurite extension by Arc**

(N147) Hitomi Donai (Fac. of Pharm. Sci., The Univ. of Tokushima, Tokushima, Japan)

- MS6-3 The regulatory mechanisms of CaM kinases I and IV in the hippocampal neurons.**

(N148) Jiro Kasahara (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Tohoku Univ., Sendai, Japan)

- MS6-4 Mechanism of mPer1 induction through CaM kinase II activation in the suprachiasmatic nucleus**

Kohji Fukunaga (Dept. Pharmacol. Grad. Sch. Pharm. Scis. Tohoku Univ. Sendai, Japan)

- MS6-5 Identification of MLK 3 as a hippocalcin-binding protein**

(N149) Masaaki Kobayashi (Dept. of Physiol., Toho Univ. Sch. of Med., Tokyo, Japan)

September 25 (Thur.) 10:00~11:15 ROOM302

MS7 Neuron-Glia

Chairpersons : Shinichi Kohsaka (Natl. Inst. of Neurosci.)

Hiroko Baba (Tokyo Univ. of Pharm. and Life)

- MS7-1 The N-terminal membrane-associated domain of RB3, a neural-specific member of the SCG10/stathmin family proteins, affects the microtubule dynamics**

Chitose Nakao (Dept. of Mol. Genet., Natl. Inst. for Longevity Sci. (NILS), Aichi, Japan)

- MS7-2 Real-time observation of the effect of dephosphorylation on neurofilament gel (N167) formation using microbeads**
 Rei Ono (Dept. of Biochem., Coll. of Sci. and Eng., Aoyama Gakuin Univ., Sagamihara, Japan)
- MS7-3 Screening of the downstream targets of Olig2 by PCR-based cDNA subtraction (N174) analysis**
 Noritaka Masahira (Div. of Mol. Neurobiol., Natl. Inst. for Physiol. Sci., Okazaki, Japan)
- MS7-4 Expression and activity of extracellular superoxide dismutase in cultured (N175) astrocytes**
 Yoichi Nakamura (Lab. of Integrative Physiol. in Veterinary Sci., Osaka Pref. Univ., Sakai, Japan)
- MS7-5 The dynamic state of progenitor cells in brain injury (N176)**
 Kouko Tatsumi (The Second Dept. of Anat., Nara Med. Univ., Kashihara, Nara, Japan)
- MS7-6 Functional analysis of a novel ER stress sensor, CREB/ATF family member, (N252) OASIS**
 Shinichi Kondo (Div. of Structural Cellular Biol., Nara Inst. of Sci. and Technol., Nara, Japan)

September 25 (Thur.) 10:00~11:15 ROOM301

MS8 Cell differentiation and cell lineage

Chairpersons : Kazuhiro Ikenaka (Natl. Inst. Physiol. Sci.)

Ichiro Matsuoka (Hokkaido Univ., Grad. Sch. Pharm. Sci.)

- MS8-1 Astrocyte-derived factors instruct differentiation of mouse and primate (N208) embryonic stem cells into neurons**
 Takashi Nakayama (Dept. of Biochem., Yokohama City Univ. Sch. of Med., Yokohama, Japan)
- MS8-2 NRSF/REST and DNA methylation regulate cell type specific expression of (N209) BRINP1 (BMP-2 and Retinoic acid Inducible Neural-specific Protein 1)**
 Toshiyuki Nakatani (Lab. of Neurosci., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan)
- MS8-3 Histological and biochemical study of Sox21 transcriptional facto (N210)**
 Hiroyuki Ohba (Dept. of Physiol., Keio Univ. Sch. of Med., Tokyo, Japan)
- MS8-4 Stimulation of the G protein, Gi2, by endothelin B receptors enhances proliferation (N150) and migration of neural progenitor cells**
 Tomiko Asano (Dept. of Mol. Neurobiol., Inst. for Develop. Res., Aichi Human Service Center, Kasugai, Japan)

MS8-5 Lineage analysis on forebrain oligodendrocyte

(N211) Hirohide Takebayashi (Natl. Inst. for Physiol. Sci.)

**MS8-6 Filamin A-interacting protein FILIP regulates cell shape prior to radial
(N170) migration in the cortical ventricular zone.**

Takashi Nagano (Dept. of Anat. (2), Faculty of Med., Fukui Med. Univ.)

Poster

Receptors and Transporters

- N001 ANALYSIS OF EXPRESSION PROFILES OF G-PROTEIN COUPLED RECEPTOR GENES IN (MS2-1) EMBRYONIC NEURAL STEM CELLS.**
 ○Mika Nishimoto^{1,2}, Yoko Hara¹, Koichi Ayukawa¹, Hiroki Ohashi^{1,3}, Yoshihisa Kudo², Toshiaki Abe³, Shunsuke Aoki¹, Keiji Wada¹ (¹Natl. Inst. of Neurosci. N.C.N.P., ²Tokyo Univ. of Pharm. And Life Sci. Sch. Of Life Sci., ³Jikei Univ. Sch. of Med.)
- N002 NEURONAL GLUTAMATE TRANSPORTER EAAT3 (EAAC1) IS INVOLVED IN AN UNIQUE CYSTEINE TRANSPORT SYSTEM**
 ○Toshiyuki Himi¹, Masayuki Ikeda², Tadashi Yasuhara³, Ikuo Morita¹, Sei-itsu Murota¹ (¹Dept. of Physiol. Chem., Grad. Sch., Tokyo Med. and Dental Univ., Tokyo, Japan, ²Natl. Saigata Hosp., Ohgata-machi, Japan, ³Tokyo Agric. Coll.)
- N003 Expression of vanilloid receptor (VR1) in PC12 cells**
 ○Akiyoshi Someya, Kana Kunieda, Tetsuya Hirabayashi, Syunji Horie, Toshihiko Murayama (Lab. of Chem. Pharm., Grad. Sch. of Pharm. Sci., Chiba Univ., Chiba, Japan)
- N004 Developmental expression of a member of TNF receptor superfamily, TROY, in the olfactory system of mice**
 ○Tomoko Hisaoka¹, Yoshihiro Morikawa¹, Toshio Kitamura², Emiko Senba¹ (¹Dept. of Anat. and Neurobiol., Wakayama Med. Univ., Wakayama, Japan, ²Div. of Cell. Therapy, Adv. Clin. Res. Center, The Inst. of Med. Sci., The Univ. of Tokyo, Tokyo, Japan)
- N005 Effects of neuronal cell toxicity induced by bicuculline methiodide in slice cultures of rat hippocampus**
 ○Chunxi Han, Nahoko Kasai, Keiichi Torimitsu (NTT Basic Res. Lab., Atsugi, Kanagawa, Japan)
- N006 Altered sensitivity of NMDA receptor channels during in vitro maturation in cultured rat cortical neurons**
 ○Noritaka Nakamichi, Yuki Kambe, Hirotaka Oikawa, Yukio Yoneda (Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Japan)
- N007 Functional expression of particular glutamate signaling machineries in rat testis**
 ○Takeshi Takarada, Eiichi Hinoi, Hideo Taniura, Yukio Yoneda (Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Ishikawa, Japan)
- N008 Signaling through groupII metabotropic glutamate receptors to nuclear activator protein-1 in primary cultured rat cortical neurons**
 ○Chie Sugiyama, Hideo Taniura, Yukio Yoneda (Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Ishikawa, Japan)
- N009 Contribution of the N- and C-terminal domain to the functional regulation of melanin-concentrating hormone receptor 1**
 ○Yumiko Saito, Mitsue Tetsuka, Kei Maruyama (Dept. of Pharm., Saitama Med. Sch.)
- N010 Immunohistochemical detection of particular NMDA receptor subunits in murine hippocampus**
 ○Keisuke Tamaki¹, Kiyofumi Yamada¹, Masanori Yoneyama², Tomoya Kitayama³, Yukio Yoneda² (¹Lab. of Exp. Therapeutics, Kanazawa Univ. Fac. of Pharm. Sci., Kanazawa, Japan, ²Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Japan, ³Dept. of Dental Pharm., Hiroshima Univ. Grad. Sch. of Biomed. Sci., Hiroshima, Japan)
- N011 Modulation by N-methyl-D-aspartate receptors of development of cultured neural progenitor cells isolated from adult murine hippocampus**
 ○Masanori Yoneyama¹, Tomoya Kitayama², Yukio Yoneda¹ (¹Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Japan, ²Dept. of Dental Pharm., Hiroshima Univ. Grad. Sch. of Biomed. Sci., Hiroshima, Japan)

- N012 Hypertonicity stimulates expression of aquaporin 4 and 9 through a p38 mitogen activated protein kinase dependent pathway in rat astrocytes**
 ○Kazuya Sobue¹, Naoki Yamamoto², Hajime Arima¹, Hiroaki Ito¹, Masaaki Inagaki¹, Tetsuro Morishima¹, Fuminori Umenishi³, Hirotada Katsuya¹, Kiyofumi Asai² (¹Dept. of Anesthesiol. and Med. Crisis Manage., Nagoya City Univ., Grad. Sch. of Med. Sci., Nagoya, Japan, ²Dept. of Mol. Neurobiol., Nagoya City Univ., Grad. Sch. of Med. Sci., Nagoya, Japan, ³Div. of Renal Dis. and Hypertension, Dept. of Med., Univ. of Colorado Health Sci. Center, Denver, USA)
- N013 Functional expression of particular GABA transporter in cultured rat calvarial osteoblasts**
 ○Sayumi Fujimori, Eiichi Hinoi, Mika Iemata, Yasuhiro Murafuji, Yukio Yoneda (Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Ishikawa, Japan)
- N014 Effects of several 5-HT_{1B/1D} receptor agonists on [³⁵S]GTPγS binding in rat brain membranes**
 ○Yuji Odagaki, Toshio Yamauchi (Dept. of Psychiat., Saitama Med. Sch., Moroyama, Saitama, Japan)
- N015 Inhibition of dopamine D2-receptor mediated endocytosis by endophilin 3**
 ○Hiroko Sugiura¹, Ken Iwata², Takashi Yamauchi³, Tatsuya Haga², Kanato Yamagata¹ (¹Dept. Neuropharmacol., Tokyo Metropol. Inst. Neurosci., Tokyo, Japan, ²Inst. Biomol. Sci., Facul. Sci., Univ. Gakushuin, Tokyo, Japan, ³Fac. Pharm. Sci., Univ. Tokushima, Tokushima, Japan)
- N016 Mutational and Computational studies for mapping the odorant binding site of a G protein-coupled olfactory receptor**
 ○Sayako Katada¹, Takatugu Hirokawa², Makiko Suwa², Hiroshi Kataoka¹, Kazushige Touhara¹ (¹Dept. of Integrated BioSci., Grad. Sch. of Frontier Sci., The Univ. of Tokyo, Tokyo, Japan, ²Computational Biol. Res. Center, Natl. Inst. of Adv. Industrial Sci. and Technol., Tokyo, Japan)
- N017 Functional interaction between T2R bitter taste receptor and G protein alpha subunit expressed in taste receptor cells.**
 ○Takashi Ueda, Shinya Ugawa, Hisao Yamamura, Shoichi Shimada (The Dept. of Mol. Morphol., Grad. Sch. of Med. Sci., Nagoya City Univ., Nagoya, Japan)
- N018 Dopamine receptor 2 regulates L-type voltage-gated calcium channel in synchronous oscillation of intracellular calcium of primary cultured mouse midbrain neurons**
 ○Fumie Yasumoto¹, Takayuki Negishi^{1,3}, Yoshiyuki Ishii¹, Shigeru Kyuwa¹, Yoichiro Kuroda^{2,3}, Yasuhiro Yoshikawa^{1,3} (¹Dept. Biomed. Sci., Grad. Sch. of Agri. and Life Sci., The Univ. of Tokyo, Tokyo, Japan, ²Dept. of Mol. and Cell. Neurobiol., Tokyo Metrop. Inst. for Neurosci., Fuchu, Japan, ³CREST, JST, Kawaguchi, Japan)
- N019 Multiple forms of ASCT1 amino acid transporter molecule in rat brain.**
 Toshifumi Yamamoto¹, ○Hitoshi Takuma¹, Itone Nishizaki¹, Toshihide Nukada², Shigeki Furuya³, Yoshio Hirabayashi³, Kazutaka Ikeda², Hideaki Kobayashi², Ichiro Sora⁴, Hideko Yamamoto² (¹Lab. of Mol. Recognition, Grad. Sch. of Integrated Sci., Yokohama City Univ., Yokohama, Japan, ²Dept. of Mol. Psychiat., Tokyo Inst. of Psychiat., Tokyo, Japan, ³RIKEN Brain Sci. Inst., Wako-shi, Japan, ⁴Div. of Psychobiol., Tohoku Univ. Grad. Sch. of Med., Sendai, Japan)
- N020 Hzf, an RNA-binding protein binding to the 3-untranslated region of type1 inositol 1,4,5-trisphosphate receptor mRNA and its mechanism of mRNA localization in cerebellar Purkinje cells**
 ○Takatoshi Iijima^{1,2,3}, Kanako Takatsuki⁴, Taisuke Miyazaki⁵, Takao Imai^{1,2}, James-Hirofumi Okano^{1,2}, Yuki Kimura⁶, Shigetaka Kawahara⁴, Alan Bernstein⁶, Masahiko Watanabe⁵, Yutaka Kirino⁴, Hideyuki Okano^{1,2} (¹Dept. of Physiol., Keio Univ. Med. Sch., Tokyo, Japan, ²CREST, JST, Saitama, Japan, ³Dept. of Mol. and Cell. Biol., Grad. Sch. of Med., Osaka Univ., Osaka, Japan, ⁴Lab. of Neurobiophys., Grad. Sch. of Pharm. Sci., Tokyo Univ., Tokyo, Japan, ⁵Dept. of Anat., Grad. Sch. of Med., Hokkaido Univ., Hokkaido, Japan, ⁶Samuel Lunenfeld Res. Inst., Mount Sinai Hosp., Toronto, Canada)

Synapse

- N021 A novel postsynaptic scaffold protein, TANC, which contains TPR, ankyrin and coiled-coil domain. (MS4-1)**
 ○Tatsuo Suzuki, Weidong Li, Jingping Zhang (Dept. Neuroplasticity, Inst. Aging and Adapt., Shinshu Univ. Grad. Sch. Med., Matsumoto, Japan)

- N022 The ligand dependent synaptic clustering of PSD-95 and its role in neuronal function**
(MS4-2) ○Mio Nonaka¹, Ayako Tanaka¹, Tomoko Doi¹, Yoshinori Fujiyoshi¹, Sayaka Takemoto-Kimura^{2,3}, Haruhiko Bito³ (¹The Dept. of Biophys., Grad. Sch. of Sci., Kyoto Univ., Kyoto, Japan, ²Dept. of Pharm., Kyoto Univ. Fac. of Med., Kyoto, Japan, ³Grad. Sch. of Med., The Univ. of Tokyo, Tokyo, Japan)
- N023 NMDA-dependent proteolytic cleavage of stargazing in cultured neurons**
(MS4-3) ○Mihoko Inamura^{1,3}, Makoto Itakura¹, Jyun Tujimura², Yoshihisa Kudou², Hirotsugu Okamoto³, Sumio Hoka³, Saori Yamamori¹, Masami Takahashi¹ (¹Dept. Bioch, Kitasato Univ. Sch. Med., ²Tokyo Univ. Pharm., ³Dept. of Anesth., Kitasato Univ. Hosp.)
- N024 Time lapse recording of translocation of GFP-drebrin A, an actin-binding protein in dendritic spines, induced by activation of glutamate receptors in hippocampal neurons**
(MS4-4) ○Toshiyuki Mizui^{1,2}, Kenji Hanamura¹, Hideto Takahashi¹, Tomoaki Shirao¹, Yuko Sekino^{1,3} (¹Dept. of Neurobiol. and Behavior, Gunma Univ. Grad. Sch. of Med., Maebashi, Japan, ²Course of Health Sci., Gunma Univ. Grad. Sch. of Med., Maebashi, Japan, ³CREST, JST)
- N025 A week-order long-term synaptic enhancement in cultured hippocampal slice after repeated exposure to glutamate**
(MS4-5) ○Akihiko Ogura¹, Keisuke Okuhara², Keiko Tominaga-Yoshino¹ (¹Osaka Univ. Grad. Sch. of Frontier Biosci., Osaka, Japan, ²Osaka Univ. Grad. Sch. of Sci.)
- N026 Electron microscopic analysis of cell adhesion molecule L1-cam immunoreactivity in the hippocampus.**
 ○Yukiko Nakamura, Hironobu Yamasaki, Sadao Shiosaka (Div. of Structural Cell Biol., Nara Inst. of Sci. and Technol.)
- N027 Modulation of short-term synaptic plasticity by presynaptic adenosine receptors in the nucleus of the solitary tract**
 ○Noriko Tsuji¹, Eiji Shigetomi², Fusao Kato² (¹The Dept. of Pharm., Tokyo Univ. of Sci., Noda, Japan, ²Lab. of Neurophysiol., Dept. of Neurosci., Jikei Univ. Sch. of Med.)
- N028 Electrophysiological analysis for the I213T PS1 knock-in mice**
 ○Yasumitsu Ikura, Takashi Kudo, Daisuke Kanayama, Akio Fukumori, Masayasu Okouchi, Masatoshi Takeda (Psychiat. and Behav. Sci., Osaka Univ. Grad. Sch. of Med.)

Regeneration, Transplantation

- N029 A different expression of galectin-1 and galectin-3 in the fish and rat retinas after optic nerve injury**
 ○Manabu Kaneda, Masayuki Tanaka, Kayo Sugitani, Satoru Kato (Dept. of Mol. Neurobiol., Grad. Sch. of Med., Kanazawa Univ., Kanazawa, Japan)
- N030 The role of purpurin, a member of retinol binding protein family during regeneration of goldfish optic nerve**
 ○Masayuki Tanaka¹, Toru Mastukawa¹, Takashi Nakagawa¹, Kazuhiro Mawatari², Yoshiki Koriyama¹, Kunizo Arai¹, Satoru Kato¹ (¹Dept. of Mol. Neurobiol., Grad. Sch. of Med., Kanazawa Univ., Kanazawa, Japan, ²Sch. of Health Sci., Kanazawa Univ. Fac. of Med., Kanazawa, Japan)
- N031 Preservation of hematopoietic properties in transplanted bone marrow cells in brain**
 ○Kenji Ono^{1,2}, Ken Yoshihara¹, Hiromi Suzuki¹, Tetsuya Suhara², Makoto Sawada¹ (¹Joint Res. Div. for Therapies against Intractable Dis., Inst. for Compr. Med. Sci., Fujita Health Univ., Aichi, Japan, ²Brain Imaging Project, Natl. Inst. of Radiol. Sci., Chiba, Japan)
- N032 Molecular Characterization of a Novel Tetraspan Membrane Protein Up-regulated in Neurons of Axotomized Facial Nuclei**
(MS2-2) Yo Sasaki, ○Masato Hoshi, Yasuko Nakamura, Hayami Tsuzuki, Chihiro Akazawa, Shinichi Kohsaka¹ (Dept. of Neurochem., Natl. Inst. of Neurosci.)
- N033 Transplantation of neural stem cells and re-expression of PSA-NCAM in a mouse model of demyelinating disease**
(MS2-3) ○Michio Matsumoto¹, Hirohide Takebayashi¹, Tetsushi Kagawa², François Lachapelle³, Anne Baron-Van Evercooren³, Kazuhiro Ikenaka¹ (¹Div. of Mol. Neurobiol., Natl. Inst. for Physiol. Sci., Okazaki, Japan, ²Inst. of Mol. Embryol. and Genet., Kumamoto Univ., Kumamoto, Japan, ³INSERM U546, France)

- N034 Possible alteration of DNA methylation may affect fate of injured motor neurons**
(MS2-4) ○Tian Cheng Zhao, Sumiko Kiryu-Seo, Hiroshi Kiyama (Dept. of Anat. and Neurobiol., Osaka City Univ., Grad. Sch. of Med., Osaka, Japan)
- N035 Axonal Regeneration after Administration of Semaphorin 3A Inhibitor into the Injured Spinal Cord**
(MS2-5) ○Shinjiro Kaneko^{1,2}, Akio Iwanami^{1,2}, Masaya Nakamura¹, Sachiyo Miyao^{1,2}, Akiyoshi Kishino³, Kaoru Kikuchi³, Toru Kimura³, Kazuo Kumagai³, Yoshiaki Toyama¹, Hideyuki Okano² (¹Dept. of Orthop. Surg., Keio Univ. Sch. of Med., Tokyo, Japan, ²Dept. of Physiol., Keio Univ. Sch. of Med., Tokyo, Japan, ³Res. Div., Sumitomo Pharm., Osaka, Japan)
- N036 Cell survival and death signals in the goldfish and rat retinas after optic nerve injury**
○Keiko Homma, Yoshiki Koriyama, Kiyoshi Sugawara, Zhonwu Liu, Satoru Kato (Dept. of Mol. Neurobiol., Grad. Sch. of Med., Kanazawa Univ., Kanazawa, Japan)
- N037 SH3 binding domain glutamic acid rich protein like 3 (SH3BGRL3) is expressed in neurons of CNS and upregulated in axotomized facial nucleus in rat**
○Masato Hoshi, Yo Sasaki, Chihiro Akazawa, Shinichi Kohsaka (Dept. of Neurochem., Natl. Inst. of Neurosci., Tokyo, Japan)
- N038 Neuronal glutamate transporter, EAAC1/EAAT3 determines neuronal fate in injured motor neurons**
○Sumiko Kiryu-Seo¹, Ryuichi Kato^{1,2}, Teruhisa Hirayama^{1,3}, Hiroshi Kiyama¹ (¹Dept. of Anat. and Neurobiol., Osaka City Univ., Grad. Sch. of Med., Osaka, Japan, ²Dept. of Urol., Sapporo Med. Univ., Sapporo, Japan, ³Dept. of Orthop. Surg., Asahikawa Med. Coll., Asahikawa, Japan)
- N039 Restoration of dopamine function in a primate model of Parkinson's disease after transplantation of neuronal stem cells derived from embryonic stem cells**
○Shin-ichi Muramatsu¹, Takashi Nakayama², Mihoko Nagata¹, Yutaka Suzuki³, Yasushi Kondo³, Fumiko Ono⁴, Kunihiro Ikeguchi¹, Ken-ichi Fujimoto¹, Keiji Terao⁴, Nobuo Inoue², Hideo Tsukada⁵, Imaharu Nakano¹ (¹Div. of Neurol., Jichi Med. Sch., Tochigi, Japan, ²Dept. of Biochem. 1, Yokohama City Univ. Sch. of Med., ³Tanabe Seiyaku Co., Ltd., ⁴Tsukuba Primate Center, Natl. Inst. of Infectious Dis., ⁵Hamamatsu Photonics K.K.)
- N040 Characterization of two monoclonal antibodies, Gal3D11 and Gal5E5, to galectin-1**
○Kazunori Yoshimura¹, Fuyuki Kametani², Kayo Fujimaki¹, Toshihiko Kadoya³, Hiroaki Asou⁴, Masahiko Nomura¹ (¹Dept. Physiol., Saitama Med. Sch., Saitama, Japan, ²Dept. Mol. Neurobiol., Tokyo Inst. Psychiat., Tokyo, Japan, ³R&D Center, Prod. Dept., Pharm. Div., Kirin Brewery Co., Ltd., Gunma, Japan, ⁴Glia Cell Res. Group, Tokyo Metrop. Inst. Gerontol., Tokyo, Japan)
- N041 Injection of adult mouse neurospheres ameliorated behavioral abnormality in brain-injured mice.**
○Katsushige Mizuno, Yasuhiro Watanabe (Dept. of Pharm., Natl. Defense Med. Coll.)
- N042 Administration of FGF-2 into the transected spinal cord enhances axonal regeneration and improves locomotion activity in adult rats**
○Takahiro Jikoh, Hidefumi Fukumitsu, Shoei Furukawa (Lab. of Mol. Biol., Gifu Pharm. Univ., Gifu, Japan)

Aging

- N043 Age-related changes in brain synaptic function and effects of carnitine supplementation**
○Yasukazu Tanaka, Machiko Iwamoto, Hatsue Waki, Kazuo Kon, Susumu Ando (Neuronal Function Res. Group, Div. of Neurosci. and Brain Function, Tokyo Metrop. Inst. of Gerontol., Tokyo, Japan)
- N044 Expression of histone deacetylase Sir2 in neural stem cells**
○Yoshiyuki Horio, Shin Hisahara (Dept. of Pharm., Sapporo Med. Univ., Sch. of Med., Sapporo, Japan)

Animal Models

- N045 Involvement of Epidermal Growth Factor in cognitive functions**
○Makoto Mizuno, Shinya Hashimoto, Romulo Malta, Hiroyuki Nawa (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)

- N046 Comparison of Dopaminergic Neuronal Damages in MPTP-treated Young and Aging C57BL/6 Mice**
Atsushi Mori^{1,2}, ○Satoshi Ohashi¹, Masami Nakai¹, Naoki Kurihara¹, Yasuhide Mitsumoto¹, Tetsuji Moriizumi² (¹Second Inst. of New Drug Discovery, Otsuka Pharm. Co., Ltd., ²Dept. of Anat., Shinshu Univ. Sch. of Med.)
- N047 An inducible transgenic mouse model of Huntington disease harboring full-length huntingtin**
○Yuji Tanaka¹, Shuichi Igarashi², Masayuki Nakamura³, Hokuto Morita³, Gabriele Schilling⁴, Tracy Wanner³, Yujin Kim³, Jonathan D Wood⁵, David R Borchelt⁴, Christopher A Ross^{3,6} (¹Dept. of Neuropsychiat., Okayama Univ. Grad. Sch. of Med. and Dentistry, Okayama, Japan, ²Dept. of Mol. Neurosci., Center for Bioresource-based Res., Niigata Univ. Brain Res. Inst., Niigata, Japan, ³Dept. of Psychiat., Johns Hopkins Univ. Sch. of Med., Baltimore, USA, ⁴Dept. of Pathol., Johns Hopkins Univ. Sch. of Med., Baltimore, USA, ⁵Academic Neurol. Unit, The Univ. of Sheffield, Sheffield, UK, ⁶Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, USA)
- N048 Amiodarone affected open field behaviors and an activity rhythm during dark phase in F344 rats**
○Shingo Suzuki¹, Takayuki Negishi^{1,4}, Katsuyoshi Kawasaki^{2,4}, Yoshiyuki Ishii¹, Shigeru Kyuwa¹, Yasuhiro Yoshikawa^{1,4}, Yoichiro Kuroda^{3,4} (¹Dept. of Biomed. Sci., Grad. Sch. of Agric. and Life Sci., The Univ. of Tokyo, Tokyo, Japan, ²Dept. of Psychol., Hoshi Univ., Tokyo, Japan, ³Dept. of Mol. and Cell. Neurobiol., Tokyo Metrop. Inst. for Neurosci., Tokyo, Japan, ⁴CREST, JST)
- N049 Production of transgenic mice expressing Cre-ERT in the brain**
○Masayo Kojima¹, Narumi Kamiya², Chiho Sumi-Ichinose², Takahide Nomura², Daniel Metzger³, Pierre Chambon³, Hiroshi Ichinose¹ (¹Dept. of Life Sci., Grad. Sch. of Biosci. and Biotechnol., Tokyo Inst. of Technol., Yokohama, Japan, ²Dept. of Pharm., Sch. of Med., Fujita Health Univ., Toyoake, Japan, ³IGBMC, CNRS, INSELM, Coll. de France, Universite Louis Pasteur, Illkirch, France)
- N050 Functional analysis of the gene, CHAC responsible for chorea-acanthocytosis, using gene-targeted model mouse**
○Yuuko Tomemori¹, Mio Ichiba¹, Akira Kusumoto¹, Emiko Morita¹, Shu-ichi Ueno², Akira Sano¹ (¹Dept. of Psychiat. Kagoshima Univ. Grad. Sch. of Med. and Dental Sci., Kagoshima, Japan, ²Dept. of Psychiat., Course of Integrated Brain Sci., Univ. of Tokushima Sch. of Med., Tokushima, Japan)
- N051 Sodium Butyrate Ameliorates Phenotypic Expression in a Transgenic Mouse Model of Spinal and Bulbar Muscular Atrophy**
○Makoto Minamiyama, Masahisa Katsuno, Hiroaki Adachi, Yasushi Kobayashi, Manabu Doyu, Gen Sobue (Dept. of Neurol., Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan)

Developmental Disorders

- N052 Development of a quantitative oligo-DNA microarray for monitoring synaptic status**
○Yuta Wakayama¹, Masaki Takahashi¹, Yasumitsu Kondo², Hideo Tashiro², Tomoko Tashiro^{1,3} (¹Dept. of Biochem., Coll. of Sci. and Eng., Aoyama Gakuin Univ., ²Adv. Eng. Center, RIKEN, ³CREST, JST)
- N053 Effect of perinatal hypothyroidism on gene expression in the developing mouse cerebellum**
○Masaki Takahashi¹, Yuta Wakayama¹, Yasumitsu Kondo², Hideo Tashiro², Misae Ohta^{3,4}, Noriyuki Koibuchi^{3,4}, Tomoko Tashiro^{1,4} (¹Dept. of Biochem., Sch. of Sci. and Eng., Aoyama Gakuin Univ., ²Adv. Eng. Center, RIKEN, ³Dept. of Physiol., Fac. of Med., Gunma Univ., ⁴CREST, JST)

Neurodegenerative Diseases (Parkinson's Disease and Others)

- N054 Targeted Disruption of Mouse DRPLA Gene to Investigate Molecular Pathophysiology of (MS1-1) dentatorubral-pallidolusian atrophy (DRPLA)**
○Tetsuya Kimura¹, Yasuhisa Akaiwa¹, Mitsunori Yamada², Masahiko Takano¹, Toshiya Sato³, Mutsuo Oyake¹, Motoya Katsuki⁴, Masatoyo Nishizawa¹, Shoji Tsuji⁵ (¹Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Dept. of Pathol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ³Center for Bioresource-Based Res. Animal Resources Branch, Brain Res. Inst., Niigata Univ., Niigata, Japan, ⁴Natl. Inst. for Basic Biol., Aichi, Japan, ⁵Dept. of Neurol., Grad. Sch. of Med., Univ. of Tokyo, Tokyo, Japan)

- N055 A molecular therapy for polyglutamine diseases targeting the toxic conformational transition and aggregate formation of the expanded polyglutamine protein using the inhibitor peptide QBP1**
 ○Yoshitaka Nagai¹, Helena A. Popiel¹, Nobuhiro Fujikake¹, Takashi Inui², Kenji Fukui¹, Masamitsu Yamaguchi³, Yoshihiro Urade⁴, Hironobu Naiki⁵, Tatsushi Toda¹ (¹Div. Functional Genomics, Dept. Post-Genomics & Dis., Osaka Univ. Grad. Sch. Med., Suita, Japan, ²Dept. Food & Nutri., Tsu City Coll., Tsu, Japan, ³Chr Tech. Group, Div. Biotechnol., Kyoto Inst. Tech., Kyoto, Japan, ⁴2nd Dept., Osaka Biosci. Inst., Suita, Japan, ⁵2nd Dept. Pathol., Fukui Med. Univ., Yoshida, Japan)
- N056 Inhibitory effects of 4-phenylbutyrate on Pael receptor accumulation and endoplasmic reticulum (MS1-3) stress induced cell death**
 ○Kyoko Kubota, Yoshifumi Niinuma, Masayuki Kaneko, Yasuyuki Nomura (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan)
- N057 ALS2, a novel guanine nucleotide exchange factor for the small GTPase Rab5 is implicated in (MS1-4) endosomal dynamics**
 ○Asako Otomo^{1,2,3}, Shinji Hadano^{1,2}, Takeya Okada², Hikaru Mizumura¹, Ryota Kunita¹, Hitoshi Nishijima⁴, Junko Showguchi-Miyata², Yoshiko Yanagisawa¹, Eri Kohiki¹, Etsuko Suga¹, Masanori Yasuda⁵, Hitoshi Osuga^{1,2}, Takeharu Nishimoto⁴, Shuh Narumiya⁶, Joh-E Ikeda^{1,2,3,7} (¹Solution Oriented Res. for Sci. and Technol. (SORST), JST, ²Dept. of Mol. Neurosci., The Inst. of Med. Sci., Tokai Univ., ³Grad. Sch. of Med. Sci., Tokai Univ., ⁴Grad. Sch. of Med. Sci., Kyushu Univ., ⁵Tokai Univ. Sch. of Med., ⁶Dept. of Pharm., Kyoto Univ. Fac. of Med., ⁷Dept. of Paediatrics, Fac. of Med., Univ. of Ottawa.)
- N058 Aprataxin, the causative gene for early-onset ataxia with ocular motor apraxia and (MS1-5) hypoalbuminemia (EAOH) as a member of ssDNA repair machinery. -Implication of impaired DNA repair systems in neurodegeneration-**
 ○Hidetoshi Date¹, Shuichi Igarashi¹, Toshiaki Takahashi¹, Hiroki Takano¹, Osamu Onodera¹, Masatoyo Nishizawa¹, Yasuteru Sano², Shoji Tsuji³ (¹Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, JAPAN, ²Dept. of Neurol. Yamaguchi Univ., ³Dept. of Neurol., The Univ. of Tokyo, Grad. Sch. of Med.)
- N059 ALS2 C-terminal like (ALS2CL): identification and characterization of the novel conserved gene that encodes a protein highly homologous to the carboxy-terminal half of the ALS2 protein**
 ○Shinji Hadano^{1,2}, Asako Otomo¹, Yoshiko Yanagisawa², Junko Showguchi-Miyata¹, Kyoko Suzuki¹, Ryota Kunita², Hikaru Mizumura², Joh-E Ikeda^{1,2} (¹Dept. of Mol. Neurosci., The Inst. of Med. Sci., Tokai Univ., Kanagawa, Japan, ²SORST, Japan Sci. and Technol. Corp. (JST), Kanagawa, Japan).
- N060 Full-length DRPLA proteins suppress CREB- and p53- dependent transcriptional activation**
 ○Takayoshi Shimohata¹, Kaori Ogura¹, Satoshi Naruse¹, Shuichi Igarashi², Toshiya Sato³, Osamu Onodera², Masatoyo Nishizawa¹, Shoji Tsuji^{1,4} (¹Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Resource Branch for Brain Dis. Res., Center for Bioresouce-based Res., Brain Res. Inst., Niigata Univ., Niigata, Japan, ³Animal Resources Branch, Center for Bioresouce-based Res., Brain Res. Inst., Niigata Univ., Niigata, Japan, ⁴Dept. of Neurol., Univ. of Tokyo, Grad. Sch. of Med., Tokyo, Japan)
- N061 An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells**
 ○Wakako Maruyama¹, Makoto Naoi² (¹Lab. of Biochem. and Metabolism, Dept. of Basic Gerontol., Natl. Inst. for Longevity Sci., Obu, Japan, ²Int. Inst. of Biotechnol., Kakmigahara, Gifu 504-0838, Japan)
- N062 N-Propargyl-1(R)-aminoindan, rasagiline, increases glial cell line-derived neurotrophic factor (GDNF) and BCL-2 in neuroblastoma SH-SY5Y cells through activation of NF-kappaB transcription factor**
 ○Makoto Naoi¹, Wakako Maruyama², Atsumi Nitta³, Yoko Hirata⁴ (¹Gifu Int. Inst. of Biotechnol., Kakmigahara, Japan, ²Natl. Inst. for Longevity Sci., Obu, Aichi, Japan, ³Dept. of Pharm., Nagoya Univ. Sch. of Med., Nagoya, Japan, ⁴Dept. of Biomol. Sci., Fac. of Eng., Gifu Univ., Gifu, Japan)
- N063 Proteasome inhibitor-induced insolubilization of ubiquitinated proteins and Hsp27 followed by cell death are mediated by heat shock factor activation**
 ○Kanefusa Kato, Hidenori Ito, Ikuko Iwamoto, Yutaka Inaguma, Takenori Takizawa (The Inst. for Dev. Res., Aichi Human Serv. Center)

- N064 Activation of JNK/SAPK pathway by trimethyltin in murine hippocampus**
 ○Norito Nishiyama¹, Yuhki Nitta¹, Mami Watanabe¹, Yukio Yoneda², Kiyokazu Ogita¹ (¹Dept. of Pharm., Setsunan Univ., Hirakata, Osaka, Japan, ²Lab. Mol. Pharmacol., Grad. Sch. Natl. Sci. & Tech. Kanazawa Univ., Ishikawa, Japan)
- N065 Expression of high-molecular-weight heat shock proteins by endoplasmic reticulum stress in SH-SY5Y cells**
 ○Naoko Iwamoto¹, Akiko Yamomuro², Reiko Nagashima¹, Sadaaki Maeda², Fumiaki Ito³, Yukio Yoneda⁴, Kiyokazu Ogita¹ (¹Dept. of Pharm., Setsunan Univ., Hirakata, Osaka, Japan, ²Dept. of Pharmacotherapeutics, Setsunan Univ., Hirakata, Osaka, Japan, ³Dept. of Biochem., Setsunan Univ., Hirakata, Osaka, Japan, ⁴Lab. Mol. Pharmacol., Kanazawa Univ. Grad. Sch. Natl. Sci. & Tech., Kanazawa, Ishikawa, Japan)
- N066 Effect of methamphetamine on gene expression of Parkin and Pael-receptor in rat striatum**
 ○Hidetaka Yamada¹, Tatsuo Nakahara¹, Toshihide Kuroki², Kijiro Hashimoto¹, Tetsuyuki Tsutsumi¹, Toshio Kajihata², Makoto Hirano¹ (¹Centre for Emotional and Behav. Disord., Hizen Natl. Mental Hosp., Saga, Japan, ²Dept. of Neuropsychiat., Fac. of Med., Kyushu Univ., Fukuoka, Japan)
- N067 Novel Zinc finger-RING finger proteins, Momo and Sakura, are enriched in Neurons and Glial cells, respectively**
 ○Kazuaki Araki¹, Meiko Kawamura¹, Daiji Kanbe¹, Kyoko Ishii¹, Tomio Ichikawa², Toshiro Kumanishi², Keiji Tanaka³, Nobuyuki Takei¹, Hiroyuki Nawa¹ (¹Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Dept. of Mol. Pathol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ³Mol. Oncol., Tokyo Metrop. Inst. of Med. Sci., Bunkyo-ku, Tokyo, Japan)
- N068 Enhanced binding to the antioxidant-response element through formation of Nrf2/Fos-B complex after kainate treatment**
 ○Kiyokazu Ogita¹, Norito Nishiyama¹, Mami Watanabe¹, Yukio Yoneda² (¹Dept. of Pharm., Setsunan Univ., Hirakata, Osaka, Japan, ²Lab. Mol. Pharmacol., Grad. Sch. Natl. Sci. & Tech. Kanazawa Univ., Ishikawa, Japan)
- N069 Ubiquitin ligase activity and palmitoylation of the membrane-associating RING finger proteins, Momo and Sakura**
 ○Meiko Kawamura¹, Kazuaki Araki¹, Toshiaki Suzuki², Noriyuki Matsuda², Daiji Kanbe¹, Tomoki Chiba², Keiji Tanaka², Hiroyuki Nawa¹ (¹Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Mol. Oncol., Tokyo Metrop. Inst. of Med. Sci., Bunkyo-ku, Tokyo, Japan)
- N070 Transplantation of tyrosinase-producing cells into the striatum of hemi-parkinsonian model**
 ○Masato Asanuma, Ikuko Miyazaki, Norio Ogawa (Dept. of Brain Sci., Okayama Univ. Grad. Sch. of Med. and Dentistry, Okayama, Japan)
- N071 Amyloid beta-Protein (Abeta)1-40 Protects Neurons from Damage Induced by Abeta1-42 in Culture and in Rat Brain**
 Kun Zou¹, Daesung Kim², Atsuko Kakio³, Kyunghee Byun², Jian-Sheng Gong^{1,4}, Myeongju Kim², Naoya Sawamura^{1,5}, Sei-ichi Nishimoto³, Katsumi Matsuzaki⁶, Bonghee Lee², Katsuhiko Yanagisawa¹, ○Makoto Michikawa¹ (¹Dept. of Dementia Res., Natl. Inst. for Longevity Sci., Obu, Japan, ²Dept. of Anat. and Neurobiol., Coll. of Med. and Inst. of Med. Sci., Cheju Natl. Univ., Jeju, Republic of Korea, ³Dept. of Energy and Hydrocarbon Chem., Grad. Sch. of Eng., Kyoto Univ., Kyoto, Japan, ⁴Org. for Pharm. Safety and Res. of Japan, Tokyo, Japan, ⁵Japan Soc. for the Promot. of Sci., Tokyo, Japan, ⁶Grad. Sch. of Biostud., Kyoto Univ., Kyoto, Japan)
- N072 Hsp105 suppresses cell death causally expansion of the polyQ tract in cellular model of SBMA**
 ○Keiichi Ishihara¹, Nobuyuki Yamagishi¹, Youhei Saito¹, Hiroaki Adachi², Yasushi Kobayashi², Gen Sobue², Kenzo Ohtsuka³, Takumi Hatayama¹ (¹The Dept. of Biochem., Kyoto Pharm. Univ., Kyoto, Japan, ²The Dept. of Neurol., Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan, ³The Dept. of Environ. Biol., Coll. of Biosci. and Biotechnol., Chubu Univ., Kasugai, Japan)
- N073 Approach to the identification of the causative substance in an endemic neurodegenerative disease in Guadeloupe, the French West Indies**
 ○Yaichiro Kotake¹, Machiko Kamizono¹, Katsuhiro Okuda¹, Naoki Matsumoto¹, Takao Tanahashi^{1,2}, Hiroshi Hara³, Dominique Caparros-Lefebvre⁴, Shigeru Ohta¹ (¹Grad. Sch. of Biomed. Sci., Hiroshima Univ., ²Kobe Pharm. Univ., Kobe, Japan, ³Fac. of Pharm. Sci., Tokyo Univ. of Sci., Noda, Japan, ⁴Dept. of Neurol., Centre Hospitalier Universitaire des Antilles et de la Guyane, Guadeloupe, French West Indies)

- N074 The involvement of glial cells and neurons in the neurodegenerative disease model rat**
 ○Masatoshi Ide, Sachiko Tanaka, Satoshi Numazawa, Takemi Yoshida (Dept. of Biochem. Toxicol., Sch. of Pharm. Sci., Showa Univ., Tokyo, Japan)
- N075 Peroxynitrite induces endoplasmic reticulum stress in human neuroblastoma SH-SY5Y cells**
 ○Satoko Morita, Akiko Yamamuro, Rumiko Kuwada, Yasuhiro Yoshioka, Sadaaki Maeda (Dept. of Pharmacotherapeutics, Fac. of Pharm. Sci., Setsunan Univ., Osaka, Japan)
- N076 In vitro aggregate formation by expanded polyglutamine**
 ○Itaru Toyoshima, Michio Kobayashi, Koji Obara, Satoshi Okawa, Masashiro Sugawara (Dept. of Intern. Med., Akita Univ. Sch. of Med., Akita, Japan)
- N077 Differential effect of MK-801 on protease activities and glial cell expression in PTZ-induced male and female rat brain.**
 ○Md. Mahiuddin Ahmed¹, Toshiyuki Chikuma², Takeshi Kato¹ (¹Lab. of Natural Inf. Sci., Grad. Sch. of Integrated Sci., Yokohama City Univ., Yokohama, Japan, ²Dept. of Hygienic Chem., Showa Pharm. Univ., Machida, Japan)
- N078 Neuroprotective Mechanism of Theanine, a Green Tea Component, in Rat Cortical Neurons**
 Sadaki Fujimoto¹, ○Hiromitsu Aoki¹, Katsuhito Nagai¹, Yasuyuki Sazuka², Shun Shimohama³, Kazuki Nagasawa¹ (¹The Dept. of Environ. Biochem., Kyoto Pharm. Univ., Kyoto, Japan, ²Fac. of Pharm. Sci., Sizuoka Univ., Sizuoka Japan, ³Dept. of Neurol., Grad. Sch. of Med., Kyoto Univ., Kyoto Japan)
- N079 Antioxidant Effect of Plant Lycopene on Neuronal Process in CNS of Motor Neuron Degeneration (Mnd) Mouse during Postnatal Growth**
 ○Nobuko Yoshimoto¹, Kimikazu Fujita², Youko Murakami¹, Hiroko Ikai¹, Hiroyuki Suganuma³, Takahiro Inakuma³, Hidemi Imada², Yutaka Nagata², Eiichi Miyachi² (¹Nagoya Bunri Coll., Nagoya, Japan, ²Fujita Health Univ. Sch. of Med. Dept. of Physiol. Toyoake, Aichi, Japan, ³Kagome Co.,Ltd. Nishinasuno, Tochigi, Japan)
- N080 An in vitro model for aceruloplasminemia with neurodegeneration : iron deposition in glial cells**
 ○Satoru Oshiro¹, Kazuyuki Nakajima² (¹Dept. of Biochem. Genet., Med. Res. Inst., Tokyo Med. and Dental Univ., Tokyo, Japan, ²Dept. of Neurochem., Inst. of Life Sci., Soka Univ., Tokyo, Japan)
- N081 Involvement of autophagy in the degradation of polyglutamine proteins.**
 ○Atsushi Iwata¹, Ron Kopito², Shoji Tsuji¹ (¹Dept. of Neurol., Univ. of Tokyo, Grad. Sch. of Med., ²Stanford Univ. Dept. of Biol. Sci.)
- N082 Expression of an acyl-CoA synthetase, Lipidosin, in the organs involved in X-linked adrenoleukodystrophy and its change in the process of experimental demyelination and remyelination**
 ○Si-Young Song¹, Chieko Kato¹, Eijiro Adachi², Masayo Inagawa-Ogashiwa¹, Naohiro Hashimoto¹ (¹Mitsubishi Kagaku Inst. of Life Sci., Machida, Japan, ²Kitasato Univ., Dept. of Mol. Morphol., Grad. Sch. of Med. Sci., Sagamihara, Japan)
- N083 Functional Analysis of Novel Ubiquitin Ligase, Potential Target Antigen of Paraneoplastic (MS1-2) Neurologic Disorder**
 ○Hirobumi Tada^{1,2,3}, Hirotaka James Okano^{1,3}, Haruo Kashima², Hideyuki Okano^{1,3} (¹Dept. of Physiol., Sch. of Med., Keio Univ., Tokyo, Japan, ²Dept. of Neuropsychiat., Sch. of Med., Keio Univ., Tokyo, Japan, ³CREST-JST)
- N084 Expanded polyglutamine stretches, in vivo interfere with CREB-dependent transcriptional activation in DRPLA.**
 ○Masahiko Takano¹, Yasuhisa Akaiwa¹, Tetsuya Kimura¹, Toshiya Sato², Mutsuo Oyake¹, Masatoyo Nishizawa¹, Shoji Tsuji³ (¹Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Dept. of Comparative and Exp. Med., Animal Resources, Brain Res. Inst., Niigata Univ., Niigata, Japan, ³Dept. of Neurol., Univ. of Tokyo, Tokyo, Japan)
- N085 Altered gene expression of neurotrophins, GDNF family members and their receptors in a peptide-delivery model of polyglutamine-induced neuronal death**
 ○Akihiro Satake, Tatsuro Koike (Mol. Neurobiol. Lab., Hokkaido Univ. Grad. Sch. Sci., Sapporo, Japan)

- N086 Establishment of functional assays system for polyglutamine disease.**
 ○Toshiaki Takahashi¹, Kenkichi Nozaki¹, Osamu Onodera¹, Masatoyo Nishizawa¹, Shyoji Tsuji²
 (¹Dept. of Neurol., Brain Res. Inst., Univ. of Niigata, Niigata, Japan, ²Dept. of Neurol., Grad. Sch. of Med., Univ. of Tokyo, Tokyo, Japan)
- N087 Analyses of biochemical functions of aprataxin in DNA single-strand break repair**
 ○Tetsuya Takahashi¹, Shuichi Igarashi¹, Hidetoshi Date¹, Osamu Onodera¹, Masatoyo Nishizawa¹, Shoji Tsuji² (¹Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Dept. of Neurol., Tokyo Univ., Tokyo, Japan)
- N088 Degradation system of aggregation in SCA6: ubiquitin-proteasomal and lysosomal pathways.**
 ○Kinya Ishikawa¹, Takao Makifuchi², Eiki Kominami³, Hidehiro Mizusawa¹ (¹Dept. of Neurol., Tokyo Med. and Dental Univ., Tokyo, Japan, ²Dept. of Lab. Med., Natl. Saigata Hosp., ³The 1st Dept. of Biochem., Fac. of Med., Juntendo Univ.)
- N089 Property of binding between synphilin-1 and phospholipids**
 ○Tetsuya Takahashi, Yoshito Nagano, Takeshi Nakamura, Hiroshi Yamashita, Masayasu Matsumoto (The Third Dept. of Intern. Med., Univ. of Hiroshima, Hiroshima, Japan)
- N090 Microarray analysis of brain RNA in DRPLA knockout mice**
 ○Yasuhisa Akaiwa¹, Masahiko Takano¹, Tetsuya Kimura², Toshiya Satou³, Mutuo Oyake¹, Shoji Tsuji⁴ (¹Dept. of Neurol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Sch. of Health Sci. Biomed. Sci., Fac. of Med., Niigata Univ., Niigata, Japan, ³Center for Bioresouce-based Res. Animal Resources Branch, Brain Res. Inst., Niigata Univ., Japan, ⁴Dept. of Neurol., Univ. of Tokyo, Tokyo, Japan)

Psychiatric Diseases

- N091 An investigation on anxiogenic drug-induced gene expressions in the brain of postnatally developing rodents**
 ○Akeo Kurumaji, Asami Umino, Masakazu Tanami, Atsushi Ito, Michiko Asakawa, Takashi Ito, Sumikazu Ishii, Toru Nishikawa (Section of Psychiat. and Behav. Sci., Tokyo Med. and Dental Univ. Grad. Sch., Tokyo, Japan)
- N092 The effects of antidepressants and moodstabilizers on the differentiation of neural stem cells**
 ○Wataru Ukai, Hiroki Ozawa, Masaru Tatenno, Masato Konno, Megumi Yamamoto, Rie Sakai, Hiroshi Ikeda, Toshikazu Saito (Dept. of Neuropsychiat., Sch. of Med., Sapporo Med. Univ., Sapporo, Japan)
- N093 Expression Analysis of Neuregulin-1 in the Dorsolateral Prefrontal Cortex in Schizophrenia**
 ○Ryota Hashimoto¹, Richard Straub², Cynthia Weickert², Thomas Hyde², Joel Kleinman², Daniel Weinberger² (¹Dept. of Mental Disord. Res., Natl. Inst. of Neurosci., Natl. Center of Neurol. and Psychiat., ²Clin. Brain Disord. Branch, Natl. Inst. of Mental Health, NIH, Bethesda, MD, USA)
- N094 Peripheral treatment with interleukin-1 α to rats reduced pre-pulse inhibition of acoustic startle response**
 ○Manavu Tohmi, Hiroyuki Nawa (Div. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)

Muscle Disorders

- N095 Mammalian O-mannosyl glycan and relationship to muscular dystrophy and neuronal migration disorder**
 ○Tamao Endo¹, Hiroshi Many¹, Kazuhiro Kobayashi², Kiyomi Taniguchi², Tatsushi Toda²
 (¹Glycobiol. Res. Group, Tokyo Metrop. Inst. of Gerontol., Tokyo, Japan, ²Div. of Functional Genomics, Dept. of Post-Genomics and Dis., Osaka Univ. Grad. Sch. of Med., Osaka, Japan)
- N096 Molecular mechanism of myasthenia gravis induced by autoantibodies against MuSK**
 ○Kazuhiro Shigemoto¹, Sachiho Kubo², Mitsuhiro Ohta³, Kiyoe Ohta⁴, Naoki Maruyama² (¹Dept. of Hygiene, Ehime Univ. Sch. of Med., Ehime, Japan, ²Tokyo Metrop. Inst. of Gerontol., Organ Disord. and Aging Res. Group, Tokyo, Japan, ³Dept. of Clin. Chem., Kobe Pharm. Univ., Kobe, Japan, ⁴Clinic. Res. Center, Utano Natl. Hospital, Kyoto, Japan)

Ischemia

- N097 Dynamic change of AQP expression in the brain cold injury model**
 ○Naoki Yamamoto¹, Kazuya Sobue², Toyohiro Tada³, Kiyofumi Asai⁴ (¹Dept. Dementia Res., Natl. Inst. for Longevity Sci., Aichi, Japan, ²Dept. Anesthesiol. Med. Crisis Manage., Nagoya City Univ. Gran. Sch. Med. Sci., ³Nagoya City Univ. Nursing, ⁴Dept. Mol. Neurobiol., Nagoya City Univ. Gran. Sch. Med. Sci.)
- N098 Changes of cerebral glucose metabolism after 30 min middle cerebral artery occlusion in rats - studied by ex vivo ¹³C-NMR spectroscopy -**
 ○Tomoyuki Kanamatsu¹, Hiromi Takahara¹, Hironaka Igarasi², Seiji Okubo², Yukiyo Mizuguchi², Yasuo Katayama² (¹Dept. of Evniron. Eng. for Symbiosis, Fac. of Eng., Soka Univ., Tokyo, Japan, ²Second Dept. of Intern. Med., Nippon Med. Sch., Tokyo, Japan)
- N099 Neuroprotective effect of DY-9760e, a calmodulin antagonist, on microsphere embolism-induced ischemic brain damage**
 ○Takashi Shirakura¹, Toshiyuki Sato², Yasufumi Shirasaki², Jiro Kasahara¹, Yusuke Takeuchi¹, Koji Fukunaga¹ (¹Dept. of Pharm., Grad. Sch. of Pharm. Sci. Tohoku Univ., Miyagi, Japan, ²Daiichi Pharm. Co., Ltd., Tokyo, Japan)
- N100 Upregulation of HRD1, an endoplasmic reticulum-associated degradation related molecule, in the mouse brain following hypoxic cerebral ischemia**
 ○Xin Qi, Yosunobu Okuma, Masayuki Kaneko, Toru Hosoi, Yasuyuki Nomura (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan.)
- N101 Poly(ADP-ribose) synthetase activation and mitochondrial injury in an experimental model of cerebral ischemia**
 ○Seigo Tanaka, Masanori Takehashi, Shinya Iida, Kunihiro Ueda (Lab. of Mol. Clin. Chem., Inst. for Chem. Res., Kyoto Univ., Uji, Kyoto, Japan)

Trauma

- N102 Effect of anti-Interleukine-6 receptor antibody in spinal cord injury**
 ○Seiji Okada¹, Masaya Nakamura², Yoshiyuki Ohsugi³, Kazuyuki Yoshizaki⁴, Yoshiaki Toyama², Hideyuki Okano¹ (¹Dept. of Physiol., Sch. of Med., Keio Univ., Tokyo, Japan, ²Dept. of Orthop. Surg., Sch. of Med., Keio Univ., Tokyo, Japan, ³Chugai Pharm. Co., LTD. Tokyo, Japan, ⁴Sch. of Med., Osaka Univ., Osaka, Japan)

Dementia and Alzheimer's Disease

- N103 Regulation of tau exon 10 splicing by a double stem-loop structure in mouse intron 10 (MS3-1)**
 ○Takenari Yamashita¹, Takami Tomiyama¹, Hideharu Numata², Hiroshi Mori¹ (¹Dept. of Neurosci., Osaka City Univ. Med. Sch., Osaka, Japan, ²Dept. of Bio- and Geosciences Grad. Sch. of Sci., Osaka City Univ., Osaka, Japan)
- N104 Phosphorylation of FTDP-17 tau mutants by Cyclin-dependent kinase 5 (MS3-2)**
 ○Fumika Sakaue¹, Masato Hasegawa², Akiko Asada¹, Taro Saito¹, Shin-ichi Hisanaga¹ (¹Dept. of Biol. Sci., Grad. Sch. of Sci., Tokyo Metrop. Univ., Tokyo, Japan, ²Dept. of Mol. Neurobiol., Tokyo Inst. of Psychiat., Tokyo, Japan)
- N105 Alzheimer's beta-secretase (BACE1) cleaves alpha2,6sialyltransferase as a physiological substrate. (MS3-3)**
 ○Yasuhiro Hashimoto, Yuriko Tachida, Ritsuko Oka, Norihiro Kotani, Kazuko Ogawa, Minoru Suzuki, Naoshi Dohmae, Koji Takio, Takaomi Saido, Shinobu Kitazume (RIKEN Inst.)
- N106 PEN-2 enhances gamma-secretase activity without the stimulation of presenilin endoproteolysis (MS3-4)**
 Xiaorei Sai^{1,2}, Hirohisa Shiraishi^{1,3}, Hua-Qin Wang⁴, Yasuhiro Maeda⁵, Masaki Nishimura⁴, Katsuhiko Yanagisawa¹, ○Hiroto Komano¹ (¹Dept. of Dementia Res., Natl. Inst. for Longevity Sci., ²Bio-mimetic Control Res. Center, The Inst. of Phys. and Chem. Res., Nagoya, Japan, ³Organization for Pharm. Safety and Res. of Japan, Tokyo, Japan, ⁴Mol. Neurosci. Res. Center, Shiga Univ. of Med. Sci., Otsu, JAPAN, ⁵Fac. of Pharm. Sci., City Univ., Nagoya, JAPAN)

- N107 Dual-cleavage mechanism of betaAPP by Cell Free PS/gamma-secretase assay.**
(MS3-5) ○Fukumori Akio¹, Masayasu Okochi¹, Harald Steiner², Hisashi Tanii¹, Shinji Tagami¹, Jingwei Jiang¹, Nurun Nessa Begum¹, Daisuke Kanayama¹, Takshi Kudo¹, Christian Haass², Masatoshi Takeda¹ (¹Div. of Psychiat. and Behav. Proteomics, Dept. of Post-Genomics and Dis., Course of Adv. Med., Osaka Univ. Grad. Sch. of Med. Suita Japan, ²Dept. of Biochem., Adolf Butenandt-Inst., Ludwig-Maximilians-Univ., Munich, Germany)
- N108 Full-length, but not N- nor C-terminal fragment of Presenilin 1, 2 interact with Syntaxin 5**
○Kei Suga¹, Takami Tomiyama², Hiroshi Mori², Kimio Akagawa¹ (¹The Dept. of Physiol., Kyorin Univ. Sch. of Med., Tokyo, Japan, ²The Dept. of Neurosci., Osaka City Univ. Med. Sch., Osaka, Japan)
- N109 Elevated BACE1 levels affect the generation of APP intracellular domain.**
○Fuyuki Kametani¹, Hideaki Kume^{1,2}, Kei Maruyama³ (¹Dept. of Mol. Neurobiol., Tokyo Inst. of Psychiat., ²Dept. of Mol. Neurobiol., Tokyo Inst. of Psychiat., ³Dept. of Pharm., Saitama Med. Sch.)
- N110 An increase in Abeta generation by the high expression of GATE-16, mammalian homologue of yeast Apg 8 essential for autophagy**
○Hirohisa Shiraishi^{1,2}, Ryo Suzuki³, Yasuhiro Maeda³, Xiaorei Sai⁴, Eiki Kominami⁵, Isei Tanida⁵ (¹Dept. of Dementia Res., Natl. Inst. for Longevity Sci., Obu, Japan, ²The Organ. for Pharm. Safety and Res., Tokyo, Japan, ³Fac. of Pharm. Sci., Nagoya City Univ., Nagoya, Japan, ⁴Bio-mimetic Control Res. Center, The Inst. of Phys. and Chem. Res., Nagoya, Japan, ⁵The Dept. of Biochem., Juntendo Univ. Sch. of Med., Tokyo, Japan)
- N111 Analysis of processing and protein interaction of β -secretase**
○Kiyoko Murayama¹, Fuyuki Kametani², Noriko Takahashi¹, Shinya Saito¹, Wataru Araki¹ (¹Dept. of Demyelinating Dis. and Aging, Natl. Inst. of Neurosci., NCNP, Tokyo, Japan, ²Tokyo Inst. of Psychiat., Tokyo, Japan)
- N112 Immunohistochemical study of b-amyloid protein(1-40, 1-42, 1-43) in old dog brain**
○Tatsuki Itoh, Takao Satou, Yoshiyuki Hayashi, Hiroyuki Ito (Second Dept. of Pathol., Kinki Univ. Sch. of Med., Osaka, Japan)
- N113 DNA chip study on mRNA expression profiles in the brain regions of MK-801 treated rat:Alzheimer's disease model**
○Yukiko Kumabe¹, Md. Mahiuddin Ahmed¹, Toshiyuki Chikuma², Takeshi Kato¹ (¹Lab. of Mol. Recognition, Grad. Sch. of Integrated Sci., Yokohama City Univ., ²Dept. of Hygienic Chem., Showa Pharm. Univ., Machida, Japan)
- N114 Identification and characterization of molecules induced by beta amyloid in cultured cortical neurons**
○Yoko Uchida, Fujiya Gomi (Gene Expression Res. Group, Tokyo Metrop. Inst. of Gerontol., Tokyo, Japan)
- N115 Modification of Epitopes of Tau Protein Specific to Alzheimer's Disease by Sequential Phosphorylation**
○Mitsuko Hashiguchi, Toshio Hashiguchi (Dept. of Physiol., Sch. of Med., Tokyo Med. Univ., Tokyo, Japan)
- N116 Dose-dependent effect of MK-801 on the levels of neuropeptide regulating enzymes in rat brain regions**
○Takeshi Kato¹, Md. Mahiuddin Ahmed¹, Yoshiyuki Chikuma², Md. Khalilur Rahman³ (¹Lab. of Natural Inf. Sci., Grad. Sch. of Integrated Science, Yokohama City Univ., Japan, ²Dept. of Hygienic Chem., Showa Pharm. Univ., Japan, ³Dept. of Biochem. & Mol. Biol., Univ. of Dhaka, Bangladesh)
- N117 The effect of PS1 mutation on glycosphingolipid metabolism in neuroblastoma cells**
○Tatsuro Mutoh¹, Shigeaki Yano¹, Tadanori Hamano³, Takeshi Tabira², Hiroko Yamamoto¹ (¹The Dept. of Neurol., Fujita Health Univ. Sch. of Med., Nagoya, Japan, ²Natl. Inst. of Longevity Sci., ³2nd Dept. of Intern. Med., Fukui Med. Univ.)
- N118 The role of phosphorylated PKR in ER-stress**
○Reiko Onuki^{1,2}, Mototsugu Itoh¹, Chihiro Kondo¹, Yoshio Bando^{3,5}, Masaya Tohyama^{4,5}, Kazunari Taira^{2,6}, Yuichi Sugiyama¹ (¹Grad. Sch. of Pharm. Sci., Univ. of Tokyo, Tokyo, Japan, ²Gene Function Res. Center, AIST, Ibaraki, Japan, ³Dept. of Anat. I, Asahikawa Med. Coll., Hokkaido, Japan, ⁴Dept. of Anat. and Neurosci., Grad. Sch. of Med., Osaka Univ., Osaka, Japan, ⁵CREST, JST, Saitama, Japan, ⁶Dept. of Chem. and Biotechnol., Sch. of Eng., The Univ. of Tokyo, Tokyo, Japan)

Drug Abuse and Psychopharmacology (Intoxication, Addiction)

N119 Effects of methamphetamine on cultured rat astrocytes

○Ichiro Isobe, Yoshitaka Maeno, Hiroyoshi Koyama, Yoshimi Nakamura, Jun Ohtaki, Masataka Nagao (Forensic Med. Sci., Nagoya City Univ. Grad. Sch. of Med. Sci., Nagoya, Japan)

N120 Circadin rhythms alters antipsychotics-induced acetylcholine release in rat prefrontal cortex

○Hidekazu Sotoyama¹, James Gitzen³, Yongxin Zhu³, Qin Zhou³, Fuming Xie³, Hiroyuki Nawa¹, Toshiyuki Someya², Peter Kissinger³ (¹Dept. of Mol. Neurobiol., ²Dept. of Psychiat., Niigata Univ., Niigata, Japan, ³Bioanalytical Systems, Inc, West Lafayette, IN47906, U.S.A.)

Neurotoxicity

N121 Effects of neonatal exposure of endocrine disruptors on rat myelin membranes.

○Yoshiko Tokuyama¹, Hisako Kojima¹, Kazuo Nakamura¹, Tsugumi Ogitan¹, Masahiro Kuwada¹, Yoichi Tamai² (¹Kitasato Univ. Sch. of Med., ²Univ. of Human Arts and Sci.)

Neuro-oncology

N122 The epigenetic silenced gene, RFX1, in human gliomas.

○Yohei Ohashi^{1,2}, Masakazu Ueda³, Takeshi Kawase⁴, Yutaka Kawakami², Masahiro Toda^{1,2,4} (¹Neuro-immunol. Res. Group, Keio Univ. Sch. of Med., Tokyo, Japan, ²Div. of Cell. Signaling, Inst. for Adv. Med. Res., Keio Univ. Sch. of Med., Tokyo, Japan, ³Dept. of Surg., Keio Univ. Sch. of Med., Tokyo, Japan, ⁴Dept. of Neurosurg., Keio Univ. Sch. of Med., Tokyo, Japan)

N123 A mouse glioma antigen recognized by T cells

○Yukihiko Iizuka^{1,2}, Hidefumi Kojima⁴, Tetsuji Kobata⁴, Takeshi Kawase³, Yutaka Kawakami², Masahiro Toda^{1,2,3} (¹Neuroimmunol. Res. Group, Keio Univ. Sch. of Med., Tokyo, Japan, ²Div. of Cell. Signaling, Inst. for Adv. Med. Res., Keio Univ. Sch. of Med., Tokyo, Japan, ³Dept. of Neurosurg., Keio Univ. Sch. of Med., Tokyo, Japan, ⁴Div. of Immunol., Inst. for Med. Sci., Dokkyo Univ. Sch. of Med., Tochigi, Japan)

Epilepsy

N124 Involvement of inducible COX-2 in the rapid kindling development

○Kanato Yamagata¹, Takako Takemiya^{1,2}, Kyoko Suzuki¹, Yoriko Kawakami² (Dept. of Neuropharm., Tokyo Metro. Inst. for Neurosci., Tokyo, Japan, ²Dept. of Physiol., Tokyo Women's Med. Univ., Tokyo, Japan)

Others

N125 Neurotoxicity of acetaldehyde-derived advanced glycation end-products (AA-AGE) for cultured cortical neurons

○Masayoshi Takeuchi¹, Mina Iwaki¹, Takayuki Watai¹, Yukihiko Kameda¹, Sho-ichi Yamagishi², Nobuyuki Sasaki³, Toshikazu Saito³ (¹Dept. of Biochem., Hokuriku Univ., Kanazawa, Japan, ²Dept. of Med., Kurume Univ. Sch. of Med., Kurume, Japan, ³Dept. of Neuropsychiat., Sch. of Med. Sapporo Med. Univ.)

N126 Neuroprotective effect of FK506 on axotomy induced motoneuron death

Kiyonobu Komai¹, ○Yasuo Kumakura², Masahito Yamada¹ (¹Dept. of Neurol. and Neurobiol. of Aging, Grad. Sch. of Med. Sci., Kanazawa Univ., Kanazawa, Japan, ²Lab. of Neuropsychopharm., Dept. of Clin. Pharm., Fac. of Pharm. Sci., Kanazawa Univ., Kanazawa, Japan)

N127 Three-dimensional culture of the rat neural stem cell in collagen gel

○ Kota Watanabe¹, Masaya Nakamura¹, Yuto Ogawa¹, Kazuhiro Chiba¹, Hideyuki Okano², Yoshiaki Toyama¹ (¹The Dept. of Orthop. Surg., Kieo Univ. Sch. of Med., Tokyo, Japan, ²Dept. of Physiol., Kieo Univ. Sch. of Med., CREST, Tokyo, Japan)

N128 Search for factors associated with neuroprotection in the retina.

○ Takayuki Mababe^{1,2,3}, Hiroaki Okuda^{1,3}, Taiichi Katayama^{1,2,3}, Masaya Tohyama^{1,3} (¹Dept. of Anat. and Neurosci., Grad. Sch. of Med., Osaka Univ., Suita, Osaka, Japan, ²Innovation Plaza Osaka, Japan Sci. and Technol. Corp. (JST), ³CREST, JST)

Ion Channels and Excitable Membranes

- N129** **Slo2, sodium-activated K⁺ channel, binds to PDZ domain of PSD-95**
 ○Shigeo Uchino, Hidenori Wada, Shizuyo Honda, Takae Hirasawa, Shigeki Yanai, Yasuko Nakamura, Yumiko Ondo, Shinichi Kohsaka (Dept. of Neurochem., Natl. Inst. of Neurosci., Tokyo, Japan)
- N130** **Cellular localization and distribution of Nax sodium channel**
 ○Eiji Watanabe^{1,2,3}, Takeshi Hiyama^{1,4}, Ryuji Kodama¹, Masaharu Noda^{1,2,4} (¹Natl. Inst. for Basic Biol., Aichi, Japan, ²Grad. Univ. for Adv. Stud., Aichi, Japan, ³PREST of JST, Aichi, Japan, ⁴CREST of JST, Aichi, Japan)
- N131** **A region of the $\alpha 1A$ subunit critical for modulation of P/Q-type Ca²⁺ channels by protein kinase A**
 ○Toshihide Nukada¹, Taiji Furukawa², Yoshiko Namiki¹, Yasuo Mori³, Mitsunobu Yoshii⁴ (¹Dept. of Neuronal Signaling, Tokyo Inst. of Psychiat., Tokyo, Japan, ²Dept. of Intern. Med., Fac. of Med., Teikyo Univ., Tokyo, Japan, ³Div. of Mol. and Cell. Physiol., Center for Integrative Biosci., Okazaki Natl. Res. Inst., Okazaki, Japan, ⁴Dept. of Neural Plasticity, Tokyo Inst. of Psychiat., Tokyo, Japan)
- N132** **Colocalization of acid-sensing ion channels and vanilloid receptor subtype-1 in rat dorsal root ganglion neurons**
 ○Shinya Ugawa, Takashi Ueda, Shoichi Shimada (Dept. of Anat. II, Nagoya City Univ. Med. Sch., Aichi, Japan)

Neurotransmitters and Modulators (Function, Release, Uptake and Metabolism)

- N133** **Egr1 and AP1 factors in transcription of tyrosine hydroxylase**
 ○Akira Nakashima^{1,2}, Akira Ota¹, Esther Sabban² (¹Dept. of Physiol., Fujita Health Univ. Sch. of Med., Toyoake, Aichi, Japan, ²Dept. of Biochem. and Mol. Biol., New York Med. Coll., Valhalla, NY, USA)
- N134** **Effect of Over-expression of the Sigma-1 receptor molecule on the dopaminergic cellular functions**
 ○Hideko Yamamoto¹, Toshihide Nukada², Etsuko Kamegaya¹, Haowei Shen¹, Tohru Yamakuni³, Fuyuki Kametani⁴, Motsunobu Yoshii¹, Kazutaka Ikeda¹, Ichiro Sora^{1,5}, Toshifumi Yamamoto^{1,6} (¹Dept. Mol. Psychiat., Tokyo Inst. Psychiat., Tokyo, Japan, ²Dept. Neuronal Signaling, Tokyo Inst. Psychiat., Tokyo, Japan, ³Dept. Pharm. Mol. Biol., Grad. Sch. of Pharm. Sci., Tohoku Univ., Sendai, Japan, ⁴Dept. of Mol. Neurobiol., Tokyo Inst. Psychiat., Tokyo, Japan, ⁵Dept. Neurosci., Tohoku Univ. Sch. Med., Sendai, Japan, ⁶Lab. of Mol. Recog., Grad. Sch. of Interated Sci., Yokohama City Univ., Yokohama, Japan)
- N135** **Tree-dimensional structure of the interior of chromaffin cells and chromaffin granule motion.**
 ○Konosuke Kumakura¹, Alessandro Riva², Mica Ohara-Imaizumi³, Masataka Murakami⁴ (¹Life Sci. Inst., Sophia Univ., Tokyo, Japan, ²Dept. of Cytomorphol., Univ. of Cagliari, Italy, ³Dept. of Biochem. II, Kyorin Univ. Sch. of Med., Tokyo, Japan, ⁴Dept. of Mol. Physiol., Natl. Inst. of Physiol. Sci., Okazaki, Japan)
- N136** **Serotonin_{2A} receptor stimulation by DOI, a serotonin_{2A/2C} receptor agonist, potentiates amphetamine-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens.**
 ○Toshihide Kuroki¹, Junji Ichikawa², Meltzer Herbert², Kijiro Hashimoto³, Makoto Hirano³ (¹Dept. of Neuropsychiat., Kyushu Univ. Grad. Sch. of Med. Sci., Fukuoka, Japan, ²Dept. of Psychiat. and Pharm., Vanderbilt Univ. Sch. of Med., Nashville, U.S.A., ³Hizen Natl. Mental Hosp., Kanzaki-Saga, Japan)
- N137** **Negative regulation of neurotransmitter release through the specific cleavage of SNAP-25 by calpain**
 ○Kosuke Ando^{1,2}, Yoshihisa Kudo¹, Masami Takahashi² (¹The Dept. of Life Sci., Univ. of Pharm. and Life Sci., Tokyo, Japan, ²The Dept. of Biochem., Sch. of Med., Univ. of Kitasato, Kanagawa, Japan)
- N138** **Amperometric detection and characterization of exocytosis from single PC12h cells**
 ○Nobuyuki Sasakawa, Norie Murayama, Konosuke Kumakura (Lab. of Neurochem. and Neuropharm., Life Sci. Inst., Sophia Univ., Tokyo, Japan.)

- N139 Purification of pChAT, a novel splice variant of choline acetyltransferase, from porcine small intestine**
 ○Jean-Pierre Bellier, Yoshinari Aimi, Akinori Matsuo, Osamu Yasuhara, Ikuo Tooyama, Hiroshi Kimura (Mol. Neurosci. Res. Center, Shiga Univ. of Med. Sci., Japan)
- N140 A high efficient transfection method for chromaffin cells**
 ○Norie Murayama, Nobuyuki Sasakawa, Natue Yoshimura, Konosuke Kumakura (Lab. of Neurochem. and Neuropharm., Life Sci. Inst., Sophia Univ., Tokyo Japan)
- N141 Effect of antipsychotic drugs haloperidol and risperidone on altered psychomotor behaviors in PACAP knockout mice**
 ○Kazuhiro Tanaka¹, Hitoshi Hashimoto¹, Norihito Shintani¹, Akiko Yamamoto¹, Chihiro Kawaguchi¹, Akemichi Baba^{1,2} (¹Lab. of Mol. Neuropharm., Grad. Sch. of Pharm. Sci., Univ. of Osaka, Osaka, Japan, ²Lab. of Mol. Pharm. Grad. Sch. of Med., Univ. of Osaka, Osaka, Japan)
- N142 Regulation by serotonin_{1A} receptors of *in vivo* release of serotonin and dopamine in mouse cortex**
 ○Yukio Ago¹, Shigeo Nakamura¹, Yutaka Koyama¹, Akemichi Baba², Toshio Matsuda¹ (¹Lab. of Med. Pharm., Grad. Sch. of Pharm. Sci., Osaka Univ., Osaka, Japan, ²Lab. of Mol. Neuropharm., Grad. Sch. of Pharm. Sci., Osaka Univ., Osaka, Japan)
- N143 Human interferon-alpha Associated Decrease of BrdU positive cells in Rat Hippocampus**
 ○Naoko Kaneko, Koutaro Kudo, Keiko Takemoto, Chunxiang Quao, Henny Waty, Hironobu Iguchi, Shigenobu Kanba (Dept. of Neuropsychiat. and Clin. Ethics, Fac. of Med., Univ. of Yamanshi, Yamanashi, Japan)
- N144 Assay of PRMT(protein arginine methyltransferase)function by using siRNA during neuronal differentiation of PC12cells.**
 ○Tatsuji Fujiwara, Shingo Miyata, Yasutake Mori, Masaya Tohyama (Dept. of Anat. and Neurosci., Grad. Sch. of Med., Osaka Univ., Osaka, Japan)
- N145 Effects of botulinum neurotoxin and nitric oxide on the exocytosis in rat cerebellum granule cells**
 ○Hiroyasu Tsutsuki^{1,3}, Hideshi Ihara^{2,3}, Tomoko Kohda^{3,4}, Masafumi Mukamoto^{3,4}, Shunji Kozaki^{3,4} (¹Dept. of Materials Sci., Grad. Sch. of Sci., Osaka Prefect. Univ., ²Dept. of Earth and Life Sci., Coll. of Integrated Arts and Sci., Osaka Prefect. Univ., ³Res. Inst. for Adv. Sci. and Technol., Osaka Prefect. Univ., ⁴Dept. of Vet. Sci., Grad. Sch. of Agric. and Biol. Sci., Osaka Prefect. Univ.)

Signal Transduction and Modulation

- N146 Autophosphorylated, inactivated and sedimentable Ca²⁺/calmodulin-dependent protein kinase II (MS6-1) during acute brief seizure activity in rats *in vivo***
 ○Yoko Yamagata, Kunihiro Obata (Natl. Inst. for Physiol. Sci.)
- N147 Stimulation of CaM kinase II-dependent neurite extension by Arc (MS6-2)**
 ○Hitomi Donai¹, Hiroko Sugiura², Yosiyuki Yoshimura¹, Kanato Yamagata², Takashi Yamauchi¹ (¹Fac. of Pharm. Sci., The Univ. of Tokushima, Tokushima, Japan, ²Tokyo Metrop. Inst. for Neurosci.)
- N148 The regulatory mechanisms of CaM kinases I and IV in the hippocampal neurons. (MS6-3)**
 ○Jiro Kasahara¹, Akiyoshi Uezu², Kohji Fukunaga¹ (¹Dept. of Pharm., Grad. Sch. of Pharm. Sci., Tohoku Univ., Sendai, Japan, ²Dept. of Pharm., Kumamoto Univ. Sch. of Med. Sci., Kumamoto, Japan)
- N149 Identification of MLK 3 as a hippocalcin-binding protein (MS6-5)**
 ○Masaaki Kobayashi, Ken Takamatsu (Dept. of Physiol., Toho Univ. Sch. of Med., Tokyo, Japan)
- N150 Stimulation of the G protein, Gi2, by endothelin B receptors enhances proliferation and migration of (MS8-4) neural progenitor cells**
 ○Tomiko Asano¹, Haruo Shinohara², Rika Morishita¹, Hiroshi Ueda¹, Reiji Semba², Kanefusa Kato¹ (¹Dept. of Mol. Neurobiol., Inst. for Dev. Res., Aichi Human Service Center, Kasugai, Japan, ²Dept. of Anat., Mie Univ. Sch. of Med., Tsu, Japan)
- N151 Sterol regulatory element-binding proteins are involved in the human brain acyl-CoA hydrolase gene transcription.**
 ○Mitsuhiro Takagi, Fumitaka Suto, Takafumi Watanabe, Tetsuya Suga, Junji Yamada (Dept. Clin. Biochem., Tokyo Univ. of Pharm. & Life Sci., Tokyo, Japan)

- N152 THE EFFECTS OF ACUTE AND REPEATED RESTRAINT STRESS ON ACTIVATION OF ERK IN THE ROSTRAL VENTROMEDIAL MEDULLA**
 ○Hiroki Imbe, Shuji Murakami, Emiko Senba (Dept. of Anat. and Neurobiol., Wakayama Med. Univ.)
- N153 Protection by repetitive exposure to static magnetic fields against neurotoxicity of MK-801 in cultured rat hippocampal neurons**
 ○Takao Hirai, Yukio Yoneda (Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Ishikawa, Japan)
- N154 Suppression by SOCS3 of leptin-induced NPY gene transactivation**
 ○Tsuyoshi Yamaguchi, Ayumi Hasegawa, Katsura Ohtani, Hiroshi Higuchi (Div. of Pharm., Niigata Univ. Grad. Sch. of Med. and Dental Sci., Niigata, Japan)
- N155 Identification and Characterization of Novel Human Ubiquitin Ligases Involved in Endoplasmic Reticulum-Associated Degradation (ERAD)**
 ○Mai Uesugi, Masayuki Kaneko, Yasuyuki Nomura (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan)
- N156 Vitamin D responsive element binding in rat brain**
 ○Minoru Ito¹, Hiroshi Ohno¹, Nobuyuki Kuramoto², Chie Sugiyama², Hideo Taniura², Yukio Yoneda² (¹Div. of Mol. Membrane Biol., Cancer Res. Inst., Kanazawa Univ., Kanazawa, Ishikawa, Japan, ²Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Ishikawa, Japan)
- N157 Regulation of calcium/calmodulin-dependent protein kinase I activity by protein phosphatases in cultured rat hippocampal neurons**
 ○Akiyoshi Uezu¹, Jiro Kasahara², Shinri Tamura³, Hideyuki Yamamoto¹, Eishichi Miyamoto¹, Kohji Fukunaga² (¹Dept. of Mol. Pharm., Kumamoto Univ., Kumamoto, Japan, ²Dept. of Pharm., Grad. Sch. of Pharm. Sci., Tohoku Univ., Sendai, Japan, ³Dept. of Biochem., Inst. of Development, Aging and Cancer, Tohoku Univ., Sendai, Japan)
- N158 Regulation of estrogen receptor function by heat shock protein 90 in HT22 cells.**
 ○Shozo Kito, S.Akiko Shingo (Hyogo Univ. Sch. of Health Sci., Hyogo, Japan)
- N159 Activation of ATF6, an Endoplasmic reticulum (ER) stress sensor, through 6-hydroxydopamine in human neuroblastoma SH-SY5Y cells.**
 ○Akiko Yamamuro¹, Satoko Morita¹, Rumiko Kuwada¹, Yasuhiro Yoshioka¹, Fumiaki Ito³, Kiyokazu Ogita², Sadaaki Maeda¹ (¹Dept. of Pharmacotherapeutics, Setsunan Univ., Osaka, Japan, ²Dept. of Pharm., Setsunan Univ., Osaka, Japan, ³Dept. of Biochem., Setsunan Univ., Osaka, Japan)
- N160 Mechanisms of IL-20 induction in the primary cultured glial cells**
 ○Sawako Suzuki, Sachiyo Wada, Toru Hosoi, Yasunobu Okuma, Yasuyuki Nomura (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan)
- N161 Mechanisms of estrogen-induced elevation of PLA activity in immortalized hippocampal neurons.**
 ○S. Akiko Shingo, Shozo Kito (Hyogo Univ. Sch. of Health Sci., Hyogo, Japan)
- N162 Decrease in histamine H₁ receptor signaling through m3 muscarinic receptor-induced H₁ receptor down-regulation**
 ○Hiroyuki Fukui, Katsuhiro Miyoshi, Nozomi Kawakami, Hatsumi Yokouchi, Shuhei Horio (Dept. of Pharm., Univ. of Tokushima Fac. of Pharm. Sci., Tokushima, Japan)
- N163 Phosphorylation of a p35 Cdk5 activator being inhibitory to the cleavage by calpain**
 ○Mirai Ozawa, Taro Saito, Fujita Yuichi, Kumiko Suzuki, Akiko Asada, Shin-ichi Hisanaga (Dept. of Biol. Sci., Grad. Sch. of Sci., Tokyo Metrop. Univ., Tokyo, Japan)
- N164 Effect of methamphetamine on expression of Homer mRNAs in the rat brain**
 ○Kijiro Hashimoto¹, Tatsuo Nakahara¹, Toshihide Kuroki², Hidetaka Yamada¹, Toshio Kajihata², Tetsuyuki Tsutsumi¹, Makoto Hirano¹ (¹Center for Emotional and Behav. Disord., Hizen Natl. Hosp., Saga, Japan, ²Dept. of Neuropsychiat., Kyushu Univ. Grad. Sch. of Med. Sci., Fukuoka, Japan)
- N165 The role of G protein subtypes in type 5 adenylyl cyclase-null mice**
 ○Tamio Iwamoto, Kousaku Iwatsubo, Yoko Hashimoto, Aki Izumitani, Kouji Ohtsu, Yoshihiro Ishikawa (Dept. of Physiol., Yokohama City Univ., Yokohama, Japan)

Axonal Transport, Cell Motility and Cytoskeleton

- N166 (MS7-1) The N-terminal membrane-associated domain of RB3, a neural-specific member of the SCG10/stathmin family proteins, affects the microtubule dynamics**
 ○Chitose Nakao¹, Tomohiko Itoh², Hirokazu Hotani², Nozomu Mori¹ (¹Dept. of Mol. Genet., Natl. Inst. for Longevity Sci. (NILS), Aichi, Japan, ²Div. of Biol. Sci., Grad. Sch. of Sci., Nagoya, Japan)
- N167 (MS7-2) Real-time observation of the effect of dephosphorylation on neurofilament gel formation using microbeads**
 ○Rei Ono¹, Kazuya Nakabayashi¹, Taisuke Morita¹, Masashi Kurachi², Yoshiaki Komiya², Tomoko Tashiro^{1,3} (¹Dept. of Biochem., Coll. of Sci. and Eng., Aoyama Gakuin Univ., Sagamihara, Japan, ²Dept. of Mol. and Cell. Neurobiol., Fac. of Med., Gunma Univ., Maebashi, Japan, ³CREST, JST)
- N168 Coordinated cytoskeletal interactions in neuritogenesis**
 ○Nobuyuki Fukushima (Dept. of Mol. Biochem., Hokkaido Univ., Sapporo, Japan)
- N169 Domain analysis of Drebrin-associated protein 1, Drap1**
 ○Hiroyuki Yamazaki, Toshiyuki Mizui, Chiho Kobayashi, Tomoaki Shirao (Dept. of Neurobiol. and Behavior, Gunma Univ. Grad. Sch. of Med., Maebashi, Japan)
- N170 (MS8-6) Filamin A-interacting protein FILIP regulates cell shape prior to radial migration in the cortical ventricular zone.**
 ○Takashi Nagano¹, Soichi Morikubo^{1,2}, Hideshi Yagi¹, Makoto Sato¹ (¹Dept. of Anat. (2), Fac. of Med., Fukui Med. Univ., ²Dept. of Ophthalmol., Fac. of Med., Fukui Med. Univ., Fukui, Japan)
- N171 Preparation of the antibody specific for tau phosphorylated by CaM kinase II.**
 ○Hideyuki Yamamoto, Hiroyuki Nakanishi (Dept. of Mol. Pharm., Grad. Sch. of Med. Sci., Kumamoto Univ., Kumamoto, Japan)
- N172 Positive and negative effects of neurosteroids and endocrine disruptors on MAP2-dependent microtubule assembly and neurite extension**
 ○Hayato Matsunaga, Akira Yoshida, Kiyonobu Mizuno, Hiroshi Ueda (Div. of Mol. Pharm. and Neurosci., Nagasaki Univ., Grad. Sch. of Biomed. Sci.)
- N173 Migration of young neurons in the adult mouse and monkey subventricular zone**
 ○Kazunobu Sawamoto^{1,5}, Yoshika Hayakawa¹, Akio Iwanami^{1,2}, Shinjiro Kaneko^{1,2}, Hitoshi Kawano³, Hajime Ishii⁴, Tatsuji Nomura⁴, Hynek Wichterle⁵, Marc Tessier-Lavigne⁶, Arturo Alvarez-Buylla⁵, Hideyuki Okano¹ (¹Dept. of Physiol., Keio Univ. Sch. of Med., ²Dept. of Orthop. Surg., Keio Univ. Sch. of Med., ³Tokyo Metrop. Inst. for Neurosci., ⁴Central Inst. for Exp. Animals, ⁵Univ. of California San Francisco, San Francisco, USA, ⁶Stanford Univ., Stanford, USA)

Neuron and Glia

- N174 (MS7-3) Screening of the downstream targets of Olig2 by PCR-based cDNA subtraction analysis**
 ○Noritaka Masahira^{1,2}, Hirohide Takebayashi¹, Keiji Shimizu², Kazuhiro Ikenaka¹ (¹Div. of Mol. Neurobiol., Natl. Inst. for Physiol. Sci., Okazaki, Japan, ²Dept. of Neurosurg., Kochi Med. Sch., Kochi, Japan)
- N175 (MS7-4) Expression and activity of extracellular superoxide dismutase in cultured astrocytes**
 ○Yoichi Nakamura¹, Takashi Kitagawa¹, Koji Murakami², Yukio Yoneda² (¹Lab. of Integrative Physiol. in Vet. Sci., Osaka Prefect. Univ., Sakai, Japan, ²Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Japan)
- N176 (MS7-5) The dynamic state of progenitor cells in brain injury**
 ○Kouko Tatsumi, Satomi Haga, Akio Wanaka (The Second Dept. of Anat., Nara Med. Univ., Kashihara, Nara, Japan)
- N177 Differential subcellular distributions of Ca²⁺/calmodulin-dependent protein kinase II delta isoforms**
 ○Yusuke Takeuchi, Kohji Fukunaga (Dept. of Pharm., Grad. Sch. of Pharm. Sci., Tohoku Univ.)
- N178 A potential role of PKC-signaling in neuronal maturation**
 ○Hiroshi Hama¹, Chikako Hara², Takako Kogure², Atsushi Miyawaki¹ (¹Lab. for Cell Function Dynamics, ATDG, Brain Sci. Inst. (BSI), RIKEN, CREST JST(Japan Sci. and Technol.), Wako-shi, Saitama, Japan, ²Lab. for Cell Function Dynamics, ATDG, Brain Sci. Inst. (BSI), RIKEN, Wako-shi, Saitama, Japan)

- N179 Cellular properties of microglia isolated from axotomized facial nucleus of adult rat**
 ○Kazuyuki Nakajima¹, Yoko Tohyama¹, Sinichi Kohsaka², Tadashi Kurihara¹ (¹Dept. of Bioinformatics, Fac. of Eng., Soka Univ., Hachioji, Japan, ²Natl. Inst. of Neurosci., Tokyo, Japan)
- N180 Influence of dibutyryc cyclic AMP on differentiation and development of glial cells in primary cultures of embryonic rat cerebral hemisphere**
 ○Tatsumi Adachi¹, Hiromi Takanaga², Manabu Kunimoto², Hiroaki Asou³ (¹Dept. of Basic Med. Sci., Natl. Inst. for Minamata Dis., Minamata, Kumamoto, Japan, ²Sch. of Pharm. Sci., Kitasato Univ., Tokyo, Japan, ³Tokyo Metrop. Inst. of Gerontol., Tokyo, Japan)
- N181 Translocation of protein kinase C to cytosol in astrocytes by apolipoprotein A-I**
 ○Jinichi Ito, Yuko Nagayasu, Shinji Yokoyama (The First Dept. of Biochem., Cell Biol. and Metabolism, Nagoya City Univ., Grad. Sch. of Med. Sci.)
- N182 Prevention by pyruvate of cell death induced by hydrogen peroxide in cultured rat cortical neurons**
 ○Yuki Kambe, Noritaka Nakamichi, Maki Inoue, Eiichi Hinoi, Katsura Takano, Chie Sugiyama, Yukio Yoneda (Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Japan)
- N183 Evaluation of cellular maturation following sustained exposure to static magnetic fields in cultured rat hippocampal neurons and astrocytes**
 ○Yasuaki Goto¹, Kiyofumi Yamada¹, Takao Hirai², Yukio Yoneda² (¹Lab. of Exp. Therapeutics, Kanazawa Univ. Fac. of Pharm. Sci., Kanazawa, Ishikawa, Japan, ²Lab. of Mol. Pharm., Kanazawa Univ. Grad. Sch. of Natural Sci. and Technol., Kanazawa, Ishikawa, Japan)
- N184 Dopamine receptors in the striatal astrocytes**
 ○Ikuko Miyazaki, Masato Asanuma, Norio Ogawa (Dept. of Brain Sci., Okayama Univ. Grad. Sch. of Med. and Dentistry, Okayama, Japan)
- N185 The expression patterns of mouse brain serine proteinase mRNA and protein in mouse development**
 ○Mineyoshi Aoyama¹, Takashi Yokoi^{1,2}, Naoki Yamamoto¹, Toyohiro Tada⁴, Yuichi Oka^{1,3}, Masataka Fujita^{1,3}, Akihiko Moriyama⁵, Yutaka Miura¹, Kiyofumi Asai¹ (¹Dept. of Mol. Neurobiol., Nagoya City Univ. Grad. Sch. of Med. Sci., Nagoya, Japan, ²Dept. of Pediatr., Neonatol. and Congenital Disord., Nagoya City Univ. Grad. Sch. of Med. Sci., Nagoya, Japan, ³Dept. of Neurosurg. and Restorative, Nagoya City Univ. Grad. Sch. of Med. Sci., Nagoya, Japan, ⁴Nagoya City Univ. of Nursing, Nagoya, Japan, ⁵Nagoya City Univ. Grad. Sch. of Natural Sci.)
- N186 Oligomer formation is essential for secretion of Pancortins**
 ○Koichi Ando¹, Akira Nakamura², Takashi Nagano¹, Makoto Sato¹ (¹Anat.2, Fukui Med. Univ., ²Div. of Cell Struct. Biol., Dept. of Biosci., Nara Inst. of Technol.)
- N187 Distinct characteristics of astrocyte precursors according to the domain structure in the spinal cord**
 ○Yasuhiro Ogawa¹, Matthew Rasband², Hirohide Takebayashi¹, Yasuno Iwasaki¹, James Trimer², Kazuhiro Ikenaka¹ (¹Natl. Inst. for Physiol. Sci., Okazaki, Japan, ²SUNY Stony Brook, NY, USA)
- N188 Enhanced protein staining and immunoreactivity of Purα induced by PUR element in parallele with its DNA binding activity**
 ○Che-Hui Kuo, Ling-Hui Zeng, Naomasa Miki (Dept. of Pharm., Med. Sch., Osaka Univ., Osaka, Japan)
- N189 Glial cell responses after peripheral nerve injury**
 ○Mizue Takahara, Eriko Kuramoto, Shinobu Inagaki (Group Neurobiol., Sch. Allied Health Sci., Osaka Univ. Fac. Med., Osaka, Japan)
- N190 A high concentration of K⁺ enhances LPS-induced nitric oxide production in cultured astrocytes**
 ○Takashi Kitagawa, Eri Asai, Yukiko Kannan, Mituaki Moriyama, Yoichi Nakamura (Lab. of Integrative Physiol. in Vet. Sci., Osaka Prefect. Univ., Sakai, Japan)
- N191 Roles of a tetraspanin protein CD9 in the nervous system**
 ○Tomoko Ishibashi, Hitoshi Kajigaya, Hiroko Baba (Dept. of Mol. Neurobiol., Sch. of Pharm., Tokyo Univ. of Pharm. and Life Sci.)

