



神経化学

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第48回日本神経化学会(福岡)大会

抄録号

平成 17 年 8 月

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第48回日本神経化学会(福岡)大会 抄 録 集

会 期：2005年9月28日(水)～30日(金)

会 場：JALリゾート シーホークホテル福岡
(福岡市ホークスタウン内)

TEL 092-844-8111 FAX 092-844-7776

大会長：神庭 重信
(九州大学大学院医学研究院)

大会事務局：九州大学大学院医学研究院精神病態医学分野内
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TEL 092-642-5627 FAX 092-642-5644
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運営事務局：株式会社コングレ内
〒810-0001 福岡市中央区天神1-9-17
ダヴィンチ福岡天神5F
TEL 092-716-7116 FAX 092-716-7143
E-mail neurochem48@congre.co.jp

大会役員一覧

会 長

神庭 重信 九州大学大学院医学研究院

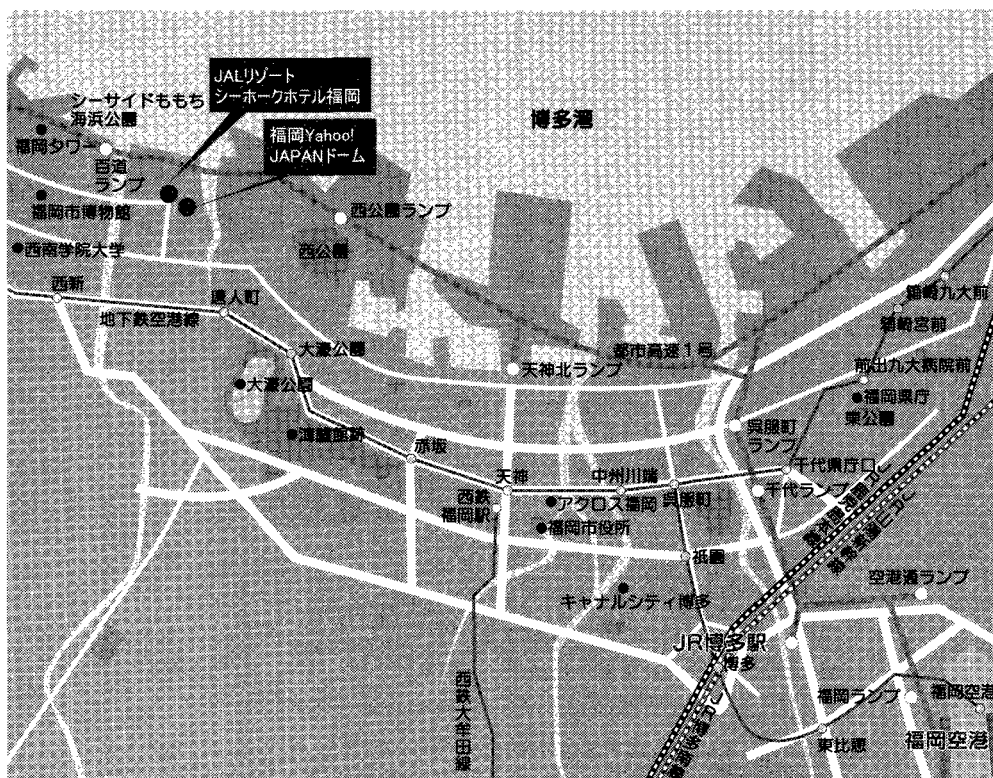
組織委員会委員

久保 千春	九州大学大学院医学研究院	服巻 保幸	九州大学生体防御医学研究所
渡辺 繁紀	九州大学／第一薬科大学	小財健一郎	久留米大学高次脳疾患研究所
前田 久雄	久留米大学医学部	森田喜一郎	久留米大学高次脳疾患研究所
内村 英幸	肥前精神医療センター／福岡心身クリニック		
野田 百美	九州大学大学院薬学研究院	山田 茂人	佐賀大学医学部
石田 康	宮崎大学医学部	大森 哲郎	徳島大学医学部
樋口 輝彦	国立精神神経センター武蔵病院	吉村 恵	九州大学大学院医学研究院
井林 雪郎	九州大学大学院医学研究院	西本 毅治	九州大学大学院医学研究院
中山 敬一	九州大学生体防御医学研究所	宮本 英七	熊本大学

プログラム委員

吉良 潤一	九州大学大学院医学研究院	中西 博	九州大学大学院歯学研究院
中別府雄作	九州大学生体防御医学研究所	黒木 俊秀	九州大学大学院医学研究院
鍋島 俊隆	名古屋大学大学院医学研究科	田中 正敏	久留米大学医学部
渡辺 義文	山口大学医学部	佐野 輝	鹿児島大学大学院
井上 和秀	九州大学大学院薬学研究院	武田 雅俊	大阪大学大学院医学系研究科
加藤 進昌	東京大学大学院医学研究科	小山 司	北海道大学大学院医学研究科
西川 徹	東京医科歯科大学大学院医学系研究科	三國 雅彦	群馬大学医学部
山脇 成人	広島大学医学部		

会場へのアクセス



●市内バス

博多駅（交通センター）	⇒	シーホークホテル福岡	約 20 分（220 円）
天神（バスセンター）	⇒	シーホークホテル福岡	約 15 分（220 円）

●地下鉄

福岡空港駅	⇒	唐人町駅	約 35 分（290 円）
博多駅	⇒	唐人町駅	約 25 分（250 円）
天神駅	⇒	唐人町駅	約 20 分（200 円）

※唐人町駅よりシーホークホテル福岡まで徒歩 15 分含む

●タクシー

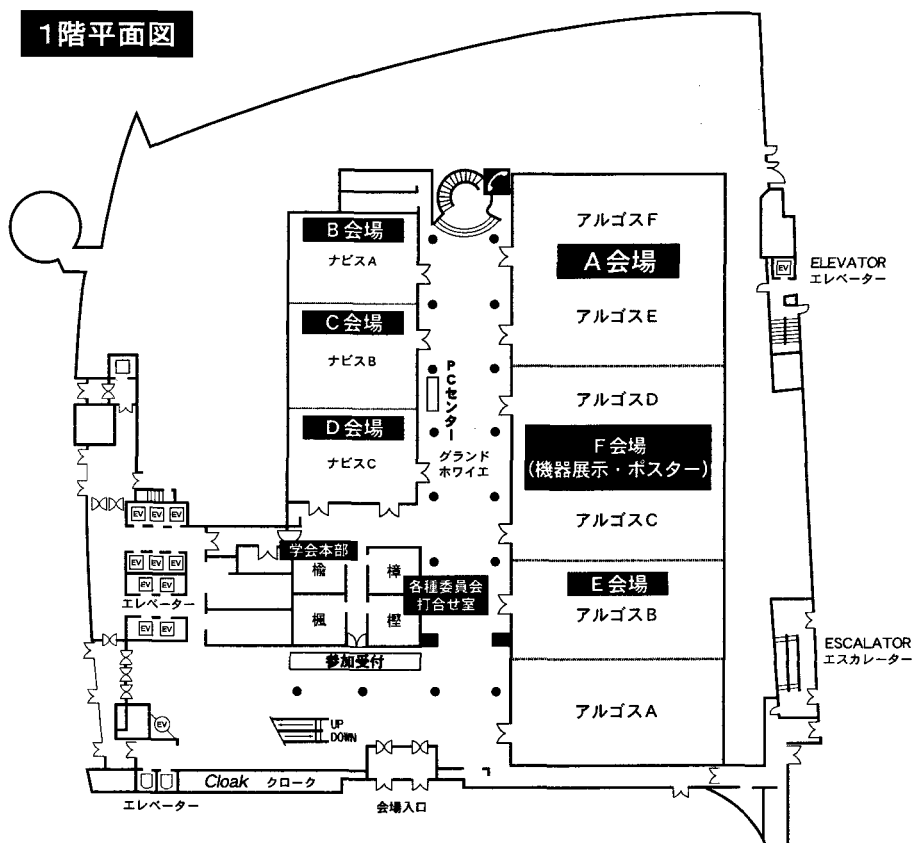
福岡空港	⇒	都市高速百道ランプ	⇒	シーホークホテル福岡	約 15 分
博多駅	⇒	都市高速百道ランプ	⇒	シーホークホテル福岡	約 15 分
天神	⇒	都市高速百道ランプ	⇒	シーホークホテル福岡	約 5 分