Myelin

- N192 New insights into myelin abnormality in brain aging.**
 ○Tomomi Sakai^{1,2}, Chika Seiwa², Taka Osanai³, Kayoko Tanaka⁴, Makoto Sugawa², Yutaka Sanai³, Isamu Matsumoto¹, Hiroaki Asou² (¹Dept. of Chem., Fac. of Sci., Ochanomizu Univ., Tokyo, Japan, ²Glial Cell Res. Group, Tokyo Metrop. Inst. of Gerontol., Tokyo, Japan, ³Dept. of Biochem. Cell Res., The Tokyo Metrop. Inst. of Med. Sci. (RINSHOKEN), Tokyo, Japan, ⁴Saitama Med. Sch., Biomed. Res. Center, Saitama, Japan)
- N193 The environmental chemicals bisphenol A exerts thyroid hormone like effects on mouse oligodendrocyte precursor cell**
 ○Chika Seiwa¹, Jin Nakahara¹, Tomomi Sakai¹, Taisen Iguchi^{2,3}, Hiroaki Asou^{1,3} (¹Glial Cell Res. Group, Tokyo Metrop. Inst. of Gerontol., ²Center for Biosci., Okazaki Natl. Res. Inst., Okazaki, Japan, ³CREST)
- N194 Expression of serine protease Protease M/neurosin/zyme in demyelination**
 ○Yoshio Bando, Yoshiko Nagai, Yuji Sakamaki, Yutaka Tadano, Shigetaka Yoshida (Dept. of Anat. I, Asahikawa Med. Coll., Hokkaido, Japan)
- N195 The role of myelin sulfatide on the axonal organization may be different in the CNS and PNS axons.**
 ○Tomiko Hoshi^{1,2}, Tomoko Ishibashi¹, Ayaka Suzuki¹, Hiroko Baba¹ (¹Dept. of Mol. Neurobiol., Tokyo Univ. of Pharm. and Life Sci., Tokyo, Japan, ²Lab. of Environ. Chemodynamics, Tokyo Univ. of Pharm. and Life Sci., Tokyo, Japan)
- N196 The complete structures of two novel multi-sulfated oligosaccharides containing HNK-1 carbohydrate epitope(s) in bovine P0 glycoprotein**
 ○Kunio Kitamura, Jianhong Yan, Masahiko Nomura (Dept. Physiol., Saitama Med. Sch., Saitama, Japan)
- N197 The proteolipid protein promoter is activated in tangentially migrating GABAergic neurons and oligodendrocytes during development of the cerebral cortex**
 ○Yuko Fujita¹, Wendy Macklin² (¹Dept. of Physiol., Keio Univ., Sch. of Med., Tokyo, Japan, ²Dept. of Neurosci., Lerner Res. Inst., The Cleveland Clinic Foundation, Cleveland, USA)

Blood-Brain Barrier

- N198 Characterization of aluminum citrate transport at the blood-brain barrier**
 ○Kazuki Nagasawa¹, Shingo Itoh¹, Ikumi Tamai², Akira Tsuji³, Sadaki Fujimoto¹ (¹Dept. of Environ. Biochem., Kyoto Pharm. Univ., Kyoto, Japan, ²Fac. of Pharm. Sci., Tokyo Univ. of Sci., Tokyo, Japan, ³Fac. of Pharm. Sci., Kanazawa Univ., Kanazawa, Japan)

Neuroimmunology

- N199 Peripheral injection of lipopolysaccharide has effect on the expression of inflammatory cytokine at locus coeruleus**
 ○Yoko Kaneko¹, Keiji Mori¹, Akira Nakashima¹, Kentaro Fujiwara², Ikuko Nagatsu³, Akira Ota¹ (¹Dept. of Physiol., Fujita Health Univ. Sch. of Med., Toyoake, Japan, ²Dept. of Intern. Med., Fujita Health Univ. Sch. of Med., Toyoake, Japan, ³Dept. of Anat., Fujita Health Univ. Sch. of Med., Toyoake, Japan)
- N200 Effect of peripheral lipopolysaccharide treatment on murine olfactory bulb**
 ○Keiji Mori¹, Kaneko Yoko S.¹, Akira Nakashima¹, Kentaro Fujiwara², Ikuko Nagatsu³, Akira Ota¹ (¹Dept. of Physiol., Fujita Health Univ. Sch. of Med., Toyoake, Aichi, JAPAN, ²Dept. of Intern. Med., Fujita Health Univ., Toyoake, Aichi, JAPAN, ³Dept. of Anat., Fujita Health Univ. Sch. of Med., Toyoake, Aichi, JAPAN)
- N201 PEDF stimulates expression of inflammatory-related genes in glial cells**
 ○Tomomi Sanagi¹, Masako Nishio¹, Joan P Schwartz³, Takeshi Yabe^{1,2}, Haruki Yamada^{1,2} (¹Kitasato Inst. for Life Sci., Kitasato Univ., Japan, ²Oriental Med. Res. Center of Kitasato Inst., Tokyo, Japan, ³Neurotrophic Factor Section, NINDS, NIH, Bethesda, MD 20892)

- N202 Inbred mouse strain difference affects in Interleukin-1 response in the brain.**
 ○Noriko Tsuda, Hiroyuki Nawa (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ.)
- N203 Neuroimmunology of neurosteroids and endocrine disruptors through common Gq/11 coupled receptor**
 ○Akira Yoshida, Hitoshi Uchida, Makoto Inoue, Kaori Mizota, Hiroshi Ueda (Div. of Mol. Pharm. and Neurosci., Nagasaki Univ., Grad. Sch. of Biomed. Sci.)
- N204 Peripheral myeline protein P0 is one of the autoantigens for human inflammatory polyneuropathies**
 ○Akiko Hayashi¹, Naoaki Masuo¹, Yoshihide Yamaguchi¹, Masato Ohnishi¹, Toshihide Takeda¹, Keiichiro Susuki², Nobuhiro Yuki², Hiroko Baba¹ (¹Dept. of Mol. Neurobiol., Sch. of Pharm., Tokyo Univ. of Pharm. and Life Sci., Tokyo, Japan, ²Dept. of Neurol., Dokkyo Univ. Sch. of Med.)

Pattern Formation

- N205 Alignment of interneurons in the developing cerebral cortex**
 ○Masato Yozu^{1,2}, Hidenori Tabata^{1,2}, Kazunori Nakajima^{1,2} (¹Dept. of Anat., Keio Univ. Sch. of Med., Tokyo, Japan, ²Dept. of Mol. Neurobiol., Inst. of DNA Med., Jikei Univ. Sch. of Med., Tokyo, Japan)
- N206 Cell adhesion properties of the migrating cortical neurons**
 ○Itsuki Ajioka^{1,2}, Hidenori Tabata^{1,2}, Kazunori Nakajima^{1,2} (¹Dept. of Anat., Keio Univ. Sch. of Med., Tokyo, Japan, ²Dept. of Mol. Neurobiol., Inst. of DNA Med., Jikei Univ. Sch. of Med., Tokyo, Japan)
- N207 A new strategy for brain cell fate mapping by in utero DNA electroporation**
 ○Tetsushi Kagawa¹, Toshihiro Inoue¹, Kimi Araki², Eiko Nakahira³, Kazuhiro Ikenaka³, Tetsuya Taga¹ (¹Div. of Cell Fate Modulation, Inst. of Mol. Embryol. and Genet., Kumamoto Univ., Kumamoto, Japan, ²Div. of Dev. Genet., Inst. of Mol. Embryol. and Genet., Kumamoto Univ., Kumamoto, Japan, ³Div. of Mol. Neurobiol., Natl. Inst. for Physiol. Sci., Okazaki, Japan)

Cellular Differentiation

- N208 Astrocyte-derived factors instruct differentiation of mouse and primate embryonic stem cells into neurons (MS8-1)**
 ○Takashi Nakayama¹, Tomoko Momoki-Soga¹, Kazuhiko Yamaguchi², Yutaka Suzuki³, Yasushi Kondo³, Nobuo Inoue¹ (¹Dept. of Biochem., Yokohama City Univ. Sch. of Med., Yokohama, Japan, ²Lab. for Memory and Learning, Brain Sci. Inst., RIKEN, Wako, Japan, ³Adv. Med. Res. Lab., Tanabe Seiyaku Co., Ltd., Osaka, Japan, 532-8505)
- N209 NRSF/REST and DNA methylation regulate cell type specific expression of BRINP1 (BMP-2 and Retinoic acid Inducible Neural-specific Protein 1) (MS8-2)**
 ○Toshiyuki Nakatani, Ichiro Matsuoka (Lab. of Neurosci., Grad. Sch. of Pharm. Sci., Hokkaido Univ., Sapporo, Japan)
- N210 Histological and biochemical study of Sox21 transcriptional factor (MS8-3)**
 ○Hiroyuki Ohba¹, Tatsuyuki Chiyoda¹, Emmy Endo¹, Masato Yano¹, Yoshika Hayakawa¹, James Hirotaka Okano^{1,2}, Hideyuki Okano^{1,2} (¹Dept. of Physiol., Keio Univ. Sch. of Med., Tokyo, Japan, ²CREST, JST)
- N211 Lineage analysis on forebrain oligodendrocyte (MS8-5)**
 ○Hirohide Takebayashi¹, Noritaka Masahira^{1,2}, Kenji Tanaka¹, Keiji Shimizu², Kazuhiro Ikenaka¹ (¹Natl. Inst. for Physiol. Sci., ²Dept. of Neurosurg., Kochi Med. Sch.)
- N212 Characterization of cellular response to cortical cryo-injury**
 ○Satomi Haga, Kouko Tatsumi, Akio Wanaka (The Second Dept. of Anat., Nara Med. Univ., Kashihara, Nara, Japan)
- N213 Transcriptional regulation of the tyrosine hydroxylase gene by Ras-MEK cellular signaling**
 ○Takahiro Suzuki¹, Hiroshi Ichinose^{1,2} (¹The Inst. for Compr. Med. Sci., Fujita Health Univ., Toyoake, Japan, ²Dept. of Life Sci., Grad. Sch. of Biosci. and Biotechnol., Tokyo Inst. of Technol., Yokohama, Japan)

- N214 Electric homeostasis and the cell fate decision in stem cells**
 ○Masahisa Yamada^{1,2}, Kentaro Tanemura³, Michiru Ozawa³, Hideaki Mizuno⁴, Atsushi Miyawaki⁴, Kyoko Takeuchi², Masako Kawano², Masaharu Ogawa², Takashi Kondo³ (¹Mol. Neuropathol. Group, Brain Sci. Inst., RIKEN, 2-1 Hirosawa, Wako, Saitama, Japan, ²Lab. for Cell Culture Development, Brain Sci. Inst., RIKEN, 2-1 Hirosawa, Wako, Saitama, Japan, ³Brain Development Res. Group, Brain Sci. Inst., RIKEN, 2-1 Hirosawa, Wako, Saitama, Japan, ⁴Lab. for Cell Function Dynamics, Brain Sci. Inst., RIKEN, 2-1 Hirosawa, Wako, Saitama, Japan)
- N215 Genetic and Biochemical Analyses of Neuron-Specific RNA Binding Protein Hu**
 ○James Hirotaka Okano^{1,2}, Wado Akamatsu^{1,2}, Masato Yano¹, Hideyuki Okano^{1,2} (¹Dept. of Physiol., Keio Univ. Sch. of Med., Tokyo, Japan, ²CREST, JST)

Axonal Outgrowth and Network Formation

- N216 Polarized localization of SHPS-1 and its ligand CD47 in hippocampal neurons**
 ○Hiroshi Ohnishi, Yuka Sakazume-Kaneko, Ryuji Sato, Akiko Hayashi, Kyoko Tomizawa, Hisae Kobayashi, Hideki Okazawa, Takashi Matozaki (Biosignal Res. Center, Inst. for Mol. and Cell. Regul., Gunma Univ., Gunma, Japan)
- N217 Expression of NDRG4 protein isoforms by alternative promoter usage and alternative splicing in rat brain**
 ○Shigeki Hongo, Akihiko Maeda, Akira Miyazaki (Dept. of Biochem., Showa Univ. Sch. of Med., Tokyo, Japan)
- N218 Aβ(25-35)-induced axonal atrophy, synaptic loss and memory impairment were recovered by ginsenoside Rb₁ and its metabolite M1**
 ○Chihiro Tohda, Noriaki Matsumoto, Kun Zou, Meselhy Meselhy, Itsuki Hashimoto, Katsuko Komatsu (Res. Center for Ethnomed., Inst. of Natural Med., Toyama Med. and Pharm. Univ.)
- N219 Neurotrophic effect of Sema4D on neurite outgrowth**
 ○Chie Kobayashi¹, Kenta Masuda², Tatsuo Furuyama³, Shinobu Inagaki¹, Shinobu Inagaki² (¹1st Dept. Oral and Maxilla-Facial Surg., Osaka Univ. Grad. Sch. Dentistry, Osaka, Japan, ²Group Neurobiol., Sch. Allied Health Sci., Osaka Univ. Fac. Med., Yamadaoka 1-7, Suita, Osaka 565-0871 Japan, ³Dept. 2nd Anat. and Neurosci., Osaka Univ. Fac. Med., Suita, Osaka 565-0871 Japan)
- N220 Synaptic reconstructing effects of Withanolide A and Withanoside VI in rat cortical neurons degenerated by Aβ25-35**
 ○Tomoharu Kuboyama, Chihiro Tohda, Katsuko Komatsu (Res. Center for Ethnomedicines, Inst. of Natural Med., Toyama Med. & Pharm. Univ., Toyama, Japan)
- N221 Proteomic analysis of regionally specific molecules in rat embryonic cerebral neocortex**
 ○Yoshihide Yamaguchi, Tomonori Mashiba, Saori Yamada, Hiroko Baba (Dept. of Mol. Neurobiol., Tokyo Univ. of Pharm. and Life Sci., Tokyo, Japan)

Trophic Factor

- N222 Regulated Release of EGF-like Molecules from Rat Striatal Culture: Their Trophic Activity on (MS5-1) Midbrain Dopaminergic Neurons.**
 ○Yuriko Iwakura, Ying-Shan Piao, Nobuyuki Takei, Hiroyuki Nawa (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)
- N223 BDNF activates translation elongation in cultured cortex neurons. (MS5-2)**
 ○Naoko Inamura, Hiroyuki Nawa, Nobuyuki Takei (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)
- N224 Adenoviral gene transfer of growth inhibitory factor (metallothionein-III) prevents degeneration of (MS5-3) injured adult rat motoneurons**
 ○Tsuyoshi Sakamoto¹, Yoko Kawazoe¹, Yoko Uchida², Isao Hozumi³, Takashi Inuzuka³, Kazuhiko Watabe¹ (¹Dept. of Mol. Neuropathol., Tokyo Metrop. Inst. for Neurosci., ²Gene Expression Res. Group, Tokyo Metrop. Inst. of Gerontol., ³Dept. of Neurol., Gifu Univ. Sch. of Med.)

- N225 The role of calbindin-D28k in the neuroprotective action of basic fibroblast growth factor -in vitro (MS5-4) assay by using neurons derived from calbindin-D28k KO mice-**
 ○Taisuke Kadoshima, Norihito Murayama, Tetsushi Oka, Keiji Sugimura, Shizuo Nakamura, Tomochika Ohno (Daiichi Suntory Biomed. Res. Co., Ltd., Osaka, Japan)
- N226 PITUITARY ADENYLATE CYCLASE- ACTIVATING POLYPEPTIDE (PACAP) REGULATES NEURAL STEM CELL FATE IN VITRO AND IN VIVO (MS5-5)**
 ○Shigeki Ohta¹, Weiss Samuel² (¹Neuro-immunol. Res. Group, Keio Univ. Sch. of Med., ²Genes & Development Res. Group, Univ. of Calgary Fac. of Med., Calgary, Canada)
- N227 Signal transduction pathways involved in riluzole-stimulated BDNF production in the rat hippocampus**
 ○Ritsuko Katoh-Semba, Ritsuko Kaneko, Satoko Kitajima, Kanefusa Kato (Inst. for Dev. Res., Aichi Human Service Center, Aichi, Japan)
- N228 A DIPEPTIDE, LEU-ILE, HAS NEUROPROTECTIVE EFFECTS AGAINST DOPAMINERGIC DENERVATION**
 ○Atsumi Nitta¹, Hirofumi Nishioka², Takuya Hori², Keiko Maruyama², Yoshiko Furukawa², Toshitaka Nabeshima¹, Shoei Furukawa² (¹Dept. of Neuropsychopharm. and Hosp. Pharm., Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan, ²Lab. of Mol. Biol., Gifu Pharm. Univ., Gifu, Japan)
- N229 Coexpression of a chemokine, MCP-1, with a neurotrophic factor, GDNF, in microglia/macrophages around the transection site of the rat spinal cord**
 ○Manabu Hashimoto, Yuichiro Nishimura, Shoei Furukawa (Lab. of Mol. Biol., Gifu Pharm. Univ., Gifu, Japan)
- N230 Epidermal growth factor (EGF)/ErbB signaling regulates the expression of synaptic proteins in rat cerebral cortex**
 ○Daisaku Yokomaku, Hussam Jourdi, Tadasato Nagano, Makoto Mizuno, Nobuyuki Takei, Hiroyuki Nawa (Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan)
- N231 The outgrowth of neurites was induced by radicicol and geldanamycin in NG108-15 cells and Nero2A cells.**
 ○Mamoru Sano (Dept. of Biol., Kyoto Prefect. Univ. of Med., Kyoto, Japan)
- N232 Supportive function of meninges in cortical development**
 ○Takao Honda^{1,2}, Hidenori Tabata^{1,2}, Kazunori Nakajima^{1,2} (¹Dept. of Anat., Keio Univ. Sch. of Med., Tokyo, Japan, ²Dept. of Mol. Neurobiol., Inst. of DNA Med., Jikei Univ. Sch. of Med., Tokyo, Japan)
- N233 Chronic Epidermal growth factor (EGF) application Down-regulates Synaptic Function in Neocortical GABAergic Neurons**
 ○Tadasato Nagano, Hisaaki Namba, Nobuyuki Takei, Hiroyuki Nawa (Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata 951-8585, Japan)
- N234 The role of calbindin-D28k in the neuroprotective action of basic fibroblast growth factor**
 ○Takafumi Noshita, Norihito Murayama, Ryoko Ogino, Tetsushi Oka, Shizuo Nakamura, Tomochika Ohno (Daiichi Suntory Biomed. Res., Osaka, Japan)
- N235 PEDF stimulates expression of survival-related genes in cerebellar granule cells**
 ○Kazuko Kanemitsu¹, Mayumi Shimizu¹, Joan P Schwartz³, Takeshi Yabe^{1,2}, Haruki Yamada^{1,2} (¹Kitasato Inst. for Life Sci., Kitasato Univ., Tokyo, Japan, ²Oriental Med. Res. Center of Kitasato Inst., Tokyo, Japan, ³Neurotrophic Factors Sect., NINDS, NIH, Bethesda, MD 20892)
- N236 Development of nociceptive neurons of dorsal root ganglia in oncostatin M-deficient mice**
 ○Yoshihiro Morikawa¹, Shinobu Tamura¹, Atsushi Miyajima², Emiko Senba¹ (¹Dept. of Anat. & Neurobiol., Wakayama Med. Univ., Wakayama, Japan, ²Inst. of Mol. and Cell. Biosci., Univ. of Tokyo, Tokyo, Japan)
- N237 Change of p40BBP in degenerating neuronal cells**
 ○Tokiko Hama¹, Ritsuko Katoh-Semba² (¹Mitsubishi Kagaku Inst. of Life Sci., Tokyo Japan, ²Aichi Human Serv. Center, Aichi Japan)
- N238 Oncostatin M receptor β is expressed in nociceptive primary sensory neurons**
 ○Shinobu Tamura¹, Yoshihiro Morikawa¹, Atsushi Miyajima², Emiko Senba¹ (¹Dept. of Anat. & Neurobiol., Wakayama Med. Univ., Wakayama, Japan, ²Inst. of Mol. and Cell. Biosci., Univ. of Tokyo, Tokyo, Japan)

- N239 Analysis of neuroprotective effects of pigment epithelium-derived factor (PEDF) on animal model of Parkinson's disease.**
 ○Toru Yasuda¹, Keiichiro Wada¹, Ying Liu¹, Tsuyoshi Furuya¹, Masafumi Onodera², Hideki Mochizuki¹, Yoshikuni Mizuno¹ (¹Dept. of Neurol., Juntendo Univ. Sch. of Med., Tokyo, Japan, ²Dept. of Hematol., Inst. of Clin. Med., Univ. of Tsukuba, Tsukuba, Japan)
- N240 Genipin, a herbal neurotrophic iridoid compound, directly binds to and activates of nitric oxide synthase**
 ○Kenzo Chiba¹, Tadatoshi Ohkubo², Matsumi Yamazaki¹, Tetsuro Mohri¹ (¹Dept. of Biodynamics, Fac. of Pharm. Sci., Hokuriku Univ., Kanazawa, Ishikawa, Japan, ²Kyukyu Pharm. Co., Ltd., Kosugimati, Toyama, Japan,)
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 ○Yuji Shishido¹, Takayuki Tanaka¹, Yuriko Iwakura¹, Shigeki Higashiyama², Nobuyuki Takei¹, Hiroyuki Nawa¹ (¹Dept. of Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan, ²Dept. of Med. Biochem., Ehime Univ. Sch. of Med., Ehime, Japan)

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 ○Keiko Kohama (Dept. of Pharm.1, Osaka Univ. Med. Sch., Osaka, Japan)
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 ○Hironobu Yamasaki¹, Yukiko Nakamura¹, Kazutada Watanabe², Sadao Shiosaka¹ (¹Dept. of Biosci., Nara Inst. of Sci. and Technol. (NAIST), Nara, Japan, ²Dept. of BioEngineering, Nagaoka Univ. of Technol., Niigata, Japan)
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 ○Tsuji Lyuji, Yamashita Toshihide, Tohyama Masaya (Dept. of Anat. and Neurosci., Osaka Univ. Grad. Sch. of Med., Osaka, Japan)
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 ○Tetsuya Fujisawa¹, Yuri Kasama¹, Daisuke Ochiai¹, Akira Okuno¹, Yasushi Shimoda¹, Yasuo Takeda², Kazutada Watanabe¹ (¹Dept. of Bioeng., Nagaoka Univ. of Technol., Nagaoka, Japan, ²Dept. of Clin. Pharm., Kagoshima Univ. Fac. of Med., Kagoshima, Japan)
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 ○Machiko Mataumoro, Hiroko Togashi, Ken-ichi Ueno, Hiroshi Otani, Taku Yamaguchi, Mitsuhiro Yoshioka (Dept. of Pharm., Hokkaido Univ. Sch. of Med., Sapporo, Japan)

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 ○Naoko Takeshima, Yasuhiro Yoshioka, Kunitomo Imazu, Akiko Yamamuro, Sadaaki Maeda (Dept. Pharmacother., Fac. Pharmaceut. Sci., Setsunan Univ., Osaka, Japan)
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 ○Takayuki Negishi^{1,3}, Yoshiyuki Ishii¹, Shigeru Kyuwa¹, Yoichiro Kuroda^{2,3}, Yasuhiro Yoshikawa^{1,3} (¹Dept. of Biomed. Sci., Grad. Sch. of Agric. and Life Sci., The Univ. of Tokyo, Japan, ²Dept. of Mol. and Cell. Neurobiol., Tokyo Metrop. Inst. for Neurosci., Japan, ³Core Res. for Evolutional Sci. and Technol., Japan Sci. and Technol. Corp., Japan)

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- N255 Mechanism of mPer1 induction through CaM kinase II activation in the suprachiasmatic nucleus (MS6-4)**
 ○Kohji Fukunaga¹, Kazumi Nomura², Shun Yamaguchi³, Hitoshi Okamura³, Yusuke Takeuchi¹ (¹Dept. Pharmacol. Grad. Sch. Pharm. Scis. Tohoku Univ. Sendai, Japan, ²Dept. Pharmacol. Kumamoto Univ. Sch. of Med. Kumamoto, Japan, ³Dept. Brain Scis. Kobe Univ. Grad. Sch. of Med. Kobe, Japan)
- N256 Abnormal light-induced phase shift in mice lacking pituitary adenylate cyclase-activating polypeptide (PACAP)**
 ○Hitoshi Hashimoto¹, Chihiro Kawaguchi¹, Yasushi Isojima², Katsuya Nagai², Kazuhiro Tanaka¹, Norihito Shintani¹, Akemichi Baba^{1,3} (¹Lab. of Mol. Neuropharm., Grad. Sch. of Pharm. Sci., Osaka Univ., Osaka, Japan, ²Div. of Protein Metabolism, Inst. for Protein Res., Osaka Univ., Osaka, Japan, ³Lab. of Mol. Pharm., Grad. Sch. of Med., Osaka Univ., Osaka, Japan)

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- N257 Insulin-mediated glucose transport system in the hypothalamus of ob/ob mice**
 ○Tadasuke Komori¹, Yoshihiro Morikawa¹, Shinobu Tamura¹, Kishio Nanjo², Emiko Senba¹ (¹Dept. of Anat. and Neurobiol., Wakayama Med. Univ., Wakayama, Japan, ²The First Dept. of Intern. Med., Wakayama Med. Univ., Wakayama, Japan)

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会長講演

Researches on Neurological Diseases in the New Millennium.

Shoji Tsuji

President of the 46th Annual Meeting of Japanese Society for Neurochemistry

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In the past 46 years since the establishment of Japanese Society for Neurochemistry, we have experienced marvelous achievements in our understanding of neurological diseases. In particular, rapid progresses in molecular genetics have made it possible to identify the causative genes for a number of hereditary neurological diseases. Neurodegenerative diseases including Huntington disease and most of the autosomal dominant spinocerebellar ataxias can now be understood on the basis of expansion of CAG trinucleotide repeats coding for polyglutamine stretches. There are now accumulating evidences indicating that nuclear transport and intranuclear accumulation of mutant proteins with expanded polyglutamine stretches lead to transcriptional dysregulation of genes including cAMP responsive genes. Development of therapeutic measures for polyglutamine diseases aiming at the molecular targets is not any more a dream, but a reality. Given the entire nucleotide sequences of the whole human genome, we foresee explosion of our researches in the near future. Identification of susceptibility genes in sporadic neurological diseases will be the main focus of the researches. This is particularly important, since sporadic neurological diseases comprise the majority of neurological diseases. Another development will be in the field of psychiatric diseases. The molecular dissection of the disease mechanisms of psychiatric diseases will soon be accomplished based on modern disciplines of molecular genetics. To make these approaches fruitful, development of multicenter-based research paradigm will be crucial. Overall, the research focus in the new millennium will be changed from "how to care neurological diseases" to "how to cure neurological diseases". To make this dream come true, we need to change our research paradigm. In developing new therapeutic measures, we need new research frameworks integrating various disciplines including *in vitro* studies, cellular biology, animal models, neuropathology, and clinical neurology. It should be noted that "*in vitro*" experiments observe phenomenon occurring in minutes to hours, while human diseases take place in the order of decades. Without such integration as a research paradigm, understanding of the processes of diseases would be difficult.

PL-1

Searching for Novel Alzheimer's Disease Genes on Chromosome 10

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Using plasma amyloid β protein (A β 42) levels as an intermediate, quantitative phenotype for late onset Alzheimer's disease (LOAD), we previously obtained significant linkage at ~ 80 centimorgans (cM) on chromosome 10. Linkage to the same region was obtained independently in a study of affected LOAD sib-pairs. Together, these two studies provide strong evidence for one or more novel LOAD loci on chromosome 10 that act to increase A β 42. Several strong candidate genes (*VR22*, *PLAU*, *IDE*) lie within the 1-lod support interval for linkage. *VR22* is a large (1.7 Mb) gene located at 80 cM that encodes α -T catenin, which is a binding partner of β catenin. This makes *VR22* an attractive candidate gene because β catenin interacts with presenilin 1, which has many mutations that elevate A β 42 and cause early onset familial AD. We identified two intronic *VR22* SNPs (4360 and 4783) in strong linkage disequilibrium (LD) that showed highly significant association ($p=0.0001$ and 0.0006) with plasma A β 42 in 10 extended LOAD families. This association clearly contributed to the linkage at ~ 80 cM because the lod scores decreased when linkage analysis was performed conditional upon the *VR22* association. Bounding of the association region using multiple SNPs showed *VR22* to be the only confirmed gene within the region of association. These findings indicate that *VR22* has variant(s) which influence A β 42 and contribute to the previously reported linkage for plasma A β 42 in LOAD families. The *PLAU* gene encodes urokinase-type plasminogen activator (uPA), which converts plasminogen to plasmin. *PLAU* is an attractive candidate because A β aggregates, which are widely believed to play an important role in AD, induce *PLAU* expression thereby increasing plasmin, which degrades both aggregated and non-aggregated forms of A β . We analyzed a missense C/T polymorphism in exon 6 of *PLAU* (*PLAU*_1=rs2227564) in which the minor T allele causes a proline to leucine change (P141L) within the kringle domain of *PLAU* at the junction between two β -pleated sheets. We analyzed *PLAU*_1 for association with AD in six case-control series and performed meta-analysis to evaluate these six series in conjunction with four additional case-control series reported by Riemenschneider et al. The CT and TT *PLAU*_1 genotypes showed significant association ($p<0.001$) with an overall estimated OR (CT+TT vs. CC) of 1.4 (1.2-1.7). The CT and TT genotypes of *PLAU*_1 were also associated with significant, age-dependent elevation of plasma A β 42 in twenty-four extended LOAD families that we analyzed ($p=0.0006$, analyzing CT+TT and CC genotypes). In knockout mice lacking the *PLAU* gene, plasma A β was significantly elevated. The insulin degrading enzyme is known to degrade brain A β in vivo, and the Brookes group in the Karolinska Institute has identified haplotypes on the chromosome 10q region harboring *IDE* that show highly significant association with intermediate AD phenotypes and with risk for AD in multiple LOAD case control series. One series (MCR, 183 age-matched case-control pairs) that we analyzed did not show association ($p=0.43$) with the six haplotypes in the 276 kb region spanning three genes (*IDE*, *KNSL1*, and *HHEX*), previously shown to associate with LOAD. The other series (MCJ, 93 age-matched case-control pairs) showed significant ($p=0.003$) association with these haplotypes. In our extended LOAD families, these haplotypes also showed significant association with plasma A β 42. In summary, we studied three strong candidate genes within the linkage region on chromosome 10 and all three had genetic variants that showed significant association with plasma A β 42 and/or LOAD. These genes are widely spaced so the associating variants in each gene were independent and not in linkage disequilibrium with one another. The associating variants in *VR22* and *IDE* involved intronic SNPs unlikely to have deleterious functional effects, and we have so far been unable to identify putative functional variants (susceptibility alleles) in linkage disequilibrium with the associating variants. The significant associations we observed replicated far more than would be expected statistically when they were analyzed in multiple case-control series involving more than 1500 cases and 1500 controls, but this replication was not as reliable or consistent as that for ApoE alleles. There are a number of factors that can make true associations difficult to replicate and susceptibility alleles difficult to identify. In the three genes studied, we believe the major factor confounding definitive identification of susceptibility alleles may be that each gene has a large mutational target and a multiplicity of rare susceptibility alleles, which collectively confer risk for LOAD. We are testing this hypothesis by searching for all variants in the conserved region of these genes in a large number of AD cases from series showing highly significant association.

PL-2

Regulatory mechanisms of synaptic transmission in the neural circuit

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Glutamatergic neurotransmission is mediated by AMPA/kainate receptors, NMDA receptors and G protein-coupled metabotropic receptors (mGluRs). We characterized the family of mGluRs and NMDA receptors by a functional cloning that combined *Xenopus* oocyte expression system and electrophysiology. However, how glutamatergic transmission is regulated in the neural circuit largely remains elusive. We first discuss synaptic mechanisms of photoreceptors-bipolar cells in the retina, indicating that mGluR6 and AMPA receptor discriminate light and dark signals in response to a common glutamate transmitter. We then discuss how the cerebellar circuit is regulated with different types of neurotransmitter receptors. The cerebellar network consists of mossy fibers, granule cells, parallel fibers and Purkinje cells. Besides this main network, Golgi cells cause feed-back inhibition on granule cells. Golgi cells were selectively ablated with immunotoxin-mediated cell targeting and this ablation revealed that the glutamatergic and GABAergic transmissions are concertedly and adaptively regulated at the mossy fiber-granule cell synapses and play a pivotal role in motor coordination. Besides AMPA receptors, mGluR1 and mGluR2 are highly distributed postsynaptically at Purkinje cells and Golgi cells, respectively. Our study indicated that mGluR1 and P-type Cav 2.1 Ca^{2+} channel form a direct protein assembly and contribute to spatiotemporal regulation of intracellular Ca^{2+} signaling in Purkinje cells. Our study also disclosed that the cooperative actions of AMPA receptors and inhibitory mGluR2 are essential for dynamic modulation of the Golgi cell excitability. The regulatory synaptic mechanisms in the neural circuit will be discussed in my presentation.

PL-3

ASSEMBLY OF A NERVOUS SYSTEM — THE INITIAL STRATEGY

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One of the central problems of neurobiology is to understand the principles that are used to assemble the central nervous system during embryonic development. Recent studies have revealed the initial strategy at the molecular level for constructing part of the central nervous system of *Drosophila*, although many details are unknown. The discussion will focus on the *vnd/NK-2* homeobox gene, which encodes a DNA binding protein that regulates gene expression. Neural pathways of development are initiated independently in three longitudinal columns of neuroectodermal cells that give rise to the ventral nerve cord. The Vnd/NK-2 homeodomain protein initiates neural development of the ventral portion of the neuroectoderm, and Intermediate neuroblast defective (Ind) homeodomain protein initiates neural development in the intermediate column of neuroectoderm. The mechanism of initiating neural development in the dorsal neuroectoderm column has not been identified; however, Muscle segment homeodomain (Msh) is expressed in the dorsal column of neuroectoderm and is required for specification of some dorsal neuroblasts. A pattern of cells that express the *vnd/NK-2* gene is generated by activation and repression of the *vnd/NK-2* gene. Vnd/NK-2 protein was detected in 11 of the 30 neuroblasts per hemisegment in *Drosophila* embryos. Fragments of DNA from the 5'-flanking region of the *vnd/NK-2* gene were inserted upstream of an enhancerless β -galactosidase gene in P-element and used to generate transgenic fly lines. Antibodies directed against Vnd/NK-2 and β -galactosidase proteins then were used in double-labeled experiments to correlate the expression of β -galactosidase and Vnd/NK-2 proteins in identified neuroblasts. The results show that at least three regions of DNA regulate the expression of the *vnd/NK-2* gene, that the *vnd/NK-2* gene can be activated in different ways in different neuroblasts, and that the pattern of *vnd/NK-2* gene expression in neuroblasts of the ventral nerve cord is the sum of partial patterns. Hence, part of the information that determines a pattern of neural cells in the central nervous system of developing embryos resides in the nucleotide sequences that regulate the expression of the *vnd/NK-2* gene.

ISN-1

Polyglutamine toxicity in spinal and bulbar muscular atrophy

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Spinal and bulbar muscular atrophy is a hereditary motor neuron disease caused by expansion of a polyglutamine tract in the androgen receptor. A toxic gain of function mechanism for this disorder is likely shared with other polyglutamine expansion neurodegenerative diseases, including Huntington's disease. Evidence indicates that the neuronal nucleus may be the primary site of pathology, and that transcriptional dysregulation due to sequestration and depletion of CREB binding protein and other important nuclear factors may be involved. The downstream effects of altered transcription are currently under investigation. Possible therapeutic approaches include histone deacetylase inhibition and androgen depletion. We have done a screen for drugs that block toxicity of the mutant androgen receptor in cell culture as part of a drug screening consortium sponsored by our institute, and hits from this screen are now being confirmed and further characterized.

A family with a related phenotype, autosomal dominant distal spinal and bulbar muscular atrophy with vocal fold paralysis, was found to have a mutation in the gene for the major subunit of dynactin, a protein that mediates retrograde axonal transport. This finding indicates that defects in axonal transport may play a role in this and other forms of motor neuron disease.

ISN-2

Intervention of nuclear transport of androgen receptor

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Spinal and bulbar muscular atrophy (SBMA) is a late-onset motor neuron disease affecting only males. Both heterozygous and homozygous females are usually asymptomatic. The molecular basis of SBMA is the expansion of a trinucleotide CAG repeat in the first exon of the androgen receptor (AR) gene, which encodes the polyglutamine (polyQ) tract. The precise pathophysiology has not been elucidated, and there has been no therapy for the polyQ diseases.

We generated Tg mice carrying full-length AR containing 97 CAGs driven by a chicken β -actin promoter. The male Tg mice exhibited marked progressive motor impairment and nuclear accumulation of mutant AR, but neurological phenotypes were not observed or far less severe in the females. Castration dramatically prevented the phenotypic expression in the male Tg mice by diminishing the nuclear accumulation of mutant AR. In contrast, the female Tg mice demonstrated marked deterioration of symptoms by testosterone administration. Leuporelin, an LHRH agonist that reduces testosterone release from the testis, also rescued motor dysfunction and nuclear accumulation of mutant AR in the male Tg mice.

Molecular chaperones, HSP70 and HSP40, showed preventive effects in a SBMA cell model. To analyze therapeutic effects of the molecular chaperone in vivo, we crossbred these Tg mice with mice over-expressing HSP70. High levels of HSP70 expression rescued motor impairments by re-folding mutant AR and accelerating its degradation.

Transcriptional dysregulation is implicated in the pathogenesis of polyQ diseases. Nuclear localized polyQ proteins interact transcriptional factors, resulting in the decreased acetylation of histone. Sodium butyrate, a histone deacetylase inhibitor, ameliorated neurological dysfunction in our mouse model, although its therapeutic dose appears to be in a narrow range.

Our findings reiterate the importance of nuclear localized and misfolded mutant protein in the disease mechanism, and indicate approaches to effective treatment for SBMA as well as other polyQ diseases.

ISN-3

Exploring RNA interference as a therapeutic strategy in polyglutamine disease

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At least nine inherited neurodegenerative diseases are caused by expanded CAG repeats that encode abnormally long polyglutamine tracts in the respective disease proteins. Although the precise molecular events underlying polyglutamine neurodegeneration are still uncertain, growing evidence indicates that polyglutamine expansion confers a neurotoxic property on the disease proteins that is closely linked to protein misfolding and aggregation. Accordingly, efforts to decrease expression of the dominant-acting disease protein may be beneficial. I will describe our laboratories' efforts to develop a novel therapeutic approach for these currently untreatable disorders: the use of small interfering RNAs (siRNA) to suppress expression of dominant disease genes. Using various strategies ranging from in vitro synthesized siRNAs to virally expressed small hairpin RNAs (shRNAs), we have accomplished robust suppression of genes encoding mutant polyglutamine proteins. We further have shown that allele-specific silencing of disease genes with siRNA can be achieved by targeting either a linked single nucleotide polymorphism (SNP) or the disease mutation directly. For the polyglutamine diseases, in which we first determined that preferential targeting of the expanded CAG repeat is not possible, we took advantage of an associated SNP to generate siRNA that exclusively silenced the mutant Machado-Joseph Disease/Spinocerebellar Ataxia Type 3 (MJD/SCA3) allele while sparing expression of the wild type allele. Allele-specific suppression of other dominant disease genes will also be described, including a tau mutation in frontotemporal dementia and the DYT1 mutation in inherited dystonia. These studies establish that siRNAs can be engineered to silence disease genes differing by as little as a single nucleotide, and highlight a potentially important role for SNPs in extending the utility of siRNA in dominantly inherited disorders.

ISN-4

Inhibition of protein aggregation in Alzheimer's and Huntington's disease: implications for therapy

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Neurodegenerative diseases are a group of late-onset progressive diseases in which symptoms may vary significantly. In some cases dementia is the leading symptom, e.g. in Alzheimer's disease (AD), whereas in other diseases such as Huntington's (HD) or Parkinson's disease the loss of motor control is the most prominent symptom. Nevertheless, all these diseases are characterized by the deposition of abnormal proteins that quite frequently show a fibrillar morphology. Hence, the process of aggregate formation may be a major event in the pathogenesis of all neurodegenerative diseases. It has been shown for mouse models of AD and HD that the treatment with small molecules such as β -sheet breaker peptides or the dye Congo red interferes with aggregate formation and slows down disease progression. The insoluble protein aggregates that accumulate in various neurodegenerative diseases have common features such as the formation of cross β sheets. Therefore, it is tempting to speculate that small molecules may be able to hinder the assembly of β sheet structures irrespective of the primary sequence of the aggregating proteins. Recently, screening a library of $\sim 184,000$ small molecules we identified several chemical compounds that inhibit htt fibrillogenesis in a dose-dependent manner. Among these, we identified some molecules that are also able to inhibit the aggregation of the Alzheimer peptide A β . These molecules do not only reduce the amount of aggregates formed but also lead to a perturbation of fibril morphology. We could show that some of these chemicals significantly inhibit HD exon 1 aggregation in a cell culture model of HD as well. Furthermore, these molecules are able to reduce the toxicity of A β fibrils when applied to neuronal cells. These findings provide the basis for a better understanding of the underlying pathomechanisms in AD and HD and may allow the development of novel therapeutic strategies.

OS-1

Molecular base of "attraction" and "aversion" in the nematode *Caenorhabditis elegans*

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How animals sense, discriminate and associate multiple stimuli in the nervous system is a fundamental question in neurobiology. To address this question, we are studying the behavioral plasticity induced by temperature and feeding state in *C. elegans*. After cultivation at a certain temperature under well-fed condition, *C. elegans* migrates to that temperature on a temperature gradient. This thermotaxis behavior turns into cultivation temperature avoidance after being cultivated under food-deprived condition. Wild type animals that had been conditioned to be starved become fully capable of re-migrating to cultivation temperature after they were re-cultivated with food only for a short time (ten minutes). Wild type animals that had been conditioned to migrate to a certain temperature (fed at X) and were re-cultivated under food-deprived condition at a new temperature (starved at Y) avoided the previous cultivation temperature (fed temperature X). Intriguingly, wild type animals that had been cultivated under food-deprived condition at a certain temperature (starved at X) and were re-cultivated with food for a short time (ten minutes) at a new temperature (fed at Y) migrated to the previous temperature (starved temperature X). These results suggest that a switch between attraction and aversion with respect to cultivation temperature occurs very quickly and is induced by change in feeding state. It is also likely that temperature memory and feeding state memory are biologically distinct and work independently, although both mechanisms interact with each other. We isolated mutants defective in some of these responses. Molecular cloning of several genes possibly underlying temperature-feeding state association process is underway.

OS-2

Diversity of cadherin-related neuronal receptor (*CNR*) genes in the brain

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Through development and evolution, the brain is generated as a complex and well-organized system. The human brain is composed of enormous number of diverse cells and their neural networks. Therefore, elucidation of the mechanisms which give rise to the highly organized functions of the mammalian brain warrants an investigation into the molecular mechanisms that generate the huge number of differentiated neurons and govern their specific interactions. Using loss of function in mice we have firstly demonstrated that Fyn tyrosine kinase has significant for generating the brain structure and function. Fyn protein locates under plasma membrane and enriched in growth cone and synapse. In synapse, Fyn regulates synaptic function through phosphorylation of NMDA receptor. To realize molecular function of Fyn in the brain, we have searched Fyn binding receptors from mouse brains and then identified diverse *CNR* family. The *CNR* genes belong to gene clustered protocadherin (*Pcdh*) family. The *CNR/Pcdh* are significant for their genomic organization in gene clusters, their roles in gene regulation, their synaptic localization and genetic diversity in vertebrates, and the frequent somatic mutations in their transcripts. Recently we also detect variation of *CNR/Pcdh* family in the human population. Thus, characterization of *CNR/Pcdh* genes will provide key insights into our understanding of the diversity and specificity of neural networks in the central nervous system during phylogeny and ontogeny.

OS-3

Audiogenic seizure and the brain development: lessons from Neurepin-KO mice

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Fukui Medical University

Epileptic seizures and syndromes, that are estimated to affect 1-3 % of the population, are defined as the occurrence of recurrent seizures. Although most seizures are unprovokable and unforeseen, some stimuli induce seizures even when there exist no obvious structural, metabolic or neurological abnormalities. It has been demonstrated that some strains of mice and rats are susceptible to audiogenic seizures; loud noise induces the seizure when animals were primed (exposed to loud noise during the development) before and these strains were used as one of good experimental models to study epilepsy. In this symposium, I will introduce our Neurepin-KO mice which are susceptible to audiogenic seizure without priming; we identified Neurepin (neuroepithelium-notable) as a novel molecule that is expressed predominantly in the neuroepithelium (ventricular zone) of the developing murine brain. To explore the potential role of Neurepin, we made the Neurepin knockout mice. We also generated the Neurepin-EYFP knock-in mice that expressed N-terminal product of Neurepin followed by EYFP. Although no apparent abnormalities were found in their brains by our conventional histological examinations, they exhibited high susceptibility to the audiogenic seizure: 95 % of these knockout mice and knock-in mice showed wild running, typical feature of the preconvulsive phase of audiogenic seizure triggered by loud noise (11 kHz, 110 dB) and 80 % of these knockout mice and knock-in mice exhibited tonic-clonic convulsion or tonic convulsion at 3 weeks after birth. Possible mechanisms and/or details underlying this susceptibility will be discussed.

OS-4

Genes regulating sexual behavior

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Sexual behavior of *Drosophila* is highly stereotypic. When a male encounters a female, he typically chases and approaches her from behind, touching her abdomen with his foreleg. Then the male generates courtship songs, licks her genitalia, and attempts to copulate. When successful, the copulation persists for about 15 min. We isolated 8 mutants with defects in specific aspects of mating behavior. For example, the *satori* mutant males rarely court females but insistently court males. In addition, the *satori* mutant males are devoid of the male-specific muscle of Lawrence (MOL). It is known that the MOL is formed only in males as it is innervated by male motoneurons. Since the homosexual courtship in *satori* is likely to result from perturbed sex determination of central neurons, the two phenotypes of *satori* can be interpreted as caused by a failure in neural sex determination. *fruitless(fru)* was identified as the gene harboring the *satori* mutation by molecular cloning. The *fru* gene was clearly an element in the sex determination cascade because it has binding sites for Transformer (Tra), a female-determining protein that functions as a splicing factor. Tra-binding to the pre-mRNA of *fru* produces a female-specific mRNA. Subsequently, Tra appears to bind to the female-type mRNA, inducing female-specific translation inhibition. We consider that the presence of Fru masculinizes the neuron while its absence feminizes. In consistent with this, ectopic expression of Fru in females leads to the formation of MOL. We conclude that the absence of Fru in *satori* males results in sexual transformation of a subset of neurons, accompanied by the phenotypic outcome, homosexual courtship and the failure in the MOL formation.

OS-5

Neuronal activities in the primate orbitofrontal cortex in relation to reward expectancy

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The orbitofrontal cortex (OFC) plays important roles in motivation and emotion. I examined delay and pre-instruction activity in primate OFC during the performance of a delayed reaction time task in relation to reward expectancy. In this task, an instruction cue indicated whether reward would be present or absent in the trial. Each set of four consecutive trials constituted one block within which three different kinds of rewards and one trial with no reward were given in a fixed order.

1) Properties of delay activity: Delay activities represented the expectancy of delivery or no-delivery of a reward, the expectancy of a preferred or no-preferred reward, or the expectancy of a specific reward. These delay activities reflected the preference of the animal for each kind of reward and were modulated by the motivational state of the animal. **2) Pre-instruction activity:** There were two types of pre-instruction activities. Step-type activities showed stepwise changes (increase or decrease) toward a trial with a particular outcome within each block of four trials, while Pref-type activities showed changes according to preference of the monkey for the outcome of current trial. These two types of activities may be related to future- and current-reward expectancy, respectively. Although Step-type and Pref-type activities were equally observed during the pre-instruction period, it was found that Pref-type activities were predominant during the delay period. These results suggest that the OFC is considered to play important roles in goal-directed behavior by adjusting the motivational level toward a certain (future or current) outcome throughout the task based on the two kinds of reward expectancy processes.

S1-1

Stress-induced Apoptosis by the ASK1-MAP Kinase Signal

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Actions of pro- and anti-apoptotic factors are often modulated by phosphorylation and dephosphorylation, and thus protein kinases and protein phosphatases contribute to the regulation of life and death decisions made in response to various stresses. Apoptosis signal-regulating kinase 1 (ASK1) is a member of the mitogen-activated protein (MAP) kinase kinase kinase family, which activates both the MKK4/MKK7-JNK and MKK3/MKK6-p38 MAP kinase pathways and constitutes a pivotal signaling pathway in various types of stress-induced apoptosis. We have recently shown by deletion of *Ask1* gene in mice that ASK1 plays essential roles in oxidative stress- and endoplasmic reticulum (ER) stress-induced apoptosis. These stresses are closely linked to various physiological phenomena in the control of cell fate, and the resultant apoptosis is implicated in the pathophysiology of a broad range of human diseases. Moreover, ASK1-p38 pathway was recently found to play essential roles in the innate immune responses. In this presentation, I will review our new findings on the pathophysiological roles of ASK1 in stress responses. Molecular mechanisms by which ASK1 determines cell fate such as differentiation and apoptosis will be also discussed.

S1-2

Nitric Oxide- and ER stress-mediated Apoptosis and Its Regulation by hsp70/DnaJ Chaperone Pairs

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Nitric oxide (NO) is a multifunctional biomolecule involved in a variety of physiological and pathological processes. Excess NO induces apoptosis in some cell types including pancreatic beta-cells, microglia and macrophages. Under these conditions, p53 accumulation was not observed, indicating that DNA damage is not the main trigger of NO-mediated apoptosis. In fact, NO induced apoptosis in microglia from p53 knockout mice. We found that NO depletes ER Ca²⁺, causes ER stress, and leads to apoptosis through the ER stress-pathway, including ATF6 activation and CHOP induction. CHOP is a C/EBP family transcription factor, which is involved in ER stress-mediated apoptosis. Actually NO-mediated apoptosis was prevented by disruption of the CHOP gene.

We also found that cytosolic hsp70/DnaJ (hsp40) chaperone pairs prevent NO-mediated apoptosis. Under these conditions, intrinsic NO production by immunostimulation and CHOP induction was not affected. Apoptosis induced by CHOP over-expression was also prevented by co-expression of hsp70 and DnaJ family member dj1 or dj2. Expression of the hsp70/DnaJ chaperone pair prevented cytochrome c release from mitochondria and pro-apoptotic Bax translocation to mitochondria. These results show that the hsp70/DnaJ chaperone pair prevents NO- and ER stress-mediated apoptosis pathway between CHOP induction and Bax translocation to mitochondria. The precise mechanisms of ER stress-mediated apoptosis and anti-apoptotic effect of molecular chaperones are under investigation.

S1-3

Caspase induced by endoplasmic reticulum (ER) stress

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Recent studies have suggested that neuronal death in Alzheimer's disease (AD) or ischemia could arise from dysfunction of the endoplasmic reticulum (ER). Although caspase-12 has been implicated in ER stress-induced apoptosis and amyloid- β peptides ($\text{A}\beta$)-induced apoptosis in rodents, it is controversial whether similar mechanisms operate in humans. Here, we searched for caspases those are specifically involved in ER stress in human cells. Consequently, we found that human caspase-4 is localized in the ER, and is cleaved when cells are treated with ER stress-inducing reagents, but not with other apoptotic reagents. Cleavage of caspase-4 is not affected by over-expression of Bcl-2, which prevents signal transduction in the mitochondria, suggesting that caspase-4 is primarily activated in ER stress-induced apoptosis. Furthermore, a reduction of caspase-4 expression by siRNA decreases ER stress-induced apoptosis, but not other types of apoptosis. In addition, caspase-4 is cleaved by administration of $\text{A}\beta$ 1-40, and $\text{A}\beta$ -induced apoptosis is reduced by siRNAs to caspase-4. The expression of caspase-4 is observed in hippocampal CA1 neurons of AD brains. Thus, caspase-4 is an ER stress-specific caspase in humans, and it may contribute to the pathogenesis of AD.

S1-4

Cell survival and death regulated on the ER membrane after ER stress

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The endoplasmic reticulum (ER) is susceptible to various stresses that provoke the accumulation of unfolded proteins in the ER. Excessive or long-term stresses in the ER result in apoptotic cell death involving activation of caspase-12 and -3, and Ask-1-JNK pathway. Eukaryotic cells can adapt for survival to deal with an accumulation of unfolded proteins in the ER by increasing transcription of genes encoding ER-resident chaperones such as GRP78/BiP to facilitate protein folding. The induction system is termed the unfolded protein response (UPR). It has been reported that IRE1, a transmembrane kinase, and ATF6, a transmembrane transcription factor, are mediators of the UPR through sensing accumulation of unfolded proteins. Cell fates after ER stress are regulated by the balance of both apoptosis and the UPR signaling. In the nervous systems, glial cells are well known to be resistant to ER stresses induced by ischemia and hypoxia. These findings raise the possibility that glial cells possess a novel UPR signaling different from that of neuronal cells. Recently, we identified a novel ER stress sensor, OASIS, which is specifically expressed in astrocytes. This protein is a transmembrane protein containing bZIP domain. The functional analyses of OASIS showed that 1) it was cleaved within the ER membrane in response to the ER stress. 2) overexpression of OASIS induced the transcription of GRP78/BiP mRNA through the activation of ER stress responsive element (ERSE), 3) its stable cell lines were resistant to ER stress compared with the control cells. These results indicate that the ER-resident transcription factor OASIS may be a candidate for leading astrocytes to protect against ER stress.

S1-5

Impairment of retrieval by the KDEL receptor sensitizes cells to ER stress

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Proteins destined for the secretory pathway are inserted into the endoplasmic reticulum (ER) cotranslationally and subjected to quality control. ER molecular chaperones facilitate the correct folding of newly synthesized proteins. The accumulation of misfolded proteins in the ER evokes the unfolded protein response (UPR) that upregulates the production of ER chaperones and reduces the level of protein misfolding. Although misfolded proteins had been considered to remain in the ER, recent yeast genetic analyses have revealed that the UPR affects gene transcriptions of a wide variety of proteins functioning not only within the ER but also in the early secretory pathway. In fact, some misfolded proteins in mammalian cells as well as in yeast have been shown to leak out from the ER, then being retrieved to the ER. However, the significance of this retrieval during the UPR remains uncertain. Here we show that an overload of misfolded proteins and ER chaperones in the lumen of the

ER upon ER stress induced their secretion out of the ER in mammalian cells. Those proteins did not escape from the early secretory pathway entirely, because the KDEL receptor retrieved them from post-ER compartments and returned them to the ER. When the retrieval was limited during ER stress, as demonstrated by the expression of a mutant KDEL receptor, ER chaperones escaped further down to the secretory pathway, hence intense UPR was induced to compensate for their loss. The increased synthesis of ER chaperones did not rescue the cells because the intense UPR also caused cell death. These results indicate that retrieval by the KDEL receptor and synthesis of ER chaperones have distinct roles in the UPR. (1702)

S2-1

Involvement of interferon- α and serotonin system in the immunologically induced fatigue in rats

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The immunologically induced fatigue was conducted in rats by intraperitoneal (IP) injection of a synthetic double-stranded RNAs, poly I:C. An IP injection of poly I:C (3 mg/kg) decreased the spontaneous running wheel activity to about 40-60% of the preinjection level until day 9, then gradually returned to the baseline level by day 14. In the open field test, the locomotor activity was unaffected by poly I:C treatment on day 7, suggesting that the fatigue was not due to the peripheral problems such as muscle/joint pain. Quantitative analysis of mRNA levels using a real-time capillary reverse transcriptase (RT)-PCR method revealed that the amount of mRNA for interferon- α (IFN- α) increased in the medial preoptic, paraventricular, ventromedial hypothalamic nuclei, and cortex on day 1 and 7. Serotonin transporter (5-HTT) mRNA also increased in the same brain regions on day 7. Interleukin-1 β (IL-1 β) mRNA increased on day 1, but recovered within a week. In vivo brain microdialysis revealed that the extracellular concentration of 5-HT in the prefrontal cortex decreased after poly I:C injection. Since this decrease in 5-HT was blocked by selective 5-HT reuptake inhibitor, fluoxetine, it was thought to be due to an enhanced expression of 5-HTT. Furthermore, the poly I:C-induced fatigue was attenuated by fluoxetine and 5-HT1A receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetraline (8-OH-DPAT). Finally, the poly I:C-induced fatigue was conditioned using poly I:C as an unconditioned stimulus and saccharin drinking as a conditioned stimulus, and this conditioned response was completely blocked by 8-OH-DPAT. These findings suggest that brain IFN- α and 5-HT systems play important roles in the neuronal mechanisms of the immunologically induced fatigue by poly I:C.

S2-2

UV-irradiation Down-regulates Immune Functions and Causes Fatigue by Photo-Optico-Neuronal Network: Lessons From iNOS-knockout Mice

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Ultraviolet B and A stimulate melanin synthesis by melanocytes and inhibit immune functions of the skin locally at a site of irradiation, respectively. We found that topical irradiation of UVB to the eye increased plasma levels of α -MSH and stimulated melanocytes to proliferate and synthesize melanin pigment systemically by a mechanism that was specifically inhibited by either hypophysectomy or ciliary while UVA systemically down-regulated immune functions by a mechanism which was selectively inhibited by optic nerve resection. These observations suggested that UVB selectively stimulated α -MSH secretion by the hypothalamo-pituitary pro-opiomelanocortin system via the first branch of the trigeminal nerve, thereby stimulating dermal melanocytes. Systemic irradiation of UV-B and/or UVA has been known to suppress immune functions. We recently found that topical irradiation of UVA also suppresses immune functions of dermal Langerhans cells and induced apoptosis of B-cells in lymph nodes. UV-A-induced suppression of immune functions was inhibited by either optic nerve denervation or hypophysectomy, but not ciliary ganglionectomy. These results suggest that UVA reached to the retina stimulates the hypothalamo-pituitary network through the optic nerves. The dermal reactions and immunosuppression induced by topical irradiation of UVA and UVB to the eye were not observed with animals that lack the activity of inducible-type of NO synthase (iNOS). These observations suggest that biological reactions induced by topical UV-irradiation of the eye are mediated by NO-dependent signaling mechanism. Based on such experiments, pathophysiological roles of the photo-optico-neuronal network in the modulation of immune functions and induction of fatigue will be discussed.

S2-3

Effects of hexenal and hexenol on 5-HT and DA Metabolisms in the Brain and/or on Food Intake under Immobilization Stress and Foot Shock Stress in Rats

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Trans-2- hexenal (hexenal) and cis-3-hexenol (hexenol) are two main components that constitute odor of green leaves. We examined here effects of hexenal and hexenol on serotonin (5-HT) and dopamine (DA) metabolisms in the brain and/or on food intake under immobilization stress and foot shock stress in rats. Immobilization stress was applied for 200 min and foot shock stress (1 s, 2 mA) was applied every 30 s for 50 min. The levels of 5-HT, 5-HIAA, DA, DOPAC and HVA in perfusates obtained from the lateral hypothalamic area (LHA) through a microdialysis probe were measured by HPLC. Both of 5-HT and DA metabolisms were increased under immobilization stress. Inhalation of 0.03% of hexenal and hexenol during immobilization stress blocked the increase in 5-HT metabolism, but had relatively no effect on DA metabolism. On feeding, immobilization stress inhibited food intake for 3 h from 18:00 (light off) to 21:00 and for night time from 18:00 to 06:00. Inhalation of hexenal and hexenol restored the decrease of 3 h food intake. The levels of 5-HT and DA did not change by foot shock stress, but those of 5-HIAA, DOPAC and HVA increased significantly. Inhalation of 0.03% and 0.3% hexenal had no effects on the levels of 5-HT, DA and their metabolites. However, when 3% hexenal was inhaled, the level of 5-HIAA significantly decreased to control level without any change on DOPAC and HVA levels. These results suggest that hexenal and hexenol have an antistress effect by inhibiting the increase of 5-HT metabolism, and that these agents may be used as substances for aromatherapy.

S2-4

Development of Advanced Trail Making Test for evaluating mental function -ATMT: a computer-assisted system for assessment of fatigue-

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Fatigue and feeling of fatigue (malaise) are different. Feeling of fatigue is a measure of subjective evaluation, and can be easily masked by motivation and a sense of accomplishment. Quantification of fatigue requires a different objective evaluation index from feeling of fatigue. Evaluation should be made at least using multiple markers, such as biochemical, physiological and immunological markers, to quantify fatigue.

We developed a computer-assisted system to physiologically quantify fatigue. Advanced Trail Making Test (ATMT) is a mental function test developed for the purpose of evaluating mental function objectively without receiving effect of intelligence quotient and experience. The test consists of the visual search response task to be challenged by pushing, as quickly as possible, the figure of 1 to 25 explored on the touch panel display of the personal computer. It can measure the search response time for every target during execution of the task. It can also rearrange all targets at every response or delete the responded target and add a new target. An ATMT experiment in patients with chronic fatigue syndrome (CFS) revealed that search response time was significantly delayed with the course of task performance time, showing the characteristic of fatigability. A study in subject taking caffeine showed a transient decrease in the search response time, suggesting that caffeine may temporarily help recovery from fatigue. Furthermore, quantification of the rate of delay in the search response time enables comparison of the effect of an anti-fatigue component and another component. We will further investigate a correlation with immunological and biochemical markers, which have been suggested to be associated with fatigue, to establish a method of evaluation for fatigue.

S2-5

Neural circuits for fatigue sensation revealed by neuroimaging techniques

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Recently, a number of studies which mainly used neuroimaging techniques have been performed to aim to explore the functional brain regions and neurochemical targets in fatigue sensation in normal volunteers and patients with chronic fatigue syndrome (CFS) and multiple sclerosis. Here, first we would like to review such articles in this field, and then introduce our results with CFS patients and normal subjects loaded with fatigue, mostly using positron emission tomography (PET). Apparently, triangular circuit, prefrontal cortex, orbitofrontal cortex, and anterior cingulate, might be the key to understand the fatigue sensation and behavior. We propose that the quantitative measures in these neuroimaging studies might be used as a good scale of extent of fatigue for evaluation of anti-fatigue methods including therapeutic drugs.

S2-6

The pathophysiology of Chronic Fatigue Syndrome (CFS)

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CFS is an operational concept to clarify the unknown etiology of the syndrome characterized by the abnormally prolonged fatigue. Recently, we found that most CFS patients showed low levels of serum acetylcarnitine, which correlates closely with the fatigue rating score, and that a significant quantity of acetyl moiety of serum acetylcarnitine is taken up into the brain. Metabolite analysis of the mouse brain revealed that an acetylcarnitine taken up into the brain is mainly utilized for the biosynthesis of glutamate. When we studied the cerebral uptake of acetylcarnitine by using [2-¹¹C]acetyl-L-carnitine, a significant decrease was detected in several regions in CFS group, namely in the prefrontal and temporal cortices, anterior cingulate and cerebellum. These findings suggest that the levels of biosynthesis of neurotransmitters through acetylcarnitine might be reduced in some regions of the brain of CFS patients and that this abnormality might be one of the key elements to unveiling the mechanisms of the chronic fatigue sensation. Furthermore, when we examined a serotonin transporter (5-HTT) gene promoter polymorphism, which affects the transcriptional efficiency of 5-HTT, in 70 CFS patients using PCR amplification of the blood genomic DNA, a significant increase of longer (L and XL) allelic variants was found in CFS patients ($p < 0.05$). When we used the Selective Serotonin Reuptake Inhibitor for the treatment of 28 CFS patients, 1/3 of them recovered enough to return to work. Therefore, a serotonergic dysfunction might also be involved as one of the pathogenesis of CFS despite the patients not being in a depressed state. We are now investigating the brains uptake of 5-HTP using PET. On the other hand, when we focused on immunological abnormalities against neurotransmitter receptors in CFS, it became clear that the autoantibody to anti-muscarinic cholinergic receptor 1 were detected in a large number (34/60) of CFS patients and were related to CFS symptoms. Therefore, these antibodies may also play an important role in the clinical characteristics of CFS.

S3-1

Mechanisms of drug-induced BDNF synthesis in the rat brain

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Brain-derived neurotrophic factor (BDNF) is known to be synthesized in an activity-dependent manner. In fact, BDNF levels in the rat hippocampus and entorhinal cortex are enhanced by glutamate agonists such as kainic acid and AMPA. However, the signaling pathway of BDNF synthesis in the brain unexpectedly remains unclear. Therefore, we, first, examined the effects of ion channel modulators on BDNF levels in vivo. Bay K8644, an activator of L-type calcium channels, stimulated BDNF production in the rat neocortex. CREB, a transcription factor, was found to be involved in this process. Moreover, we found that riluzole, an inhibitor of a voltage-dependent sodium channel, markedly stimulated BDNF synthesis in the rat hippocampus and entorhinal cortex. Enhanced BDNF protein was specifically found in the hippocampal region, where mossy fibers make synapses. Riluzole-induced enhancement of BDNF was inhibited by CCPA, an agonist of the adenosine receptor, and by omega-conotoxin GVIA, a blocker of N-type voltage-dependent calcium channels being abundant in the mossy terminals and regulating the calcium influx by coupling with adenosine receptors. By contrast, antagonists of the adenosine receptors stimulated BDNF production, suggesting regulation of BDNF synthesis by the adenosine receptors. In the next step, we examined the intracellular signaling pathway of BDNF production induced by riluzole. We focused on ERK, p38 MAPK and IP3K pathways. Riluzole activated p38 MAPK and SB203580, a blocker of p38 MAPK, decreased BDNF levels, indicating involvement of p38 MAPK in BDNF synthesis.

S3-2

Transcriptional Regulation of Brain-derived Neurotrophic Factor (BDNF) Gene in Neurons

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Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, plays an important role in promoting neuronal survival, neuronal differentiation and synaptic plasticity. The BDNF gene consists of four short 5'-exons (exon I, II, III and IV) and a common 3'-exon V encoding a prepro-BDNF protein. Among BDNF promoters (BDNF-PI, -PII, -PIII and -PIV), BDNF-PI is markedly activated by Ca²⁺ signals evoked via neuronal activity. Using rat cortical neurons in culture, we found that the Ca²⁺ signal-responsive elements of BDNF-PI were mainly located in the proximal region (-100 ~ -80) containing cAMP-responsive element (CRE), which is overlapped by the upstream stimulatory factor1/2 (USF1/2)-binding element (UBE). Both the CRE and UBE elements were responsible for the activation of BDNF-PI. CREB and USF1/2 bound to this overlapping site, depending upon their preferred sequences which also control the magnitude of the activation. Thus, not only CREB but also USF1/2 contributes to the Ca²⁺ signal-mediated activation of BDNF-PI. However, CREB and USF2 were able to form a heterodimer in HeLa cells, which was inhibitory for the CRE-mediated transcription. On the other hand, both the CRE- and the UBE-mediated transcription showed an optimum activation at 75 mM KCl whereas the BDNF-PI and -PIII did it at 25 mM KCl, suggesting that some mechanisms which make the promoter sensitive to the Ca²⁺ signals could be associated with the BDNF promoters. Elucidation of these phenomena would reveal some aspects concerning the transcriptional regulation evoked via synaptic inputs.

S3-3

Intracellular processing and secretion of neurotrophins

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Neurotrophins, including NGF and BDNF, are first generated as precursor

Proteins of molecular weight 30-35 kDa. The proneurotrophins possess clusters of basic amino acids in the middle of them, which are then cleaved by processing proteases like furin, releasing mature neurotrophins (molecular weight 12-14 kDa). Recently it was suggested that proneurotrophins and mature neurotrophins may differentially activate pro- and antiapoptotic cellular responses, through preferential activation of p75 and Trk receptors, respectively. This leads to the prediction that the proneurotrophin-p75 system works to eliminate damaged cells after an injury or a disease. It is well known that p75 is induced in such occasions and recent reports describe that the level of proNGF is increased in the brains of Alzheimer's patients or following spinal cord injury. Thus it is indispensable to study the detail of the intracellular processing of neurotrophins and the regulation of their secretion. There are considerable structural similarities between NGF and BDNF, but their subcellular localization and secretion mechanisms are suggested to be different: cells with a regulated secretory pathway release mature NGF mainly via a constitutive secretory pathway, whereas mature BDNF is released mainly through a regulated pathway. When we transfected PC12 cells with NGF or BDNF cDNA, we found the intracellular processing of BDNF was less efficient than NGF. Comparing the processing of chimera neurotrophins, the processing efficiency was found to be dependent on their propeptides. NGF has 2 more additional clusters of basic amino acids in its propeptide region, but they were not responsible for the high efficiency of NGF processing. PC12 cells transfected with NGF cDNA differentiated in response to the self-secreting NGF. NGF was secreted constitutively and also in a regulated fashion on day 2 of the transfection and also on day 7, but on day 7 the constitutive secretion of NGF decreased. Such a change in the neurotrophin secretion pathway might have an important role in the development of neurons.

S3-4

A novel molecule that mediates neurotrophin release in cerebellar neurons

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Neurotrophins are key modulators of various neuronal functions including differentiation, survival, and synaptic plasticity, but molecules that regulate their secretion are poorly understood. We isolated a clone CERAIN that is predominantly expressed in granule cells of postnatally developing mouse cerebellum and that turned out to be a paralog of CAPS (Ca²⁺-dependent Activator Protein for Secretion). CERAIN is enriched on vesicular structures of presynaptic parallel fiber terminals of granule cells connecting postsynaptic spines of Purkinje cell dendrites. Vesicle fractions affinity-purified by the CERAIN antibody from mouse cerebella contained significant amounts of neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF) and chromogranin B but not marker proteins for synaptic vesicles synaptophysin and synaptotagmin. In cerebellar primary cultures, punctate CERAIN immunoreactivities are largely colocalized with those of NT-3 and BDNF and near those of a postsynaptic marker PSD-95 around dendritic arborization of Purkinje cells. Exogenously expressed CERAIN enhanced release of exogenous NT-3 and BDNF from PC12 cells and of endogenous NT-3 from cultured granule cells in a depolarization-dependent manner. Moreover, the over-expression of CERAIN in granule cells promotes the survival of Purkinje cells in cerebellar cultures. Thus, we suggest that CERAIN mediates the depolarization-dependent release of NT-3 and BDNF from granule cells, leading to regulation in cell differentiation and survival during cerebellar development.

S3-5

Functional SNPs in human BDNF gene: roles in BDNF secretion and processing

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We examined the effects of single nucleotide polymorphism (SNP) in the human BDNF gene on the molecular and cellular function, and brain function. Recently, we studied an SNP, which replaces valine (Val) to methionine (Met) in the pro-region of BDNF. In human subjects, the met allele was associated with poorer episodic memory, abnormal hippocampal activation. Neurons transfected with Met-BDNF showed lower depolarization-induced secretion. Met-BDNF also failed to localize to secretory granules or synapses. These data demonstrate a role for BDNF and its val/met polymorphism in human hippocampal function, intracellular trafficking and activity-dependent secretion of BDNF. Second, we studied the effects of the SNPs located at nucleotide 372 and 378 of the human BDNF gene, causing amino acid substitution (Arg125Met and Arg127Leu) near the cleavage site of pro-BDNF. Constructs with these mutations were transfected to cultured hippocampal neurons. Western blot analysis of the lysates and supernatants demonstrated that these mutations reduced the cleavage of pro-BDNF in these neurons. Double mutation also markedly reduced the secretion of the mature BDNF, as measured by a BDNF ELISA assay. To determine the biological consequences of the cleavage mutations, cerebellar granule cells were transfected with each construct. The cells were exposed to low potassium (LK)-containing medium for 24-48 hr, and their viability was assessed by LDH assay and Hoechst staining. As is expected, wild BDNF-expressing cells survived well. In the cells expressing mutant BDNF constructs, however, LK-induced apoptosis was significantly enhanced, compared to non-transfected cells. We also found that transfection of mutant BDNF constructs into granule cell cultures prepared from p75^{NTR}-knock out mice did not cause enhanced apoptosis. Therefore, secretion of uncleaved pro-BDNF induces p75^{NTR}-mediated cell death in cerebellar granule neurons. These results identify important structural determinants for intracellular cleavage of pro-BDNF, and suggest a critical role of the pro-BDNF cleavage in the survival-apoptosis decision for certain CNS neurons.

S4-1

Functional anatomy of the γ -secretase complex

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Mutations in presenilin (PS) 1 and 2 genes cause early-onset familial Alzheimer's disease (FAD) by altering γ -cleavage of APP to increase the production of the amyloidogenic A β 42 peptide. Although it still remains unclear how PS proteins regulate the γ -secretase activity, the high molecular weight (HMW) protein complex harboring PS fragments is regarded as the active form of γ -secretase. Recent biochemical and genetic studies revealed that nicastrin (NCT), APH-1 and PEN-2 are required for the Notch signaling, γ -secretase activity and the accumulation of PS fragments. To study the individual roles of PS cofactors in the formation and activation of γ -secretase, we employed *Drosophila* S2 cells that are useful in overexpression of transgenes as well as inactivation of gene expression by RNAi. We found that overexpression of *Drosophila* APH-1 (dAPH-1) increases the stabilization of *Drosophila* PS (Psn) holoproteins that are incorporated into a HMW protein complex. Inactivation of *Drosophila* PEN-2 (dPEN-2) abrogates the accumulation of Psn fragments, whereas promoted stabilization of Psn holoprotein as seen in overexpression of dAPH-1. Accumulation of PS1 holoprotein by PEN-2 RNAi was observed in mammalian neuronal cells, including primary neurons, suggesting that the molecular mechanism of PS cofactors in the assembly of PS complex is highly conserved. And finally, co-expression of dPEN-2 with dAPH-1 and *Drosophila* NCT increased the formation of Psn fragments as well as γ -secretase activity to generate A β . Mutation in conserved glycine residue within the transmembrane region of dAPH-1 abolished the formation of HMW protein complex as well as the γ -secretase activity. These data illustrate the differential roles of PS cofactors in PS complex formation, APH-1 as the stabilizing co-factor of PS and PEN-2 as a factor conferring γ -secretase activities and facilitating the formation of PS fragments.

S4-2

Relationship between γ - and ϵ -cleavage

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So called regulated intramembranous proteolysis (RIP) of amyloid precursor protein (APP) mediated by γ -secretase produces amyloid β -protein (A β), and concomitantly carboxyl terminal fragment (CTF) γ . Because A β is a key molecule for the pathogenic progression to Alzheimer's disease (AD), the control of A β production is one of the most important targets for the therapeutic strategies. We and others recently found that there are two cleavage sites within the transmembrane domain of APP: In addition to γ -cleavage, which produces A β , APP is cleaved at the cytoplasmic membrane boundary (ϵ -cleavage), releasing predominantly CTF γ 50-99. The ϵ -cleavage shares several characteristics with the cleavages of other γ -secretase substrates, such as Notch site-3 cleavage. Although both γ - and ϵ -cleavages appear to depend on presenilin-associated γ -secretase, whether ϵ -cleavage occurs independently of, or is coordinated with, γ -cleavage is unknown. Using a cell-free system and culture cells expressing wild-type or mutant APP and/or presenilins, we have investigated the relationship between γ -cleavage and ϵ -cleavage. Familial AD-associated mutations of APP and presenilins, which cause enhanced production of A β 42, were found to increase the production of CTF γ 49-99, a minor species of CTF γ . This suggests a potential link between the production of A β 42 and CTF γ 49-99, and thus between that of A β 40 and CTF γ 50-99. The expression of A β 49, a putative product generated by the ϵ -cleavage at CTF γ 49/50, generated predominantly A β 40 in a presenilin-dependent manner. Moreover, A β species longer than A β 42/43 were found in the cell lysate. From these observations, the mechanism of γ -cleavage will be discussed.

S4-3

NSAIDs and Alzheimer's disease

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Epidemiologic studies have shown that patients who are chronic users of nonsteroidal anti-inflammatory drugs (NSAIDs) have a reduced risk of developing Alzheimer's disease. Although NSAIDs may be protective because of their anti-inflammatory properties in the CNS, we recently showed certain NSAIDs, including ibuprofen, sulindac, and indomethacin, selectively lower the levels of Ab42 in cultured cells and in brains of transgenic mice. This activity is mediated through an unknown, non-cyclooxygenase (COX) mediated pathway. My talk will focus on recent results to define the mechanism by which NSAIDs reduce the production of Ab42 from in vitro and in vivo systems. We now find that there is a consistent increase in the levels of Ab38 and shorter Ab species that accompany the reduction in Ab42 levels in cultured cells given a variety of NSAIDs. Moreover, NSAIDs and derivative compounds have been found to increase Ab42 levels. In the latter setting, Ab38 levels are consistently decreased. This suggest that there is a subtle shift in the g-secretase activity that affect these Ab species. We also found that presenilin and APP mutations modulate the NSAID effect on Ab42 both positively and negatively. The fact that others (Takahaski et al, JBC 278:18664, 2003) and we have shown that Ab42 generation is altered an in vitro g-secretase assay argue that NSAIDs may affect g-secretase activity at or near the cleavage site. This is consistent with our negative findings from a systemic survey of other known targets of NSAIDs to determine if these pathways may be involved in the Ab42 reduction. We find that neither alterations of lipoxygenase activity nor increasing levels of arachidonic acid reduce Ab42 levels. Some transcription factors have been reported to be sensitive to NSAIDs. However, our studies suggest that the Ab reduction is not mediated the NF-kB pathway. Our continuing efforts will hopefully define the mechanisms by which certain NSAIDs and other compounds preferentially reduce Ab42 production and determine whether this approach will prove to be useful in reducing Ab deposition and other AD-associated pathology in vivo.

S4-4

Abeta metabolism and Alzheimer's disease

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Amyloid beta peptide (Abeta), the primary pathogenic agent of Alzheimer's disease (AD), is a physiological metabolite in the brain. We focused our attention on elucidation of the unresolved aspect of Abeta metabolism, proteolytic degradation, or catabolism. Among a number of Abeta-degrading enzyme candidates, we identified neprilysin as the major catabolic enzyme using a novel in vivo paradigm. Consistently, neprilysin deficiency resulted in defects in the metabolism of endogenous Abeta, notably, in a gene dose-dependent manner. Our observations suggest that even partial down-regulation of neprilysin activity, which could be caused by aging, can contribute to AD development by promoting Abeta accumulation. Moreover, we describe that an aging-dependent decline of neprilysin activity, leading to elevation of Abeta levels in the brain regions closely associated memory formation. We not only hypothesize the likely role of neprilysin down-regulation in sporadic AD (SAD) pathogenesis but also propose that the knowledge itself be used for developing novel preventive and therapeutic strategies through utilization of a G protein-coupled receptor (GPCR), presuming that the neprilysin expression level in brain may be regulated by a neuropeptide-neuropeptide receptor mechanism. One candidate medication is a non-peptidic agonist of somatostatin receptor(s) although there are likely to be other targets as well.

S4-5

Inhibition of GSK-3 — A possible therapeutic target in Alzheimer's disease

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Neurofibrillary tangles (NFT) are found in a wide range of neurodegenerative disorders, including Alzheimer's disease (AD). Hyperphosphorylated microtubule-associated protein tau comprises a major part of these tangles; however, its precise role in NFT formation has remained elusive. We developed an FTDP-17 mutant tau Tg mouse model exhibiting NFT-like tau inclusions. In tau accumulated neurons of this mouse, we found GSK-3 β and phosphor-JNK accumulation. The same phenomena were confirmed in FTDP-17 human samples suggesting that GSK-3 β and JNK might be involved in NFTs formation. The adenovirus-mediated gene expression of tau, Δ MEKK, JNK3, and GSK-3 β in COS-7 cells produces most of the pathological phosphorylation-epitopes of tau including AT100. Furthermore, this co-expression resulted in the formation of tau aggregates having short fibrils that were detergent insoluble. These results suggested that aberrant tau phosphorylation by a combination of these kinases may be involved in tau fibril formation *in vivo*. To investigate the effects of kinase activation in NFT formation, we used an A β paradigm that accelerates NFT formation. Injecting A β into 3-month old tau Tg mice activated GSK-3 β which then induced NFT-like hyperphosphorylated tau accumulation. Thus, tau hyperphosphorylation by GSK-3 β is essential to form NFTs in AD and other neurodegenerative disorders.

S5-1

Proteomic approach of the growth cone functions

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The growth cone is responsible for axonal growth, axon guidance, and synaptogenesis. For achievement of these complicated functions precisely, the growth cone should be equipped with proteins organizing and regulating cytoskeletons, those for vesicular trafficking, and for signal transduction. In mammalian growth cones, however, the number of the proteins that have been reported to be localized there, is small. To clarify the overview of the growth cone functions, we chose the proteomic analysis of the growth cone. We prepared the growth cone particle fraction and the growth cone membrane fraction from developing rat brain, and analyzed those proteins using LC-MS-MS system. As the results, we identified more than 600 kinds of proteins in each fraction, respectively. In this symposium, we discuss the profiles of these growth cone proteins and the relationship to the growth cone functions.

S5-2

Dynamics of actin filaments and actin associate proteins revealed by polarized light and fluorescence microscopy.

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Growth cones at the tip of growing nerves, crawl around, find the path for neuronal elongation and recognize targets for synapse formation. The motile activity is powered by some actin-based systems, details of which are still in debate.

To know the motile mechanism of growth cones, we visualized and analyzed behavior of filamentous actin (f-actin) and of actin associate proteins in living growth cones. Our movies recorded with a new Polscope revealed vigorous movements of f-actin in living unstained growth cones¹. Moreover, analysis of the movies lead to findings that 1) shape of the actin bundles was determined near the leading edge and was kept during the retrograde flow², 2) the shape of actin bundles exhibited short history of filopodial behavior in the recent past², 3) filopodial behavior was controlled by three parameters: rate of actin polymerization, rate of retrograde flow, and orientation of actin polymerization³. Since actin associate proteins are candidate molecules that control actin dynamics, we visualized dynamics of actin associate proteins in living growth cones by using GFP. We recorded time-lapse movies of GFP- α actinin, GFP-fascin, GFP-tropomyosin, and GFP-caldesmon and compared them with f-actin dynamics. Regulatory mechanism of dynamics of actin associate will be also discussed.

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References

1. *Mol Biol Cell* (1999) 10 p197-210. 2. *Proc. Natl. Acad. Sci. USA* (1999) 96 p7928-7931. 3. *Biophys. J.* (2000) 78 p1176-1182.

S5-3

Regulation of N-WASP by Src-Family Tyrosine Kinases and Proteasome in Neurite Extension

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Neurite extension is a key process for constructing neuronal circuits during development and remodeling of the nervous system, in which actin cytoskeletal dynamics is essential. Here we show that Src family tyrosine kinases and proteasome-degradation signals synergistically regulate actin regulatory protein N-WASP, leading to neurite extension. Src family kinases activate N-WASP through tyrosine phosphorylation, which induces nucleation of actin polymerization through the Arp2/3 complex. Tyrosine phosphorylation of N-WASP also initiates its degradation through ubiquitination, providing the tight control of activated N-WASP levels. Under proliferating condition that inhibits neurite growth, N-WASP is rapidly degraded by proteasome. When neurite growth is stimulated in culture, degradation of N-WASP is markedly inhibited, leading to accumulation of the phosphorylated, activated N-WASP and resulting in neurite extension. In this process, HSP90 serves as a chaperon that maintains activated state of N-WASP. Collectively, neurite extension appears to be regulated by the balance of N-WASP phosphorylation (activation) and degradation (inactivation), which are induced by tyrosine phosphorylation.

S5-4

Plexin mediates bifunctional signals

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Precise growth cone guidance is the consequence of a continuous reorganization of actin filament structures within filopodia and lamellipodia in response to inhibitory and promoting cues. The small GTPases Rac1 and RhoA are critical for regulating distinct actin structures in growth cones and in non-neural cells. Collapse, a retraction of filopodia and lamellipodia, is a typical growth cone behavior on contact with inhibitory cues and is associated with depolymerization and redistribution of actin filaments. Several semaphorins are shown to induce growth cone collapse via plexins. This action on growth cone likely corresponds to cell contraction in non-neural cells as described by others using COS cell-transfectants (He and Tessier-Lavigne, 1997). Interestingly, intracellular and extracellular environments can convert repulsive actions to attractive of some guidance molecules. Plexin B1 is proposed as a high affinity receptor for Sema4D, a transmembrane semaphorin. We examined whether small GTPases mediate semaphorin-plexin signaling accompanied with any alterations of morphology in non-neural cells transfected with expression vectors encoding wild-type and deletion mutants of plexin B1. Cells expressing wild type of plexin B1 induced lamellipodia-formation and moderately cell-compaction in non-neural cells, while extracellular domain-deleted mutant of plexin B1 did not induce lamellipodia or compaction. Sema4D ligand induced additional cell compaction of wild-type plexin B1 transfectants, while no effect on cells expressing extracellular domain-deleted nor intracellular domain-deleted mutant. We further analyzed whether these actions mediated Rac1 or RhoA signaling.

S5-5

THE REGULATION OF MICROTUBULE DYNAMICS IN GROWTH CONES BY SCG10

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SCG10, a member of the stathmin family, is a neuronal growth cone protein which has microtubule destabilizing activity. The expression of SCG10 is closely associated with neuronal growth during development as well as regeneration and structural plasticity in the adult. The protein contains an N-terminal targeting domain that mediates its transport and accumulation in the central domain of the growth cone, a region that also contains highly dynamic microtubules, known to be crucial for growth cone advance. Since overexpression of SCG10 strongly enhances neurite outgrowth, SCG10 appears to be an important factor for the dynamic assembly and disassembly of growth cone microtubules during axonal elongation. In vitro studies have previously identified four serine residues that are phosphorylated, and pseudo-phosphorylated mutant SCG10 showed decreased microtubule-destabilizing activities in living cells suggesting that SCG10 activity is negatively regulated by phosphorylation. To analyze the in vivo phosphorylation of SCG10, we have developed phospho(P)-isoform specific antibodies which we used for Western blot analysis in two-dimensional gels and for immunohistochemistry. In mouse brain, the phosphorylation pattern was found to be very complex with several different P-isoforms, and in layer V of the cortex, a specific subcellular localization of P-isoforms was found. Experiments using anti-SCG10 function blocking antibodies inhibited axonal elongation of retinal neurons suggesting that the microtubule-destabilizing activity of SCG10 is essential for growth cone advance in these neurons.

S5-6

Exocytosis and contact formation in neuronal growth cones

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The cell-substrate adhesion molecule, integrin, localizes at growth cones and contributes to the formation of adhesive contacts at growth cones (Wu et al., 1996; Grabham and Goldberg, 1997; Grabham and Goldberg, 1997). Neurite extension is accelerated when neurons are plated on a cover slip coated with fibronectin, a natural ligand of integrin. When cells move, adhesive molecules, such as integrin, are in general taken up into intracellular space by endocytosis and transported to the extending regions (Bretscher and Aguado-Velasco, 1998; Bretscher, 1996). Our recent study has shown that integrin molecules are incorporated into the cell membrane by exocytosis in endothelial cells (Kawakami et al., 2001). We have also demonstrated a close correlation between the exocytosis of neurotransmitter and the formation of adhesive contacts between a growth cone and a neuron in contact (Tatsumi and Katayama, 1999). Using TIRF, EpiF and confocal microscopy, we examined the relationship between the exocytosis and the supply of integrins to the bottom of the growth cones of NGF treated PC12 cells. Time-lapse imaging of exocytosis of integrin containing vesicles at growth cones showed that exocytosis occurred at or near the growth cones followed by incorporation of integrin molecules into the bottom surface of the cell. Taken together with the observations of dynamic movement of growth cones, we concluded that there is a close relationship among vesicle-exocytosis, formation of adhesive contacts and movements of growth cones.

S6-1

Development of a temporal and cell-specific gene knockout mouse and its application to brain research

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The methods of gene targeting have greatly contributed to understanding the brain function. However, it has also become clear that the methods have some limitations. 1) Its innate molecular loss hinders normal development and causes death, making analysis impossible. 2) Abnormal formation of tissues and organs caused by knockout (for instance, abnormal nerve network etc.) does not correctly reflect the molecular function in adults. 3) Functional compensation could be made by other molecules prohibiting correct evaluation. Moreover, knockout mice made by prevalently used 129 strain-ES cells have a congenital hypoplasia in the corpus callosum, for which they are unsuitable for behavioral analysis. A back-cross was not able to clear up the problems of genetic background completely. In order to solve these problems, we have developed a new system. As the first step, we established a method of producing a gene-manipulated mouse using the C57BL/6 origin embryonic stem cell. Then we adopted the CrePR/loxP recombination system to generate mutant mice, where the recombinase activity of the CrePR protein was induced by the synthetic steroid, RU486 but not by endogenous hormones. By generating mutant mice in which the CrePR gene is expressed in a region-specific or cell-type specific manners, it has become feasible to achieve a spatially and temporally regulated gene targeting system. With this technique, we recombined a gene in hippocampus CA3, cerebellar Purkinje cells, cerebellar granular cells, etc. We present these results and its usefulness in brain research.

S6-2

Role of scaffold proteins interacting with the carboxyl-terminal domain of mGluR1a

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mGluR1 is a G-protein coupled glutamate receptor and activates Gq-PLC β -PKC pathway. mGluR1 is implicated in modulation of synaptic transmission and plasticity. mGluR1 knockout [mGluR1(-/-)] mice have characteristic cerebellar symptoms such as ataxic gait, intention tremor and motor discoordination. We have previously introduced the transgene of mGluR1 α , the longest and most abundant splice variant of mGluR1, into mGluR1 (-/-) mice using a Purkinje cell specific promoter. The mGluR1a transgenic mice homozygous mutant for endogenous mGluR1 allele (mGluR1a-rescue mice) showed normal cerebellar long-term depression and regression of multiple climbing fiber innervation, events significantly impaired in mGluR1 (-/-) mice. In this study we introduced the transgene that express mGluR1b, an mGluR1 splice variant that lack the long carboxyl-terminal domain specific for mGluR1a, into the mGluR1 (-/-) mice to clarify the role of Homer/Vesl proteins and PDZ-binding proteins that could interact with the carboxyl-terminal domain specific for mGluR1a in the motor coordination and synapse elimination. One line of mGluR1b transgenic mice homozygous mutant for endogenous mGluR1 allele (mGluR1b-rescue mice) showed no ataxic gait or tremor and could walk along a straight line as do wild-type littermates. We are investigating whether climbing fiber synapse elimination is restored in the mGluR1b-rescue mice. The role of scaffold proteins that interact with the carboxyl-terminal domain specific for mGluR1a in the mGluR1-signal transduction will be discussed.

S6-3

Generation and analysis of striatum-selective NMDA receptor knockout mice

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The basal ganglia are involved in the control of movements. The striatum, the input nucleus of the basal ganglia, receives glutaminergic inputs from the all area of cortex and the intralaminar nuclei of the thalamus. To investigate the molecular mechanisms underlying motor control, we generated a mouse line expressed Cre recombinase gene selectively in the developing striatum with the knockin strategy in ES cells derived from the C57BL/6 strain. We also produced a target mouse line carrying loxP sites in the NMDA receptor GluR ζ 1 (NR1) gene by homologous recombination in C57BL/6 ES cells. Crossing of the two mouse lines yielded striatum-selective NMDA receptor knockout mice. The NMDA receptor GluR ζ 1 protein expression was diminished in the striatum of the mutant mice by postnatal day 14. The mutant mice were smaller in size than the wild-type littermates and died by postnatal week 5. In the striatum, dopaminergic inputs from the substantia nigra pars compacta converge with glutaminergic inputs. Dopamine-deficient mutant mice also died by postnatal week 4 and the dopamine deficiency reduced the expression of substance P and dynorphin. However, in situ hybridization analysis showed that the striatum-selective NMDA receptor GluR ζ 1 knockout exerted little effects on the expression of dopamine receptors and these neuropeptides. These results suggest that NMDA receptors are essential for proper functioning or organization of the developing striatum.

S6-4

Emx1-Cre Mice Reveal Cortical Mechanisms Involved in the Barrel Formation

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The rodent somatosensory system is an excellent model to study molecular mechanisms underlying the establishment of patterned topographic connections between the sensory periphery and the brain. In the cortex, the configuration of whiskers on the snout is topographically represented as "barrels", discrete modules of layer IV granule cells (post-synaptic patterns) and thalamocortical afferent terminals (pre-synaptic patterns).

To understand the cortical mechanisms of the barrel formation, we generated the Emx1-Cre mice, in which the Cre recombinase gene is expressed under control of the dorsal telencephalon-specific Emx1 promoter. Using these mice, one could disrupt any target gene in virtually all excitatory neurons of the cerebral cortex but not in the inhibitory cortical neurons or neurons of the thalamus or brainstem. By crossing Emx1-Cre mice with NR1-flox mice, in which the essential NMDAR subunit (NR1) gene is flanked by two loxP sequences, we generated the cortex-restricted NR1 knockout (CxNR1KO) mice. In the somatosensory cortex of CxNR1KO mice, the pre-synaptic patterns formed though they were not as distinct as those of normal mice. By contrast, the post-synaptic patterns failed to form in the CxNR1KO cortex. Furthermore, we found that the dendritic fields of spiny stellate cells (excitatory neurons) of CxNR1KO layer IV do not orient toward thalamocortical afferent patches as in normal mice.

Thus, the Emx1-Cre conditional gene targeting system is a powerful tool to dissociate the cortical mechanisms of the pre- and post-synaptic barrel formation from the subcortical mechanisms.

S6-5

Roles of Hippocampal CA3 NMDA Receptors in Learning and Memory

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Marr postulated that a recurrent collateral network could act in an auto-associative memory capacity if the efficacy of their excitatory synapses was plastic. He also pointed out the recurrent network as a site of Hebbian learning, which could be useful for binding together features active at the same time within the same episode. Among various types of hippocampal subfields that are involved in learning and memory, a CA3 recurrent network seemed to be capable of such functions, with a quick and large storage capacity and good retrieval of an entire memory trace from partial memory input. To address the function of NR-dependent CA3 networks in mnemonic processes, we generated and analyzed a genetically engineered mouse strain in which the NR subunit 1 (NR1) gene is ablated specifically in the CA3 pyramidal cells of adult mice (CA3-NR1 KO mice). Here we show that the CA3 NRs are necessary for the retrieval of spatial memory when limited external cues are present, *i.e.* involvement of spatial pattern completion, at both behavioral and neural network levels. We also show that CA3-NR1 KO mice are impaired in the rapid acquisition of spatial memory of novel locations of the hidden platform with just one visiting trial, with its potential underlying mechanism at neural network level. It seems that hippocampal CA3 NR networks make animals capable of rapidly acquiring, associating and storing a variety of information of external stimuli as a daily episode, allowing animals to respond adaptively to new environments in the ever changing world.

References:

- Nakazawa, K., Quirk, M. C., Chitwood, R. A., Watanabe, M., Yeckel, M. F., Sun, L. D., Kato, A., Carr, C. A., Johnston, D., Wilson, M.A., and Tonegawa, S. (2002) Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science* **297**, 211-218.
Nakazawa, K., Sun, L. D., Quirk, M. C., Rondi-Reig, L., Wilson, M. A., and Tonegawa, S. (2003) Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. *Neuron* **38**, 305-315.

S7-1

Regulation of exocytotic events in single adrenal chromaffin cells

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Exocytotic release of neurotransmitters is a calcium-dependent process that requires the interaction of multiple proteins. However, the precise mechanism of the exocytosis remains unclear. Because of biochemical and functional similarities to neuronal cells, adrenal chromaffin cells have been often employed as a model system for studying the molecular mechanisms of exocytotic transmitter release. Carbon-fiber amperometry is excellent in temporal resolution and allows detailed analysis of the kinetics of exocytosis from single vesicles that is detected as single current spikes. By use of this system, we characterized single exocytotic events in bovine adrenal chromaffin cells. Exposure of the chromaffin cells to 60 mM KCl for 5 min and for 4 s evoked a train of events with the frequency of 285 ± 32 (number of spikes/5 min, $n=25$) and 28 ± 7 (number of spikes/15 s, $n=33$), respectively. Kinetics of the events were; rise time = 3.7 ± 0.19 ms, middle width = 18.3 ± 4.4 ms, area = 0.78 ± 0.19 pC and the spikes with a "foot" = 16.5 ± 2.7 % of total spikes. We examined the effects on the kinetics of several factors implicated in the regulation of exocytosis. The frequency and the kinetics of the events were affected distinctively by treatment with inhibitors of actin-myosin interaction, phorbol ester, fatty acid and microinjection of VAMP peptides. Since each parameter corresponds to the distinct steps of exocytotic process, these results may provide dynamic insights of their regulatory role in vesicle recruitment and fusion process in adrenal chromaffin cells.

S7-2

A Genetic Dissection of the Roles of Synaptotagmin and Eps15 in *Drosophila*

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Neurotransmitters are stored in lipid bound organelles known as synaptic vesicles. The fusion of these vesicles with the plasma membrane is regulated by the influx of Ca^{2+} . We have introduced mutations into the Ca^{2+} binding domains of one protein, synaptotagmin, which is thought to act as the transducer for the Ca^{2+} signal and studied the consequences of these mutations on synaptic transmission. Following the fusion of synaptic vesicles with the plasma membrane components of the vesicles are recycled and used for further rounds of membrane fusion. We have recently begun a reverse genetic approach to study proteins implicated in the recycling pathway. In particular we are examining the role of Eps15 in this process.

Synaptotagmin is postulated to be the Ca^{2+} sensor for fast, evoked neurotransmitter release. Genetic tests remain equivocal as to its role as the Ca^{2+} sensor. We have mutated one of the essential aspartates (D229N) of the Ca^{2+} binding site of the *Drosophila* synaptotagmin I C2A domain and expressed it in a synaptotagmin I null background. Despite the disruption of the C2A domain no alterations were observed in the Ca^{2+} -dependent properties of synaptic transmission. Synaptotagmin IV, a related isoform that does not bind Ca^{2+} in the C2A domain, is proposed to be an inhibitor of release. Similarly, we found that synaptotagmin IV could substitute for synaptotagmin I. By contrast mutating two of the Ca^{2+} -binding aspartate residues in the C2B domain (D416,418N) decreased evoked transmitter release by >95%. We conclude that the C2B but not the C2A domain of synaptotagmin is required for Ca^{2+} -dependent synaptic transmission and that synaptotagmin IV promotes rather than inhibits synaptic transmission.

Eps15 is a protein that interacts with other proteins of the endocytic machinery, including α -adaptin and epsin. Mutant and dominant negative studies have implicated it in vesicle recycling in *Caenorhabditis* synapses and in endocytosis in mammalian cells. To understand further the molecular function of Eps15, we have initiated an analysis of the gene and its product in *Drosophila*. We have sequenced a full-length cDNA of *Drosophila* eps15 and used this to predict the protein sequence, which is highly conserved with that of homologs in *Caenorhabditis* and humans. We have identified a severe loss-of-function allele of eps15 in *Drosophila*. Homozygous mutants show reduced survival to adult stages, and survival is increased by expression of an eps15 transgene. Mutant larvae are sluggish and have an abnormal body posture. Prolonged stimulation of neuromuscular junctions (NMJs) leads to a more severe rundown in amplitude of excitatory junction potentials (EJPs) in mutant larvae than in wild-type. This indicates a possible defect in replenishment of synaptic vesicles, similar to that of *shibire* mutants, which lack dynamin function. Consistent with this interpretation, Eps15 is present presynaptically at *Drosophila* larval NMJs. Therefore, Eps15 appears to be required for normal synaptic physiology in *Drosophila*, possibly by acting in vesicle recycling.

S7-3

Dynamics of postsynaptic density

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Remodeling of synaptic structure is important in both development of functional neural circuits and modulation of preexisting connections. A variety of proteins are recruited to the postsynaptic density (PSD), an electron dense thickening of the postsynaptic membrane, and are thought to play critical roles in the modulation of synaptic functions. We previously showed continual remodeling of the PSD-95 containing postsynaptic structure and synchronized accumulation of synaptic vesicle proteins and PSD-95 at synaptic junctional sites. To further explore mechanisms governing the formation and remodeling of the PSD, we utilized dissociated cultures of hippocampal neurons isolated from transgenic embryos expressing GFP-tagged PSD proteins. Expression of GFP-tagged PSD molecules was stable and the remodeling process of PSDs could be followed for more than a week. Repetitive imaging of the same cell populations revealed both monotonous increase of PSD number and its complex fluctuation, including short decremental stages. Comparison of the temporal profiles from multiple cells in the same culture preparation revealed synchronized assembly and disassembly of PSDs in single cells. Pharmacological manipulations indicated the involvement of cAMP-dependent signaling in this process. These observations suggest presence of signaling mechanisms that control the total number of postsynaptic structure in a single neuron. This process is possibly involved in activity-dependent, neuron-wide synaptic homeostasis, which is important for promoting stability of neural circuits.

S7-4

Potential roles of synaptic scaffolding molecule (S-SCAM) in the molecular organization of synapses

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Neural synapses have two microdomains, the neurotransmission domain and the cell adhesion domain. These domains are closely related to each other. Synaptic activity modifies the strength of cell adhesion, while the modification of cell adhesion changes the efficacy of synapses for neurotransmission. Our major interest is the molecular mechanism to link the neurotransmission domain and the cell adhesion domain. The initial focus is on synaptic membrane-associated proteins that interact with cell adhesion molecules and neurotransmitter receptors. Synaptic scaffolding molecule (S-SCAM) is composed of multiple PDZ domains, a guanylate kinase (GK) domain, and two WW domains. The molecular structure of S-SCAM is similar to that of PSD-95, which has three PDZ domains, one SH3 domain, and one GK domain. Moreover, both of S-SCAM and PSD-95 interact with N-methyl-D-aspartate receptor subunits and a cell adhesion molecule, neuroligin. We previously reported that β -catenin binds S-SCAM and recruits it to synapses. Thereby, it is likely that S-SCAM is initially targeted to the cadherin-based cell adhesion domain at synapses. I will report here that S-SCAM recruits neuroligin to synapses, and that neuroligin is involved in the synaptic targeting of PSD-95. The findings imply that S-SCAM and PSD-95 play roles at different stages in the assembly of synaptic components in spite of striking similarities of both proteins. I will also describe the effect of S-SCAM on the degradation of β -catenin in neurons and discuss the potential roles of S-SCAM in the molecular organization of synapses.

S7-5

Structural plasticity of dendritic spines associated with short and long-term potentiation in hippocampal CA1 pyramidal neurons

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Dendritic spines of pyramidal neurons in cerebral cortex undergo structural remodeling during tetanic stimulation that induces long-term potentiation of synapse. It has not been clarified, however, whether the structural remodeling occurs in only spines that received glutamate repetitively from opposing presynaptic terminals, or how these structural alterations are associated with changes in spine functions. Here, we have investigated structural alteration of dendrites of hippocampal CA1 pyramidal neurons by stimulation of single spine with repetitive application of glutamate by two-photon uncaging of a caged-glutamate compound. We found that the enlargement of spine head could be induced in 90% of thin spines, about half of which lasted more than an hour and selective to the stimulated spines. The structural plasticity required activation of NMDA receptors and actin polymerization. In addition, the long-lasting spine enlargement was reduced by a blocker of CaM kinase II, KN62. Three dimensional mapping of glutamate sensitivity using two-photon excitation revealed that the potentiation of glutamate sensitivity was induced specific to the spines undergoing enlargement of spine head. We have thus demonstrated that both short and long-term potentiation can be postsynaptically induced at the level of single spine, and that most of them are associated with enlargement of spine head.

S8-1

The role of ATP in neuro-glio-endothelial interaction - ATP-induced chemokine production in astrocytes -

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The brain is composed of various types of cells including neurons, glial cells (astrocytes, microglia and oligodendrocytes) and endothelial cells. In addition, under some inflammatory conditions, leukocytes such as neutrophils, macrophages and lymphocytes invade into the brain parenchyma. Intercellular communication across these cell species is supposed to play crucial roles in both the brain functions and dysfunctions. However, the molecular basis of such intercellular communication remains to be elucidated. Chemokines are produced in the ischemic or injured brain, and supposed to mediate the activation of microglia and/or invasion of leukocytes. As the first step to identifying the molecule(s) regulating the chemokine production in the damaged brain, we screened several bioactive substances and found that ATP and its related compounds acted on the enriched glial cultures to induce the production of chemokines. Production of monocyte chemoattractant protein-1 (MCP-1) was increased by ATP-treatment in the cultured astrocytes, but not microglia. On the other hand, production of cytokine-induced neutrophil chemoattractant-1 (CINC-1) was upregulated by ATP in both the cultured astrocytes and microglia. In addition, ATP and its hydrolysis-resistant analogue ATPγS induced the production of MCP-1 in the cortico-striatal slice culture with a peak at 3-4h after the treatment. Almost all of the MCP-1 immunoreactivity was located on astrocytes. MCP-1 concentration in the culture media markedly increased by these compounds at 24h. ATP is a potential candidate of the molecule that causes glial inflammatory responses in the ischemic or injured brain.

S8-2

Intracellular Proteases and ATP-induced Apoptosis of Neuronal and Glial Cells

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It is well known that Ca^{2+} influx through P2X_7 receptors activates various intracellular signaling systems. In antigen presenting cells, P2X_7 receptors are associated with secretion of cytokines such as interleukin 1- β (IL-1 β) and induction of apoptosis. Cytokines and possibly other substances released through activation of P2X_7 receptors facilitate immune responses by activating helper T cells and induce protective and/or harmful effects on neurons. Recently, we have found that ATP or Bz-ATP, an agonist of P2X_7 receptors, activated μ -calpain in primary cultured rat microglia. When microglia were treated with calpain inhibitors such as calpain inhibitor-1, Bz-ATP-induced secretion of IL-1 β and apoptosis were significantly suppressed, suggesting the involvement of μ -calpain in these processes. On the other hand, microglia treated with pepstatin A, an aspartic protease inhibitor, exhibited a lysosomal accumulation of subunit c of mitochondrial ATPase. In pepstatin-treated microglia, the amounts of reactive oxygen species induced by Bz-ATP or phagocytosis of opsonized zymosan were markedly increased. These results suggest that lysosomal dysfunction may make microglia more harmful to neurons. This may have a significant implication in pathogenesis of neurodegenerative diseases such as Alzheimer's disease and lysosomal storage disease. These results strongly suggest that some of P2X_7 receptor-mediated responses are regulated by intracellular proteases.

S8-3

Microglial activation by ATP through Gi/o-coupled purinoceptor, P2Y_{12}

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Accumulating lines of evidence indicated that activated microglia exhibit proliferation, morphological changes, phagocytosis and release of bioactive factors, suggesting that the cells play important roles in tissue repair and neural regeneration. Recently extracellular ATP have been shown to activate microglia through various types of ATP receptors. For example, ATP stimulates the release of neuroprotective factors, such as plasminogen, IL-1 β , TNF- α and IL-6 by means of ionotropic and metabotropic ATP receptors. Recently we have shown that ATP and ADP induced membrane ruffling and chemotaxis of cultured microglia. These phenomena were inhibited by pertussis toxin (PTX) and AR-C69931MX, a selective antagonist against of P2Y_{12} receptor. We examined expression of P2Y_{12} in adult rat brains using in situ hybridization. P2Y_{12} -expressing cells showed small cell bodies and distributed throughout the brain. The cells increased in the facial nucleus following axotomy, and expressed microglia-specific protein Iba1, indicating that P2Y_{12} -expressing cells in the brain are microglia. We further showed that the small G-protein Rac was activated in microglia by ATP stimulus, and its activation was inhibited by pretreatment with PTX. Iba1, which has been reported to participate specifically in Rac signaling in microglia, was accumulated in membrane ruffles and was phosphorylated under the stimulus of ATP. These findings suggest that Iba1 and Rac are involved in the signaling downstream of P2Y_{12} receptor during microglial activation.

S8-4

Diverse consequences of the ATP application in the hippocampal synaptic transmission

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Molecules underlying extracellular purine signaling including the P1 and P2 receptors and families of ectonucleotidase are widely expressed in the central nervous system including the hippocampus, however, their functional role in the brain function remains largely undetermined. To identify the functional consequence of a rise in extracellular ATP concentration in the hippocampal network, spontaneous inhibitory and excitatory postsynaptic currents (IPSCs and EPSCs, respectively) were simultaneously recorded in isolation from each other from CA3 pyramidal neurons in the hippocampal slices of young rats. ATP (0.1-0.3 mM) as well as adenosine, but not α,β -methylene ATP ($\alpha\beta$ mATP) and 2-methyl-thio-ATP significantly decreased the EPSC frequency. In contrast, ATP at a higher concentration (0.3-1 mM) significantly increased the IPSC frequency, an effect being mimicked by 2-methyl-thio-ATP, ATP γ S and $\alpha\beta$ mATP, but not by adenosine. PPADS, tetrodotoxin, but not kynureic acid significantly attenuated these effects. Fluorometric measurement using Fluo-4 revealed CA3 interneurons responding to 2-methyl-thio-ATP with a marked rise in the intracellular calcium concentration. These results suggest that in CA3 pyramidal cells ATP attenuates excitability and excitatory transmission through activation of A₁ receptors after extracellular breakdown and concurrently promotes inhibitory transmission through activation of P2X receptors in the interneurons. All these consequences of a rise in ATP concentration reduce the pyramidal cell excitability, which might have important protective role under massive cell damage in the hippocampus.

S8-5

Bi-directional regulation of neuronal activities by extracellular ATP

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The energy currency "ATP" is now known as an important neurotransmitter in the CNS. Recent studies have suggested that ATP also mediates communications among glial cells or even those of so-called "tripartite synapses". In the present study, we show that extracellular ATP has a central role to mediate communications (1) between astrocytes and glutamatergic neurons in hippocampal cultures, and (2) between epidermis keratinocytes and small-sized DRG neurons. In hippocampal astrocytes, intercellular communication "Ca²⁺ wave" was elicited by release of ATP and activation of P2Y1 receptors in astrocytes. Since numerically superior astrocytes are located closely in neurons or synapses, astrocytic ATP could act on adjacent neurons and inhibited presynaptic functions, leading to dynamic inhibition of excitatory synaptic transmission. Epidermis keratinocytes revealed propagating Ca²⁺ waves, which was dependent on release of ATP and activation of P2Y2 receptors. DRG neurons are known to terminate peripherally in skin cells, and especially small-sized unmyelinated DRG neurons directly contact with basal layer of keratinocytes. The ATP-dependent Ca²⁺ wave in keratinocytes activated small-sized DRG neurons, which resulted in nociceptive signal transduction. Thus, non-neuronal cells or tissues could communicate with adjacent neurons by releasing ATP, and show either inhibitory or excitatory regulation of neuronal functions. Such dynamic communications mediated by extracellular ATP would be of great consequence for the study of neuronal functions.

S9-1

Dysfunction of the ubiquitin proteasome system in neurodegenerative disease

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Most neurodegenerative diseases share common cytopathological features including intracellular accumulation of aggregated protein in inclusion bodies and massively elevated levels of ubiquitin conjugates. Because multiubiquitinated proteins are usually efficiently degraded by cellular proteasomes, their accumulation in diseased neurons has long suggested a link between cellular pathogenesis and dysfunction of the ubiquitin-proteasome system (UPS). We have previously shown that a destabilized variant of green fluorescent protein (GFP) can be used as a non-invasive reporter of UPS activity and that cells with large aggregate burdens exhibit impaired UPS function. However this reporter, GFPu, is expressed in both nuclear and cytoplasmic compartments. Because localization of disease-associated inclusion bodies to either the nuclear or cytoplasmic compartments appears to be a consistent property tightly linked to pathogenesis, we have developed variants of the original GFPu that are restricted to either nuclear or cytoplasmic compartments. We have used these compartmentalized reporters to assess the effect of protein aggregation in one compartment on UPS activity in both compartments. Cells with cytoplasmic huntingtin inclusions exhibited increased fluorescence of both reporters, suggesting that cytoplasmic aggregation can influence UPS activity in both nuclear and cytoplasmic compartments. Similarly, cells with nuclear ataxin-1 inclusion bodies exhibit enhanced fluorescence of both reporters, indicating that nuclear aggregation can influence UPS activity in both nuclear and cytoplasmic compartments. These data suggest that the impairment of UPS function by protein aggregation can cross compartmental boundaries.

S9-2

Parkin and Parkinson's disease

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Park2, which is an autosomal recessive form (AR-JP) by parkin gene mutations, is the most common form of Familial PD. Moreover, we know that the role of parkin protein in the brains is to break down misfolded proteins as an ubiquitin-protein ligase, and the mutations appear to prevent it from doing its job due to the loss-of-function effects. Recently, although the presence of Lewy bodies have been reported in one case, the lack of Lewy bodies in parkin-mutated brains suggests us a fundamental pathology for Lewy bodies formation. Considering the absence of Lewy bodies in AR-JP brains, the parkin function could be essential for the Lewy bodies formation. Thus, the elucidation of the exact role of parkin protein provides us the mechanisms of the formation of Lewy bodies in sporadic PD. Therefore, it is important to detect the substrates for the parkin protein. Recently, several candidate substrates have been reported including CDCrel-1, synphilin-1, *o*-glycosylated α -synuclein, PAEL-receptor, cyclin E, and α/β tubulin. The question is accumulation of which substrates are responsible for the nigral neuronal death in Park2 linked brain.

In addition, the localization of parkin protein provides us the information to elucidate the mechanism of nigral neuronal death. The distribution of parkin in the nerve terminals suggests its role in some synaptic activities. Furthermore, CDCrel-1, one of candidate substrates, functions as a regulator of exocytosis. We also show the overexpression of parkin mutants in the pancreatic cell line HIT-T15 exhibit a reduced release of the reporter human growth hormone. Parkin knockdown with siRNA resulted in the same consequence, suggesting parkin functions as a positive regulator of exocytosis. In addition, parkin interacted with some neuronal SNARE proteins such as syntaxin 1, SNAP-25, and VAMP2 in COS1 cells. These results suggest SNAREs are involved in parkin function in exocytosis. The impaired exocytosis may underlie the pathogenesis of Park2 brains.

S9-3

Parkinson's disease and ER stress -from a study of autosomal recessive juvenile parkinsonism (AR-JP)

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Recent growing evidence has shown that neurodegenerative diseases including Parkinson's disease (PD) are caused by accumulation of various kinds of misfolded proteins. The presence of an abnormal neuronal inclusion, Lewy body (LB), which is a neuropathological hallmark of common PD, strongly suggests that this disease indeed involves disturbances in protein degradation system. Although a rare autosomal recessive juvenile parkinsonism is not usually accompanied by LBs in the affected regions, Parkin, the disease gene product, has turned out to be a proteolysis-related enzyme - a ubiquitin ligase. One of the substrates for Parkin is an integral membrane protein, Pael receptor (Pael-R). Pael-R has unique properties to be easily misfolded even in physiological conditions. Misfolded Pael-R is eliminated by wild-type Parkin, but not AR-JP-related mutants. When the degradation of Pael-R is blocked, it accumulates in the endoplasmic reticulum (ER), resulting in ER stress-induced cell death. I will present the recent findings in molecular mechanism of ER stress-induced neuronal death caused by misfolded Pael-R.

S9-4

Pathophysiological role of ubiquitin C-terminal hydrolase L1 in neurodegeneration

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Ubiquitin C-terminal hydrolase L1 (UCH-L1) is a constituent of cellular aggregates that are indicative of neurodegenerative diseases, such as Lewy bodies in Parkinson's disease. I93M mutation was reported in a family with a dominant form of Parkinson's disease. We recently identified that an intragenic deletion of mouse UCH-L1 gene causes gracile axonal dystrophy (*gad*), a recessive neurodegenerative disease. These two examples of neuro-dysfunction from UCH-L1 mutations prompted us to investigate the function of UCH-L1 in neuronal cells. We found that UCH-L1 associated with monoubiquitin and elongates ubiquitin half-life. The *gad* mouse exhibited the reduced level of monoubiquitin in neurons. In contrast, overexpression of UCH-L1 caused an increase in the level of ubiquitin in both cultured cells and mice. These data suggest that UCH-L1, with avidity and affinity for ubiquitin, insures ubiquitin stability within neurons. We further investigated the possible pathological role of UCH-L1. We constructed recombinant human UCH-L1 variants, and examined their structure (using circular dichroism) and hydrolase activities. I93M substitution resulted in a decrease in *k_{cat}* coincident with an alteration in alpha-helical content. In contrast, an S18Y substitution resulted in an increase in *k_{cat}* without altering the circular dichroistic spectrum. These data suggest that UCH-L1 hydrolase activity may be inversely correlated with Parkinson's disease risk and that the hydrolase activity is protective against the disease. Furthermore, we found that oxidation of UCH-L1 by 4-hydroxynonenal, a candidate for endogenous mediator of oxidative stress-induced neuronal cell death, resulted in a loss of hydrolase activity. Further studies of altered UCH-L1 hydrolase function would provide new insights into a possible common pathogenic mechanism between familial and sporadic Parkinson's disease.

S9-5

Mechanisms to control degradation of polyglutamine-containing protein

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Machado-Joseph disease (MJD) is neurodegenerative disease which is caused by polyglutamine expansion in a responsible gene product, MJD1. MJD1 is degraded by ubiquitin-proteasome pathway. MJD1 with expanded polyglutamine tract was more resistant to degradation than normal MJD1. We established an in vitro system of ubiquitylation of MJD1, thereby biochemically purified activity to mediate polyubiquitylation of MJD1. An AAA-family ATPase VCP, and a mammalian ubiquitin-chain assembly factor (E4), UFD2a, are critical for polyubiquitylation of MJD1. UFD2a markedly promoted ubiquitylation and degradation of MJD1 with expanded polyglutamine tract, resulting in the clearance of MJD1 protein. In contrast, dominant-negative mutant UFD2a reduced the degradation rate of MJD1, leading to the formation of intracellular aggregation. In *Drosophila* model, overexpression of UFD2a significantly suppressed the neurodegeneration induced by expression of MJD1 with expanded polyglutamine tract. These findings suggest that E4 is a rate-limiting factor of degradation of pathologic polyglutamine-containing proteins, and may give a potential tool for gene therapy to control the clinical conditions of MJD.

To study the role of UFD2a in mammals, we have generated mice lacking UFD2a. The mutant mice died at embryonic day 12, manifesting enlarged heart. Histopathological examination revealed thinning of the myocardial layer of the heart with massive apoptosis. These data indicate that UFD2a plays a crucial role in cardiac growth and development as a mammalian E4 enzyme. Interestingly, UFD2a^{+/−} mice show impaired locomotion and abnormal histopathology in the terminal of sensory neurons. We are currently investigating the neurology and pathology in UFD2a^{+/−} MJD1-transgenic mice.

S10-1

Gene Expression Changes and Loss of Neuronal Plasticity in the Aged Brain

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A central question in the neurobiology of aging is why brains from aged organisms have reduced plasticity when compared with those from young adults. Answers to this question will present a hint for effective therapy for memory loss and delayed recovery from damage in the aged brain. We hypothesize that key molecules for understanding the mechanisms of loss of neuronal structural plasticity would be the so-called neuronal growth-associated proteins (nGAPs) and the signaling molecules that are relevant for the induction of plasticity-related molecules such as nGAPs. We isolated a neural-specific phosphotyrosine signal adapter N-Shc, which is induced in central neurons following the stimulation by neurotrophins such as BDNF. The BDNF-dependent induction of N-Shc is followed by subsequent induction of RB3, a neuronal homolog of SCG10/stathmin family. We find RB3 and N-Shc play a crucial role in regulating the neuronal microtubule and actin cytoskeleton reorganization. We further found the N-Shc-induced actin reorganization is mediated by a novel brain-enriched p250 Rho-GAP, which we referred to GRIT, a GTPase regulator interacting with TrkA. Indeed, GRIT interacted with TrkA, and GRIT-overexpression promoted NGF-induced neurite outgrowth of PC12 cells. While these neural enriched molecules, including N-Shc, GRIT, and RB3, are crucial players for neuronal cytoskeletal rearrangement or structural plasticity, we further found that N-Shc also relates to neuronal functional plasticity. Interestingly, N-Shc gene deficient mice were altered in hippocampal function, and N-Shc seems to have a modulatory role on NMDA receptor at synapse. Functional roles and gene expression changes of these molecules will be discussed with the special interest to the aging brain.

S10-2

Brain aging and Humanin

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Alzheimer's disease (AD) is a major cause of senile dementia. Although the responsible molecule for sporadic AD has been unidentified yet, aging is generally recognized as the greatest risk factor. Humanin (HN) is 24 amino acids polypeptide that suppresses AD-relevant neuronal cell death (Proc. Natl. Acad. Sci. USA 98, 6336-6341, 2001). HN antagonizes against all AD-related toxic insults including familial AD-linked mutant genes and A β at 10 microM, and amino acid substitution promotes its effective dose as low as femtoM. HN also protects cerebrovascular smooth muscle cells from A β toxicity observed in amyloid angiopathy (J. Neurochem. 84, 266-272, 2003). HN is ubiquitinated and degraded by the TRIM11-dependent mechanism (Eur J. Neurosci 17, 1150-1158, 2003). In immunohistological analysis, HN-immunopositive neurons and glia cells were detected in occipital lobe and all over the brain, respectively, in the AD brain, whereas little immunopositive cells were detected in age-matched control. HN immunoreactivity was also observed in senile plaques in brain sections of Tg2576, Swedish type A β PP mutant-overexpressing transgenic mice. In immunoblot analysis with normal mouse samples, the 3kDa HN-immunopositive band was detected in the testis and the colon in 3 week-old mice, but only in the testis in 12 week-old mice (Neurosci. Lett. 324, 227-231, 2002). These results suggest that in vivo expression of HN is regulated by age and/or pathological conditions. In addition, HN recovers amnesia caused by scopolamine and A β 25-35 in mice. Rattin, the HN homolog identified in the rat, antagonizes glutamate-induced toxicity (FASEB J. 16, 1331-1333, 2002). These findings imply that HN has a wide range of neuroprotective effect in vivo. Potential roles of HN in aging brain and other organs will be further discussed.

S10-3

Roles of neurotrophic factors in aged brain

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The aging of brain based on neuronal dysfunction and decrease in neuronal cell number is focused. Neurotrophic factors including brain-derived neurotrophic factor (BDNF) are noticed as endogenous factors that regulate the brain aging. BDNF belongs to the well-characterized neurotrophin family, and is widely expressed in neuronal populations of central nervous system. BDNF synthesis/secretion is regulated by glutamate or GABA neurotransmission, and thus seems to participate in various activity-dependent events including synapse plasticity. In facts, there are several reports showing that BDNF content or its mRNA expression is lower in the particular brain regions of the aged animals. Immunohistochemical analysis found BDNF is predominantly distributed in the regions expressing a high level of mRNA, or in the synapse-associated structures. What mechanisms are involved in the regulation of BDNF production in the aged animals? Glucocorticoids may be a candidate. Basal corticosterone level increases with age in rats as a result of decreased negative-feedback inhibition of hypothalamic-pituitary-adrenal activity. We found that corticosterone reduced BDNF production in cultured rat hippocampal neurons, which suggests that the failure of BDNF production induces neuronal dysfunction and/or vulnerability. Further, BDNF content was markedly reduced in brains of the rat type I diabetes mellitus. In these rats, the memory/learning ability was impaired, and the spine structures of the dendrite of cerebral pyramidal neurons were destroyed, resembling partly to those of the aged rats. To elucidate a relationship between BDNF expression and neuronal function or structure, we are examining the effects of BDNF gene transfection into neural stem cells of embryonic rats.

S10-4

Synaptic Plasticity and Cognitive Enhancement by Enriched Environment

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Hebb (1949) was the first to develop the concept that an enriched environment has an effect on the brain. In the 1960s, environmental stimulation was reported to change anatomical measures of the brain such as cortical thickness. The morphological plasticity of synapses responding to an enriched environment was further confirmed. This type of plasticity was shown to be synaptic strengthening rather than synaptogenesis (1). Activity-dependent neurogenesis (Nature Rev Neuroscience, 1: 191-8, 2000) and gene expression (Mol Brain Res, 91: 50-6, 2001) were recently reported.

Enriched environmental rearing was reported to enhance the cognitive function of developing rats and mice in the literature. However, it has been controversial whether the similar effect is observed with aged animals. We have attempted to determine the effect of environmental enrichment on the learning ability of aged rats. Even short-term (3 M) exposure to an enriched environment was effective in aged rats, although the effect of long-term exposure starting at weaning was much greater than that of short-term exposure (2). The results show that aged animals still have appreciable plasticity in cognitive function, and suggest that environmental stimulation could benefit aging humans as well.

- 1) Nakamura H, Kobayashi S, Ohashi Y and Ando S: Age-changes of brain synapses and synaptic plasticity in response to an enriched environment. J Neurosci Res, 56: 307-315 (1999)
- 2) Kobayashi S, Ohashi Y and Ando S: Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. J Neurosci Res, 70: 340-346 (2002)

S10-5

Neurogenesis in the hippocampus of aged rats

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In general, neurogenesis occurs during embryonic and early postnatal stages and ceases at the adult stage. Further the number of neurons in the brain declines with aging. However, the dentate granule cells continue to be produced during the adult period in mammals, including humans. In this sense, the dentate gyrus is an exceptional brain region. Although the precise function of the adult neurogenesis is unknown, recent studies have shown that the production and survival of new neurons are modulated by stress, a rich environment, exercise, and brain damage. These studies suggest that hippocampal adult neurogenesis may play an important physiological role and may contribute to the treatment of brain damage and disease occurring with aging. Here we examine the development of newly generated dentate granule cells in young and older rats using cell proliferation markers (BrdU and Ki67) and immature neuronal markers (polysialic acid-neural cell adhesion molecule; PSA-NCAM). In young adult rats newly generated cells first make clusters and then disperse in the subgranular zone and deep part of the granular cell layer. PSA-NCAM-positive developing neurons express strongly NeuroD which is a bHLH transcription factor and is required for differentiation of hippocampal granule cells, while they do weakly mature neuronal markers such as NeuN and MAP2. The numbers of the PSA-NCAM- and the NeuroD-positive neurons decrease in older rodents, but no qualitative difference is found in the expression patterns of these molecular markers between young and older rats. Further, clustering and dispersion of newly generated cells also are found in older rats. These results suggest that newly generated neurons in young adult and older rats have similar properties and imply that dysfunction of the aged brain may be restored by the stimulation of adult neurogenesis.

S11-1

Diversity of astrocytes.

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Brain cells are composed of three major cell types; neuron, astrocyte and oligodendrocyte. It is well known that neurons generated from distinct domains or developmental time course of brain have different character and are named differently, such as pyramidal or granule neurons of hippocampus. On the other hand diversity of astrocytes is not recognized. Recently, however, astrocytes have been shown to possess many functions and it is becoming more and more convincing that there are subtypes in the astrocyte lineage cells. At present most common definition of astrocytes is "cells expressing GFAP", which totally ignores the presence of its diversity. We have been screening for novel monoclonal antibodies that label astrocyte lineage cells from early development from a pool of newly isolated monoclonal antibodies. We found several antibodies that label radial glial cells in mouse spinal cord from as early as E12. Interestingly, some of them labeled different populations of radial glial cells along the dorso-ventral axis. This suggests that at least in the E12 spinal cord there are distinct subpopulation of astrocyte lineage cells. We are trying to understand how these diversity of astrocytes are reflected to their functional diversity.

S11-2

Regulation of axonal functional domain organization by glia

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Myelinated axons consist of four distinct regions, including the node, paranodal and juxtaparanodal regions and internode, which are determined by specific distributions of distinct channels and adhesion molecules. Voltage-gated sodium channels are concentrated at the node of Ranvier, while potassium channels are at the juxtaparanodal region. These characteristic localizations as well as specific expression of channel subtypes are strictly influenced by myelination. The node and juxtaparanodal region are separated by the septate-like paranodal axo-glial junction, which is formed between axonal adhesion proteins, Caspr and contactin, and glial counterpart, Neurofascin155 (NF155). Myelin glycolipid sulfatide and two tetraspanins CD9 and CD81 are also involved in the paranodal formation. Our recent study shows that these tetraspanins form complex with other glial proteins and probably act on targeting these proteins to the appropriate membranes. The mutants which lack any one of each paranodal molecules cause paranodal disruption, resulting the significant changes of axonal surface organization. In addition, the abnormal sodium channel subtype switch occurs with age, and it cause subsequent loss of channel clusters from the nodes. Thus, the paranodal axo-glial junction may mediate signals between axon and glia to form and stabilize each axonal domain characteristics in addition to be just an electrical insulator. Such unusual rearrangement of channel subtypes is not observed in the mutant sciatic nerve where paranodal disruption is also observed. Thus, the presence of paranodal junction significantly influence axonal protein organization, however, such importance may be different between the CNS and PNS axons.

S11-3

Possible roles of glia-neuron networks in brain function

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Recent studies on optical measurements, especially calcium imaging, revealed the dynamic profiles of glial cells. Those cells were found to express receptors for many types of neurotransmitters, such as glutamate, acetylcholine, monoamines, ATP and peptides and responded to those neurotransmitters by oscillatory increase in calcium concentration. Furthermore the glial cells were found to release neurotransmitters, such as glutamate and ATP. The concept of "tripartite synapse" formed among presynaptic neuron, postsynaptic neuron and surrounding astrocyte was derived from those findings. Since the calcium signaling can propagate into the other astrocytes using gap junction and also ATP dependent process, the activities at one synapse may not cease in a local response at a tripartite synapse, but spread widely into surrounding synapses through astrocyte-networks. Our experiments on fresh and also organotypic culture of rat hippocampus loaded with fluo-4, a calcium indicator, showed that the activation of astrocytes by t-ACPD, a metabotropic glutamate receptor agonist, induced oscillatory sipCa^{2+} changes in astrocytes and synchronized oscillatory activations of a group of neuronal cells. The oscillatory activities of neuronal cells were blocked by the antagonists for ionotropic glutamate receptors. Intracellular Ca^{2+} concentration of a single astrocyte in fresh slice preparation loaded with fluo-4 showed delayed, but obvious increase during tetanic stimulation to cause long term potentiation. Our findings demonstrated the participation of astrocyte-neuron networks to the synaptic plasticity and the other higher brain function.

S11-4

Functions of Ca^{2+} -permeable AMPA receptors and glutamate transporters in Bergmann glia

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Bergmann glia (BG) in the cerebellum elaborately ensheathes Purkinje cell (PC) synapses, and express Ca^{2+} -permeable AMPA receptors. We converted these Ca^{2+} -permeable AMPA receptors into Ca^{2+} -impermeable receptors by adenoviral-mediated delivery of the GluR2 gene. This conversion retracted the glial processes ensheathing both parallel fiber (PF) and climbing fiber (CF) synapses on PC dendritic spines, and retarded the removal of synaptically released glutamate. Thus, the glial Ca^{2+} -permeable AMPA receptors are indispensable for proper structural and functional relations between BG and glutamatergic synapses.

Since BG express a high-affinity glutamate transporter, GLAST, most abundantly, this transporter may be responsible in large part for the uptake of synaptically released glutamate. To clarify the role of GLAST, we examined the decay time constants of CF- and PF-EPSCs in GLAST-deficient mice in the presence of cyclothiazide (CTZ) that eliminates the desensitization of AMPA receptors. Under this condition, the amplitude of the EPSCs increased and their decay phase was markedly prolonged in GLAST-deficient mice. We also found that the decay of CF- and PF-EPSCs was prolonged by much lower concentrations of DL-threo- β -benzyloxyaspartate (DL-TBOA), a specific blocker of glutamate transporters, in GLAST-deficient mice, suggesting that GLT-1, another glial transporter present in BG at lower levels, also participated the removal of glutamate. GLAST-deficient mice were provided by Dr. Kohichi Tanaka (Tokyo Medical and Dental University).

N001 (MS2-1)

ANALYSIS OF EXPRESSION PROFILES OF G-PROTEIN COUPLED RECEPTOR GENES IN EMBRYONIC NEURAL STEM CELLS.

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G-protein-coupled receptors (GPCRs) constitute the largest family of cell-surface receptors. GPCRs respond to molecular signals including neurotransmitters, hormones, peptides, nucleotides, lipids and other chemicals, and are involved in the regulation of cell growth, differentiation, survival, motility, hormone secretion and neurotransmission, among other processes. It has been demonstrated that the activation of GPCRs such as muscarinic receptors induces embryonic neural stem cell growth via activation of extracellular-regulated kinase 1/2 (ERK1/2). However, little is known about the expression of other GPCRs in embryonic neural stem cells, and therefore we analyzed the expression profiles of GPCR genes in these cells. We prepared neuroepithelial cells from the E14.5 mouse telencephalon and cultured nestin-positive cells (embryonic neural stem cells) in serum-free medium containing basic FGF. Specific primer sets were synthesized for 598 mouse GPCR genes (identified in GenBank and the GPCR database, [www.cmbi.kun.nl/7tm/]) and we analyzed GPCR gene expression using SYBR green-based quantitative reverse transcription-polymerase chain reaction (SYBR green QRT-PCR). We identified 38 known and 7 orphan GPCR genes that are highly expressed in embryonic neural stem cells. Furthermore, we tested whether specific agonists for these GPCRs elicit biological effects on these cells. Several agonists were found to regulate cell growth and motility, suggesting that these GPCRs and specific ligands play important roles in these neuronal stem cell processes as well as in embryonic neurogenesis and gliogenesis.

N002

NEURONAL GLUTAMATE TRANSPORTER EAAT3 (EAAC1) IS INVOLVED IN AN UNIQUE CYSTEINE TRANSPORT SYSTEM

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Glutamate transporters (EAATs) has been reported to contribute in regulating the extracellular Glu levels. Here we show the evidence that EAAT3 is involved in neuronal Cys uptake, and this Cys transport system shows unique pharmacological profiles compared with other cysteine uptake systems.

Neural cell cultures were exposed to Glu (0.1 mM) for 5 min, and incubated for 24 h in the presence or absence of EAAT inhibitors, such as PDC and TBOA. PDC (0.2 mM) increased the Glu-induced neuronal death to 147% of that induced by Glu alone. The cells treated with EAAT inhibitors showed reduced level of intracellular glutathione (GSH) and generation of reactive oxygen species. NAC and Glu receptor antagonists additively reduced the death enhanced by EAAT inhibitors. These facts suggest that EAATs inhibitors enhances Glu-toxicity not only via activation of Glu receptors but also reduces intracellular GSH levels.

The neuronal Cys uptake was enhanced by the extracellular sodium and Cys levels. EAAT inhibitors suppressed the Cys uptake, whereas inhibitors of Cys transporters did not affect the neuronal Cys uptake. Increased level of extracellular Cys enhanced Cys uptake, and increased level of extracellular Glu and aspartate, substrates of EAATs, suppressed Cys uptake, though substrates for the Cys transporters, such as Ala and Ser, did not affect Cys uptake. Intracellular GSH level was decreased in the presence of EAAT inhibitors and substrates of EAATs, but was not affected by those of Cys transporters. Knock down expression using antisense oligonucleotide decreased Cys uptake and GSH level, and increased neuronal vulnerability against oxidative stress. These facts indicate that EAAT3 plays an important role in this unique Cys uptake system in neurons.

N003

Expression of vanilloid receptor (VR1) in PC12 cells

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Capsaicin, a pungent ingredient of chili pepper, activates vanilloid receptor subtype 1 (VR1). VR1 is a nonselective cation channel with high Ca^{2+} permeability, and is expressed mainly in primary sensory neurons. However, many studies suggest that VR1 exists in various tissues including the central nervous system and peripheral, non-sensory neuronal cells. Various pharmacological effects induced by capsaicin are reported in these non-sensory neuronal cells. In PC12 cells, a rat pheochromocytoma-derived cell line, we have shown that capsaicin and anandamide, which is endogenous ligand for VR1, activated phospholipase A₂ and induced arachidonic acid release in concentration-dependent manner, although underlying mechanisms are still unknown. These pharmacological studies suggested the possibility of the existence of VR1 in PC12 cells. Here, we investigated whether VR1 is expressed in PC12 cells. VR1 mRNA and the protein were detected in PC12 cells by reverse transcriptase-polymerase chain reaction and western blotting analysis, respectively. Capsaicin induced increase of intracellular Ca^{2+} concentrations concentration-dependently at more than 100 μM . The effect by capsaicin was dependent on extracellular CaCl_2 , and was blocked by capsazepine, a selective antagonist of VR1. The increase by capsaicin was transient, and the level of intracellular Ca^{2+} concentrations returned to the basal level at 3-4 min after the addition. In addition, anandamide also increased intracellular Ca^{2+} concentrations. These findings indicate that VR1 was expressed, and activated by capsaicin in PC12 cells.

N004

Developmental expression of a member of TNF receptor superfamily, TROY, in the olfactory system of mice

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We previously reported that TROY, a member of the tumor necrosis factor (TNF) receptor superfamily, is expressed in the olfactory system, in addition to the germinal zones during the neural development. The olfactory system is unique in its ability to continuously turn over olfactory receptor neurons (ORNs) throughout life by division of undifferentiated precursor cells located in the olfactory epithelium. In the present study, we examined the characteristics of TROY-expressing cells in the developing olfactory system. TROY mRNA and protein were first detected in the olfactory nerve layer (ONL) and the glomerular layer (GL) at embryonic day 13.5 and neonatal stage, respectively. In particular, TROY expression was most intense in the inner part of the ONL (ONL-i) during late embryonic stages. In the ONL-i, TROY was colocalized with neuropeptide Y, but not with S-100 or p75 low affinity nerve growth factor receptor, indicating that TROY was expressed in olfactory ensheathing cells (OECs) of the ONL-i, but not in OECs of the outer part of ONL (ONL-o). In addition, some TROY-expressing cells in the ONL-i were astrocyte-like cells (GFAP-positive, NPY-negative). In the GL, TROY was also expressed in the astrocytes of the GL during postnatal stages because TROY-expressing cells were positive for GFAP. These data indicate that TROY may play some roles in the developing and adult olfactory system.

N005

Effects of neuronal cell toxicity induced by bicuculline methiodide in slice cultures of rat hippocampus

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Fast synaptic inhibition in the vertebrate central nervous system (VCNS) is mediated primarily by the neurotransmitter GABA interacting with the GABAA receptors. Impaired GABA transmission can lead to neuronal hyperexcitability in VCNS. To test the effects of the hyperexcitability, the hippocampal slices from postnatal days 9-10 (P9-P10) rats were cultivated for 7-14 days and then exposed to bicuculline methiodide (BMI, 100 micromole), a GABAA receptor antagonist, for 12-24h. Non-exposed slice cultures served as a control. Selective neuronal cell death was induced by BMI in the CA3 pyramidal layer and cell death was inhibited by muscimol (20 micromole), a GABAA receptor agonist. The death can be reduced by both the NMDA receptor antagonist MK-801 (20 micromole) and the non-NMDA antagonist CNQX (20 micromole). Furthermore, when used in combination these two antagonists the cell death was inhibited completely. These observations suggest that the GABAA receptor was blocked by BMI, which caused an imbalance between excitation and inhibition in the CA3 region in the slice culture of rat hippocampus.

N006

Altered sensitivity of NMDA receptor channels during in vitro maturation in cultured rat cortical neurons

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Both cell bodies and neurites were more immunoreactive to the anti-MAP2 antibody in cortical neurons cultured for 9 days in vitro (DIV) in the absence of fetal calf serum than those for 3 DIV. These cortical neurons were incubated with fluo-3 AM for determination of intracellular free Ca^{2+} ions on fluorescence image analysis. Cultured neurons were briefly exposed to NMDA, followed by washing and subsequent second brief exposure to NMDA at the same concentration. In neurons cultured for 9 to 15 DIV, the second exposure to NMDA led to a less potent increase in the number of fluorescent cells than that found after the first exposure. In neurons cultured for 3 DIV, however, the second exposure to NMDA induced a similarly potent increase in the fluorescence intensity. Nifedipine was similarly potent in inhibiting the increase after the second exposure in neurons cultured for 3 or 9 DIV, while dantrolene slightly inhibited the increase by the second exposure to NMDA in neurons cultured for 3 to 9 DIV. These results suggest that the increase in intracellular free Ca^{2+} by NMDA may partly involve Ca^{2+} influx across the voltage-sensitive Ca^{2+} channels rather than Ca^{2+} release from intracellular stores and that in vitro maturation may lead to desensitization of NMDA receptors in cultured rat cortical neurons.

N007

Functional expression of particular glutamate signaling machineries in rat testis

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In order to elucidate a possible role of Glu as a signal mediator in testis, we have attempted to examine the possible expression and localization of particular subtypes of molecular machineries responsible for glutamatergic signaling in rat testis using different techniques. Using reverse transcription polymerase chain reaction techniques, we found the constitutive expression of mRNA for 5 different subtypes of Glu transporters required for regulation of extracellular Glu concentrations in the brain, in addition to that for particular subtypes of ionotropic and metabotropic Glu receptors, in rat testis. These included NR1, NR2A-C, NR2D, GluR1-4, GluR7, KA1, KA2, mGluR1, mGluR2, mGluR3, mGluR4, mGluR5, mGluR6 and mGluR8. The splice variant of glutamate aspartate transporter (GLAST) -1a was also expressed in both brain and testis. In situ hybridization as well as immunohistochemistry analysis showed localized expression of GLAST and glutamate transporter-1 (GLT-1) at interstitial spaces and elongated spermatids, respectively. [³H]Glu was markedly accumulated in testicular crude mitochondrial fractions, in a temperature-dependent manner. The accumulation was significantly inhibited by the addition of different transport inhibitors known to date. These results suggest that particular subtypes of central Glu transporters could be constitutively and functionally expressed for regulation of extracellular Glu concentrations in rat testis.

N008

Signaling through group II metabotropic glutamate receptors to nuclear activator protein-1 in primary cultured rat cortical neurons

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Cortical neurons were isolated from 18-days old embryonic rat brain, and cultured in DMEM/F-12 containing 10% fetal calf serum for the initial 3 days in vitro (DIV). Cultured neurons were treated with cytosine beta-D-arabinofuranoside for 24 h on 2 DIV, followed by medium change to DMEM every 3 days for consecutive 15 DIV until the day of harvest. RT-PCR analysis revealed the constitutive expression of mRNA for metabotropic glutamate receptor (mGluR) -1 to mGluR8 in cultured cortical neurons irrespective of the duration of cultivation. Cells cultured for 14 DIV were exposed to an agonist at particular mGluR for 5 min in HKR buffer, followed by further incubation for 120 min before harvest and subsequent determination of DNA binding on gel retardation electrophoresis. Of mGluR agonists tested, only the group II mGluR agonist DCGIV significantly increased AP1 DNA binding at a concentration range of 1 to 100 μM in a manner sensitive to prevention by the antagonist APICA at 100 μM. The potentiation by DCGIV was significantly prevented by both nifedipine and BAPTA-AM, but not by dantrolene. These results suggest that activation of group II mGluR subtype could lead to signaling to nuclear AP1 complex for long-term signal consolidation through mechanisms associated with voltage-sensitive Ca²⁺ channels rather than intracellular Ca²⁺ stores in cultured rat cortical neurons.

N009

Contribution of the N- and C-terminal domain to the functional regulation of melanin-concentrating hormone receptor 1

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Recently, the understanding of the role of melanin-concentrating hormone (MCH) in food intake has grown in an accelerated rate and MCH was found to act through two G-protein-coupled receptors MCHR1 and MCHR2 by reverse pharmacology. The importance of MCH system in the control of food intake has been confirmed by findings of lean phenotypes of mice with targeted deletion of MCH or MCHR1. However, the receptor domains critical for signaling are unknown. To explore the role of the N- and C-terminus, mutant receptors were constructed and expressed in HEK293T cells, and cell surface expression, immunofluorescence, radioligand binding, internalization assay and calcium influx assay were performed. MCHR1 has three potential sites for N-linked glycosylation in the extracellular amino-terminus that may regulate its activity. Site-directed mutagenesis of the rat MCHR1 cDNA at single or multiple combinations of the three potential glycosylation sites was used to examine the role of the putative carbohydrate chains on receptor activity. It was found that all three potential N-linked glycosylation sites in MCHR1 were indeed glycosylated, and that N-linked glycosylation at Asn23 was especially important for correct delivery to the cell surface and signal transduction. Next we constructed 15 mutant receptor species comprising substitutions and deletions in the C-terminal domains, and we have determined that the N-terminal region of the cytoplasmic tail is required for optimal Gq-mediated signaling pathway. On the other hands, the distal of MCHR1 is involved in internalization. We are currently investigating which amino acids are responsible for increasing calcium influx and regulating receptor activity on the cell surface.

N010

Immunohistochemical detection of particular NMDA receptor subunits in murine hippocampus

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Marked immunoreactivities were detected with NMDA receptor subunits along the CA1 to CA4 pyramidal and dentate granular layers in sections prepared after perfusion with 4% paraformaldehyde (PA) and Zamboni, but not Carnoy, solutions. Frozen coronal sections were at first made from mouse brains, followed by immersion fixation with 10% formalin or Carnoy solution for subsequent immunohistochemistry. Immunoreactivities were detected with NR1 and NR2C subunits in pyramidal and dentate granule layers on sections fixed with 10% formalin, whereas immersion fixation with Carnoy solution resulted in detection of immunoreactive NR1, NR2A and NR2B, but not NR3C, subunits in the stratum oriens and radiatum of the CA1 subfield as well as the stratum moleculare of the dentate gyrus, but not in pyramidal and granular layers. Immunoblotting analysis using the same antibodies revealed the absence of immunoreactive NR3C subunit from hippocampal membranous preparations. These results suggest that immersion fixation by Carnoy fixative may be more suitable than perfusion with 4% PA fixative for immunohistochemical detection of particular NMDA receptor subunits in murine brain.

N011

Modulation by N-methyl-D-aspartate receptors of development of cultured neural progenitor cells isolated from adult murine hippocampus

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Hippocampus was dissected from adult ddY strain mouse brain, followed by preparation of neural progenitor cells using the percoll density gradient method. In vitro culture of these progenitor cells led to formation of round spheres immunoreactive to nestin within 12 days in vitro (DIV) when cultured in the presence of basic fibroblast growth factor. These neurospheres cultured for 12 DIV were differentiated into cells immunoreactive to MAP-2 and GFAP within 20 DIV upon stimulation by all-trans retinoic acid and ciliary neurotrophic factor, respectively. An RT-PCR analysis revealed constitutive expression of NMDA receptor subunits required for assembly of functional heteromeric NMDA receptor channels in neurospheres cultured for 4 to 12 DIV. Similarly, high immunoreactivities were detected to NR-1 and NR-2 subunits in neurospheres cultured for 4 to 12 DIV on immunocytochemistry. Brief exposure to NMDA resulted in high expression of immunoreactive c-Jun, c-Fos, Fos-B and Fra2 proteins in neurospheres cultured for 12 DIV, which occurred in a manner sensitive to antagonism by MK-801. These results suggest that functional heteromeric NMDA receptor channels would be rapidly expressed to modulate mechanisms associated with cellular proliferation and/or differentiation in cultured neural progenitor cells isolated from adult murine hippocampus.

N012

Hypertonicity stimulates expression of aquaporin 4 and 9 through a p38 mitogen activated protein kinase dependent pathway in rat astrocytes

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Membranous pore proteins, aquaporins (AQPs), facilitate the osmotically driven passage of water and, in some instances, small solutes. Under hypertonic conditions, the expression of some AQPs changes and some studies have shown that the expression of AQP1 and AQP5 is regulated by MAPKs. However, the mechanisms regulating the expression of AQP4 and AQP9 induced by hypertonic stress remain poorly understood. In this study, we observed that hypertonic stress induced using mannitol increased the expression of AQP4 and AQP9 in cultured rat astrocytes (in vitro), and intraperitoneal infusion of mannitol increased AQP4 and AQP9 in the rat brain cortex (in vivo). In addition, the p38 MAPK inhibitor suppressed their expressions in cultured astrocytes. An ERK inhibitor and a JNK inhibitor did not suppress the expression of AQP4 and AQP9. After brain ischemia or injury, some studies have shown that the p38 MAPK is activated and AQP4 and AQP9 expressions are changed. Clinically, mannitol is commonly used to reduce brain edema. Determining the regulation of AQPs and p38 MAPK under hypertonic condition induced with mannitol might lead to a control of the water movements and a new treatment for brain edema.

N013

Functional expression of particular GABA transporter in cultured rat calvarial osteoblasts

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In the central nervous system (CNS), glutamate (Glu) and γ -aminobutyric acid (GABA) are major excitatory and inhibitory neurotransmitters, respectively. Previous findings that central Glu signaling machineries mediate intercellular communication in bone, led us to examine the possible expression of GABA signaling system in bone cells. We have previously reported that functional metabotropic GABA-B receptor is expressed in cultured calvarial osteoblasts. In this study, we investigated the possible functional expression of GABA transporters (GAT) required for termination of central GABA signaling in cultured rat calvarial osteoblasts. RT-PCR analysis revealed expression of a GAT-3 subtype in osteoblasts cultured in α -MEM containing 10% fetal calf serum for 7 to 21 DIV, while the GAT-3 subtype was detected at a molecular weight position lower than that of central GAT-3 subtype on immunoblotting assays. In osteoblasts cultured for 7 DIV, [^{3} H]GABA was accumulated in a temperature- and sodium-dependent manner with a saturable profile. Moreover, [^{3} H]GABA accumulation was significantly inhibited by the selective inhibitor of rat GAT-3 subtype (S) -SNAP-5114, in addition to by nipecotic acid and β -alanine, in a concentration dependent fashion. These results suggest that GABA may play an unidentified role in mechanisms associated with cellular proliferation, differentiation and/or development through central GABA signaling machineries expressed in cultured rat calvarial osteoblasts.

N014

Effects of several 5-HT_{1B/1D} receptor agonists on [^{35} S]GTP γ S binding in rat brain membranes

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Agonist-induced [^{35} S]GTP γ S binding is now widely used to investigate the functional coupling between several receptors and their coupled G proteins. In the present study, the effects of several 5-HT_{1B/1D} receptor agonists on [^{35} S]GTP γ S binding were examined in rat striatal, hippocampal, and cerebral cortical membranes as a part of pharmacological characterization of 5-HT receptor subtype (s) through which 5-HT stimulated the binding in these brain regions. In the striatal membranes, a potent 5-HT_{1B/1D} receptor agonist L-694,247 stimulated the binding in a concentration-dependent manner with a mean pEC₅₀ value of 9.11. The [^{35} S]GTP γ S binding in the striatal membranes was also stimulated by another potent 5-HT_{1B/1D} receptor agonist GR46,611 with a mean pEC₅₀ value of 8.12. CP93,129, the selective 5-HT_{1B} receptor agonist, stimulated the binding with a mean pEC₅₀ of 7.10. On the other hand, L-694,247 was almost 100 times less potent agonist in the hippocampus (pEC₅₀=6.82) and cerebral cortex (pEC₅₀=7.27). GR46,611 stimulated the binding both in the hippocampal and cerebral cortical membranes with a mean pEC₅₀ value of 6.54 and 6.89, respectively. CP93,129 failed to stimulate the binding in the both brain regions. These results, together with the extremely high EC₅₀ value obtained with a selective 5-HT_{1A} receptor agonist 8-OH-DPAT in the striatum, strongly support the conclusion that 5-HT stimulates [^{35} S]GTP γ S binding through 5-HT_{1B} receptor subtype in rat striatum whereas 5-HT_{1A} receptors are mainly involved in 5-HT-stimulated [^{35} S]GTP γ S binding in hippocampus and cerebral cortex. This method provides useful and convenient strategy to investigate the functional activation of G proteins coupled with 5-HT_{1B} receptors in rat striatal membranes.

N015

Inhibition of dopamine D2-receptor mediated endocytosis by endophilin 3

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Endophilin 1 (endo1) is known to participate in synaptic vesicle endocytosis through SH3 domain-mediated interactions with the IP3 phosphatase synaptojanin and the GTPase dynamin. However, other endophilin family members have not been analyzed as regulators of endocytosis. Here, we show that endophilin 3 (endo3) is highly expressed in olfactory nerve terminals, where dopamine D2 receptor is also localized, and suppresses D2 receptor (D2R) -mediated endocytosis. In contrast, endo1 did not show any inhibitory effect on D2R-mediated endocytosis. To investigate which domain of endophilin is responsible for the regulation of endocytosis, we exchanged the variable and SH3 domains between endo1 and endo3 proteins. Two resultant chimeras (endo1-3 and endo3-1) were introduced into COS-7 cells, and a transferrin uptake assay was performed. Endo3-1 showed an almost identical level of transferrin uptake as compared with endo1, whereas endo1-3 showed almost no transferrin in the cytoplasm, suggesting that the variable domain of endophilin is important for the regulation of receptor-mediated endocytosis. Moreover, to verify whether endo3 inhibits D2R-mediated endocytosis in neurons, we used an olfactory epithelial cell line (13.S.1.24), which differentiates into bipolar neurons by addition of dopamine. We over-expressed the EGFP-endo3 plasmid in this cell line and stimulated it with dopamine. Endo3-expressing cells differentiated into bipolar cells faster than EGFP-transfected cells. These results indicate that over-expression of endo3 proteins inhibits D2R-mediated endocytosis in 13.S.1.24 cells and permits their differentiation into bipolar cells.

N016

Mutational and Computational studies for mapping the odorant binding site of a G protein-coupled olfactory receptor

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To recognize and discriminate thousands of odorants, the vertebrate olfactory system has evolved to acquire a large number of olfactory receptor (OR) genes. In mammals, there are about 1000 OR genes comprising the largest super-family of rhodopsin-like G protein-coupled-receptors. We recently succeeded in functional reconstitution of mouse ORs in HEK293 cells, and provided molecular evidence that structurally related ORs recognize overlapping sets of odorants with distinct ligand specificities. The propose of this study was to determine the odorant binding site of a mouse olfactory receptor, mOR-EG, that recognized a spicy smell, eugenol and a vanillic aroma, vanillin. We first constructed a molecular model of mOR-EG using the recent atomic-level structure of bovine rhodopsin. We then introduced site-directed mutations within a potential ligand-binding pocket that was found in the transmembrane (TM) portions of the receptor. Mutations of some amino acid residues in TM3, TM5, and TM6 dramatically affected the EC₅₀ values of eugenol in Ca²⁺ imaging or cAMP assay of mOR-EG-expressing HEK293 cells. These residues were also found to interact with eugenol, vanillin, and other agonists according to computational ligand-docking analysis. The present study is the first to reveal molecular environment of the active site of an OR, providing insight into molecular basis for odor recognition with high specificity and sensitivity in the olfactory system. The excellent agreement in computer modeling and mutational studies suggest reliability of the current approach that could be applicable to perform active site mapping of various G protein-coupled receptors and to design novel agonists and agonists for therapeutic application.

N017

Functional interaction between T2R bitter taste receptor and G protein alpha subunit expressed in taste receptor cells.

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Bitter taste perception is a conserved chemical sense against the ingestion of poisonous substances in mammals. T2R (TAS2R/TRB) receptors are candidate G protein-coupled receptors that function as bitter taste receptors, but most of the receptors remain orphan receptors. In addition, a G protein alpha subunit, gustducin is believed to be key molecules for its perception, but little is known about the molecular basis for its interaction with T2R receptors. Here, we use a heterologous expression system to determine a specific domain of gustducin necessary to T2R coupling. Two chimeric G alpha16 proteins harboring 37 and 44 gustducin-specific sequences at their C termini (G16/gust37 and G16/gust44) responded to different T2R receptors with known ligands, but G16/gust 23, G16/gust11 and G16/gust5 did not. The former two chimeras contained a predicted beta 6 sheet, an alpha 5 helix and an extreme C-terminus of gustducin, and all the domains were indispensable to the expression of T2R activity. We also expressed G16 protein chimeras with the corresponding domain from other G alpha i proteins (G16/i2 and G16/z). As a result, G16/i2 produced specific responses of T2Rs, but G16/z did not. Since G alpha i2 is expressed in the taste receptor cells, the G protein alpha i2 subunit may also be involved in bitter taste perception via T2R receptors. The present G alpha 16-based chimeras could be useful tools to analyze the functions of many orphan G protein-coupled taste receptors.

N018

Dopamine receptor 2 regulates L-type voltage-gated calcium channel in synchronous oscillation of intracellular calcium of primary cultured mouse midbrain neurons

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Synchronous oscillation of intracellular Ca²⁺ in cultured midbrain neurons was thought to result from spontaneous and synchronous neural bursts accompanying glutamatergic transmissions in a synaptic neural network. We previously reported that raclopride, a dopamine receptor 2 (D2R) antagonist, induced a transient increase of intracellular Ca²⁺ and inhibited synchronous oscillation. We consider that endogenous dopamine maintains synchronous oscillation in midbrain neurons through D2R, and D2R regulates intracellular Ca²⁺ in a suppressive way. In the present study, we investigated whether D2R regulated L-type voltage-gated calcium channel in synchronous oscillation.

Midbrain neurons were prepared from ICR mouse fetus (E17). We detected a few TH-positive (dopaminergic) neurons by immunocytochemistry. In primary cultured midbrain neurons, synaptophysin and D2R expressions were confirmed by western blot analyses. Raclopride alone induced a transient increase of intracellular Ca²⁺ and inhibited synchronous oscillation. Nifedipine, a L-type voltage-gated calcium channel blocker, inhibited synchronous oscillation. In the presence of nifedipine, raclopride did not induce a transient increase of intracellular Ca²⁺. We think that, in primary cultured midbrain neurons, D2R down-regulates the overinflux of Ca²⁺ through mainly L-type voltage-gated calcium channel.

N019

Multiple forms of ASCT1 amino acid transporter molecule in rat brain.

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L-Serine has been well-known as a nonessential amino acid, and can be synthesized in many cells. Recently, we have demonstrated that the cerebellar Purkinje cells essentially require extracellular L-serine for their survival, and that L-serine is predominantly transported into neuron through a neutral amino acid transporter ASCT1. However, it has not been described regional distributions and biochemical properties of ASCT1 in the brain. In the present study, to analyze the functional roles of ASCT1 in brain, we have cloned ASCT1 from rat primary cultured neurons and characterized its expression and molecular forms in rat various brain regions. Northern blot analysis has demonstrated that the mRNAs (5.2 and 3.3 kb) of ASCT1 were ubiquitously expressed in brain. High levels of the 5.2 kb mRNA transcript was detected in olfactory bulbs, striatum and hippocampus, whereas the 3.3 kb mRNA transcript was predominantly expressed in cerebral cortex and cerebellum. In Western blot analysis, antibody against ASCT1 recognized multiple bands between 65 and 75 kDa in the membrane fraction prepared from rat various brain regions. The patterns of the bands were different among in brain regions. Moreover, in astroglial cultures, higher molecular forms (more than 70 kDa) were detected as compared with in primary neuron. Taken together, these findings suggest that these variations of brain ASCT1 molecules are likely to make distinct contributions to cellular transport properties.

N020

Hzf, an RNA-binding protein binding to the 3'-untranslated region of type1 inositol 1,4,5-trisphosphate receptor mRNA and its mechanism of mRNA localization in cerebellar Purkinje cells

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In neuronal cells, specific mRNAs are localized in the dendrites. It has been proposed that the dendritic localization of mRNAs and the locally translational regulation in synaptic region are involved in certain aspects of synaptic plasticity. *Type1 inositol 1,4,5-trisphosphate receptor (IP₃R1)* mRNA is one of dendritically localized mRNAs. IP₃R1, an intracellular Ca²⁺ channel, is highly expressed in cerebellar Purkinje cells and required for long-term depression (LTD), a model of synaptic plasticity in cerebellum. However very little has been shown on the mechanisms of the dendritic localization of IP₃R1 mRNA. Here we identified one gene, *hzf (hematopoietic zinc finger)*, encoding a protein that might be involved in the localization of IP₃R1 mRNA into dendrites. *hzf* encodes three C2H2 type zinc-finger motifs. RNA-binding experiment showed that Hzf binds to 3' untranslated region (3' UTR) of IP₃R1 mRNA *in vitro*. Furthermore, in cerebellum, *hzf* was predominantly expressed in Purkinje cells, corresponding to the expression pattern of IP₃R1, and its products were localized in the dendrites of Purkinje cells, where IP₃R1 mRNAs are localized. Additionally it was revealed that the amount of IP₃R1 mRNA in dendrites of Purkinje cells could dramatically reduce in *hzf*-deficient mice. These results suggest the possibility that Hzf could be involved in intracellular localization of IP₃R1 mRNA in Purkinje cells. Furthermore, *hzf*-deficient mice exhibit ataxia like symptoms. Then we are investigating the relation between the mRNA localization and cerebellar LTD *in vivo*.

N021 (MS4-1)

A novel postsynaptic scaffold protein, TANC, which contains TPR, ankyrin and coiled-coil domain.

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From the rat brain, we cloned a novel gene that encoded a protein containing three tetratricopeptide repeats (TPR), ten ankyrin repeats and coiled-coil regions, and termed this protein TANC (GenBankTM Accession No. AB098072). The deduced TANC protein consisted of 1,849 amino acids. Northern blot analysis showed the 8 kb mRNA expressed widely in various tissues. Western blotting using anti-TANC antibody detected a protein with 200 kDa in the rat brain, in particular, it was enriched in the postsynaptic lipid raft and postsynaptic density fractions. Immunohistochemical study showed the localization of the protein in dendrites of neurons in the cerebral cortex and the hippocampus. The mRNA for TANC was also localized to the dendrites, as well as somas, of neuronal cells. Pull-down assay showed binding to PSD-95, SAP97, and ves11/Homer via C-terminal PDZ-binding motif, ESNV. Immunoprecipitation study also showed binding of the protein with alpha subunit of C2+/calmodulin-dependent protein kinase II and various postsynaptic proteins. These results suggest that this protein is synthesized, at least partly, locally at the postsynaptic sites and may play a role as a scaffold at the postsynaptic sites.

N022 (MS4-2)

The ligand dependent synaptic clustering of PSD-95 and its role in neuronal function

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PSD-95 is a PDZ domain-containing scaffolding protein enriched in the Post Synaptic Density of excitatory synapses, and is thought to play a pivotal role in clustering specific ion channels into a signaling complex at the synapses. One of its essential components is the NMDA-type glutamate receptor, which directly binds to the PDZ1,2 of PSD-95. Previous studies have shown the requirements of the palmitoylation of two cysteines and at least one PDZ domain of PSD-95 for its localization at synapses. However, the precise mechanism that initiates and regulates synaptic clustering by PSD-95 is not fully understood. We used a series of PSD-95 mutant proteins lacking the β B- β C loop in the PDZ domain, which is essential for their ligand binding. These mutants had been confirmed to reduce channel co-clustering efficiencies in heterologous cells. We overexpressed these mutant proteins tagged with GFP in hippocampal primary cultures and examined their localization. A PSD-95 mutant in which the β B- β C loops were deleted in both PDZ1 and PDZ2 was able to induce distinct clusters at synaptic sites, though the clustering efficiency was one third compared to the wild-type. In addition, we observed elongated spines, as reported for various mutant synaptic proteins. Furthermore, the immunostaining of GluR1 showed its slightly reduced assembly at synaptic sites. Finally, the overexpression of a membrane-unbound form of PSD-95 delayed the presynaptic maturation when expressed in younger neurons. Taken together, our data indicate that the ligand binding of PDZ1,2 of PSD-95 plays a critical role in the clustering of synaptic signaling complex. Furthermore, regulation of the clustering efficiency may be important for the formation of intact synapses as well as the presynaptic maturation.

N023 (MS4-3)

NMDA-dependent proteolytic cleavage of stargazing in cultured neurons

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Many kinds of protease contributes both to developmental remodeling of neuronal contacts and to memory consolidation. Recent studies showed that various serine proteases including tissue plasminogen activator and neuropsin are implicated in correlates of learning including long term potentiation (LTP), however, little is known on the protein substrate essential for these regulations. Stargazin is a postsynaptic glycoprotein, which is critical for surface expression and synaptic targeting of AMPA receptors. We found that a brief treatment of cultured hippocampal and cortical neurons with NMDA resulted in a marked reduction of apparent molecular size of stargazing in concentration- and time-dependent manners. The NMDA-induced molecular shift was abolished in the presence of AP-5, a specific NMDA receptor antagonist, and was markedly suppressed by a serine protease inhibitor, AEBSF. N-endoglycosidase F causes further reduction in the molecular size of truncated stargazing. Since the truncated stargazing could be recognized by an antibody to C-terminal sequence of stargazing, and was smaller by 5kDa than native stargazin, the cleavage site was assumed to locate in first extracellular loop. These results suggested that proteolytic cleavage of stargazin at the extracellular site was implicated in regulation of synaptic transmission.

N024 (MS4-4)

Time lapse recording of translocation of GFP-drebrin A, an actin-binding protein in dendritic spines, induced by activation of glutamate receptors in hippocampal neurons

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In the previous study, we have shown that the activation of NMDA receptors result in the loss of drebrin-like immunoreactivity from the dendritic spines and the appearance of the immunoreactivity in the dendritic shafts using primary cortical neuronal culture. Although the immunohistochemical data suggest the translocation of drebrin from the spine to the shaft, it is still unclear whether drebrin is actually redistributed by the receptor activity in live neurons. In the present study, we analyzed the effects of glutamate (100μM, 20 sec) on the localization of expressed drebrin A tagged with GFP in live cultured hippocampal neurons using time-lapse recording. We prepared low density cultures of rat hippocampal neurons from 18-day embryo. After 14 days in vitro, we injected cDNA of rat drebrinA tagged with GFP into the neurons. The neurons were examined with fluorescent microscopy 24 hours after the cDNA injection. GFP-drebrin A was observed mainly in filopodia and spines, and faintly in the dendritic shafts. Dancing of dendritic spines and dynamic movements of GFP-drebrin A in filopodia and spines were observed in non-treated neurons. Time lapse imaging at 10 sec intervals revealed that glutamate treatments inhibited the dancing and redistributed GFP-drebrin A from filopodia and spines to the dendritic shafts immediately after the treatment. 10 min after the treatments, GFP-drebrin was mainly concentrated at dendritic shaft in addition to slight accumulation at dendritic spines. Our observations suggest that glutamate receptor activity regulates morphology of filopodia and spines through the localization of drebrin A.

N025 (MS4-5)

A week-order long-term synaptic enhancement in cultured hippocampal slice after repeated exposure to glutamate

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Synaptic plasticity, a cellular basis for brain memory, consists of two phases. A short-term plasticity occurring in existing synapses lasting for minutes-hours and a long-term one accompanied by the formation of new synapses lasting for days. The former has been well analyzed using an excellent model, long-term potentiation (LTP) in hippocampus, whereas the latter remains unchallenged due mainly to the lack of model. We recently reported that repeated application of forskolin (an adenylyl cyclase activator) to cultured hippocampal slice produced an enhancement of synaptic transmission which lasted for 2 weeks. This enhancement should differ from the so-called late-phase LTP, since the enhancement developed gradually in 1 week after LTP had occurred and disappeared. The enhancement was accompanied by the increases in the amount of synaptic proteins and morphologically identified synaptic structures.

Here we changed the stimulus to a transient exposure to glutamate, a signal upstream of adenylyl cyclase, and found that the repeated glutamate exposure resulted in a similar long-term enhancement of synaptic transmission. This enhancement was dependent on the times (requiring 3) and the interval (requiring 2hr but 24hr) of the exposure, abolished by inhibitors for PKA and MAPK kinase, and accompanied by the increase in immunochemically identified synaptic structures. To reveal a qualitative difference between the 1st and 3rd stimulus, we quantified MAPKs. The kinase proteins accumulated by the repeated exposures and their phosphorylated form also increased. Nuclear translocation of phosphorylated MAPKs was induced by the 3rd stimulus. Correspondingly, the inhibition of MAPK kinase at the 3rd stimulus sufficed to block the synaptic enhancement.