●各方面から航空機での福岡空港までの所要時間

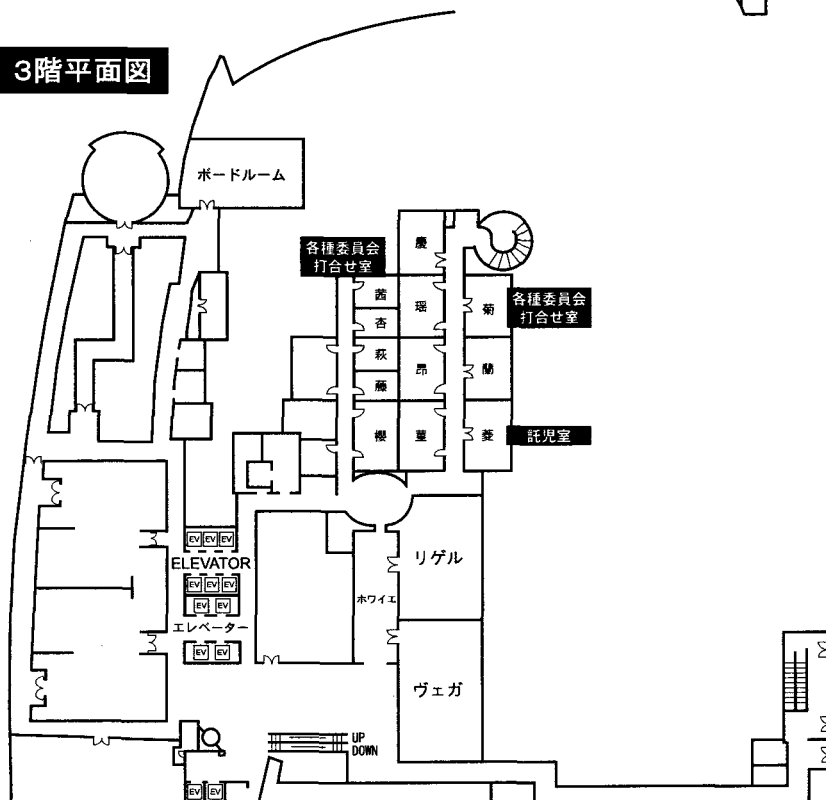
札 幌	2 時間 10 分
東 京	1 時間 30 分
大 阪	1 時間 00 分

会場案内図

1階平面図



3階平面図



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いたしました参加証（ネームカード）を必ずご持参ください。会期中はネームカードを必ず着用してください。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。公開シンポジウムを除き、ネームカードのない方の入場はお断りいたします。

●当日参加登録される方へ

受付は1Fロビーにおいて、午前8時00分より開始いたします。お渡ししたネームカードを着用のうえ、ご入場ください。参加費は以下の通りです。学生の方は受付に学生証を提示してください。

【当日受付参加費】	会員（一般）	11,000 円
	非会員（一般）	12,000 円
	学生（会員・非会員）	4,000 円
	懇親会（一般）	6,000 円
	懇親会（学生）	3,000 円

●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きます。非会員の筆頭発表者は速やかに正会員の入会手続きをお取りください。詳細は下記事務局までお問合せください。抄録集は会員の方のみ送付されます。抄録集は学会当日に総合受付でも販売いたしておりますので、ご希望の方はお買い求めください。

【入会申込連絡先】 〒160-0016
東京都新宿区信濃町 35 信濃町煉瓦館
(財) 国際医学情報センター内 日本神経化学会事務局
TEL 03-5361-7107 FAX 03-5361-7091
E-mail jsn@imic.or.jp

●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00分にならないと入場できません。ご注意ください。

●クローク

会期中は受付付近にクロークを設けますが、スペースに限りがございます。できるだけ、ホテル等のクロークをご利用いただくようお願いいたします。

●呼び出し、伝言

アナウンスでの参加者の呼び出し、お電話の取次ぎ等は一切いたしません。1階ロビーに伝言掲示板を設けておりますので、ご利用ください。

●宿泊・交通・観光案内

1階ロビーにJTBのトラベルデスクを設置します。また、会期前のお問合せは下記までお願いします。

連絡先：JTB コンベンションサポートセンター 「第48回日本神経化学学会大会」係

〒810-0072 福岡市中央区長浜 1-1-35 新KBCビル 6F

TEL 092-751-2102 FAX 092-751-4098

(営業時間)

月～金 9:30～17:30

土・日、祝祭日 休業

●学会本部

会期中は1階の楡(にれ)を学会本部にいたします。連絡先などの詳細は第48回日本神経化学学会大会ホームページにてお知らせいたします。ご確認ください。

URL: <http://www.congre.co.jp/neurochem48/>

●懇親会

大会2日目・29日(木)の19時15分よりJALリゾートシーホークホテル福岡<5F ソトコトクラブ>にて行いますので、是非ご参加ください。(参加費：一般・6,000円、学生・3,000円)

3. 大会行事

●市民公開講座

日時：9月28日(水) 17:00～20:00 会場：A会場(アルゴスE・F)

テーマ：うつ病の克服に向けて－心と脳の科学の挑戦－

司会：中根 允文(長崎国際大学)

1. うつ病－予防と治療の最前線

樋口 輝彦(国立精神神経センター武蔵病院)

2. 家族や同僚がうつ病になった時

大野 裕(慶應義塾大学・保健管理センター)

3. 心と体のミステリー

夏樹 静子(作家)

●特別講演

日時：9月28日(水) 14:30～15:20

会場：A会場(アルゴスE・F)

座長：前田 久雄(久留米大学医学部)

内因性摂食調節因子の脳高次機能活性化

大村 裕(九州大学・名誉教授)

日時：9月28日(水) 15:20～16:10

会場：A会場(アルゴスE・F)

座長：黒木 俊秀(九州大学大学院医学研究院)

The Molecular basis of monogamy

Larry Young(Emory University)