N026

Electron microscopic analysis of cell adhesion molecule L1-cam immunoreactivity in the hippocampus.

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Our previous studies indicated that the cell adhesion molecule L1-cam is present in synapse and is cleaved specifically by neuropsin, a serine protease at an activity-dependent manner. The proteolytic activity of neuropsin is activated from non-active precursor form to active form in several minutes after long-term potentiation of Schaffer-collateral in the hippocampus. These evidences strongly suggest that the cleaving system of L1-cam by neuropsin might be involved in synaptic plasticity. To elucidate the involvement of neuropsin-L1 system on synaptic plasticity, it is important to reveal where L1 is localized at the ultrastructural level and how the protein is interacted by neuropsin. We therefore analyzed and compared L1-cam immunoreactive structure between neuropsin knock out mice and wild type mice in the hippocampus. We found that L1 immunoreactivity is concentrated in the presynaptic active zone of the asymmetry synapses. However, we did not detect postsynaptic L1-immunoreactivity in hippocampus. L1-positive synapses were located in a region where the stratum radiatum of CA1 subfield which is projected from the CA3 pyramidal neurons. In the neuropsin knock out mice, it was found that immunoreactive presynaptic active zone was marked loss in the middle layer of the stratum radiatum. Taken together, it might be suggested that the presence of neuropsin regulates the existence of L1 synapses in layer specifically.

N027

Modulation of short-term synaptic plasticity by presynaptic adenosine receptors in the nucleus of the solitary tract

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The nucleus of the solitary tract (NTS) receives various types of afferent signals from widely distributed visceral receptors. The glutamatergic transmission from the primary afferents to the second-order neurons shows strong frequency- and repetition-dependent suppression. We have already demonstrated that the amplitude of EPSCs evoked by the solitary tract (TS) stimulation is decreased by activation of A1 receptors (Kato and Shigetomi, 2001). Here we investigated how adenosine affects the repetition-dependent suppression of the glutamate release from the TS termini in thick brainstem slices of the young rats. TS was stimulated repeatedly 2-10 times at an interval of 20 ms. The amplitude of EPSC elicited by the first stimulus decreased to $70.6 \pm 3.6\%$ ($n=31$) with adenosine ($100 \mu\text{M}$), whereas that by the second stimulus was unaffected ($105.6 \pm 15.4\%$) and that by the third stimulus was rather increased to $171.3 \pm 32.4\%$. The paired-pulse ratio increased from 0.36 ± 0.06 to 0.49 ± 0.06 . These effects were abolished by DPCPX. The decay rate constant for the EPSC amplitude during the course of repeated stimulation increased from 1.4 ± 0.6 to 2.9 ± 1.3 with adenosine, indicating a significant slowing of the repetition-dependent suppression. These results indicate that, despite strong reduction of the release elicited by the first action potential, activation of presynaptic A1 receptors assure stable responses to the repeated slowly-adapting afferent inputs.

N028

Electrophysiological analysis for the I213T PS1 knock-in mice

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We previously described a Japanese family with familial Alzheimer disease (FAD) caused by the I213T mutation of presenilin-1 (PS1) and established the knock-in mice with the same missense mutation. These mice were found to develop increased level of amyloid β ($\text{A}\beta$) 42 proteins in the whole brain at the age of 16-20 weeks and could be a useful animal model for studying abnormal processing of APP caused by the PS1 mutation. However, the functional and cognitive feature of those mice has not yet to be determined. The latest findings suggest that the $\text{A}\beta$ 42 oligomer have the potent neurotoxic effect by disturbing synaptic activity such as long-term potentiation (LTP). Those results have the limitation in their experimental method as the $\text{A}\beta$ 42 are extrinsically added to the brain slice at the extremely high dose which are not found in physiological condition. Here, we report the results of electrophysiological analysis found in the hippocampal slice from our I213T knock-in mice. The significance of our study is that we measured the effect of intrinsic $\text{A}\beta$ 42 for the synaptic activity. We prepared the $450 \mu\text{m}$ thick slice of hippocampus from the mice at the age of 20 weeks using the standard method. The basal synaptic activity was tested by comparing the slope for field EPSP and is found no significant difference. However, the LTP from the knock-in mice are significantly reduced compared with that from control mice after the high frequency stimulation (100Hz, 1s). Those reduction is remarkable in the homozygous PS1 knock-in mice but not in the heterozygous one. These results suggest that our I213T PS1 knock-in mice should be the useful animal models for understanding the synaptic toxicity of $\text{A}\beta$ 42 oligomer and the pathophysiology of AD.

N029

A different expression of galectin-1 and galectin-3 in the fish and rat retinas after optic nerve injury

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The retinal ganglion cells (RGCs) of goldfish can survive and regrow their axons after optic nerve injury, whereas RGCs of rat cannot survive and become apoptotic 7days after optic nerve injury. Galectin, a beta-galactoside binding lectin which is classified at least 14 subfamilies, has been implicated for various biological phenomena. Recently, among of them, galectin-1,3 was identified as a candidate substance for promoting neurite outgrowth. Therefore, in the present study we compared the galectin-1,3 expression in the goldfish and rat retinas after optic nerve crush. An immunohistochemical study revealed that the fish and rat RGCs were labeled with galectin-1,3 antibody after injury. However, the time course of labeling after optic nerve crush was different from each other. In goldfish retina, the increase of expression of galectin-3 was initiated at 3 days, peaked at 7-20 days and continued for 50 days after injury. The staining of galectin-1 was gradually decreased. In rat retina, the increase of expression was initiated at 2-3 days, peaked at 5-6 days and suddenly lost at 7-9 days after optic nerve injury. The staining of galectin-1 was gradually decreased. The immunohistochemical data were quantitatively confirmed by western blot analysis. The long lasting increase of galectin-3 expression in the goldfish RGCs reflects a regenerative potential of fish to CNS injury. The transient increase of galectin-3 expression in the rat RGCs is not thoroughly understood at present. Galectin-3 will offer some clues for solving the difference in CNS regeneration between fish and mammals.

N030

The role of purpurin, a member of retinol binding protein family during regeneration of goldfish optic nerve

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The mammalian central nervous system, CNS, fails to regenerate after lesions, however, the lesions of CNS neurons of fish are followed by successful recovery. We have investigated this recovery mechanism, by using goldfish as a model system. After transection of optic nerve, the retinal ganglion cells begin to grow their axons to tectum within a week, and we have asked which genes involved in this process. We have cloned several genes of which expression level increased after optic nerve transection in goldfish. After cloning by subtracted hybridization, we obtained purpurin, a retina specific retinol binding protein, cDNA. Its mRNA and protein amount increased roughly 2 times, 2 to 5 days after optic nerve transection in retina. The purpurin mRNA was expressed in photoreceptor cells. In explant culture of retina, the extension of neurites was enhanced after addition of recombinant purpurin, and inhibited after addition of the antibody against to the medium. It has been reported that the chick purpurin was able to promote cell adhesion and prolong the survival of cultured embryonic retinal neural cells (Schubert *et al.*, 1985). The purpurin is also required for neurite regeneration of retinal ganglion cells in goldfish.

N031

Preservation of hematopoietic properties in transplanted bone marrow cells in brain

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In recent studies, it has been discussed that the possible trans-differentiation of bone marrow cells (BMC) into neural cells when they migrate to the brain. We have reported that some immature BMC migrating into the brain parenchyma in an early phase after bone marrow transplantation (BMT) express early hematopoietic markers but not neural markers. The present study further characterizes transplanted BMC that migrate to the brain. Immuno-double labeling confirmed that BMC migrating to the brain expressed hematopoietic, but not neural markers such as nestin, MAP-2 and GFAP, even four and eighteen weeks after BMT. BMC that expressed GFP also expressed hematopoietic, but not neural markers when cultured with mixed brain cells according to immuno-double labeling and single cell dissection using a laser. Analysis of the DNA content indicated that most of the migrated BMC were arrested at the G0/G1 phase and aneuploidy or tetraploidy was undetectable. Thus, BMC that migrate to the brain are probably preserved hematopoietic properties under the appropriate conditions.

N032 (MS2-2)

Molecular Characterization of a Novel Tetraspan Membrane Protein Up-regulated in Neurons of Axotomized Facial Nuclei

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Facial nerve axotomy of adult rats provides us of a useful model to study the molecular mechanisms of axonal regeneration. We have screened up-regulated genes following unilateral facial nerve axotomy by PCR-based subtraction between cDNAs obtained from operated and unoperated sides of facial nuclei. Here we identified a novel cDNA fragment, which was highly up-regulated in axotomized facial nucleus. Subsequently we screened a rat brain cDNA library to isolate the full coding region of this clone. Five clones were isolated from the 1.5×10^6 population of the rat brain cDNA library. We designated clone-48 for a cDNA containing an upstream stop codon of open reading frame and poly (A'). A database search showed that clone-48 was a novel tetraspan membrane protein with a partial homology to peripheral myelin protein 22 (PMP-22). Northern blot analysis revealed that clone-48 was ubiquitously expressed in various tissues. The expression of clone-48 was high in heart, moderate in brain, lung, liver, kidney, skeletal muscle, testis, and low in spleen. Localization of mRNA for clone-48 in the adult rat brain was examined by in situ hybridization. The mRNA expression of clone-48 was prominent in neurons in the hippocampus, purkinje cell layer, and facial nucleus. Northern blot analysis showed that the expression of clone-48 in the facial nuclei was up-regulated from 24 hours after axotomy, peaked at postoperative day 3, and gradually decreased by 14 days after axotomy. EGFP tagged clone-48 that expressed in HEK293 and PC12 cells were N-linked glycosylated and localized at plasma membrane. Our results suggest that clone-48 might play an important role in regenerating motor neurons.

N033 (MS2-3)

Transplantation of neural stem cells and re-expression of PSA-NCAM in a mouse model of demyelinating disease

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Dysmyelination or demyelination causes severe CNS diseases, such as multiple sclerosis (MS). Transplantation of neural stem cells into demyelinated lesions is a potent therapy for the disease. We previously generated PLP-4eTg mouse, an animal model of demyelinating disease, overexpressing the plp gene by introducing extra wild-type mouse plp gene. It is known that MS patients show increased levels of TNF- α and TGF- β 1 mRNA compared to healthy controls. We studied both cytokines mRNA levels expressed in whole brains of wild type and PLP-4eTg mice. Increased levels of the cytokines were demonstrated in PLP-4eTg mice compared to wild type mice. Next we transplanted neural stem cells into PLP-4eTg mice and investigated whether the grafted cells differentiate into oligodendrocyte. Not many of the grafted cells seemed to differentiate into oligodendrocyte at 20 days post-transplantation. We considered that polysialylated form of the neural cell adhesion molecule (PSA-NCAM), act as an inhibitor of myelination at the surface of axons in the developing CNS and could participate in disease progression in MS, may be re-expressed on demyelinated axons and responsible for the inefficient differentiation of neural stem cells. Thus we investigated whether PSA-NCAM was expressed in demyelinated lesions of PLP-4eTg mice. PLP-4eTg mice showed significant increase of its expression level.

N034 (MS2-4)

Possible alteration of DNA methylation may affect fate of injured motor neurons

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Recent powerful gene-targeting study revealed that genetic background of the mice strain could be a crucial factor in determining the expression of gene and subsequent phenotype. This might be caused by the different level of DNA methylation among mice strains, because the methylation level varies among mouse species. The present study revealed that the expression level of neuronal glutamate transporter, EAAC1 mRNA in response to nerve injury varied among mice species. Even opposing expression pattern of EAAC1 mRNA between rat and mouse is seen in injured neuron. The more highly methylated mouse strain showed the more significant down-regulation of EAAC1 mRNA and accelerated neuronal death following nerve injury. DNA methylation thus seems crucial for controlling expression of some genes in injured neurons. In addition, we identified that injured motor neurons in mouse up-regulated DNA methyltransferase1 (Dnmt1) expression, which is essential for maintaining DNA methylation after DNA replication, whereas those in rat did not. Dnmt1 was highly expressed even in the postmitotic CNS neurons and its activity was elevated during transient ischemia. These data suggests that additional role of Dnmt1 contribute to the gene expression regulation even in postmitotic neurons, and that the modification by DNA methylation promote EAAC1 transcriptional repression within injured motor neurons in mouse.

N035 (MS2-5)

Axonal Regeneration after Administration of Semaphorin 3A Inhibitor into the Injured Spinal Cord

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Axons of the adult mammalian central nervous system (CNS) exhibit little regeneration after injury. It has been suggested that several axonal growth inhibitors prevent axonal regeneration in CNS. Recent research has demonstrated that semaphorin 3A (Sema3A) is one of the inhibitors of axonal regeneration that plays central roles after CNS injury. We extracted a substance from a fungus that inhibits functions of Sema3A in vitro such as chemorepulsive effect to neurite extension and growth cone collapse. To examine the effect of the Sema3A inhibitor in vivo, we made spinal cord transection model using adult rats, and administered Sema3A inhibitor into the lesion site for 4 weeks using osmic mini pump (treatment group). In the control animals, phosphate buffer saline was administered into the lesion site (control group). In the both groups, open-field walking was assessed using the BBB scale up to 14 weeks after the injury. Immunostainings for neurofilaments, GAP43 and CGRP were performed after the perfusion with 4% paraofrmaldehyde at 14 weeks after the injury. The immunohistochemical analysis revealed that more extensive axonal regeneration was observed in the treatment group compared to the control group. Furthermore, significantly better functional recovery was observed in the treatment group than the control group. These findings suggest that Sema3A plays a central role in inhibition of axonal regeneration after CNS injury, and Sema3A inhibitor is a possible therapeutic reagent for human spinal cord injury.

N036

Cell survival and death signals in the goldfish and rat retinas after optic nerve injury

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Mammalian CNS neurons die by apoptosis following nerve injury. In contrast, fish and amphibian CNS neurons can survive and regrow their axons throughout their life. Thus, using a model system of goldfish and rat optic nerve, we studied neuronal responses of retinal ganglion cells (RGCs) to optic nerve crush. We particularly compared cell death and survival signals of both RGCs after injury. Fish RGC could survive permanently, whereas rat RGCs were gradually lost 6 days after injury. The enzyme activity of caspase-3 in rat retina was significantly activated 6 days after treatment, whereas the caspase-3 activity in the goldfish retina was reduced 10-20 days after treatment. We further measured levels of antiapoptotic Bcl-2 and proapoptotic Bax proteins in both goldfish and rat retinas after optic nerve injury by Western blotting analysis. In goldfish, the retinal level of Bcl-2 but not Bax significantly increased 10-20 days after injury. By contrast, in rat the level of Bax but not Bcl-2 significantly increased 6 days after injury. These opposing results of Bcl-2 and Bax in the goldfish and rat retinas were confirmed by immunohistochemical analysis with localizing limited to the RGCs. The present data will offer a clue for solving the mystery of CNS regeneration.

N037

SH3 binding domain glutamic acid rich protein like 3 (SH3BGRL3) is expressed in neurons of CNS and upregulated in axotomized facial nucleus in rat

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Neuronal regeneration after peripheral nerve axotomy is a well-known phenomenon in adult rat. We performed axotomy on one side of adult rat facial nerve and obtained a subtraction cDNA library subtracting mRNA of no-operating side from that of axotomized, and analyzed upregulated cDNA clones which seem to contribute to a promotion of axonal regeneration. SH3BGRL3 was originally identified as a human homologue of SH3BGR, and showed a significant similarity to *E. coli* glutaredoxin 1. SH3BGRL3 was thought to be a member of thioredoxin super-family, but its function was not elucidated. Rat SH3BGRL3 had 98% identity to human and mouse homologue in amino acid level and had no consensus sequence of SH3 binding domain and also lacked the conserved consensus sequence essential for glutaredoxin enzymatic activity. Northern analysis showed ubiquitous expression in all tissues analyzed except for skeletal muscle. *In situ* hybridization revealed that SH3BGRL3 was expressed in the neurons of cortex, hippocampus, and especially in the motoneurons of trigeminal motor nucleus, facial nucleus, and anterior horn of spinal cord. *In situ* hybridization also showed SH3BGRL3 up-regulation in the axotomized facial nucleus. The up-regulation was observed within a day after axotomy, and significantly elevated from day 3 to day14, and returned to the basal level by day 21. Although the function of SH3BGRL3 is still unclear, the protein may play certain roles in the axonal regeneration of facial motor neurons.

N038

Neuronal glutamate transporter, EAAC1/EAAT3 determines neuronal fate in injured motor neurons

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Rats and mice are concordant animals, and most of their genotypes and phenotypes can be considered similar. However, this is not the case for motor neuron regeneration. Nerve-injured motor neurons of the adult rat can survive, whereas similar axotomy causes gradual cell death of the adult mouse in p53-dependent manner. Here, we identified that the expression of a neuronal glutamate transporter, EAAC1/EAAT3, in response to nerve injury was up-regulated in the rat, but down-regulated in the mouse, although most of the other molecules associated with cell survival responded similarly. These findings suggest that the opposing expression of EAAC1 in response to nerve injury between rats and mice results in the marked difference in their fate. The recovery of EAAC1 expression using EAAC1 transgenic mice rescued numerous motor neurons after axotomy. Neuronal glutamate transporter, EAAC1 has less uptake activity than glial glutamate transporters, although it is generally believed that glutamate transporters have capacity in taking up extracellular glutamate to finish synaptic transmission and/or prevent glutamate toxicity. However, EAAC1 over-expression diminished p53-induced cell death and reduced the protein oxidative level in PC12 cells. In this respect, it is likely that EAAC1 may have some additional role, which is distinct from the ordinary glutamate uptake in preventing nerve injured motoneuron death in mice.

N039

Restoration of dopamine function in a primate model of Parkinson's disease after transplantation of neuronal stem cells derived from embryonic stem cells

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Parkinson's disease (PD) is a progressive movement disorder marked by selective degeneration of nigrostriatal dopaminergic pathways. In advanced stages, surgical therapies such as neural transplantation may help. However, short supply of donor cells limits clinical applications. Embryonic stem (ES) cells can generate large numbers of dopaminergic neurons, and are good candidates for sources of donor cells. To investigate the therapeutic potential of ES cells, we grafted neural stem cells derived from primate ES cells into striatum in a primate model of PD. Primate ES cells established from blastocysts of cynomolgus macaques (*Macaca fascicularis*) were cultured in astrocyte-conditioned medium under free-floating conditions to induce differentiation into neuronal stem cells. Differentiation into dopaminergic neurons was efficient in culture. Three cynomolgus macaques were chronically treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to form bilateral striatal lesions. Animals showed stable parkinsonian motor symptoms for at least two months. Neuronal stem cells derived from ES cells were then stereotactically injected into the left putamen. Culture medium was injected into the right putamen as a control. Striatal dopamine function was evaluated using positron emission tomography. After 12 weeks, [¹¹C]-L-dopa uptake was significantly increased in the left putamen. Methamphetamine challenge induced significant reduction in D₂ receptor antagonist [¹¹C]-raclopride binding potential in the left putamen, suggesting increased synaptic dopamine release. Although behavioral recovery was modest at 12 weeks, improvement may be gradual rather than immediate. No side effects were observed. Transplantation of primate ES cell-derived cells might offer a feasible therapy for PD.

N040

Characterization of two monoclonal antibodies, Gal3D11 and Gal5E5, to galectin-1

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Galectin-1, which belongs to a family of galectin, is a kind of lectin. Only reduced form of galectin-1 homodimer has lectin activity. Recently, Horie and colleagues reported that oxidized galectin-1 promoted nerve regeneration after axotomy. But no detailed informations are yet available for the kinetics of galectin-1 during repair of DRG after axotomy. Therefore, here we generated two monoclonal antibodies, Gal3D11 and Gal5E5, to galectin-1 and tried to explore the expression and the localization for galectin-1 in DRG of rat with these monoclonal antibodies. In this study, we characterized two kinds of monoclonal antibody, Gal3D11 and Gal5E5. Enzyme-linked immunoadsorbent assay revealed that both antibodies recognized recombinant human galectin-1. These antibodies showed different immunoreactivity in the adult rat central nervous system. Gal3D11 reacted primarily with astrocytes in CNS, whereas Gal5E5 recognized astrocytes including with probably oligodendrocytes in white matter of CNS. Immunohistochemistry of DRG from adult rats showed that Gal3D11 and Gal5E5 recognize cell body of DRG neuron with similar pattern. Especially, Gal3D11 showed strong immunoreactivity on regenerating DRG compared with healthy DRG. Western blot analysis of DRG with Gal3D11 or Gal5E5 showed that Gal3D11 weakly recognized reduced form of rat galectin-1 in DRG compared with that of recombinant human galectin-1 and that Gal5E5 strongly recognized reduced form of rat galectin-1 compared with that of recombinant human galectin-1. Epitope analysis of Gal3D11 showed that this antibody recognized N-terminal portion (29-48) of reduced form of galectin-1. Gal5E5 failed to recognize amino acid sequence of galectin-1. Taken together, Gal3D11 and Gal5E5 are suggested to recognize different epitope.

N041

Injection of adult mouse neurospheres ameliorated behavioral abnormality in brain-injured mice.

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Multipotent neural precursors have been shown to exist in the adult brains and to generate neurospheres in culture. Recent study reported that injection of neurospheres from adult mice brains induced recovery in a chronic mouse model of multiple sclerosis. In this study, we investigated whether the neurospheres from adult mice brains induced recovery when those were injected into the physically damaged mice brains. A brain region was unilaterally removed from each mouse. The mice were allowed to recover for one week. Intraperitoneal injection of apomorphine caused strong body bending with dysfunctions of limbs. At the same time, the brain-damaged mice hardly showed rearing after the injection of apomorphine, although sham-operated control mice showed frequent rearing. The number of rearing was counted. Neurospheres were prepared from the brains of 12-week old mice. The neurospheres showed an ability to form new spheres when passaged in fresh medium and showed strong immunoreactivity to anti-nestin antibody, suggesting that the obtained spheres contained immature neural precursor cells. The obtained neurospheres were injected into the damaged area of the mice brains. After 8 weeks of the injection, the number of rearing increased to indistinguishable level from that of control mice. These results imply that the injected neurospheres recovered physically injured brain functions.

N042

Administration of FGF-2 into the transected spinal cord enhances axonal regeneration and improves locomotion activity in adult rats

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Neurotrophic factors such as neurotrophins have been regarded as substances for nerve regeneration of the injured spinal cord. Transplantation of neural stem cells has been also conducted, and reported to be promising for neuronal regeneration. Therefore, the effects of fibroblast growth factor (FGF) -2 on the regeneration of the transected rat spinal cord were examined, because FGF-2 is a potent neurotrophic factor for various types of neurons including motor neurons, and a potent mitogen for neural stem cells. The rat spinal cords were completely transected at the position of T10, and 1 ml each of FGF-2 (1 mg/ml) or vehicle solution was injected three times into rostral and caudal sites of the injury. Rats were then fed maximally for 42 days. The locomotion activity was evaluated with Basso, Beattie, and Bresnahan (BBB) rating scale. The score was zero at the day of the operation. The score of the FGF-2-treated group started to increase 7 days and attained maximally to score 8 till 42 days after the operation, but the score of the vehicle-treated rats was still zero during all experimental period, demonstrating a marked improvement of locomotion activity, and suggesting an effective axonal regeneration by FGF-2. Most of the FGF-2-treated rats, but none of the vehicle-treated ones, showed fluorogold (FG) -positive nerve fibers in the rostral side or FG-positive cells in the brainstem nuclei when FG was administered into the caudal side of the transection. Apoptosis was also suppressed by FGF-2 when evaluated by TUNEL assay. Present results demonstrate that FGF-2 enhances axonal regeneration in the transected spinal cord probably via its widely active neurotrophic effect and the activation of neural stem cells.

N043

Age-related changes in brain synaptic function and effects of carnitine supplementation

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Aging decreases the efficacy of synaptic neurotransmission in the brain. We found that brain aging reduced depolarisation-induced Ca^{2+} influx into cortical synapses. Our previous data indicate that the density of voltage dependent calcium channel (VDCC) are significantly decreased in aged synaptic plasma membranes. In addition, brain aging alters the relative contribution of certain types of VDCC to depolarization-induced Ca^{2+} influx (Tanaka and Ando, 2001). The present study was conducted to reveal the age-related changes in the expression of alpha1-subunit proteins of VDCCs in cortical synapses using immunoblotting. We also investigated the effects of long-term supplementation of acetyl-L-carnitine (ALCAR) on synaptic functions in aged rats. Synaptosomes prepared from cerebral cortices of adult and aged rats were used for immunoblotting analyses. The results indicated that alpha1-A (P/Q-type) and alpha1-B (N-type) subunit expressions were significantly decreased with advancing age. However, aging did not alter L-type VDCC expression. These changes in VDCCs may lead to age-related hypofunction of synaptic neurotransmission in brain cortices. Carnitine and its acyl derivatives, which play a vital role in beta-oxidation of long-chain fatty acids in the mitochondrial matrix, are reported to have many beneficial effects on brain function. Aged rats were given ALCAR (100 mg/kg) per os for 3 months. The high-affinity choline uptake, acetylcholine (ACh) synthesis and depolarization-induced ACh release were all enhanced in the ALCAR-treated group. However, ALCAR did not changes the VDCC expressions in cortical synapses. These results indicate that ALCAR exerts its beneficial effects on cholinergic neurotransmission in aged rats.

N044

Expression of histone deacetylase Sir2 in neural stem cells

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The yeast silent information regulator 2 (Sir2) is an NAD-dependent histone deacetylase and silences transcription at the mating type loci, telomeres and the ribosomal DNA. Over-expression of Sir2 extends the life span of yeast, while Sir2 knockout shortened the life span by about 50%. Mammalian cells also express several Sir2 homologues. Recently, mammalian Sir2a (SIRT1) has been shown to deacetylate p53, suggesting that Sir2a has some functional roles in P53-mediated apoptosis. However, most of physiological functions of Sir2 homologues seem to be unknown. We found that Sir2a was highly expressed in mouse embryo. In the adult mouse brain, ependymal cells and some cells of subventricular zone expressed Sir2a. To identify proliferating neural cells in the adult brain, BrdU was administered in the drinking water for 2 weeks. Immunostaining of BrdU, nestin and Sir2a showed that BrdU-positive and nestin-positive cells expressed Sir2a. Furthermore, cultured neurosphere derived from E14 mouse striatum expressed Sir2a. The expression of Sir2a in neurosphere disappeared, when neurosphere differentiated into neuron, astrocyte and oligodendrocyte. Nicotinamide and splitomicin, potent inhibitors of Sir2a, inhibited the growth of neurosphere. These results suggest that Sir2a has a pivotal role in the proliferation of neural stem cells.

N045

Involvement of Epidermal Growth Factor in cognitive functions

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Epidermal growth factor (EGF) and its structurally related proteins are involved in the developmental regulation of various brain neurons, including midbrain dopaminergic neurons. Previously we reported that there are EGF and EGF receptor abnormalities in brain tissues and blood of schizophrenic patients. In agreement, peripheral administration of EGF to neonatal rats induced overactivation of EGF receptors in the brain, and leading to behavioral abnormalities such as prepulse inhibition of acoustic startle and locomotor activity after development. The enhanced locomotor and stereotypic responses of the EGF neonatal-treated rats would be considered to be an animal model of positive schizophrenia symptoms. In the present study, we investigated whether EGF neonatal-treated rats might also elicit abnormal cognitive behaviors consistent with the animal models of schizophrenia, using some behavioral tasks. In the radial arm maze task, we found that the EGF-treated rats exhibited a similar acquisition in spatial memory to control rats, but higher persistency behavior to the previous acquired memory when the position of food pellets have been changed. In the two-way active avoidance task, control groups showed significant latent inhibition during the test sessions, as reflected by reduced avoidance rates of the tone preexposed rats. In contrast, animals treated with EGF showed much stronger latent inhibition than control. In context fear conditioned task, however, their latent inhibition was disrupted conversely. These results show that EGF neonatal treatment provides a model of cognitive disorders. Our findings suggest that the cognitive dysfunctions of the EGF neonatal-treated rats appear to have many behavioral aspects in psychotic patients.

N046

Comparison of Dopaminergic Neuronal Damages in MPTP-treated Young and Aging C57BL/6 Mice

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The neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) produces clinical, biochemical and pathological features similar to those observed in idiopathic parkinsonism and has been used to create an animal model for Parkinson's disease (PD) in nonhuman primates and mice. Here we compared the damages of dopamine (DA) neurons between young and aging C57BL/6 mice, which were treated with several doses of MPTP, using biochemical, neurochemical, immunohistochemical and behavioral technique.

Both young (10 weeks old) and aging (14 months old) male C57BL/6 mice were administered i.p. with different doses of MPTP (1 to 4 injections of 20 mg/kg at 2 h intervals). Three days after MPTP treatment, dopaminergic neuronal degeneration was analyzed by tyrosine hydroxylase (TH) immunoblotting and immunohistochemistry. Behavioral abnormality in MPTP-treated mice was evaluated using the tail suspension test. Mice were suspended by the tail for 6 min and the total duration of immobility was measured. Monoamine contents were assayed by HPLC-ECD.

In MPTP-treated young mice, which showed no mortality at any dose, striatal DA contents and TH protein levels decreased dose-dependently. The duration of immobility in the tail suspension test was significantly increased only at the four injections (4×20 mg/kg) of MPTP as compared with saline-treated control mice. On the other hand, in MPTP-treated aging mice, survival rates (%) for mice that received MPTP of 1, 2, 3, and 4 injections were 100, 77, 15, and 0, respectively. Even 1 or 2 injections of MPTP induced a large loss of striatal DA contents and TH protein levels as compared with those in young mice. We are now analyzing what factor is mostly associated with this age-related vulnerability for MPTP toxicity.

N047

An inducible transgenic mouse model of Huntington disease harboring full-length huntingtin

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Huntington disease (HD) is an autosomal dominant inherited, progressive, neurodegenerative disorder caused by an expansion of a CAG repeat in the huntingtin gene. To study the pathogenesis of HD, we have created transgenic mice inducibly expressing either full-length wild-type (23Q) or mutant (148Q) huntingtin using the tet-off gene expression regulatory system. We kept mice in uninduced conditions in the presence of doxycycline (Dox) until birth of offspring, at which time Dox treatment was discontinued to induce transgene expression. Mice expressing 148Q huntingtin showed weight loss and neurological abnormalities including loss of coordination, gait disturbance, fore- and hind-limb claspings, tremors, and hypoactivity. The neurological abnormalities were progressive, leading to early death. In pathological studies, mice expressing 148Q huntingtin showed intranuclear aggregates in cerebral cortex, hippocampus, striatum, and cerebellar granule cells. In immunoblot analyses of cytosolic and nuclear protein extracts, we detected a cleavage band of huntingtin in the nuclear fractions taken from mice expressing 148Q huntingtin. Mice expressing 23Q huntingtin or uninduced conditions did not show the cleavage band or abnormal neurological symptoms. This mouse model shows a clear phenotype and should be useful for studies on the pathogenesis of HD. In addition, these data suggest that the proteolytic cleavage detected in mice expressing 148Q huntingtin may be involved in HD pathogenesis and help find clues to potential therapeutics.

N048

Amiodarone affected open field behaviors and an activity rhythm during dark phase in F344 rats

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It has been reported that PCBs and dioxins might disrupt thyroid function as thyroid hormone (TH) -like chemicals and cause abnormal central nervous system (CNS) development. Amiodarone, a drug treating for tachyarrhythmias, is known to have adverse effects on TH synthesis and conversion from T4 to T3. Moreover, amiodarone is thought to directly antagonize TH because of its TH-like structure. In this study, we tried to establish a novel perinatal TH disrupting animal model using amiodarone and evaluate the effects of amiodarone on CNS development by neurobehavioral tests. Pregnant female F344 rats (n=5 in each group) were daily exposed to amiodarone (10mg/kg/day) by oral administration from 3 to 20 days of gestation. The offspring were weaned at the postnatal day 21, then they were subjected to behavioral tests, open field test (7 w), spontaneous motor activity (12 w) and active avoidance test (only males to avoid sexual cycle, 25-27 w). In female offspring, amiodarone had no effect on the behavioral tests conducted in this study. There was significant decrease in locomotion of the amiodarone-treated male offspring compared with control males. During dark phase, although the total motor activity did not change in the amiodarone-treated males, the activity rhythm of this group markedly differed from that of control males. In amiodarone-treated males, the durations of non-active phase were elongated. Active avoidance learning behavior of the male offspring was not impaired by amiodarone administration. These findings revealed that perinatal exposure to amiodarone affected locomotor behavior of grown-up males. We are now investigating the expressions of the factors (deiodinases, actin and tubulin etc.) susceptible to TH disruption in the brain.

N049

Production of transgenic mice expressing Cre-ERT in the brain

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Catecholaminergic neurons, which include dopaminergic, noradrenergic, and adrenergic neurons, are located in discrete regions of the central nervous system and have an important role in a wide range of brain function, such as locomotion, behavior, sleep, memory, and learning. Tyrosine hydroxylase (TH, EC 1.14.16.2) is a monooxygenase that catalyzes the conversion of tyrosine to 3,4-dihydroxyphenylalanine (DOPA). Homozygous TH knockout mice died at a late stage of embryonic development. Conditional knock out is a powerful technique to analyze function of the gene-product in a specific region at a specific developmental stage, even if the gene-product is essential for normal development. Here we produced transgenic mice expressing tamoxifen-inducible Cre-ERT, a fusion protein composed of Cre recombinase and a mutated ligand-binding domain of the estrogen receptor under the control of the human dopamine beta-hydroxylase (DBH) promoter. We used a DNA fragment of the 5.8 kb promoter region that was reported to express a reporter gene in dopaminergic, noradrenergic, and adrenergic neurons. We establish 14 lines of transgenic mice, and analyzed expression of Cre-ERT in the brain and the adrenal immunohistochemically. We detected Cre-ERT positive cells in the brain of 11 out of 14 transgenic mice. The expression patterns were different in each transgenic mouse. Most of the mice expressed Cre-ERT in locus ceruleus, adrenal medulla, and mesencephalic trigeminal nucleus. In two lines, we detected Cre-ERT in the substantia nigra. We are crossing the Cre-ERT transgenic mice with floxed TH mice.

N050

Functional analysis of the gene, CHAC responsible for chorea-acanthocytosis, using gene-targeted model mouse

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Chorea-acanthocytosis (CHAC) is a hereditary neurodegenerative disorder with autosomal recessive transmission, showing Huntington disease-like neuropsychiatric symptoms and peripheral blood red cell acanthocytosis. Recently, we have identified the gene, CHAC encoding a newly discovered protein, chorein, in which a deletion mutation was found in Japanese CHAC families (Nature Genet. 2001; 28: 121-122). In the present study, we have cloned the mouse CHAC cDNAs and identified the exon-intron structures of the gene. A novel alternative spliced mRNA isoform (Transcript C) was identified as well as Transcripts A and B which have been already reported. Expression of the CHAC gene was studied using in situ hybridization and real time PCR. Transcript A was ubiquitously expressed in various tissues, but Transcript B was exclusively expressed in the brain, and Transcript C in tissues except the brain. Further, we produced the CHAC-model mouse using gene-targeting technique introducing #60-61 exons-deletion corresponding to the human Ehime-deletion mutation liable to CHAC. At 72 weeks old, there was no significant difference in weight between wild and homozygously mutation-bearing CHAC-model mice, and no involuntary movement was observed in the model mice. However, acanthocytosis was found in their peripheral blood and the fragility of their red cells was demonstrated in osmotic test. Splenomegaly like in human CHAC patients was observed in CHAC-model mice at autopsy. In behavioral observation, total locomotor activity was not different, but the duration of the time, in which the mice were around the edge of the field, was significantly increased and the contact time was decreased significantly at social interaction test in the CHAC-model mouse.

N051

Sodium Butyrate Ameliorates Phenotypic Expression in a Transgenic Mouse Model of Spinal and Bulbar Muscular Atrophy

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Purpose: In polyglutamine (poly Q) disease, mutant protein containing poly Q is thought to inhibit histone acetyltransferase (HAT) activity resulting in transcriptional dysfunction. Histone deacetylase (HDAC) inhibitors have been reported to reactivate transcriptional function in fly and mouse models of Huntington disease. We studied therapeutic effects of sodium butyrate (SB), a HDAC inhibitor, in a transgenic mouse model of spinal and bulbar muscular atrophy (SBMA). **Method:** SBMA model mice were orally administered SB solution (800mg/100ml water). We analyzed histopathology and symptomatic phenotypes such as rotarod task, cage activity, survival rate, and body weight. We also evaluated nuclear accumulation of the mutant androgen receptor protein. **Results:** Rotarod task, cage activity, and survival rate were ameliorated in SB administered mice. These effects however, were seen only in narrow range of SB dosage. SB did not change nuclear accumulation of mutant androgen receptor (AR). Acetylation of nuclear histone was enhanced in the spinal cord and brain of the SB treated mice. SB did not alter phenotypes of wild type mice. **Conclusion:** SB ameliorated phenotypic expression in a SBMA mouse model. Our results indicate that SB is a therapeutic candidate of SBMA and other polyQ disease although its therapeutic window is narrow.

N052

Development of a quantitative oligo-DNA microarray for monitoring synaptic status

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Though DNA microarrays have proven to be powerful tools for large scale screening of gene expression changes, their further use for the more quantitative analyses is hampered by the limited reproducibility and sensitivity. To overcome these problems and further to be able to detect alterations in mRNA splicing which are common in the nervous system, we developed an original, Stanford-type oligoDNA microarray covering approx.100 genes involved in the construction and functioning of the synapse. In addition to the use of high-precision arrayer developed at RIKEN, following measures were taken to increase the reliability of the array: (1) selecting 45mer probes with GC content in the distinct range, (2) employing 2 spots/probe, 2 different probes/gene, triplicate grids/slide, (3) optimizing the hybridization and wash conditions, (4) normalizing with data from a set of 10 standard genes of different expression levels. Performance of the microarray was tested by competitive hybridization using mRNAs extracted from the cerebellum of rats at postnatal day 4 (P4) and 6 weeks (6w) which were reverse-transcribed and labeled with the fluorescent dye Cy3 or Cy5. The results show that differential expression ratios for the same probe fall within the variance of plus or minus 20 percent, making it possible to detect 50 percent changes in gene expression with confidence. These values were also in good accordance with expression ratios measured by realtime PCR for more than 20 representative genes. With such a quantitative array, it will be possible to efficiently monitor the time course of changes in synaptic status due to disease or exogenous agents such as environmental chemicals.

N053

Effect of perinatal hypothyroidism on gene expression in the developing mouse cerebellum

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To study the roles of thyroid hormone in brain development, we analyzed gene expression differences in the cerebellum of experimentally hypothyroid and control mice during a critical perinatal period of up to 15 days after birth. Two types of DNA microarrays were used; a conventional high-density cDNA microarray with probes for 15,000 genes and an original oligoDNA microarray (Synapto-array) with probes for approx. 100 genes involved in the construction and functioning of the synapse. Messenger RNAs extracted from mouse cerebellum at different time points were reverse-transcribed, labeled with Cy3 or Cy5, and compared by competitive hybridization. At postnatal day 7 (P7), overall differences between cDNA from hypothyroid and control mice were small on both types of arrays, but were significantly increased at postnatal day 15 (P15). Large scale screening and comparison of the differentially expressed genes during normal development (P7-control vs. P15-control) with those between hypothyroid and control mice at P15 (P15-hypo vs. P15-control) using high-density arrays revealed that several groups of genes were specifically up-regulated by hypothyroidism. These included genes involved in cell cycle regulation, apoptosis, cell stress and the ubiquitin-proteasome pathway, suggesting that the stress response is taking place. Analyses using the more quantitative Synapto-array showed that distinct groups of synaptic proteins were differentially down-regulated by hypothyroidism; compared with the pre- and post-synaptic structural proteins, proteins involved in synaptic vesicle docking were more severely down-regulated. The results indicate that thyroid hormone mainly influences the synaptogenic process, more severely on the functional than on the structural aspect.

N054 (MS1-1)

Targeted Disruption of Mouse DRPLA Gene to Investigate Molecular Pathophysiology of dentatorubral-pallidolusian atrophy (DRPLA)

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The physiological functions of the gene products of the causative genes for polyglutamine diseases remain to be determined, except for the androgen receptor (SBMA), the alpha 1A voltage-depended calcium channel (SCA6) and TATA-binding protein (SCA17). To gain insight into the physiological roles of the wild-type DRPLA protein, a widely expressed protein with no known homology to any of the proteins, we generated mice with a targeted disruption of the DRPLA gene with insertion of LacZ gene. The mutant mice grow into adulthood although mice heterozygous and homozygous for this mutation displayed neurological phenotypes including involuntary movements and the feet clasping posture when suspended by the tail. We analyzed the motor performance ability of mutant mice on the rotating rod test. Heterozygous mice of the C57BL/6J-129SvJ hybrid background revealed a significant decrease in the rotating rod test at 18 weeks. Homozygous mice were consistently smaller than their normal littermates. The morphology of the central nervous system (CNS) in the mutant mice appeared normal with no focal areas of malformation or neurodegeneration. However, sections of the brains of the homozygous mice were consistently smaller than their normal littermates. Staining of the brain sections derived from mutant mice with X-gal, interestingly revealed strongly stained neuronal cells, but we did not detect blue cells in the other organs, including heart, lung, liver, spleen, kidney, and ovary. These results suggest that DRPLA protein has physiological functions essential for the CNS, and furthermore, that even half dose of wild-type of DRPLA gene results in phenotypic expression. The mice should be highly useful for investigating physiological functions of DRPLA protein.

N055

A molecular therapy for polyglutamine diseases targeting the toxic conformational transition and aggregate formation of the expanded polyglutamine protein using the inhibitor peptide QBP1

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Polyglutamine (polyQ) diseases are a class of inherited neurodegenerative diseases including Huntington's disease, various types of spinocerebellar ataxia, and spinobulbar muscular atrophy, which are caused by abnormal expansions of the polyQ stretch in each unrelated disease protein. Expansion of the polyQ stretch is thought to confer toxic properties on the disease proteins through alterations in their conformation, leading to pathogenic protein-protein interactions including aggregate formation. Based on the hypothesis that molecules which bind the expanded polyQ stretch may interfere with its pathogenic interactions, we previously identified Polyglutamine Binding Peptide 1 (QBP1), a peptide sequence that preferentially binds the expanded polyQ stretch from combinatorial peptide libraries by phage display screening. We showed that QBP1 inhibits polyQ protein aggregation *in vitro* and cytotoxicity in cell culture. In this study, we show that QBP1 expression inhibits polyQ aggregation and suppresses polyQ-induced compound eye degeneration in *Drosophila* polyQ disease models. Moreover, QBP1 rescues polyQ-induced premature death in *Drosophila*, suggesting that QBP1 can prevent polyQ-induced neurodegeneration *in vivo*. Structural analysis using circular dichroism suggests that QBP1 inhibits aggregation by preventing the toxic conformational transition of the polyQ protein to a beta-sheet rich structure. Furthermore, electron microscopy revealed that QBP1 prevents amyloid-like fibril formation of the polyQ protein. Selective inhibition of the toxic conformational transition and aggregate formation of the expanded polyQ protein by QBP1 is a useful strategy for developing potential therapies for the currently untreatable polyQ diseases.

N056 (MS1-3)

Inhibitory effects of 4-phenylbutyrate on Pael receptor accumulation and endoplasmic reticulum stress induced cell death

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A class of compounds called chemical chaperone, an example of which is 4-phenylbutyrate (4-PBA), has been demonstrated to repair unfolded proteins including cystic fibrosis transmembrane conductance regulator (CFTR) and alpha 1-antitrypsin. The most frequent mutation of CFTR causes misfolding and trafficking arrest in the endoplasmic reticulum (ER). Therefore, we hypothesized that 4-PBA may be useful in preventing the accumulation of unfolded protein in the ER. We initially demonstrated that 4-PBA prevented death induced by tunicamycin (Tm), an ER stress inducing agent, in neuroblastoma SK-N-MC cells. IRE1, an ER stress transducer, recognizes unfolded proteins that accumulate in the ER, and eventually induces the transcription of ER chaperone genes. 4-PBA restored the growth rate of the yeast delta *ire1* strain treated with Tm. The up-regulation of ER resident chaperones, GRP78 and GRP94, in response to Tm was decreased by treatment with 4-PBA. PERK, another ER stress transducer, is also phosphorylated in response to ER stress. We showed that 4-PBA attenuated the phosphorylation of PERK in response to Tm. Furthermore, we investigated the effects of 4-PBA on the Parkin-associated endothelin receptor-like receptor (Pael-R) that is involved in autosomal recessive juvenile Parkinsonism (AR-JP). The expression of ER chaperones induced by the overexpressed Pael-R was decreased by 4-PBA treatment, indicating that 4-PBA suppressed ER stress induced by the overexpression of Pael-R. In addition, 4-PBA prevented the accumulation of Pael-R in the ER induced by thapsigargin, an ER stressor. These results suggest that the suppression of ER stress by 4-PBA is caused by the decrease in the amount of unfolded proteins that accumulated in the ER.

N057 (MS1-4)

ALS2, a novel guanine nucleotide exchange factor for the small GTPase Rab5 is implicated in endosomal dynamics

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ALS2 mutations account for a number of recessive motor neuron diseases including forms of amyotrophic lateral sclerosis, primary lateral sclerosis, and hereditary spastic paraplegia. Although computational predictions suggest that ALS2 encodes a protein containing multiple guanine nucleotide exchange factor (GEF) domains [RCC1-like domain (RLD), the Db1 homology and pleckstrin homology (DH/PH), and the vacuolar protein sorting 9 (VPS9)], the functions of the ALS2 protein have not been revealed as yet. Here we show that the ALS2 protein specifically binds to small GTPase Rab5 and functions as a GEF for Rab5. Ectopically expressed ALS2 protein localizes with Rab5 and early endosome antigen-1 (EEA1) onto early endosomal compartments, and stimulates the enlargement of endosomes in the cultured cortical neurons. The carboxy-terminus of ALS2 protein carrying a VPS9 domain mediates not only the activation of Rab5 via a guanine-nucleotide exchanging reaction but also the endosomal localization for the ALS2 protein, while the amino-terminal half containing RLD acts suppressive in its membranous localization. Further, the DH/PH domain in the middle portion of ALS2 protein enhances the VPS9 domain-mediated endosome fusions. Taken together, the ALS2 protein as a novel Rab5-GEF, ALS2rab5GEF, seems to be implicated in the endosomal dynamics in vivo. Notably, a feature common to eight reported ALS2 mutations among motor neuron diseases is the loss of VPS9 domain resulting in the failure of Rab5 activation. Thus, a perturbation of the endosomal dynamics caused by loss of ALS2 rab5GEF activity might underlie neuronal dysfunction and degeneration in a number of motor neuron diseases.

N058 (MS1-5)

Aprataxin, the causative gene for early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH) as a member of ssDNA repair machinery. - Implication of impaired DNA repair systems in neurodegeneration-

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Early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH/AOA1) is an autosomal recessive neurodegenerative with clinical presentations partly similar to those of Friedreich's ataxia. By a positional cloning approach, we have recently identified the causative gene, aprataxin. Aprataxin has two major mRNA species coding for short and long forms as a result of alternative splicing of a part of exon 3. Both forms of aprataxin mRNAs are expressed at comparable levels in various human tissues. From the Western blotting analysis, the long form of APTX (LAPTX) is a major form in human central nervous system. In patient's brain, however, the total amount of LAPTX has been remarkably decreased. From these results the loss of function of LAPTX may contribute to neurodegenerative process in this disease. The N-terminus portion of LAPTX shows homology to the polynucleotide kinase-3'phosphatase (PNKP), a subtype of single-strand DNA (ssDNA) break repair, through interaction of XRCC1, DNA polymerase β , DNA ligase III, poly (ADP-ribose) polymerase. We identified XRCC1 as APTX interacting protein by yeast two hybrid system and immunoprecipitation. We also determined the direct binding region of LAPTX that interacts with XRCC1 using truncated APTX construct. The present study suggests that the long form of aprataxin, the major form of the APTX gene products, is involved in the repair of single strand DNA break repair machinery. The gradual accumulation of DNA damages might occur as the result of dysfunction of the long-form aprataxin and cause the neuronal dysfunction in EAOH/AOA1.

N059

ALS2 C-terminal like (ALS2CL) : identification and characterization of the novel conserved gene that encodes a protein highly homologous to the carboxy-terminal half of the ALS2 protein

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The loss-of-functional mutations in the *ALS2* gene account for a number of recessive motor neuron diseases including forms of amyotrophic lateral sclerosis (ALS2), primary lateral sclerosis, and hereditary spastic paraplegia. Here we report a novel *ALS2* homologous gene, *ALS2 C-terminal like (ALS2CL)*, as a candidate functional modulator for the ALS2 protein. The sequence of the *ALS2CL* transcript encompasses 4,741 nt with a single open reading frame (2,862-nt long). Consistent with this result, the transcript of approximately 5 kb was detected, by northern blotting, in various adult human tissues. Computational predictions have shown that *ALS2CL* encodes a 108-kD protein (953 amino acids) comprising several domains and motifs including pleckstrin homology (PH), membrane occupation and recognition nexus (MORN), and vacuolar protein sorting 9 (VPS9). The entire amino acid sequence of ALS2CL is highly homologous to the carboxy-terminal half, corresponding to Dbl homology/PH/MORN/ VPS9 domains, of ALS2 (33% identity and 51% similarity). The presence of VPS9 domain suggests that ALS2CL is a putative Rab5-guanine nucleotide exchange factor (GEF) and might play roles in endocytosis and membrane trafficking in the cells. Genomic analysis has revealed that the *ALS2CL* gene comprises 26 exons and resides within 24.5 kb of genomic DNA mapping to chromosome 3p21. Further, the intron-exon boundaries of 25 coding exons for *ALS2CL* were completely matched with those (corresponding to exons 10-34) for *ALS2*, indicating that *ALS2CL* and *ALS2* have evolved from the same ancestral gene of origin. Future studies on the molecular functions both of ALS2CL and ALS2 will give us further insights into the neurodegeneration and pathogenesis for a number of motor neuron diseases.

N060

Full-length DRPLA proteins suppress CREB- and p53- dependent transcriptional activation

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At least nine neurodegenerative diseases, including dentatorubral pallidoluysian atrophy (DRPLA), have been known to be caused by expanded CAG repeats encoding polyglutamine (polyQ) stretches. Recently, it has been demonstrated that interference with CREB-dependent transcription due to the binding of expanded polyQ stretches with transcriptional co-activators, such as TATA-binding protein associated factor (TAFII130) or CREB-binding protein (CBP), is involved in the pathogenetic mechanisms underlying neurodegeneration. It remains, however, unclear whether full-length DRPLA proteins have physiological functions on transcriptional regulation. To investigate the effects of DRPLA proteins on transcriptional regulation, we performed a reporter assay (dual luciferase assay) using cultured cells expressing full-length or truncated DRPLA proteins containing 19 or 82 glutamines, and found that full-length DRPLA proteins suppressed CREB-dependent transcriptional activation. There are no apparent differences of the suppression levels between the cells expressing DRPLA proteins containing 19 or 82 glutamines. We also found that p53-dependent transcriptional activation was suppressed by full-length DRPLA proteins, while AP1- or NFκB-dependent transcriptional activation was not suppressed. Taken together, these results raise the possibility that physiological function of DRPLA proteins is the transcriptional regulation that depends on CREB or p53.

N061

An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells

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In Parkinson disease, characteristic pathological features are the cell death of nigro-striatal dopamine neurons and the formation of Lewy bodies composed of degraded proteins including oxidized proteins. Mitochondrial dysfunction and aggregation of abnormal proteins have been proposed to cause these pathological changes. However, the relation between these two factors remains to be clarified. In this paper, the effect of mitochondrial dysfunction on the oxidative modification and accumulation of protein were studied using an inhibitor of mitochondrial complex I, rotenone, and antibodies against acrolein- and dityrosine-modified proteins. Under the conditions inducing mainly apoptosis in human dopaminergic neuroblastoma SH-SY5Y cells, rotenone markedly increased oxidized proteins, especially those modified with acrolein, even though increase in the intracellular reactive oxygen and nitrogen species was only transient and not so marked. In addition, the activity of proteasome degrading oxidized proteins reduced profoundly after treatment with rotenone. The 20S beta subunit of proteasome was modified with acrolein, to which other acrolein-modified proteins were found to bind, as shown by the co-precipitation with the antibody against 20S beta subunit. These results suggest that mitochondrial dysfunction, especially decreased activity of complex I, may reduce proteasome activity through the oxidative modification of proteasome itself and the aggregation with other oxidized proteins. This mechanism might account for the accumulation of modified protein, and at least partially for the death of the dopamine neurons in Parkinson disease.

N062

N-Propargyl-1 (R) -aminoindan, rasagiline, increases glial cell line-derived neurotrophic factor (GDNF) and BCL-2 in neuroblastoma SH-SY5Y cells through activation of NF-kappaB transcription factor

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N-Propargyl-1 (R) -aminoindan (rasagiline), an anti-Parkinson drug, was found to increase the protein and mRNA levels of BCL-2 and glial cell line-derived neurotrophic factor (GDNF) in human neuroblastoma SH-SY5Y cells, whereas an analogue without a propargyl residue, aminoindan, did not. In this paper, intracellular mechanism underlying the induction of neuroprotective proteins was studied. Rasagiline induced phosphorylation of nuclear factor-kappaB (NF-kB) inhibitory subunit (IκB) and translocation of active p65 subunit from cytoplasm into nuclei. Activation of NF-κB, was also quantitatively determined by NF-κB p65 transcription assay. Sulfasalazine, an inhibitor of IκB kinase, suppressed the activation of NF-κB and the increase of BCL-2 and GDNF by rasagiline simultaneously, indicating further the involvement of the IκB kinase-NF-κB pathway. In addition, rasagiline was found to activate neuroprotective Erk1/2 MAP kinase, but p38 and JNK were not affected. These results suggest that the neuroprotective action of rasagiline may be due to activation of a kinase to induce neuroprotective genes. Rasagiline, which can cross the blood-brain barrier into the brain, may be effective as a neuroprotective drug to halt decline of neurons in neurodegenerative disorders, such as Parkinson and Alzheimer diseases. The activation of transcription factors to increase anti-apoptotic and pro-survival genes suggests the possibility to apply rasagiline as a causal therapy in neurodegenerative disorders, including Parkinson and Alzheimer diseases.

N063

Proteasome inhibitor-induced insolubilization of ubiquitinated proteins and Hsp27 followed by cell death are mediated by heat shock factor activation

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Exposure of U251 MG human glioma cells to MG-132, a proteasome inhibitor, induces accumulation of Hsp27 and ubiquitinated proteins in the insoluble fraction of cells, together with phosphorylation of Ser-15, Ser-78 and Ser-82 in Hsp27 molecules. MG-132 induces necrotic cell death, which is enhanced by the presence of nocodazole, a microtubule-disrupting drug. However, the coexistence of cycloheximide, which inhibits protein synthesis and activation of heat shock factors (HSFs) by MG-132, suppressed the MG-132-induced formation of insoluble protein complexes (IPC) and subsequent cell death, even though cycloheximide did not inhibit the enhanced phosphorylation of Hsp27 nor the accumulation of ubiquitinated proteins in the soluble fraction induced by MG-132. In contrast, nordihydroguaiaretic acid, which activates HSE-binding activity of HSF, enhanced the MG-132-induced accumulation of IPC and ubiquitinated proteins. Immunocytochemically, Hsp27 and ubiquitinated proteins were found located in the inclusion bodies, formed preferentially in the perinuclear regions of cells treated with MG-132. These inclusions were not found in cells treated with cycloheximide, suggesting that the formation of IPC by proteasome inhibition is correlated with the activation of HSF. Diffuse distribution of insoluble protein complexes in cytoplasm may injure cells and their collection into inclusion bodies, with the aid of microtubules, might be a protective mechanism against cell insult. Whatever, phosphorylation of Hsp27 seems to be unnecessary for formation of IPC.

N064

Activation of JNK/SAPK pathway by trimethyltin in murine hippocampus

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Trimethyltin (TMT), which is used in fungicides and chemostabilizers, selectively damages neurons in human and rodent central nervous system after a single exposure. Our previous reports have demonstrated that a systemic injection of TMT into mouse induced neuronal damage specific for the dentate granule neurons of the hippocampus. To elucidate possible mechanism underlying TMT-induced neuronal damage in mouse, we investigated on expression of the transcription factor activator protein-1 (AP-1) after the systemic administration of TMT. Electrophoresis mobility shift analysis revealed that TMT treatment leads to enhancement of AP-1 DNA binding in the hippocampus at least 1-3 days afterward. Supershift and immunoblot analyses using specific antibodies showed that TMT-induced enhancement of AP-1 DNA binding results from expression of Fra-2 and c-Jun in the hippocampus. Further analyses indicated that TMT treatment induces marked expression of phosphorylated c-Jun (Ser63) in the hippocampus, but not in the cerebellum, at least 16 to 24 h later. In addition, phosphorylated c-Jun N-terminal kinases (JNKs) as well as phosphorylated SEK1 (MKK4) were increased in the hippocampus after the treatment. These results suggest that TMT may induce neuronal cell damage through the activation of JNK pathway in murine hippocampus.

N065

Expression of high-molecular-weight heat shock proteins by endoplasmic reticulum stress in SH-SY5Y cells

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Several lines of evidence indicate that endoplasmic reticulum (ER) dysfunction may induce neuronal cell injury in some neurodegenerative disorders. ER dysfunction has been known to activate ER-overload and unfolded-protein responses. Recent studies have also shown that the inhibition of ubiquitin-proteasome pathway induces an increase in expression of HSPs, such as cytosolic HSP70 and glucose-regulated proteins, which are involved in many cellular metabolic processes including protein synthesis, folding/assembly, membrane translocation and degradation in normally growing cells. However, very little is known about expression of high-molecular-weight HSPs, including HSP105, APG-1 and APG-2, under the ER stress. By means of an immunoblot analysis, we determined the levels of the high-molecular-weight HSPs in the cytosol of human neuroblastoma SH-SY5Y cells treated with tunicamycin (50 μ M) and the proteasome inhibitor MG132 (1 μ M). Treatment with tunicamycin and MG132 led to more than 50% cell death for a period of 24 h. Tunicamycin was effective in decreasing the levels of HSP105, APG-1, and APG-2, but not HSP70 level, in a time-dependent manner. MG132 treatment markedly increased the levels of both HSP70 and HSP105, without significantly affected APG-1 and APG-2 levels. These results suggest that expression of the high-molecular-weight HSPs may be regulated by the ER stress.

N066

Effect of methamphetamine on gene expression of Parkin and Pael-receptor in rat striatum

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We previously reported that haloperidol, a dopamine-D(2) receptor antagonist, induced striatal expression of parkin gene, which mutations cause autosomal recessive juvenile parkinsonism. Because of an involvement of the parkin gene defect in selective degeneration of dopaminergic neurons, we herein examined the effect of the neurotoxic dose of methamphetamine (METH; 40 mg/kg, i.p.) on gene expression of parkin and its substrate Pael-receptor (R) in the dopamine-rich areas of the rat brain, using reverse transcription-polymerase chain reaction. parkin mRNA levels in the striatum, but not in other regions, decreased at 1 and 2 h and returned to the pre-drug basal levels at 4 h after METH administration. METH also decreased Pael-R mRNA levels in the striatum and substantia nigra within 2 h after METH, while haloperidol (2 mg/kg, s.c.) increased Pael-R mRNA levels in the substantia nigra at 2 h after administration. These results suggest that temporary suppression of gene expression of parkin and Pael-R may be associated with the METH-induced dopaminergic neurotoxicity. Taken together with our previous report, dopaminergic modulation of the expression of parkin and Pael-R genes in the nigro-striatal pathway may have significant implication for pathophysiology and treatment of parkinson disease.

N067

Novel Zinc finger-RING finger proteins, Momo and Sakura, are enriched in Neurons and Glial cells, respectively

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There are more than 100 members of the family containing RING finger structure and most of them are suggested to function as a E3 ubiquitin ligase. Here, we report two novel ubiquitin ligases, Momo and Sakura, both of which associate with the membranes of neuronal and/or glial cells and carry double zinc finger motif and RING finger domain. Momo cDNA (2224 bp) encodes 381 aa (42695 Da), while Sakura cDNA (3107 bp) encoded a protein of 362 aa (40407 Da) (Genbank #AY157968 and #AY157969). The overall nucleotide homology between Momo and Sakura was 62% and their amino acid identity was 46%. Although the RING finger sequence of Momo exhibited a 42% amino acid identity and 64% similarity to that of IAP, and that of Sakura 51% identity and 70% similarity to that of IAP, we failed to detect an influence of Momo or Sakura overexpression on the cell survival of neurons. Sakura mRNA was detected in the brain, liver, kidney, lung and spleen, while Momo mRNA expression was more restricted to the brain. In situ hybridization analysis confirmed that Momo mRNA was detected in the pituitary as well as in the molecular layer of the cerebellar cortex and Sakura mRNA was detected in the corpus callosum, brain stem, spinal cord and cerebellar white matter. In agreement, Momo immunoreactivity was most enriched in the gray matter fractions of the cerebral cortex and cerebellar cortex while Sakura immunoreactivity was recovered mainly in the white matter fractions. As Momo and Sakura carry putative palmitoylation site (s), the immunoblotting revealed that almost all immunoreactivity for Momo and Sakura was both recovered in the membrane fraction (P3). These results suggest specific roles of Momo and Sakura in ubiquitination of neuronal and glial membrane components, respectively.

N068

Enhanced binding to the antioxidant-response element through formation of Nrf2/Fos-B complex after kainate treatment

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Activation of glutamate signals has been well known to generate reactive oxygen species which elicit oxidative stress in the neurons. It may be possible that glutamate signals induce expression of antioxidant molecules through activation of antioxidant-response element (ARE) in the genes. However, little is known about changes in ARE binding after activation of glutamate signals. To determine whether glutamate signals activate antioxidant-response element (ARE) in the hippocampus, in this study, ARE binding was examined in nuclear extracts obtained from mouse hippocampus after a systemic injection of kainate or NMDA. Electrophoretic mobility shift analyses were carried out using a radiolabeled oligonucleotide with ARE in glutathione-S-transferase Ya subunit promoter. NMDA and kainate has the ability for enhancing ARE binding in the hippocampal nuclear extracts. ARE binding enhanced by kainate treatment was significantly inhibited by an antibody against Nrf2, which has shown to associate with ARE. Furthermore, antibodies against c-Fos and Fos-B induced mobility shift of probe/protein complex when used the hippocampal nuclear extracts from kainate treated animals. Probe/protein complex shifted by the anti-Fos-B antibody was inhibited by further addition of the anti-Nrf2 antibody. However, the complex shifted by anti-c-Fos antibody was unaffected by the anti-Nrf2 antibody. Immunoblot analyses revealed kainate treatment enhanced marked expression of Fos-B and c-Fos, but not of Nrf2, in the hippocampus. Taken altogether, kainate signals could activate ARE in the hippocampus at least in part through association of Nrf2 with Fos-B expressed by the treatment.

N069

Ubiquitin ligase activity and palmitoylation of the membrane-associating RING finger proteins, Momo and Sakura

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We identified two genes designated Momo and Sakura that encode novel RING finger protein and are highly expressed in the brain (see accompanying presentation; K. Araki et al). To examine their potential Ub ligase activity, viral expression vectors carrying myc-tagged Momo and Sakura together with FLAG-tagged Ub were transfected into mixed cortical cultures. Overexpression of either Momo or Sakura increased polyubiquitination levels as monitored by anti-FLAG immunoblotting. Momo-dependent or Sakura-dependent ubiquitination also occurred in vitro. The immunoprecipitates from culture lysates containing Momo or Sakura were co-incubated with E1 Ub activating and E2 Ub conjugating (Ubc) enzymes in the presence of 125I-Ub. Ubiquitination required the combination of Momo and UbcH4 and H5c, or of Sakura and UbcH4, H5c and H6. The purified recombinant Momo and Sakura caused their self-ubiquitination in the presence of E1 and UbcH4 in reconstitution Ub assay. Deletion mutagenesis suggested that the E3 Ub ligase activity of Momo and Sakura depended on their C-terminal domains containing RING finger motif, while their N-terminal domains determined sensitivity to a proteasome inhibitor or their membrane association. In agreement, an incorporation study of [3H]-palmitate revealed that Sakura associating with the membrane was palmitoylated. Although the molecular targets of their Ub ligation remain to be identified, these findings imply a novel function of the brain-enriched E3 Ub ligases, Momo and Sakura, in the cell membrane.

N070

Transplantation of tyrosinase-producing cells into the striatum of hemi-parkinsonian model

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Tyrosinase, which catalyzes both the hydroxylation of tyrosine and the oxidation of L-DOPA to form melanin in melanocytes, is also expressed in the brain, and oxidizes not only L-DOPA but dopamine (DA). The replacement of DA synthesis by tyrosinase has been reported in tyrosine hydroxylase-null mice. We previously reported that inhibition of tyrosinase reduced viability of DAergic neuronal cells to enhance DA-induced cell death. To investigate the possible effects of tyrosinase-producing cell transplantation in parkinsonian models, we performed intrastriatal transplantation of B16-F1 melanoma cells, as tyrosinase-producing cells, into hemi-parkinsonian rats. Apomorphine-induced rotation behavior towards contralateral side was markedly ameliorated 7-14 days up to 40 days after the transplantation, coinciding with expression of DA-positive signals around survived transplant. Furthermore, we performed transplantation of melanocytes into the striatum of hemi-parkinsonian mice. In the transplanted group with melanocytes from the back of newborn black mice, the rotation behavior was markedly ameliorated at 7 days up to 2 months after the transplantation. Taken together with the previous studies showing DA synthesis and metabolism by tyrosinase, these results suggest a therapeutic potency of tyrosinase which may complement tyrosine hydroxylase when DAergic neurons are degenerated, and may normalize L-DOPA-induced abnormal DA turnover.

N071

Amyloid beta-Protein (Abeta) 1-40 Protects Neurons from Damage Induced by Abeta1-42 in Culture and in Rat Brain

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We previously reported that Abeta1-40 serves as an antioxidant molecule by quenching metal ions and inhibiting metal-mediated oxygen radical generation (Zou, K, et al, J. Neurosci. 22, 4833-4841, 2002). Here we show another neuroprotective action of monomeric Abeta1-40 against Abeta1-42-induced neurotoxicity in culture and in vivo. Neuronal death was induced by Abeta1-42 at concentrations higher than 2 microM and the Abeta1-42-induced neuronal death was prevented by concurrent treatment with Abeta1-40. However, metal chelators did not prevent Abeta1-42-induced neuronal death. Circular dichroism spectroscopy, electron microscopy analysis, and thioflavin-T assay showed that Abeta1-40 inhibited the fibril formation of Abeta1-42. Injection of Abeta1-42 into the rat entorhinal cortex (EC) caused hyperphosphorylation of tau on both sides of EC and hippocampus, which were prevented by the concurrent injection of Abeta1-40. These results indicate that Abeta1-40 protects neurons from Abeta1-42-induced neuronal damage in vitro and in vivo by inhibiting the beta-sheet transformation and fibril formation of Abeta1-42. Our data suggest a mechanism underlying elevated Abeta1-42/Abeta1-40 ratio accelerates development of Alzheimer's disease (AD) in familial AD.

N072

Hsp105 suppresses cell death causally expansion of the polyQ tract in cellular model of SBMA

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Spinal bulbar muscular atrophy (SBMA) is a neurodegenerative disorder caused by the expansion of a polyglutamine (polyQ) tract in the androgen receptor (AR). The N-terminal fragment of AR containing the expanded polyQ tract aggregates in cytoplasm and/or in nucleus, and induces cell death. Hsp105, expressed at especially high levels in mammalian brain, has been shown to suppress apoptosis in neuronal cells, and prevent the aggregation of protein caused by heat shock *in vitro*. To elucidate the role of Hsp105 on SBMA, we used a cellular model of SBMA. Although the transient expression of truncated ARs containing an expanded polyQ tract (tAR97) caused aggregates to form in COS-7 cells and concomitantly apoptosis in the cells with the nuclear aggregates, this aggregation and cell toxicity were markedly reduced when Hsp105 was over-expressed with tAR97. The analysis using various deletion mutants of Hsp105 revealed that both β -sheet and α -helix domains of Hsp105 were necessary to suppress the formation of aggregates *in vivo* and *in vitro*. In addition, although endogenous Hsp105 was not co-localized to aggregates of tAR97 in COS-7 cells, Hsp105 was co-localized when Hsp105 was over-expressed with tAR97. Thus, the increased amounts of Hsp105 seemed necessary for the interaction with and binding to the tAR97. Furthermore, Hsp105 was found to localize in nuclear inclusions formed by ARs containing an expanded polyQ tract in tissues of patients and transgenic mice with SBMA. These findings suggest that over-expression of Hsp105 suppresses cell death caused by expansion of the polyQ tract without chaperone activity, and the enhanced expression of the essential domains of Hsp105 in brain may provide an effective therapeutic approach for CAG repeat diseases.

N073

Approach to the identification of the causative substance in an endemic neurodegenerative disease in Guadeloupe, the French West Indies

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In Guadeloupe, the French West Indies, patients with atypical parkinsonism or progressive supranuclear palsy are frequent. Local inhabitants consume the fruits of the *Annonaceae* family, and they also have customs to drink tea boiled up from leaves of the *Annonaceae* family. We started the research described below, in order to identify the low-molecular-weight neurotoxic substances like tetrahydroisoquinoline derivatives in *Annona muricata* (soursop), one of the *Annonaceae* family and to elucidate the cause of the local disease. We extracted the total alkaloid fraction from seeds, pulps, and leaves of the fruits, and tried to detect and determined reticuline, norreticuline, and N-methylcoculaurine as representative alkaloids having tetrahydroisoquinoline structure with LC/MS/MS. In addition, we examined the toxicity on SH-SY5Y neuroblastoma cells and the inhibitory effect on mitochondrial respiratory complex I. As the result, we detected reticuline and N-methylcoculaurine in each part. N-methylcoculaurine weakly exerted the cytotoxicity in SH-SY5Y cells. These results raise the possibility that these neurotoxic TIQ derivatives are taken up into the human body and accumulated in the brain, and it might be related with the pathogenesis of the endemic disease.

N074

The involvement of glial cells and neurons in the neurodegenerative disease model rat

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Inflammatory process in the brain may involve the activation of microglial cells and then lead to the development of neurodegenerative disease such as Alzheimer's disease and Parkinson's disease. Activated microglial cells release inflammatory cytokines such as IL-1 β and TNF α that contribute to neurodegenerative process. On the other hand, astrocytes are capable of producing various trophic factors that are beneficial to the survival of neurons. However, interactions between neuronal cells and glial cells during the development of neurodegenerative disease remains to be determined. We prepared the experimental model rat which induced the activation of microglial cells by the LPS resulted in the degeneration of neurons. Male Wistar rats were injected with LPS into hippocampus CA1 region. Total RNA from the hippocampus were extracted after 4, 8, 24 hr and 5 days after LPS injection. Northern blot analysis was employed to quantitate the levels of mRNA for IL-1 β , HO-1, BDNF, TrkB and some of GABA_A receptor subunits (α 1, α 5 and β 2). IL-1 β mRNA levels in the hippocampus increased in the initial stage of LPS administration, and HO-1 mRNA levels increased in the time-dependent manner. On the other hand, mRNA expressions of BDNF, its receptor TrkB and GABA_A receptor subunits decreased time-dependently. LPS-induced neurodegenerative alterations in rat hippocampus were occurred in the concentration-dependent and time-dependent manners. The present results suggest that the activation of microglial cells by LPS administration might induce the subsequent neurodegeneration such as the lowering of GABA_A receptors expression.

N075

Peroxynitrite induces endoplasmic reticulum stress in human neuroblastoma SH-SY5Y cells

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Peroxynitrite, which is a powerful biological oxidant produced by a diffusion-limited reaction of superoxide with nitric oxide (NO), is involved in a wide range of pathological processes including brain ischemia and neurodegeneration such as Parkinson disease, and is also reported to cause neuronal cell death. It is widely accepted that the toxicity of peroxynitrite and NO is mediated by mitochondrial dysfunction or the DNA damage-p53 pathway. On the other hand, several reports suggested that the functional disturbances induced by ischemia-like insult is mediated by endoplasmic reticulum (ER) dysfunction. GRP75 and GRP78/Bip is a member of the family of glucose-related proteins which are thought to act as molecular chaperones. GRP75 is located exclusively in the mitochondria, and GRP78/Bip is an ER lumen protein whose expression is induced during ER stress. In the present study, we investigated the effect of exposing human neuroblastoma SH-SY5Y cells to peroxynitrite or NO on the levels of GRP75 and GRP78/Bip by means of Western blot analysis. Treatment with a peroxynitrite generator 3-morpholinosydnonimine (SIN-1) for 12 h induced cell death and a significant increase in the level of GRP78/Bip. Treatment with an NO generator NOC18 also induced cell death, but did not increase the level of GRP78/Bip. The level of GRP75 was increased by treatment with SIN-1 but not NOC18. These results suggest that ER dysfunction may be partly involved in the mechanism of peroxynitrite-induced neuronal cell death.

N076

In vitro aggregate formation by expanded polyglutamine

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[Background] Filamentous aggregates are induced by expansion of polyglutamine stretch in polyglutamine diseases. Although macroaggregates are thought to be innocent for the pathogenesis of polyglutamine diseases, a major consequence of mutation in polyglutamine disease is filamentous aggregate formation. [Method] We constructed fusion protein, polyglutamine and thioredoxin, expressed in E coli and affinity purified in 8 M urea. We examined the process of aggregate formation by differential interference contrast (DIC) microscopy and electron microscopy after dialysing fusion protein against phosphate buffered saline. Controls were mutant SOD1s that are responsible for the pathogenesis of some of familial amyotrophic lateral sclerosis (FALS). Mutant SOD1s were A4T, G85R and G93A. [Results] In the dialysate of polyglutamine stretch, numerous microaggregates forming filamentous structure were found together with macroaggregates consisting spheres 3-5 microns in the diameter. Each filament resembled filamentous structure in macroaggregates in cultured cells. Mutant SOD1s resulted in microspherical aggregates. [Conclusion] Polyglutamine stretch fusion protein with thioredoxin induced filamentous aggregates that were characteristic and distinguished from SOD1 aggregates. This result indicates that polyglutamine stretch is solely enough for filamentous aggregate formation relating pathogenic process in neurons.

N077

Differential effect of MK-801 on protease activities and glial cell expression in PTZ-induced male and female rat brain.

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Pentylenetetrazol (PTZ) is one of the antagonists of the GABA receptor-coupled chloride ionophore that decreases the inhibitory control of GABA receptor and finally increases the cholinergic and glutamatergic inputs. PTZ causes seizures or kindling in rodents and is associated with a variety of behavioral, neurophysiological and neurochemical alterations, resulting in long-lasting changes in hippocampal and cortical glutamate receptor density. MK-801, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which has the neuroprotective effects on the glutamate-induced hyperactivation of the neurons, that causes hypoxic-ischemia, hypoglycemia, epilepsy and stroke-related brain damage. However, a high dose administration of MK-801 to mammals induces memory deficits, and neuronal vacuolization and necrosis in the PC/RSC neurons. It has been reported that MK-801 has anticonvulsant actions on the kindling model of epilepsy. Since PTZ treatment uses as a model of epilepsy, the aim of the present study is whether systemic administration of MK-801 (0.5mg/kg, i.p.) prior to PTZ (60 mg/kg, i.p.) treatment could protect the kindling/seizures of male and female rats. In order to investigate the protective effect of MK-801 on PTZ induced seizures, we have observed the changes of proteases levels and the expression of astrocytes and microglial cells in both sexes of rat brain tissues. Our comparative study in both sexes suggests that different effects of MK-801 on protease level and glial proliferation was observed in PTZ-induced male and female rat brain tissues.

N078

Neuroprotective Mechanism of Theanine, a Green Tea Component, in Rat Cortical Neurons

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[Purpose] Excessive activation of glutamate (Glu) receptors is neurotoxic, leading to neuronal degeneration and death. Although we previously reported the neuroprotective effect of theanine, of which chemical structure is similar to that of Glu, its molecular mechanism remains unclear. In general, phospholipase C (PLC) -beta1 and -gamma1 are protective molecules against oxidative stresses and their expression levels are increased by stimulation of mGluRs. In this study, we examined whether or not theanine showed the neuroprotective effect via stimulation of mGluR (s). [Methods] Rat cortical neurons were cultured in B-27-supplemented EMEM. The neurons were treated with Glu and/or theanine for 10 min in Mg²⁺-free Lockes solution, and cultured in HS-supplemented EMEM for 24 hr. Then, the protein levels of PLC isozymes were determined by western blot, and the viability of neurons was assessed by trypan blue exclusion. Effect of theanine on binding of [³H]D-aspartate (Asp) and [³H]Glu to membrane fraction of rat brain was evaluated by radio-ligand assay. [Results and Discussion] Glu-induced neuronal death was suppressed by simultaneous treatment of theanine dose-dependently, while nitric oxide-induced neuronal death was not affected. The decreased PLC-beta1 and -gamma1 protein levels in Glu-treated neurons were increased to the control levels by treating with theanine simultaneously. On the other hand, theanine had no effect on the binding of [³H]D-Asp and [³H]Glu to the membrane. These results suggest that theanine has no effect on Glu binding to the major Glu receptors, such as NMDA receptor, but it might act as an agonist to the minor Glu receptor, such as mGluR, coupled to PLC isozymes.

N079

Antioxidant Effect of Plant Lycopene on Neuronal Process in CNS of Motor Neuron Degeneration (*Mnd*) Mouse during Postnatal Growth

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In the CNS tissue of the mutant motor neuron degeneration (*Mnd*) mouse, progressive neuronal death is under way during postnatal growth, manifesting gait disturbances leading to premature death up to 10 month old. Although origins of these motor dysfunctions are not clarified yet, we have already measured activities of some enzymes relevant to neuronal degenerations; tissue type transglutaminase (tTGase), a marker enzyme of tissue degeneration process was increasing, whereas cytochrome c oxidase (CO) went down, and superoxide dismutase (SOD) was initially high but decreased in later stages in the spinal cord and cerebral cortex tissues of the *Mnd* mouse. Per oral administration of plant lycopene to the mutant mouse showed considerable delay of the appearance of motor dysfunctions, and recoveries of enzymatic activities of CO, a related enzyme to aerobic energy metabolism, and SOD, a detoxicating factor for toxic reactive oxygen species (ROS). Furthermore, delay of neuronal death was confirmed by reduced tTGase activity and glutamate transporter system, which is implicating to eliminate harmful excitatory glutamate, was recovered in spinal cord after lycopene administration to *Mnd* mouse. These results suggest that per oral lycopene administrations can eliminate cytotoxic ROS which affect motor neurons to cause motor dysfunctions in the mutant mouse.

N080

An in vitro model for aceruloplasminemia with neurodegeneration : iron deposition in glial cells

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Disruption in the expression of iron metabolim-related proteins, divalent cation transporter, ceruloplasmin, iron regulatory protein in brain is one of the important cause of the altered brain iron metabolism in neurodegenerative diseases such as Alzheimer's, Parkinson's diseases, amyotrophic lateral sclerosis and aceroplasminemia. We previously reported that microglia (MG) and astrocytes (AS) protect neurons (N) from both iron- and H₂O₂-induced neuronal cell death. In the present study, we report an in vitro model for aceruloplasminemia with iron deposition in glial cells. **METHODS** The purity of rat primary cortical N, MG and AS obtained by the methods of Shimojo et al and Nakajima et al was estimated to be 96-97% and over 99.9 and 97-98%. **RESULTS AND CONCLUSION** Not only N, MG but AS took up non-transferrin (Tf) iron (⁵⁵Fe) over binding capacity of serum Tf. There was no difference between N and MG in the total radioactivity. However, specific radioactivity of MG was more than 10 times as high as that of N. Total radioactivity of AS was twice, compared to that of N, but specific radioactivity of AS was less than 7 times as high as N. For coculture of N and MG, or N and AS, total radioactivities of coculture N and MG (N/MG) were similar to those of N and that of coculture N and AS (N/AS) approached to that of AS. The specific radioactivities of N/MG and N/AS were similar to those of N and AS, respectively. AS has a large capacity for the non-Tf Fe uptake, however, non-Tf Fe was mainly concentrated in MG rather than in AS. Thus, in the present in vitro experiment, we observed the similar phenomena that the cerebral cortex from patients with aceruloplasminemia shows iron deposition in glial cells.

N081

Involvement of autophagy in the degradation of polyglutamine proteins.

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Polyglutamine diseases are caused by expansion of polyglutamine tract in various responsible genes. Expanded polyglutamine somewhat modifies the structure of the protein affect proper folding and generate intracellular aggregates. Aggregated protein is thought to be toxic to the cells through numbers of mechanisms, thus the cells can be expected to have some protective mechanism against the accumulation of the aggregated proteins. Intracellular aggregated proteins are known to be ubiquitinated, suggesting that aggregated proteins are recognized by ubiquitin proteasome system (UPS) and subjected to degradation by the system. However, intracellular aggregation itself inhibits UPS, which might result in the abnormal accumulation of cellular proteins to cause cell death. Other than UPS, there are several possible mechanisms for the degradation of aggregated proteins, one of which is autophagy. There are reports to show the presence of the autophagic lysosomal vacuoles in the diseased brain. We found that intracellular polyglutamine inclusions are recognized by autophagic pathway and the inhibition of the system resulted in the accumulation of the aggregated proteins. We are now investigating the precise relationships between aggregated proteins and the autophagic pathway.

N082

Expression of an acyl-CoA synthetase, Lipidosin, in the organs involved in X-linked adrenoleukodystrophy and its change in the process of experimental demyelination and remyelination

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X-linked adrenoleukodystrophy (ALD) is a neurodegenerative disease showing demyelination of CNS, adrenal insufficiency and male infertility associated with accumulation of very long chain fatty acids (VLCFA). ALD gene product adrenoleukodystrophy protein (ALDP) -deficient mice exhibit accumulation of VLCFA, but fail to express neurodegenerative changes. Thus, additional mediator (s) may be required to induce ALD-specific histopathological lesions. The *Drosophila* mutant *bubblegum* exhibits neurodegeneration, which resemble pathological findings of ALD. Lipidosin is a novel long-chain acyl-CoA synthetase and was shown to be a murine homologue of bubblegum. Northern and Western blot analyses have shown that Lipidosin is selectively expressed in the brain, adrenal gland and testis of mouse, which are known to be involved in ALD. In the present study, we examined its cellular localization by immunohistochemical technique. In the brain, we confirmed the expression of Lipidosin in astrocytes by double immunostaining with GFAP. Its expression increased postnatally and was extensively detected in soma, endfeet on the vascular basement membrane and perisynaptic processes of astrocytes in the adult brain. More dense immunoreactivities were detected in the gray matter than in the white matter at this stage. Strongly Lipidosin-immunoreactive astrocytes were accumulated in the region where remyelination occurred after demyelination by p.o. administration of 0.45% cuprizone to mice. In peripheral tissues, Lipidosin was expressed in spindle-shaped perisinusoidal cells of the adrenal cortex, Leydig cells of the testis and in theca-interstitial cells of the ovary. These findings suggest that Lipidosin may be involved in lipid metabolism for myelin formation and steroidogenesis.

N083 (MS1-2)

Functional Analysis of Novel Ubiquitin Ligase, Potential Target Antigen of Paraneoplastic Neurologic Disorder

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PNDs (paraneoplastic neurologic disorders) are rare neurologic disorders caused by the remote effects of cancer and are thought to be immune-mediated. A high titer of autoantibodies in the patient's serum and cerebrospinal fluid, directed against both neurons and tumor, have been detected in some forms of PNDs. We had identified novel potential PND target genes by expression screening using autoimmune antiserum from a patient with stomach cancer (Borrmann type 4), associated with psychiatric symptoms including severe depression, involution and amnesia. One of the cloned target genes, named Kspot (Keio Stomach cancer Psychiatry Onconeural Target) encodes 286 amino acids protein with F-box domain and SPRY domain, which is thought to be a novel ubiquitin ligase. Kspot is localized in cytoplasm and its expression is restricted in brain. We have demonstrated that Kspot interacts with Skp1 and Cull1 as ubiquitin ligase and mediates ubiquitination of cellular proteins by pull-down assay. These results indicate that Kspot is nervous system-specific substrate recognition component of SCF complex. Ubiquitin-Proteasome pathway of protein degradation plays an important role in control of the abundance of short-lived regulatory proteins. Recently many neurodegenerative disorders have been thought to be caused by accumulation of harmful proteins in CNS because of malfunction of ubiquitin-proteasome system. We suggest that identification of substrate of Kspot may explain the pathophysiology of the psychiatric disorders associated with malignancy.

N084

Expanded polyglutamine stretches, in vivo interfere with CREB-dependent transcriptional activation in DRPLA.

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Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder characterized by various combinations of cerebellar ataxia, choreoathetosis, myoclonus, epilepsy, dementia and psychiatric symptoms. In previous studies, we have shown that polyglutamine stretches strongly suppresses CREB-dependent transcriptional activation through interaction with TAF130, a co-activator involved in CREB-dependent transcriptional activation, suggesting that the interference of CREB-dependent transcription by expanded polyglutamine stretches is involved in the neuronal dysfunction in DRPLA. As the mouse model for DRPLA, our laboratory has created transgenic mice for DRPLA, carrying full-length mutant DRPLA gene with expanded CAG repeats (Q76 and Q129). To directly study the effect of expanded polyglutamine stretches on the CREB-dependent transcriptional activation in vivo, transgenic mice harboring a CRE-LacZ reporter gene are interbred with the DRPLA transgenic mice. To establish the assay systems to evaluate the CREB-dependent transcription in the transgenic mice, preliminary studies employing nicotine administration have been conducted. Administration of nicotine 4mg/Kg, i.p. resulted in strong increase of beta-galactosidase activities in hippocampus and cerebral cortices. Detailed analyses of CRE-LacZ expression in the double transgenic mice should be highly useful to investigate the effect of expanded polyglutamine stretches on the CREB-dependent transcriptional activation and to understand the molecular mechanisms of neuronal dysfunction in polyglutamine diseases.

N085

Altered gene expression of neurotrophins, GDNF family members and their receptors in a peptide-delivery model of polyglutamine-induced neuronal death

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Expanded polyglutamine (polyQ) is the cause of nine inherited neurodegenerative disorders including Huntington's disease (HD). The protective effects of neurotrophins and GDNF family members have been investigated in several HD models including an excitotoxic model with quinolinic acid. Here, we examine the gene expression of these neurotrophic factors in cultured cortical neurons following intracellular delivering of polyQ peptides (Qn=22). Upon treatment of cortical neurons with these peptides, neuronal death occurred within 24 hours. The gene expression of neurotrophins, receptors, neuropeptides, cytokines and growth factors was examined using Gene microarrays (GEArray kit). As an *in vivo* model, HD model mouse (R6/2) was employed for comparison. We found that the gene expression of GDNF and GDNF family receptors (GDFR- α 1, 2, 3) decreased after treatment for 6 hours, whereas that of artemin, CNTF, TrkA and TrkB increased in cortical neurons. It has been postulated that artemin is one of GDNF family members and interacts with GDFR- α 3. In R6/2 mice (14 week-old), the level of GDNF mRNA was decreased, whereas that of artemin and persephin mRNAs, GDNF family members, was increased. These results suggest that polyQ may have a neurotoxic effect in an early stage of neurodegeneration by down-regulating gene expression for neuronal survival. Moreover, enhanced expression of artemin and persephin mRNAs in the striatum of R6/2 mice suggests a compensatory effect of glial cells on the down-regulation of GDNF mRNA expression.