日 時：9月29日（木）14:30～15:20

カテコールアミン研究の回顧と展望

会 場：A会場（アルゴスE・F）

座 長：宮本 英七（熊本大学）

永津 俊治

（名古屋大学・藤田保健衛生大学 名誉教授）

日 時：9月29日（木）15:20～16:10

Temporal and spatial regulation by CaM kinase II

会 場：A会場（アルゴスE・F）

座 長：遠山 正彌（大阪大学大学院医学系研究科）

Howard Schulman（Stanford University）

● 招待講演

日 時：9月29日（木）9:00～9:50

脳の左右差—分子レベルからのアプローチ

会 場：A会場（アルゴスE・F）

座 長：御子柴克彦（東京大学医科学研究所）

伊藤 功（九州大学大学院理学研究院）

日 時：9月29日（木）9:50～10:40

変異型プリオン病の分子病理

会 場：A会場（アルゴスE・F）

座 長：武田 雅俊（大阪大学大学院医学系研究科）

北本 哲之（東北大学医学部創生応用医学研究センター）

● 奨励賞選考シンポジウム

日 時：9月28日（水）9:00～11:30

座 長：西澤 正豊（新潟大学医学部）、仲嶋 一範（慶応義塾大学医学部）

会 場：A会場（アルゴスE・F）

● 理事会企画オープンシンポジウム

日 時：9月29日（木）16:40～19:10

座 長：鍋島 俊隆（名古屋大学医学部）、岡野 栄之（慶応義塾大学医学部）

テーマ：オルガネラ機能異常と神経疾患

会 場：A会場（アルゴスE・F）

● 躁うつ病の薬理生化学的研究懇話会合同シンポジウム

日 時：9月29日（木）8:30～11:30

座 長：第1部 齊藤 利和（札幌医科大学）、鈴木 映二（北里大学医学部）

第2部 樋口 輝彦（国立精神神経センター武蔵病院）

門司 晃（九州大学大学院医学研究院）

テーマ：向精神薬の作用機序に関する新しい見解

会 場：D会場（ナビスC）

● ISN シンポジウム

日 時：9月30日（金）9:00～11:30

座 長：神庭 重信（九州大学大学院医学研究院）、Yong-Sik Kim（Seoul National University）

テーマ：Recent advance in molecular psychiatry: A viewpoint of ethnicity

会 場：A会場（アルゴスE・F）

● 日本精神行動遺伝学会合同シンポジウム

日 時：9月30日（金）9:00～11:30

座 長：佐野 輝（鹿児島大学大学院）、服巻 保幸（九州大学生体防御医学研究所）

テーマ：精神神経疾患の分子遺伝学的研究

会 場：B会場（ナビスA）

4. 関連行事

● 理事会

日 時：9月27日（火）13：00～17：00 会 場：3F・菊（きく）

● 評議員会

日 時：9月28日（水）12：00～13：00 会 場：A会場（アルゴスE・F）

● 総 会

日 時：9月29日（木）11：00～12：00 会 場：A会場（アルゴスE・F）

● 懇親会

日 時：9月29日（木）19：15～20：45
会 場：5F・ソトコトクラブ

5. 各種委員会

● 出版・広報委員会

日 時：9月28日（水）13：30～14：30 会 場：1F・樟（くす）

● 研究助成金等候補者選考委員会

日 時：9月28日（水）13：30～14：30 会 場：1F・櫟（かし）

● 将来計画委員会

日 時：9月28日（水）13：30～14：30 会 場：3F・菊（きく）

● シンポジウム企画委員会

日 時：9月28日（水）13：30～14：30 会 場：3F・茜（あかね）

● 奨励賞選考委員会

日 時：9月28日（水）17：00～18：00 会 場：1F・樟（くす）

● 国際対応委員会

日 時：9月29日（木）12：00～13：00 会 場：1F・樟（くす）

● 第49回大会実行委員会

日 時：9月29日（木）13：30～15：30 会 場：3F・菊（きく）

口演発表要項

1. 会場

A～F会場において同時進行で行われます。

2. 発表・討論、進行

- 1) シンポジウム及びミニシンポジウムの発表・討論は**英語**を使用して下さい。
- 2) 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、時間厳守をお願いします。
- 3) 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。
- 4) 演者は講演時間開始 10 分前までに、次演者席にお着きください。
- 5) 座長はご担当のシンポジウムの開始 20 分前までに、「座長・演者受付」(1F ロビー) までお越しください。
- 6) 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。
- 7) ミニシンポジウムの口演時間は発表 10 分、討論 5 分です。時間厳守をお願いします。シンポジウムは座長の指示に従って下さい。

3. 発表機材

本大会の発表は PC プレゼンテーションに限らせていただきます。以下の項目についてご確認ください。

PC プレゼンテーションのご案内

- 1) パソコンはご自身で持参してください。
- 2) mini-D Sub15pin の出力端子が、本体にあることが必要です。本体にない場合には、変換ケーブルをご持参ください。
- 3) ソフトウェアは、Power Point の使用を強く推奨いたします。それ以外のソフトウェアをご使用の方は、あらかじめ運営事務局 (E-mail:neurochem48@congre.co.jp、Tel 092-716-7116、Fax 092-716-7143) までご相談ください。
- 4) パソコン持参ではなく、MO、CD-R、USB フラッシュメモリーなどでご持参予定の方は、あらかじめ運営事務局にご相談ください。
- 5) 発表の 60 分前までに PC センターにて出力をチェックしてください。
- 6) 発表中にスクリーンセーバーや省電力モードにならないよう、事前に設定してください。
- 7) プレゼンテーションに静止画・動画・グラフ等のデータをリンクさせている場合は、データも必ず保存していただき、事前に動作確認を行ってください。
- 8) 動画データを使用の場合は、必ず発表データが作動するノートパソコンをお持ち込みください。
- 9) 演題上にモニターとマウスをご用意しておりますので、発表時の操作はご自身でお願いいたします。

4. オーガナイザー、座長の方へ

- 1) 担当される各セッション開始 15 分前までには各会場入りし、次座長席にお着きください。
- 2) 時間厳守に留意していただき、進行してください。
- 3) シンポジウムでは、最後にまとめの時間をとって、フロアーを交えて討論を行ってください。

[illegible]

託児所の開設

1. 対象

学会参加者の子ども（乳幼児から就学前まで）。

2. 期間

学会会期中（9月28日～30日）の9時から17時までを予定いたしております。
（ただし、最終日30日は12時までのご利用となります。）

3. 場所

3F「菱（ひし）」

4. 利用状態

保母さんによる託児サービス（有料）。

5. 保育料

保育料は有料ですが、一部を大会事務局で負担いたします。

6. 利用方法

利用者は予約が必要です。9月9日（金）までに学会ホームページより予約を行ってください。
（学会ホームページアドレス）<http://www.congre.co.jp/neurochem48/>

大会日程概要

●Sep 28(Wed)

会場	A会場 (アルゴスE・F)	B会場 (ナビスA)	C会場 (ナビスB)	D会場 (ナビスC)	E会場 (アルゴスB)	F会場 (アルゴスC・D)
8:00						
9:00	45 大会長あいさつ 00 奨励賞受賞 シンポジウム 座長：西澤 正豊 仲嶋 一範	45 MS 1 Neurotransmitters, channels and receptors 座長：熊倉鴻之助 高坂 新一 15 MS 2 Diversity of cellular signaling systems 座長：米田 幸雄 山本 秀幸	45 MS 3 Neuron-glia interaction 座長：野田 百美 丹羽 正美 30 MS 4 Neuronal death and rebirth 座長：木山 博資 和中 明生	45 MS 5 Neuronal differentiation and development I 座長：高松 研 吉川 和明 15 MS 6 Neuronal differentiation and development II 座長：田中 英明 佐藤 真	45 MS 7 Molecular pathology of dementia and ischemia 座長：柳澤 勝彦 井林 雪郎 00 MS 8 Molecular basis of neuropsychiatric disorder 座長：大森 哲郎 山田 茂人	00
10:00						
11:00						ポスター掲示 P1-001~116
12:00	30 00 評議員会	45 00 ランチョンセミナー (GSK,吉富薬品共催) 張 賢徳 座長：渡辺 義文	45 00 ランチョンセミナー (ヤンセンファーマ共催) 下濱 俊 座長：鍋島 俊隆	45	45	
13:00						00 ポスター討論 (奇数)
14:00						45 ポスター討論 (偶数)
15:00	30 特別講演1 大村 裕 座長：前田 久雄 20 特別講演2 Larry Young 座長：黒木 俊秀	30 SY 1 アルツハイマー病 発症の危険因子と 防御因子—予防と 創薬の展開— 座長：道川 誠 駒野 宏人	30 SY 2 転写因子による 脳の構造と 機能の制御 座長：尾藤 晴彦 中別府雄作	30 SY 3 うつ病・ストレス 関連障害の 分子病理 座長：久保 千春 田中 正敏		30 ポスター掲示
16:00	40					
17:00	00 市民公開講座 「うつ病の克服に 向けて—心と脳の 科学の挑戦」 樋口 輝彦 大野 裕 夏樹 静子 司会：中根 允文					00
18:00						
19:00						
20:00	00					