N086

Establishment of functional assays system for polyglutamine disease.

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Purpose: Until now, several neurological disorders have been reported as caused by expanded polyglutamine stretch. The mechanism of gain of function of expanded polyglutamine stretch is uncertain. Recently others and we proposed that the dysfunction of neuronal cell system has preceded neuronal cell death in these disorders. Especially dysregulation of CRE (cAMP responsible element) mediated transcription system has been considered as one of the major cell dysfunction process in polyglutamine diseases. However when and how occur this dysregulation is uncertain. To clarify the mechanism of expanded polyglutamine stretch disorders and screen drugs, we have to establish the cell dysfunction assay system specially attend to polyglutamine disease. Here we have developed the rapid and convenient cell assay system which can evaluate dysfunction of CRE mediated transcription caused by polyglutamine stretch. **Method:** We established the stable cell lines (HEK293) which expressed hcRED (Clontech) polyglutamine stretch (Q12&Q79) fusion protein under control of tetracycline inducible promoter. We have also integrated GFP with degron sequence under control of CRE element. In this system we have integrated these plasmids at the exactly same locus on chromosome to eliminate the chromosomal localization effect on expression of integrated foreign cDNA. **Result & consideration:** Under expression of polyglutamine stretch (Q12&Q79), the CRE-mediated transcription was remarkably decreased. The decrement of CRE mediated transcription has been observed before detection of visible aggregate of expanded polyglutamine stretch. We have clarified the CRE mediated transcription has been strongly interfered by polyglutamine stretch regardless of their length and their formation of intra nuclear aggregate.

N087

Analyses of biochemical functions of aprataxin in DNA single-strand break repair

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Aprataxin (APTX) has been identified as the causative gene for Early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH). The physiological functions of aprataxin, however, remains to be elucidated. APTX has two splicing variants, long form (LAPTX) and short form (SAPTX). LAPTX has a homology to polynucleotide kinase-3' phosphatase (PNKP) and interacts with XRCC1, which is required for single-strand DNA break repair (SSBR), in a yeast two-hybrid study. To investigate the functions of the aprataxin in SSBR, we conducted an SSBR assay using oligonucleotide duplex with a 1 bp gap and three recombinant SSBR-related proteins (DNA polymerase β (Pol β), DNA ligase III α (Lig3) and PNKP). The short fragment of the oligonucleotides was end-labelled with fluorescein isothiocyanate, and the length of ligated oligonucleotide products was analyzed by an automated DNA sequencer. In this experiment, however, ligation products that are produced upon addition of LAPTX were undetectable. To elucidate the physiological roles of aprataxin in SSBR, further investigations on other SSBR systems will be needed.

N088

Degradation system of aggregation in SCA6: ubiquitin-proteasomal and lysosomal pathways.

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Spinocerebellar ataxia type 6 (SCA6) is an autosomal-dominant neurodegenerative disorder caused by a small expansion of polyglutamine in the α 1A (P/Q-type) -calcium channel protein (Cav2.1). We have shown that calcium channel protein and polyglutamine-containing protein are aggregated in SCA6 Purkinje cells. To understand the degradation system of aggregation in SCA6, we studied association of ubiquitin-proteasomal system and lysosomal enzymes, the two major protein degradation systems in cells, with microscopic aggregations immunohistochemically. Similar analysis was undertaken in other polyglutamine diseases, Machado-Joseph disease and dentato-rubral and pallidolusian atrophy (DRPLA). While nuclear inclusions in MJD and DRPLA were labelled with anti-ubiquitin antibodies, intracytoplasmic aggregations in MJD and DRPLA brains were labelled with lysosomal marker, cathepsin. In SCA6 Purkinje cells, aggregations were barely labelled with anti-ubiquitin antibodies. In contrast, cytoplasmic aggregations in SCA6 Purkinje cells were labelled with cathepsins, indicating that lysosomal pathway is involved in the degradation of polyglutamine aggregates in SCA6. Ubiquitin-proteasome pathway may not have significant role in SCA6, although further studies are needed.

N089

Property of binding between synphilin-1 and phospholipids

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Synphilin-1 was initially identified as alpha-synuclein binding protein. The function of alpha-synuclein is not fully understood, but is reported to associate with phospholipid bilayers, and thought to be a potent inhibitor of phospholipase D. We hypothesized that synphilin-1 might also be able to bind to lipid membrane. A variety of lipids (L-alpha-lysophosphatidylcholine, sphingomyelin, L-alpha-phosphatidylcholine, L-alpha-phosphatidic acid, L-alpha-phosphatidylinositol, L-alpha-phosphatidyl-L-serine, cardiolipin, L-alpha-phosphatidylethanolamine, L-alpha-phosphatidyl-DL-glycerol) was dot blotted onto membrane, and the membrane was incubated with solution containing GST-fusion protein of four parts of synphilin-1. Attached protein was demonstrated with anti-GST antibody and ECL system. Precipitation assay with multilamellar phospholipid vesicles was also used for analysis of binding property of synphilin-1 to phospholipids. In this study, we report that synphilin-1 binds to multilamellar phospholipid vesicles with negatively charged phospholipids (phosphatidic acid and phosphatidyl-L-serine), but not to vesicles with a net neutral charge. Mapping analysis revealed that C-terminal region was involved in the binding between synphilin-1 and phospholipids. Such binding property of synphilin-1 was similar to that of alpha-synuclein. These results suggest that the membrane binding capacity of complex of synphilin-1 and alpha-synuclein should vary according to the phospholipid composition of membrane.

N090

Microarray analysis of brain RNA in DRPLA knockout mice

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DRPLA (dentato-rubral pallidoluysian atrophy) is an autosomal dominant neurodegenerative disorder characterized by various combinations of symptoms including cerebellar ataxia, choreoathetosis, myoclonus, epilepsy, mental retardation and dementia and post mortal examination shows selective neuronal loss observed in dentate nucleus, red nucleus, globus pallidus and subthalamic nucleus. DRPLA is one of the neurodegenerative disorders caused by expanded polyglutamine (polyQ) stretches and the causative gene was identified in 1994, however, the physiological function of the gene product remains to be unknown. However, recent studies showed DRPLA protein might function as a transcriptional factor, particularly a transcriptional co-repressor in early developmental stage of *Drosophila*. Recently developed DNA microarray technology allows us to rapidly investigate transcriptional changes of great number of genes. To gain insight into the physiological roles of the DRPLA protein, we compared expression profile of approximate 6000 genes between the brains of DRPLA knockout mice and wild-type mice (6 weeks of age) using oligonucleotide DNA arrays (GeneChip Murine genome U74Av2; Affimetrix). We detected 284 genes up regulated and 135 genes down regulated in the brain of DRPLA deficient mice. Interestingly, several neurotransmitters, specific subunit of ion channels and RNA processing related proteins were down regulated. These results demonstrate that the lack of DRPLA protein directly or indirectly changes the expression of a specific group of genes involved in transcriptions and signaling pathways.

N091

An investigation on anxiogenic drug-induced gene expressions in the brain of postnatally developing rodents

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N-methyl-beta-carboline-3-carboxamide (FG 7142) acts at benzodiazepine site of the GABA_A receptor as a partial inverse agonist. The drug causes anxiety in humans and rodents, and produces a various physiological and neurochemical changes which are very similar to the effects of stress, e.g. an increase in the plasma corticosterone, the selective activation of mesocortical dopaminergic transmission, and deficits of cognition. Thus, the FG compound has been called a pharmacological stressor and used as a tool for investigating the neurobiological basis of stress responses. In addition, the networks and molecular cascades specifically related to a stressor may mature around a certain developmental period, e.g. the stress hyporesponsive period of the HPA axis.

We investigated the effects of FG 7142 on the regional brain activity by monitoring the c-fos gene expression as the c-Fos immunoreactivity in the infant (8-day-old) rats as well as in the young adult (56-day-old) rats to obtain an insight into the stress-responsive neuron system.

FG 7142 (20mg/kg) induced a dense nuclear c-Fos-like immunoreactivity in the cingulate cortex and retrosplenial cortex, the neocortex, lateral septum, paraventricular nucleus of the thalamus, striatum, central and medial nucleus of the amygdala in the brain of 56-day-old rats. However, the 8-day-old rats expressed much fewer c-Fos-positive cells in the neocortex, lateral septum and medial nucleus of the amygdala, while a marked increase in the positive cells was observed in other areas. These differences may reflect the postnatal development of the stress-related neuron circuits and molecular responses. Further studies are required to search for the candidate genes that play an important role on the system of the brain.

N092

The effects of antidepressants and moodstabilizers on the differentiation of neural stem cells

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It has been emerged that the abnormality of cell turnover is exist in the pathophysiology of CNS disease including neuropsychiatric disorders. In the present study, we examined the influences of antidepressants and moodstabilizers on the differentiation activity of rat embryonic neural stem cells that give rise to neurons in vitro. Initially, we showed that BDNF and IGF-1 stimulate neuronal differentiation of neural stem cells, and combined treatment of cAMP-signal cascade activator, forskolin, accelerated the neuronal differentiation by these trophic factors. The promoting effects of neuronal differentiation were found by some kinds of antidepressants and moodstabilizers in the evaluation using MAP2 ELISA. In addition to the analysis of cellular responses, we attempted to investigate the molecular changes of ERK and Akt, those are known to be activated in response to trophic factors in neurons, and alternation of transcription factor activity including CREB and STATs in the neural stem cells. These results may suggest that the different potential of neural stem cell differentiation by several kinds of antidepressants and moodstabilizers relate to their differences of clinical responses, and the alternation of cAMP-CREB signaling play a key role in neural stem cell differentiation by these drugs.

N093

Expression Analysis of Neuregulin-1 in the Dorsolateral Prefrontal Cortex in Schizophrenia

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Genetic linkage and association have implicated Neuregulin-1 (NRG-1) as a schizophrenia susceptibility gene. NRG-1 plays crucial roles in neuronal and glial development and plasticity. NRG-1 has multiple alternative splicing variants, which comprise three major isoforms: Type I (heregulin / ARIA / NDF), Type II (glial growth factor) and Type III (sensory and motor neuron-derived factor). We measured mRNA expression levels of the three major isoforms of NRG-1 in postmortem dorsolateral prefrontal cortex (DLPFC) from matched patients and controls using real-time quantitative RT-PCR (ABI; TaqMan Assay). Expression levels of three internal controls - GAPDH, cyclophilin and b-actin - were unchanged in schizophrenia. Type I expression was increased in schizophrenia DLPFC and positively correlated with antipsychotic medication dosage. Type II / Type I and Type II / Type III ratios were significantly decreased, suggesting relative down-regulation of Type II expression levels. There was no effect of genotype, for two SNPs previously associated with schizophrenia, on NRG1 mRNA levels suggesting that these alleles are not functionally responsible for abnormal NRG-1 expression patterns in our sample of patients. Abnormalities in NRG-1 mRNA expression patterns in DLPFC may be associated with schizophrenia.

N094

Peripheral treatment with interleukin-1 α to rats reduced pre-pulse inhibition of acoustic startle response

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The proinflammatory cytokine interleukin-1 in the periphery acts on the central nervous system to alter monoamine transmission and induce sickness behaviors. Although abnormal dopamine release is implicated in abnormal cognitive functions such as sensory motor gating disruption, correlation between interleukin-1 signal and cognitive functions has yet been unclear. To assess the effect of peripheral administration of interleukin-1 on cognitive function, pre-pulse inhibition of acoustic startle response that reflects sensory-motor gating was tested, following intraperitoneal injection to young adult Sprague-Dawley rats with 50 μ g human recombinant interleukin-1 α . We also measured monoamine levels in the frontal cortex, serum corticosterone, and open field activity. We found that the peripheral injection of interleukin-1 α suppressed pre-pulse inhibition without any alteration of startle amplitude. The dihydroxyphenylacetic acid (DOPAC) to dopamine ratio, which reflects dopamine metabolism, was elevated in frontal cortex, however the 5-hydroxyindoleacetic acid (5-HIAA) to 5-hydroxytryptamine (5-HT) ratio was not. In parallel, locomotor activity was decreased and serum corticosterone was increased. Results of dopamine metabolism and locomotor activity are in agreement with previous findings. Accordingly, the influence of interleukin-1 α on the decrease of pre-pulse inhibition may be via alteration of dopamine metabolism. These results suggest that the impaired cognitive function caused by peripheral inflammation may originate partially from peripherally interleukin-1 release.

N095

Mammalian O-mannosyl glycan and relationship to muscular dystrophy and neuronal migration disorder

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Muscular dystrophies are a heterogeneous group of inherited single-gene disorders, characterized clinically by progressive muscle weakness and wasting. Muscle-eye-brain disease (MEB) is an autosomal recessive disorder characterized by congenital muscular dystrophy, ocular abnormalities, and lissencephaly. Mammalian O-mannosyl glycosylation is a rare type of protein modification that is observed in a limited number of glycoproteins of brain, nerve, and skeletal muscle. We isolated a human cDNA for protein O-mannose β -1,2-N-acetylglucosaminyltransferase (POMGnT1). POMGnT1 participates in the synthesis of O-mannosyl glycan, a modification that is known to be a laminin-binding ligand of α -dystroglycan. We identified 13 disease-causing mutations of the *POMGnT1* gene in patients with MEB. Expression of these mutant proteins revealed a great loss of the enzymatic activity. These results clearly demonstrate that MEB is inherited as a loss-of-function of POMGnT1. We also found a selective deficiency of α -dystroglycan in MEB patients. These findings suggest that α -dystroglycan is a potential target of POMGnT1 and that altered glycosylation of α -dystroglycan may play a critical role in the pathomechanism of MEB. Since the MEB phenotype overlaps substantially with those of Fukuyama-type congenital muscular dystrophy (FCMD) and Walker-Warburg syndrome (WWS), these three diseases are thought to results from a similar pathomechanism, aberrant glycosylation of α -dystroglycan.

N096

Molecular mechanism of myasthenia gravis induced by autoantibodies against MuSK

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Myasthenia gravis (MG) is a prototypic antibodies-mediated autoimmune disease and most of MG patients have autoantibodies against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction (NMJ). These antibodies cause loss of AChR number and function of neuromuscular transmission, and induce clinical symptom such as muscle weakness. Recently, it was shown that MG patients, who are seronegative for AChR-antibodies, have serum autoantibodies against Muscle specific kinase (MuSK). (Hoch et al., 2001. Nature Medicine) MuSK is a receptor tyrosine kinase expressing at the postsynaptic membrane of NMJ and activated by agrin secreted from motoneuron. In addition, MuSK is indispensable and plays multiple roles in clustering of AChR, thus the autoantibodies against MuSK may cause severe defect of AChR clustering at postsynaptic membrane of NMJ. We already reported our results of the screenings of autoantibodies against MuSK in MG patients in this meeting (2001). We have shown that the serum containing MuSK autoantibodies actually inhibited AChR clustering by using in vitro assay. We are currently studying the blocking mechanism of AChR clustering by the autoantibodies.

N097

Dynamic change of AQP expression in the brain cold injury model

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Aquaporins (AQPs), water channels, transport water through the membranes of numerous tissues. In the brain, we recently found that five subtypes of AQPs (3, 4, 5, 8, 9) were expressed in neural cells and that AQPs in astrocytes participated with brain oedema. Moreover, we also found that AQP4, 5 and 9 protein expression in cultured astrocytes upregulated by hypoxia / reoxygenation, and we concluded that AQPs participated with a progress and/or a healing process of brain oedema after ischaemia or injury.

In this study, we examined the effect of the expression of AQP4 and 9 proteins in rat brain cold injury model, and reviewed possibility of the participation with brain oedema. The expression of AQP4 and 9 decreased comparing with contralateral side in one day after injury by western blot. However, The expression of AQP4, 9 enhanced in astrocytes around injury in one week after injury, and increased continuously and overexpressed in a healing process after 4 and 8 weeks after injury. In addition, the expression of GFAP decreased after injury as well as AQP4 and 9, and increased in astrocytes around injury in one week after injury.

From these results, both AQP4 and 9 may participate with the progression of an oedema from brain damage and/or the healing process.

N098

Changes of cerebral glucose metabolism after 30 min middle cerebral artery occlusion in rats - studied by ex vivo ¹³C-NMR spectroscopy -

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Changes of cerebral glucose metabolism were examined in rats subjected to focal cerebral ischemia as induced by 30 min of intraluminal thread occlusion of the left middle cerebral artery (MCA), followed by 2, 5 and 8 hrs of reperfusion. Glucose metabolism was studied by ex vivo ¹³C nuclear magnetic resonance spectroscopy (¹³C-NMRS). The rats were killed by exposure to microwaves at 20 min after intravenously bolus injection of [1-¹³C] glucose (1 g/kg) at various reperfusion times. The cerebrum was divided into two hemispheres and each hemisphere was dissected into cortex (including hippocampus; region 1) and the other region (region 2). The supernatants obtained from both regions by deproteinization were vacuum-dried and dissolved in deuterium oxide. The solution was employed for ¹³C-NMRS and HPLC measurement. The glutamine concentration and the ¹³C incorporation into lactate from [1-¹³C] glucose increased in the MCA occlusion side (region 2) throughout the experiment. The ¹³C incorporation into glutamate and glutamine, however, decreased in the MCA occlusion side (region 2) at 5 and 8 hrs after reperfusion. These data indicate that cerebral glucose metabolisms are altered at early time after reperfusion by a short term MCA occlusion in rats.

N099

Neuroprotective effect of DY-9760e, a calmodulin antagonist, on microsphere embolism-induced ischemic brain damage

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Calmodulin (CaM) antagonists and inhibitors of Ca²⁺/CaM-dependent enzymes have been known to have neuroprotective effects on ischemic brain damage. A novel CaM antagonist, DY-9760e, which inhibits various CaM-dependent enzymes, had powerful neuroprotective effects in vivo. However, the mechanism underlying neuroprotection is not clear. Nitric oxide (NO) is generated by NO synthase (NOS), which is a Ca²⁺/CaM-dependent enzymes. An excessive production of NO following ischemia partly accounts for the neuronal injury. To determine whether DY-9760e exerts neuroprotective effects by inhibiting NO production, we investigated the effect of DY-9760e on nitric oxide production and protein nitration by peroxynitrite (ONOO⁻) formation in the striatum after microsphere embolism in rats.

In freely moving rats, NO production after ischemia was monitored consecutively with in vivo brain microdialysis. NO_x levels (NO metabolites, NO₂⁻ plus NO₃⁻) significantly increased immediately after and 24 hours after ischemia. Intraperitoneal injection of DY-9760e (50 mg/kg) significantly decreased the increased levels of NO after cerebral ischemia to the control levels in sham-operated animals. Concomitant with the increased NO levels, Western blotting using an anti-nitrotyrosine antibody indicated a marked increase in nitrotyrosine immunoreactivity in the striatum 24 hours after ischemia, and DY-9760e significantly inhibited the increased nitrotyrosine immunoreactivity. Coincident with the inhibition of the NO production and protein tyrosine nitration, pretreatment with DY-9760e rescued cells from neuronal death in the striatum. These results suggest that the inhibitory effects of DY-9760e on the NO/ONOO⁻ pathway partly account for its neuroprotective effects on ischemic brain damage.

N100

Upregulation of HRD1, an endoplasmic reticulum-associated degradation related molecule, in the mouse brain following hypoxic cerebral ischemia

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Hrd1p in yeast plays an important role in endoplasmic reticulum-associated degradation by transferring ubiquitin from the ubiquitin-conjugating enzymes to target substrates that will be subjected to degradation in the cytosol. Human HRD1, a homologue of yeast Hrd1p, has been recently identified and characterized in our laboratory. In the present study, we used a model of hypoxic ischemic brain injury in mice to study the expression of the murine homologue of human HRD1. The levels of mHRD1 mRNA were measured by RT-PCR at various times (3, 6, 12, 24, 48, 96 h) after hypoxic cerebral ischemia. The level of mHRD1 mRNA was significantly increased at 12 to 48 h with a peak at 24 h (approximate 3-fold) in the injured cerebral cortex and significantly elevated at 3 - 12 h (p<0.05) in the ipsilateral striatum after the hypoxic ischemia. Likewise, we also detected the changes of MyD116 and CHOP mRNA levels which belong to a gene family implicated in growth arrest and apoptosis induced by ER dysfunction and were upregulated after transient forebrain ischemia. The mRNA levels of both MyD116 and CHOP were remarkable upregulated at 3 to 24 h in the cortex and striatum after hypoxic ischemia. On the other hand, no changes of these molecules were observed in contralateral hemisphere after hypoxic ischemia. These results indicate that hypoxic cerebral ischemia caused ER stress and induced the expression of mHRD1 in different brain regions, suggesting that mHRD1 seems to be involved in the rescue of hypoxic ischemia induced neuronal death.

N101

Poly (ADP-ribose) synthetase activation and mitochondrial injury in an experimental model of cerebral ischemia

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Poly (ADP-ribose) synthetase (PARS), a nuclear enzyme also known as poly (ADP-ribose) polymerase-1, is activated by DNA strand breaks and involved in their repairs. Here, we studied a possible role of PARS activation in the mitochondrial injury, using an experimental model of cerebral ischemia. Cortical neurons of rat brain primary culture were subjected to oxygen-glucose deprivation (OGD) for 2 hours. In this model, PARS was activated, resulting in the decrease of NAD⁺ content. The OGD treatment induced mitochondrial injuries; 1) enhanced ROS generation indicated by oxidation of chloromethyl-tetramethyl rosamine, 2) reduction of mitochondrial membrane potential shown by flow cytometry with JC-1 probe, and 3) permeability transition pore opening indicated by a release of cytochrome c from mitochondria. Addition of PARS inhibitors such as 1,5-dihydroxyisoquinoline and benzamide suppressed NAD⁺ depletion, and also attenuated the above-mentioned mitochondrial injuries. These results suggest that PARS activation plays a critical role in the mitochondrial injury in the ischemic neuronal cell death.

N102

Effect of anti-Interleukine-6 receptor antibody in spinal cord injury

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Endogenous or transplanted neural stem/progenitor cells (NSPCs) have recently been shown to differentiate exclusively into astrocytes, but not into neurons even after spinal cord injury (SCI), and then associate with glial scar formation. The microenvironment of spinal cord, especially inflammatory cytokines that dramatically increase in acute phase at injury site can be considered as this important cause. Interleukin-6, which has been proved to induce neural stem cells to the astrocytic differentiation through the JAK/STAT pathway in vitro study, also play a central role as pro-inflammatory cytokines. In this study, we investigated whether blockade of IL-6 signaling pathway could diminish the scar formation and ameliorate functional recovery in SCI. To demonstrate the effect of rat anti-mouse interleukin-6 receptor antibody (MR16-1), we obtained NSPCs from spinal cord of adult mice and allowed them differentiate in presence IL-6 and soluble IL-6 receptor with or without MR16-1 for 3 days in vitro. Then we demonstrated the validity of this blocking agent to the mouse SCI model in vivo. Immediately after inducing SCI by a modified NYU Impactor, mice were single injected 2g/g of MR16-1 intraperitoneally, and we assessed histological and functional evaluation for 6 weeks. Our result demonstrated that MR16-1 suppressed not only the astrocytic differentiation-promoting effect caused by IL-6 signal in vitro but also gliosis after SCI in vivo. In addition, MR16-1 decreased the number of inflammatory cells and connective tissue scar formation. Furthermore, we observed significant functional recovery in mice treated with MR16-1 compared with control mice. These findings suggest that neutralization of IL-6 in acute phase represents an attractive therapeutic option in SCI.

N103 (MS3-1)

Regulation of tau exon 10 splicing by a double stem-loop structure in mouse intron 10

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Tau is one of the microtubule-associated proteins (MAPs) that play a role in promoting the polymerization and stabilization of neuronal microtubules and is involved in both maintenance of the neuronal cytoskeleton and axonal transport. Human tau is encoded by a single gene (TAU) in chromosome 17 from which six isoforms are produced in adult brain by alternative splicing of exons 2, 3 and 10. Tau exon 10 (E10) encodes the second microtubule-binding domain, and alternative splicing of this exon results in isoforms with three (E10-) or four (E10+) microtubule-binding domains referred to as three-repeat tau (3R-tau) and four-repeat tau (4R-tau), respectively. The pattern of expression of the 3-repeat and 4-repeat tau isoforms has been shown to differ among developmental stages, species and neuropathological states, indicating that E10 splicing is closely associated with physiological and pathological functions of tau. To investigate the mechanism of regulation of E10 splicing in mouse tau, we isolated mouse genomic fragments to include tau E10 and its flanking introns and examined its splicing in a term of the ratio of 3R-tau/4R-tau isoforms. We found that mouse intron 10 (I10) has a human intron splicing modulator (ISM) -like sequence to enhance E10 splicing and unexpectedly has the potential to form a unique hairpin structure, unlike human I10, which has a single stem-loop structure. The second stem-loop formation involves the ISM-like sequence, and results in inhibition of ISM-like activity and suppression of E10 splicing. These results suggest a new model of regulation of tau E10 splicing in which both linear sequence like ISM and secondary RNA structure in I10 have regulatory functions.

N104 (MS3-2)

Phosphorylation of FTDP-17 tau mutants by Cyclin-dependent kinase 5

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Major pathological hallmarks of Alzheimer's disease are senile plaques and neurofibrillary tangles (NFTs). NFTs are aggregates of paired helical filaments (PHF) composed of hyperphosphorylated tau. The question is what makes tau form PHF. Various exonic and intronic mutations of tau have been found in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Mutations are indicated to change tau's ability of binding to microtubules but it is not still clear why these mutations cause intracellular tau inclusions. On the other hand, although PHF tau is well known to be hyperphosphorylated, it has not yet been determined how phosphorylation works in PHF formation. Cyclin-dependent kinase 5 (Cdk5) is one of tau protein kinases, which increase PHF epitopes of tau by phosphorylation. Recently it was shown that the cleavage of a p35 Cdk5 activator to p25 by calpain led to increased Cdk5 activity, resulting in higher phosphorylation of tau. However, these two factors have not been examined together yet. Our interest is whether p25/Cdk5 displays much higher phosphorylation activity to mutant tau.

All tau variants (wild-type, K257T, P301L, P301S and R406W) were synthesized in *E.coli* and purified from the heat stable cell extracts. p35/Cdk5 or p25/Cdk5 was prepared from Sf9 cells. These recombinant tau proteins were phosphorylated by p25/Cdk5 or p35/Cdk5 *in vitro* and the phosphorylation was compared among tau mutants. When tau was phosphorylated by p35/Cdk5, no difference in phosphorylation was found in tau variants. On the other hand, when tau was phosphorylated by p25/Cdk5, tau mutants were phosphorylated more than wild-type tau. The R406W mutant was particularly highly phosphorylated by p25/Cdk5.

N105 (MS3-3)

Alzheimer's beta-secretase (BACE1) cleaves alpha2,6sialyltransferase as a physiological substrate.

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The deposition of amyloid beta-peptide (A-beta) in the brain is a hallmark of Alzheimer disease pathogenesis. A-beta is generated from the amyloid precursor protein (APP) by the sequential actions of proteases, beta-secretase (BACE1) and gamma-secretases. BACE1, a membrane-bound aspartic protease, is considered to be a major therapeutic target of Alzheimer's disease. We previously found that BACE1 also cleaved a membrane-bound sialyltransferase, ST6Gal I. By BACE1 overexpression in COS cells, the secretion of ST6Gal I markedly increased and the amino terminus of the secreted ST6Gal I started at Glu-41 (E41-form). A similar form of soluble ST6Gal I was also present in rat plasma. Here we report that BACE1-Fc chimera protein cleaved the protein A-ST6Gal I fusion protein, or ST6Gal I-derived peptide, between Leu-37 and Gln-38 in vitro, suggesting that an initial cleavage product by BACE1 was three amino acids longer than the secreted (E41-) form. The three amino acids, Gln-38/Ala-39/Lys-40, were found to be truncated by aminopeptidase activity, which was detected in detergent extracts of microsomal fraction from COS cells. The fact that only the truncated (E41-) form but no Q38-form is detected in extracellular fluid, suggesting that the amount of aminopeptidase exceeds that of the substrate. Alternatively, the aminopeptidase-dependent truncation may be prerequisite for the secretion of ST6Gal I. Identification and further characterization of the aminopeptidase will be required for a better understanding of the molecular mechanisms underlying the cleavage and secretion of glycosyltransferases.

N106 (MS3-4)

PEN-2 enhances gamma-secretase activity without the stimulation of presenilin endoproteolysis

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The presenilin (PS) complex, including the endoproteolytic processed forms of PS and nicastrin (NCT), is essential for gamma-cleavage, which is required for the generation of amyloid beta-protein (Abeta) from the beta-amyloid precursor protein (APP). It was shown that APH-1 and PEN-2 are additional components of the functional PS complex. However, the precise role of APH-1 and PEN-2 in the PS complex, with regard to PS endoproteolysis and Abeta generation, remains unclear. Here, we determined the effect of the expression of exogenous PEN-2 and/or APH-1 on Abeta generation and endoproteolysis of exogenous PS using fibroblasts. The enhancement of PS endoproteolysis required the three exogenous components, PEN-2, APH-1 and NCT. However, the expression of PEN-2 alone resulted in a marked increase in the extent of Abeta generation, which was not associated with the stimulation of PS endoproteolysis. These results indicate that the mechanism underlying the stimulation of gamma-cleavage and that of PS endoproteolysis are distinct. Moreover, the expression of PEN-2 significantly altered IC50 of a specific gamma-secretase inhibitor, a transition state analogue L-685458, on Abeta42 generation, suggesting that the expression of PEN-2 modulates gamma-secretase activity. Thus, PEN-2 is not only an essential component of the gamma-secretase complex, but also an enhancer of gamma-secretase activity.

N107 (MS3-5)

Dual-cleavage mechanism of betaAPP by Cell Free PS/gamma-secretase assay.

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Cell-free gamma-secretase assay was established from membrane fraction of betaAPPsw and wt PS1 expressing human cells. *De novo* generation of both NTF (Abeta P3) and CTF (CTFgamma) were recognized by means of IP-autoradiography, IP-blot and IP-MS. At least, gamma-cleavage at gamma33, gamma34, gamma37, gamma38, gamma39, gamma40, gamma41, and gamma42 were detected as C-terminus of NTF and that at gamma48, gamma49, and gamma51 were seen as N-terminus of CTF. However, so far we could detect any trace of neither gamma42-49 peptide nor its degradation. Thus, we could directly observe Dual cleavage of betaAPP in cell free assay. It was clearly shown that gamma-secretase complex containing PS and nicastrin is located on plasma-membrane, indicating active gamma-cleavage on the plasma-membrane. Nevertheless, it is not fully elucidated whether active gamma-cleavage predominantly occurs on plasma-membrane. Here we show that gamma-cleavage of betaAPP on plasma-membrane was hardly detectable, rather it occurred predominantly on microsomal membrane and *de novo* Abeta is liberated into luminal space of these vesicles. Therefore, PS/gamma-secretase complex on plasma membrane might function other than gamma-cleavage of betaAPP-CTF stubs.

N108

Full-length, but not N- nor C-terminal fragment of Presenilin 1, 2 interact with Syntaxin 5

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Mutations in presenilin 1 and 2 (PS1 and PS2) account for the majority of early-onset familial Alzheimer's disease. However, trafficking and interaction of PSs with other proteins are poorly understood. By using co-immunoprecipitation and pull down studies, we examined the interaction of PSs with syntaxin (Syx) proteins that are involved in intracellular vesicular transport. We found that, when expressed in HeLa and COS7 cells, both PS1 and PS2 bind Syx5 involved in ER-Golgi transport. In contrast, Syx1A, 2, 3 and 4 that are located at the plasma membrane did not show specific binding to PS1. Syx5 interacted only with the full-length PS holoproteins, but not with naturally occurring N-terminal fragments nor C-terminal fragments. Interaction domain was mapped to the cytoplasmic loop region for PS1. The interaction domain in Syx5 was mapped to the alpha-helical region that is distinct from SNARE (soluble N-ethylmaleimide-sensitive factor-attachment protein receptor) motif. Immunofluorescence and sucrose density gradient fractionation analyses showed that both full-length holoproteins of PS1 and PS2 were co-localized with Syx5 at ER and Golgi compartments. Taken together, these results indicate that Syx5 binds to full-length PSs at ER and *cis*-Golgi compartment via the cytoplasmic region. Syx5 may play a role in trafficking of the PSs from ER to Golgi compartment in the early secretory pathway.

N109

Elevated BACE1 levels affect the generation of APP intracellular domain.

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A significant accumulation of Abeta is major pathological feature in the brain in patients with Alzheimer's disease (AD). Abeta is derived from amyloid precursor protein (APP) by sequential proteolytic processing involving two proteases, called BACE1 and gamma-secretase. gamma-Secretase cleavage results in the generation of the APP intracellular domain (AICD), as well as Abeta. AICD binds to a DNA binding protein, Fe65, and translocates to the nucleus, suggesting that AICD plays a role in signal transduction. Recently, it was reported that in sporadic AD brain beta-secretase expression and its enzymatic activity were elevated. In this presentation, we show that elevated BACE1 levels induce an increase of Abeta generation and a reduction of AICD generation in vitro. This suggests that Abeta generation and AICD generation are regulated independently, and that the decreased AICD levels due to elevated BACE1 expression in AD brain induce signal transduction failure.

N110

An increase in Abeta generation by the high expression of GATE-16, mammalian homologue of yeast Apg 8 essential for autophagy

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Amyloid beta-protein (Abeta), which is the major component of senile plaques in the brain of patients with Alzheimer's disease (AD), is generated from the beta-amyloid precursor protein through proteolytic cleavages catalyzed by beta- and gamma-secretases. Although the presenilin complex is responsible for gamma-secretase activity, it remains to be clarified how the gamma-cleavage is regulated. Recently, we have established a new screening system for isolating cDNAs that enhance Abeta generation by modulating the gamma-cleavage (Komano et al., J. Biol. Chem. 277: 39627, 2002). Using this method, we isolated the cDNA encoding GATE-16 which is one of the mammalian homologues of yeast Apg8p essential for autophagy. Autophagy is a process involved in the bulk degradation of cytoplasmic components by a lysosomal/vacuole system. Although elevated levels of autophagy have been reported in several neurodegenerative disorders, including AD, its pathological significance remains to be clarified. We found that the high expression of GATE-16 in fibroblasts enhances the generation of Abeta40/42 by approximately twofold. The high expression of another autophagy-related factor, a human homologue of yeast Apg4p, which is involved in proteolytic activation of GATE-16, also enhances Abeta generation. Moreover, the fibroblasts treated with an autophagy inducer, rapamycin, increase Abeta generation, while the treatment with an autophagy inhibitor, 3-methyladenine, reduces Abeta generation. Thus, autophagy is likely to be involved in the Abeta generation pathway mediated by mammalian homologues of yeast Apg8 such as GATE-16.

N111

Analysis of processing and protein interaction of β -secretase

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The amyloid β -peptide (A β) appears to play a critical role in the pathogenesis of Alzheimer's disease. A β is produced from sequential endoproteolytic processing of amyloid precursor protein (APP) by β - and γ -secretases. γ -Secretase activity resides in a high molecular weight complex containing presenilin 1, nicastrin and other factors. β -Secretase has been identified as BACE (Beta-site APP cleaving enzyme or BACE1). BACE1 and its homologue BACE2 are membrane-bound aspartic proteases. BACE proteins are partly processed in the extracellular domain, generating soluble BACE. In order to better understand BACE processing and the regulation of BACE activity, we attempted to determine the cleavage site within BACE and explored specific factors interacting with BACE. We established human neuroblastoma and HEK293 cells stably expressing BACE with a C-terminal tag. Membrane preparations from the cells were subjected to glycerol density gradient centrifugation, and separated fractions were immuno-precipitated with an antibody to the tag. C-terminal fragments of BACE1 and BACE2 and a possible BACE-interacting protein were detected. Analysis of their amino acid sequences is in progress. We are also investigating the relationship between BACE and γ -secretase.

N112

Immunohistochemical study of b-amyloid protein(1-40, 1-42, 1-43) in old dog brain

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Introduction: In recent years, we reported that the aging change induces deposition of b-Amyloid protein (Ab) in the dog brain, and that a dementia. In last year study, we reported immunohistochemical study of Ab deposited ratio, aging, memory and learning. In this study, we examined immunohistochemical study of Ab1-40(Ab40), Ab1-42(Ab42), Ab1-43(Ab43) deposited ratio, aging, memory and learning. **Methods:** Whole dog 16 brains were removed (3years old-19 years old), and the resected brains were immersed in 4% paraformaldehyde. Cerebral frontal cortex were serially sliced at a thickness of 50um with a micro slicer. Immunohistochemistry was performed using against Ab40, Ab42 and Ab43. Ab positive area was measured by Olympus VM30 Ver. 2.01. Ab positive number of blood vessels were counted under the microscopy. **Results:** Ab40 was positive correlation with blood vessel number, score and age, however the correlation was not shown with positive area. Ab43 was positive correlation with blood vessel number, score, age and positive area. Ab42 was positive correlation with score and age. **Discussion:** Ab40 was positive correlation with blood vessel number, score and age. It was reported that the deposition of Ab40 to the brain reflected the degree of the disease state in the human, but in this study, we did not indicated. Ab 40 positive blood vessel number was positive correlation with score and age, and then the possibility in which the deposition to the blood vessel preceded was indicated the deposition of Ab40. Ab42 and Ab43 were positive correlation with score and age. We suggested that the deposition first step was long Ab deposited and these deposition was become diffuse plaque core.

N113

DNA chip study on mRNA expression profiles in the brain regions of MK-801 treated rat:Alzheimer's disease model

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MK-801 is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) subtype glutamate receptor. MK-801 administration induces nucleal vacuolation and neuronal cell death in the posterior cingulate / retrosplenial (PC/RS) cortex of rat. Olney et al. proposed that NMDA receptor antagonist induces the decrease of the GABAergic presynaptic inhibition of cholinergic and glutamatergic neurons, and leads to the over-stimulation of the neurons, resulting in the induction of neurotoxicity at mainly PC/RS cortex and hippocampus. This model is similar to the brain in Alzheimer's disease. MK-801 (more than 1.0 mg/kg,i.p.) administration increased prolyl endpeptidase (PEP) activity in the PC/RS cortex.MK-801 treatment also increased immunoreactive GFAP and CD11b, indicating the increases of astrocyte and microglial cells. In order to investigate changes of mRNA expression in the cortex of the rat, a pilot study was carried out using liver and genital DNA chips attached over 10000 genes. More than 3 times increases were shown in 300 spots including the proteins of Alzheimer's disease and various enzymes.We are currently studying mRNA expression in some brain regions, specially in the hippocampus using DNA chip for rat.

N114

Identification and characterization of molecules induced by beta amyloid in cultured cortical neurons

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Beta-amyloid (A beta) may play a important role in pathogenesis of AD, because A beta has toxic effect to cultured neuronal cells. However, about half of non-demented aged individuals have A beta plaques in neocortex but do not show neuronal loss in neocortex. These controversial findings in vitro and in vivo suggests that A beta induces molecules not only activating cell death pathway but also protecting neurons from A beta toxicity in neocortex. To understand the molecular mechanisms of A beta actions, we have applied cDNA subtraction between A beta1-42 treated and non-treated cerebral cortical neurons to generate A beta-induced cDNA pools. Three hundred clones were used for screening by cDNA macroarray. A total of 40 clones were identified. Out of 40 cDNAs, differential regulation of 5 genes was confirmed by Northern blot and RTQ-PCR. These clones, which were not known to be overexpressed by A beta-treatment, included a postsynaptic membrane protein and EST clones. Effects of overexpression of these molecules in cultured cortical neurons are currently under investigation.

N115

Modification of Epitopes of Tau Protein Specific to Alzheimer's Disease by Sequential Phosphorylation

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Hyperphosphorylation of microtubule-binding protein tau is thought to induce dissociation of tau from microtubules and irreversible tau aggregation resulting in tauopathies. In Alzheimer's disease (AD) patient brain, hyperphosphorylated tau (found in NFT) is characterized by double phosphorylation of closely located residues such as Ser202 and Thr205, Thr212 and Ser214.

Manifestation of such double phosphorylation seems to require complex conditions. For example, involvement of more than two tau kinases or activators is considered. Recently we have found that cleavage of p35 to p25 dramatically promotes phosphorylation of Ser202 and Thr205. Phosphorylation of Thr205 occurs only after the completion of Ser202 phosphorylation. This double phosphorylation is essential to a PHF-tau specific monoclonal antibody AT-8 reactivity.

We have also examined possible involvement CDK5, GSK3beta and PKA in expression of AD-specific epitopes including AT-8, AT-100 and PHF-1.

N116

Dose-dependent effect of MK-801 on the levels of neuropeptide regulating enzymes in rat brain regions

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The appropriate levels of neuropeptides and their processing enzyme activities are required to continue a normal cell life, and the dysfunction of these peptides and enzymes are responsible for many neuronal abnormalities. Systemic administration of MK-801, a noncompetitive NMDA receptor antagonist, causes both neuroprotective and neurotoxic activities depending on doses and conditions. In the present study, we investigated the dose dependent effects of MK-801 on prolyl endopeptidase (PEP), endopeptidase EC 24.15 (EP 24.15) and b-D-glucuronidase activities as well as the protein level of EP 24.15 in the posterior cingulate/retrosplenial cortices (PC/RSC), hippocampus, frontal cortex and striatum of female rats 3 days after the treatment. The activity of PEP was significantly increased compared with controls (saline) in the PC/RS at 1.0 and 5.0 mg/kg doses, and in the frontal cortex at 5.0 mg/kg dose. b-D-Glucuronidase activity was dose-dependently increased in all brain regions examined. The activity of EP 24.15 was unchanged in all regions after the treatment, whereas the Western blot analysis for EP 24.15 showed the increased protein levels in the PC/RS. These results suggest that a low dose treatment with MK-801 causes neurotoxicity in the PC/RS and hippocampus, and the high dose treatment causes neurotoxicity in all the brain regions examined.

N117

The effect of PS1 mutation on glycosphingolipid metabolism in neuroblastoma cells

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AimTo elucidate the effect of presenilin 1 (PS1) mutation on the metabolism of glycosphingolipids in neuroblastoma cells. **Method**Cell culture; Human neuroblastoma cell-line, SH-SY5Y, expressing wild (SH20-3) and mutant (SH34-5) ratPS1cDNA as well as mock-transfected (SH33-1) were cultured in DMEM with serum. Lipid extraction and radioisotope labeling of cellular lipids; Total lipids of cells were isolated by chloroform/methanol and further fractionated followed by TLC analyses as described. To analyze glycosphingolipids biosynthesis, cellular lipids were labeled by incubating cells in DMEM containing 3H-palmitic acid for overnight. Confocal laser microscope: To examine the distribution and quantity of GM1 in these cells, we used a fluorescein isothiocyanate-conjugated B subunit of cholera toxin (FITC-TB) as a probe. Cells were stained with FITC-CTB for 10 min at in the incubator and fixed with 3% paraformaldehyde for 15 min. **Results and Discussion** Lipids extraction analyses revealed that the biosynthesis of GM1 and polysialogangliosides was dramatically decreased in SH34-5 cells, while neutral glycosphingolipids were unchanged except glucosylceramide. There was no significant difference in glycosphingolipids pattern between mock-transfected and wild PS1 expressing cells. Confocal laser microscopic examination revealed the decreased FITC-CTB staining in SH34-5 cells. These results strongly suggest that mutation of PS1 gene would affect not only protein modification but also impair gangliosides biosynthesis, which are thought to be neuroprotective lipids.

N118

The role of phosphorylated PKR in ER-stress

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The endoplasmic reticulum (ER) is susceptible to various cellular stresses that provoke the accumulation of unfolded proteins in the ER. Excessive and/or long-term stress in the ER results in apoptosis. Recent studies have shown that ER-stress is associated with certain genetic and/or neuronal degenerative diseases, such as Alzheimer's disease (AD).

To identify the pro-apoptotic factors in ER-stress, we employed the gene discovery system using randomized ribozyme (Rz) library. The Rz is a small RNA molecule that can catalyze cleavage of RNAs in a sequence-specific manner. When the phenotype of cells changes upon introduction of a Rz library, genes that are responsible for the changes in phenotype can be identified by sequencing the active Rz that is expressed in the cell. In our previous report, isolated Rzs were suppressed Tunicamycin (Tm)-induced apoptosis and it recognized mRNA of double stranded RNA dependent protein kinase (PKR). This result indicates that PKR involved in Tm-induced ER-stress.

In general, double stranded RNA facilitates autophosphorylation of PKR and phosphorylated PKR inhibits the translation against virus infection. In this work, phosphorylated PKR was increased in Tm-mediated SK-N-SH cells and in autopsy brains of AD. Furthermore, many phosphorylated PKR was detected in nuclear fraction. Dominant negative (DN) type of PKR was also constructed and stably expressed in SK-N-SH cells. The cells were incubated with Tm and apoptotic cells were evaluated by TUNEL staining. DN-PKR hardly induced apoptosis. This result indicates that phosphorylated PKR is important to facilitate cell death. Interestingly, we found another role of PKR that may affect the stability of mRNA in ER-stress. We are planning to investigate further analysis.

N119

Effects of methamphetamine on cultured rat astrocytes

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Methamphetamine (MAP), a central nervous system (CNS) stimulant, can induce various malfunctions of CNS including confusion, hallucinations and delusions. Effects of MAP can usually be attributed to an indirect activation of sympathomimetic systems, that is, MAP facilitates release of monoamine neurotransmitters from nerve terminals and inhibits their re-uptake. Dopamine neurons are considered as a main target of MAP. Nowadays, however, astrocytes are thought to play important roles in brain function and some pathological conditions, and astrocytes express a wide range of monoamine receptors and transporters, thus, it seems reasonable to hypothesize that MAP affects astrocyte functions. In this study, we investigated the effects of MAP on cultured rat astrocytes to clarify whether the drug influences the glial cells directly. Treatment of the cells with 0.5mM MAP caused the formation of distinctive granules probably in the cytoplasm after 24 h of incubation, then the number of the granule increased until 7-10 days of incubation. Interestingly, the formation of granule by MAP was inhibited with 30 μ M U0126, an inhibitor of MEK (extracellular signal-regulated kinase (ERK) kinase). Western blotting using anti-phospho-ERK1/2 antibody revealed incubation with 0.5 mM MAP for 24 or 48 hours increased ERK activity compared with that of the control at each time point. Incubation with 0.5 mM MAP also induced elongation of astrocytic processes in about 10 days. Moreover, under a low glucose condition (5.5 mM glucose in DMEM), 0.5 mM MAP accelerated cytoplasmic vacuolation. These data suggest that MAP affects the morphology and metabolic state of astrocytes directly.

N120

Circadin rhythms alters antipsychotics-induced acetylcholine release in rat prefrontal cortex

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Extracellular acetylcholine (ACh) concentrations in medial prefrontal cortex (mPFC) have diurnal variations. In order to examine if such a diurnal variation impacts on effects of antipsychotic drugs (APDs) on ACh release in rat mPFC were investigated in nocturnal and diurnal phases using intracerebral microdialysis. The extracellular ACh concentration in mPFC increased with the transition from the diurnal phase to the nocturnal phase. In the nocturnal phase, haloperidol (1 mg/kg) and olanzapine (10 mg/kg) decreased extracellular ACh levels whereas, in the diurnal phase, haloperidol (1 mg/kg) did not. Clozapine (10 and 20 mg/kg) produced no significant effect on extracellular ACh levels in the nocturnal phase, whereas it increased extracellular ACh in the diurnal phase. Because haloperidol, which has higher affinities for dopamine receptors, decreased extracellular ACh in the nocturnal phase, we raised a hypothesis that the ACh-decreasing ability of APDs might be associated with antagonism at dopamine receptors. Both D1-like receptor antagonist, SCH23390 (0.25 and 0.5 mg/kg), and D2-like receptor antagonist, raclopride (1 mg/kg), decreased ACh concentration in the nocturnal phase. Pretreatment of SCH23390 (0.5 mg/kg), but not raclopride (5 mg/kg), inhibited the haloperidol-induced decrease in ACh concentration in the nocturnal phase. In contrast, olanzapine (10 mg/kg) and clozapine (10 and 20 mg/kg) increased conversely extracellular ACh levels under the same condition. These results suggest that APDs may produce different effects between day and night and that antagonism at D1-like receptors may be important for the ability of APDs to decrease extracellular ACh levels in the nocturnal phase, although further studies are necessary to characterize details.

N121

Effects of neonatal exposure of endocrine disruptors on rat myelin membranes.

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Neonatal exposure of endocrine disruptors induces developmental abnormalities in the reproductive and neuronal systems. To elucidate whether the neonatal exposure affects neuronal functions in juvenile and pubertal rat brains, Sprague-Dawley rats were given tributyltin (TBT) or be-ta-estradiol, by a single injection on the day of birth at a dose of 60 nmol /kg (TBT) or 60 umol/ kg (be-ta-estradiol), and the offspring brains were collected on 21 (juvenile), 35 (prepuberty), and 49 (puberty) days of age. The body weight of be-ta-estradiol treated groups was lower than that of control groups on the respective days of age, whereas no differences were shown between TBT-treated group and control group. Testis weight was affected by TBT and be-ta-estradiol, being paarticularly sensitive to TBT. 2', 3' - cyclic nucleotide 3'-phosphodiesterase (CNP) activity in all TBT-exposed groups (21, 35, 49 days of age) were significantly decreased compared with that of the control groups. Densitometric patterns of SDS-PAGE of myelin proteins in TBT-treated groups showed talteration in CNP content compared with the control groups. These results imply that neonatal exposure of TBT affects the brain myelination and male reproductive system, even by the relatively low level exposure.

N122

The epigenetic silenced gene, RFX1, in human gliomas.

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The status of CpG island methylation is characteristic of tumor type, suggesting that distinct sets of genes are suppressed by methylation during development of each tumor type. To identify CpG islands differentially methylated in human glioma, we performed the restriction landmark genomic scanning (RLGS) with a methylation sensitive enzyme, Not I. We found 12 spots, of which intensity were loss or decreased in human glioma tissues compared with matched normal lymphocytes, indicating that these CpG islands were aberrantly methylated in gliomas. The expression of RFX1, one of genes associated with the methylated CpG islands, was frequently lost or decreased in human glioma tissues and cell lines. The isolated CpG island located in the 7th intron of RFX1 gene has been shown to be an enhancer activity and hypermethylated in all of glioma tissues and cell lines analyzed, but not in normal brains and lymphocytes. Treatment of human glioma cells with a demethylating agent, 5-azacytidine, resulted in an expression of RFX1, indicating that the silencing of RFX1 gene is attributable to methylation. Furthermore, the proliferation of glioma cells were suppressed by transfection of the RFX1 gene. RFX1 has been implicated in transcriptional down-regulation of the proto-oncogene c-myc. Taken together, these results suggest that the transcriptional regulator gene RFX1 may be epigenetically silenced in gliomas and involved in glioma tumorigenesis.

N123

A mouse glioma antigen recognized by T cells

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The success of the immunotherapy depends upon its capability to induce specific T cell responses against the tumor antigens. For the development of immunotherapy against glioma, the identification of tumor antigens recognized by cytotoxic T lymphocytes (CTL) is required. In this study, we established a mouse CTL line (GCL-1) specific for a mouse glioma cell line, GL261, from spleen cells of immunized mice. The tumor-reactive CTL, GCL-1, was shown to recognize specifically the mouse glioma, GL261, in an MHC class I (H2-D^b) -restricted fashion. To isolate antigens recognized by the CTL, a mouse glioma cDNA library was screened by transfecting cDNA clones into 293 cells expressing H2-D^b and co-incubating these cells with GCL-1. We identified a new gene encoding tumor antigen, designated as GARC-1, recognized by the tumor-reactive CTL on the glioma cells. This mouse gene was expressed ubiquitously and showed homology with the human mitochondrial ribosomal protein S4. Sequence analysis revealed that the GARC-1 gene has several point mutations including a mutation in the open reading frame that causes amino acid change (Asp to Asn at amino acid residue 81). To characterize T cell epitopes in the GARC-1 antigen, we synthesized peptides carrying an H-2D^b binding motif from the putative protein and analyzed the recognition of the GCL-1. The peptide GARC-1 (77-85), which is encoded by the mutated sequence, was suggested to be the dominant target antigen of the GCL-1. The wild type peptide without the mutation was not recognized by GCL-1. In conclusion, we identified a mouse glioma antigen recognized by T cells and the use of the antigen in a preclinical model of tumor immunotherapy may be helpful in suggesting optional vaccination strategies for glioma therapy in patients.

N124

Involvement of inducible COX-2 in the rapid kindling development

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Brain cyclooxygenase-2 (COX-2), the rate-limiting enzyme in prostaglandin synthesis, is rapidly and transiently induced by convulsions in hippocampal and cortical neurons. Therefore, we examined the effects of COX-2 on the rapid kindling development in COX-2 knockout mice and in mice treated with nimesulide, a COX-2-selective inhibitor. Rapid kindling development was examined based on the incidence of hippocampal EEG seizures and behavioral seizures following repetitive electrical stimulation of the perforant path at an interval of 40 sec, and on the total afterdischarge (AD) duration induced by 50 stimulations. In addition, we measured COX-2 mRNA expression by in situ hybridization and PGE₂ concentration using enzyme immunoassay following rapid kindling stimulation. The results suggested that brain COX-2 mRNA levels were markedly increased in the hippocampal neurons and the concentration of PGE₂ was elevated significantly, and that the incidence of AD and seizure behavior induction and the total AD duration were significantly decreased under conditions of COX-2 deficiency. Therefore, we concluded that inducible COX-2 facilitates the recurrence of hippocampal seizures.

N125

Neurotoxicity of acetaldehyde-derived advanced glycation end-products (AA-AGE) for cultured cortical neurons

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The Maillard reaction that leads to the formation of advanced glycation end-products (AGEs) plays an important role in the pathogenesis of angiopathy in diabetic patients, in aging and in neurodegenerative processes. We hypothesize that acetaldehyde (AA), one of the main metabolites of alcohol, may be involved in alcohol-induced neurotoxicity in vivo by formation of AA-derived AGEs (AA-AGE) with brain proteins. Incubation of cortical neurons with AA-AGE produced a dose-dependent increase in neuronal cell-death, and the neurotoxicity of AA-AGE was neutralized by the addition of an anti-AA-AGE specific antibody, but not by anti-N-ethyllysine (NEL) antibody. The AA-AGE epitope was detected in human brain of alcoholism. We propose that the structural epitope AA-AGE is an important toxic moiety for neuronal cells in alcoholism.

N126

Neuroprotective effect of FK506 on axotomy induced motoneuron death

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Tacrolimus (FK506) is a potent immunosuppressive drug. It has been reported that FK506 has a neuroprotective effect when administered after ischemia and increases the rate of axonal regeneration after axotomy in vivo. In the present study, we examined a possible protective effect of FK506 on spinal motoneurons after axotomy. Male Sprague-Dawley rats (4 weeks old) were subjected to right sciatic nerve transection and then received daily subcutaneous injections of FK506 at a dose of 1 mg/kg for 7 days. One week after cessation of the drug treatment (2 weeks after axotomy), the animals were killed by perfusion of fixative and the spinal cord was examined in serial frozen sections (10-mm thickness). Number of motoneuron was counted in 20 serial sections (the first out of every five) of spinal segment L4 stained with cresyl violet. All motoneurons in lamina IX were counted. Neuronal survival ratio (NSR) was defined as the ratio between the number of motoneurons counted in the operated and control sides. NSR was 0.69 ± 0.05 (mean $\pm$ S.E.) in saline-treated control animals while it was 0.93 ± 0.02 (mean $\pm$ S.E.) in FK506-treated group. These results suggest that FK506 significantly suppresses motoneuron death after axotomy.

N127

Three-dimensional culture of the rat neural stem cell in collagen gel

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Recently we have reported the usefulness of neural stem cells (NSCs) transplantation for spinal cord injury in adult rat. To improve the transplantation of NSCs, we have been seeking scaffolds, neurotrophic factors, and blockage of the inhibitory molecules of axonal regeneration. We focused on type 1 collagen as a scaffold. Purpose of the present study is to determine the culture condition of NSCs in type 1 collagen gel prior to transplantation.

Methods NSCs derived from embryonic day 14 fetal green rat forbrain were cultured using neurosphere method as reported previously. Then NSCs were seeded with variety of density in type 1 collagen, then the survival rate of NSCs was quantified. To analyze the phenotype of NSCs after culture, immunostaining with anti-Tuj1, anti-GFAP or anti-CNPase was performed and the number of each type of cells was quantified. To determine the effect of BDNF on NSCs cultured in the gel, BDNF was added to the culture medium at a concentration of 50ng/ml.

Results The appropriate culture conditions of NSCs in type 1 collagen gel were, cell density: 3×10^6 – 2×10^7 cells/ml, collagen gel concentration: 0.05%. The immunostaining of NSCs after differentiation revealed that the ratio of GFAP⁺ cells, Tuj1⁺ cells and CNPase⁺ cells were 62%, 37% and 2% respectively. BDNF increased the number of Tuj1⁺ cells and the lengths of neuronal dendrites in collagen gel compared to the NSCs cultured without BDNF.

Discussion Our findings suggest that NSCs can survive and differentiate into neurons, astrocytes and oligodendrocytes in type 1 collagen gel, and that BDNF promote the neuronal differentiation and neurite extension. It is plausible that type 1 collagen may be an appropriate scaffold for NSCs transplantation with neurotrophic factors.

N128

Search for factors associated with neuroprotection in the retina.

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We had reported that the high mobility group protein A1a (HMGA1a) was induced by hypoxic stimulation in human neuroblastoma SK-N-SH cells. Further, the induced HMGA1a expression causes aberrant splicing of presenilin-2 pre-mRNA, that lack exon 5 (PS2V), observed in sporadic Alzheimer disease. The PS2V-expressing SK-N-SH cells became fragile in response to several endoplasmic reticulum (ER) stresses. On the other hand, it was reported that the high level expression of HMGA1a were detected in the photoreceptor of mouse retina. However, the PS2V expression and neuronal cell death were not induced by these HMGA1a in the retinal photoreceptor. Therefore, we searched factors that associated with HMGA1a and inhibited the expression of PS2V in mouse retina, but not hippocampus. Cell lysates from mouse retina and hippocampus were applied on pull-down assay using *e.coli*-expressed recombinant GST-HMGA1a. As a result, we obtained three HMGA1a-binding factors in the retinal lysates. These results suggest that the factors may have neuroprotective functions against the neuronal cell death underlying PS2V expression.

N129

Slo2, sodium-activated K⁺ channel, binds to PDZ domain of PSD-95

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Slo2 is a class of sodium-activated K⁺ channels widely expressed in nervous system, yet the neuronal function of these channels has been largely unknown. Here, we attended to the PSD-95/Dlg/ZO-1 (PDZ) binding motif at the carboxy (C) -terminal end of Slo2, since other subtypes of K⁺ channels, such as voltage-gated and inward rectifier K⁺ channels, bind to postsynaptic density-95 (PSD-95) via PDZ binding motif and are involved in the excitatory synaptic transmission. To examine the biochemical interaction of Slo2 and PSD-95 by Glutathione S-transferase (GST) pulldown assay, we cloned the mouse Slo2 (mSlo2) cDNA and constructed GST-fused proteins using the C-terminal 145 amino acid segment. Using the extract prepared from cultured cortical neurons, we clearly showed the interaction of mSlo2 and PSD-95. In addition, mutational analysis revealed that mSlo2 bound to the first PDZ domain of PSD-95 by means of PDZ binding motif. Furthermore, anti-PSD-95 antibody brought down mSlo2 from brain lysate on immunoprecipitation assay. *In situ* hybridization studies showed that Slo2 mRNA was expressed in excitatory neurons including cerebral cortex and hippocampus, where K⁺ current activated by sodium has been detected on electrophysiological studies. To investigate the expression of mSlo2 protein in the primary cortical neurons, we produced anti-mSlo2 antibody and immunostained the cortical neurons. mSlo2 was expressed in both dendrite and axon, and partly present at synaptic site, determined by the co-immunostaining with anti-PSD-95 or anti-synaptophysin antibodies. These findings suggest that mSlo2 will interact with PSD-95 in mouse brain.

N130

Cellular localization and distribution of Nax sodium channel

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Previous our knockout-mouse studies suggested that Nax is an extracellular sodium-level sensitive sodium channel in the brain, which is essential for the control of the salt intake behavior. Here, we examined the cellular localization and distribution of Nax throughout the visceral organs and the central nervous system. In visceral organs including lung, heart, intestine, bladder, kidney and tongue, a subset of Schwann cells within the peripheral nerve trunks were highly positive for Nax. An electron microscopic study indicated that these Nax-positive cells were non-myelinating Schwann cells, which maintain ionic levels in the extracellular space. In the lung, Nax-positive signals were also observed in the alveolar type II cells, which actively absorb sodium and water to aid gas exchange through the alveolar surface. In the brain circumventricular organs, Nax was expressed in the GABAergic inter-neurons. An electron microscopic study using spinal cord tissues demonstrated that synaptic terminals are positive for Nax. It was thus suggested that Nax sodium channel is involved in controlling the local extracellular sodium level in the peripheral organs and modulating neuronal activity in the CNS through its sodium-level sensing activity.

N131

A region of the $\alpha 1A$ subunit critical for modulation of P/Q-type Ca^{2+} channels by protein kinase A

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To understand the functional and structural basis for the modulation of neuronal Ca^{2+} channels by cyclic AMP-dependent protein kinase (PKA), $\alpha 1A$ (Cav2.1) and $\alpha 1B$ (Cav2.2) Ca^{2+} channels were expressed in *Xenopus* oocytes and also in baby hamster kidney cells. PKA inhibitors applied to the external medium decreased $\alpha 1A$ (P/Q-type) channel activities, and this effect was abolished by protein phosphatase inhibitors. On the other hand, intracellular application of PKA catalytic subunit increased the channel activities. In cell-attached patches, PKA inhibitors applied to the bathing medium significantly decreased single-channel activity of $\alpha 1A$ without affecting unitary conductance. The PKA inhibitor-induced inhibition of $\alpha 1A$ channels was potentiated by coexpression of the β subunit, but not of the $\alpha 2/\delta$ subunit. By contrast, $\alpha 1B$ (N-type) Ca^{2+} channels were not markedly affected by PKA inhibitors, even together with the β subunit. Chimeric channels between $\alpha 1A$ and $\alpha 1B$, and mutant $\alpha 1A$ channels with C-terminal deletions or point mutations revealed that one threonine residue in the C-terminus of $\alpha 1A$ is critical for the PKA-dependent regulation of P/Q-type Ca^{2+} channels.

N132

Colocalization of acid-sensing ion channels and vanilloid receptor subtype-1 in rat dorsal root ganglion neurons

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Many painful inflammatory and ischemic conditions are accompanied by local tissue acidosis, and extracellular protons provoke the pain by opening acid-sensing ion channels (ASICs) and vanilloid receptor subtype-1 (VR1) in nociceptors. Here we report the cellular colocalization and/or distinct localization of ASIC transcripts with those of VR1 in rat dorsal root ganglion (DRG) neurons. We selected ASIC1a and ASIC3 as target molecules for experiments, because ASIC1a, ASIC2b, and ASIC3 are main molecular entities present in murine primary sensory neurons and ASIC2b is predominantly colocalized with ASIC3 in the same population of the neurons. *In situ* hybridization revealed that both ASIC1a and ASIC3 transcripts were expressed in 30-35% of the DRG neurons. The ASIC1a transcripts were mainly expressed in small-diameter neurons, while the ASIC3 transcripts were located in (small-to-) medium-diameter cells. Intense expression signals for ASIC1a and ASIC3 transcripts were detected in 55-60% and approximately 20% of VR1-positive neurons, indicating that ASIC1a considerably contributes to pH-sensitivity of VR1-expressing polymodal nociceptors and that ASIC3 and VR1 are basically localized in the distinct populations of DRG neurons.

N133

Egr1 and AP1 factors in transcription of tyrosine hydroxylase

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Several treatments which regulate tyrosine hydroxylase (TH) transcription, such as stress *in vivo*, or 12-O-tetradecanoylphorbol-13-acetate (TPA) in cell culture, induce both Egr1 and AP1 factors. Previously, we identified that a functional Egr1 motif overlapped with Sp1 site in the rat TH promoter and determined that induction of TH promoter activity by Egr1 also required an AP1/Ebox motif in addition to the Egr1 motif. In this report, we examined the mechanism of the cross-talk between these motifs. Introduction of Egr1 expression vector into PC12 cells stimulated luciferase reporter gene controlled by proximal 272 nucleotides of the rat TH promoter. Insertion of 10- or 20-bp between the AP1/Ebox and the Sp1/Egr1 motifs, as well as mutation of either or both motifs, reduced the ability of Egr1 to up-regulate luciferase activity. Electrophoretic mobility shift assays with nuclear extract from TPA treated PC12 cells and labeled Sp1/Egr1 oligonucleotide revealed a complex that was not competed with excess AP1/Ebox oligonucleotide. The complexes formed with labeled AP1/Ebox oligonucleotide were reduced or supershifted with antisera to Fos family, Fra-2, c-Fos and Jun D. Excess Sp1/Egr1 oligonucleotide or anti Egr1 antisera did not compete. Fra-2 was a major component of the complexes after 2-4 hrs TPA. Transfection of PC12 cells with Fra-2 induced reporter activity requiring the AP1, but not the Egr1 motif. However, when cotransfected with Fra-2, Egr1 expression vectors elicited lower induction of luciferase activity than observed with Egr1 alone. These results indicate that although Egr1 does not compete for binding of AP1 factors to the promoter, it can modulate the regulation of TH transcription by AP1 factors.

N134

Effect of Over-expression of the Sigma-1 receptor molecule on the dopaminergic cellular functions

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To evaluate the function of dopaminergic neuron involved in Sigma-1 receptors (SigmaR1), we examined the effects of overexpressions of V-1, a catecholamine biosynthesis regulatory protein, or SigmaR1 in PC-12 cells on cellular functions. High K⁺-induced dopamine secretion in V-1 overexpressing PC-12 (V-1 cell) was markedly increased while the amount of [³H]dopamine uptake was decreased. Although, in PC-12 cells, extracellular dopamine uptake is via norepinephrine transporters (NET), immunoreactive activities of NET in V-1 cells were not altered. In V-1 cells increased expression of SigmaR1 was found as well as catecholamine biosynthesizing enzymes. Of interest, high K⁺-induced dopamine secretion and enhanced neuritis elongation were observed in only SigmaR1-overexpressed PC-12 cells (SigmaR1/DsRed). The high K⁺-induced dopamine secretion was not affected in the presence of SigmaR1 ligands. Semi-quantitative analysis showed that SigmaR1-overexpression (1.5 - 2-fold) caused increases in the immunoreactivity of phosphorylated (⁹Ser)synapsin. These data raises an intriguing possibility that an increase in synapsin phosphorylation in response to overexpressed SigmaR1 through intracellular cascade might contribute to enhance dopamine release. Such a pathway is further supported by the coexistence with the enhanced dopamine release and SigmaR1 expression in V-1 cells. Given the ability of SigmaR1 to modulate efficacy in dopamine release, we propose that activation of SigmaR1 may potentiate the dopaminergic transmission.

N135

Tree-dimensional structure of the interior of chromaffin cells and chromaffin granule motion.

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Molecular mechanisms of exocytosis has been well elucidated, if not fully, from biochemical and physiological studies on the exocytosis in adrenal chromaffin cells. However, conventional biochemical and physiological studies sometimes fail to elucidate the mechanism of tempo-spatial regulation of exocytosis in the living cells. For understanding the tempo-spatial regulation, visualizing analysis of exocytotic event and of secretory granule movement in living cells are advantageous in addition to the amperometrical analysis of single exocytotic events. Our previous studies with cultured adrenal chromaffin cells by such newly developed techniques revealed implications of actin-myosin interaction and PKC in the recruitment of the secretory granules for exocytosis. In this study, three-dimensional (3D) structure of the interior of bovine adrenal chromaffin cells was examined by scanning electron microscopy (SEM) with a newly improved maceration technique for further understanding of the tempo-spatial regulation. The 3D images revealed, for the first time, that the secretory granules are distributed adjacently to the plasma membrane with a variety of micro components such as filamentous structures and micro vesicular structures. We also obtained 3D images of the secretory vesicles connected with the inner surface of the plasma membrane by a tubular structure which suggest a compound exocytosis by three to four vesicles. Analysis of chromaffin granule motion in a living cells by a fluorescence microscopy showed images that may indicate also a compound exocytosis. To our knowledge, these are the first SEM images of secretory vesicles and of the compound exocytosis in adrenal chromaffin cells.

N136

Serotonin_{2A} receptor stimulation by DOI, a serotonin_{2A/2C} receptor agonist, potentiates amphetamine-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens.

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Modulation of stimulant-induced dopamine (DA) release by serotonin (5-HT)_{2A} receptors is of considerable interest for its role in the pathophysiology and treatment of schizophrenia and the relevance to psychosis and drug abuse as well. We previously reported that DOI, a 5-HT_{2A/2C} agonist, significantly potentiated D-amphetamine (AMPH)-induced DA release in rat striatum (STR) and nucleus accumbens (NAC) (Ichikawa & Meltzer, 1995). The present study further investigated the effects of DOI on AMPH-induced DA release in the medial prefrontal cortex (mPFC) and NAC, using in vivo microdialysis of awake, freely moving rats. DOI (2.5 mg/kg) significantly potentiated AMPH (1 mg/kg)-induced DA release in the mPFC and NAC. This effect of DOI was completely prevented by M100907 (0.1 mg/kg), a selective 5-HT_{2A} antagonist, which by itself had no significant effect on basal and AMPH-induced DA release in either region. These results demonstrate that the stimulation of 5-HT_{2A} receptors by DOI facilitates AMPH-induced DA release in three major DA terminal areas, the mPFC, NAC, and STR. The modest ability of 5-HT_{2A} receptor antagonism by M100907 to affect basal and AMPH-induced DA release in the mPFC and NAC suggests that 5-HT_{2A} receptors may play no tonic role in regulating basal DA release, only modulating activated DA release in these regions, as occurs following administration of antipsychotic drugs, amphetamine or DOI. Moreover, the combination of DOI with M100907 significantly decreased AMPH-induced DA release in the NAC, but not in the mPFC. Difference in 5-HT_{2A} and 5-HT_{2C} receptor stimulation by DOI in the NAC and mPFC may account for these results.

N137

Negative regulation of neurotransmitter release through the specific cleavage of SNAP-25 by calpain

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Synaptic transmission is conducted by neurotransmitters released from presynaptic nerve terminals by means of a Ca^{2+} -dependent exocytosis of synaptic vesicles. Recent studies showed that so-called SNARE proteins including vesicle-associated membrane protein 2 in synaptic vesicle membrane, and syntaxin 1 and synaptosome associated protein (SNAP-25) in plasma membrane, are essential for exocytosis. Synaptic transmission could be modified through the post-translational modifications of SNARE proteins, and these regulation is believed to be one of the mechanisms of synaptic plasticity underlying learning and memory.

We found in the present study that ionomycin treatment of cultured rat cerebellar granule cells and cortical neurons resulted in the reduction of molecular size of SNAP-25 from 25 to 20 kDa. The reduction was also induced by NMDA-treatment, and was not occurred in the absence of extracellular Ca^{2+} . Calpain inhibitors abolished Ca^{2+} -dependent cleavage of SNAP-25. By using various site-specific antibodies to SNAP-25, the cleavage site was suggested to be near N-terminal of cysteine-rich region of SNAP-25. Ca^{2+} -dependent glutamate release from culture cerebellar granule cells was increased markedly in the presence of calpeptin and calpain inhibitor IV. Immunoblotting of rat brain P2 membrane of various ages revealed that 20kDa fragment was also transiently appeared in brain and the content reached a maximal level around two weeks after birth. These results suggested that proteolytic cleavage of SNAP-25 by calpain may play an important role in the regulation of synaptic transmission through the inhibition of neurotransmitter release especially in developing brain. Partially supported by CREST, JST

N138

Amperometric detection and characterization of exocytosis from single PC12h cells

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Exocytosis in PC12h cells was analysed using a carbon fiber amperometry. PC12h cells cultured onto poly-L-lysine coated glass-base dish were incubated with dopamine (1 mM) and ascorbic acid (1 mM) for 90 min. The cells were washed with Locke's solution and incubate for another 90 min. Single-cell amperometric recording was performed under an inverted microscope at 25°C, and released dopamine were monitored with a carbon fiber microelectrode (5 micrometer diameter). The applied voltage was +700 mV versus the reference electrode. The amplified current signal was digitized at 4 kHz by a MacLab/4s system coupled to a computer. To characterize a single exocytotic event that is detected as a single current spike event, the spike number, spike parameters (rise time, middle width and area) and spike shape were analyzed. Exposure of PC12h cells to 60 mM KCl (1000 hps, 5 min) and (1000 hps, 4 s) evoked a train of events with the frequency of 118 ± 22 (number of spike/5 min, n=6) and 12 ± 4 (number of spike/15 s, n=11), respectively. We observed distinctive kinetics in the events (rise time = 0.78 ± 0.17 ms, middle width = 2.38 ± 0.42 ms, area = 58 ± 9.7 fC and the spikes with a foot = 14.7 ± 2.8 % of total spikes). The rise time and middle width in PC12h cells were approx. 5- and 10-fold small than those observed in cultured adrenal chromaffin cells, suggesting much faster exocytotic events in PC12h than adrenal chromaffin cells.

N139

Purification of pChAT, a novel splice variant of choline acetyltransferase, from porcine small intestine

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Choline acetyltransferase (ChAT) is a 67 kDa protein that catalyzes the biosynthesis of the neurotransmitter acetylcholine. Our laboratory recently reported the expression of a splice variant mRNA of ChAT that lacks coding exons 6 to 9. Because of its preferential expression in peripheral nervous system the 50 kDa protein encoded by the mRNA variant was termed ChAT of a peripheral type (pChAT). Immunohistochemical studies, using an antiserum raised against a recombinant peptide specific to pChAT, have confirmed its preferential localization in peripheral cholinergic neurons such as pterygopalatine ganglion, larynx and intestine. Although these observations provide the first demonstration of the expression of a ChAT isoform in situ, it remains to be solved whether pChAT still conserves an enzymatic activity. For this purpose, we have undertaken to purify pChAT protein from the enteric nervous system of porcine small intestine. Knowledge concerning the intracellular localization, its solubility, isoelectric point and behavior in the presence of pChAT antibody, all allowed us to establish a scheme for the purification of pChAT using conventional methods of fractionation combined with immunoaffinity chromatography. Our SDS-PAGE analysis in the final purification step revealed a major band of about 50kDa with pChAT immunoreactivity. In each step of purification, pChAT exhibited a significant activity for acetylcholine synthesis. These results indicate that pChAT is an active enzyme, having biochemical properties different from the 67kDa ChAT. Since, in the intestine, pChAT and the 67kDa ChAT have been shown to be differentially expressed in subclasses of enteric neurons, roles of pChAT may be understood through chemical coding of functionally distinct enteric neurons.

N140

A high efficient transfection method for chromaffin cells

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Gene transfection seems useful to investigate possible roles of exogenous proteins for regulated secretion in intact cells, and lipid-mediated gene delivery is the most widely used technique in cell biologic research. So far, unfortunately, this method is generally inefficient for adrenal chromaffin cells, though the cells have been extensively used in this field. We adapted the high efficient lipofection technique to transiently express the gene which encoding proteins implicated in secretion in chromaffin cells. We examined the cationic lipid reagent, LipofectAMINE 2000, Effectin, Neuroporter and Eugene, which formed complex with plasmid DNA. The transfection efficiency was estimated from the expression level of EGFP. Primary dissociated chromaffin cells from bovine adrenal medulla were prepared by differential plating with the culture medium without uridine, FUDR and cytosine arabinoside. This step was important to get higher transfection efficiency and stability. When we carried out the transfection 12-120 hr after plating the cells, we observed a high EGFP expression. Among the examined reagents, LipofectAMINE 2000 was most effective resulting 10 to 30% transfection efficiency. Effectin was also effective reagent, although the efficiency was a little low than LipofectAMINE 2000. The transfection efficiency of Neuroporter and Eugene was below 1/5 of LipofectAMINE 2000, but cell toxicity appeared weaker. Amperometric measurement of catecholamine release was performed in EGFP-expressed single chromaffin cells. There was no difference in the amperometric data between the transfected cells and control cells.

N141

Effect of antipsychotic drugs haloperidol and risperidone on altered psychomotor behaviors in PACAP knockout mice

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We have recently generated mice lacking PACAP (PACAP^{-/-} mice), and demonstrated that PACAP^{-/-} mice shows phenotypic changes including increased exploratory locomotor activity, explosive jumping behavior, and a deficit in sensorimotor gating (as assessed by a reduced prepulse inhibition (PPI) of the acoustic startle response). In addition, we have showed that the typical antipsychotic haloperidol, a potent dopamine D2 receptor antagonist with relative high specificity, effectively suppressed the hyperlocomotion of PACAP^{-/-} mice to the control level in wild-type mice, suggesting the involvement of dopaminergic neurotransmission. In the present study, we examined the effect of haloperidol on the two phenotypes, explosive jumping behavior and a deficit in PPI, in PACAP^{-/-} mice. We also examined the effect of an atypical antipsychotic risperidone (a serotonin 2A-dopamine D2 receptor antagonist). Both haloperidol (0.2 mg/kg) and risperidone (0.1 mg/kg) completely blocked the jumping behavior of PACAP^{-/-} mice. Risperidone normalized the deficit in PPI in PACAP^{-/-} mice, however, haloperidol did not reverse the PPI deficit. These results suggest that D2 dopaminergic pathways are responsible for the abnormal jumping behavior in PACAP^{-/-} mice, while serotonin 2A receptor system are also involved in the deficit in PPI in PACAP^{-/-} mice. We postulate that PACAP^{-/-} mice may serve as an useful animal model for screening potential antipsychotic drugs.

N142

Regulation by serotonin_{1A} receptors of *in vivo* release of serotonin and dopamine in mouse cortex

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Serotonin (5-HT) _{1A} receptors are localized presynaptically on 5-HT cell bodies or dendrites in the raphe nuclei and postsynaptically on non-5-HT neurons in various brain regions. The study on pre- or postsynaptic receptor mechanism should contribute to better understanding of pharmacology of 5-HT_{1A} receptor agonists. The present study using an *in vivo* microdialysis technique examined whether the pre- and postsynaptic 5-HT_{1A} receptors have different sensitivity to the selective 5-HT_{1A} receptor antagonist WAY100635 to develop a new strategy for studies on the 5-HT_{1A} receptor mechanism in mice. 5-HT and dopamine (DA) in dialysates were simultaneously quantified by HPLC with electrochemical detection. Oral administration of MKC-242 and 8-OH-DPAT, 5-HT_{1A} agonists, decreased cortical 5-HT release at low and high doses, while only the high dose increased DA release. MKC-242-induced increase in DA release but not the decrease in 5-HT release was attenuated by local application of WAY100635. Furthermore, cortical 8-OH-DPAT application increased DA release, but did not affect 5-HT release. These results suggest that cortical 5-HT release was regulated by presynaptic 5-HT_{1A} receptors, and DA release was regulated by postsynaptic 5-HT_{1A} receptors. We also examined the effects of WAY100635 at different doses on 5-HT_{1A} receptor agonist-induced changes in DA and 5-HT release in the cortex. The 5-HT_{1A} receptor agonist-induced decrease in 5-HT release was blocked by low and high doses of WAY100635, while the agonist-induced increase in DA release was blocked by only high dose of WAY100635. These findings may suggest that a low dose of WAY100635 antagonizes preferentially presynaptic 5-HT_{1A} receptors and this drug is a useful reagent to study the roles of presynaptic 5-HT_{1A} receptors.

N143

Human interferon-alpha Associated Decrease of BrdU positive cells in Rat Hippocampus

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Human interferon alpha (hIFNa) is a cytokine that is produced in the early immuno response to viral infections. hIFNa clinically applied to treatment for infections and malignant diseases. Despite the theraputic effects, hIFNa administration frequently induces depression, sometimes leads to discontinuation of hIFNa therapy. For the hIFNa associated depression, antidepressant therapy is shown to be effective. In the rat forced swimming test, hIFNa was reported to increase the immobility time. Previous studies revealed that antidepressant administration prevented the hIFNa induced increase of the immobility time. In the dentate gyrus, granule cells proliferate even in adulthood. Stress decreases neurogenesis, and antidepressants prevent stress related decrease of that. Therefore we hypothesized that hIFNa inhibits neurogenesis in the dentate gyrus, that causes the prolongation of the immobility time by hIFNa administration. Adult rats were administrated hIFNa or vehicle for 7days, and 24 hours before the last administration, BrdU was started to be injected. In all groups administrated hIFNa, the numbers of BrdU positive cells in the dentate gyrus were significantly smaller than that of the control group. These findings suggest that the hIFNa induced prolongation of the immobility time in the forced swimming maybe related to decrease of neurogenesis by hIFNa. This phenomenon maybe one mechanism of the hIFNa associated depression.

N144

Assay of PRMT (protein arginine methyltransferase) function by using siRNA during neuronal differentiation of PC12cells.

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Protein Methylation is a posttranslational modification that can potentially regulate signal transduction pathways in a similar manner as protein phosphorylation.. Although phosphorylation has mainly researched in signal transduction so far, previous studies by Cimato et al have implied that protein methylation could mediate neurite extension of PC12cell by NGF. Protein methylation occurs on the polar group of amino acids, like arginine and lysine residues, and the carboxyl-termini of proteins, like small G-proteins. It has not been known at all what kind of methylation is necessary for the phenomenon, because it is the lack of specific methyltransferase inhibitors. Recent progress in the identification of PRMT (protein arginine methyltransferase) provides a clue for analyzing physiological roles of protein arginine methylation. We noted that RGG boxes that are characteristic of some RNA-binding proteins were known to undergo methylation at the first arginine residues. During NGF-induced differentiation, an RNA-binding protein, HuD, elongates the half-life of GAP-43 and p21 transcripts and elevates their protein levels. We imagine that its methylation may regulate the events on these mRNA species to stabilize them, because other family member of HuD has been reported to undergo methylation in response to inflammation. To elucidate the link between protein arginine methylation and neurite outgrowth of PC12 cell, we knocked down each of PRMT members using interference (RNAi), by which 20-23 nucleotide double-stranded RNA (small interfering RNA; siRNA) triggers posttranscriptional silencing of the corresponding gene. We report the effect of RNAi-inducing PRMT knock down on the neurite outgrowth of PC12 cell in response to NGF.

N145

Effects of botulinum neurotoxin and nitric oxide on the exocytosis in rat cerebellum granule cells

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[Purpose]

Nitric oxide (NO) modulates the neurotransmitter release, which is thought to be involved in neuronal plasticity. The main focus of our study is to reveal the molecular mechanism of the modulation of exocytosis by NO. In this study, Botulinum neurotoxin (BoNT), which inhibits neurotransmitter release by cleavage of SNARE-complex, was examined as a tool for analysis of the modulation of exocytosis by NO in rat cerebellum granule cells.

[Methods]

Rat cerebellum granule cells were incubated for 5 days after diluting to 2×10^6 cell / ml culture medium composed of high-K⁺ (25 mM) Minimum Essential Medium containing 5% FCS and 5% horse serum (HK-MEM / HFCS). After treatment with botulinum type B neurotoxin (BoNT/B) and NOC7 which was NO donor, L-NAME and L-NMMA which were NO synthase (NOS) inhibitor, cultures were depolarized with high-K⁺ ringer solution. Glutamate content was determined by reverse-phase HPLC. SNARE-complex formation was analyzed by 2D-SDS-PAGE and Westernblotting using antibodies specific for VAMP, SNAP25 and syntaxin.

[Result and discussion]

Our result of treatment with 1 mM NOS inhibitor and NO donor, K⁺-induced glutamate release was increased to 138%, and decreased to 70%, respectively. And BoNT/B inhibits the glutamate release in concentration dependent manner, whose EC₅₀ was 0.085 nM. From these results, in cultured rat granule cells it became clear that NO affects inhibitory for glutamate release and BoNT/B could be a powerful tool. Further studies including co-treatment with NO donor and BoNT/B, and analysis of SNARE-complex formation are in progress.

N146 (MS6-1)

Autophosphorylated, inactivated and sedimentable Ca²⁺/calmodulin-dependent protein kinase II during acute brief seizure activity in rats *in vivo*

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Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) is highly enriched in the central nervous system, and proposed to play a central role in activity-dependent changes in neuronal functions. It is activated by binding of Ca²⁺/calmodulin, undergoes rapid autophosphorylation at Thr-286 (α) / 287 (β) and substrate phosphorylation in response to Ca²⁺ influx into neurons. Recent studies indicate macromolecular complex formation of CaMKII in cultured neurons under ischemia-like conditions, which may be related to a cellular self-defense mechanism in pathological conditions. However, whether such CaMKII clustering actually occurs under certain conditions *in vivo*, whether it is reversible, what the activity state is and how autophosphorylation at Thr-286/287 is involved remain to be elucidated. Here we employed electroconvulsive treatment in rats to induce acute, brief seizure activity, and biochemically examined the distribution, autophosphorylation and activity states of CaMKII in homogenate from hippocampus and parietal cortex during and after seizure activity. We found an increase in sedimentable, particulate CaMKII with increased autophosphorylation at Thr-286/287 and decreased kinase activity at 30 sec after the electrical stimulation during brief seizure activity. Such CaMKII was no longer detected several minutes after the termination of seizure activity, indicating its reversible nature. Combined with previous observations, we propose a mechanism for reversible formation of such autophosphorylated, inactivated and sedimentable CaMKII during excessive neuronal excitation *in vivo*. Such a mechanism may be a novel physiological process indispensable for normal functioning of the brain.

N147 (MS6-2)

Stimulation of CaM kinase II-dependent neurite extension by Arc

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CaM kinase II (Ca²⁺/calmodulin-dependent protein kinase) plays an important role in synaptic plasticity, including learning and memory. It is one of the major proteins in the PSD (postsynaptic density) of the cerebral cortex and hippocampus. It has been demonstrated that one set of mRNAs, such as CaM kinase II, Arc (activity-regulated cytoskeleton-associated protein) and MAP2, is prominent in the dendrites of neurons in the cortex and hippocampus. The translation of dendritic mRNAs is regulated by signaling events at synapses, and local protein production during long-term synaptic plasticity has focused attention on the mechanism involved. Therefore, it is of particular interest to see whether Arc affects CaM kinase II action. In present study, we demonstrated that Arc and CaM kinase II were accumulated in the PSD after electroconvulsive treatment. To investigate the effect of Arc on CaM kinase II, GFP-Arc fusion protein was expressed in Nb2a cells expressing alpha CaM kinase II (Nb2a/alpha cells). Cells expressing and not expressing Arc were present in the same culture dish and both cells could be easily distinguished by fluorescence microscopy. The morphological change to Nb2a/alpha cells expressing Arc was compared using cells not expressing Arc. The cells expressing both Arc and CaM kinase II had longer neurites than those expressing CaM kinase II alone. The growth of neurites by Arc was completely blocked by treatment with KN62. Arc itself did not promote neurite outgrowth. The interaction of Arc with CaM kinase II was demonstrated using GST-Arc fusion protein, and confirmed in neuroblastoma cells by immunoprecipitation. These results indicated that Arc potentiated the action of CaM kinase II for neurite extension.