機器展示

大会日程概要

●Sep 29(Thu)

会場	A会場 (アルゴスE・F)	B会場 (ナビスA)	C会場 (ナビスB)	D会場 (ナビスC)	F会場 (アルゴスC・D)		ソトコト クラブ
8:00							
9:00	招待講演1 伊藤 功 座長：御子柴克彦	SY4 神経幹細胞の 発生・維持の 分子機構 座長：等 誠司 岡澤 均	SY5 精神疾患における カルモデュリン依存性 キナーゼシグナル 伝達役割 座長：福永 浩司 宮川 剛	躁うつ病の 薬理生化学的 研究懇話会合同 シンポジウム 第1部座長： 斉藤 利和 鈴木 映二 第2部座長： 樋口 輝彦 門司 晃	00	00	
10:00	招待講演2 北本 哲之 座長：武田 雅俊						
11:00	総 会				ポスター掲示 P2-001~119		
12:00		ランチョンセミナー (大塚製薬共催) 尾崎 紀夫 座長：加藤 進昌	ランチョンセミナー (旭化成ファーマ、ヤンセンファーマ共催) 吉田 契造 座長：小澤 寛樹	ランチョンセミナー (日本イーライリリー共催) 兼子 直 座長：小山 司			
13:00					ポスター掲示 P2-001~119		
14:00					ポスター掲示 P2-001~119		
15:00	特別講演3 永津 俊治 座長：宮本 英七	SY6 モデルマウスは 精神神経疾患の モデルたり得るか？ 座長：一瀬 宏 笹岡 俊邦	SY7 統合失調症の 分子病態 座長：西川 徹 那波 宏之	SY8 精神神経 疾患の新展開 座長：池中 一裕 吉良 潤一	ポスター掲示 P2-001~119		
16:00	特別講演4 Howard Schulman 座長：遠山 正彌						
17:00	理事会企画 オープン シンポジウム ：オルガネラ 機能異常と 神経疾患 座長：鍋島 俊隆 岡野 栄之						
18:00							
19:00							
20:00							19:15~20:45 〈懇親会〉

大会日程概要

●Sep 30(Fri)

会場	A会場 (アルゴスE・F)	B会場 (ナビスA)	C会場 (ナビスB)	D会場 (ナビスC)
8:00				
9:00	00	00	00	00
10:00	ISNシンポジウム: Recent advance in molecular psychiatry: A viewpoint of ethnicity 座長: 神庭 重信 Yong-Sik Kim	日本精神行動 遺伝学会合同 シンポジウム: 精神神経疾患の 分子遺伝学的研究 座長: 佐野 輝 服巻 保幸	SY9 疼痛関連分子研究 の最前線 座長: 井上 和秀 吉村 恵	SY10 神経突起形成 の分子機構 座長: 中山 敬一 貝淵 弘三
11:00	30	30	30	30
12:00				
13:00				
14:00				
15:00				
16:00				
17:00				
18:00				
19:00				
20:00				

学会からのお知らせ

1. 評議員会

日 時：9月28日（水）12:00～13:00

会 場：A会場（アルゴスE・F）

平成17年度評議員会議題（案）

「合同学会の今後」

2. 総会

日 時：9月29日（木）11:00～12:00

会 場：A会場（アルゴスE・F）

日本神経化学会 2005年度総会議題（案）

1. 平成17年度理事改選結果報告
2. 理事長報告
3. 庶務報告
4. 会計報告
5. 出版広報報告
6. プログラム編成報告
7. 各種委員会報告
 - ①将来計画委員会
 - ②脳研究推進委員会
 - ③国際対応委員会
 - ④出版広報委員会
 - ⑤研究助成金等委員会
 - ⑥シンポジウム企画委員会
8. 平成17年度奨励賞選考結果報告
9. 平成16年度決算の件
同 監査報告
10. 平成18年度予算の件
11. 評議員選任の件
12. 名誉会員推薦の件
13. 監事選任の件
14. 次期大会の件
15. その他

理事会議事録

2005 年度第 1 回理事会議事録

日 時：2005 年 3 月 24 日（木） 13:00 ～ 17:00

会 場：（財）国際医学情報センター 第 4 会議室

出席者：御子柴克彦、熊倉鴻之助、岡野 栄之、神庭 重信、池中 一裕、井上 和秀、木山 博資
黒木 俊秀、佐藤 真、島田 昌一、武田 雅俊、辻 省次、遠山 正彌、仲嶋 一範
鍋島 俊隆、野村 靖幸、東田 陽博、柳澤 勝彦、米田 幸雄
植村 慶一、宮武 正（監事）
岡野 ジェイムス洋尚（選挙管理委員長）

欠席者：高坂 新一、高松 研、馬場 明道

議事に先立ち、御子柴理事長より挨拶がなされた。

議 題

1. 理事改選結果について

平成 17 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岡野ジェイムス洋尚委員長から以下の通り報告された。

理事選挙結果報告について

日本神経化学会細則第 2 条および同代 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) 選挙結果

①選挙日程 神経化学 第 43 巻 4 号（2004 年 12 月 20 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 1,322 通（但し受取人不明で 4 通は返送された）

投票通数 379 通（投票率 28.7%）

有効通数 370 通

無効数 締切日後到着 5 通

小封筒に入っていなかったもの 4 通

白票 52 通

無効票 2 通

③開票場所

（財）国際医学情報センター 3 階 会議室

④開票立会人

田畑 秀典

久永 真市

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 池中 一裕（自然科学研究機構生理学研究所）

同 2 米田 幸雄（金沢大学大学院自然科学研究科）

当 選	3	木山 博資	(大阪市立大学大学院医学研究科)
同	4	武田 雅俊	(大阪大学大学院医学系研究科)
同	5	仲嶋 一範	(慶應義塾大学医学部)
同	6	東田 陽博	(金沢大学大学院医学系研究科)

2. 理事長・副理事長選出の件

出席理事による協議の後、理事長に遠山正彌 氏（大阪大・院・医学系研究科）が、副理事長に池中一裕 氏（自然科学研究機構生理学研究所）がそれぞれ選出された（任期は2007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、理事選挙結果を参考に理事による投票を行い下記の通り補充理事候補を選出した。

補充理事は細則第2条により3名と定められ、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。

田代 朋子	(青山学院大・理工・化学)
西川 徹	(東京医科歯科大・院)
和中 明生	(奈良県立医科大)

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	: 田代 朋子
会計担当	: 井上 和秀
出版広報担当	: 柳澤 勝彦

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。

将来計画委員会	: 御子柴克彦
国際対応委員会	: 池中 一裕 (副理事長)
研究助成金等候補者選考委員会	: 佐藤 真
脳研究推進委員会	: 辻 省次
シンポジウム企画委員会	: 東田 陽博
出版広報委員会	: 柳澤 勝彦 (出版広報担当理事)

なお、将来計画委員会と脳研究推進委員会は連携して運営することとなった。

6. 庶務報告

岡野庶務担当理事より、庶務報告が行われた。

- ・総会員数 1,631 名 (2005 年 3 月 22 日現在)

名誉会員	19 名
一般会員	1,318 名
学生会員	262 名
賛助会員	22 名
団体会員	10 名
- ・会員異動状況 (2004 年 1 月 1 日～2004 年 12 月 31 日)

新入会者	86 名
退会者	99 名

尚、入退会者の会員種別内訳は新入会員 86 名（正会員 33 名・学生会員 52 名、賛助会員 1 社）退会会員 99 名（正会員 75 名・学生会員 23 名、賛助会員 1 社）だった。会員数を増加するために島田理事を中心に小委員会を作り会員の動向を検討する。将来計画委員会においても必要であれば検討することとした。

7. 会計報告

高坂会計理事欠席のため同理事の指示により事務局から平成 16 年度決算案ならびに、参考として平成 18 年度予算案について報告が行われた。

8. 出版・広報報告

柳澤出版広報担当理事より以下の報告がなされた。

- (1) 学会誌「神経化学」44 巻 1 号の校正が終了。
- (2) 機関誌の予算オーバーについては若手研究者の研究成果を発表する企画を試み、カラー印刷が増えたためと予想される。
- (3) 学会ホームページについては今まで三木直正氏が作成していたが、2005 年 4 月から学会事務局に移管された。今後は国際化に対応したホームページ英語版の作成、会員検索システムの構築等をしていく予定であるが、昨今の個人情報保護の問題もあるが、鋭意作業を進めて行きたい。
- (4) E メール配信についての対応について
E-mail アドレスを学会からの連絡に使用するため、個々の会員に同意を求める記事を雑誌に掲載したが、メール返信が 31 通と少なく、今後も雑誌にも掲載することとした。検討の結果、会員の同意を得るため以下 3 通りなどの方法をも含め、対応を検討することとした。
 - a) 次回大会の受付に緊急時の連絡先としてアドレスを記入してもらうようボックスを用意する
 - b) 入会登録、参加登録する際にアドレスを記入してもらう
 - c) 会費振込み用紙にアドレスを記入するようにする
- (5) 国際化に対応するため、ISN の入会案内を毎号掲載する。
- (6) ISN の機関誌に日本神経化学会の活動を掲載する方向で検討を行う。
諸活動については出版広報委員会、第 48 回日本神経化学会大会については神庭大会長が原稿を作成し広報でまとめる。その際に学会設立年度を強調するようにする。
- (7) 機関誌発行と広報の役割を委員長一人で行うにはかなり負担になるため出版広報委員会を設立し、委員会メンバーで役割を分担し体制を強化する。

9. 委員会報告

(1) 国際対応委員会

池中委員長より以下の報告がなされた。

文部科学省はアジアを重視しており、今後は国際的なアジアを中心とした学術セミナーやアジアの研究教育拠点形成を考えた予算を組んでいる。今後はアジアとの関係をどうするかがポイントである。しかし、本学会の予算には限界があり国に働きかけるなどいかんして APSN に対応できるか委員を選び検討をすすめて行きたい。

(2) 研究助成金等候補者選考委員会

馬場委員長欠席のため特に報告はなかった。

(3) 脳研究推進委員会

辻委員長より以下の報告がなされた。

2004 年 9 月に評議員にアンケートをお願いし、現在まとめている最中である。

(4) シンポジウム企画委員会

鍋島委員長より以下の報告がなされた。

理事会企画オープンシンポジウムは 9 月 29 日 16 : 00 ~ 18 : 30 に開催する。

座長は鍋島俊隆（名古屋大学医学部）、岡野栄之（慶應義塾大学医学部）の両氏

10. 評議員推薦の件

今回、評議員に2名の申請があり候補者を審査し了承された為、次回総会に諮ることとした。また、現在の評議員の任期は本年度の総会までとなっているため、次期（任期は2009年総会終了迄）も引き続き評議員を引き受けていただけるかの諾否を全評議員に諮ることとした。

11. 第48回（2005年度）日本神経化学会の件

神庭重信理事より大会の進捗状況の報告がなされた。

12. 第49回（2006年度）日本神経化学会の件

鍋島俊隆理事より、会期は2006年9月14日～16日開催、会場は名古屋国際会議場とする報告がなされた。

13. 第50回（2007年度）日本神経化学会の件

高坂新一理事欠席のため、熊倉鴻之助理事より以下の報告がなされた。

会期は2007年9月10日～12日 会場はパシフィコ横浜である。日本神経科学学会との合同大会により神経化学会として会期が3日では短いのではないかと意見もあるため、1日延期する場合は9日とする方向で、高坂大会長が検討を進めている。この点については次回理事会において検討する。

14. プログラム編成ガイドラインの件

熊倉鴻之助理事より報告がなされた。

前理事会の要請により日本神経化学会大会プログラム編成のガイドライン（最終案）を作成。将来計画委員会が行ったアンケート結果をもとに、従来の利点を生かしつつ、今後の大会プログラムの編成に役立てるために作成した。ガイドラインの内容に関しては理事会で検討し、必要であればワーキンググループを立ち上げる。

15. 特許申請のための抄録公開開始日の件

岡野理事より報告がなされた。第30条の抄録公開開始日について抄録集印刷日とするか、日本神経科学学会と発行日が異なる場合もあり、検討の上報告する。

16. 名簿のホームページ掲載の件

過去の理事選挙の有権者名簿が掲載されていたため問い合わせがあり、個人情報保護の観点からホームページから削除した。

17. 余剰金の繰入の件

辻理事の申し出により平成15年度大会（新潟）の決算余剰金を日本神経化学会一般会計へ繰入ることとした。

以 上

平成17年 8 月

日本神経化学会
会員各位

日本神経化学会
理事長 遠山 正 彌

第48回日本神経化学会・総会の開催について

謹 啓

時下ますますご清祥のこととお慶び申し上げます。

さて、下記の通り日本神経化学会総会を開催致したくご案内申し上げます。

尚、総会に欠席される方は委任状（ハガキ）に必要な事項をご記入の上、事務局宛にご送付下さるか、学会当日、受付までご提出下さいますようお願い申し上げます。

敬 白

記

日 時 : 平成17年 9 月 29 日 (木) 11:00~12:00

場 所 : A会場 1F「アルゴスE・F」

議 題 : 1. 平成17年度理事改選結果報告 9. 平成16年度決算の件(同監査報告)
(予定) 2. 理事長報告 10. 平成18年度予算の件
3. 庶務報告 11. 評議員選任の件
4. 会計報告 12. 名誉会員推薦の件
5. 出版広報報告 13. 監事選任の件
6. プログラム編成報告 14. 次期大会の件
7. 各種委員会報告 15. その他
8. 平成17年度奨励賞選考結果報告

(切り離して「投函」下さい)



平成17年
日本神経化学会
総会

委 任 状

(ご欠席の方はご記入ください)

平成17年日本神経化学会総会の議決権の行使に
関する一切の権限を

代理人 _____ に委任します。

平成 17 年 月 日

所属

氏名

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日本神経化学会平成17年度奨励賞受賞シンポジウム（最優秀奨励賞選考会） Young Scientists Lectureship Award

日本神経化学会では2000年度より優秀な神経化学若手研究者を対象に日本神経化学会奨励賞を贈っております。本年度も書類審査を経て、下記の4名の奨励賞受賞者が選出されました。4名の奨励賞受賞者（シンポジスト）に研究成果を発表していただいた後、選考委員会で本年度の最優秀奨励賞受賞者を決定いたします（奨励賞の表彰及び最優秀奨励賞受賞者の発表は総会で行います）。

奨励賞受賞シンポジウム（最優秀奨励賞選考会）は一般の参加者にも公開されますので是非ともご参加ください。尚、本シンポジウムの抄録は当日会場で配布致します。

日時：2005年9月28日（水）9：00～11：30

会場：JALリゾートシーホークホテル福岡 A会場 1F 「アルゴスE・F」

座長：西澤 正豊（奨励賞選考委員長/新潟大・脳研・神経内科）

Chairperson: Masatoyo Nishizawa (Dep. of Neurology, Brain Research Inst., Univ. of Niigata)

仲嶋 一範（奨励賞選考委員/慶應大・医・解剖学）

Commission member: Kazunori Nakajima (Dep. of Anatomy, Keio Univ. School of Medicine)

発表者（平成17年度奨励賞受賞者）

1. 上原 孝（北海道大・院・薬学研究科薬理学分野）

Takashi Uehara (Dep. of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido Univ.)