N148 (MS6-3)

The regulatory mechanisms of CaM kinases I and IV in the hippocampal neurons.

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The CaM kinase cascade is consisted by CaM kinase kinase (KK), CaM kinase I and CaM kinase IV. CaMKK is activated by calcium/calmodulin, and phosphorylates Thr-177 of CaMKI and Thr-196 of CaMKIV. In the rat hippocampal neurons, CaMKI is localized in the cytosol whereas CaMKIV is mainly localized in the nuclei. We compared the basal and the glutamate-induced activities of these kinases. The basal activity of CaMKI showed higher than that of CaMKIV, and both kinases were significantly activated by glutamate through the NMDA receptor. The time course of the glutamate-induced CaMKI activity was sustained after the activation, whereas that of CaMKIV was transient. Two possible mechanisms were thought to cause these differences between CaMKI and CaMKIV. (1) The differential regulatory mechanisms by protein phosphatases for each kinases: in fact, cyclosporin A, an inhibitor for calcineurin, increased the glutamate-induced activity of CaMKIV but not of CaMKI. (2) The differential regulation by CaMKK isoforms: CaMKK alpha was localized both in the nuclei and the cytosol, whereas beta was only in the cytosol. Alpha is strictly regulated by Ca/CaM and never showed the Ca-independent activity, while beta showed the significant Ca-independent activity. The strict CaM dependency of CaMKK alpha may also contribute to the lower basal activity of CaMKIV in the nuclei. On the other hand, the cytosolic CaMKI is thought to be regulated by both CaMKKs alpha and beta, especially the basal CaMKI activity would be defined by the Ca-independent activity of CaMKK beta.

N149 (MS6-5)

Identification of MLK 3 as a hippocalcin-binding protein

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Hippocalcin is a member of the neuronal calcium sensors (NCS) family predominantly expressed in the hippocampal pyramidal cells. Hippocalcin deficient mice showed impairments in NMDA-induced ERK2- and CREB-phosphorylation in the hippocampal slices, and in learning ability of the visual-discrimination.

Here we screened to search for proteins, which interact with hippocalcin by using yeast two-hybrid system composed of mouse brain cDNA library. From screening, 76 positive clones were obtained. Reporter (beta-galactosidase) expression analysis revealed that 13 clones showed positive interaction with hippocalcin. These clones were classified by sequence analysis to be mixed-lineage kinase (MLK) 3 (7 clones), protein 1B; a transcription factor having f-box/WD40 domain (3 clones), NAIP (neuronal apoptosis inhibitory protein) 3 (2 clones) and complexin 2. MLK3 displayed the strongest interaction in reporter expression analysis, and then binding profile between hippocalcin and MLK3 was examined. Immunoprecipitation study using antigen-purified anti-hippocalcin antibody displayed the co-precipitation of MLK3 in 1% TritonX-100 soluble hippocampal lysate. In vitro co-precipitation analysis using domain specific constructs of MLK3 revealed that hippocalcin bound with C-terminal Pro/Ser/Thr-rich region of MLK3. Recombinant fragments for each EF-hand domain of hippocalcin failed to bind with MLK3, indicating that conformation of whole hippocalcin molecule involves in the interaction with MLK3. Neural visinin-like protein (NVP) 1, 2 and 3, structurally related proteins to hippocalcin, did not show binding ability to MLK3, suggesting that members in NCS family may have their own target proteins and may play specialized roles in neurons.

N150 (MS8-4)

Stimulation of the G protein, Gi2, by endothelin B receptors enhances proliferation and migration of neural progenitor cells

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Our previous study showed that the pertussis toxin (PTX) -sensitive G protein, Gi2, is selectively localized in the ventricular zone of embryonic brains, where the neuroepithelial cells undergo active proliferation. In order to clarify the role of Gi2 in this site, we first administered PTX, by an exo-utero manipulation method, into the lateral ventricle of mouse brains at embryonic day 14. Examination at embryonic day 18 revealed that PTX-injected embryos had brains with thinner cerebral cortices made up of fewer constituent cells, indicating impaired development. Then we cultured neural progenitor cells from rat embryonic brains and evaluated the mitogenic effects of agonists for several Gi-coupled receptors, which are known to be expressed in the ventricular zone. Among agonists tested, endothelin (ET) most effectively stimulated the incorporation of [³H]thymidine via the ET-B receptor and this was associated with phosphorylation of extracellular signal regulated kinase (ERK). PTX partially inhibited ET-stimulated DNA synthesis and ERK phosphorylation. Next we examined whether Gi2 is also involved in cell migration, and ET, again, most effectively stimulated cell migration among agonists for Gi-coupled receptors tested. PTX and ET-B receptor antagonist completely inhibited ET-stimulated cell migration. These findings indicate that Gi2 mediates signaling from the ET-B receptor to enhance mitogenic activity and migration of the neural progenitor cells in developing brain.

N151

Sterol regulatory element-binding proteins are involved in the human brain acyl-CoA hydrolase gene transcription.

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Long-chain acyl-CoA hydrolases, a group of enzymes that catalyze the hydrolysis of acyl-CoA thioesters to free fatty acids and CoA-SH, could provide a mechanism via their potency to mediate cellular concentrations of acyl-CoAs for the regulation of various cellular events including lipid metabolism membrane trafficking, and gene expression. The brain acyl-CoA hydrolase (BACH) is markedly distributed in the brain and localized in neurons, however, the physiological significance of BACH is unclear. To study the gene function, we characterized the human BACH gene promoter. Deletion analysis of the human BACH gene promoter at -7277 to +35 base pairs, employing a nested series of luciferase constructs, in the SK-N-SH neuroblastoma cells demonstrated that the some regions of the gene promoter contain the information required for the transcriptional regulation. The region from -515 to -57, with eight clustered GC-boxes, was responsible for 70% of maximum transcriptional activity of the BACH promoter. The 5'-ATCACACCAG-3, at -1577 to -1568 base pairs of the BACH promoter was perfectly matched to the sterol regulatory element (SRE) of LDL receptor promoter and corresponded to the region required for the transcriptional activation by sterol depletion. Electronic gel mobility shift assay showed that active forms of recombinant sterol regulatory element-binding protein (SREBP) -1a, -1c, and -2 bound to the SRE of the BACH promoter. These findings suggested that SREBPs may mediate transcription of the BACH gene. Further characterization of the roles of BACH may provide new insight into acyl-CoA and cholesterol metabolism in neurons.

N152

THE EFFECTS OF ACUTE AND REPEATED RESTRAINT STRESS ON ACTIVATION OF ERK IN THE ROSTRAL VENTROMEDIAL MEDULLA

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Extracellular signal-regulated kinase (ERK) is the key molecule in numerous cellular and physiological processes in the CNS, which is activated by many neurotransmitters and neurotrophins, such as excitatory amino acid and brain-derived neurotrophic factor. Exposure to stressors causes an important effect to the perception and response to pain. Although acute stress elicits antinociception, there is some evidence to indicate that chronic stress elicits hyperalgesic effects in several behavioral tests. The rostral ventromedial medulla (RVM) that includes the nucleus raphe magnus (NRM), the adjacent gigantocellularis pars alpha (NGCα) and ventral nucleus reticularis gigantocellularis (NGC) plays a crucial role in descending pain modulation. In the present study, the activation of ERK in the RVM in rat following acute and repeated restraint stress was examined in order to characterize the mechanisms underlying stress induced analgesic and hyperalgesic response. The rats were stressed by restraint 6h daily for 3 weeks. The brainstem tissues were dissected and sections were processed for phospho-ERK (pERK) immunohistochemistry. The pERK-immunoreactive (IR) cells were observed in the NRM and NGCα. In these area, the number of pERK-IR cells per section in the 3 week stressed rats was 14.3 ± 1.2 , significantly higher than that in naive rats (8.9 ± 0.7) [$p < 0.05$]. However there was no significant difference in the activation of ERK between the acute stressed and naive rats. About 80% of pERK-IR cells in the RVM in the 3 week stressed rats were serotonin neurons. These findings suggest that the repeated restraint induced-increase on the activation of ERK in serotonin neurons in the RVM may be involved in the modulation of the pain threshold by chronic stress.

N153

Protection by repetitive exposure to static magnetic fields against neurotoxicity of MK-801 in cultured rat hippocampal neurons

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Hippocampal neurons were cultured in DMEM for consecutive 8 days in vitro (DIV) with medium change every 3 days under repetitive exposure to static magnetic fields at 100 mT generated by permanent ferrite magnets equipped at both sides of culture dishes for 15 min per day. Repetitive exposure to static magnetic fields significantly decreased the expression of microtubule-associated protein 2 (MAP2) without markedly affecting that of neuronal nuclei on Western blotting analysis. Repetitive magnetism did not markedly affect cell survivability quantified by MTT assay in hippocampal neurons cultured for 8 DIV, while a significant increase was seen in expression of the particular subunit for assembled heteromeric N-methyl-D-aspartate (NMDA) receptor channels NR2B subunit but not in that of both NR1 and NR2A subunits with concomitant potentiation of the ability of NMDA to increase intracellular free Ca^{2+} ions as revealed by fluo-3 fluorescence in hippocampal neurons cultured under repetitive magnetism for 8 DIV. By contrast, repetitive exposure to static magnetic fields led to significant protection against the loss of MAP2 in hippocampal neurons cultured under sustained exposure to the NMDA receptor antagonist MK-801 for 8 DIV. These results suggest that repetitive exposure to static magnetic field may modulate mechanisms associated with cellular maturation as well as with expression of particular NMDA receptor subunits without affecting survivability in cultured rat hippocampal neurons.

N154

Suppression by SOCS3 of leptin-induced NPY gene transactivation

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Leptin is an adipose tissue-derived secretory hormone that suppresses appetite by inhibition of neuropeptide Y (NPY) gene expression in arcuate nucleus (ARC) in CNS. Increase in body fat mass causes augmented production of leptin from adipose tissue. To investigate the transcriptional regulation of NPY gene by leptin, we carried out the neural cell culture experimental systems using NPY gene promoter-luciferase plasmid (NPY-luc) in N18TG2, NG108-15 and PC12 cells. Under these experimental conditions, NPY gene was transactivated by leptin in these cells that expressed the functional leptin receptor through JAK-STAT signaling pathway.

In this study, we showed that leptin-induced transactivation was mediated through the 221-bp region of NPY gene promoter, which possesses two putative STAT3 binding sites. Moreover, to investigate the mechanism of suppression of NPY gene expression in ARC by leptin in vivo, the effect of SOCS members on the leptin-induced transactivation of NPY gene was studied in the neural cell system. Although treatment with leptin (125 ng/ml) induced significant increase in NPY-luc reporter activity by 3-fold in mock-transfected cells, NPY-luc reporter activity was not activated by leptin stimulation in SOCS3-transfected cells. NPY-luc reporter activity was also inhibited by transfection of SOCS1 cDNA. These finding suggested that SOCS3 is the negative regulator on the NPY gene expression in neural cells.

N155

Identification and Characterization of Novel Human Ubiquitin Ligases Involved in Endoplasmic Reticulum-Associated Degradation (ERAD)

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Endoplasmic reticulum-associated degradation (ERAD) is a system, in which unfolded proteins that are drained from the ER lumen to the cytosol are ubiquitinated by ubiquitin ligase (E3) and then degraded by 26S proteasome. We report here largely unknown human E3 proteins that are involved in ERAD, their functions and their induction mechanisms. We have identified and characterized human HRD1 as a typical E3 involved in ERAD, with a RING-H2 finger motif required for its ubiquitin ligase-activity, being localized to the ER membrane and up-regulated in response to ER stress. We searched protein databases for other novel E3s involved in ERAD, similar to HRD1, using bioinformatic tools. Finally, a candidate RING-H2 finger protein, human KF-1, was determined. KF-1 was predicted to have three transmembrane regions and to be localized to the ER. In fact, transient overexpressed KF-1 was found to be localized to the ER in cos-1 cells. Although KF-1 has already been reported to be an E3 with a RING-H2 finger motif, its involvement in ERAD remains unknown. We demonstrated the up-regulation of KF-1 in response to such ER stress-inducing agents, as thapsigargin and tunicamycin, and the transient overexpression of human IRE1 and ATF6, which are ER stress-sensor molecules in the ER membrane. Furthermore, we isolated and investigated the KF-1 promoter region, and found that it was responsive to ER stress. The results indicate that similarly to HRD1, KF-1 is an E3 involved in ERAD.

N156

Vitamin D responsive element binding in rat brain

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Vitamin D receptor (VDR) is a transcription factor of zinc finger domain with ability to specifically recognize vitamin D responsive element (VDRE) on inducible target genes after hetero-dimerization with retinoid X receptor (RXR) in the cell nucleus. Oligonucleotide containing VDRE was synthesized and radiolabeled with [α -³²P]dCTP using Klenow fragment of DNA polymerase I as a probe for determination of DNA binding activity on gel retardation electrophoresis. DNA binding was detected in nuclear extracts prepared from rat brain discrete structures, but not in cytosolic fractions, with cerebellum being higher than that in other brain regions examined. Unlabeled VDRE probe was effective in competing for VDRE binding in a concentration-dependent manner in cerebral and cerebellar nuclear extracts, while unlabeled mutant VDRE probe was ineffective in competing for binding at the concentration range used. In rat cortical neurons cultured for 9 days in vitro, brief exposure for 5 min to the group II metabotropic glutamate receptor (mGluR) subtype DCGIV led to a marked increase in VDRE binding when determined 120 min later. However, no significant change was found in VDRE binding in cultured cortical neurons briefly exposed to agonists for group I and III mGluR subtypes. These results suggest that crosstalk could be seen between signals mediated by VDR and mGluR in cultured rat cortical neurons.

N157

Regulation of calcium/calmodulin-dependent protein kinase I activity by protein phosphatases in cultured rat hippocampal neurons

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We have focused on activation mechanisms of calcium/calmodulin-dependent protein kinase I (CaM-KI) in the hippocampal neurons. We recently reported that stimulation of glutamate receptors potentiated CaM-KI activity in cultured rat hippocampal neurons. To define protein phosphatases involved in regulation of CaM-KI activity in the hippocampal neurons, we here tested effects of phosphatase inhibitors on the basal and the glutamate-induced CaM-KI activity. Treatment with cyclosporin A, an inhibitor of calcineurin, showed no effects on CaM-KI activity. In contrast, treatment with okadaic acid, an inhibitor of protein phosphatase (PP) 1 and PP2A, decreased the basal and glutamate-induced activities in CaM-KI. We next purified CaM-KI as a immuno-complex with the specific antibodies from cell extracts and treated with PP2A. Consistent with the results *in situ*, the treatment with PP2A *in vitro* increased the glutamate-induced activity in CaM-KI, whereas PP1 decreased its activity. *In vitro* assay for dephosphorylation of phosphorylated CaM-KI with major PPs revealed that PP2C had the highest activity for dephosphorylation, followed by PP1 and PP2A. Dephosphorylation rate by calcineurin was apparently low and did not affect on the CaM-KI activity. When CaM-KI was immunoprecipitated from NG108-15 cells transfected with CaM-KI and treated with PP2A, its activity increased without change in phosphate incorporation. These results suggest that protein phosphatases including calcineurin, PP2A, PP1 and PP2C differently regulate the CaM-KI activity in neurons.

N158

Regulation of estrogen receptor function by heat shock protein 90 in HT22 cells.

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Estrogen-induced upregulation of estrogen receptor (ER) and activation of estrogen response element (ERE) binding in relation with heat shock protein (hsp) 90 were examined with use of HT22 hippocampal cell line. HT22 cells which lack ERs were transfected with ER-expressed vector. ER-expressed HT22 cells (ER-HT cells) were stimulated by various doses of 17beta-estradiol. Then, ER and ERE bindings were examined by Biacore system and gel shift assay, respectively before and after the stimulation. In addition, same experiments were done on hsp90-overexpressed ER-HT cells. In ER-HT cells, estradiol induced upregulation of ER and elevation of ERE bindings dose-dependently. As for hsp90 overexpressed ER-HT cells, the results were different depending on dose of estradiol. These results show that hsp90 is not merely inhibitory on ER-ERE complex formation but is playing roles in modulating ER activation and ERE binding.

N159

Activation of ATF6, an Endoplasmic reticulum (ER) stress sensor, through 6-hydroxydopamine in human neuroblastoma SH-SY5Y cells.

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Although exact etiology of Parkinson disease is not clear to date, oxidative stress and mitochondria dysfunction have been shown to induce damage of particular neurons. Recently some reports have demonstrated that oxidative stress enhances accumulation of unfolded proteins in the endoplasmic reticulum (ER). Accumulation of misfolded proteins within ER induces a highly specific unfolded protein response (UPR) which involves ATF6 proteolysis, followed by expression of ER stress-response genes, including those that encode Grp78 and GADD153. To elucidate whether ER stress is involved in cell death induced by 6-hydroxydopamine (6-OHDA), which has been used to prepare Parkinsonian rats, we tested changes in levels of ATF6, GADD153 and Grp78 through treatment with 6-OHDA in the human neuroblastoma SH-SY5Y cells. 6-OHDA induced the cell death in a concentration-dependent manner, with complete protection by an antioxidant N-acetylcystein. 6-OHDA treatment induced a decrease in the proteasome activity, as well as an increase in the levels of high molecular ubiquitin-conjugated proteins. Western blot analyses revealed that 6-OHDA treatment markedly proteolysed ATF6 and increased the levels of both GADD153 and Grp78. Levels of these proteins reached a maximum 9 h after treatment with 50 mM 6-OHDA. N-acetylcystein absolutely prevented the increases in 6-OHDA-induced expression of both GADD153 and Grp78. These results suggest that ER dysfunction may be at least in part involved in mechanisms underling the cell death induced by 6-OHDA in SH-SY5Y cells. Finally, this study could provide a new and important information on the mechanisms underling neuronal cell death in Parkinson disease.

N160

Mechanisms of IL-20 induction in the primary cultured glial cells

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Recently discovered cytokine IL-20 has been reported to have a role in epidermal function and psoriasis. However, the regulatory mechanisms leading to IL-20 expression during infection and inflammation of the central nervous system has not been elucidated. In the present study, we have found that bacterial lipopolysaccharide (LPS) and double-stranded RNA, poly I:C, induces IL-20 expression in the mouse primary cultured glial cells. LPS induced an increase in IL-20 mRNA expression at 1hr, which peaked at 2 hr and decreased thereafter. The expression of IL-20 was not inhibited by pretreatment with protein synthesis inhibitor puromycin indicating that the expression was not dependent on de novo protein synthesis. LPS activated p38 kinase, subgroup of mitogen-activated protein (MAP) kinases, in primary cultured glial cells. Since p38 MAP kinase inhibitor, SB203580 inhibited the LPS-induced expression of IL-20 mRNA, it is suggested that p38 MAP kinase is involved in transcriptional regulation of IL-20 gene expression in endotoxin-activated glial cells. It is known that LPS transduces the signal via MyD88, an adaptor protein mediating Toll-like receptor signaling. Next, we demonstrated using MyD88 deficient glial cells. Expression of IL-20 induced by both LPS and poly I:C was abolished. Therefore, it is suggested that MyD88 and p38 MAP kinase may play an important role in IL-20 induction in the glial cells.

N161

Mechanisms of estrogen-induced elevation of PLA activity in immortalized hippocampal neurons.

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In our previous studies, we confirmed that beta-estradiol evoked an immediate PKA activation in the living immortalized hippocampal neural cell, H19-7 by means of DR2 fluorometry. The DR2 is a cell-permeable fluorescent PKA substrate. This study was undertaken to clarify the mechanism of this estrogen-induced PKA elevation.

Instead of beta-estradiol, we added either BSA-conjugated beta-estradiol or alpha-estradiol to H19-7 cell and then DR2 fluorometry was done. The BSA-conjugated beta-estradiol caused as much PKA elevation as beta-estradiol, while alpha-estradiol induced no change in PKA activity.

Intracellular Ca ion concentration was also imaged by Fura2 fluorometry on the same cell in which estrogen-stimulated PKA elevation was confirmed. As the result, it was observed that PKA activation followed Ca ion elevation. Effects of PKA inhibitor, Ca channel antagonist and ICI 182,780 were observed in this experimental system of estrogen-induced PKA activity assay.

N162

Decrease in histamine H₁ receptor signaling through m3 muscarinic receptor-induced H₁ receptor down-regulation

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Both histamine H₁ receptors (H₁Rs) and muscarinic receptors are distributed in the central nervous system and peripheral tissues. Heterologous desensitization between H₁Rs and muscarinic receptors has been extensively studied by pharmacological methods. Recent studies at the molecular level show that desensitization mechanism contains three steps, namely i) uncoupling with effectors, ii) internalization and iii) down-regulation. Strong down-regulation of H₁Rs with 40% of the initial level was induced by the stimulation of H₁Rs. Then muscarinic receptor stimulation-induced H₁R down-regulation was studied using Chinese hamster ovary cells stably expressing both H₁Rs and one of muscarinic receptor subtypes. Among m1-m5 muscarinic receptor subtypes, no H₁R down-regulation was not induced through m1, m2 and m4 receptors in 24 hours. In contrast, the stimulation of m3 muscarinic receptors induced remarkable H₁R down-regulation with 60% of the initial level. Intermediate down-regulation was induced by m5 receptor stimulation. The down-regulation mediated by m3 receptors was completely blocked by the pretreatment with atropine. Ro 31-8220, a protein kinase C inhibitor, showed negligible effect on the down-regulation. KT5823, a protein kinase G inhibitor, showed partial but significant inhibition. Accumulation of inositol phosphates by the stimulation of histamine was remarkably lower in down-regulated cells than non-treated cells. These results clearly showed that H₁R signaling is regulated by m3 muscarinic receptor-dependent H₁R down-regulation mechanism. It is suggested that long-term depression of H₁R signaling due to m3 muscarinic receptor-mediated H₁R down-regulation play important roles in the central and peripheral functions of histamine.

N163

Phosphorylation of a p35 Cdk5 activator being inhibitory to the cleavage by calpain

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Cyclin-dependent kinase 5 (Cdk5) is a member of the Cdk family but is activated in post-mitotic neurons by a brain-specific activator p35. p35 is cleaved into p25 by calpain in cultured neurons undergoing cell death. p25 was reported to accumulate in brains of Alzheimer's patients. The cleavage to p25 changes the subcellular distribution of active Cdk5 from the particulate to the cytosolic fraction, thereby allowing aberrant phosphorylation of neuronal cytosolic proteins. Thus, the cleavage of p35 to p25 could be toxic for neurons. We previously reported that phosphorylation of p35 suppressed the proteolysis by calpain. The phosphorylated form of p35 was prevalent in the fetal brain, but p35 became unphosphorylated in the adult brain. To prevent p25-induced neuronal cell death in adult brains, it is important to know the mechanism of protective phosphorylation on p35. Here, we investigated the phosphorylation site involved in suppression of the p35 cleavage by calpain. We cultured cortical neurons in the presence of [³²P] orthophosphate, and isolated p35 by immunoprecipitation from the cultured neurons extract. p35 was labeled with ³²P and the incorporation of ³²P was suppressed by roscovitine, a Cdk5 inhibitor, indicating that p35 was phosphorylated by Cdk5 in cultured neurons. When phosphorylated p35 was subjected to 2D phosphopeptide mapping after tryptic digestion, a single phosphopeptide was detected. When p35/Cdk5 prepared from Sf9 cells was incubated with ATP, the identical phosphopeptide was detected. However the phosphopeptide was not detected with p25/Cdk5. One of Cdk5-dependent phosphorylation sites in p35 appeared to be present in the N-terminal p10. We are now analyzing whether phosphorylation at this site indeed inhibits the proteolysis of p35 by calpain.

N164

Effect of methamphetamine on expression of Homer mRNAs in the rat brain

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Homer proteins, which regulate the signaling pathway of metabotropic glutamate receptors, may contribute to the glutamatergic modulation of dopamine neurons in the basal ganglia. In this study, we examined whether the induction of Homer 1 genes is or not associated with the methamphetamine-induced dopaminergic neurotoxicity in the discrete brain regions of rats. Basal levels of Homer 1a and 1c mRNAs in the forebrain regions were higher than those in the substantia nigra, whereas Homer 1b mRNA levels were higher in the substantia nigra than those in the forebrain regions examined. A neurotoxic dose (40 mg/kg, i.p.) of methamphetamine increased Homer 1a mRNAs in the striatum and nucleus accumbens, but not in the medial prefrontal cortex or the substantia nigra. Both Homer 1b and 1c mRNAs were not affected in any brain regions examined. These results suggest that the induction of Homer 1a gene may be involved at least in part in the methamphetamine-induced dopaminergic neurotoxicity, possibly through the glutamate-dopaminergic interaction.

N165

The role of G protein subtypes in type 5 adenylyl cyclase-null mice

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Type 5 adenylyl cyclase (AC5) is dominantly expressed in the striatum while negligibly in other brain regions. In mice with the disrupted AC5 gene (AC5KO), we found the AC activity of the striatum decreased by 80% while that of other brain regions showed a marginal decrease. AC5KO showed a major defect in motor function represented by impaired Rotarod performance and the presence of bradykinesia, mimicking human Parkinson's disease. Selective D1 dopaminergic stimulation, which activates Gs α /olf protein to increase intracellular cAMP, partially improved motor dysfunction, suggesting the restoration of cAMP signal in the striatum is essential for its improvement. Motor dysfunction was most readily recognized in adult mice, such as by the presence of abnormal gait, while this was not seen in young mice. Striatal AC activity of AC5KO was only 20% of that of wild type (WT) in adult mice, while that was more than 50% in newborn mice, indicating the difference in AC activity between WT and AC5KO increased with development. We found that this increase was, at least partially, due to the developmental changes in the expression of G protein subtypes. We examined the expression of striatal Golf protein at postnatal day 0, 2, 4, and 14 of WT and AC5KO. The amount of expression was 100, 186, 209 and 491%, respectively, in WT while 103, 174, 192 and 330% in AC5KO. In contrast, the amount of other G protein subtypes, such as Gi, Gs, G β , remained similar between WT and AC5KO. Because Golf is the major stimulatory G protein subtype in the striatum, it is likely that the developmental decrease in the striatal Golf expression in AC5KO relative to that in WT contributes to the development of motor dysfunction.

N166 (MS7-1)

The N-terminal membrane-associated domain of RB3, a neural-specific member of the SCG10/stathmin family proteins, affects the microtubule dynamics

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Microtubules (MTs) are polar polymers composed of ab tubulin heterodimers that are inherently dynamic, a property referred to as dynamic instability. The MT dynamism is regulated by MT-stabilizing and -destabilizing factors, such include the so-called MAPs and stathmin, respectively. RB3 is a neural-specific homologue of the SCG10/stathmin family proteins, possessing a unique N-terminal membrane-associated domain and the stathmin-like domain at the C-terminus, which promotes MT catastrophe and/or tubulin sequestering. We have been interested in the structural and functional relationships of the SCG10 family members as to neuronal plasticity, and examined how RB3 sub-domains contributes to MT regulation. To begin with, we determined the effects of full-length (RB3-f) and short truncated (RB3-s) forms of RB3 on MT polymerization in vitro. RB3-s had a deletion of 1-75 amino acids from the N-terminus, leaving the so-called stathmin-like domain. Both RB3-f and RB3-s revealed MT-depolymerizing activity; however, RB3-f was apparently less effective, suggesting the N-terminal domain masks, at least in part, the tubulin-interacting and/or MT-depolymerizing activity, which is evoked by the stathmin-like domain. Indeed, RB3-f bound tubulin less efficiently than RB3-s. Direct observation of individual MTs using dark-field microscope revealed that RB3-s reduced the MT-elongation velocity and rescue frequency, and thus the catastrophe frequency was increased. In contrast, addition of RB3-f increased the MT-elongation rate and rescue frequency, but still increasing the catastrophe frequency. These results indicate that the N-terminal domain of RB3 has a modulatory role on MT-depolymerization activity executed by its stathmin-like domain.

N167 (MS7-2)

Real-time observation of the effect of dephosphorylation on neurofilament gel formation using microbeads

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Highly cross-linked arrays of neurofilaments (NFs) observed in the mature axon are thought to determine the mechanical properties of the axoplasm as well as NF transport rates and NF aggregate formation. To investigate the mechanisms regulating the formation of such higher order structures, we developed a sensitive method to follow the time course of NF-NF interaction based on the analyses of the Brownian movements of Latex microbeads trapped in the forming gel using video-enhanced differential interference contrast (DIC) microscopy. Compared with the conventional falling-ball viscometer which measures resistance of the gel against mechanical forces and applicable only to NF protein concentrations higher than 3mg per ml, our method is capable of detecting viscosity changes at concentrations of 0.3 to 1.5mg per ml in less than 10 microliter of volume and during formation of the gel. Two types of measurements were carried out; (a) measurement of mean square displacement (MSD) values for individual beads, and (b) measurement of the total area covered by moving beads in the observation field for a fixed time interval at higher bead concentration, which give an average bead movement. After warming to 25 degrees, native NFs extracted from rat spinal cords and purified by sucrose density gradient centrifugation showed time- and concentration-dependent decrease in bead movement by both measurements, indicating viscosity increase due to NF association. When NFs were enzymatically dephosphorylated, the decrease in bead movement became more rapid and heterogeneous within the field; some areas in the field had higher density of moving beads than others. Dephosphorylation thus results in the rapid but more irregular association of NFs.

N168

Coordinated cytoskeletal interactions in neuritogenesis

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Neurons begin to extend neurites when they differentiate. Neuritogenesis requires rearrangement of cytoskeletal elements, which are mechanically and functionally integrated each other. Cytoskeletal rearrangement is both intrinsically and extrinsically regulated. We previously reported that lysophosphatidic acid (LPA), an extracellular lipid mediator, induced neurite retraction through actin polymerization in young cortical neurons undergoing neuritogenesis. Here we examine the effects of LPA on microtubules (MTs) in these neurons and immortalized neuroblast TR cells. LPA treatment resulted in rapid retraction of MT-containing neurites, accompanied by an increase of MT contents within rounded cell bodies. This MT collapse in neurites was inhibited by pretreatment with cytochalasin D (CD), an actin polymerisation inhibitor, but not with taxol, an MT stabiliser. These results indicated that LPA affected the interactions between actin microfilaments (MFs) and MTs primarily through actin polymerization to influence neuritogenesis of neuronal cells. To further examine these interactions, we overexpressed MT-binding domains of MACF (microtubule actin-crosslinking factor) in TR cells. These cells showed colocalization of the domains with MTs and resistance to LPA-induced MT collapse. The present study provides first evidence that MF-MT interactions are regulated through actions of cytoskeletal crosslinkers during extracellular signal-induced changes of cell dynamics.

N169

Domain analysis of Drebrin-associated protein 1, Drap1

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Drebrin associated protein 1, Drap1, was identified in a yeast two-hybrid screening by using Drebrin as bait. To characterize Drap1 protein, we generated polyclonal antibodies against the recombinant Drap1 protein. Immunocytochemistry in rat primary cultured hippocampal neurons revealed that Drap1 was located primarily in nucleus, and lesser amounts in the cytoplasm of soma, dendritic shafts, and dendritic spines. In this study, we constructed variety of GFP-tagged Drap1 fragments and performed a domain analysis by introducing them into COS-7 cells. Domain analysis indicated that there were three distinguishable domains concerning with intracellular localization; a nuclear localization signal (NLS), a nuclear export signal (NES), and a vesicle associate domain. All fragments containing short N-terminal region were concentrated in nucleus. Amino acid sequence of this region had continuous five basic amino acids. It is known as a consensus sequence of NLS. When two amino acids of the NLS were exchanged to other amino acids, this mutant was not located in nucleus. NES was found in coiled-coil domain of the C-terminal region. While most of the short fragments have entered into nucleus, fragments with coiled-coil domain were localized in cytoplasm. This domain did not have any obvious consensus sequence with known NES sequences. Vesicle associate domain was seen in upstream of the coiled-coil domain. This fragment was transiently expressed in cultured hippocampal neurons. Immunocytochemistry by using antibodies against various vesicular proteins exhibited that it was localized in non-clathrin coated vesicles. These results suggest that Drap1 functions by shuttling between cytoplasm and nucleus and is involved in non-clathrin coated vesicles.

N170 (MS8-6)

Filamin A-interacting protein FILIP regulates cell shape prior to radial migration in the cortical ventricular zone.

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One neural stem cell in the developing cerebral cortex typically divides to yield one postmitotic neuron and one neural stem cell. These two siblings show distinct behavior after their birth: while a neural stem cell stays within the ventricular zone, a postmitotic neuron quickly starts migration toward the cortical plate. It is a matter of interest how the start of migration is regulated in cell-autonomous manner. Previously, we identified a novel protein FILIP in the ventricular zone. FILIP is a negative regulator for cell migration start through interacting with, and inducing the degradation of, an actin-binding protein Filamin A. Here we assessed cell-biological significance of FILIP by suppressing its expression using RNA interference (RNAi). Short interfering RNA (siRNA) for FILIP was expressed in rat embryonic neocortical neuroepithelial cells together with GFP and maintained them as slice culture. We found that FILIP siRNA-expressing cells exhibited radially-oriented spindle-shape more frequently compared with control cells in the vicinity of the ventricular surface. Because their radially-oriented spindle-shape is characteristic of radially migrating postmitotic neurons normally found in the cortical plate, the result suggests that FILIP prevents the ventricular zone cells from exhibiting migratory shape prior to radial migration start.

N171

Preparation of the antibody specific for tau phosphorylated by CaM kinase II.

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The paired helical filaments (PHF) found in Alzheimer's disease (AD) brain are composed mainly of the hyperphosphorylated form of microtubule-associated protein tau. It is well known that tau is a good *in vitro* substrate for Ca^{2+} /calmodulin-dependent protein kinase II (CaM kinase II). We previously reported that CaM kinase II phosphorylates tau at serines 262 and 356, numbered according to the longest human tau isoform (hTau40), in its tubulin binding sites. While these sites are phosphorylated by other protein kinases *in vitro*, serine 416 has been reported to be phosphorylated only by CaM kinase II. To examine the phosphorylation of tau by CaM kinase II *in vivo*, we produced a specific antibody against tau phosphorylated at serine 416. We synthesized a phosphopeptide which contained phosphoserine 416 and prepared the antibody specific for this phosphopeptide. The antibody was purified by antigen-affinity chromatography. Immunoblot analysis revealed that the antibody reacted with tau purified from porcine brain only after phosphorylation by CaM kinase II. In contrast, the antibody reacted with bacterially expressed hTau40 after phosphorylation by cAMP-dependent protein kinase as well as CaM kinase II. When we prepared the cytosol fraction from rat brain without protein phosphatase inhibitors, the antibody reacted with tau only after phosphorylation by CaM kinase II. Interestingly, when we prepared the cytosol fraction in the presence of protein phosphatase inhibitors, the antibody strongly reacted only with tau in the fraction. These results suggest that tau is phosphorylated by CaM kinase II *in vivo* and that the antibody is useful for examination of phosphorylation of tau by CaM kinase II in AD brain.

N172

Positive and negative effects of neurosteroids and endocrine disruptors on MAP2-dependent microtubule assembly and neurite extension

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We found some non-genomic molecular targets for neurosteroids. Here we report that some endocrine disruptors (EDs) act on microtubule-associated protein 2 (MAP2), which is one of the targets of neurosteroids. Pregnenolone (PREG), a representative neurosteroid stimulated MAP2-dependent microtubule assembly *in vitro*. The enhancement by PREG was inhibited by progesterone (PROG), an antagonistic neurosteroid. In contrast to PREG, dehydroepiandrosterone (DHEA), another neurosteroid, suppressed the MAP2-dependent microtubule assembly. No neurosteroid influenced the tau-dependent microtubule assembly. PREG also increased the length and number of dendrites of rat primary cultured hippocampal neurons, and PROG inhibited the effect. It has been reported that some neurosteroids affected the neurite extension through NMDA receptor activation. However, NMDA receptor antagonists did not affect the present neurosteroid-induced neurite extension. On the other hand, 4-nonylphenol (4-NP), a representative ED, inhibited the MAP2-dependent microtubule assembly like DHEA. Bisphenol A (BPA) blocked the PREG-enhanced assembly like PROG. In the primary hippocampal culture, 4-NP inhibited the stimulatory effect of PREG on the dendritic neurite extension. Furthermore, the intracerebroventricular injection (i.c.v.) of PREG increased the density of basal dendrites of mouse CA1 neurons, while 4-NP decreased it. In the step-through-type passive avoidance test, 4-NP (i.c.v.) caused marked decrease in the test latency. Co-injection of PREG showed a dose-dependent reversal of 4-NP-induced amnesic actions. All these findings suggest that 4-NP inhibits the hippocampal dendritic extension and memory and learning by its inverse agonistic effect on MAP2-dependent microtubule assembly.

N173

Migration of young neurons in the adult mouse and monkey subventricular zone

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Adult mammalian subventricular zone (SVZ) contains stem cells that give rise to both neurons and glia. The newly generated neurons migrate tangentially through the SVZ to join a restricted path called the rostral migratory stream (RMS) that leads to the olfactory bulb. In the olfactory bulb, the new neurons differentiate into granule and periglomerular neurons. The young neurons move closely associated with each other, forming chains without radial glial or axonal guidance. This migration occurs throughout the lateral wall of the lateral ventricle, where the neuroblasts form an extensive network of chains. We studied the SVZ and RMS of the adult marmoset monkeys using immunohistochemical detection of BrdU and several cell-type specific markers. Our results suggest that adult primates have mechanisms of neuronal migration similar to those in rodents. Previous studies identified some candidate molecules that might be involved in chain migration of neuroblasts. However, the directional mechanism of neuroblast migration in SVZ and RMS is largely unknown. We recently found that Slit proteins secreted from choroid plexus into the ventricular cerebrospinal fluid play an important role in directional control of neuronal migration in the adult mouse SVZ and RMS. Based on these results, we will propose a novel model of neuronal migration in the adult mammalian brain.

N174 (MS7-3)

Screening of the downstream targets of Olig2 by PCR-based cDNA subtraction analysis

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Olig2 is the basic helix-loop-helix transcriptional factor that is essential for development of oligodendrocytes and motoneurons. Olig2 is expressed in the pMN-precursor region of the ventral neural tube, which is known to give rise both to motoneurons and oligodendrocytes. The Olig2-null mice entirely lack motoneurons and OLPs in the spinal cord and lack almost all OLPs except for small pockets of OLPs in the forebrain. Recent studies that Olig2 is highly expressed in human oligodendrogliomas suggest the possibility that Olig2 might participate in the oncogenesis. Olig2 is induced by floorplate-derived Sonic hedgehog (Shh) but little is known about the downstream transcriptional targets of Olig2. So we attempted to identify downstream genes of Olig2 by use of PCR-based cDNA subtraction analysis that permits the isolation of cDNA that are present in one DNA sample but absent in another. We compared transcripts of the wild type mouse and the Olig2-null mouse and identified several genes that expressed differentially. Expression patterns of these genes were investigated by in situ hybridization in spinal cords of wild type mice and Olig2-null mice, respectively. These genes may provide important insights into molecular mechanisms of oligodendrocytes and motoneurons development and contribute to unravel Olig2-related oncogenic mechanism.

N175 (MS7-4)

Expression and activity of extracellular superoxide dismutase in cultured astrocytes

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Under the pathological conditions such as brain ischemia, a large amount of superoxide anion (O₂⁻) is produced and released. Extracellular superoxide dismutase (EC-SOD), known to be an ectoenzyme, should play a role to detoxify superoxide in extracellular space; however, little is known about EC-SOD in brain.

We examined the mRNA expression of three isozymes of SOD by RT-PCR method; mitochondrial Mn-SOD, cytosolic Cu/Zn-SOD, and EC-SOD, in three types of cultured brain cells from embryo or newborn rats; astrocytes, neurons, and microglia. EC-SOD activity was evaluated by the inhibition of color development of a water-soluble tetrazolium (WST-1) due to O₂ generation by xanthine oxidase/hypoxanthine added into extracellular medium of cultured intact cells.

The three kinds of SOD mRNA could be detected in all three types of the cells examined; however, the semiquantitative analysis revealed that the level of EC-SOD mRNA in astrocytes was significantly higher than that in neurons and microglia. The expression levels of the other two isozymes of SOD mRNA were not significantly different among three types of the cells. The activity of EC-SOD in cultured neuron and microglia was below the range of detection limit; however, in astrocyte, it was high enough to measure and to compare with that in erythrocytes. The specific activity of EC-SOD in cultured astrocytes per cell protein was as high as 8% of the specific activity of Cu/Zn-SOD observed in cytosolic fraction of erythrocytes after removal of hemoglobin.

These results suggest that EC-SOD of astrocyte plays a role for detoxication of extracellular superoxide and is responsible for an important defensive mechanism against oxidative brain injury.

N176 (MS7-5)

The dynamic state of progenitor cells in brain injury

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Damage of the central nervous system causes reaction of various kinds of cells, including damaged oligodendrocytes, reactive astrocytes, activated microglia, oligodendrocyte precursor cells (OPCs), meningeal cells and proliferating vascular endothelial cells. Although these cellular reactions have been repeatedly described over the last two decades, the dynamic states of the newly generated cells in the post-injury remodeling tissues have not been fully elucidated. The present study was undertaken to characterize proliferation and differentiation of newly generated cells after brain injury. We employed cortical cryo-injury model and pulse-labeled proliferating cells with BrdU on the second day after injury. The mice were perfused after various periods (3, 7, 14 days after injury) and brain sections were cut and subjected to double-labeling study. The BrdU-labeled cells were simultaneously labeled for various cell markers immunohistochemically; nestin (for neural progenitor cells), NG2 proteoglycan (OPCs), Notch-1 and CNPase (oligodendrocytes), GFAP (reactive astrocytes), NeuN and Tuj-1 (neuron) and Iba-1 (microglia/macrophage). Spatio-temporal analyses of the double-labeled cells (cell marker and BrdU) revealed that the most of the newly generated cells had characters of neural progenitor cells and tendency to differentiate into astrocytes, but not to oligodendrocytes or neurons. To address the origin of the progenitor cells, we labeled proliferating cells in the intact adult brain by injecting BrdU once a day for two weeks and made cryo-injury. Nestin-positive cells in the tissue surrounding the necrotic region were hardly double-labeled for BrdU, suggesting that the progenitor cells found in the vicinity of the lesion were not derived from the preexisting progenitor pools in the adult brain.

N177

Differential subcellular distributions of Ca²⁺/calmodulin-dependent protein kinase II delta isoforms

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Four subunits of Ca²⁺/calmodulin-dependent protein kinase II (CaM KII) have been identified including several isoforms, which differ in the variable domains. CaM KII comprises holoenzyme of 8-12 subunits with the carboxyl-terminal association domains. To examine subcellular distributions of these subunits, we performed immunoblot analysis for each subunit in the extracts from the rat frontal cortex after subcellular fractionation in a continuous sucrose density gradient. Only alpha subunit was clearly co-localized with synapsin I, and each subunit showed different subcellular distributional patterns. We further examined subcellular distribution between delta isoforms in the NG108-15 cells stably expressing delta 1, delta 4 and delta 3. The delta 1, delta 3 and delta 4 isoforms showed different distributional patterns in the subcellular fractions each, and in addition, the endogenous delta 2 isoform was clearly co-localized with the overexpressed delta 1, delta 4 and delta 3 isoforms although the endogenous gamma B and gamma C isoforms were not co-localized with the overexpressed delta isoforms. From these results, CaM KII can comprise oligomer between other isoforms but not between other subunits and the variable domains are responsible for their subcellular distributions.

N178

A potential role of PKC-signaling in neuronal maturation

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In a dissociated neuronal culture, local contact with astrocytes elicited PKC activation in an integrin-mediated manner, which spreads over an entire neuron, resulting in global and augmented synaptogenesis. The synapse-formation was significantly suppressed by a PKC inhibitor. Thus, the local contact with astrocytes triggers propagation of PKC-signaling within a neuron. Moreover, phosphorylation of adducin, a substrate of PKC, was restrictedly detected by immunohistochemistry in immature neurons of subgranular zone of adult dentate gyrus, where they started to be exposed to astrocytes. It was suggested that PKC-activation post-contact with astrocytes might play a cue role for maturation of newly generated neurons in adult. To test this hypothesis, we are making further trial to test the effects of PKC on neuronal maturation by using culture of hippocampus-derived neural progenitor cells.

N179

Cellular properties of microglia isolated from axotomized facial nucleus of adult rat

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In order to characterize activated microglia in matured brain, we isolated the microglia into culture system from axotomized adult rat facial nucleus by explant culture. The isolated cells exhibited the immunoreactivity similar to that of newborn rat brain-derived microglia. The purity of the microglia was estimated to be almost 100%. Interestingly, the cultured microglia increase in cell number during the culture time (~2 weeks). Actually, the microglia incorporated bromodeoxyuridine (BrdU), indicating their ability to divide. The analysis of their conditioned medium revealed that they produce macrophage colony stimulating factor (M-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF). The mRNA of both factors was also expressed in the cells, supporting the results of immunoblotting. These results indicate that isolated microglia from axotomized facial nucleus proliferate in autocrine fashion *in vitro*. Therefore, it is suggested that activated microglia produce their own mitogens in axotomized facial nucleus *in vivo*.

N180

Influence of dibutyric cyclic AMP on differentiation and development of glial cells in primary cultures of embryonic rat cerebral hemisphere

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The influence of dibutyric cyclic AMP (dbcAMP) on differentiation and development of astrocytes and oligodendrocytes was investigated in primary cultures prepared from rat cerebral hemisphere on embryonic day 18, because cyclic AMP is critical for the fate of neural cells. The cells were cultured in serum-free defined medium containing thyroid hormone with or without dbcAMP for 2 days, and expression levels of glial fibrillary acidic protein (GFAP), a specific marker of astrocytes, and the number of O1-positive oligodendrocytes were investigated. Both the level of GFAP expression and the number of oligodendrocytes increased with the addition of dbcAMP. Then, the influence of the inhibition of platelet-derived growth factor (PDGF) on oligodendrocyte differentiation was also examined in the presence and absence of dbcAMP, since it is well known that cultured astrocytes release PDGF into the culture medium, and that PDGF is a mitogen for oligodendrocyte progenitors and represses the differentiation of oligodendrocytes. When PDGF was inhibited using its neutralizing antibody, the number of oligodendrocytes increased regardless of the presence of dbcAMP, suggesting that the differentiation of some oligodendrocytes is delayed by PDGF. In addition, after neutralization of PDGF, the number of oligodendrocytes in the presence of dbcAMP was still higher than in the absence of dbcAMP. These results suggest that dbcAMP accelerates the differentiation and/or development of both astrocytes and oligodendrocytes.

N181

Translocation of protein kinase C to cytosol in astrocytes by apolipoprotein A-I

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Newly synthesized cholesterol is translocated to the cytosolic lipoprotein particle fraction from the endoplasmic reticulum in astrocytes treated with apolipoprotein (apo) A-I, followed by cholesterol release. We examined apoA-I-induced signal transduction for intracellular cholesterol trafficking. Astrocytes stimulated with apoA-I produced transiently diacylglyceride at 5 min. A phospholipase C inhibitor, U73122, suppressed apoA-I-mediated cholesterol release, cholesterol synthesis and cholesterol translocation to the cytosol. The diacylglyceride production was increased in the cytosolic lipoprotein particle fraction after apoA-I stimulation.. The phospholipase C and protein kinase C were translocated to the cytosolic lipoprotein fraction also. The protein kinase C binds to caveolin-1 through scaffolding domain of caveolin-1 on the cytosolic lipoprotein particle. It is suggested that these intracellular reactions in astrocytes by apoA-I stimulation are important for intracellular cholesterol trafficking.

N182

Prevention by pyruvate of cell death induced by hydrogen peroxide in cultured rat cortical neurons

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Hydrogen peroxide (H₂O₂) is believed to at least in part participate in mechanisms underlying delayed neuronal cell death after ischemia as well as a variety of neurodegenerative disorders such as Alzheimer,s and Parkinson,s diseases. In this paper, we have attempted to evaluate the mechanism for the neuronal cell death induced by H₂O₂ using primary cultured rat cortical neurons. Cerebral cortex was isolated from fetal rats at 18 days after gestation and cultured in DMEM/F12 in the absence of fetal calf serum (FCS) for the initial 3 days in vitro (DIV), followed by cultivation in DMEM in the absence of FCS for subsequent different periods with medium change every 3 days. Neurons cultured for 3 DIV were exposed to H₂O₂ at a concentration range of 10 μM to 1 mM, followed by determination of cell viability on MTT assay. Exposure to H₂O₂ led to a marked decrease in cell viability in a concentration-dependent manner at the concentrations used irrespective of the timing for determination between 6 and 24 h after addition. Pyruvate was effective in preventing the neuronal cell death at a concentration above 500 μM when added 30 min prior to or simultaneously with H₂O₂, but ineffective when added 1 h after the addition of H₂O₂. These results suggest that pyruvate could be neuroprotective through prevention of neuronal cell death by H₂O₂ in a particular situation.

N183

Evaluation of cellular maturation following sustained exposure to static magnetic fields in cultured rat hippocampal neurons and astrocytes

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Hippocampal neurons and astrocytes were cultured for different days in vitro (DIV) under sustained exposure to static magnetic fields at 100 mT generated by permanent ferrite magnets equipped at both sides of culture dishes. Sustained exposure to static magnetic field significantly decreased the expression of microtubule-associated protein 2 and neuronal nuclei in hippocampal neurons cultured for 1 to 9 DIV, without markedly affecting that of growth associated protein-43. Although sustained exposure led to a significant increase in the expression of glial fibrillary acidic protein (GFAP) in hippocampal neuronal preparations cultured for 6 to 9 DIV under sustained exposure to magnetism, sustained exposure did not markedly affect the expression of both GFAP and proliferating cell nuclear antigen in cultured astrocytes irrespective of cellular maturity. No significant alteration was seen with the cell survivability in hippocampal neurons and astrocytes cultured under sustained magnetism. These results suggest that cultured rat hippocampal neurons may be more sensitive to sustained exposure to static magnetic fields than cultured rat hippocampal astrocytes in terms of modulation of mechanisms associated with cellular maturation and development, but not with cellular survivability.

N184

Dopamine receptors in the striatal astrocytes

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To clarify possible localization of dopamine (DA) receptors in glial cells, especially astrocytes surrounding synapse, we examined the expression of DA receptors (D1-D5) in primary cultured astrocytes from rat striatum, using RT-PCR and Western blot analysis. Messenger RNAs of DA D1, D2, D4 and D5 receptors were expressed in the astrocytes from the striatum, whereas, the striatal astrocytes showed protein expression of DA D4, D5 receptors. To elucidate DA receptor-mediated signal transduction in the astrocytes, we examined changes in DA-induced phosphorylated cAMP responsive element binding protein (p-CREB) expression in the astrocytes after the pretreatment of DA receptor antagonists using Western blot analysis. Primary cultured astrocytes were treated with SCH23390 (D1, D5 antagonist), sulpiride (D2, D3 antagonist), clozapine (relative D4 antagonist) or L-745,870 (selective D4 antagonist) for 2 hr, and then treated with DA for 4 hr. The p-CREB expression, as an index of receptor-mediated signal transduction, was induced with the 4-hr DA treatment in the astrocytes. This induction of p-CREB in the striatal astrocytes was dramatically inhibited by pretreatment of L-745,870, D4 receptor antagonist. These results suggest that astrocytes express DA receptors as well as the post-synaptic neurons to respond to DA. Such DA response of astrocytes may play an important role in L-DOPA metabolism of damaged dopaminergic neural system.

N185

The expression patterns of mouse brain serine proteinase mRNA and protein in mouse development

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Serine proteases are known to be involved in neural development and various functions in the central nervous system. Mouse brain serine proteinase (mBSP) is expressed almost exclusively in the mouse brain and it has been characterized at the molecular and biochemical levels. In this study we analyzed the developmental changes and localization of mBSP mRNA and protein in the mouse brain, using reverse transcription PCR, western blotting, and immunohistochemistry. Expression of mBSP was strong in the white matter and the nerve tracts after postnatal day 30, especially in the cerebellum and the medulla oblongata. These results suggest that mBSP contributes to development and sustaining the functions in the mouse brain.

N186

Oligomer formation is essential for secretion of Pancortins

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We previously identified Pancortin as dominantly expressed molecules in the adult cerebral cortex; Pancortin comprise 4 members (Pancortin-1 to -4), sharing a common B part in the middle of their structure, having two pairs of alternative spliced 5, parts, A1 and A2, and 3, parts, C1 and C2. In the present study, we revealed that Pancortin-3 (A2-B-C1) was transiently but distinctly expressed in the developing thalamus using in situ hybridization with part-specific (A1, A2, C1 or C2-specific) probe, although no substantial expression of any Pancortins in the thalamus was observed in the adult. Interestingly, Pancortin-3 appeared to be very stable in vivo, since our Western blot analyses uncovered that Pancortin-3 exists much, even on the postnatal day 7 when no substantial amount of its mRNA is expressed. This observation prompted us to study on the molecular forms of Pancortin-3. Our Western blot analyses under non-reducing condition disclosed that Pancortin-3, and other Pancortins, formed a complex of large molecular mass. The following in vitro study showed that Pancortins were capable of forming oligomer with each other through their cysteine residues located in the common B part. When their disulfide bonds were removed by cysteine substitution, they were not secreted. Moreover, mutated Pancortin, that lost abilities to form oligomer, were rapidly sorted to the degrading machinery. Therefore, that process is strictly monitored, and it is possible that such oligomerization is important for the molecular stability after secretion.

N187

Distinct characteristics of astrocyte precursors according to the domain structure in the spinal cord

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Central nervous system (CNS) consists of many types of neurons and glial cells. The diversities of many cell types become more and more complicated in the brain of animals with higher brain function. The mechanism that generates diversity of neurons is well studied, which is thought to depend on graded inductive and repressive signals derived from local organizing centers. Analysis of neuronal lineage alone is insufficient to understand the regulation of CNS functions, because astrocytes consist of a major portion of the CNS and play important roles in the CNS functions. However, astrocyte lineage have not been studied well due to a lack of specific markers that label its lineage throughout their development from early to mature stage. To overcome this problem, it is necessary to establish markers expressed in the astrocyte-lineage. We reported several antibodies that stained astrocyte lineages in this meeting last year. Some antibodies of them labeled radial glial fibers in dorsal spinal cord at mouse embryonic day 12.5, which also expressed well-known radial glial cells maker, RC2. These expression patterns of dorsal domain were complementary with GLAST which are expressed in ventral domain at this stage. These results indicate that astrocytes are generated from multiple precursors that have distinct characteristics.

N188

Enhanced protein staining and immunoreactivity of Purα induced by PUR element in parallel with its DNA binding activity

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We have reported by the gel shift assay that calmodulin (CaM) stimulates GST-Purα binding to a single stranded cyclic AMP response element (ssCRE) containing (GGN) 2 sequence, PUR element. During the study on the interaction between Purα and CaM in the presence of ssCRE by using a non-denatured gel, we found that intensity of GST-Purα protein staining by silver was increased by the preincubation with ssCRE. CaM further enhanced it. Immunoblot analysis of GST-Purα blotted to PVDF filter from the non-denatured gel also revealed increase of Purα immunoreactivity, which was enhanced by the preincubation with ssCRE in a dose-dependent and a sequence-specific manners. CaM further enhanced GST-Purα immunoreactivity only in the presence of ssCRE. When GST-Purα was applied on SDS-PAGE, enhanced immunoreactivity was not observed.

The enhanced immunoreactivity on GST-Purα and endogenous Purα prepared from mouse brain was also observed with other ssDNA containing PUR element such as myelin basic protein (MB1A) and nicotinic ACh receptor (β 4-E1), which are shown to form Purα-DNA complex by gel shift assay. We also found that a sequence of AA. 50-215, DNA-binding domain, was required for the enhanced immunoreactivity. CREB preincubated with double stranded CRE did not show the enhanced immunoreactivity.

From these results, we concluded that increase of the Purα immunoreactivity by ssCRE and/or CaM is based on a unique structure of Purα which probably resides on the DNA-binding domain.

N189

Glial cell responses after peripheral nerve injury

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Injury to peripheral nerve axons results in a series of molecular and structural modifications in the affected nerve cell bodies, the so-called axon reaction. This reaction includes several components: 1) down regulation of functions associated with synaptic transmission, 2) support to regrow the injured axon, 3) adaptations to survive and recover from the cellular stress imposed by the lesion. The non-neural responses to axon injury most likely decide whether axotomized neurons can survive to regrow axon or degenerate to die. Peripheral axotomy invokes a rapid and extensive microglial response. Within the first day after this injury, microglial cells proliferate in the vicinity of the axotomized motor neuron perikarya and in central termination areas of peripherally axotomized dorsal root ganglion cells. A reaction peaks about 1 to 2 weeks postinjury. Concomitantly, astrocytes undergo hypertrophy, as evidenced by the marked increase in immunoreactivity for the major astroglial cell intermediate filament protein, glial fibrillary acidic protein, GFAP. The microglial cells responding to peripheral nerve injury secrete several cytokines and complement factors to lead to death or survival of the axotomized neurons. Since the axotomy in mice induced delayed neuronal cell death 6~8 weeks after injury, we study microglial and astroglial responses in such late stages after injury. In addition, we observed the responses of oligodendroglial cells, because these cells are likely affected by microglial responses.

N190

A high concentration of K⁺ enhances LPS-induced nitric oxide production in cultured astrocytes

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Astrocytes play various important roles in CNS. Excess K⁺ ion excreted by overly active neurons into the extracellular space is shunted to an area of lesser K⁺ concentration by astrocytes. The extracellular K⁺ elevation within damage areas has been observed under the CNS pathological conditions, such as epileptic seizures, ischemia, and hypoxia. Therefore, we hypothesize that high-K⁺ may be a signal involving in astrocyte activation. On the other hand, it is well known that activated astrocytes release nitric oxide (NO), although endogenous stimulants under pathological and physiological conditions have not been well established. In the present study, we examined whether high-K⁺ regulates the NO production in cultured astrocytes from rat embryo, which is experimentally stimulated by lipopolysaccharide (LPS). NO production was evaluated by the fluorometric assay of nitrite accumulation in the medium. NO production induced by 1 ng/ml LPS for 48 hr increased about 2 fold by the addition of 40 mM KCl compared with that in normal medium (5.4 mM K⁺). The increase in the NO production was dependent on added KCl concentration (to 40 mM). Addition of 40 mM NaCl or Na-gluconate did not show any effect on LPS-induced NO production. When 40 mM K-gluconate was added, LPS-induced NO production increased; whereas the extent of the enhancement was about a half of that by KCl. These results suggest that the increase in extracellular concentrations of K⁺ up-regulates the NO production in astrocytes and Cl⁻ also plays an important role for the regulation. Such potentiation of NO production from astrocytes by a change in ionic environment may aggravate neuronal damage in some CNS diseases.

N191

Roles of a tetraspanin protein CD9 in the nervous system

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CD9 is a member of tetraspanin family, which has some roles in cell signaling, adhesion, cell growth and motility by forming complexes with a variety of membrane proteins. In the nervous system, CD9 is enriched in myelin, especially along the outermost membrane of myelin as well as in the paranodal region both in the CNS and the PNS. CD9-deficient mouse showed the disruption of the paranodal junction both in the CNS and the PNS in addition to the abnormally thick myelin predominantly observed in the PNS. The function and partners of CD9 in the myelin are still poorly characterized. In the present study, to identify the molecular mechanism of such abnormalities in the mutant, we examined CD9 complex in the nervous system. Immunoprecipitation with anti-CD9 antibody resulted in coprecipitation of CD81, which is the most closest member of CD9 in the same family, from CNS myelin and sciatic nerve. In addition to CD81, several myelin proteins including myelin oligoglycoprotein (MOG), which are localized in non-compact myelin, also coprecipitated with CD9. Immunohistochemistry of sciatic nerves showed that CD9 was more enriched in the membrane between each paranodal loop than the paranodal junction. These results suggested that CD9 forms complex with several myelin proteins and may play a role on targeting these proteins to the specific regions in the myelin.

N192

New insights into myelin abnormality in brain aging.

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Recent studies demonstrate that during aging, the cortical gray matter remains preserved, while a significant loss of the white matter occurs, particularly due to myelin break down in the white matter of normal and healthy adults. It is important in obtaining insights into the mechanism underlying myelin repair in the aging brain.

In the present study, we investigate an age-related alteration of the myelin structures and the molecular characteristics of myelin sheaths. We have found severe alterations of myelinated fibers observed in 31-month-old mice.

The elucidation of the characteristics composition of myelin will contribute to the understanding of myelin destruction in old age. Therefore, we analyzed myelin sheaths related proteins and lipids from young and old mouse brains.

The major glycolipids were greatly enriched in myelin from both 30-month-old mice, but the component distribution of these acidic glycolipids was changed.

The major protein constituents were expressed in both of mice. The expression of myelin basic proteins (MBPs) was different from 31-month-old and 5-month-old mice. Only of the 21.5kDa isoforms of MBP was not observed in the aged mice. Our findings suggest that the concept of age-related myelin loss may be due to the 21.5kDa MBP, which is expressed during myelinogenesis and myelin repair, specifically correlating with remyelination.

N193

The environmental chemicals bisphenol A exerts thyroid hormone like effects on mouse oligodendrocyte precursor cell

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Thyroid hormone plays a critical role in normal development of the mammalian central nervous system. In developing brain, oligodendrocyte precursor cells differentiate into premyelinating oligodendrocyte that myelinated axons. It is known that OPCs acquire sensitivity to the proliferation-stopping and differentiation-promoting action of thyroid hormone with maturation. On the other hand, bisphenol A is known to mimic the action of estrogenic compound. Little is known about these environmental chemicals action on the development of oligodendrocyte, and the differentiation of OPCs. The present work reports the effects of BPA on the differentiation of OPCs into myelinating oligodendrocytes. Treatment of OPCs with T3 had significant effect on the differentiation of OPCs that became galactocerebroside expressing mature oligodendrocytes. The number of OPCs were inhibited for differentiation, when the cells were administrated with BPA *in vitro* and the expression of thyroid hormone receptors also decreased. No significant effect of BPA on the expression of estrogen receptors of OPCs differentiation was detected. These findings suggest that BPA has a potential endocrine disrupter effect on the differentiation of OPCs thyroid hormone regulate OPCs maturation.

N194

Expression of serine protease Protease M/neurosin/zyme in demyelination

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Few proteases have been identified to be oligodendrocyte-specific, though there are phenomena in which proteases may be committed. Recently, we have cloned serine protease, Protease M/Neurosin/Zyme. Protease M/neurosin/zyme is expressed by mature oligodendrocyte and may serve a variety of functions in the central nervous system. Therefore, protease M/neurosin/zyme may be important to the processes occurring after the maturation of oligodendrocytes such as myelination or turn over of the protein in the myelin. In the present study, we have examined the expression of protease M/neurosin/zyme in a model of demyelination/ remyelination in which these events could be carefully controlled using the oligodendrocyte-specific toxin, cuprizone (bis-cyclohexanone oxaldihydrazone). This copper-chelating agent produces demyelination in the corpus callosum and superior cerebellar peduncles, and when treatment is stopped, rapid remyelination occurs. Seven day treatment with cuprizone increased the amount of this protease in the mouse brain. Immunohistochemical analysis also showed that protease M/neurosin/zyme was induced in the corpus callosum during demyelination. In cultured oligodendroglioma cells, both oxidative- and ER-stress induced the expression of Protease M/Neurosin/Zyme. These observations indicate that this protease has some roles in the turn over of the proteins in the myelin during demyelination in some neurodegenerative diseases.

N195

The role of myelin sulfatide on the axonal organization may be different in the CNS and PNS axons.

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The cerebroside sulfotransferase (CST) -deficient mice lack sulfatide, which is a major glycolipid in myelin. The CST-deficient mice are born healthy and develop normally, but begin to display progressive neurological deficits by 6 weeks of age. The mutant CNS shows the disruption of paranodal axo-glial junctions, whereas compact myelin is well preserved. We previously reported the abnormal localization of axonal ion channels in the mutant. The replacement of Na⁺ channel subtypes from Nav1.6 to Nav1.2 become prominent with age, and these clusters were progressively disappeared from the CNS nodal regions. In the present study, we examined the functional role of sulfatide on PNS myelin using sciatic nerves from the CST-deficient mice. As results, glial paranodal protein, neurofascin155 and ezrin-radixin-moesin proteins in Schwann cell microvilli were mislocated in the mutant. The disappearance of Caspr clusters and replacement of K⁺ channels in the presumptive paranode suggested that paranodal junction was disrupted in the mutant sciatic nerves as well. Unlike CNS axons, however, no remarkable changes of Na⁺ channel clusters in their shapes or number were observed, and Na⁺ channel subtype was not unusually replaced in the sciatic nerves. The spinal roots, which were believed to be the part of PNS, showed the similar changes observed in the CNS, suggesting that Schwann cells in spinal roots and sciatic nerves may act differently to the axonal protein organization. These results indicate that myelin sulfatide is important for the axo-glial junctional formation as well as proper localization and subtype determination of axonal channels. However, such importance may be different between the CNS and PNS axons.

N196

The complete structures of two novel multi-sulfated oligosaccharides containing HNK-1 carbohydrate epitope (s) in bovine P0 glycoprotein

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Sulfated oligosaccharides occur in glycoproteins, such as P0 and PASII/PMP22, in myelin in the PNS. These glycoproteins are involved in the interaction of cell membranes and play important roles in the formation and maintenance of myelin sheaths. These functions are due in part to the oligosaccharides in their molecules. Recently, the structures of the oligosaccharides of bovine peripheral myelin P0 were reported, and some of these carry the HNK-1 epitope (SO₄-3GlcAβ1-3Galβ1-4GlcNAc). We isolated two extremely acidic glycopeptides, MS1p and MS2p, from bovine PNS myelin and determined their complete structures. Amino acid sequence analyses revealed that they were from P0 protein. Structural analyses on the oligosaccharide part of MS1p and MS2p demonstrated that MS1 and MS2 contained three moles of sulfate and that MS1 and MS2 contained one and two moles of the HNK-1 carbohydrate epitope, respectively. The structures of the oligosaccharides are: MS1: SO₄-3GlcAβ1-3Galβ1-4GlcNAcβ1-2Manα1-6 (SO₄-3GlcAβ1-3Galβ1-4[SO₄-6]GlcNAcβ1-2Manα1-3) Manβ1-4GlcNAcβ1-4 (Fucα1-6) GlcNAc. MS2: Manα1-2Manα1-6 (SO₄-3GlcAβ1-3[SO₄-6]Galβ1-4[SO₄-6]GlcNAcβ1-2Manα1-3) Manβ1-4GlcNAcβ1-4 (Fucα1-6) GlcNAc. It is interesting to note that MS2 contained a 6-O-sulfated galactose. This implies that Gal-6-O-sulfotransferase must be in peripheral nervous tissues.

N197

The proteolipid protein promoter is activated in tangentially migrating GABAergic neurons and oligodendrocytes during development of the cerebral cortex

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Plp gene encodes two proteins, proteolipid protein (PLP) and its smaller isoform DM-20, major membrane proteins of myelin in the CNS. Plp gene expression is detected during early embryonic development in the mouse, although it is much higher in mature oligodendrocytes. In order to characterize the embryonic plp-expressing cells, transgenic mice expressing EGFP driven by the plp promoter have been examined. In this study, we focused on telencephalic development. In the embryonic telencephalon, PLP-EGFP cells initially appeared only in restricted regions of ventral telencephalon, as well as in the lateral ganglionic eminence, the medial ganglionic eminence (MGE) and the anterior entopeduncular area at E11-13, where neural precursor s are generated. However, PLP-EGFP cells failed to express nestin and RC2, which are markers for neural stem cells or radial glia. Most, but not all, PLP-EGFP cells in the ventricular zone of the MGE were labeled with Olig2, which has been reported to be involved in the differentiation of motor neurons and oligodendrocytes in the spinal cord. By E16, PLP-EGFP expression expanded into the cortex, suggesting that PLP-EGFP may migrate from ventral to dorsal telencephalon. At E16, PLP-EGFP was not expressed only in oligodendroglial progenitor cells but also in progenitor cells of GABAergic interneurons, which are defined as the expression of GABA, TuJ1 and MAP2. At later stages, PLP-EGFP was not detected in neuronal lineage. These findings suggest that the earliest plp may be expressed by progenitor cells, which can give rise to GABAergic interneurons and/or oligodendrocytes in the ventral telencephalon.

N198

Characterization of aluminum citrate transport at the blood-brain barrier

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[Purpose] Aluminum (Al) is shown to be involved in etiology of neurodegenerative disorders because it causes neuronal cell death resulting from inducing oxidative stress. In the brain, a predominant form of Al is Al citrate, and its accumulation is regulated by blood-brain barrier (BBB), but a very little information is available. We previously reported that Al citrate was incorporated into RBEC1, which is a model cell line originated from rat brain capillary endothelial cells for BBB, via a specific transport system, except for proton-coupled monocarboxylate transporters. The aim of this kinetic study was to identify what kind of transporter handled Al citrate transport at the BBB.

[Materials & Methods] In uptake study, RBEC1 was incubated with Al citrate in an appropriate HEPES-HBSS in the presence or absence of inhibitors for the indicated times and temperature, and the reaction was terminated by adding excess volume of ice-cold buffer. The cellular Al concentration was determined using ICP-MS.

[Results & Discussion] The uptake of Al citrate by RBEC1 in the presence of an inwardly directed sodium-gradient was greater than that in the absence of it, demonstrating requirement of sodium-gradient as a driving force partially. The sodium-dependent uptake of Al citrate was concentration dependent, the kinetic analysis showing involvement of a single component. This uptake was inhibited by some organic anions, and was stimulated by their preload of the cells. On the other hand, the substrates for sodium-dependent glutamate transporter had no effect on the Al citrate uptake. These findings indicated that Al citrate was taken up into RBEC1 by a sodium-dependent transporter common to some organic anions, except for the substrates of glutamate transporter.

N199

Peripheral injection of lipopolysaccharide has effect on the expression of inflammatory cytokine at locus coeruleus

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Recently the presence of the crosstalks among neuro-, immune- and endocrine systems involved in maintaining the homeostasis has been established. According to the crosstalks, nervous system can regulate immune response and immune system exerts an effect upon nervous system vice versa. Cytokines constitute a significant portion of the neuro- and immunomodulatory networks. Lipopolysaccharide (LPS), an endotoxin released from the outer membranes of gram-negative bacteria, acts as a nonspecific activator of the immune system by stimulating the secretion of cytokines from macrophages. We previously reported the mechanism that peripheral injection of LPS increased norepinephrine (NE) turnover at locus coeruleus (LC). We then examined the alteration of transcription factor and inflammatory cytokine expression levels at LC after LPS injection.

The mRNA expression levels of genes encoding *IκBα*, *IL-1β*, *TNF-α* within the LC of C3H/HeN mice (male, 8W) were measured. The mRNA expression level of *IκBα* increased within 1 hr and reached a maximum level at 2 hr after the LPS injection. The mRNA expression levels of *IL-1β* and *TNF-α* increased within 2 hr, and reached a maximum level at 4 hr after the LPS injection. Pretreatment of corticotropin releasing factor (CRF) receptor type 1 antagonist CP-154 had no effects on the increase in mRNA expression by LPS treatment. Collectively, the quick up-regulation of inflammatory cytokine mRNA expression after peripheral LPS injection may be caused not via humoral factors transmitted through blood-brain barrier but by the activation of neural circuit. The research is currently in progress in order to elucidate the relationship between the increase of NE turnover and inflammatory cytokine upregulation at the LC.

N200

Effect of peripheral lipopolysaccharide treatment on murine olfactory bulb

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A large number of studies have demonstrated that the central nervous system (CNS) and the immune system are functionally interconnected. This relationship is clearly observed in phenomena like sickness behavior induced by an immune challenge. The central structures that have been implicated in immune-to-brain communication are the nucleus of the solitary tract, parabrachial nucleus, central nucleus of amygdala, paraventricular hypothalamic nucleus, and the insular and prefrontal cortices. But, less attention has been paid to the neuroimmune interactions on olfactory system.

Recently we found that the endotoxemia in mice caused by an intraperitoneal (i.p.) injection of lipopolysaccharide (LPS) enhanced the contents of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid in the anterior olfactory nucleus. Therefore, to address the physiological derangements in olfactory system caused by peripheral LPS treatment, we investigated the effect of peripheral LPS treatment on mRNA expression levels in the olfactory bulb (OB) of the genes encoding the substances involved in inflammatory perturbation. Following 50 μg/mice i.p. injection of LPS to C3H/HeN male mice, slices of OB was removed at multiple time points and used as samples for analysis. LPS treatment enhanced the mRNA expression levels in OB of the genes encoding *TNFα*, *IκBα*, *NF-κB*, *iNOS* and *caspase-8*. Collectively, a series of events leading to apoptosis in OB might be triggered by an immune challenge following peripheral LPS treatment.

N201

PEDF stimulates expression of inflammatory-related genes in glial cells

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Pigment epithelium-derived factor (PEDF) is a 50-kDa glycoprotein and a member of the serine protease inhibitor (SERPIN) gene family. We have shown previously that PEDF acts as a survival factor for cerebellar granule cell neurons in culture, as well as protecting them against glutamate toxicity or induced apoptosis. Some of the effects of PEDF reflect specific changes in gene expression, mediated via activation of the transcription factor NF- κ B in neurons. However, little is known about the effects of PEDF on glial cells. To investigate whether PEDF also modulates gene expression in glial cells, we analyzed transcription factor-DNA binding activity using EMSA and differential gene expression using RT-PCR. RT-PCR analysis revealed that rhPEDF induces inflammatory-related genes (iNOS, IL-1 β , IL-6, TNF α , MIP1 α etc.) in both astrocytes and microglia. Time- and dose-dependent increase of NF- κ B-DNA binding activity and the decreased levels of I κ B proteins were observed in PEDF treated astrocytes. Moreover immunocytochemically analysis revealed that the nuclear translocation of RelA was observed in both PEDF treated astrocytes and microglia. PEDF-induced inflammatory-related genes were blocked by the addition of MG-132, which blocks proteasome degradation of I κ B. Time- and dose-dependent increase of AP-1-DNA binding activity was also observed in PEDF treated astrocytes. AP-1 related genes (fra-1, fra-2, junB, c-jun and junD) were up-regulated by PEDF in both astrocytes and microglia. Taken together, these results demonstrate that PEDF is a multipotent factor, capable of affecting not only neurons but also glial cells such as astrocytes and microglia, suggesting that it may act as a neuro-immune modulator in the central nervous system.

N202

Inbred mouse strain difference affects in Interleukin-1 response in the brain.

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Interleukin (IL) -1 regulates stress response through the elevation of steroid levels, the alternation of catecholine amine metabolisms, and the induction of prostaglandins. Therefore we evaluated the genetic influence of the IL-1 responsiveness in the brain. Several inbred mice (C3H/He, DBA/2, C57BL/6, BALB/c) were treated with recombinant Interleukin-1 alpha (0.1mg/kg, s.c.) systemically. Catecholineamines and their metabolites were measured one hour after injection. The expression of cyclooxygenase-2 (COX-2) was measured in the hypothalamus, hippocampus and frontal cortex. In analysis of COX-2 expression on postnatal day 2, C3H/He strain exhibited no response to IL-1, while the other mice strains were induced of COX-2 expression. Regional induction of COX-2 also differed among the mouse strains. IL-1 induced COX-2 expression in all the brain regions of BALB/c mice whereas not in the frontal cortex of DBA/2 and C57BL/6. This suggests that genetic background influence the sensitivity for IL-1. Abnormal products of Cytokine are implicated in various psychiatric or brain diseases. As one of pathophysiology of schizophrenia, activation of inflammatory response system have been suggested by several recent studies. In schizophrenic peripheral blood or cerebrospinal fluid, the levels of proinflammatory Cytokines, such as interleukin (IL) -1, -6, and tumor necrosis factor (TNF) alpha have been influenced by pathology. In newborn mice, C3H/He was not induced COX-2. This agree with the fact ; In clinical therapy, COX-2 inhibitors including celecoxib are effective, though individual differences exist.

N203

Neuroimmunology of neurosteroids and endocrine disruptors through common Gq/11 coupled receptor

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We identified various non-genomic molecular targets for neurosteroids. Here we report that endocrine disruptors (EDs) share the membrane receptor target with neurosteroids. In previous studies we found neurosteroids share G_i coupled membrane receptor with sigma receptor agonists (Neurosci Res. 41, 33-40, 2001). This mechanism was also observed in the bioanalytical *in vivo* nociception tests (JPET, 299, 213-219, 2001). In the latter study we have found another membrane target for neurosteroid, which mediates histamine release from mast. Our goal is to clone novel neurosteroid receptors and to clarify mechanisms for transmitter release regulation. So we decided to characterize the membrane neurosteroid GPCR in the mast cell line in order to examine its validity for the source of cDNA library. Dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and pregnenolone (PREG), representative neurosteroids, caused rapid degranulation of mast cell line and the DHEAS-induced degranulation was blocked by progesterone, an antagonistic neurosteroid. The degranulation was mediated through G_{q/11}, phospholipase C and intracellular calcium mobilization. In a course of study, we found that EDs share the common targets with neurosteroids. Many representative EDs including bisphenol A showed antagonistic actions for the DHEAS-induced degranulation. However, atrazine, a pesticide ED caused degranulation. As the degranulation by neurosteroids and atrazine was all inhibited by BSA-conjugated PROG, the degranulation seem to be mediated through a membrane receptor. Recently the role of brain mast cells has been attracting the concerns of neurochemists. Together with the stimulation of sensory neurons, neuroimmunological roles of neurosteroids and EDs would be more important targets.

N204

Peripheral myeline protein P0 is one of the autoantigens for human inflammatory polyneuropathies

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Autoantibodies to neural components have been implicated in the pathogenesis of inflammatory polyneuropathies. A variety of glycolipids have already been identified as autoantigens, however, target antigens are still unknown in most of the demyelinating polyneuropathy cases. In order to find the role of myeline proteins as target molecules for demyelination, we examined sera from 50 patients with acute and chronic demyelinating polyneuropathies as well as from 10 normal (NC) and 10 disease control (DC) sera using western blot analysis. As results, sera from 8 patients contained IgG which reacted with 30 KDa protein in rat sciatic nerve but not in rat brain homogenates. One serum from the patient with motor neuron disease also reacted with the same protein, however, the antibody titer was significantly low. None of NC sera reacted with this protein. Since this 30 KDa protein was concentrated in membrane fraction of PNS and specific monoclonal antibody against P0 reacted with the same protein, these patients, sera contained IgG antibodies against P0 protein in myelin. Glycoprotein P0 is a main myelin protein only in the PNS. The main function of this glycoprotein is to adhere each myelin lamella to form compact myelin. The loss of P0 cause severe hypomyelination as well as demyelination both in mice and human, suggesting that these autoantibodies to P0 found in the patients may cause demyelination. Several recent reports also showed that the sera from polyneuropathy patients reacted with P0. Taken together, IgG autoantibodies to P0 may play a role on the pathogenesis in the subgroup of inflammatory demyelinating polyneuropathies.

N205

Alignment of interneurons in the developing cerebral cortex

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In the developing cerebral cortex, projection neurons and interneurons arise in distinct places and migrate into the pallium in different ways. While the projection neurons are born in the pallial ventricular zone and migrate radially toward the pial surface, most interneurons are known to derive from the ganglionic eminences and migrate tangentially into the pallium in mice. To clarify the mechanisms of the cortical histogenesis, we have labeled the interneurons with bromodeoxyuridine at each developmental stage, and analyzed their ultimate locations in this study. Here, we show that both the projection neurons and the interneurons that are born at the same embryonic day, tend to locate in a common layer of the cerebral cortex. The relationship between the migration of the projection neurons and the interneurons in the cortical histogenesis will be discussed.

N206

Cell adhesion properties of the migrating cortical neurons

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The mammalian cerebral cortex is organized into six-layered neurons. These neurons are born in the ventricular zone (VZ) and migrate through the intermediate zone (IMZ). Finally, they stop migration beneath the marginal zone (MZ), where they form the cortical plate (CP). The migrating neurons in the cerebral cortex undertake two main types of radial migration: locomotion and somal translocation. Locomotion is the cell movement along a radial glial fiber and the length of the leading process of the migrating cell is maintained. In contrast, somal translocation is the cell movement that is independent of glial fibers, and the cell nucleus moves toward the MZ by shortening the leading process. Recently, we found that a novel type of migration, multipolar migration, which was observed for more than 80% of the radially migrating neurons in the IMZ. After the migrating neurons invade into the CP, these neurons change their migration mode into locomotion. To explore the cell biological properties of the migrating neurons in the IMZ, we have investigated the cell behavior of those cells by time-lapse microscopy in this study, and found that the multipolar migrating neurons had a tendency to adhere to each other. Also, the reaggregation culture of the dissociated IMZ cells showed that these cells tended to form larger aggregates than the dissociated VZ or CP cells. These results suggest that the multipolar migrating neurons in the IMZ have characteristic cell adhesion properties among each other.

N207

A new strategy for brain cell fate mapping by in utero DNA electroporation

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Cell migration is an important determinant for brain structure, and was classically examined in the explant culture of brain slices; however, it was difficult to trace them through the adult stages. Any cell labeling materials, such as DiI, are quickly dilute during cell proliferation. Retroviral infection cannot determine the position of the firstly infected cells. Thus, we established a new strategy for in utero fate mapping using DNA electroporation combined with Cre/loxP reporter mouse system. The reporter mouse embryos were electroporated in utero with a plasmid containing Cre recombinase gene, triggering a permanent expression of EGFP in the Cre-expressing cells. By positioning of electrodes, Cre plasmid was able to introduce in a dorsal- or ventral-specific manner. To put a label on the farther regionally restricted cells, we examined region specific promoter activity for controlling Cre expression. Enhancer/promoter regions of *Dlx5/6*, *Tbr2* and *Pax6* were connected to *lacZ* gene, and introduced into embryonic brain by in utero DNA electroporation. The *lacZ* expression derived from *Dlx5/6* enhancer was comparable to the endogenous *Dlx5/6* expression, suggesting *Dlx5/6* enhancer cloned in the plasmid kept its region specific activity, even though plasmid DNA was not incorporated into the chromosome.

N208 (MS8-1)

Astrocyte-derived factors instruct differentiation of mouse and primate embryonic stem cells into neurons

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We have managed to coax pluripotent embryonic stem (ES) cells into differentiating into neurons in vitro. This should prove immensely valuable in studying neurogenesis and for generating donor cells for neuronal transplantation. Mouse and primate ES cells differentiated into neurons following stimulation by astrocyte-derived soluble factors. Cultured in astrocyte-conditioned medium (ACM) under free-floating conditions, within 4 days, colonies of undifferentiated ES cells gave rise to floating spheres with a concentric stratiform structure. The spheres had a periphery of neural stem cells, a core of dividing ES cells and an intermediate layer of cells in a transitional stage of differentiation. The internal structure of the spheres differed from that of embryoid bodies, as confirmed by RT-PCR analyses. We termed them Neural Stem Spheres. Subsequent culture of the Neural Stem Spheres on an adhesive substrate in ACM promoted neurogenesis. The attached spheres gave rise to circular clusters of cells containing neurons at the periphery. Many neurons with neurites, including dopaminergic neurons, migrated from the clusters within 5 days. Gene expression analyses and electrophysiology confirmed the neuronal properties of the cells. In contrast, neither astrocytes nor oligodendrocytes were formed. The procedure developed for mouse ES cells could be applied to monkey ES cells. This is the first report on effects of astrocyte-derived humoral factors instructing ES cells to differentiate into neural stem cells. This neurogenesis pathway provides a new insight into mechanisms of specification of cell fates in early development and also provides a new simple procedure for fast and efficient generation of vast numbers of neural stem cells and neurons.

N209 (MS8-2)

NRSF/REST and DNA methylation regulate cell type specific expression of BRINP1 (BMP-2 and Retinoic acid Inducible Neural-specific Protein 1)

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We have recently identified a novel neural-specific family of proteins, BRINPs. Chromosomal location of BRINP1 (also known as DBCCR1: Deleted in Bladder Cancer Chromosome Region candidate 1) has suggested its role as a tumor suppressor. On the other hand, we have shown that BRINP1 is highly expressed in various regions of mammalian nervous system, although its expression is observed also in some non-neural tissues and cell types at low levels. But molecular basis for the cell-type specific expression of BRINP1 gene has not been clarified. In the present study, we investigated the transcriptional mechanisms regulating the expression of BRINP1. In the first series of experiments, it was revealed that the CpG island surrounding BRINP1 exon 1 is hypermethylated in a non-neural cell line, NIH 3T3. Furthermore, treatment of NIH 3T3 cells with a demethylating agent up-regulated BRINP1 gene. It is, therefore, suggested that hypermethylation of the CpG island suppress BRINP1 expression in this cell line. However, methylation levels of the BRINP1 CpG island in the normal non-neural tissues were as low as those of neural tissues expressing BRINP1 at higher levels. We, then, analyzed the promoter activity of 7kb region surrounding BRINP1 Exon1 in different cell contexts. Consequently, we found a non-neural-specific silencing region containing NRSE/RE-1 (neuron-restrictive silencing element/repressor element 1), whose mutation restored the BRINP1 promoter activity in non-neuronal cells. Furthermore, NRSF/REST bound to the BRINP1 NRSE/RE-1. In conclusion, it is suggested that hypermethylation of the CpG island suppress the BRINP1 expression in NIH 3T3 cells and tumor cells, while NRSE/RE-1 plays a major role in the neuron-selective expression.

N210 (MS8-3)

Histological and biochemical study of Sox21 transcriptional factor

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The paraneoplastic neurologic disorders (PND,s) are neurologic diseases occurring in the setting of non-neuronal tumors that express neuronal antigens. The expression of such onconeural antigens in tumor cells is thought to induce an immune response which suppresses tumor growth, but causes neuronal degeneration. We performed expression screening by using the antiserum from PND patient with small cell lung cancer and identified a target antigen, Sox21, an HMG box transcriptional factor belonging to the Sox B1 family. To determine Sox21 expression in mouse CNS, we performed in situ hybridization and immunohistochemical analysis using the PND serum and polyclonal antibody produced against Sox21 fusion protein and revealed that the expression is restricted to the subventricular zone of E14 mouse embryo. To address the function of Sox21 in the nervous system, we have constructed recombinant retroviruses of full length and mutant Sox21. Overexpression of Sox21 in PC12 cells inhibited the induction of neurite outgrowth by NGF. These results suggest that Sox21 may play an important role in neural stem/progenitor cells to prevent the differentiation. Most Sox proteins appear to work as context-dependent transcriptional regulators that require other proteins for activity. To identify Sox21 binding partners, we have constructed Sox21 fusion protein-affinity column and purified at least 6 proteins from E14 mouse brain extract. Mass spectrometry analysis revealed that one of them is a transcriptional factor YB-1. Furthermore, we demonstrated that Sox21 specifically interacts with YB-1 through the HMG domain in vitro.