「内在性ストレス抵抗性蛋白質の単離・同定とその細胞内機構」

Identification of endogenous protective proteins against ischemic stress

2. 鶴川 眞也（名古屋市立大・院・医学研究科分子形態学）

Shinya Ugawa (Dep. of Molecular Morphology, Graduate School of Medical Sciences, Nagoya City Univ.)

「味覚・痛覚における酸感受性イオンチャンネル（ASIC）の機能解析」

Functional analyses of acid-sensing ion channels in taste and pain transductions

3. 大西 浩史（群馬大・生体調節研究所・バイオシグナル分野）

Hiroshi Ohnishi (Lab. of Biosignal Sciences, Institute for Molecular and Cellular Regulation, Gunma Univ.)

「新規細胞間シグナルシステムCD47-SHPS-1系の神経系における機能解析」

Functional analysis of a novel intercellular communication system, the CD47-SHPS-1 system, in nervous system

4. 新田 淳美（名古屋大・院・医学系研究科医療薬学）

Atsumi Nitta (Dep. of Neuropsychopharmacology and Hospital Pharmacy, Nagoya Univ. Graduate School of Medicine)

「疎水性ジペプチドLeu-Ileの神経保護および薬物依存抑制作用に関する研究」

Actions of hydrophobic dipeptide Leu-Ile on the neuroprotection and drug dependence

（発表は原則として50音順ですが他のセッションとの関係で順番が入れ替わる場合もあります。予めご了承下さい。）

郵便はがき

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東京都新宿区信濃町35番地信濃町煉瓦館

(財) 国際医学情報センター内

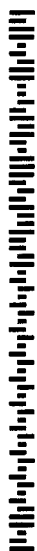
日本神経化学会行

差出有効期間
平成19年8月
9日まで

7072

新
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料金受取人払



- 特別講演
- 招待講演
- ISN シンポジウム
- 理事会企画オープンシンポジウム
- 躁うつ病の薬理生化学的研究懇話
会合同シンポジウム
- 日本精神行動遺伝学会合同シンポ
ジウム
- 奨励賞受賞シンポジウム
- シンポジウム
- 一般演題プログラム
(ミニシンポジウム、ポスター)

◆◆◆ 特別講演－ Plenary Lecture ◆◆◆

Sep 28 (Wed)

14:30 ~ 15:20 A会場

PL-01

座長：前田 久雄（久留米大学医学部神経精神医学）

内因性摂食調節因子の脳高次機能活性化

Activation of the higher brain function by endogenous satiety substances increased during food intake

大村 裕¹¹九州大学 名誉教授

Sep 28 (Wed)

15:20 ~ 16:10 A会場

PL-02

座長：黒木 俊秀（九州大学大学院医学研究院精神病態医学分野）

The Molecular basis of monogamy

Larry J.Young¹¹Dept.of Psychiatry and Behavioral Sciences, Center for Behavioral Neuroscience, Emory University, Atlanta, USA

Sep 29 (Thu)

14:30 ~ 15:20 A会場

PL-03

座長：宮本 英七（熊本大学名誉教授）

カテコールアミン研究の回顧と展望

Catecholamine research: Present, past, and future

永津 俊治¹¹名古屋大学・藤田保健衛生大学名誉教授

Sep 29 (Thu)

15:20 ~ 16:10 A会場

PL-04

座長：遠山 正彌（大阪大学大学院医学系研究科）

Temporal and spatial regulation by CaM kinase II

Howard Schulman¹¹Dept.of Neurobiology, Stanford University School of Medicine and PPD Biomarker Discovery Sciences, Stanford, USA



◆◆◆ 招待講演 – Invited Lecture ◆◆◆

Sep 29 (Thu)

9:00 ~ 9:50 A会場

IL-01

座長：御子柴克彦（東京大学医科学研究所）

脳の左右差－分子レベルからのアプローチ

Molecular Asymmetry of hippocampal circuitry

伊藤 功¹

¹九州大学大学院理学研究院

Sep 29 (Thu)

9:50 ~ 10:40 A会場

IL-02

座長：武田 雅俊（大阪大学大学院医学系研究科）

変異型プリオン病の分子病理

Biology in the prion infections: From BSE to variant Creutzfeldt-Jakob disease

北本 哲之¹

¹東北大学医学部創成応用医学研究センター

◆◆◆ ISN シンポジウムー ISN Symposium ◆◆◆

Sep 30 (Fri)

9:00 ~ 11:30 A会場

ISN-01 ~ ISN-05

Recent Advance in Molecular Psychiatry:A viewpoint of ethnicity

座 長：神庭 重信 (九州大学大学院医学研究院精神病態医学分野)

Yong-Sik Kim (Seoul National University)

- ISN-01 Dizocilpine (MK-801) induced phosphorylations of the GSK-3 β and ERK signal pathway
Yong-Sik Kim¹
¹Dept.of Psychiatry and Behavioral Science and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul, Korea
- ISN-02 The molecular and cellular basis of non-dopamine systems in addiction
Wei Hao¹
¹Mental Health Institute, Central South University, Changsha, China
- ISN-03 Ethnicity, culture and pharmacogenetics
Keh-Ming Lin¹
¹Division of Mental Health and Drug Abuse Research, National Health Research Institutes (NHRI), Zhunan Town, Taiwan
- ISN-04 The association of gene expression in anxiety, depression and suicide
Tan Chay Hoon¹, Zhu YZ¹, Sherrin T¹, Tang YM², Lau G²
¹Dept.of Pharmacology, National University of Singapore, Singapore, ²Institute of Forensic Science and Medicine, Singapore General Hospital, Singapore
- ISN-05 Ginseng enhances contextual fear conditioning and neurogenesis in rats
Kotaro Kudo¹, Kanba Shigenobu²
¹Dept.of Psychiatry, Tokyo University Graduate School of Medical Science, Tokyo, Japan, ²Dept. of Neuropsychiatry Kyushu University Graduate School of Medical Sciences

◆◆◆ 理事会企画オープンシンポジウム ◆◆◆ — Open Symposium

Sep 29 (Thu)

16:40 ~ 19:10 A会場

OS-01 ~ OS-05 オルガネラ機能異常と神経疾患

Organelle dysfunction and neurological disease

座 長：鍋島 俊隆（名古屋大学大学院医学研究科）

岡野 栄之（慶応義塾大学医学部）

- OS-01 Neurological disorder and AP complex-mediated post-Golgi membrane traffic
大野 博司^{1,2}、中津 史¹
¹理化学研究所 免疫アレルギー科学総合研究センター 免疫系構築研究チーム
²横浜市立大学 大学院国際総合科学研究科 生体超分子科学専攻
- OS-02 Deficiency of autophagy and the pathogenesis of neurodegenerative disorders
木南 英紀¹
¹順天堂大学 医学部 生化学第一講座
- OS-03 Deficiency of lysosomal proteases and disorders of neuronal and microglia I functions
中西 博¹
¹九州大学 大学院歯学研究院 加齢口腔科学分野
- OS-04 The role of mitochondrial dysfunction in selective degeneration of dopamine neurons in Parkinson disease
丸山和佳子¹
¹国立長寿医療センター 老年病研究部
- OS-05 Diversity of endoplasmic reticulum stress response
今泉 和則¹
¹宮崎大学 医学部 解剖学講座 分子細胞生物学分野

◆◆◆ 躁うつ病の薬理生化学的研究懇話会合同シンポジウム ◆◆◆ — Joint Symposium with Pharmacobiochemical Research on Bipolar Disorder Conference

Sep 29 (Thu)

8:30 ~ 11:30 D会場

向精神薬の作用機序に関する新しい見解

New insight for mechanisms of action of psychotropic drugs

第1部 JS1-01 ~ JS1-04

座長：齋藤 利和（札幌医科大学神経精神科）

鈴木 映二（北里大学医学部）

JS1-01 The Effects of Antipsychotics on Neurogenesis and survival

鶴飼 渉¹、黒澤 茂樹¹、石井 貴男¹、今井 智之¹、吉永 敏弘¹、齋藤 諭¹、
橋本 恵理¹、池田 官司¹、齋藤 利和¹¹札幌医科大学 医学部 神経精神科

JS1-02 Stress vulnerability of the hippocampus in developing rat brain.

丹生谷正史¹、鈴木 豪¹、戸田 裕之¹、脇園 智宜¹、中井 完治²、清水 邦夫²、
須田 治彦³、野村総一郎¹¹防衛医科大学 精神科、²防衛医科大学 行動科学、³首都大学東京 健康福祉学部
作業療法学科JS1-03 Human Interferon-alpha suppressed cell proliferation through interleukin-1
production in adult rat dentate gyrus金子菜穂子^{1,2,3}、工藤耕太郎⁴、馬淵 正宗⁵、竹本 恵子³、藤巻康一郎⁶、
Wati Henny³、井口 博登³、神庭 重信⁷¹慶應義塾大学医学部 ブリヂストン神経発生・再生学寄附講座、²慶應義塾大学医学
部生理学教室、³山梨大学大学院医学工学総合教育部、⁴東京大学医学部精神神経科、
⁵山梨大学医学部生化学教室、⁶県立広島大学保健福祉学部、⁷九州大学大学院精神病
態医学JS1-04 Mechanisms of action of antidepressants from the viewpoint of adult
hippocampal neurogenesis中川 伸¹、井上 猛¹、加藤亜紀子¹、西川 弘之¹、北市 雄士¹、小山 司¹¹北海道大学 医学部 精神科

第2部 JS1-05 ~ JS1-10

座長：樋口 輝彦（国立精神神経センター武蔵病院）

門司 晃（九州大学大学院医学研究院）

JS1-05 Expression of neurotrophic factor by antidepressant via mitogen-activated
protein kinase (MAPK) activation竹林 実¹、久岡 一恵¹、土岡 麻美^{1,2}、前田奈津子¹¹国立病院機構 呉医療センター・中国がんセンター 臨床研究部、²広島大学院 医
歯薬学総合 薬効解析科学

JS1-06 Neuron-Glia interaction as a novel target system for antidepressant

山田 光彦¹¹国立精神・神経センター 精神保健研究所 老人精神保健部

- JS1-07 The neurochemical mechanism of action of the anxiolytic effect of selective serotonin reuptake inhibitor: its effect on the amygdala
井上 猛¹、小山 司¹
¹北海道大学大学院医学研究科神経機能学講座精神医学分野
- JS1-08 Regulation of TH activity in rat locus coeruleus after chronic variable stress
田中 大輔¹、朝倉 幹雄¹、金井 重人¹、菱沼 拓児¹、藤井佐知子¹、長島 秀明¹、五十嵐潤子²、貴家 康男¹、御園生篤志¹、長田 賢一¹、金子 律子²
¹聖マリアンナ医科大学 医学部 神経精神科学教室、²聖マリアンナ医科大学 医学部 解剖学教室
- JS1-09 Effects of Haloperidol, Lithium, Imipramine and Diazepam on Amygdalic Nitrate Levels
鈴木 映二¹、丸田 修史¹、横山 正宗¹、佐藤 拓¹、稲田 健¹、渡辺 滋²、宮岡 等¹
¹北里大学 医学部 精神科、²北里大学 医学部 生物物理系
- JS1-10 THE long-term lithium treatment increased GAP-43 mRNA by bHLH transcription factor in rat brain
長田 賢一^{1,2}、御園生篤志¹、高橋 清文^{1,2}、長谷川 洋¹、中野 三穂¹、高橋 美保¹、小川百合子¹、金井 重人¹、田中 大輔¹、菱沼 拓児¹、貴家 康男¹、山田 光彦²、朝倉 幹雄¹
¹聖マリアンナ医科大学 神経精神科、²国立神経精神センター 老人精神保健部

◆◆◆ 日本精神行動遺伝学会合同シンポジウム ◆◆◆
 — Joint Symposium with Japanese Society for Psychiatric and
 Behavioral Genetics

Sep 30 (Fri)

9:00 ~ 11:30 B会場

JS2-01 ~ JS2-05

精神神経疾患の分子遺伝学的研究

Molecular genetics of neuropsychiatric disease

座長：佐野 輝（鹿児島大学大学院医歯学総合研究科）

服巻 保幸（九州大学生体防御医学研究所）

- JS2-01 Clinical pharmacogenetics in the treatment of schizophrenia
 古郡 規雄¹、兼子 直¹
¹ 弘前大学医学部神経精神医学講座
- JS2-02 Genome-wide affected sibpair linkage analysis of schizophrenia in the Japanese Families
 有波 忠雄¹
¹ 筑波大学 大学院人間総合 遺伝医学
- JS2-03 Gene expression analysis of mitochondria-related genes in bipolar disorder using DNA microarray
 宗像 可枝¹、岩本 和也¹、文東 美紀¹、加藤 忠史¹
¹ 理化学研究所 脳科学総合研究センター 精神疾患動態研究チーム
- JS2-04 Genome-wide linkage and association studies of schizophrenia
 服巻 保幸¹
¹ 九州大学 生体防御医学研究所 遺伝情報実験センター ゲノム機能学分野
- JS2-05 Molecular Genetical Approach to Neuropsychiatric Diseases from single gene diseases
 佐野 輝¹
¹ 鹿児島大学大学院 医歯学総合研究科 精神機能病学分野

◆◇◆ 奨励賞受賞シンポジウム ◇◇◆
— Young Scientists Lectureship Award Symposium

Sep 28 (Wed)
9:00 ~ 11:30 A会場
LA-01 ~ LA-04

座 長：西澤 正豊(新潟大学脳研究所神経内科)
仲嶋 一範(慶應義塾大学医学部解剖学)

- LA-01 Identification of endogenous protective proteins against ischemic stress
上原 孝¹
¹北海道大学大学院薬学研究科薬理学分野
- LA-02 Functional analyses of acid-sensing ion channels in taste and pain transductions
鶴川 真也¹
¹名古屋市立大学大学院医学研究科分子形態学
- LA-03 Functional analysis of a novel intercellular communication system, the CD47-SHPS-1 system, in nervous system
大西 浩史¹
¹群馬大学生体調節研究所バイオシグナル分野
- LA-04 Actions of hydrophobic dipeptide Leu-Ile on the neuroprotection and drug dependence
新田 淳美¹
¹名古屋大学大学院医学系研究科医療薬学

Sep 28 (Wed) Symposium

◆◇◆ シンポジウムー Symposium ◇◇◆

14:30 ~ 17:00 B会場

SY1-01 ~ SY1-05 アルツハイマー病発症の危険因子と防御因子ー予防と創薬への展開ー

Risk and defence factors for Alzheimer's disease: Implications for the prevention and therapeutics

座長：道川 誠(国立長寿医療センター アルツハイマー病研究部)
駒野 宏人(国立長寿医療センター アルツハイマー病研究部)SY1-01 Effects of homocysteine on amyloid β -protein generation駒野 宏人¹¹国立長寿医療センター アルツハイマー病研究部