N211 (MS8-5)

Lineage analysis on forebrain oligodendrocyte

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We, together with others, had isolated a novel basic helix-loop-helix transcription factors, Olig family. Olig family consists of three family members, Olig1, Olig2 and Olig3. In the embryonic spinal cord, Olig1 and Olig2 are expressed restricted ventral domain and implicated in motoneuron and oligodendrocyte development. By gain-of-function and loss-of-function analysis, we demonstrated that Olig2 is essential for both motoneuron and oligodendrocyte development. These results show that motoneuron and oligodendrocyte are sequentially produced from neural stem cell located at ventral ventricular zone of spinal cord. Although extensive analysis was performed on spinal cord phenotype of Olig2 knockout mice, little is known about forebrain phenotype of Olig2 KO mice. Since Olig2 is expressed in ventricular zone of ganglionic eminence and ventral thalamus, it is expected that Olig2 also regulates differentiation of neural stem cell at these region. Therefore, we analyzed forebrain phenotype of Olig2 KO mice using various neuron and oligodendrocyte markers. We would like to discuss which neuronal cell type is produced in couple with forebrain oligodendrocytes.

N212

Characterization of cellular response to cortical cryo-injury

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We analyzed cellular response including cell proliferation and differentiation at a cryo-injured lesion of the cerebral cortex of either BALB/c (1 or 4 weeks after birth) or ICR (8 weeks after birth) mice. Cryo-injury was performed by applying liquid N₂-chilled lead probe onto the cranium for 30 second. Two days after injury, BrdU was injected intraperitoneally and on the next day (three days after injury) primary cell culture was performed from the injured cortex and from contralateral intact cortex (as a control). All the culture flasks, dishes and plates were coated by polyethyleneimine. At five to six days in culture, some cells from the injured cortex, but not from the intact cortex, formed clusters that resembled to neurosphere. These cell clusters were then fixed and labeled immunocytochemically with antibodies against BrdU and cell markers such as Nestin, GFAP, Iba-1 and NeuN. We found a number of BrdU-positive cells in the cell clusters and some of them were Nestin, GFAP or Iba-1-positive. These findings suggest that some cells in the clusters, if not all, had characters of neural stem cells/precursor cells, astrocytes or microglia/ macrophage. It should be noted that there was no NeuN-positive cells in the clusters. Expression differences of cell marker could not be observed between mouse strains or age. When we started primary culture at earlier periods (the first or second days of injury), cell clusters were hardly observed, suggesting that it took several days after injury to induce precursor cell characteristics.

N213

Transcriptional regulation of the tyrosine hydroxylase gene by Ras-MEK cellular signaling

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Neurotrophins are essential for the development and survival of the catecholaminergic neurons. Both Ras-MEK and PI3K-Akt pathways are suggested to be required for neurite outgrowth and neuronal survival by neurotrophins. The critical pathway for induction of the tyrosine hydroxylase (TH) gene is, however, still unclear. Here we examined the intracellular signals required for the activation of the TH gene expression in nerve growth factor (NGF)-stimulated PC12D cells. Induction of TH mRNA by addition of NGF was abolished by pretreatment with U0126, an inhibitor for MEK1/2, but not with SB203580, wortmannin, and H-89, inhibitors for p38 MAPK, PI3K, and PKA, respectively. U0126 inhibited the TH promoter activity of a reporter construct at the same concentration as it acted on ERK1/2 phosphorylation in the NGF-stimulated cells. In contrast, wortmannin had no inhibitory effect on the TH promoter activation, whereas it completely blocked phosphorylation of Akt. Transient transfection of wild type Ras and MEK1 increased the TH promoter activity. A dominant negative form of Ras, but not that of Akt, suppressed the NGF-induced TH promoter activation. Reporter assay demonstrated that the Ras-MEK-dependent TH gene transcription was mainly mediated by both the AP-1-binding motif and the cAMP-responsive element in the promoter region of the TH gene. Phosphorylation of CREB and ATF-2 and induction of AP-1 transcription factors were observed prior to the induction of TH mRNA by NGF. Both phenomena were completely blocked by pretreatment of U0126. These data suggest that the transcriptional activation by the Ras-MEK pathway is required for the expression of the TH gene induced by neurotrophins.

N214

Electric homeostasis and the cell fate decision in stem cells

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Cells receive various types of environmental cues for differentiation and patterning continuously during development. Up to now many reagents were isolated as such differentiation cues, for example, cell-cell interactions, growth factors. These cues activate signaling pathways within cells, and cause series of inevitable reactions finally result in transcription modification to produce functional and terminally differentiated cells. Electric activity is known to have function in some aspects in biological processes, mostly in neural transmission. Through ionic density gradient in and out of cells, electricity invokes biological reactions. We would like to propose that ionic density gradient or electric homeostasis is also important for developmental processes, especially, in the modulation of fate determinations for differentiating cells. ES cells initiated differentiation were given strong tendency to take neuronal cell fate by weak electric-stimulation. Those electro-stimulated cells have potential to differentiate into various types of neurons in vivo and able to contribute to animal body.

N215

Genetic and Biochemical Analyses of Neuron-Specific RNA Binding Protein Hu

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Neurons use a variety of means to regulate post-transcriptional gene expression including translational control and alternative splicing. Neural RNA-binding proteins are likely to play essential roles in mediating this regulation. Hu proteins are mammalian ELAV-like neuronal RNA-binding proteins that were identified as autoimmune antigens of human paraneoplastic encephaloneuropathies. Recently, we provided evidence that mHuB and mHuC are required for and capable of inducing neuronal phenotype in both CNS and PNS. In vitro RNA selection experiments identified RNAs harboring UGUUUGU elements to which Hu proteins bound with sequence-specificity and high affinity. Furthermore, we found that Hu binds to UGUUUGU element present in 5'UTR of p27KIP1 mRNA to regulate translation. We have used genetic and biochemical analyses to determine that Hu proteins induce neuronal differentiation by regulating the metabolism of specific target mRNAs. To examine whether Hu interacts specifically with other proteins, and to assess whether these interactions might modulate the ability of Hu to regulate translation, we have performed biochemical purification experiments using flag tagged Hu-recombinant adenovirus. We identified 6 proteins at least, including hnRNPK, NF45, Musashi and SKB1 that are expressed in the brain and interact with Hu in vitro. To determine in vivo functions of Hu, we generated HuD null and HuB null mice. Although HuD null mice are born phenotypically normal, one third of the animals show a progressive motor deficit and die in the first months of postnatal life. In contrast, HuB null mice are embryonic lethal with developmental abnormalities in cortex. Our results demonstrate that HuB is essential for terminal differentiation in developing neurons.

N216

Polarized localization of SHPS-1 and its ligand CD47 in hippocampal neurons

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SHPS-1 and its ligand CD47 are members of immunoglobulin superfamily membrane proteins. These two molecules constitute an intercellular communication system (the CD47-SHPS-1 system). Both SHPS-1 and CD47 are highly expressed in the brain, however the physiological function of the CD47-SHPS-1 system in the central nervous system is unknown yet. Here, we analyzed expression patterns of these two molecules by using primary cultured hippocampal neurons. We found that SHPS-1 and CD47 were localized in a different manner; the former predominantly on axons and the latter on dendrites, respectively. Exogenous expression of SHPS-1 and CD47 in cultured neurons also confirmed this observation. Using a series of mutant SHPS-1 constructs, we found that cytoplasmic domain was an important element for the axonal localization of SHPS-1. Furthermore, exogenously expressed SHPS-1 and CD47 were markedly accumulated at the contact sites of axon and dendrite, each of which were derived from neurons transfected separately, indicating that the interaction of these molecules also affects their localization. Thus, our results suggest a directional regulation of neuronal functions by the CD47-SHPS-1 system through polarized localization of these two molecules. The functional implication of this polarized localization in neurons is now further investigated to elucidate physiological role of the CD47-SHPS-1 system in the central nervous system.

N217

Expression of NDRG4 protein isoforms by alternative promoter usage and alternative splicing in rat brain

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Rat *Ndr4* is a member of the NDRG4 gene family and has been suggested to relate to neurite outgrowth and brain development. Subcloning and DNA sequencing analysis of a bacterial artificial chromosome clone, together with analysis of a transcriptional start site by a cap-site hunting, indicated that the *Ndr4* gene spans about 39 kilobases and consists of 19 exons. An alternative promoter usage at different transcriptional start sites may produce three types of messages, *Ndr4*-A, *Ndr4*-B, and *Ndr4*-C, and there is a variant that lacks exon 18 for each type of transcript. These six variants might explain the heterogeneity of the *Ndr4* protein in the brain. A reverse transcription-polymerase chain reaction analysis showed that expressions of *Ndr4*-A and *Ndr4*-C mRNAs increased as the brain developed from fetal to postnatal stages, whereas *Ndr4*-B mRNA was dominantly detected in the heart. Radiation hybrid mapping suggests that the rat *Ndr4* gene locates on chromosome 19 at 90.6 centirays from the top.

N218

A β (25-35) -induced axonal atrophy, synaptic loss and memory impairment were recovered by ginsenoside Rb₁ and its metabolite M1

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Previously, we screened neurite outgrowth activity of several Ginseng drugs in human neuroblastoma SK-N-SH cells for the purpose of finding anti-dementia drugs, and found that protopanaxadiol (ppd) -type saponins were active constituents. Since ppd-type saponins are mostly metabolized to 20-O- β -D-glucopyranosyl-20 (S) -protopanaxadiol (M1) by intestinal bacteria, and some of M1 are transformed to fatty acid ester (EM1) in the liver when taken orally, these metabolites should be also investigated. Therefore, M1 and EM1 in addition to ginsenoside Rb₁ as a representative of ppd-type saponins, were used in the present study for examining synaptic reconstructing effect. Ginsenoside Rb₁ and M1 extended axons, but not dendrites, even when neuritic atrophy was already progressed by the administration of 10 μ M A β (25-35). The effective dose of M1 was 10⁴ times lower than that of ginsenoside Rb₁, but EM1 had no significant effect. In a conveniently prepared mouse model of Alzheimer's disease (AD) by A β (25-35) i.c.v. injection, impaired spatial memory was recovered by p.o. administration of ginsenoside Rb₁ or M1. Although expression levels of phosphorylated NF-H (axonal marker) and synaptophysin (synaptic marker) were reduced in the cerebral cortex and the hippocampus of A β (25-35) -injected mice, their levels in ginsenoside Rb₁- and M1-treated mice were almost completely recovered up to control levels. These results suggest that both ginsenoside Rb₁ and M1 have axonal extension activity in degenerated neurons, and improve memory disorder and synaptic loss in AD. M1 as well as ginsenoside Rb₁ was shown to be effective *in vitro* and *in vivo*, indicating that Ginseng drugs containing ppd-type saponins may reactivate neuronal function in AD by p.o. administration.

N219

Neurotrophic effect of Sema4D on neurite outgrowth

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The semaphorins are a large family of secreted and membrane-bound glycoproteins characterized by conserved sema domain of ~500 amino acids. Several members of semaphorin have been implicated in mediating axonal guidance in the developing nervous system. In vitro and in vivo, some semaphorins act as potent repulsive molecules. However, at least some semaphorins are bifunctional molecules that can be attractive as well as repulsive. For example, Sema3A induces growth cone collapse of dorsal root ganglion (DRG) neurons and cortical axons, while it acts as an attractant for cortical apical dendrites. Sema3C (formerly called SemE) repels sympathetic axons but attracts cortical axons in vitro. We have also shown that Sema3E (primarily called M-SemaH) repels and inhibit axon outgrowth in DRG neurons, whereas it is neurotrophic to induce neurite outgrowth in PC12 cells. In grasshopper embryos, T1 axons are initially repelled by an invertebrate secreted-semaphorin, Sema2a, until they encounter a stripe of epithelial cells that express an invertebrate transmembrane semaphorin, Sema1a. A secreted-semaphorin acts as a repulsive factor in axon guidance in vivo in invertebrate, while a transmembrane-semaphorin can promote axon outgrowth. However, it is not well known about the function of numerous transmembrane semaphorins in the vertebrates. In this study we found that Sema4D, a transmembrane type of semaphorin functions as a neurotrophic factor on DRG neurons and PC12 cells. We further analysed what mediates this signal.

N220

Synaptic reconstructing effects of Withanolide A and Withanoside VI in rat cortical neurons degenerated by A β 25-35

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We previously found that Withanolide A and Withanoside VI isolated from *Ashwagandha* (roots of *Withania somnifera* Dunal) had neurite outgrowth activities in neuroblastoma cells. It was also shown that treatment with Withanolide A predominantly extended axons in rat cortical neurons, whereas treatment with Withanoside VI extended dendrites. To clarify effects of those two compounds on synaptic reconstruction in degenerated neurons, we investigated expression levels of synaptic markers in the present study. Cortical neurons of rats (SD, E18) were cultured for 21-23 days, and treated with A β 25-35 (partial peptide of β -amyloid, 10 μ M) for 4 days. After that, the neurons were treated with Withanolide A (1 μ M) or Withanoside VI (1 μ M) for 14-15 days without A β 25-35, and synaptophysin (presynaptic marker) or PSD-95 (postsynaptic marker) was double immunostained with MAP2 (dendritic marker). Although synaptophysin and PSD-95 were numerous localized in punctate forms along dendrites in cortical neurons, both of them were significantly reduced in A β 25-35-treated neurons. Treatment with Withanolide A significantly increased the density of synaptophysin-positive puncta, and also tended to increase PSD-95-positive ones. On the other hand, treatment with Withanoside VI remarkably increased the density of PSD-95-positive puncta, but not synaptophysin-positive ones. These results suggest that Withanolide A has an activity to extend axons, and may promote presynaptic maturation, whereas Withanoside VI extends dendrites, and may promote postsynaptic maturation in degenerated neurons by A β 25-35.

N221

Proteomic analysis of regionally specific molecules in rat embryonic cerebral neocortex

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The mammalian cerebral neocortex is divided into functionally specialized areas such as motor, somatosensory, and visual cortex. Recently, several molecules including the transcription factor Emx2, Pax6, and the fibroblast growth factor FGF8 are identified as factors which genetically regulate this arealization in the late embryonic stage. However, the downstream genes controlled by these factors are still unknown. To identify the functional molecules related to the arealization of cerebral neocortex, we analyzed differentially expressed proteins among three neocortical regions (frontal, central, and posterior regions) using the proteomic technique. In the present study, we isolated the soluble protein fractions, the growth cone fractions, other membrane-mixture fractions from three neocortical regions of rat embryonic day 18 brain. Each fraction was characterized by two-dimensional gel electrophoresis. The protein spots were visualized by silver staining. The patterns of protein spots of both soluble and other membrane-mixture fractions were identical among three regions. However, several spots were clearly enriched only in the growth cone fraction of frontal neocortex but not of other regions. In addition, these spots were not detected in other soluble and membrane fractions. These results suggest that the spots detected differentially may be crucial proteins expressed at growth cone and be related to the arealization of frontal cortex.

N222 (MS5-1)

Regulated Release of EGF-like Molecules from Rat Striatal Culture: Their Trophic Activity on Midbrain Dopaminergic Neurons.

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Epidermal growth factor (EGF), tumor growth factor alpha (TGF α) and heparin-binding EGF (HB-EGF), exert a trophic effect for mesencephalic dopaminergic neurons both in vivo and in vitro. In the rat midbrain culture, EGF remarkably increased the number of tyrosine hydroxylase (TH) -positive dopaminergic neurons. However, regulation of their production and release is poorly understood. Here we examined release of the EGF members, EGF, TGF α and HB-EGF, from rat striatal cultures that the dopaminergic neurons innervate. Amounts of these immunoreactivities, which rat striatal neurons or glia cultures release in response to various neurotransmitters, were determined by two site ELISA. The thirty minutes stimulation of dopamine or a D1R-specific agonist, SKF38393, triggered the release of the EGF-like immunoreactivities, but not that of TGF α and HB-EGF immunoreactivities. Although these stimulations to the glial culture did not stimulate the release of the EGF-like immunoreactivity. Release of EGF involves two molecular processes, exocytosis and ectodomain shedding, recruiting metalloproteases. Inhibitors for metalloproteases or exocytosis both prevented the striatal release of the EGF-like immunoreactivity. Based on these results, we conclude that this EGF-like immunoreactivity is liberated from rat striatal neurons through both shedding and exocytosis processes. These molecular processes in the striatum presumably play a crucial role in regulating the survival or maturation of midbrain dopaminergic neurons. Supported by J S P S Research Fellowships for Young Scientist.

N223 (MS5-2)

BDNF activates translation elongation in cultured cortex neurons.

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Recent studies have illuminated the importance of novel protein synthesis on synaptic plasticity. However, the mechanisms of translational control in neurons or at synapses are still largely unknown.

mRNA translation engages in initiation, elongation and release processes. In the initiation phase, an mRNA and a methionyl-tRNA are recruited to a ribosome. In the elongation phase, aminoacyl-tRNAs bind to a ribosome and translocate from the A site to the P site on a ribosome, resulting in peptide chain elongation. In the final step, a completed polypeptide chain is released from the ribosome.

We reported that BDNF activates the translation initiation to enhance protein synthesis in cortical neurons. Here we show that BDNF also accelerates the rate of elongation, another regulatory step of translation. We measured ribosomal transit time to study the BDNF influence on elongation rates, which represent the average time taken for ribosomes to complete nascent polypeptide chains. BDNF stimulation shortens the ribosomal transit time, indicating enhancement of elongation rates. In parallel, BDNF decreases the phosphorylation of eucaryotic elongation factor 2(eEF2), which means the activation of eEF2. Both the transit time and the dephosphorylation of eEF2 are suppressed by rapamycin, an inhibitor of mammalian target of rapamycin (mTOR).

Together with our previous evidence for the activation of mTOR by BDNF (JBC 2001 276, 42818-42825), these results strongly suggest that BDNF activates translation elongation via mTOR signaling. The signaling cascades of the eEF2 activation will be discussed.

N224 (MS5-3)

Adenoviral gene transfer of growth inhibitory factor (metallothionein-III) prevents degeneration of injured adult rat motoneurons

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Growth inhibitory factor (GIF), also called metallothionein-III (MT-III), a central nervous system-specific member of MT family, is a cysteine-rich protein that binds zinc and copper with high affinity. GIF shows protective effects against glutamate-, nitric oxide-, and beta amyloid-induced neurotoxicity and prevents neuronal death caused by high oxygen exposure. It has also been shown that mutant human superoxide dismutase 1 (SOD1) -transgenic mice (G93A mice) deficient of GIF exhibit reduced survival compared with G93A mice with normal GIF expression. These reports indicate that GIF may function as a neuroprotective molecule, whereas the surviving effects of GIF on injured adult motoneurons have not been demonstrated. In this study we examined neuroprotective effects of GIF on injured adult rat facial motoneurons. The right facial nerves of adult rats were avulsed and removed from the stylomastoid foramen, and an adenoviral vector encoding rat GIF and Myc epitope (AxCARGIFM) were injected into the facial canal. Animals treated with AxCARGIFM showed intense immunolabeling for GIF/Myc in injured facial motoneurons. The treatment with AxCARGIFM after avulsion significantly prevented the loss of injured facial motoneurons, improved choline acetyltransferase immunoreactivity and prevented the induction of nitric oxide synthase activity in these neurons. These results indicate that GIF may have therapeutic potential against degeneration of motoneurons in adult humans with motoneuron injury and motor neuron diseases such as amyotrophic lateral sclerosis.

N225 (MS5-4)

The role of calbindin-D28k in the neuroprotective action of basic fibroblast growth factor -in vitro assay by using neurons derived from calbindin-D28k KO mice-

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It is well known that basic fibroblast growth factor (bFGF) shows protective effects on various neuronal damages, but the mechanisms are not thoroughly understood. In this study, we examined the involvement of calbindin-D28k in neuroprotective effects of bFGF by using primary cultured neurons from homozygous knockout mice (CBKO) and wild-type (WT) mice. Primary neurons isolated from the cerebral cortex and hippocampus of fetal mice (E15) were seeded. Six days later, bFGF (1, 5 and 10 ng/mL) was applied to the culture and then glutamate (50-200 μ M) 24 hrs after bFGF treatment. Intracellular free calcium, $[Ca^{2+}]_i$, levels were measured after glutamate instillation using the Ca^{2+} indicator dye Fluo3, and cell survival was determined 1 day after glutamate treatment using MTT assay and MAP2 staining. Basic FGF increased intracellular calbindin-D28k protein, and concentration-dependently inhibited glutamate-induced $[Ca^{2+}]_i$ increase and neuronal damage of the cerebrocortical and hippocampal neuronal cells cultured from WT mice. In contrast, bFGF did neither prevent glutamate-induced $[Ca^{2+}]_i$ increase nor neuronal damage of primary neurons from CBKO mice. These data indicate that bFGF protects neurons by stabilizing intracellular Ca^{2+} level via calbindin-D28k induction. In chronic neurodegenerative disease, such as Alzheimer's disease, neuronal cell death is said to be caused by excessive Ca^{2+} influx. Basic FGF might be a potent therapeutic candidate for preventing neuronal cell death by maintaining calcium homeostasis in neurons.

N226 (MS5-5)

PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE (PACAP) REGULATES NEURAL STEM CELL FATE IN VITRO AND IN VIVO

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The PACAP receptor (PAC1-R) is expressed in the forebrain germinal zone of the rat throughout early development, suggesting a role for PACAP in the regulation of neural stem cells (NSCs). Using RT-PCR analysis we confirmed that both PACAP and PAC1-R are expressed in E14 murine ganglionic eminence. PAC1-R was also expressed in EGF-generated neurospheres, further suggesting a role in NSCs regulation. This was first investigated by the addition of PACAP to embryonic neurosphere cultures. The addition of PACAP to clonal density cultures at plating significantly increase the number of primary neurospheres generated in response to EGF and FGF-2. Primary neurospheres generated in the presence of mitogen and PACAP contained increased numbers of neurons compared to those generated in the presence of mitogen alone. These results suggest that PACAP may act to both enhance the proliferation/survival of NSCs, as well as their differentiation towards the neural lineage. These effects depended on the cAMP signaling pathways. Furthermore PACAP addition to embryonic neurosphere cultures resulted in the activation of both anti-apoptotic and neurogenic signaling pathways in vitro. Examination of PAC1-R in the adult brain revealed abundant expression in the forebrain in the subventricular zone (SVZ). To examine putative actions of the peptide in vivo, PACAP was infused into the lateral ventricle for 6 days, resulting in increased numbers of BrdU positive cells in the SVZ as well as in the hippocampus. We also observed the increase of DCX (migrating neuron marker) positive cells in the same region. These results demonstrate a role for PACAP in the proliferation and differentiation of embryonic and adult NSCs.

N227

Signal transduction pathways involved in riluzole-stimulated BDNF production in the rat hippocampus

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We have reported that riluzole markedly enhanced levels of brain-derived neurotrophic factor (BDNF) in the rat hippocampus. Moreover, we demonstrated that riluzole-induced BDNF production in this region was regulated by N-type voltage-dependent calcium channels coupled with the adenosine receptors. Then we searched for signal transduction pathways activated by riluzole, and further investigated if the pathways are involved in the BDNF production. Since BDNF synthesis seems to be stimulated by calcium influx, we focused on ERK, p38MAPK and PI3K pathways. Riluzole was intraperitoneally injected into 6-week-old rats and, if necessary, kinase inhibitors were administered into the left lateral ventricle before riluzole treatment. Amounts of phosphorylated kinases in the hippocampus were measured by Western blotting analysis. Among the three kinases tested, phosphorylation of p38MAPK in the region was significantly stimulated by riluzole. SB203580, an inhibitor of p38MAPK, blocked both riluzole-enhanced phosphorylation of p38MAPK and BDNF production. On the other hand, relative amounts of phosphorylated ERK (p42 and p44) were slightly, but not significantly, increased. Riluzole had no effect on amounts of phosphorylated Akt. Inhibitors of ERK and PI3K did not cause any reduction of BDNF levels. The present results suggest that hippocampal BDNF production is enhanced via p38MAPK in riluzole-injected rats.

N228

A DIPEPTIDE, LEU-ILE, HAS NEUROPROTECTIVE EFFECTS AGAINST DOPAMINERGIC DENERVATION

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We have already reported that FK506, one of the immunophilin ligands, has neuroprotective effects via induction of glial cell line-derived neurotrophic factor (GDNF) synthesis. However, FK506 does not seem to be proper as a therapeutic tool for neurodegenerative diseases because of its immunosuppressant activity. In this study, we attempted to find new neuroprotective immunophilin ligands without immunosuppressant effects. First, we investigated whether some hydrophobic dipeptides, Leu-Ile, Pro-Leu and Pro-Ile, which partly resemble to the binding site of FK506 to immunophilin could stimulate GDNF synthesis in cultured neurons, and found Leu-Ile as an active dipeptide, but not Pro-Leu or Pro-Ile. Next, we examined the effects of i.p. or i.c.v. administration of Leu-Ile on rats with dopaminergic denervation by unilateral 6-hydroxydopamine (6-OHDA) injection into the striatum. The number of rotation following methamphetamine challenge was lower in the Leu-Ile-treated group than in the non-treated group. Both i.p. and i.c.v. injection of Leu-Ile increased GDNF content in the striatum of mice or rats in other experiments. Leu-Ile did not suppress the ConA-induced interleukin-2 synthesis/secretion of cultured spleen cells, suggesting that the immunosuppressant activity of Leu-Ile may be negligible when used as a therapeutic tool for neurodegenerative diseases.

N229

Coexpression of a chemokine, MCP-1, with a neurotrophic factor, GDNF, in microglia/macrophages around the transection site of the rat spinal cord

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The spinal cord injury causes many kinds of inflammatory reactions such as induction of chemokines that activate and chemoattract leukocytes. We have already observed that the leukocytes, especially activated microglia/macrophages, in the injured spinal cord, express glial cell line-derived neurotrophic factor (GDNF), a potent neurotrophic factor for motor neurons. However, regulatory mechanisms or physiological significance of GDNF expression in the microglia/macrophages of the injured spinal cord have not yet been investigated. In this study, we compared the expression of chemokines with that of GDNF in the rat spinal cord after injury. The spinal cords of anesthetized rat were completely transected at the position of T10. The tissue adjacent to the transected site was collected various times after the injury. Corresponding site of the tissue was also dissected out from the uninjured rats. Expression levels of mRNA and protein were evaluated with RT-PCR and immunohistochemical technique, respectively. Level of mRNA of monocyte chemoattractant protein (MCP) -1, macrophage inflammatory protein (MIP) -1 alpha, MIP-1 beta, MIP-2 or RANTES, a family of chemokines, was remarkably increased within a few hr after the spinal cord transection. Immunohistochemical analysis revealed that MCP-1 was expressed in both macrophages and astrocytes following the injury, and that GDNF was coexpressed with MCP-1 in substantial number of macrophages. Furthermore, as GDNF mRNA expression was preceded by MCP-1 mRNA expression, it may be possible that MCP-1 takes part in regulation of GDNF expression. Some chemokines may contribute to regeneration processes of the injured spinal cord via stimulation of neurotrophic factors.

N230

Epidermal growth factor (EGF)/ErbB signaling regulates the expression of synaptic proteins in rat cerebral cortex

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Epidermal growth factor (EGF) family molecules are known to regulate cell migration and differentiation. These molecules are ubiquitously expressed in various tissues or organs including brain. However, it is still unclear whether EGF/ErbB signaling controls neuronal function. In the present study, we investigated the possibility that EGF/ErbB signaling regulated the expressions of various synaptic proteins, such as postsynaptic PDZ proteins or presynaptic proteins *in vitro* and *in vivo*. It was found that EGF/ErbB signaling down-regulated the expressions of 97 kDa synapse-associated protein (SAP97), glutamate receptor-interacting protein 1 (GRIP1), and SAP102 in cultured cortical neurons. The expression of protein interacting C kinase 1 (Pick1) was not changed, and the postsynaptic density-93 (PSD-93) expression was up-regulated by EGF/ErbB signaling. Accordingly, EGF/ErbB signaling down-regulated the expressions of SAP97, GRIP1, SAP102, PSD-95 and PSD-93 in frontal cortex of neonatal rats that were subcutaneously administered EGF. The expression of Pick1 was not altered. In conclusion, EGF/ErbB signaling tends to decrease the expression of certain types of synaptic proteins in central nervous system neurons both *in vitro* and *in vivo*.

N231

The outgrowth of neurites was induced by radicicol and geldanamycin in NG108-15 cells and Neuro2A cells.

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I previously reported that radicicol and geldanamycin, hsp90-binding antibiotics, potentiate neurite growth and survival of cultured sensory neurons from chick embryo (J. Neurochem., 72, 2256, 1999; Neuropharmacol., 40, 947, 2001). Whereas, these antibiotics did not stimulate neurite growth and survival of sensory neurons from mouse embryo. This study shows that radicicol and geldanamycin (10-200nM) induce the outgrowth of neurites in NG108-15 neuroblastoma x glioma cells and murine neuroblastoma Neuro2A cells. Treatment of NG108-15 cells with these drugs decreased protein levels of Raf1 and Akt1 time-dependently. They did not change protein levels of HSP90, Ras, Erk1/2 and p38MAPK. By the treatment, phosphorylated ERK1/2 was decreased but the level of phosphorylated p38MAPK was not changed. These results show that treatment of NG108-15 cells with radicicol and geldanamycin induce morphological differentiation and that the response may be due to the reduction of activities in Raf1 and Akt1 together with their downstream signals. In human neuroblastomas (ShSY5Y, SK-N-SH and LAN-1), geldanamycin has been reported to induce apoptosis, and it has been suggested that the response may be due to prevention of cdk activation by decreased level of Raf1 and Akt. These pathways were known to regulate proliferation and differentiation of cells. It can be interpreted that prevention of cdk activation does not cause apoptosis as a general cellular response, but induces differentiation in sensory neurons from chick embryo, NG108-15 cells and Neuro2A cells.

N232

Supportive function of meninges in cortical development

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To study the function of meninges in cortical histogenesis, E15.5 cerebral hemispheres were cultured with or without the meninges by rotation culture system. This method allowed us to study the cortical development in detail *in vitro* as the histological characteristics were preserved fairly well. After 2 days in culture, the removal of the meninges resulted in irregular brain surface. Nuclear staining of cross sections of cortices without meninges revealed ectopic invasion of numerous cells into the marginal zone (MZ), where only small number of cells should normally reside. The MZ contains Cajal-Retzius (CR) neurons that secrete Reelin, which regulates the position of cortical plate neurons. Therefore, ectopic invasion of cortical plate neurons into the MZ raised a possibility of decrease or lack of Reelin production. We examined the presence of Reelin-producing cells by immunohistochemistry. In the hemispheres with meninges, Reelin-producing cells formed a well-organized layer along the pial surface. In contrast, in hemispheres without meninges, Reelin-producing cells were almost absent. To investigate whether the CR neurons were removed by cell death by the lack of the meninges, cell viability was determined by staining the slices with membrane-impermeant chromatin dye, propidium iodide (PI), as a fluorescent viability indicator. Although the hemispheres with meninges showed only few PI-positive cells (cell death), the hemispheres without meninges showed widespread cell death within the cortical plate and the MZ. These results suggest the important role of the meninges in the cortical histogenesis.

N233

Chronic Epidermal growth factor (EGF) application Down-regulates Synaptic Function in Neocortical GABAergic Neurons

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Recent studies have shown that neurotrophic factors including BDNF enhance the efficacy of synaptic transmission. However, the negative molecules which downregulate the synaptic functions have not fully been understood. Here we report epidermal growth factor (EGF) negatively influence synaptic function in GABAergic neurons in vivo. We treated mice daily with or without EGF (s.c. 0.875mg/kg) for 15 days. Chronic treatment with EGF markedly reduced the overall expression of glutamate receptor proteins, such as GluRs and NMDARs, as well as presynaptic proteins in frontal cortex. Immunohistochemical studies revealed that EGF tended to decrease the number and intensity of GluR1-immunoreactivity in parvalbumin-containing interneurons. AMPA receptor (AMPA) -mediated synaptic transmission in slices prepared from EGF-treated mice frontal cortices were examined electrophysiologically. The miniature excitatory postsynaptic current (mEPSC) amplitude was significantly decreased in fast-spiking neurons from EGF-treated mice. Similarly, mEPSC frequency was decreased. These observations suggest that EGF downregulates synaptic formation and maturation of the GABAergic interneurons in the frontal cortex and might balance the excitatory and inhibitory synaptic circuits.

N234

The role of calbindin-D28k in the neuroprotective action of basic fibroblast growth factor

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It has been reported that calbindin-D28k, a major calcium binding protein predominantly presented in the cytosol, plays an important role in intracellular Ca^{2+} homeostasis and buffering neuronal damage induced by excitatory amino acids. On the other hand, basic fibroblast growth factor (bFGF) shows potent protective effects on various neuronal damages, but the mechanisms are not thoroughly understood.

In the present study, we examined whether calbindin-D28k is involved in the mechanisms of neuroprotective effects of bFGF by using calbindin-D28k knockout (CBKO) and wild-type (WT) mice. Neuronal damage was produced by a combinational injection of $A\beta_{1-40}$ (4 μ g/1 μ L) and ibotenate (0.3 or 0.6 μ g/0.5 μ L), into the hippocampus at the injection interval of 48 hr. Ten days after $A\beta_{1-40}$ injection, the hippocampus was removed and measured the level of peripheral type benzodiazepine binding sites (PTBBS, a gliosis marker for neuronal damage). PTBBS levels were significantly increased by $A\beta_{1-40}$ + ibotenate co-injection in CBKO and WT mice as compared with sham operated mice (WT, 225.7 $\pm$ 6.5 vs 393.1 $\pm$ 38.5 fmol/mg protein; CBKO, 282.3 $\pm$ 9.5 vs 465.9 $\pm$ 74.1 fmol/mg protein). Microinjection of bFGF (25 ng/site) into the same site of hippocampus 24hr after $A\beta_{1-40}$ injection significantly reduced the PTBBS level by 70% in WT mice (vehicle; 393.1 $\pm$ 38.5 vs bFGF; 275.9 $\pm$ 17.9 fmol/mg protein). In contrast, the neuroprotective effect of bFGF was not observed in CBKO mice (vehicle; 465.9 $\pm$ 74.1 vs bFGF; 475.9 $\pm$ 37.6 fmol/mg protein).

These results indicate that calbindin-D28k plays an important role in the neuroprotective action of bFGF.

N235

PEDF stimulates expression of survival-related genes in cerebellar granule cells

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Pigment epithelium-derived factor (PEDF) is a 50-kDa glycoprotein and a member of the serine protease inhibitor (SERPIN) gene family. We have shown previously that PEDF acts as a survival factor for cerebellar granule cells (CGCs) in culture, as well as protecting them against glutamate toxicity or induced apoptosis. NF- κ B activation has been shown to mediate these effects of PEDF in CGCs (Yabe *et al.*, *J. Biol. Chem.* 2001). It is well known that NF- κ B blocks neuronal apoptosis through the induction of survival related factors, however the effects of PEDF on the gene expression of survival related factors are not fully understood. In this study, we analyzed the gene expression of survival related genes using RT-PCR method. When CGCs (DIV2) were incubated with 10nM PEDF, the induction of survival related factors mRNA (Mn-SOD, cIAP1, cIAP2, FLIPs, A1/Bfl-1, NGF, BDNF, trkB, p75NGFR etc.) was observed in PEDF treated CGCs. In contrast, no induction of pro-apoptotic Bcl-2 family member mRNA (Bid, Bax, Bak etc.) was observed in PEDF treated neurons at any time from 3 to 24 h after PEDF addition. Up-regulation of cIAP2, FLIPs, A1/Bfl-1 and Mn-SOD mRNA was attenuated by pretreatment with proteasome inhibitor, MG-132. Furthermore, pretreatment with PI3K inhibitor, LY294002 also inhibited the ability to induce cIAP2, FLIPs and A1/Bfl-1 mRNA. Western blot analysis revealed that rapid phosphorylation of AKT and CREB protein was observed in PEDF-treated CGCs. These results suggest that the induction of survival related genes via NF- κ B activation and/or PI3K-AKT pathway is involved in neuroprotective effects of PEDF on CGCs.

N236

Development of nociceptive neurons of dorsal root ganglia in oncostatin M-deficient mice

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Oncostatin M (OSM) and leukemia inhibitory factor (LIF) are functionally and structurally related and are members of the gp130 family of cytokines. Although it has been reported that LIF is involved in the development of the neurons of dorsal root ganglia (DRGs), the roles of OSM in the development of DRGs remain unclear. We previously reported that OSM receptor β (OSMR β) was expressed in the central nervous system, such as the hypoglossal nucleus, of the perineonatal mice (Tamura *et al.*, *Neuroscience*, 2003). In the present study, we investigated the development of OSMR β -positive neurons of DRGs in OSM-deficient mice. In situ hybridization for the DRGs of the developing mice revealed that OSMR β -positive neurons began to appear at postnatal day (PN) 0 and reach to the adult level at PN 14. Immunostaining revealed that all OSMR β -positive neurons of DRGs were both VR1- and P2X3-positive (VR1/P2X3-double positive). In the DRGs of the OSM-deficient mice, we could detect few VR1/P2X3-positive neurons. OSM-deficient mice displayed significantly reduced pain responses to various stimuli such as capsaicin and α β -me-ATP. Thus, OSM appears to play some important roles in the development of a subtype of nociceptive neurons in the DRGs. This work was in part supported by Grant-in-Aid for Scientific Research (C) from The Ministry of Education, Culture, Sports, Science and Technology (15500264) and Research Grant on Primary Areas from Wakayama Medical University.

N237

Change of p40BBP in degenerating neuronal cells

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The novel membrane glycoprotein, p40BBP has been cloned as a BINP binding protein. BINP (brain injury-derived neurotrophic peptide) promotes survival of cultured neurons from postnatal rats and prevents neuronal cell death of hippocampal neurons caused by glutamate and protects hippocampal neurons from glutamate toxicity. The mRNA of rat p40BBP is specific in brain and is increased after birth. Though the expression of p40BBP protein is quite low in normal adult rat brain, it is increased in numbers of survived neurons under a condition inducing neuronal degeneration that is observed in kainic acid-administrated rats. This suggests that the lack of p40BBP in neurons may explain the vulnerability of neurons. Then we investigated the change of p40BBP in response to cell death using clonal cell line NG108-15 cells. In the presence of lasalocid (10^{-6} M), NG108-15 cells showed apoptotic cell death after 48 hrs. BINP prevents this cell death. Using this system, the change of p40BBP protein in NG108-15 cells during apoptosis was investigated. Cells were cultured with lasalocid (10^{-6} M) or BINP (10^{-7} M) in the serum free DMEM for 18 hrs. For the control, cells were cultured in serum free DMEM for 18 hrs. Then these cells were homogenized in isotonic solution and fractionated to the nuclear fraction, membrane fraction and cytosol fraction. In only membrane fractions, p40BBP protein was detected by western blotting with polyclonal anti-p40BBP antibody. When the cells were treated with lasalocid, p40BBP was observed in both soluble and insoluble membrane fractions. This suggests that the failure of plasma membrane expression of p40BBP may be related to cell death.

N238

Oncostatin M receptor β is expressed in nociceptive primary sensory neurons

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Oncostatin M (OSM), the interleukin-6 family of cytokines, plays some important roles in the definitive hematopoiesis, the development of liver, and inflammatory reactions. However, the role of OSM in the peripheral nervous system of adult mice remains unclear. Here, we examined the expression of OSM receptor β (OSMR β) in dorsal root ganglia (DRGs) of adult mice using in situ hybridization and immunohistochemical method. Approximately 13% of total DRG neurons in mice expressed OSMR β . OSMR β was expressed exclusively in small-sized DRG neurons. To further characterize OSMR β -positive DRG neurons, we performed double-immunofluorescence method for several nociceptive markers in adult DRGs. Most of OSMR β -positive neurons expressed Ret-immunoreactivity and bound isolectin B4. No OSMR β -positive neurons contained neuropeptides, such as substance P and calcitonin gene-related peptide. In addition, all OSMR β -labeled neurons were positive for both vanilloid receptor 1 (VR1, also known as TRPV1) and P2X3 purinergic receptor. OSMR β -positive fibers were detected in the inner portion of lamina II and the dermis of plantar skin. In conclusion, OSMR β was expressed in a specific subset of non-peptidergic nociceptive neurons of adult mice, suggesting that OSM is involved in the nociceptive function of DRG neurons through the modulation of VR1 and P2X3 expression. This work was in part supported by Research Grant on Primary Areas from Wakayama Medical University and Grant-in-Aid for Scientific Research (C) from The Ministry of Education, Culture, Sports, Science and Technology (15500264).

N239

Analysis of neuroprotective effects of pigment epithelium-derived factor (PEDF) on animal model of Parkinson's disease.

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Pigment epithelium-derived factor (PEDF) was initially identified as a neurotrophic factor for retinal neurons, and now has been shown to function in central nervous system beyond the retina. PEDF protein is a 50-kDa glycoprotein that belongs to serine protease inhibitor (SERPIN) family, although the SERPIN activity is not required for the neurotrophic effects. We have recently confirmed that PEDF supported the survival of primary dopaminergic neurons of mouse midbrain. In this study, aiming for the clinical treatment with Parkinson's disease (PD) patients, we assessed the neurotrophic and/or neuroprotective effects of PEDF on dopaminergic neurons by using animal model of PD. We first investigated the changes in transcriptional expression of mouse PEDF after the injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Both of the acute and chronic administration of MPTP caused rapid increases of transcripts of PEDF in the substantia nigra (SN) and the striatum, suggesting a neuroprotective role of PEDF in nigrostriatal system. Next, a recombinant adeno-associated viral (rAAV) vector containing PEDF cDNA was stereotactically injected to the SN or striatum. After the MPTP administration, although significant effect was not seen in SN, several TH-positive neurons were found around the rAAV injection site in the striatum. Gene therapy using PEDF will be useful for the treatment of PD.

N240

Genipin, a herbal neurotrophic iridoid compound, directly binds to and activates of nitric oxide synthase

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We have previously reported that geniposide and its aglucone, genipin, isolated from *Gardenia Fructus* have a neuritogenic activity in PC12h cells and suggested that the genipin-induced neurite outgrowth depends on activation of nitric oxide synthase (NOS) - soluble guanylate cyclase (sGC) - cGMP-dependent protein kinase (PKG) pathway.

To clarify the target molecule of genipin in the neuritogenic action, in this experiment we examined direct interaction between genipin and NOS, the effects of genipin to NOS-dimerization and the activity, using cytosolic fractions extracted from rat brain cortex or PC12h cells. Direct binding of genipin/geniposide to NOS was analyzed by the overlay methods with rabbit anti-genipin antisera raised against geniposide as antigen. NOS activity was measured by ³H-arginine - citrulline conversion assay using TLC or cation exchange resin. NOS dimerization was analyzed by low-temperature electrophoresis and following western blotting method with rabbit anti-neuronal NOS antisera. Geniposide-binding protein with molecular weight about 170 kDa was detected in both cortical extract and cytosolic fraction of PC12h cells. Genipin enhanced tetrahydrobiopterin (BH₄) -dependent ³H-citrulline production and dimerization at low concentration of BH₄. These results strongly suggest that the target molecule of genipin/geniposide is nNOS for the neuritogenic action of the genipin/geniposide, and support that genipin directly binds to nNOS and activates following sGC-PKG pathway in PC12h cells.

N241

Biphasic expression of CNTF in developmental chick skin, a target tissue of sensory neurons

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Ciliary neurotrophic factor (CNTF) is a potent neurotrophic factor for many types of neurons including sensory, parasympathetic, sympathetic and motor neurons. However, the physiological function of CNTF is not fully clarified yet because of the absence of signal peptide sequence in the molecule and the limited expression to specific tissues such as myelin-forming Schwann cells and ocular tissues and, in low levels, astroglia in brain. Chick CNTF has only 46% homology in amino acid sequence to rat CNTF, and is reported to be releasable from cells that produce CNTF. In this report, we found the high expression of CNTF in developmental chick skin. The mRNA expression started at embryonic 11 days (E11d), peaked at E13d, diminished at E15d, started again at postnatal 7days (P7d), peaked at P14d and declined at P21d. The peak expression levels in skin at E13d and P14d were as high as the peak expression in sciatic nerves (E20d). The neurotrophic activities of tissue extracts assayed using ciliary neurons and Western blotting using antibody against chick CNTF showed similar results. The activities in E13 skin extracts were completely absorbed by the antibody and mostly in P14d extracts. Immunohistochemical data showed that CNTF was expressed in fibroblast-like cells beneath the dermal tissues and surround the feather roots. These developmental stages coincide with those of the rapid development of skin and feather, suggesting the involvement of CNTF in sensory innervation to skin and development of neural crest-derived cells in skin.

N242

Activity-dependent shedding of EGF family molecules in CNS

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Members in the epidermal growth factor (EGF) family bind to ErbB receptors (erbB1-4) and produce mitotic and trophic actions on various types of CNS cells. They induce the proliferation of glia and neural stem cells or promote the survival of certain sets of postmitotic neurons including dopaminergic neurons. The molecules in EGF family are processed and liberated from their membrane-bound precursors by shedding. Although the regulation of processing and release of EGF-like molecules must play an important role in their actions, molecular mechanism of the regulation is yet to be elucidated in the brain. We have reported that mature HB-EGF was detected in rat brain regions including the frontal cortex, hippocampus and cerebellum but their levels were relatively low. To study the regulation of EGF family shedding in the brain, we have generated the transgenic mice that over-express HB-EGF gene in the brain. mRNA for human preproHB-EGF was expressed under a CaMK II promoter. Using the transgenic mice, we analyzed effects of various pharmacological agents, which modulate neural activity. Among those agents, subchronic administration of methamphetamine altered the processing of HB-EGF precursors. The results suggest that shedding-dependent maturation of HB-EGF protein is regulated by neural activity. Its trophic consequence to dopaminergic neurons is currently under investigation.

N243

Regulation of gicerin gene by NGF

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Gicerin is a cell adhesion molecule belonging to the immunoglobulin superfamily. Gicerin consists of five immunoglobulin-like loop structures in an extracellular domain, a single transmembrane region and a short cytoplasmic tail. Gicerin participates in neurite extension and structural organization of nervous system. Expression of gicerin is highly observed during development and dramatically decreased after birth. To elucidate the mechanisms of regulation of gicerin expression, we cloned a 14kbp mouse gicerin gene. It contained 8kbp gicerin gene composed of 16 exons and 6kbp upstream region. The gene has a TATA less promoter with several Sp1 and CREB binding site. One Ig-loop coded by two exons and cytoplasmic domain is found to be generated by alternative splicing of exon 15 resulting in either 63 or 21 amino acids. On the other hand, we found gicerin was expressed in PC12 cells and its expression was regulated by NGF. Northern blot analysis revealed that NGF induced three fold increase of gicerin mRNA after 24 hour of incubation. To characterize its promoter region activity by using luciferase as a reporter gene. Chimeric luciferase reporter gene with 1.5kbp upstream region of gicerin construct was transiently transfected in PC12 cells. This 1.5kbp region revealed the 1.5 fold increase of promoter activity responsive to stimulation by NGF compared with non-stimulated. Western blot analysis also revealed the 2 folds increase of gicerin protein. These results were consistent with the result of Northern analysis.

N244

Localization of the immunoglobulin superfamily molecules L1, contactin, TAG-1, NB-2, and NB-3 in the adult mouse hippocampus

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Adhesion molecules of the immunoglobulin (Ig) superfamily, such as NCAM, L1, contactin, TAG-1, NB-2, and NB-3, are thought to play important roles in the development, maturation, and neural plasticity of the central nervous system. The distribution patterns of these molecules may influence neuron-to-neuron and neuron-to-glial cell interactions, and hence reflect the organization of brain networks and neural functions. The rich variety of Ig-superfamily molecules in the hippocampus suggests that they may have significant roles in hippocampal function. However, little is known about their precise localization in the hippocampus, and therefore we have investigated the immunohistological localization of L1, contactin, TAG-1, NB-2, and NB-3 in the adult mouse hippocampus by light and electron microscopy. L1 immunoreactivity was detected in the strata radiatum (SR) and lacunosum-moleculare (SLM), but was very weak or undetectable in the strata oriens (SO) and pyramidal (SP). Contactin immunoreactivity was localized to the SP, SR, and SLM, and was absent in the SO. TAG-1 immunoreactivity was strong in the SLM, weaker in the SP and SR, and undetectable in the SO. NB-2 immunoreactivity was detected in the SR and the SLM, but not in the SO or the SP. For NB-3, immunoreactivity was strong in the SP, SR, and SLM, but absent in the SO. These distinctive patterns suggest that the adhesion molecules of Ig-superfamily have their respective functions in the hippocampus.

N245

FLRT3 Is Induced in Injured Nerve and Promotes Neurite Outgrowth

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Mature peripheral nervous system (PNS) has the ability to survive and to regenerate their axons following axonal injury. After nerve injury, the distal axonal and myelin segment undergoes dissolution and absorption by the surrounding cellular environment, a process called Wallerian degeneration. Then the remaining Schwann cells divide and align longitudinally within basal lamina tubes. Growth cones from regenerating axons extend along the Schwann cell bands, growing along the Schwann cell membranes and basal laminae. Such biological and morphological changes of Schwann cells are thought to be controlled by injury-induced molecules that are expressed by neurons and Schwann cells themselves. Using cDNA microarrays, we isolated FLRT3 as one of the up-regulated genes expressed in the distal segment of sciatic nerve 7 days after transection relative to those of intact sciatic nerve. FLRT3 is a putative type I transmembrane protein containing 10 leucine-rich repeats, a fibronectin type III domain and an intracellular tail. We assessed localization of FLRT3 mRNA in rat brain by in situ hybridization. Expression of FLRT3 mRNA was especially abundant in basal ganglia, substantia nigra, granular layer of cerebellum and hippocampus except CA1 region. To address the role of FLRT3 in neuronal function, we examined neurite outgrowth of cerebellar granule neurons on CHO cells expressing FLRT3. The neurons plated on CHO cells expressing FLRT3 extended significantly longer neurites than neurons plated on wild-type CHO cells, suggesting that FLRT3 contributes to axonal outgrowth. FLRT3, which is one of the cell surface adhesion molecules, may be required for proper regeneration following axonal injury.

N246

Zonal expression of neural recognition molecule NB-2 in the developing cerebellum

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During development of the central nervous system, neural recognition molecules play essential roles in cell migration, neurite outgrowth, synaptogenesis and myelination. The molecules on the plasma membrane of neurons and/or glial cells regulate interactions between neuron and neuron, neuron and glial cell, and neuron and extracellular matrix. We have been studying the functions of contactin subgroup molecules, which belong to the immunoglobulin superfamily anchoring to the plasma membrane through glycosylphosphatidyl moiety. To date, we have generated gene-deficient mice of NB-2, NB-3 and TAG-1, which are in the subgroup, and have been analyzing the function of these molecules. In this study, we examined the localization of NB-2 in the developing cerebellum of mice. NB-2 is transiently expressed between P0 and P5 with a maximum level at P2 in the developing cerebellum. To know the localization of NB-2 in the cerebellum, we examined tau-LacZ expression in the heterozygotes of the NB-2 mutant mice in which a part of NB-2 gene on an allele was replaced with tau-LacZ, thereby expressing tau-LacZ in place of NB-2. Interestingly, NB-2 expression monitored by X-gal staining was detected in a striped manner in the neonatal cerebellum. Coronal sections of the cerebellum exhibited a zonal pattern of X-gal positive regions flanked by X-gal negative regions. Recently, it has been reported that FAR-2, a chicken orthologue of NB-2, is expressed in stripes in the embryonic cerebellum. The expression pattern of NB-2 in the cerebellum is similar between two species. This suggests that NB-2 plays an essential role in cerebellar development. At present, we are staining the neonatal cerebellum and primary culture cells using anti-NB-2 antibodies.

N247

Biosynthesis of a chondroitin sulfate moiety of neuroglycan C, a CNS-specific transmembrane proteoglycan

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Neuroglycan C (NGC) is a membrane-spanning chondroitin sulfate proteoglycan that is expressed predominantly in the brain. In the cerebellum, the structure of NGC changes drastically during the development; NGC in the immature cerebellum exists in a proteoglycan form, but most NGC molecules in the mature cerebellum do not bear any chondroitin sulfate chains, indicating that NGC is a typical part-time proteoglycan in the cerebellum. However, the regulatory mechanism for the addition of the chondroitin sulfate chain to NGC core protein is not known at present. To investigate the mechanism, NGC cDNA was transfected into neuro2a and PC12D cells. The former cells expressed NGC in a proteoglycan form and the latter in a non-proteoglycan form. There were three intrinsic chondroitin sulfate proteoglycans in cultures of PC12D cells in which NGC was artificially expressed, indicating that enzymes and substrates necessary for the synthesis of chondroitin sulfate exist in PC12D cells. Genetic analysis showed that the gene of GRP78, one of stress-response proteins, bore a mutation in neuro2a cells. GRP78 with the mutation can not be retained in the endoplasmic reticulum. The result suggests that NGC would be folded by GRP78 in PC12D cells but not in neuro2a cells, and the difference between these two cells in substitution of chondroitin sulfate chain to NGC core protein may be attributed to the proposed difference in its protein folding.

N248

Involvement of serotonergic system in the stress-induced alteration of the synaptic plasticity in the rat hippocampus

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Several lines of evidence have shown that the stress alters the induction of plasticity at glutamatergic synapses in the hippocampus. The aim of the present study is to elucidate the possible involvement of serotonergic system in the emotional stress-induced changes in the long-term potentiation (LTP) in the hippocampal CA1 field. For this purpose, conditioned fear stress (CFS) subjected to the 5-HT lesioned rats treated with 5,7-dihydroxytryptamine (5,7-DHT, 200 microgram/rat, i.c.v.). LTP was recorded under 1% halothane anesthesia introduced immediately after CFS experiment. Freezing behavior observed after the foot shock (FS, 0.5 mA, 2 sec x 5 times) was similar in 5,7-DHT- and sham-treated rats, whereas the behavior during exposure to the CFS, i.e. 24 hrs after the FS, significantly decreased in 5-HT lesioned rats compared with controls. The induction of LTP was completely suppressed after FS in both groups. The blockade of LTP was still observed after exposure to the CFS, however the inhibitory effects of LTP in 5-HT lesioned rats significantly attenuated compared with controls. We observed, furthermore, that the hippocampal extracellular glutamate levels markedly increased during exposure to the CFS in 5,7-DHT treated rats, but not in sham-treated controls. Thus, deficits in freezing behavior observed in 5-HT lesioned rats may be associated with the alteration of the plasticity at glutamatergic synapses in the CA1 field. In other words, serotonergic system appears to play a key role in the retention but not acquisition in the fear related stress.

N249

NMDA-dependent proteolysis of presynaptic adhesion molecule L1 in the hippocampus by neuropsin.

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Synaptic plasticity depends on activity-dependent, rapid, and long-lasting modifications of synaptic characters such as morphology and coupling strength. Here we show that a serine protease, neuropsin, directly and specifically modifies a synaptic adhesion molecule, L1, which is located on the presynaptic side of the asymmetric synapse in the mouse hippocampus. We used two forms of N-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP): LTP induced by theta-burst stimulation (TBS-LTP) *in vivo*, and LTP induced by NMDA and the potassium channel blocker 4-aminopyridine (chemical-LTP) *ex vivo*. Induction of both TBS-LTP and chemical-LTP triggered rapid and transient activation of the precursor form of neuropsin in the CA1 region of the hippocampus. Activation was blocked by NMDA receptor antagonists. The activated neuropsin immediately cleaved L1 and released a unique extracellular 180-kDa fragment. Induction of chemical-LTP also triggered the cleavage of L1 by endogenous neuropsin *ex vivo*. Furthermore, administration of the activity-neutralizing anti-neuropsin antibody mAbB5 prevented both induction of the early phase of LTP and cleavage of L1 by neuropsin. Our results suggest that this neuropsin-specific L1-cleaving system is involved in NMDA receptor-dependent synaptic plasticity via the Schaffer-collateral pathway.

N250

Activity dependent cytoskeletal remodeling by Arc transduction

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Arc, activity-regulated cytoskeleton associated gene, is an immediate early gene whose expression level is regulated by neuronal activities. Although a variety of stimuli induce arc gene expression, the function of the protein is unknown. To examine the cellular localization of Arc in cultured hippocampal neurons, rabbit polyclonal antibody was generated. In control neuron, Arc immunostaining was hardly detected. Forskolin treatment, however, revealed intense staining of cell bodies and dendritic processes, including distal branches. No immunoreactivity was detected in regions of the axons or the terminals. Next, to investigate Arc protein functions, we carried out the overexpression with expression constructs and by the protein transduction system for the introduction of purified Arc protein in the hippocampal primary culture. Overexpression of Arc caused a decrease in MAP2 (microtubule-associated protein 2) immunoreactivity in the dendrites. This result suggests a possibility that Arc is involved in the dendritic microtubule remodeling.

N251

A key role of Rho GTPase signaling pathway through Rho-kinase in the survival of developing motor neurons prior to synaptic formation

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Neuronal survival or death during development is generally dependent on neurotrophic supports derived from synaptic targets. However, some motor neurons (MNs) undergo programmed cell death before the formation of synaptic contact at early embryonic stages, suggesting the presence of the mechanism that regulates neuronal survival or death independent of trophic supports. Recently, we reported that the Rho GTPase and its major target protein, Rho-dependent serine/threonine protein kinase (Rho-kinase/ROK/ROCK), play an important role in the survival of the spinal cord MNs at early developmental stages. In the present study, we examined the time course of apoptosis in the transgenic mice that express a dominant-negative Rho-kinase and analyzed the anatomical features of the apoptotic cells. The enhanced apoptosis of MNs in the transgenic embryos was observed at embryonic day 10.5 (E10.5) and then the number of apoptotic cells was decreased at E12.5 and E14.5. MN axons had not reached their target tissues at E10.5 in the transgenic embryo. Activation of caspase-3 was detected in some of dying MNs, indicating that the apoptosis in the transgenics is dependent on the caspase cascade. In addition, ultrastructural morphology of degenerating cells revealed the typical apoptotic features, such as condensation of chromatin structure, electron-dense cytoplasm, and shrinkage of the soma. These data support the view that Rho/Rho-kinase signaling pathway acts to promote the survival of developing MNs prior to synaptic formation independent of target-derived trophic support.

N252 (MS7-6)

Functional analysis of a novel ER stress sensor, CREB/ATF family member, OASIS

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Accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER) causes ER stress. Normal cells respond to ER stress by increasing transcription of genes encoding ER-resident chaperones such as GRP78/BiP to facilitate protein folding. This stress response is called unfolded protein response (UPR) or the ER stress response. It has been reported that IRE1, a transmembrane kinase, and ATF6, a transmembrane transcription factor, sense accumulation of unfolded proteins in the ER and trigger activation of interorganelle signaling from ER to the nucleus. In this study, we identified a novel ER stress sensor OASIS, which is specifically expressed in reactive astrocytes. OASIS is a basic leucine zipper (bZIP) transcription factor of the CREB/ATF family. It contains a transmembrane domain that allows it to associate with ER and a transcription-activating domain in its N-terminus. When C6 glioma cell lines stably expressing OASIS were stimulated by tunicamycin or thapsigargin, OASIS was cleaved within the ER membrane, and the N-terminal cytoplasmic domain, which contains bZIP domain, translocated into the nucleus. We examined the effects of overproduction of OASIS N-terminal fragment (OASIS 374) on the expression of the reporter gene carrying the ER stress responsive element (ERSE) of GRP78/BiP promoter immediately upstream of luciferase gene. The reporter activities were promoted by expression of OASIS 374. Northern blotting analysis showed that the level of endogenous GRP78/BiP mRNA was indeed elevated in cells overproducing OASIS 374. These results suggest that OASIS may be a novel ER stress sensor and play pivotal roles in the modulation of the UPR signaling in astrocytes.

N253

ERK activation by phorbol ester and forskolin attenuates hydrogen peroxide-induced death in PC12 cells

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Accumulation of reactive oxygen species (ROS) is observed in numerous human neurological diseases including ischemia and stroke, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Hydrogen peroxide (H_2O_2), one of ROS, is also known to induce cell death in a wide variety of cells, including neuronal cells. In the present study, we investigated the protective effect of PKC or PKA activation on H_2O_2 -induced cell death in rat pheochromocytoma PC12. H_2O_2 caused dose-dependent PC12 cell death that was measured by colorimetric 3,4,5-dimethylthiazol-2-yl-2,5-diphenyl tetrazolium bromide (MTT) assay. Pretreatment with neither a PKC activator phorbol 1,2-myristate 1,3-acetate (PMA, 3 nM-1 μ M) nor an adenylate cyclase activator forskolin (100-300 nM) affected the cell death. However, pretreatment with a combination of PMA (100 nM) and forskolin (300 nM) prevented the cell death. Treatment with a combination of 100 nM PMA and 300 nM forskolin increased extracellular signaling-regulated kinase (ERK) activity. The mitogen-activated protein kinase/ERK kinase inhibitor PD98059 (20-50 μ M) attenuated the cytoprotective effect of pretreatment with the combination of PMA and forskolin. These results indicate that coactivation of PKC and PKA protects PC12 cells against H_2O_2 -induced death through ERK activation.

N254

Environmental estrogens, bisphenol A and nonylphenol, inhibit staurosporine-induced cell death of primary cultured hippocampal and cortical neurons

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We examined whether estrogenic chemicals could influence neuronal cell death, since programmed cell death was a major event during normal central nervous system (CNS) development. Primary cultured cortical and hippocampal neurons prepared from E18 rats were maintained in serum-free medium without phenol red. At 4 days in culture, estradiol (E_2) (10^{-9} M and 10^{-5} M), bisphenol A (BPA) (10^{-5} M), and nonylphenol (NP) (10^{-5} M) were added to the culture medium. At 24 hr after exposure, neuronal cell death was induced by staurosporine (100nM), and LDH release for 24 hr was measured. Caspase-3 activity was assessed at 6 hr after staurosporine application. In hippocampal neurons, E_2 (10^{-9} M and 10^{-5} M), and BPA (10^{-5} M) significantly inhibited staurosporine-induced LDH release, and NP (10^{-5} M) slightly inhibited. In cortical neurons, BPA (10^{-5} M) significantly inhibited staurosporine-induced LDH release, and NP slightly inhibited. However, E_2 showed no inhibitory effect. In hippocampal neurons, E_2 (10^{-9} M), BPA (10^{-5} M) and NP (10^{-5} M) significantly inhibited staurosporine-induced increase of caspase-3 activity. In cortical neurons, BPA (10^{-5} M) and NP (10^{-5} M) significantly inhibited staurosporine-induced increase of caspase-3 activity. Furthermore, low dose BPA (10^{-8} M) also showed inhibitory effect against staurosporine-induced increase of caspase-3 activity in both cortical and hippocampal neurons. These results suggest that BPA and NP inhibit even desirable neuronal cell death for normal development, interfering with caspase-3 activation.

N255 (MS6-4)

Mechanism of mPer1 induction through CaM kinase II activation in the suprachiasmatic nucleus

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CaM kinase II activity is required for the light-induced phase delays and induction of Per1 and Per2 genes in the hamster suprachiasmatic nucleus. We here focused on intracellular mechanisms of the CaM kinase II-induced mPer1 gene expression. Immunoblotting and immunohistochemical studies with isoform specific antibodies against different isoforms of CaM kinase II and CaM kinase IV showed abundant expression of the delta isoform of CaM kinase II without significant expression of CaM kinase IV in the lateral ventral part of the rat SCN. We next defined CaM kinase II responsive region on the mPer1 promoter using luciferase reporter gene assay. Transfection of the constitutively active CaM kinase II delta largely increased the mPer1 promoter activity in NG108-15 cells and slightly but significantly in NB2A and C6 glioma cells. Similarly, transfection of a constitutively active MEKK, an upstream kinase of MAP kinase largely increased the promoter activity in NB2A cells. Deletion and mutation analyses of the mPer1 promoter revealed that 5'-GAGGGG-3' sequence motif near exon 1B, in which several zinc finger proteins seem to bind, was essential for the CaM kinase II-induced activation of the mPer1 promoter. These results suggest that CaM kinase II delta but not CaM kinase IV play an essential role for mPer1 expression through 5'-GAGGGG-3' motif on the mPer1 promoter.

N256

Abnormal light-induced phase shift in mice lacking pituitary adenylate cyclase-activating polypeptide (PACAP)

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PACAP is a member of the vasoactive intestinal peptide (VIP) /secretin/glucagon family of peptides and functions as a neuromodulator and neurotransmitter and regulates a variety of physiological processes. In an attempt to better understand the *in vivo* role of PACAP, we recently generated mice lacking the PACAP gene (PACAP^{-/-}) and showed that PACAP^{-/-} mice display remarkable behavioral changes, including exhibition of hyperactive and explosive jumping behaviors, increased exploratory behavior and/or less anxiety, and the deficit in prepulse inhibition of the acoustic startle response. PACAP is one of the neurotransmitters as well as glutamate in retinohypothalamic tract, and has been suggested to be involved in the resetting mechanism of the circadian clock. Therefore, in order to clarify the role of PACAP in the generation and resetting the circadian clock, in this study we investigated the circadian locomotor activity profiles and light-induced phase shift in PACAP^{-/-} mice.

PACAP^{-/-} mice exhibited behavioral circadian rhythm under the constant dark conditions with a slightly short free-running period. PACAP^{-/-} mice reentrained to 6h-delay and -advance of light:dark cycles similarly with wild type mice. Light stimulation at late subjective night resulted in significantly attenuated phase advance in PACAP^{-/-} mice compared with wild type mice. In contrast, light stimulation at early subjective night caused modest reduction of phase delay in PACAP^{-/-} mice against wild type mice. These different effects of PACAP deficiency to phase delay and advance suggest the unsymmetrical roles of PACAP in phase resetting of the circadian clock.

N257

Insulin-mediated glucose transport system in the hypothalamus of ob/ob mice

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In peripheral tissues, such as skeletal muscle and white adipose tissue, insulin stimulates glucose transport by inducing the translocation of glucose transporter (GLUT) 4 from an intracellular compartment to the plasma membrane via PI3K-Akt pathway. This glucose transport system is impaired in type 2 diabetes in these tissues, which is called insulin resistance. Although insulin receptor (IR) and GLUT4 proteins are also expressed in the hypothalamus of adult brain, the roles of hypothalamic GLUT4 in the pathogenesis of insulin resistance are still unknown. In this study, we investigated GLUT4 translocation pathway in the hypothalamus of ob/ob mice with hyperinsulinemia, hyperglycemia, and insulin resistance. The expression of IR and GLUT4 proteins was shown to be increased in the hypothalamus of ob/ob mice compared to lean mice by western blot analysis. Immunohistochemical studies revealed that IR- and GLUT4-positive neurons were increased in the arcuate and paraventricular nuclei in the hypothalamus of ob/ob mice. In addition, phosphorylated IR- and Akt-positive neurons were also abundant in these regions of ob/ob mice. Further, the immunoreactivity for GLUT4 was detected in the plasma membrane of hypothalamic neurons of ob/ob mice using immunoelectron microscopy. These results indicate that GLUT4 translocation pathway is activated in the hypothalamus of ob/ob mice, which may suggest the existence of novel mechanisms preventing insulin resistance in the hypothalamus of ob/ob mice. This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (C) Medical Genome Science from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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第46回日本神経化学学会大会（新潟）大会長

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グレラン製薬(株)	佐藤製薬(株)
大正製薬(株)	大鵬薬品工業(株)
帝国臓器製薬(株)	帝人(株)
富山化学工業(株)	鳥居薬品(株)
日本ケミファ(株)	日本製薬(株)
ノバルティスファーマ(株)	萬有製薬(株)
三笠製薬(株)	(株)ミノファージェン製薬
望田製薬(株)	森永乳業(株)
雪印乳業(株)	わかもと製薬(株)

アムジェン(株)	栄研化学(株)
エルメッドエーザイ(株)	大塚製薬(株)
カネボウ(株)	キッセイ薬品工業(株)
キリンビール(株)	グラクソ・スミスクライン(株)
三共(株)	第一製薬(株)
中外製薬(株)	(株)ツムラ
テルモ(株)	トーアエイヨー(株)
日研化学(株)	日本化薬(株)
日本たばこ産業(株)	日本ワイスレダリー(株)
ファイザー製薬(株)	プリストル製薬(株)
明治製薬(株)	明治乳業(株)
(株)ヤクルト本社	山之内製薬(株)

大阪医薬品協会

アストラゼネカ(株)	(株)アズウェル
興和新薬(株)	沢井製薬(株)
シェリング・プラウ(株)	塩野義製薬(株)
武田薬品工業(株)	田辺製薬(株)
日本新薬(株)	日本シェリング(株)
バイエル薬品(株)	藤沢薬品工業(株)
マルホ(株)	三菱ウェルファーマ(株)

(株)大塚製薬工場	小野薬品工業(株)
参天製薬(株)	(株)三和化学研究所
住友製薬(株)	大日本製薬(株)
東和薬品(株)	ニプロファーマ(株)
日本臓器製薬(株)	日本ベーリンガーインゲルハイム(株)
扶養薬品工業(株)	丸石製薬(株)
メルク・ホエイ(株)	ロート製薬(株)

財団等

(財)井上科学振興財団
(財)協和会
(財)三共生命科学研究振興財団
(財)内藤記念科学振興財団

新潟県医師会
新潟県

(財)上原記念生命科学財団
(財)細胞科学研究財団
(財)椿神経疾患研究基金
(財)ブレインサイエンス振興財団
International Society of Neurochemistry
新潟市

ランチョンセミナー

アフメトリクス・ジャパン(株)	日本ベーリンガーインゲルハイム(株)	エーザイ(株)	ファイザー製薬(株)
三菱ウェルファーマ(株)	大日本製薬(株)	小野薬品工業(株)	横河アナリティカルシステムズ(株)

機器・試薬・書籍展示

アフメトリクス・ジャパン(株)	アアプライドバイオシステムズジャパン(株)	インビトロジェン(株)	倉敷紡績株式会社
(株)考古堂書店	(株)西村書店	ベックマン・コールター(株)	和光純薬工業(株)

広告掲載

アストラゼネカ(株)	インビトロジェン(株)	エーザイ(株)	小野薬品工業(株)
キッセイ薬品工業(株)	協和発酵工業(株)	グラクソ・スミスクライン(株)	興和新薬(株)
塩野義製薬(株)	(株)新栄医理科	第一製薬(株)	大正富山医薬品(株)
武田薬品工業(株)	日本イーライリリー(株)	日本ベーリンガーインゲルハイム(株)	ノバルティスファーマ(株)
萬有製薬(株)	ファイザー製薬(株)	藤沢薬品工業(株)	藤本製薬(株)
三菱ウェルファーマ(株)	山之内製薬(株)	和光純薬工業(株)	

(五十音順、2003年7月29日現在)

理事会だより**～ 日本神経化学会の今後の発展をめざして ～**

日本神経化学会 理事長 御子柴克彦
(東京大学医科学研究所、理化学研究所 脳科学総合研究センター)

日本神経化学会は、精神医学研究を指向するグループと、基礎研究者（生理学、生化学、薬理学等の分野）が、脳の高次機能の物質的基盤を明らかにする目的で設立されて今年で46年目を迎えます。学会は時代の流れとともにその社会からの要請は変化してきています。

日本神経化学会は理事会の下部組織として、将来計画委員会を作り、これまでに多くの調査を行ってきています。常に将来を見据えてその方向性を先取りしていますが、その一つが日本神経化学会の「国際化」でした。この他に「他学会との交流」、「若手の育成」をはじめとして幾つかの提案がなされています。

これらは相互に強くリンクしているものであります。「他学会との交流」の第一歩として今回は新潟の地で、辻 省次大会長のもと、日本生物物理学会とのジョイント大会となったのでその意義などについても触れてみたいと思います。

日本生物物理学会とのジョイントから相互に得られるもの

これまで、他学会との合同として日本神経科学学会とのジョイントは3年に一回毎に開催しようと決めて日本神経科学学会へ提案して、相互の同意のもとに進めてきました。しかし今回の生物物理学会とのジョイントは、それとは質的に全く異なっていると言えます。日本神経科学学会とのジョイントでは、合同で行ういくつかの理由はあるにしても、一番大きな理由は同じ脳神経系という共通材料を扱う学会なので二度別々に開催するよりは、一回で両方に参加する方が開催する側も、参加する側も両方、より効果的であるということが主な理由であります。

ここで今回の日本神経化学会と日本生物物理学会のジョイントの意義を考えてみたいと思います。

「神経化学」と「生物物理」の違いと共通点

神経化学は「脳神経系の構造と機能を物質レベルで明らかにしよう」とする方向を持ち、生物物理は「生物現象を物理の言葉で語ろう」と云うことと単純化しても良いと思います。「生物」というキーワードでは共通であっても、「神経」と云う言葉は生物物理から見ると異なる領域のもの、「物理」は神経化学からはかなり離れた言葉として捉えられていると思います。共通点はというと、両学会とも「物質」を扱っていることでしょう。「物質」ということになると一見、両分野で共通性はあるにしても神経化学と生物物理では捉え方は全く異なるように思われがちです。しかし、神経化学と生物物理における「物質」の捉え方が異なるにしても実は両者ともに十分に研究が進んでいない為であって、両者はいずれ融合しあうものであると私は考えています。現時点ではまだ両学問が十分に進んでいない為、全く異次元の世界のように考えて、物の考え方や、材料の選択、方法も異なるように考えていますが、早く我々にはともに、いかに違っているのか、どう違っているのかを相互に認識する必要があるでしょう。それが両者の歩みより融合する第一歩となり、且つこれが両者が相互理解の上に飛躍的に発展する第一歩と考えています。

異分野交流から創造性へ

日本神経化学会と日本生物物理学会はともにオリジナルな成果を発信しています。日本神経化学会からは世界にこれまで多くのことが発信されています。例えばリン酸化の研究の中からプロテインキナーゼCの発見が出て来たり、カルモジュリンの発見、プロスタグランジン、各種レセプターやイオンチャネル、ペプチドの研究など、と枚挙にいとまがありません。また最近の日本生物物理学会の一分子イメージングを中心とした研究展開は素晴らしいものがあります。日本の独創的な常に新しい技術を開発してきた生物物理学会と、新しい脳内の機能分子を探求してきた神経化学会というこれらのユニークな二つの学会が合同で大会を開催することがサイエンスを更に加速させるに違いないと信じています。

若手の間の交流を期待して

生物物理学会は、大学院生の参加が圧倒的に多いのです。若手育成を考える上で今回の生物物理学会とのジョイントが、日本神経化学会の若手育成を考える上でも大きなヒントを得られるものと考えています。この大会後に、将来計画委員会の調査結果を踏まえてじっくりと、神経化学会に於いての若手育成の具体策についても、考えてゆきたいと思います。皆様方の新潟大会の参加をお願いし、今後の議論を深めて頂きたいと存じます。

日本神経化学会役員リスト

理事長

御子柴克彦 (東京大学医科学研究所)

副理事長

熊倉鴻之助 (上智大学生命科学研究所)

庶務担当理事

岡野 栄之 (慶應義塾大学医学部)

会計担当理事

高坂 新一 (国立精神・神経センター)

出版広報担当理事

柳澤 勝彦 (国立療養所中部病院長寿医療センター)

理事

井上 和秀 (国立医薬品食品衛生研究所)

神庭 重信 (山梨大学医学部)

佐藤 真 (福井医科大学医学部)

島田 昌一 (名古屋市立大学大学院医学研究科)

高松 研 (東邦大学医学部)

辻 省次 (東京大学大学院医学系研究科)

遠山 正彌 (大阪大学大学院医学系研究科)

鍋島 俊隆 (名古屋大学大学院医学研究科)

野村 靖幸 (北海道大学大学院薬学研究科)

馬場 明道 (大阪大学大学院薬学系研究科)

監事

植村 慶一 (慶應義塾大学名誉教授)

宮武 正 (昭和薬科大学)

委員会リスト

将来計画委員会

委員長 熊倉鴻之助 (上智大)

阿部 輝雄 (新潟大)、五嶋 良郎 (横浜市大)、小泉 修一 (医薬品食品衛生研)、
斎藤祐見子 (埼玉医大)、佐野 輝 (鹿児島大)、仙波りつ子 (愛知県コロニー)、
田代 朋子 (青山学院大)、中村 洋一 (大阪府大)、馬場 広子 (東京薬大)、
松岡 一郎 (北海道大)、吉田 明 (長崎大)、米田 幸雄 (金沢大)

編集委員会

委員長 柳澤 勝彦 (長寿医療センター)

木山 博資 (大阪市大)、佐野 輝 (鹿児島大)、鈴木 龍雄 (信州大)、
平 英一 (大阪大)、馬場 広子 (東京薬大)、和中 明生 (奈良県医大)

シンポジウム企画委員会

委員長 鍋島 俊隆 (名古屋大)

浅沼 幹人 (岡山大)、浅野 富子 (愛知県コロニー)、植田 弘師 (長崎大)、
岡野 栄之 (慶應大)、神庭 重信 (山梨大)、仙波恵美子 (和歌山県医大)、
武田 雅俊 (大阪大)、山田 清文 (金沢大)、渡辺 恭良 (大阪市大)

国際対応委員会

委員長 池中 一裕 (生理研)

浅井 清文 (名古屋市大)、阿相 皓晃 (都老人研)、北村 邦男 (埼玉医大)、
白尾 智明 (群馬大)、東田 博陽 (金沢大)、松岡 一郎 (北海道大)、
宮本 英七 (早稲田大)、和中 明生 (奈良県医大)

研究助成金等候補者選考委員会

委員長 馬場 明道 (大阪大)

井上 和秀 (医薬品食品衛生研)、澤田 誠 (藤田保衛大)、武井 延之 (新潟大)、
田中 稔久 (大阪大)、津田 正明 (富山医薬大)

脳研究推進委員会

委員長 辻 省次 (東京大)

高橋 正身 (北里大)、武田 雅俊 (大阪大)、古市 貞一 (理化研)、
和田 圭司 (精神・神経セ)

理事会議事録

2003年度第1回理事会

日 時：2003年3月13日（木） 13:00～17:30

会 場：都市センターホテル「607」

出席者：井上 和秀、岡野 栄之、熊倉鴻之助、高坂 新一、佐藤 真、島田 昌一、
辻 省次、遠山 正彌、鍋島 俊隆、御子柴克彦、柳澤 勝彦
植村 慶一、宮武 正（監事）
池中 一裕（前 庶務担当理事）
武田 雅俊（前 シンポジウム企画委員長）
田代 朋子（前 将来計画委員長）
五十嵐修一、成瀬 聡（第46回大会実行委員）

欠席者：馬場 明道（理事）

宮本 英七（前 副理事長）

小宮 義璋（前 科研費調査委員長）、東田 陽博（前 国際対応委員長）

議 題

議事に先立ち、御子柴前理事長より前理事会の取り組み、現在学会がおかれている状況、国際問題についての概要等が報告された。

1. 理事改選結果報告について

平成15年2月18日に開票された理事選挙結果について、選挙管理委員会 今井嘉紀委員長からの報告書が示された。

理事選挙結果報告について

日本神経学会細則第2条および同第4条の規定により理事選挙を実施しましたところ、下記の通りの結果となりましたのでご報告申し上げます。

記

1. 選挙経過

(1) 選挙日程

神経化学 第41巻4号（2002年12月1日発行）公示の要領に従い実施した。

(2) 投票用紙の開票

発送総数 1,410通（但し受取人不明で7通は返送された）

投票通数 447通（投票率31.7%）

有効通数 447通

(3) 開票場所

八重洲龍名館

(4) 開票立会人

中嶋 一行 会員

浜之上 誠 会員

(5) その他

氏名の誤記等については、特定の被選挙人と判別できる場合には有効とした。

2. 得票順位

当 選	1	遠山 正彌
同	2	井上 和秀
同	3	島田 昌一
同	4	柳澤 勝彦
同	5	鍋島 俊隆
同	6	佐藤 真

2. 理事長・副理事長選出の件

出席理事による協議の後投票が行われ、理事長に御子柴 克彦氏（東京大学医科学研究所脳神経発生・分化分野）が、副理事長に熊倉 鴻之助氏（上智大学生命科学研究所神経化学部門）がそれぞれ選出された（任期はそれぞれ2005年2月末日迄）。

3. 補充理事選出の件

得票数、専門分野および地域性等を考慮し、出席理事による協議の後、投票により下記の通りの補充理事を選出した（任期：2005年2月末日迄）。補充理事は細則第2条により評議員会の承認事項となるため、前例に倣い文書で評議員に可否を伺うこととした。

また、幅広い人材より補充理事を選出するために、理事選挙における得票順位をどの程度まで選挙管理委員会から報告していただくかを検討することとした。

神庭 重信氏（山梨大・医・精神神経医学）

高松 研氏（東邦大・医・生理学）

野村 靖幸氏（北海道大・院・薬・医療薬学）

（50音順）

4. 担当理事選任の件

協議の結果、各担当理事（任期2年）を以下の通りに選任した。

庶務担当：岡野 栄之氏

会計担当：高坂 新一氏（留任）

出版広報担当：柳澤 勝彦氏

5. 各委員会委員長選任の件

協議の結果、各委員会の委員長（任期2年）を以下の通りに選任した。尚、委員長は理事会と密接な関係を持ち重要な役割を担っていただくため、原則として理事の中から選出する事とした。また、科研費調査委員会は委員会発足当初の役割を終了したとして発展的に解消し、新たに「脳研究推進委員会」を設置することが了承された。

研究助成金等候補者選考委員会：馬場 明道氏（留任）

将来計画委員会：熊倉鴻之助氏（副理事長）

シンポジウム企画委員会：鍋島 俊隆氏

国際対応委員会：池中 一裕氏

編集委員会：柳澤 勝彦氏（出版広報担当理事）

脳研究推進委員会：辻 省次氏

6. 庶務報告

池中前庶務担当理事より、庶務報告が行われた。

・総会員数（平成14年12月31日現在） 1,714名

名誉会員 15名

一般会員 1,424名

学生会員 241名

賛助会員 21名

団体会員 13名

・会員異動状況（平成14年1月1日～12月31日）

新入会者 112名

退会者 178名

尚、入退会者の会員種別内訳は新入会員112名（正会員61名・学生会員50名、海外名誉会員1名）、退会会員178名（正会員145名・学生会員32名、賛助会員1名）だった。

7. 会計報告

高坂会計担当理事より平成14年度（平成14年1月1日～12月31日）の決算報告がなされた。引き続き植村監事より監査報告があり、了承された。

8. 出版広報報告

岡野前出版広報担当理事より、平成14年度の学会誌の刊行状況及び学会HPについて報告が行われた。

9. 委員会報告の件

(1) 将来計画委員会

田代前委員長より以下の報告がなされた。

昨年の札幌大会終了後に評議員を対象として電子メールで札幌大会での新しい試みや大会運営・今後の学会運営等についてアンケートを取り、集計したものを学会誌「神経化学」に掲載した。

今後は大会終了後に毎回アンケートを実施してはどうかという意見もあったが、アンケートをとるだけではなくアンケートで出された意見に対し理事会としてどう応えていくのかを検討し、次回理事会で具体的な方針を会員に対して出せるようにする事とした。

(2) 研究助成金等候補者選考委員会

欠席された馬場前委員長より平成14年度の各財団の褒賞・助成に対する学会内の応募状況の報告書が理事会宛に提出された。

(3) 科研費調査委員会

欠席された小宮前委員長より理事選出選挙と同時に行われた「平成16・17年度科学研究費審査委員候補者選出選挙経過」についての報告書が理事会宛に提出された。

(4) シンポジウム企画委員会

武田前委員長から提案された第46回日本神経化学会（新潟大会）でのオープンシンポジウム企画案について演者、内容を検討し最終案を取りまとめた。

今後、オープンシンポジウムは早い段階で委員会に企画案をまとめていただき、理事会で検討した後で再度委員会にフィードバックし、大会事務局が会員に対してシンポジウムを公募する前に最終案の骨子をまとめ、一般公募のシンポジウムとテーマが重複しないよ

うに配慮する事とした。

オープンシンポジウムは立ち上げ当初からシンポジウム開催の趣旨が若干異なってきたので、オープンシンポジウム（及び委員会）の名称、今後の方向性を再検討するとともに、オープンシンポジウムが他の大会プログラムの中に埋もれてしまわないように大会事務局に配慮していただくべきではないかとの意見も出された。

また、昨年の第45回大会から大会会期中に「ISNシンポジウム」を開催している。昨年及び今年の大会での「ISNシンポジウム」は理事会執行部が立案した。「ISNシンポジウム」の企画立案を誰が行うかについて議論され、今後は理事長・国際対応委員長・大会長（または大会実行委員）にオブザーバーとして参加していただき、シンポジウム企画委員会で取りまとめていただく事にした。

(5) 国際対応委員会

欠席された東田前委員長より学会誌「神経化学」次号において「ISN/APSIN Joint Meeting 2003への参加とISN会員への登録呼びかけ」を掲載することが書面で報告された。

10. 評議員推薦の件

今回、評議員に3名の申請があり、候補者を審査し了承されたため次回の総会に諮ることとした。

11. 名誉会員推薦の件

今回、名誉会員に3名の方の推薦があった。今回の審議を経て次回の理事会で再度確認の上、候補者を総会に推薦することとした。

12. 第46回日本神経化学学会大会の件

辻大会長より大会案内（案）、プログラム（案）が提案され了承された。

今回は生物物理学会との合同大会となるが、大会プログラムを生物物理学会と共通の内容で独立して作成するか、前回の神経科学学会との合同大会の時のようにプログラムと抄録を合本とするのかについて審議され引き続き検討することとした。大会では生物物理学会との合同シンポジウムも予定し、双方の会員からアンケートを取って内容を決める事としている。

昨年の札幌大会に引き続きアジア各国から参加を希望する若手研究者を対象に「Young Investigator Award」を設け、ISN/APSIN Joint Meeting 2003のWebサイトを通じて広報することとした。

国際化を考慮し、抄録は全て英文とし、タイトルは和英併記としていただくこととした。シンポジウムについては原則として英語で行っていただき、少なくともスライドは英文でご用意いただく事とした。尚、大会発表においての倫理問題については発表者の自己申告とする。

また、シンポジウムの公募方法として、シンポジウムのテーマを公募する方法の他に、シンポジウムのテーマを公開してシンポジストを広く会員から募集し大会への参加意欲を高める方法が提案され、来年以降に開催される大会において引き続き検討していく事とした。

13. 第47回日本神経化学学会の件

遠山正彌次期大会長より提出された日程案が了承された。尚、日本神経科学学会との合同大会となるため「Neuro200X」を引き続き使用し大会名称を「Neuro2004」とした。

第47回日本神経化学学会大会

会 期：2004年9月21日～23日

会 場：大阪国際会議場

14. その他

(1) ISN/APSNサテライトシンポジウムの件

鍋島理事よりISN/APSN2003に先立って開催されるサテライトシンポジウムの概要説明と日本薬学会第123年会シンポジウムの説明がなされた。

・ ISN/APSNサテライトシンポジウム

会 期：2003年7月29日～8月1日

会 場：国立京都国際会館

・ 日本薬学会第123年会 シンポジウム

会 期：2003年3月27日

会 場：長崎厚生年金会館

(2) 「世界脳週間2002」 結果報告の件

本学会が協賛した「世界脳週間」が終了し、脳の世紀実行委員会より事業報告書が提出された。

(3) 臨時理事会開催の件

今回の理事会で選任された補充理事を迎え、早急に臨時理事会を開催し、今期の学会の方針を定めることにした。

(4) ISN理事選挙の件

現在、ISNの理事には日本から御子柴克彦氏がなられているが今期で任期満了となる。近々、ISNの次期理事選挙が行われるが、日本としては池中一裕氏を次期理事候補として推薦していくこととした。

理事会議事録

2003年度第2回理事会

日 時：2003年5月21日（水） 13:00～17:00

会 場：主婦会館プラザエフ「パンジー」

出席者：御子柴克彦、熊倉鴻之助、井上 和秀、岡野 栄之、神庭 重信、
高坂 新一、佐藤 真、島田 昌一、高松 研、辻 省次、
鍋島 俊隆、野村 靖幸、馬場 明道、柳澤 勝彦
植村 慶一、宮武 正（監事）
池中 一裕（国際対応委員長）

欠席者：遠山 正彌（理事）

議 題

議事に先立ち、御子柴理事長より挨拶がなされた。

1. 補充理事選考可否の件

岡野庶務担当理事より以下の報告がなされた。前回理事会で選任された補充理事は細則第2条により評議員会の承認を得ることになっていた。郵送による持ち回りの審議で評議員に可否をお伺いしたところ、213名中159名の評議員より「可」という回答があり承認された。

2. 国際関係の件

2003年8月に香港で開催を予定されていたISN/APSN Meeting 2003はSARS（重症急性呼吸器症候群）のために中止となった。

ISN/APSN Meeting 2003 は中止となったが、ISN/APSN Meeting 2003 のアブストラクトを発行するという連絡や、2004年2月頃に香港でAPSN Meeting のみを単独で開催したいという連絡がきており対応について協議を行った。

3. 委員会構成の件

今期の委員会構成について各委員長より事前に委員候補リストが提出されている。各委員会の人員構成について各委員長より提案がなされた後、委員会構成について審議され今期の委員会委員を内定し委員候補者には可否を諮ることとした。

尚、委員会委員はなるべく若手の評議員に就任を依頼し、委員の兼任、理事の委員就任はなるべく避けることが確認された。

2003-2004年度委員会

・将来計画委員会

熊倉鴻之助（上智大／委員長・副理事長）

阿部 輝雄（新潟大）

五嶋 良郎（横浜市大）

小泉 修一（医薬品食品衛生研）

斎藤祐見子（埼玉医大）

佐野 輝（鹿児島大）

仙波りつ子（愛知県コロニー）

高橋 正身（北里大）

田代 朋子（青山学院大）

中村 洋一（大阪府大）

馬場 広子（東京薬大）

松岡 一郎（北海道大）

吉田 明（長崎大）

米田 幸雄（金沢大）

・編集委員会

柳澤 勝彦 (長寿医療センター／委員長・出版広報担当理事)

木山 博資 (大阪市大)

平 英一 (大阪大)

佐野 輝 (鹿児島大)

馬場 広子 (東京薬大)

鈴木 龍雄 (信州大)

和中 明生 (奈良県医大)

・シンポジウム企画委員会

鍋島 俊隆 (名古屋大／委員長)

神庭 重信 (山梨大)

浅沼 幹人 (岡山大)

仙波恵美子 (和歌山県医大)

浅野 富子 (愛知県コロニー)

武田 雅俊 (大阪大)

植田 弘師 (長崎大)

山田 清文 (金沢大)

岡野 栄之 (慶應大)

渡辺 恭良 (大阪市大)

・国際対応委員会

池中 一裕 (生理研／委員長)

東田 博陽 (金沢大)

浅井 清文 (名古屋市大)

松岡 一郎 (北海道大)

阿相 皓晃 (都老人研)

宮本 英七 (早稲田大)

北村 邦男 (埼玉医大)

和中 明生 (奈良県医大)

白尾 智明 (群馬大)

・研究助成金等候補者選考委員会

馬場 明道 (大阪大／委員長)

武井 延之 (新潟大)

井上 和秀 (医薬品食品衛生研)

田中 稔久 (大阪大)

澤田 誠 (藤田保衛大)

津田 正明 (富山医薬大)

・脳研究推進委員会

辻 省次 (東京大／委員長)

古市 貞一 (理化研)

高橋 正身 (北里大)

和田 圭司 (精神・神経セ)

武田 雅俊 (大阪大)

4. 名誉会員推薦の件

前回推薦のあった候補者を再度審議し了承されたため総会に推薦することとした。

5. 第46回日本神経化学会大会の件

辻大会長より大会準備の進捗状況が報告された。

今回も昨年と同様に一般演題の中から演題を選んでミニシンポジウムを行うこととした。

大会発表の英語化の問題について、将来計画委員会でのアンケート結果では「部分的に賛成」という意見が多かった。今回の大会では原則としてシンポジウムは英語で行っていただくが、来年からは英語化をより推進することとした。尚、理事会の協議で奨励賞受賞シンポジウムの発表・質疑を今年から英語で行うこととした。

また、大会で優秀な発表を行った若手研究者を表彰してはどうかという意見が出され日本神経化学会として表彰するのか大会長として表彰するのか、選考はどこが行うのかといった問題点が論じられた。本件は将来計画委員会で検討していただくこととした。

6. 第47回日本神経化学会の件

欠席された遠山正彌次期大会長より下記の日程案が書面で提示され確認された。

第47回日本神経化学会大会（「Neuro2004」として第27回日本神経科学学会との合同大会）

会 期：2004年9月21日～23日

会 場：大阪国際会議場

関連して池中国際対応委員長より以下の提案がなされ了承された。

APSN Meetingは学問的な情報交換の場というよりもアジア諸国の科学の発展のための援助や啓蒙活動をする場となることが多い。

そこで来年の合同大会前の9月19-20日に中国（香港を含む）・韓国・日本の3ヶ国で国際研究集会を日本で開催する計画を立てており、日本の公的機関に補助金を申請するとともにISN会長からも賛同され若干の資金援助も約束されている。

今後、アジア諸国をサポートしアジア諸国に対して開かれた日本神経化学会となることを目的とした研究集会を日本神経化学会の大会前に継続的に開催していきたい。この研究集会をJSNのSatellite Meeting的な位置づけで定着させれば、ISNのメンバーの参加も期待できると思われる。

7. その他

(1) 日本学術会議の件

御子柴理事長より下記の報告がなされた。

前理事会で理事各位に各研連の会員候補者として相応しい方を推薦（投票）していただき、上位者を会員候補として日本学術会議に推薦した。尚、推薦人及び推薦人予備者の選考は理事長に一任されていたので適任と思われる方に依頼した。

・細胞生物学研究連絡委員会

会員候補 宮本英七氏

推薦人 井上和秀氏

推薦人予備者 野村正彦氏

・脳・神経学研究連絡委員会

会員候補 遠山正彌氏

推薦人 木山博資氏

推薦人予備者 和中明生氏

・分子生物学研究連絡委員会

会員候補 御子柴克彦氏

推薦人 熊倉鴻之助氏

推薦人予備者 田代朋子氏

(2) 理事選挙結果報告の件

理事選挙における選挙結果報告は補充理事選出の重要な資料となるため、今後、選挙管理委員会にどの程度の順位までを報告していただくかについて協議した結果、従来通り上位20名程度をご報告いただくこととした。

(3) アメリカ神経化学会（ASN）からの提案の件

本学会に対してASNの次期会長より2006年にハワイで合同大会を開催してはどうかという打診があった。合同シンポジウム等、部分的なジョイント開催も含めて対応を検討することとした。

(4) 今後の大会開催予定の件

日本神経化学会大会開催予定は2004年の第47回大会（大阪）まで正式に決まっている。本学会は2007年に第50回大会を迎えるため、50周年記念事業をどのようにするかを念頭において今後の大会開催地や日本神経科学学会との合同大会スケジュールを検討していくこととした。

(5) 評議員の活性化の件

現行の規約では評議員の任期は4年で、任期満了ごとに次期評議員就任の諾否を諮っているが、定年を設けていないこともあり評議員の高齢化が目立っているとの指摘がなされた。

評議員の定数は会則第21条で「50名乃至250名」と定められているが、定数に達していないため、学会活動に熱心な若手研究者を積極的に評議員として推薦していただくこととした。

また、若手研究者の積極的な学会運営の参画をはかるため、昨年度までの奨励賞受賞者を理事会として今年の総会で評議員に推薦することとした。

(6) 奨励賞選考委員会の件

日本神経化学会奨励賞内規5項では「選考委員の所属する研究室から自薦者が出た場合は、選考委員を辞退すること」となっている。

第5項について検討がなされ、選考委員の所属する研究室から奨励賞の応募者が出た時は、選考委員を辞任するのではなく、その年の選考を辞退していただくことが確認された。

学会よりのお知らせ

評議員会

日 時：9月24日（水）12時00分～13時00分

会 場：Room201

平成15年度評議員会議題（案）

「日本神経化学会の今後の発展をめざして」

総 会

日 時：9月25日（木）16時55分～17時40分

会 場：マリンホール

平成15年度総会議題（案）

1. 平成15年度理事改選結果報告
2. 理事長報告
3. 庶務報告
4. 出版広報報告
5. プログラム編成報告
6. 委員会報告
7. 平成14年度決算の件
8. 平成16年度予算の件
9. 評議員選任の件
10. 名誉会員推薦の件
11. 次期大会の件
12. 奨励賞選考委員会報告
13. その他

学会掲示板**上智大学生命科学研究所教授募集**

- 専門分野：** 動物の行動発現あるいは神経回路形成に関連した分野（生理学または分子レベルで研究を推進されている方）
- 担当職務：** 当研究所は、理工学部所属の生物科学系の教員（5部門）と、神学部および文学部所属の兼任教員（2部門）により構成された組織です。公募する教授は理工学部所属となりますが、生物科学関連の学部学科はありませんので、全学共通教育（一般教育）と、理工学研究科生物科学専攻における大学院生の研究指導と教育を担当していただきます。
- 応募資格：** 博士号を持っている方で、50歳以下の方
- 着任時期：** 平成16年4月1日
- 提出書類：** (1) 履歴書、(2) 業績リスト（原著、総説等を含む）、(3) 主要論文別刷り、または、コピー（5編以内）、(4) 各種研究助成金の取得状況、(5) これまでの研究の概要（2000字以内）、(6) 今後の研究方針と教育に対する抱負（2000字以内）、(7) 応募者について問い合わせのできる方2名の所属と連絡先
- 公募締切：** 平成15年8月29日（必着）
- 書類送付先：** 〒102-8554 東京都千代田区紀尾井町7-1
上智大学生命科学研究所 所長 井内一郎
封筒に「教員募集書類」と朱書し、簡易書留で郵送してください。
- 問合せ先：** 〒102-8554 東京都千代田区紀尾井町7-1
上智大学生命科学研究所 所長 井内一郎
Tel: 03-3238-3393 E-Mail: i-iuchi@hoffman.cc.sophia.ac.jp
<http://www.st.sophia.ac.jp/seimei/>

岐阜大学工学部生命工学科・大学院工学研究科生命工学専攻教官公募**【助教授または講師】**

- 募集人員：** 助教授または講師1名
- 専門分野・仕事の内容：**
化学的素養があり、糖質や脂質などに関連する分子認識の分野で研究を行っており、学部および大学院の教育・研究を担当できる方。
- 応募資格：** 博士号取得者
- 着任時期：** 2004年4月1日
- 提出書類：** (1) 履歴書、(2) 業績リスト、(3) 代表的な原著論文別刷（5編程度）、(4) 現在までの研究の概要と将来に対する研究・教育についての抱負（1200字程度）、(5) 外部からの研究資金獲得リスト、(6) 本人について意見を求める方2名の氏名、連絡先。以上各2部ずつ（コピー可）。なお、提出書類は返却致しません。
- 応募締切：** 2003年10月10日（金）必着

書類送付先：〒501-1193 岐阜市柳戸1-1 岐阜大学工学部生命工学科

学科主任 木内一壽

封筒に「応募書類在中」と朱記し、簡易書留あるいは書留で送付のこと。

【助 手】

募集人員： 助手1名

専門分野・仕事の内容：

神経系における細胞内シグナル伝達に興味を持ち、木内一壽教授と協力して意欲的に研究を進める方。学部の生命工学実習を担当。

応募資格： 博士号取得者あるいは博士課程修了見込者（着任時）で、30歳ぐらいまでの方。

着任時期： 2004年4月1日までに着任

提出書類： (1) 履歴書、(2) 業績リスト、(3) 原著論文別刷（5編以内、筆頭著者でない場合、応募者が担当した実験が分かるように該当する場所にマークしてください）、(4) 修得した生化学・分子生物学領域における技術、(5) これまでの研究概要と将来の研究についての抱負（1200字以内）、(6) 本人について意見を求める方2名の氏名、連絡先。以上各2部ずつ（コピー可）。なお、提出書類は返却致しません。

応募締切： 2003年10月10日（金）必着

書類送付先：〒501-1193 岐阜市柳戸1-1 岐阜大学工学部生命工学科

学科主任 木内一壽

封筒に「応募書類在中」と朱記し、簡易書留あるいは書留で送付のこと。

問合せ先： 岐阜大学工学部生命工学科 学科主任 木内一壽

TEL: 058-293-2651 e-mail: kiuchi@biomol.gifu-u.ac.jp

（財）東レ科学振興会「第53回科学講演会」

日 時： 2003年9月19日（金） 18：00～20：45（開場17：30）

会 場： 有楽町朝日ホール

千代田区有楽町2-5-1 有楽町マリオン11階（JR有楽町駅前）

テーマ： 遺伝子治療と再生医療

1. インターフェロンと遺伝子治療

吉田 純（名古屋大学大学院医学系研究科 教授）

2. 中枢神経系再生医学

岡野 栄之（慶應義塾大学医学部生理学教室 教授）

その他： 入場無料・予約不要（当日会場先着順／定員630名）

ご来聴の方には後日講演記録を進呈いたします。

問合せ先：財団法人東レ科学振興会

〒279-8555 千葉県浦安市美浜1-8-1（東レビル）

TEL: 047-350-6103 FAX: 047-350-6082

E-mail: JDP00120@nifty.ne.jp

<http://www.toray.co.jp/tsf/index.html>

(財) ノバルティス振興科学財団公開シンポジウム

Pathological Pain: from Molecular to Clinical Aspects

「病態痛：分子から臨床まで」

日 時： 2003年10月3日（金）9:30～

会 場： 安田生命ホール

東京都新宿区西新宿1-9-1 安田生命ビルB1F

問合せ先：〒106-0032 東京都港区六本木7-8-4 銀嶺ビル5F

(財) ノバルティス振興科学財団

TEL：03-5414-5761 FAX：03-3796-8271

- 講 演：
- ・ Mechanisms of bone cancer pain 「骨癌痛のメカニズム」
Mantyh PW (Minnesota, USA)
 - ・ Abnormal discharges and neuropathic pain 「異常放電とニューロパシー痛」
Devor M (Jerusalem, Israel)
 - ・ Neurotrophic factors and neuropathic pain 「神経栄養因子とニューロパシー痛」
McMahon SB (London, UK)
 - ・ Sympathetic involvement in pathological pain 「病態痛における交感神経関与」
Perl ER (Chapel Hill, USA)
 - ・ Imaging brain pathophysiology of chronic pain 「慢性痛の脳イメージング」
Apkarian VA (Chicago, USA)
 - ・ Mechanistic and clinical aspects of complex regional pain syndrome
「CRPSのメカニズムと臨床」
Baron R (Kiel, Germany)

第25回 理化学研究所 科学講演会開催のお知らせ

理化学研究所では、最先端の研究を一般の方々に広く知っていただくため、科学講演会を毎年開催しています。本年度は、「～脳を知る 守る 創る 育む～脳科学総合研究センター（仮）」をテーマに、脳科学について第一線の研究者が最新的话题を分かりやすく紹介します。下記ご覧の上、奮ってご来場ください。

日 時： 平成15年10月30日（木） 14:00～17:20

会 場： 東京国際フォーラム ホールC（東京都千代田区丸の内3-5-1）

JR・地下鉄 有楽町駅 徒歩1分

参加費： 無料

講 演： 「学習と記憶の機構」

理化学研究所 脳科学総合研究センター

RIKEN-MIT脳科学研究センター長 利根川 進

「脳の設計図は果たして読めるのかー脳科学の夢」

特別顧問 伊藤 正男

「21世紀の脳科学」

センター長 甘利 俊一

参加事前申し込み：不要

問合せ先：理化学研究所 広報室 Tel.048-467-9954

koho@postman.riken.go.jp

http://www.riken.go.jp

千里ライフサイエンスセミナー 「アルツハイマー病研究の最前線と治療への挑戦」

日 時： 平成16年1月16日（金）10:00～17:00

場 所： 千里ライフサイエンスセンタービル 5階ライフホール

着眼点： アルツハイマー病研究は原因究明に向けこの10年間で飛躍的に進展した。原因遺伝子の特定から発症のしくみが解き明かされつつあり、さらに治療へとつながる応用研究も行われるに至っている。本セミナーでは特に話題性のある研究にクローズアップしてアルツハイマー病の本質に迫る。

コーディネーター：

奈良先端科学技術大学院大学 助教授 今泉 和則

大阪大学大学院医学系研究科 教授 遠山 正彌

プログラム：

1. はじめに 今泉 和則

2. A β 代謝とアルツハイマー病

理化学研究所 脳科学総合研究センター 神経蛋白制御研究チーム

チームリーダー 西道 隆臣

3. A β 凝集開始の分子基盤

国立長寿医療研究センター 痴呆疾患研究部 研究部長 柳澤 勝彦

4. γ セクレターゼの形成と機能

東京大学大学院薬学系研究科 臨床薬学教室 教授 岩坪 威

5. 小胞体ストレスとアルツハイマー病

奈良先端科学技術大学院大学 バイオサイエンス研究会

助教授 今泉 和則

6. ミクログリアとアルツハイマー病

京都大学大学院医学系研究科 臨床神経学 助教授 下濱 俊

7. 脳の老化とアルツハイマー病発症機構—タウ研究からのアプローチ

理化学研究所 脳科学総合研究センター アルツハイマー病研究チーム

チームリーダー 高島 明彦

8. おわりに 遠山 正彌

問合せ先：(財)千里ライフサイエンス振興財団 ブレインサイエンス係

〒560-0082 大阪府豊中市新千里東町1-4-2

千里ライフサイエンスセンタービル8階

TEL：06-6873-2001 FAX：06-6873-2002

E-mail：tnb-lsf@senri-lc.co.jp （注：lsfは「エルエスエフ」、lcは「エルシー」）

URL：http://www.senri-lc.co.jp

第12回日本バイオイメーjing学会学術集会

日 時： 2003年10月29日（金）～31日

会 場： 慶応義塾大学日吉キャンパス 来往舎（らいおうしゃ）会議室
横浜市港北区日吉4-1-1

プログラム：・公開シンポジウム（2003年10月29日／入場無料）

「ナノバイオロジをイメージングする」

1. 細胞・組織障害のメカニズム解析
2. ナノテクノロジーの生物・医療分野への応用
3. 生体のナノフィールド動態観察

・学術集会（2003年30-31日／参加費はHPをご覧ください）

連絡先： 第12回日本バイオイメーjing学会

〒101-0063 東京都千代田区神田淡路町2-6-2

医療法人亮友会

Tel. 03-3251-6878 Fax. 03-3251-6848

E-mail: oshio@ff.ij4u.or.jp

<http://131.113.64.36/bioimaging.html>

褒賞・助成の推薦依頼のお知らせ

1. (財) 内藤記念科学振興財団（日本神経化学会からの推薦枠 各1件）

・内藤記念科学振興賞（日本神経化学会締切日：2003年9月1日必着）

【趣旨】

人類の健康の増進に寄与し得る自然科学の基礎的領域における進歩発展に顕著な功績のあった研究者に対してほう賞を授与するものである。

【候補者資格】

- 1) 人類の健康の増進に寄与する自然科学の基礎的研究において独創的テーマに取り組み、進歩発展に顕著な功績を上げた研究者。
- 2) 候補者は単独とするが、異なる研究グループによる共同研究の場合には、連名であっても良い。
- 3) 候補者の再度の推薦は差支えない。
- 4) 褒賞：正賞 金メダル 副賞 500万円

・内藤記念海外学者招へい助成金

後期：2004年7月1日～2004年12月31日に外国の研究者を招聘するもの

（日本神経化学会締切日：2003年9月1日必着）

・資料請求／問合せ先

(財) 内藤記念科学振興財団

〒103-0033 東京都文京区本郷3-42-6 NKDビル8F

TEL：03-3813-3005 FAX：03-3811-2917

<http://www.naito-f.or.jp/> E-mail：info@naito-f.or.jp

2. (財) 東レ科学振興会 (日本神経化学会締切日: 2003年9月1日必着)

下記の2件については日本神経化学会からの推薦枠は各2件です。

第44回科学技術賞

[対象]

1) 学術上の業績が顕著なもの 2) 学術上重要な発見をしたもの 3) 重要な発明をして、その効果が大きいもの 4) 技術上重要な問題を解決して技術の進歩に大きく貢献したものの。

例年、紫綬褒章クラスの方が受賞されているそうですが、既に国家的表彰を受けられた方(例えば勲一等、勲二等や学士院賞受賞者)についてはご遠慮下さいとの事です。推薦を受けた候補者はその年度および次年度にわたって選考の対象となります。従って平成14年度に推薦された候補者は平成15年度候補者としての再度推薦の必要はありません。

[褒賞]

賞状、金メダル、賞金(500万円) 受賞者は2名前後

第44回科学技術研究助成

[対象]

国内の研究機関において自らのアイディアで萌芽的基礎研究に従事し、かつ本人が主体性をもって研究を遂行できる方で、今後の研究の成果が科学技術の進歩、発展に貢献するところが大きいと考えられる若手研究者(原則として推薦時45歳以下)。

従来の研究の多くが海外で行われていても差し支えありません。

[研究助成金]

総額1億3000万円。1件3000万円程度まで10件程度。

資料請求/問合せ先

(財) 東レ科学振興会

〒279-8555千葉県浦安市美浜1-8-1 東レビル

TEL: 047-350-6103 FAX: 047-350-6082

<http://www.toray.co.jp/tsf/index.html>

推薦書類は財団のHPからダウンロードできます。

学会事務局でも何部か申請書類をお預かりしております。

・上記1. 2. の日本神経化学会からの応募について

申請用紙は各財団に直接請求し、学会推薦を希望されます場合は、日本神経化学会事務局まで簡易書留(宅配便も可)にて9月1日必着でご送付ください。

3. ブレインサイエンス振興財団各助成・褒賞

(1) 第18回研究助成(財団への直接応募)

[対象]

ブレインサイエンスの広い分野における研究に対して助成を行いますが、特に下記の各項について、脳のメカニズムを解明する独創的な研究計画の助成に重点をおきます。研究分野は実験研究のみならず、理論、モデリング研究をも含みます。

- (1) 脳細胞の働き (2) 脳の感覚、認知、運動、情動、記憶・学習、睡眠、意識の機能 (3) 脳の制御の原理と機構 (4) 脳神経系疾患の病理 (5) 脳の老化 (6) 脳神経の発生、分化、発達 (7) 物理学から脳へのアプローチ

[研究助成金] 1件100万円 助成件数は8～10件

[応募締切日] 2003年11月27日 (木)

(2) 第17回海外派遣助成 (財団への直接応募)

[趣旨]

我が国におけるブレインサイエンスの研究促進を図るため国際学会、シンポジウム等への参加、あるいは短期間 (6ヶ月以内) の共同研究のための研究者の海外派遣を助成。平成16年4月～平成17年3月の間に出発出来るもの。

[助成額] 往復の航空運賃を主とし30万円迄を限度として若干件数

[応募締切日] 2004年1月16日 (金)

※今年より上記の研究助成と海外派遣助成は財団への直接応募となりました

(3) 第18回塚原仲晃記念賞 (日本神経化学会締切日: 2003年9月1日必着)

[対象年齢] 生命科学の分野において優れた独創的研究を行っている45歳以下の研究者

[褒賞] 賞牌ならびに副賞 (100万円) 原則として1件

[応募締切日] 2003年11月27日 (木) (日本神経化学会の学会内締切: 2003年9月1日必着)

(4) 第17回海外研究者招聘助成 (日本神経化学会締切日: 2003年11月28日必着)

[趣旨]

ブレインサイエンス研究分野において独創的テーマに意欲的に取り組んでいる外国人研究者の短期間 (3ヶ月以内) の招聘を助成。平成16年4月1日～平成17年3月31日の間に招聘するもの。

[助成額]

往復の航空運賃を主とし30万円迄を限度として若干件数。助成金は招聘する受入責任者に交付。

[応募締切日]

2004年1月16日 (金) (日本神経化学会の学会内締切: 2003年11月28日必着)

※今年から上記の塚原仲晃記念賞と海外研究者招聘助成の学会推薦枠数の制限がなくなりました。但し、本学会研究助成金候補者推薦委員会において選考を行います。

申請を希望されます場合、申請用紙は各財団に直接請求し、学会推薦を希望されます場合は、日本神経化学会事務局まで簡易書留 (宅配便も可) にてそれぞれの締切必着で送付ください。

資料請求/問合せ先

推薦要領は80円切手1枚を同封のうえ、「○○助成 (賞)」推薦要領希望を明記し、封書で下記財団宛ご送付下さい。

(財) ブレインサイエンス振興財団

〒104-0028東京都中央区八重洲2-6-20 ホンダ八重洲ビル

TEL.03-3273-2565

<http://homepage2.nifty.com/bsf/>

応募書類は財団のHPからダウンロードできます。

4. 第20回井上研究奨励賞（財団への直接応募となります）

対 象：平成12～14年度の過去3年間に理・工・医・薬・農学等の分野で博士の学位を取得した35歳未満（医学・歯学・獣医学の分野については37歳未満）の研究者で、自然科学の基礎的研究において新しい領域を開拓する可能性のある優れた博士論文を提出した研究者。

募集方法：博士論文を指導した研究者の推薦に基づき、学位を授与した大学の学長からの推薦。

褒 賞：賞状及び研究奨励金50万円

締 切：2003年9月20日

資料請求／問合せ／応募先

（財）井上科学振興財団

〒150-0036 東京都渋谷区南平台町15-15 南平台今井ビル601

TEL：03-3477-2738 FAX：03-3477-2747

E-mail：inoue01@inoue-zaidan.or.jp

5. 平成15年度「安藤百福賞」募集（財団への直接応募となります）

1. 受賞対象者

食品分野における独創的な基礎研究、食品開発、およびベンチャーを対象とします。なお、叙勲、褒章ならびに他に顕著な賞を受けられた方は原則として対象外とします。

2. 対象分野

表彰は、次の3部門に優秀賞を、特に優秀と認められた方に大賞を贈呈します。

- ① 基礎研究部門 食品の基礎科学に関する独創的かつ将来性豊かな学術的研究を対象とします。
- ② 食品開発部門 独創的な技術開発により新しい市場を創造した商品、あるいは新しい業態を創造した技術を対象とします。
- ③ ベンチャー部門 独創的かつ将来性豊かな食品加工技術や流通システムなどを開発、起業したベンチャーを対象とします。

3. 選考基準

驚きの気持ちを引き起こすような斬新で独創的なもの。

特許申請、論文著書等、知的財産として価値があり、生産性が高いもの。

科学技術の世界や、社会一般へ強い影響力のあるもの。

実績、知名度が低くても、将来性を期待できるもの。

4. 選 考

各部門ごとに審査委員会を設け、厳正な予備選考を行った上、役員会にて大賞・優秀賞を選考します。選考結果は、文書により関係者にご通知いたします。

選考の結果、該当者がいないこともあります。

5. 賞の種類

大 賞 1点 賞状及び副賞賞金 1,000万円

優秀賞 3点 賞状及び副賞賞金 200万円（各部門で1点）

6. 応募締め切り 平成15年10月末日

7. 応募要綱・応募用紙等について

本人の申請もしくは関係機関、学識経験者の推薦によりご応募下さい。

安藤スポーツ・食文化振興財団のホームページにて閲覧、ダウンロードいただけます。

8. 応募書類の送付・問合せ先

財団法人安藤スポーツ・食文化振興財団『食創会』事務局

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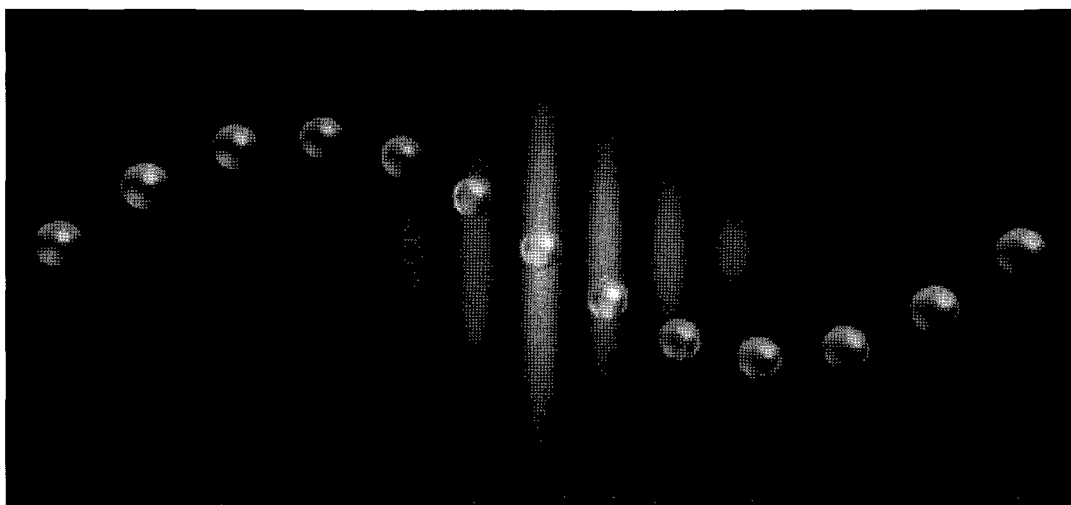
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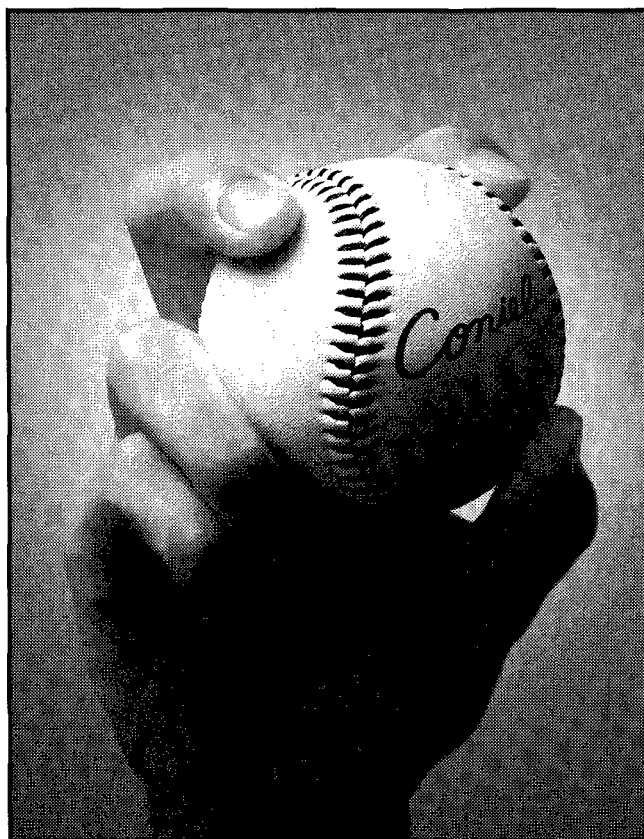
製造発売元
資料請求先



小野薬品工業株式会社

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〔資料請求先〕

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東京都千代田区大手町1-6-1

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02.10.

- メニエール病及び内耳障害に基づくめまい
- 調節性眼精疲労における調節機能の安定化
- 消化管機能低下のみられる慢性胃炎
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- 心不全

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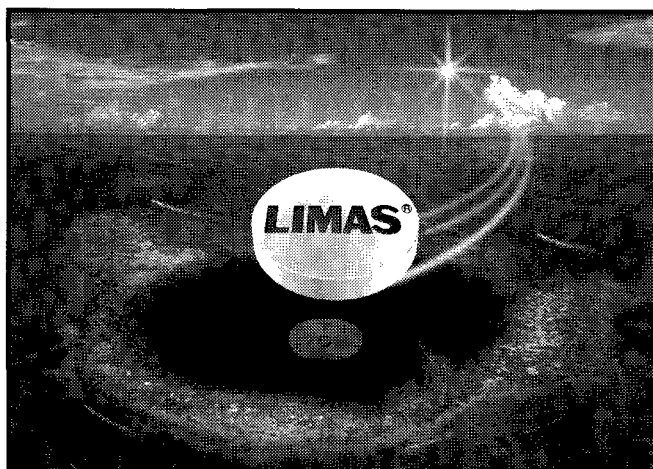
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アデホス[®]顆粒

〔用法・用量〕アデノシン三リン酸二ナトリウムとして、1回40～60mgを1日3回経口投与する。メニエール病及び内耳障害に基づくめまいに用いる場合には、アデノシン三リン酸二ナトリウムとして、1回100mgを1日3回経口投与する。なお、症状により適宜増減する。



製造元 興和株式会社 販売元 興和新薬株式会社 名古屋市中区錦三丁目6-29



創薬
指定医薬品
要指示医薬品^(注)

躁病・躁状態治療剤 薬価基準収載

リ-マス[®]錠100 錠200
LIMAS[®] tab.100 / tab.200

炭酸リチウム製剤

(注) 注意一医師等の処方せん・指示により使用すること



販売元〔資料請求先〕
大正富山医薬品株式会社
〒170-8635 東京都豊島区高田3-25-1



製造元
大正製薬株式会社
〒170-8633 東京都豊島区高田3-24-1

【禁忌(次の患者には投与しないこと)】

1. てんかん等の脳波異常のある患者〔脳波異常を増悪させることがある。〕
2. 重篤な心疾患のある患者〔心疾患を増悪し、重篤な機能障害を引き起こすおそれがある。〕
3. リチウムの体内貯留を起こしやすい状態にある患者〔リチウムの毒性を増強するおそれがある。〕
 - (1) 腎障害のある患者
 - (2) 衰弱又は脱水状態にある患者
 - (3) 発熱、発汗又は下痢を伴う疾患のある患者
 - (4) 食塩制限患者
4. 妊婦又は妊娠している可能性のある婦人〔添付文書「妊婦、産婦、授乳婦等への投与」の項参照〕

【効能・効果】

躁病および躁うつ病の躁状態

【用法・用量】

炭酸リチウムとして、成人では通常1日400～600mgより開始し、1日2～3回に分割経口投与する。以後3日ないし1週間毎に、1日通常1200mgまでの治療量に漸増する。改善がみられたならば症状を観察しながら、維持量1日通常200～800mgの1～3回分割経口投与に漸減する。

なお、年齢、症状により適宜増減する。

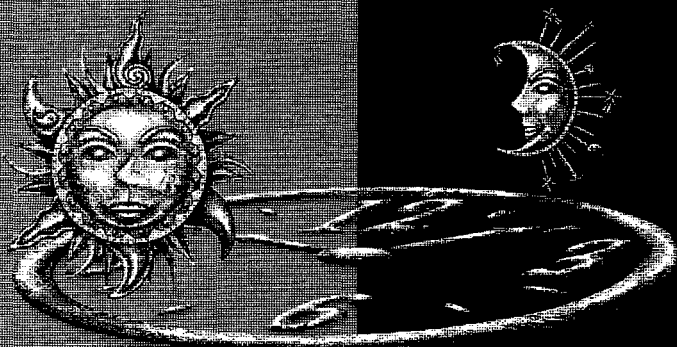
用法・用量に関連する使用上の注意

過量投与による中毒を起こすことがあるので、投与初期又は用量を増量したときには1週1ないし2回、維持量の投与中には1月1回程度、早朝服薬前の血清リチウム濃度を測定しながら使用すること。

- (1) 血清リチウム濃度が1.5mEq/Lを越えたときは臨床症状の観察を十分に行い、必要に応じて減量又は休薬等の処置を行うこと。
- (2) 血清リチウム濃度が2.0mEq/Lを越えたときは過量投与による中毒を起こすことがあるので、減量又は休薬すること。

※その他詳細は、製品添付文書をご参照ください。

BLOPRESS®



持続性アンジオテンシンⅡ受容体拮抗剤

指定医薬品
要指示医薬品*

ブロプレス錠 2・4・8・12

(カンデサルタン シレキセチル錠)* (注意・医師等の処方せん・指示により使用すること)

(資料請求先)

■効能・効果、用法・用量、禁忌・使用上の注意等については、
添付文書をご参照ください。 ■薬価基準：収載



武田薬品工業株式会社

〒540-8645 大阪市中央区道修町四丁目1番1号
<http://www.takeda.co.jp/> (0205:852)

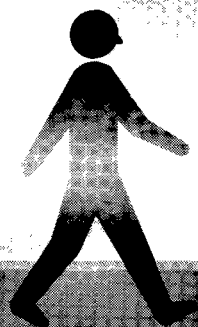
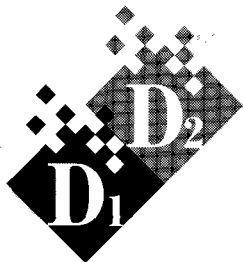
ドパミンD₁、D₂作動性パーキンソン病治療剤

ペルマックス錠 50μg 250μg

Permax® 〈メシル酸ベルゴリド錠〉

薬価基準収載

劇薬、指定医薬品、要指示医薬品 (注意・医師等の処方せん・指示により使用すること)



日本標準商品分類番号 87116

禁忌 (次の患者には投与しないこと)

既往に麦角製剤に対しての過敏症を有する患者

※「効能・効果」、「用法・用量」、「禁忌を含む使用上の注意」、「用法・用量に関する使用上の注意」等については、製品添付文書をご参照ください。また、禁忌を含む使用上の注意の改訂に十分ご注意ください。

PMX-A005 (R0)
2003年4月作成

製造発売元＜資料請求先＞

日本イーライリリー株式会社
〒651-0086 神戸市中央区磯上通7丁目1番6号

Lilly Answers

日本イーライリリー医薬情報問合せ窓口
☎0120-360-605 (医療関係者向け)
受付時間 8:45～17:30 (月～金)

医療関係者向けヘルマックス情報提供サイト
www.permax.jp
一般の方向けパーキンソン病情報提供サイト
www.parkinsons.co.jp

Lilly



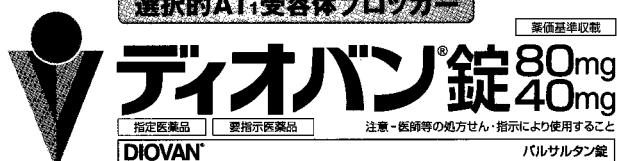
選ばれしもの。

NOVARTIS

THE ARB DIOVAN

選択的AT₁受容体ブロッカー

薬価基準収載



バルサルタン錠

- 禁忌、効能・効果、用法・用量、使用上の注意については、製品添付文書をご覧ください。

製造：日本チバガイギー株式会社

販売

(資料請求先)

ノバルティス ファーマ 株式会社
東京都港区西麻布4-17-30 〒106-8618

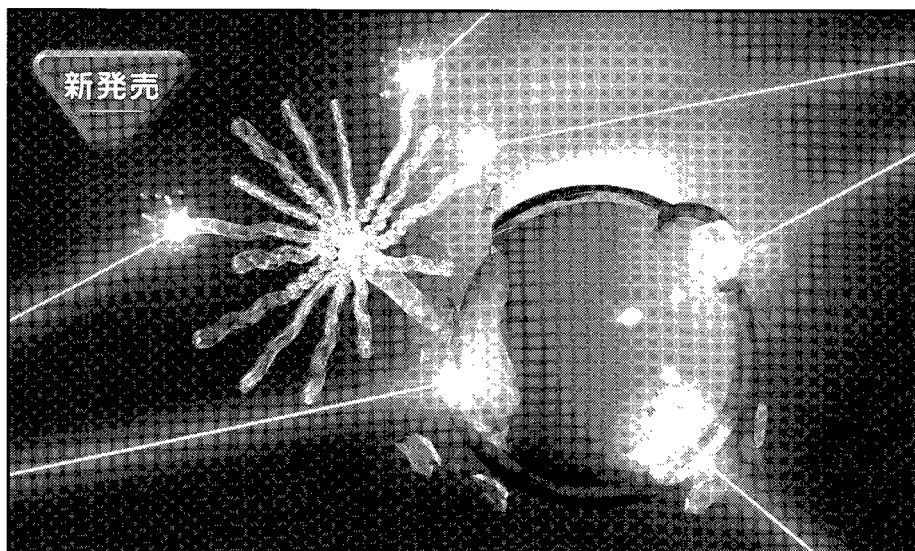
NOVARTIS DIRECT

☎ 0120-003-293

受付時間：月～金 9:00～18:00

www.diovan.jp

2002年8月作成



新発売

Fujisawa

カンディン系抗真菌剤

薬価基準収載

ファンガード® 点滴用 50mg 75mg

〈注射用ミカファンギンナトリウム〉 創薬・指定医薬品・要指示医薬品注)

Funguard® for Infusion 50mg・75mg

注) 注意一医師等の処方せん・指示により使用すること

(略号: MCFG)

- 効能・効果、用法・用量、禁忌を含む使用上の注意等につきましては、製品添付文書をご参照下さい。

製造発売元 資料請求先

藤沢薬品工業株式会社
大阪市中央区道修町3-4-7 〒541-8514

作成年月2003年1月



パーキンソン病治療剤

エピー[®]錠2.5
FP (塩酸セレギリン錠) 劇薬 覚せい剤原料 指定医薬品 要指示医薬品

薬価基準収載

●効能・効果、用法・用量、警告・禁忌を含む使用上の注意等については、製品添付文書をご参照下さい。

【資料請求先】

藤本製薬株式会社 医薬情報室

〒100-0005 東京都千代田区丸の内1丁目1番1号 (パレスビル)

☎ 0120-545-427 URL: <http://www.fujimoto-pharm.co.jp/>

製造発売元

— **藤本製薬株式会社**
 大阪府松原市西大塚1丁目3番40号

提携

Chinoin

Fo

医科器械・理化学器械・実験用器具
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株式会社 **新栄医理科**

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TEL 286-1158

FAX 286-7110



片頭痛治療薬／5-HT_{1B/1D}受容体作動薬

ゾーミック[®]RM錠2.5mg

Zomig[®]RM ゾルミトリブタン口腔内速溶錠

創薬、指定医薬品、要指示医薬品^{※1}

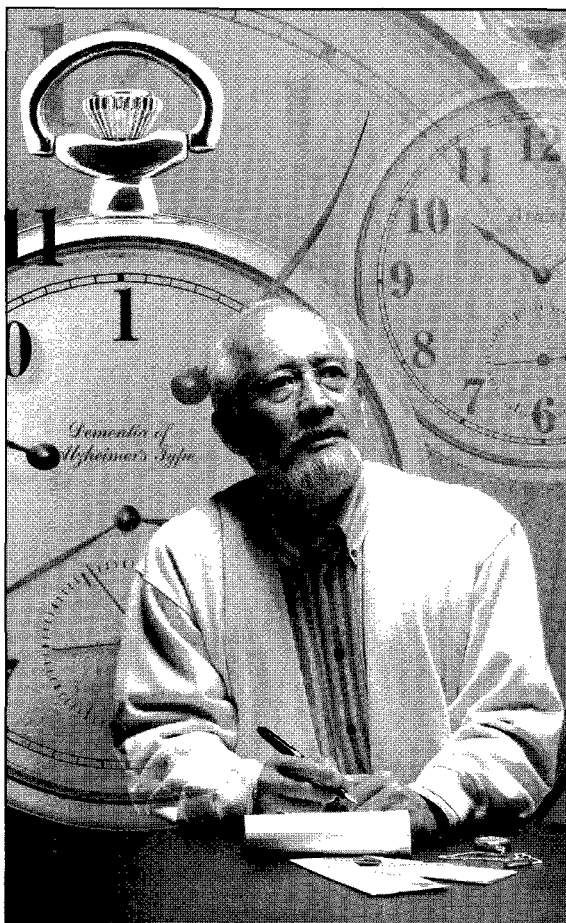
薬価基準収載

注) 注意—医師等の処方せん・指示により使用すること

●効能・効果、用法・用量、禁忌を含む使用上の注意、効能・効果に関連する使用上の注意、用法・用量に関連する使用上の注意については、製品添付文書をご参照下さい。

製造・販売元(資料請求先) **アストラゼネカ株式会社** 大阪市北区大淀中1丁目1番88号

2003年5月作成



劇薬
指定医薬品
要指示医薬品：注意—医師等の処方せん・指示により使用すること

アルツハイマー型痴呆治療剤

アリセプト® 錠3mg
錠5mg
〈塩酸ドネペジル製剤〉 細粒0.5%

【禁忌】(次の患者には投与しないこと)

本剤の成分又はピペリジン誘導体に対し過敏症の既往歴のある患者

製造発売元 **Eisai** **エーザイ株式会社**
東京都文京区小石川4-6-10

販売提携 **Pfizer** **ファイザー製薬株式会社**
ファイザー
東京都新宿区西新宿2-1-1

資料請求先：エーザイ株式会社 医薬事業部 医薬部
ファイザー製薬株式会社 マーケティングサービス部

●その他の使用上の注意等については添付文書をご参照ください。

【効能・効果】

軽度及び中等度のアルツハイマー型痴呆における痴呆症状の進行抑制

〈効能・効果に関連する使用上の注意〉

- 1) 軽度及び中等度のアルツハイマー型痴呆と診断された患者にのみ使用すること。
- 2) 本剤がアルツハイマー型痴呆の病態そのものの進行を抑制するという成績は得られていない。
- 3) アルツハイマー型痴呆以外の痴呆性疾患において本剤の有効性は確認されていない。

【用法・用量】

通常、成人には塩酸ドネペジルとして1日1回3mgから開始し、1～2週間後に5mgに増量し、経口投与する。

〈用法・用量に関連する使用上の注意〉

3mg/日投与は有効用量ではなく、消化器系副作用の発現を抑える目的なので、1～2週間を超えて使用しないこと。

なお、医療従事者、家族などの管理のもとで投与すること。

【使用上の注意】

1. 慎重投与(次の患者には慎重に投与すること)

本剤はアセチルコリンエステラーゼ阻害剤であり、コリン作動性作用により以下に示す患者に対しては症状を誘発又は増悪する可能性があるため慎重に投与すること。

- (1) 洞不全症候群、心房内及び房室接合部伝導障害等の心疾患のある患者
- (2) 消化性潰瘍の既往歴のある患者、非ステロイド性消炎鎮痛剤投与中の患者
- (3) 気管支喘息又は閉塞性肺疾患の既往歴のある患者
- (4) 錐体外路障害(パーキンソン病、パーキンソン症候群等)のある患者

2. 重要な基本的注意

他の痴呆性疾患との鑑別診断に留意すること。

3. 相互作用

本剤は、主として薬物代謝酵素CYP3A4及び一部CYP2D6で代謝される。〔添付文書「薬物動態」の項参照〕

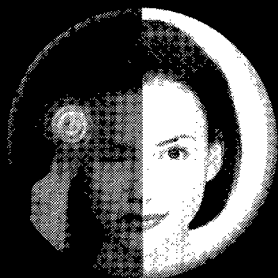
併用注意(併用に注意すること)

塩化スキサメトニウム コリン賦活剤：塩化アセチルコリン、塩化カルプロニウム、塩化ベタネコール、ナバジシル酸アクラトニウム コリンエステラーゼ阻害剤：塩化アンペニウム、臭化ジスチグミン、臭化ピリドスチグミン、ネオスチグミン等 イトラコナゾール エリスロマイシン等 硫酸キニジン等 カルバマセピン テキサメタゾン フェニトイン フェノバルビタール リファンピシン等 中枢性抗コリン剤：塩酸トリヘキシフェニジル、塩酸ピロヘプチン、塩酸マザチコール、塩酸メチキセン、塩酸ビペリデン等 アトロピン系抗コリン剤：臭化プルススコラミン、硫酸アトロピン等 非ステロイド性消炎鎮痛剤

4. 副作用

総症例457例中48例(10.5%)の副作用が報告されている。また、98例(21.4%)の臨床検査値異常変動が報告されている。(承認時)

- (1) 重大な副作用(頻度不明) 1) 失神、徐脈、心ブロック、心筋梗塞：失神、徐脈、心ブロック(房室ブロック、洞房ブロック)、心筋梗塞があらわれることがあるので、このような症状があらわれた場合には、投与を中止するなど適切な処置を行うこと。2) 消化性潰瘍、十二指腸潰瘍穿孔、消化管出血：本剤のコリン賦活作用による胃酸分泌及び消化管運動の促進によって消化性潰瘍(胃・十二指腸潰瘍)、十二指腸潰瘍穿孔、消化管出血があらわれることがあるので、このような症状があらわれた場合には、投与を中止するなど適切な処置を行うこと。3) 肝炎、肝機能障害、黄疸：肝炎、肝機能障害、黄疸があらわれることがあるので、異常が認められた場合には、投与を中止するなど適切な処置を行うこと。4) 脳性発作、脳出血、脳血管障害：脳性発作(てんかん、痙攣等)、脳出血、脳血管障害があらわれることがあるので、このような症状があらわれた場合には、投与を中止するなど適切な処置を行うこと。5) 錐体外路障害：震動、運動失調、ジスキネジア、ジストニア、振戦、不随意運動、歩行異常、姿勢異常、言語障害等の錐体外路障害があらわれることがあるので、このような症状があらわれた場合には、投与を中止するなど適切な処置を行うこと。6) Syndrome malin(悪性症候群)：無動痙攣、強度の筋強剛、嚥下困難、頻脈、血圧の変動、発汗等が発現し、それに引き続き発熱がみられる場合は、投与を中止し、体冷却、水・電解質管理等の全身管理とともに適切な処置を行うこと。本症発症時には、白血球の増加や血清CK(CPK)の上昇がみられることが多く、また、ミオグロビン尿を伴う腎機能の低下がみられることがある。7) 呼吸困難：呼吸困難があらわれることがあるので、このような症状があらわれた場合には、投与を中止し、適切な処置を行うこと。8) 急性肺炎：急性肺炎があらわれることがあるので、異常が認められた場合には、投与を中止するなど適切な処置を行うこと。9) 原因不明の突然死



点鼻液新登場
新発売



5-HT_{1B/1D}受容体作動型片頭痛治療剤 薬価基準収載

劇薬 指定医薬品 要指示医薬品(注意-医師等の処方せん・指示により使用すること)



イミグラン[®]点鼻液20

IMIGRAN[®] Nasal Spray スマトリブタン点鼻液

■ 本剤の「効能・効果」「用法・用量」「効能・効果及び用法・用量に関連する使用上の注意」「禁忌を含む使用上の注意」等につきましては、製品添付文書をご参照ください。

[資料請求・問い合わせ先]

グラクソ・スミスクライン株式会社

〒151-8566 東京都渋谷区千駄ヶ谷 4-6-15 GSKビル

TEL : 0120-561-007 (9:00~18:00/土日祝日を除く)

FAX : 0120-561-047 (24 時間受付)

<http://www.glaxosmithkline.co.jp>

2003.6.

睡眠誘導剤

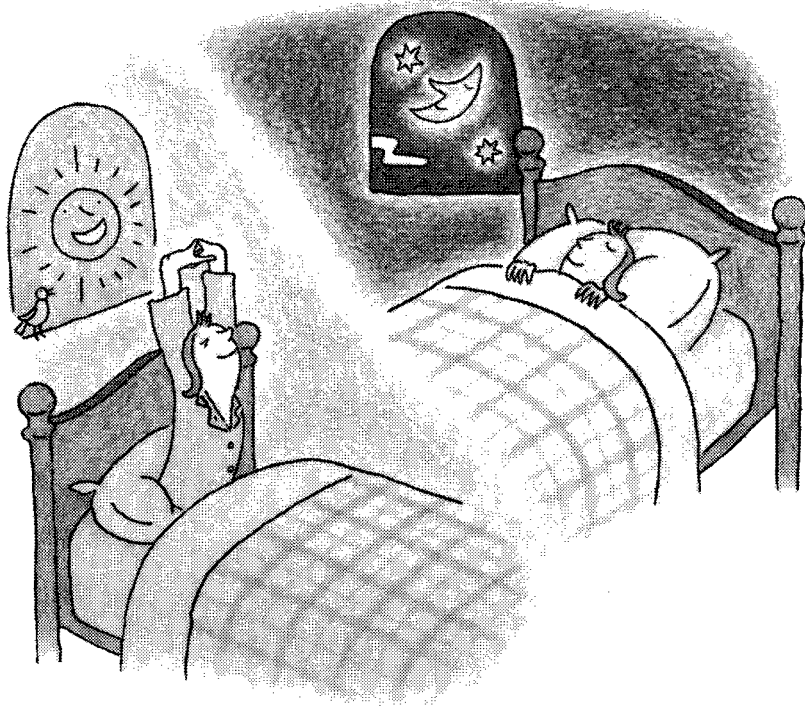
習慣性医薬品^{注1)}、指定医薬品、要指示医薬品^{注2)}

リスミー[®] 錠1mg・2mg

塩酸リルマザホン錠

Rhythmy[®]

注1) 注意-習慣性あり 注2) 注意-医師等の処方せん・指示により使用すること



■薬価基準収載

■「効能・効果」、「用法・用量」、「禁忌」、「原則禁忌」、「使用上の注意」等については添付文書をご参照下さい。

〔資料請求先〕 塩野義製薬株式会社 〒541-0045 大阪市中央区道修町 3-1-8

2003.3 作成 B51 ⑧：登録商標

 シオノギ製薬

降圧療法は、いま新時代へ。 PROGRESS in Hypertension



持続性組織ACE阻害剤

薬価基準収載

指定医薬品/要指示医薬品*

コバシル錠[®] 2mg 4mg

一般名：ペリンドプリルエルブミン (perindopril erbumine)

*注意—医師等の処方せん・指示により使用すること

【禁忌(次の患者には投与しないこと)】

1. 本剤の成分に対し過敏症の既往歴のある患者
2. 血管浮腫の既往歴のある患者(アンジオテンシン変換酵素阻害薬等の薬剤による血管浮腫、遺伝性血管浮腫、後天性血管浮腫、特発性血管浮腫等) [高度の呼吸困難を伴う血管浮腫を発現することがある。]
3. デキストラン硫酸セルロースを用いた吸着器によるLDLアフェレーシス施行中の患者(「併用禁忌」の項参照)
4. アクリロニトリルメタリルスルホン酸ナトリウム膜(AN69[®])を用いた血液透析施行中の患者(「併用禁忌」の項参照)
5. 妊婦または妊娠している可能性のある婦人(「妊婦、産婦、授乳婦等への投与」の項参照)

●効能・効果●

高血圧症

●用法・用量●

通常、成人にはペリンドプリルエルブミンとして2～4mg(錠2mg:1～2錠、錠4mg:0.5～1錠)を1日1回経口投与する。なお、年齢、症状により適宜増減するが、1日最大量は8mg(錠2mg:4錠、錠4mg:2錠)までとする。

〔用法・用量に関連する使用上の注意〕

重篤な腎機能障害のある患者では、本剤の活性代謝物の血中濃度が上昇し、過度の血圧低下、腎機能の悪化が起こるおそれがあるため、クレアチニンクリアランスが30mL/分以下または血清クレアチニンが3mg/dL以上の場合には、投与量を減らすか、もしくは投与間隔をのばすなど、経過を十分に観察しながら慎重に投与すること。

●使用上の注意●

1. 慎重投与(次の患者には慎重に投与すること)

- 1) 両側性腎動脈狭窄のある患者または片腎で腎動脈狭窄のある患者(「重要な基本的注意」の項参照)

2) 高カリウム血症の患者(「重要な基本的注意」の項参照)

3) 重篤な腎機能障害のある患者(「用法・用量に関連する使用上の注意」の項参照)

4) 高齢者[過度の血圧低下により病態を悪化させるおそれがある(「高齢者への投与」の項参照)。]

2. 重要な基本的注意

1) 両側性腎動脈狭窄のある患者または片腎で腎動脈狭窄のある患者においては、腎血流量の減少や糸球体濾過量の低下により急速に腎機能を悪化させるおそれがあるので、治療上やむを得ないと判断される場合を除き、使用は避けること。

2) 高カリウム血症の患者においては、高カリウム血症を増悪させるおそれがあるので、治療上やむを得ないと判断される場合を除き、使用は避けること。また、腎機能障害、コントロール不良の糖尿病等により血清カリウム値が高くなりやすい患者では、高カリウム血症が発現するおそれがあるので、血清カリウム値に注意すること。

3) 本剤の投与により、特に次の患者では、初回投与後一過性の急激な血圧低下を起こす場合があるので、投与は少量より開始し、増量する場合は患者の状態を十分に観察しながら徐々に行うこと。

- (1) 重症の高血圧症患者
 - (2) 血液透析中の患者
 - (3) 利尿降圧薬投与中の患者
 - (4) 厳重な減塩療法中の患者
- 4) 降圧作用に基づきめまい、ふらつきがあらわれることがあるので、高所作業、自動車の運転等危険を伴う機械を操作する際には注意させること。
- 5) 手術前24時間は投与しないことが望ましい。

3. 相互作用

1) 併用禁忌(併用しないこと)

デキストラン硫酸セルロースを用いた吸着器によるアフェレーシスの施行(LDLアフェレーシス)、アクリロニトリルメタリルスルホン酸ナトリウム膜を用いた透析(AN69[®])

2) 併用注意(併用に注意すること)

カリウム保持性利尿薬(スピロノラクトン、トリアムテレン等)、カリウム補給薬、利尿降圧薬(ヒドロクロロチアジド等)、リチウム製剤(炭酸リチウム)、非ステロイド性消炎鎮痛薬(インドメタシン等)、カリジノゲナーゼ製剤

4. 副作用

副作用発生状況の概要

承認前の調査589例中報告された副作用は11.0%(65例)で、主な副作用は咳嗽(晩発性の咳を含む)7.1%(42件)、喉頭異和感0.5%(3件)等の呼吸器症状、発疹・皮膚疹1.0%(6件)等の過敏症状であった。承認後における使用成績調査(現在実施中)1,324例中報告された副作用は10.6%(141例)で、主な副作用は咳嗽6.8%(90件)、喉頭異和感0.5%(7件)等の呼吸器症状であった。

1) 重大な副作用(頻度不明^(*))

(1) 血管浮腫

呼吸困難を伴う顔面、舌、声門、喉頭の腫脹を症状とする血管浮腫があらわれることがあるので、このような場合には直ちに投与を中止し、エドニブリン注射、気道確保等適切な処置を行うこと。

(2) 急性腎不全

急性腎不全があらわれることがあるので、腎機能に異常が認められた場合には投与を中止するなど適切な処置を行うこと。

(3) 高カリウム血症

重篤な高カリウム血症があらわれることがあるので、観察を十分に行い、異常が認められた場合には、直ちに適切な処置を行うこと。

注1) 自発報告または海外において認められている副作用のため頻度不明。

★その他の使用上の注意等につきましては、製品添付文書をご参照ください。

製造発売元

第一製薬株式会社

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in the Elderly Study II

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2002 LIFE
The Losartan Intervention For Endpoint
Reduction in Hypertension Study

2002 OPTIMAL
Optimal Therapy in Myocardial Infarction
with the Angiotensin II Antagonist Losartan

脳心腎

ニューロタンの実証

禁忌（次の患者には投与しないこと）

- (1) 本剤の成分に対し過敏症の既往歴のある患者
- (2) 妊婦又は妊娠している可能性のある婦人
- (3) 重篤な肝障害のある患者

【効能・効果】高血圧症

【用法・用量】

通常、成人にはロサルタンカリウムとして25～50mgを1日1回経口投与する。なお、年齢、症状により適宜増減するが、1日100mgまで増量できる。

【使用上の注意】

1. 慎重投与（次の患者には慎重に投与すること）

- (1) 両側性腎動脈狭窄のある患者又は片腎で腎動脈狭窄のある患者
- (2) 高カリウム血症の患者 (3) 重篤な腎機能障害のある患者
- (4) 肝機能障害又はその既往のある患者 (5) 脳血管障害のある患者
- (6) 体液量が減少している患者 (7) 高齢者

2. 重要な基本的注意

- (1) 両側性腎動脈狭窄のある患者又は片腎で腎動脈狭窄のある患者においては、腎血流量の減少や糸球体過剰の低下により急速に腎機能を悪化させるおそれがあるので、治療上やむを得ないと判断される場合を除き、使用は避けること。
- (2) 高カリウム血症の患者においては、高カリウム血症を増悪させるおそれがあるので、治療上やむを得ないと判断される場合を除き、使用は避けること。また、腎機能障害、コントロール不良の糖尿病等により血清カリウム値が高くなりやすい患者では、高カリウム血症が発現するおそれがあるので、血清カリウム値に注意すること。
- (3) 本剤の投与によって、一過性の血圧低下（ショック症状、意識喪失、呼吸困難等を伴う）を起こすおそれがあるので、そのような場合には投与を中止し適切な処置を行うこと。また、特に次の患者では投与は少量より開始し、増量する場合は患者の状態を十分に観察しながら徐々に行うこと。
ア、利尿剤投与中の患者 イ、厳重な減塩療法中の患者 ウ、血液透析中の患者
- (4) 降圧作用に基づくめまい、ふらつきがあらわれることがあるので、高所作業、自動車の運転等危険を伴う機械を操作する際には注意させること。
- (5) 手術前24時間は投与しないことが望ましい。
- (6) 本剤を含むアンジオテンシンII受容体拮抗薬投与中にまれに肝炎等の重篤な肝障害があらわれたとの報告がある。肝機能検査を実施するなど、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

3. 相互作用（併用注意）（併用に注意すること）

カリウム保持性利尿剤：スピロラクトン、トリウムテレン等
カリウム補給剤：塩化カリウム

4. 副作用

臨床試験（治験）

国内で実施された臨床試験で副作用が報告されたのは709例中71例（10.0%）であり、主な副作用は頭痛13件（1.8%）、めまい9件（1.3%）、嘔吐・悪気6件（0.8%）、ほてり5件（0.7%）であった。また、主な臨床検査値異常は、ALT(GPT)上昇19件（2.7%）、AST(GOT)上昇15件（2.1%）、CK(CPK)上昇15件（2.7%）、総コレステロール上昇11件（1.6%）、LDH上昇10件（1.4%）、赤血球減少10件（1.4%）であった。なお、65歳以上の高齢者における副作用発現率は9.6%（156例中15例）で、65歳未満の非高齢者群（553例中56例、10.1%）と同様であり、主な副作用はめまい4件（2.6%）及び頭痛2件（1.3%）であった。

(1) 重大な副作用（すべて頻度不明）

次のような副作用があらわれることがあるので、症状があらわれた場合には、投与を中止し、適切な処置を行うこと。

- 1) アナフィラキシー様症状：不快感、口内異常感、発汗、蕁麻疹、呼吸困難、全身潮紅、浮腫等が症状としてあらわれることがあるので観察を十分に行うこと。
- 2) 血管浮腫：顔面、口唇、咽頭、舌等の腫脹が症状としてあらわれることがあるので観察を十分に行うこと。
- 3) 急性肝炎または劇症肝炎
- 4) 腎不全
- 5) 失神・意識喪失：血圧低下に伴う一過性のショック症状があらわれることがある。
- 6) 横紋筋融解症：筋肉痛、脱力感、CK(CPK)上昇、血中及び尿中ミオグロビン上昇を特徴とする横紋筋融解症があらわれることがあるので、このような場合には投与を中止し、適切な処置を行うこと。また、横紋筋融解症による急性腎不全の発症に注意すること。
- 7) 高カリウム血症：重篤な高カリウム血症があらわれることがあるので、観察を十分に行い、異常が認められた場合には、直ちに適切な処置を行うこと。
- 8) 不整脈：心室性期外収縮、心房細動等の不整脈があらわれることがあるので、観察を十分に行い、異常が認められた場合には、直ちに適切な処置を行うこと。
- 9) 汎血球減少、白血球減少、血小板減少：汎血球減少、白血球減少、血小板減少があらわれることがあるので、観察を十分に行い、異常が認められた場合には、直ちに適切な処置を行うこと。

本剤のご使用にあたり、【使用上の注意】等詳細については、製品添付文書をご参照ください。

AA
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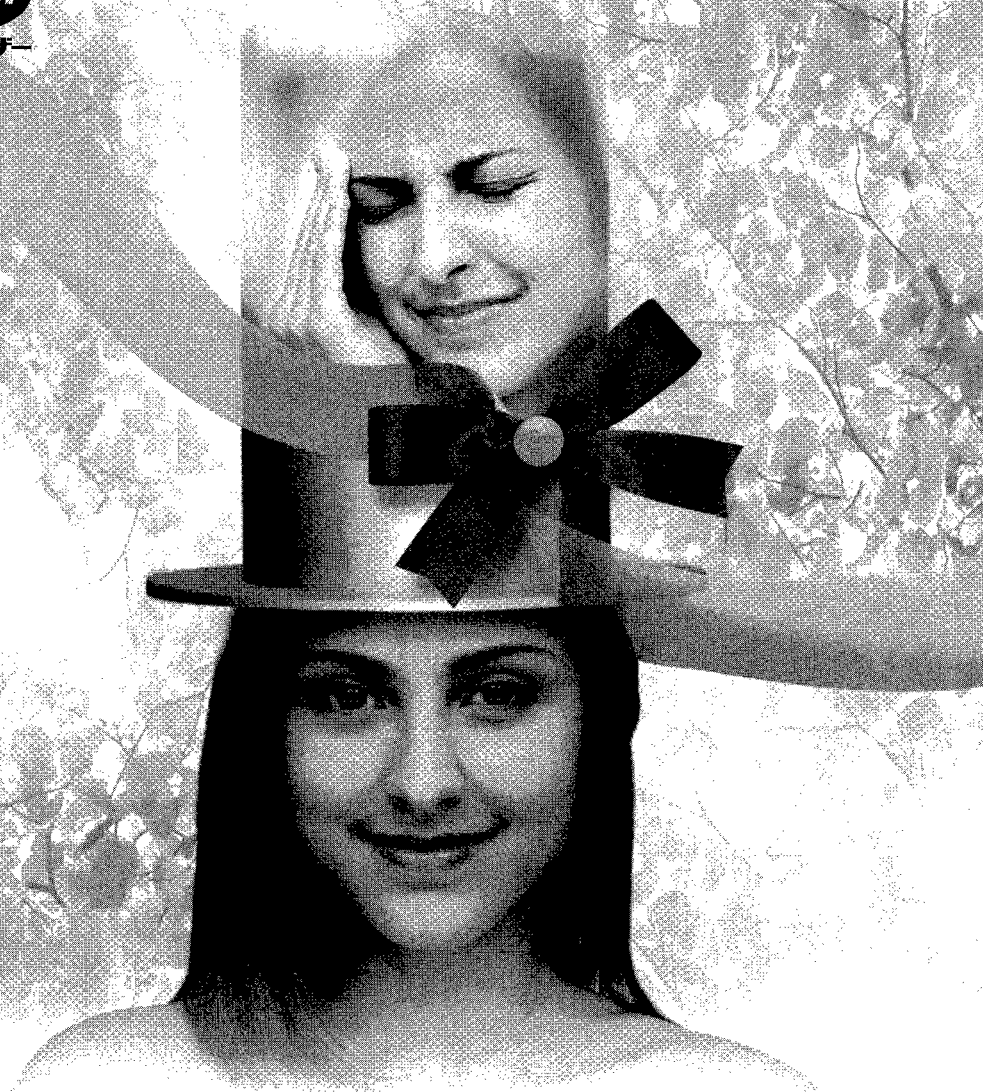
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2003年3月作成 01-04C2R03-J-3706J



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新発売

効能・効果、用法・用量及び禁忌を含む使用上の注意等は、添付文書をご参照下さい。

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資料請求先：マーケティングサービス部

2002年7月作成

■頭痛情報Web:「スッきりんのバイバイ頭痛講座」<http://www.sukkirin.com>



脳保護剤（フリーラジカルスカベンジャー）

ラジカット[®] 注30mg

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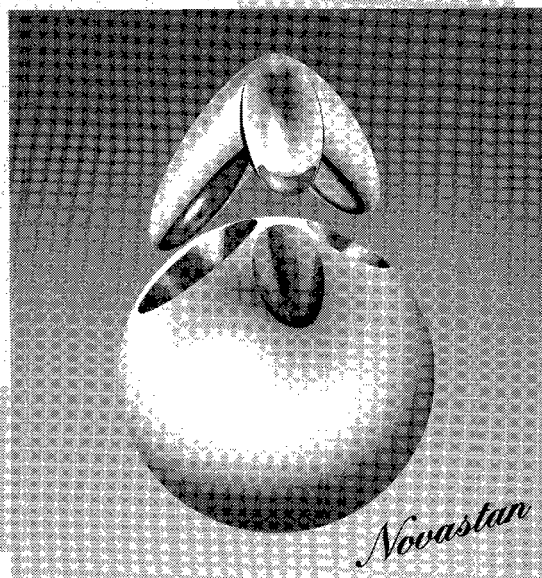
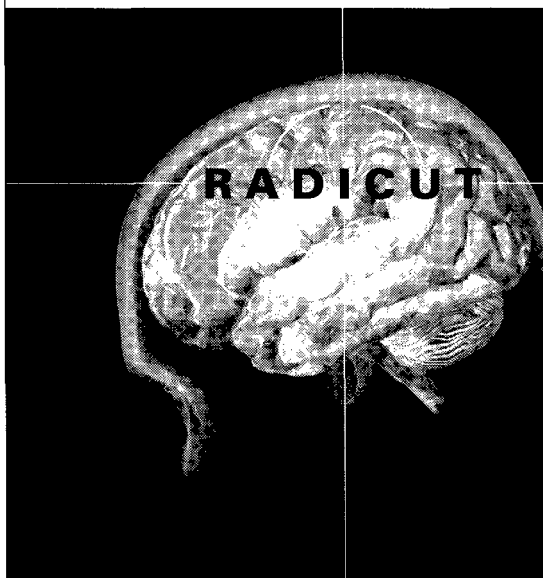
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注）注意—医師等の処方せん・指示により使用すること

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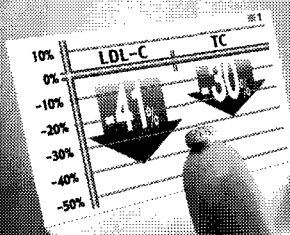
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(B5) 2003年1月作成



スタチン治療の新しい幕開け。

軽症から、重症まで、患者さん一人ひとりのコレステロール値の確かな改善に。

禁忌 (次の患者には投与しないこと) (抜粋)

(1) 本剤の成分に対し過敏症の既往歴のある患者 (2) 肝代謝能が低下していると考えられる以下のような患者
急性肝炎、慢性肝炎の急性増悪、肝硬変、肝癌、黄疸 (3) 妊婦又は妊娠している可能性のある婦人及び授乳婦
原則禁忌 (次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること) (抜粋)
腎機能に関する臨床検査値に異常が認められる患者に、本剤とフィブラート系薬剤を併用する場合には、治療上やむを得ないと判断される場合にのみ併用すること。

効能・効果

高コレステロール血症、家族性高コレステロール血症

<効能・効果に関連する使用上の注意>

(1) 適用の前に十分な検査を実施し、高コレステロール血症、家族性高コレステロール血症であることを確認した上で本剤の適用を考慮すること。
(2) 家族性高コレステロール血症ホモ接合体については、LDL-アフェレシス等の非薬物療法の補助として、あるいはそれらの治療法が実施できない場合に本剤の適用を考慮すること。

用法・用量

○高コレステロール血症 通常、成人にはアトルバスタチンとして10mgを1日1回経口投与する。なお、年齢、症状により適宜増減するが、重症の場合は1日20mgまで増量できる。○家族性高コレステロール血症 通常、成人にはアトルバスタチンとして10mgを1日1回経口投与する。なお、年齢、症状により適宜増減するが、重症の場合は1日40mgまで増量できる。

使用上の注意 (抜粋)

1. 慎重投与 (次の患者には慎重に投与すること) (1) 肝障害又はその既往歴のある患者、アルコール中毒の患者 (2) 腎障害又はその既往歴のある患者 (3) フィブラート系薬剤 (ベザフィブラート等)、免疫抑制剤 (シクロスポリン等)、ニコチン酸製剤 (ニセリトール等)、アゾール系抗真菌薬 (イトラコナゾール等)、エリスロマイシンを投与中の患者 (4) 糖尿病の患者 (5) 甲状腺機能低下症の患者、遺伝性の筋疾患 (筋ジストロフィー等) 又はその家族歴のある患者、薬剤性の筋障害の既往歴のある患者 (6) 高齢者

2. 重要な基本的注意 (1) あらかじめ高コレステロール血症治療の基本である食事療法を行い、更に運動療法や高血圧、喫煙等の虚血性心疾患のリスクファクターの軽減等も十分考慮すること。(2) 投与中は血中脂質値を定期的に検査し、治療に対する反応が認められない場合には投与を中止すること。(3) 投与中は投与開始又は増量時より12週までの間に1回以上、それ以降は定期的に (半年に1回等) に肝機能検査を行うこと。

3. 相互作用 本剤は、主として肝の薬物代謝酵素CYP3A4により代謝される。【原則併用禁忌】(原則として併用しないこと) 腎機能に関する臨床検査値に異常が認められる患者では原則として併用しないこととするが、治療上やむを得ないと判断される場合にのみ慎重に併用すること。フィブラート系薬剤 (ベザフィブラート等) 【併用注意】(併用に注意すること) フィブラート系薬剤 (ベザフィブラート等)、免疫抑制剤 (シクロスポリン等)、ニコチン酸製剤 (ニセリトール等)、アゾール系抗真菌薬 (イトラコナゾール等)、エリスロマイシン、クラリスロマイシン、陰イオン交換樹脂、ジゴキシン、経口避妊薬 (ルエチンドロン

エチニルエストラジオール)、HIVプロテアーゼ阻害剤 (メシル酸ネフィナビル等)

4. 副作用 総症例897例中で、副作用が78例(8.7%)に認められた。主な副作用は胃不快感、痒痒感、手指しびれ、不眠、下痢、胸やけ、便秘、頭痛、全身倦怠であった。また、主な臨床検査値異常変動はγ-GTP上昇、ALT(GPT)上昇、テストステロン低下、AST(GOT)上昇、CK(CPK)上昇であった。(承認時)

(1) 重大な副作用 (頻度不明) 1) 横紋筋融解症、ミオパシー: 筋肉痛、脱力感、CK(CPK)上昇、血中及び尿中ミオグロビン上昇を特徴とする横紋筋融解症があらわれ、急性腎不全等の重篤な腎障害があらわれることがあるので、観察を十分に行い、このような症状があらわれた場合には直ちに投与を中止すること。また、ミオパシーがあらわれることがあるので、広範な筋肉痛、筋肉圧痛や著明なCK(CPK)の上昇があらわれた場合には投与を中止すること。2) 肝機能障害、黄疸: 定期的に検査を行うなど観察を十分に行い、異常が認められた場合には投与を中止し適切な処置を行うこと。3) 過敏症: 血管神経性浮腫、アナフィラキシー反応、蕁麻疹を含む過敏症状があらわれたとの報告があるので、このような症状があらわれた場合には投与を中止すること。4) 血小板・出血性障害: 血小板減少症が発生したとの報告があるので、このような症状があらわれた場合には投与を中止すること。5) 皮膚・皮膚付属器障害: 多形紅斑、Stevens-Johnson症候群、中毒性表皮壊死症等の水疱性発疹があらわれたとの報告があるので、このような症状があらわれた場合には投与を中止すること。6) 高血糖、糖尿病: 高血糖、糖尿病があらわれることがあるので、口渴、頻尿、全身倦怠感等の症状の発現に注意するとともに、定期的に検査を行うなど十分な観察を行い、異常が認められた場合には投与を中止するなど、適切な処置を行うこと。

●その他の使用上の注意等については製品添付文書をご参照ください。

Treat to GOAL
— 治療目標値をめざして —



【指定医薬品】 HMG-CoA還元酵素阻害剤
リピットール錠 5mg 10mg
アトルバスタチンカルシウム水和物 【薬価収載】

※1) LDL-C低下率・TC低下率 [10mg投与時・489例 承認時社内集計] ※2) 2002年6月現在

製造発売元 **山之内製薬株式会社**
【調剤請求先】
〒103-8411 東京都中央区日本橋本町2-3-11

販売提携 **ファイザー株式会社**
〒151-8588 東京都港区代々木3-2-2 新文化ビルビル

高脂血症に関する情報提供サイト **LIPID NET**

<http://www.lipid.ne.jp/>

●詳しい情報をご入力の方は山之内製薬株式会社またはファイザー製薬株式会社、医療情報担当者 (MR) にお申し付け下さい。



神経細胞へ高い遺伝子導入効率を実現

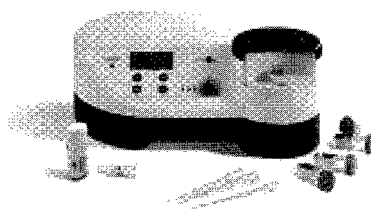
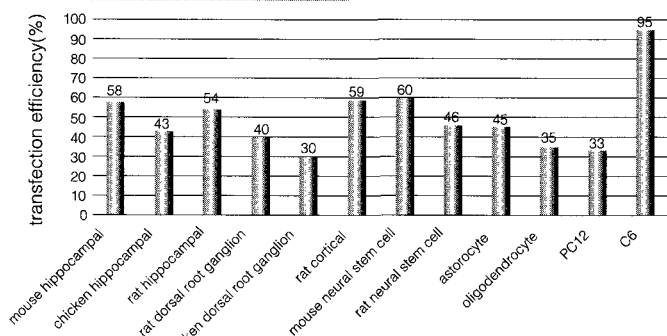
ama x a biosystems

Nucleofector™ System

Nucleofector™はエレクトロポレーション法を応用したNucleofector™ Device(導入装置)と細胞ごとに特化したNucleofector™ Solution(専用試薬)により、神経細胞にて高い導入効率を得られます。

- 《特長》 ● 神経幹細胞から中枢神経、グリア細胞と幅広い細胞への導入が可能
● プラスミドの他にsiRNAの導入も可能

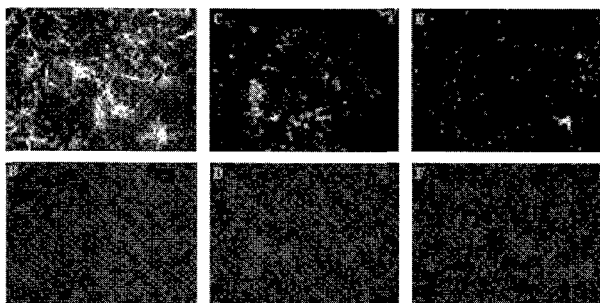
神経細胞系導入効率一覧



Nucleofector™ Deviceと専用試薬

神経細胞へのpEGFP(pEYFP)の導入効率

siRNAの導入例



Mouse cortical neurons (E17) にEGFP plasmid, EGFP発現阻害のsiRNAをco-transfectionした。導入後4日経過時に蛍光顕微鏡像にて観察した。

- A)pEGFP 3 μ g使用時のGFPの発現
B)pEGFP 3 μ g使用時のDAPI染色
C)pEGFP 3 μ g, siRNA 1.5 μ g使用時のGFPの発現
D)pEGFP 3 μ g, siRNA 1.5 μ g使用時のDAPI染色
E)pEGFP 3 μ g, siRNA 3 μ g使用時のGFPの発現
F)pEGFP 3 μ g, siRNA 3 μ g使用時のDAPI染色

Data generated by Hyun-Ju Kim and Tim Vartanian, Beth Israel Deaconess Medical Center, Dept. of Neurology, Boston, MA, USA

コード	メーカーコード	品名	内容
570-35521	VPG-1001	Nucleofector™ for Mouse Neurons	25回用
577-35531	VPG-1002	Nucleofector™ for Chicken Neurons	25回用
570-38681	VPG-1003	Nucleofector™ for Rat Neurons	25回用
572-72341	VPG-1004	Nucleofector™ for Mouse Neural stem cells	25回用
579-72351	VPG-1005	Nucleofector™ for Rat Neural stem cells	25回用
近日発売予定	VPG-1006	Nucleofector™ for Mouse Astrocytes	25回用
近日発売予定	VPG-1007	Nucleofector™ for Rat Astrocytes	25回用
近日発売予定	VPG-1008	Nucleofector™ for Mouse Oligodendrocytes	25回用
近日発売予定	VPG-1009	Nucleofector™ for Rat Oligodendrocytes	25回用
500-98921	AAD-1001	Nucleofector™ Device	1台

*株化細胞用キットも販売しています。お問い合わせ下さい。

和光純薬工業株式会社

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営業所: 北海道・東北・北関東・筑波・横浜・東海・中国・九州

問い合わせ先

フリーダイヤル: 0120-052-099 フリーファックス: 0120-052-806

URL: <http://www.wako-chem.co.jp>

E-mail: labchem-tec@wako-chem.co.jp



口腔内崩壊錠の特徴

- 高齢者や錠剤の嚥下が困難な患者でも服用しやすい。
- 就寝直前の服用に便利である。
- 麻酔前や他の治療で水分補給が制限されている患者への投薬が可能である。
- 介護者が患者の服用を援助しやすい。

【禁忌（次の患者には投与しないこと）】

- (1) 急性狭隅角緑内障のある患者 (2) 重症筋無力症のある患者

【原則禁忌（次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること）】

肺性心、肺気腫、気管支喘息及び脳血管障害の急性期等で呼吸機能が高度に低下している場合
「重大な副作用」の項参照

【効能・効果】

不眠症、麻酔前投薬

【用法・用量】

本剤の用量は、年齢、症状、疾患などを考慮して適宜増減するが、一般に成人には次のように投与する。

・不眠症

1回プロチゾラムとして0.25mgを就寝前に経口投与する。

・麻酔前投薬

手術前夜：1回プロチゾラムとして0.25mgを就寝前に経口投与する。

麻酔前：1回プロチゾラムとして0.5mgを経口投与する。

【使用上の注意】

1. 慎重投与（次の患者には慎重に投与すること）

- (1) 衰弱患者
- (2) 高齢者「高齢者への投与」の項参照
- (3) 心障害、肝障害、腎障害のある患者
- (4) 脳に器質的障害のある患者

2. 重要な基本的注意

- (1) 本剤の影響が翌朝以後に及び、眠気、注意力・集中力・反射運動能力等の低下

が起こることがあるので、自動車の運転等の危険を伴う機械の操作に従事さないよう注意すること。

(2) レンドルミンD錠0.25mg：

本剤は口腔内で崩壊するが、口腔粘膜からの吸収により効果発現を期待する製剤ではないため、崩壊後は唾液又は水で飲み込むこと。

3. 相互作用

本剤は、主として薬物代謝酵素CYP3A4で代謝される。

【併用注意】（併用に注意すること）

薬剤名等/アルコール（飲酒）、中枢神経抑制剤：フェノチアジン誘導体、バルビツール酸誘導体、イトラコナゾール、ミコナゾール、シメチジン、モノアミン酸化酵素阻害剤

4. 副作用

レンドルミン錠（普通錠）について、臨床試験及び再審査終了時の調査症例数6,548例中、副作用が報告されたのは256例（3.91%）であった。主な副作用は、残眠感・眠気144件（2.20%）、ふらつき66件（1.01%）、頭痛感50件

（0.76%）、だるさ48件（0.73%）、めまい25件（0.38%）、頭痛8件（0.12%）、倦怠感7件（0.11%）等であった。また、臨床検査値においては特に一定の傾向を示す変動は認められていない。

(1) 重大な副作用

肝機能障害、黄疸（頻度不明）：AST（GOT）、ALT（GPT）、γ-GTP上昇等の肝機能障害、黄疸があらわれることがあるので、異常が認められた場合には、直ちに投与を中止し、適切な処置を行うこと。

(2) 重大な副作用（類案）

呼吸抑制（頻度不明）：ベンゾジアゼピン系薬剤の投与により、呼吸抑制があらわれることが報告されているので、このような場合には気道を確保し、換気をはかるなど適切な処置を行うこと。

※詳細は添付文書等をご覧ください。

睡眠導入剤（プロチゾラム口腔内崩壊錠）

レンドルミン®D錠0.25mg

睡眠導入剤

レンドルミン®錠



Lendormin® D Tablets 0.25mg・Tablets

（プロチゾラム製剤）

※1）注意—習慣性あり、※2）注意—医師等の処方せん—指示により使用すること

薬価基準収載

製造販売元

日本ベーリンガー・インゲルハイム株式会社

本社・研究所／〒686-0193兵庫県川西市矢間3-10-1

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2003年6月作成（D錠0.25mg：2002.3／普通錠：2001.2）



ゴールドスタンダードな Gateway®テクノロジー

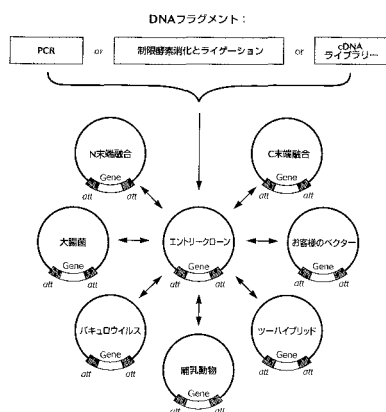


誰でもやってるGateway®クローニング

※ Gateway® は国家プロジェクトではありません。
ほら、隣の研究室でもお使いいただいています ※ ※ ※

Gateway は簡単です。

目的遺伝子のエントリークローンを作製さえすれば、その遺伝子を多種類の発現ベクター（デスティネーションベクター）に簡単に移し換えることができます。



目的遺伝子のエントリークローンを作製さえすれば、その遺伝子を複数のデスティネーションベクターに方向性とリーディングフレームを維持したままでも移入することができる。

エントリークローンの構築方法（4種類あります）

- ① PCR Directional TOPO® クローニング：PCR産物を目的の方向で迅速・効率的にクローニング。5分間室温インキュベーション
- ② PCR産物のBP反応：PCR産物の両端にattB配列が必要なため、目的遺伝子の増幅の際にはattB配列をつなげたプライマーを使用。
- ③ 制限酵素とリガーゼによるクローニング：DNAフラグメントを制限酵素で処理し、リガーゼでGateway® エントリーベクターにつなげる方法。
- ④ Gateway® 対応ライブラリー/ソースクローンから作製：Gateway® 対応ライブラリーなら簡単にエントリークローンの作製ができます。

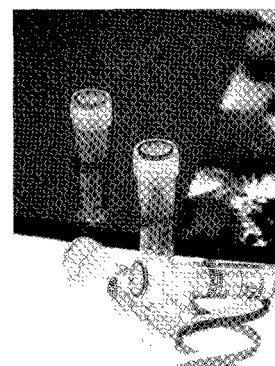
さあ、いろいろな発現系へ

目的遺伝子のエントリークローンを構築すれば多種類の発現系を同時・容易に利用することができます。

インビトロジェンでは細菌・酵母・昆虫・哺乳類細胞など、Gateway® 対応の発現システムを取扱っております。

Gateway® 用のカスタムプライマーならインビトロジェンへ

→ attB配列を含むプライマー作製の特許を所有している当社のみが製造できます。



<http://www.invitrogen.co.jp/>

製造元

Invitrogen Corporation

輸入総発売元

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