SY1-02 How do omega-3 fatty acids effect Alzheimer's disease

植木 彰¹¹自治医科大学附属 大宮医療センター 神経内科

SY1-03 Cholesterol and Alzheimer's disease: Apolipoprotein E-mediated cholesterol metabolism in the central nervous system

道川 誠¹¹国立長寿医療センター 研究所 アルツハイマー病研究部

SY1-04 Anti-amyloidogenic effects of polyphenols: implications for the prevention and therapeutics of Alzheimer's disease

山田 正仁¹、小野賢二郎¹、浜口 毅¹、内木 宏延²¹金沢大学大学院 医学系研究科 脳老化・神経病態学(神経内科)、²福井大学 医学部 病理学

SY1-05 Mitochondrial genome polymorphisms associated with longevity or Alzheimer's disease

田中 雅嗣¹、福 典之¹、西垣 裕¹¹東京都老人総合研究所 健康長寿ゲノム探索

14:30 ~ 17:00 C会場

SY2-01 ~ SY2-05 転写因子による脳の構造と機能の制御

Transcription factors: Critical determinants of brain structure and function

座長：尾藤 晴彦(東京大学医学研究科)

中別府雄作(九州大学生体防御医学研究所)

SY2-01 Do-it-all or simply single minded? The role of Zic genes in neural development

有賀 純¹¹理研脳科学総合研究センター 比較神経発生研究チーム

SY2-02 A role of PTF1a, a bHLH transcription factor, in neuronal subtype specification

星野 幹雄¹¹京都大学 医学研究科 腫瘍生物学講座

Sep 28 (Wed) Symposium

- SY2-03 Using Chemical Probes to Dissect the Calcineurin/NFAT Pathway Signaling in Neural Development
Graef Isabella¹, Haggarty Stephen², Wang Fan³, Crabtree Gerald¹, Devasthali Vidusha¹
¹Department of Pathology and Developmental Biology, Stanford University School of Medicine, ²Eli & Edythe Broad Institute of MIT-Harvard University, ³Department of Cell Biology, Duke University
- SY2-04 Regulation of brain functions by δ FosB, a naturally occurring truncated form of FosB
中別府雄作¹、大西 克典¹、本田(大西) 陽子¹、作見 邦彦¹
¹九州大学 生体防御医学研究所 脳機能制御学分野
- SY2-05 Regulation of memory formation by transcription factor CREB
喜田 聡¹、鈴木 章円¹
¹東京農業大学 応用生物科学部 バイオサイエンス学科

14:30 ~ 17:00 D会場

SY3-01 ~ SY3-05 うつ病・ストレス関連障害の分子病理

Molecular pathology of depression and stress-related disorder

座 長：久保 千春(九州大学大学院医学研究院)
田中 正敏(久留米大学医学部)

- SY3-01 The physiological mechanisms behind psychosomatic disease
千田 要一¹、須藤 信行¹、久保 千春¹
¹九州大学大学院 医学研究院 心身医学
- SY3-02 Stress responses and depression under the influence of environmental chemicals
栗生 修司¹、藤本 哲也¹、久保 和彦²、畑中 顯和³
¹九州工業大学大学院 生命体工学研究科、²千鳥橋病院 耳鼻咽喉科、³山口大学 農学部 農芸化学科
- SY3-03 Neonatal isolation induces susceptibility to learned helplessness, an animal model of depression, in adulthood rats
山脇 成人¹、高橋 輝道¹、岩本 泰行¹、森信 繁¹
¹広島大学大学院 医歯薬学総合研究科 精神神経医科学
- SY3-04 Molecular pathophysiology of bipolar disorder
加藤 忠史¹
¹理化学研究所 脳科学総合研究センター 精神疾患動態研究チーム
- SY3-05 Novel candidate genes for stress responses in the brain
車地 暁生¹、伊藤 卓¹、海野 麻未¹、石井 澄和¹、西川 徹¹
¹東京医科歯科大学 大学院 精神行動医科学分野

Sep 29 (Thu) Symposium

8:30 ~ 11:00 B会場

SY4-01 ~ SY4-05 神経幹細胞の発生・維持の分子機構

Molecular mechanism for genesis and survival of neuronal stem cells

座長：等 誠司(自然科学研究機構 生理学研究所)

岡澤 均(東京医科歯科大学難治疾患研究所)

SY4-01 Expression and function of Oct-3/4 in neural stem/progenitor cells

岡澤 均¹¹東京医科歯科大学 難治疾患研究所 神経病理学分野

SY4-02 Accelerated demethylation in an astrocyte specific gene promoter mediated by Notch-signaling

波平 昌一¹、神山 淳¹、田賀 哲也²、中島 欽一¹¹奈良先端科学技術大学院大学 バイオサイエンス研究科 分子神経分化制御学講座、²熊本大学 発生医学研究センター 転写制御分野

SY4-03 Hormonal regulation of neural stem cells

新郷 哲郎¹¹岡山大学医学部

SY4-04 Fate regulation of neural precursor cells in the embryonic mouse neocortex

後藤由季子¹¹東京大学 分子細胞生物学研究所

SY4-05 Molecular mechanisms underlying the maintenance of neural stem cells in the adult brain

等 誠司¹¹自然科学研究機構 生理学研究所 分子神経生理

8:30 ~ 11:00 C会場

SY5-01 ~ SY5-05 精神疾患におけるカルモデュリン依存性キナーゼシグナル伝達の役割

Role of calmodulin-dependent kinase signaling system in neuropsychiatric disease

座長：福永 浩司(東北大学 薬学研究科)

宮川 剛(京都大学 医学研究科)

SY5-01 Expression and functional significance of Ca²⁺calmodulin-dependent protein kinase I in neuronal differentiation阪上 洋行¹、鎌田 暁史^{1,2}、福永 浩司²、近藤 尚武¹¹東北大学大学院 医学系研究科 細胞生物学講座、²東北大学大学院 薬学研究科 薬理学分野SY5-02 The role of Ca²⁺calmodulin-dependent protein kinase II in neuronal activity and seizure山肩 葉子^{1,2}¹自然科学研究機構 生理学研究所 神経シグナル研究部門、²総合研究大学院大学

SY5-03 Dopamine receptor signaling through CaM kinase II and calcineurin, and psychiatric disorders

福永 浩司¹、鎌田 暁史¹、塩田 倫史¹、竹内 有輔¹¹東北大学 薬学研究科 薬理学分野

Sep 29 (Thu) Symposium

- SY5-04 Visualization of synaptic Ca^{2+} -calmodulin-dependent protein kinase II activity in living neurons
 高雄 啓三^{1,2,3}
¹マサチューセッツ工科大学 RIKEN-MIT 脳科学研究センター、
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 神経構築技術開発チーム、³京都大学 情報学研究科 知能情報学専攻
- SY5-05 Calcium/calmodulin signaling and psychiatric disorders
 宮川 剛¹
¹京都大学 医学研究科 先端領域融合医学研究機構

14:30 ~ 17:00 B会場

- SY6-01 ~ SY6-05 モデルマウスは精神神経疾患のモデルたり得るか？
 Can mice be animal model for neuropsychiatric disorders?
 座長：一瀬 宏(東京工業大学)
 笹岡 俊邦(基礎生物学研究所)
- SY6-01 Genetic analysis of schizophrenia-related trait in mice
 吉川 武男¹
¹理化学研究所 脳科学総合研究センター 分子精神科学
- SY6-02 An endocrine activin regulates anxiety-related behavior and postnatal neurogenesis
 井ノ口 馨¹、上田 洋司¹
¹三菱化学生命科学研究所
- SY6-03 Noradrenaline transmission and memory retrieval deficits
 小林 和人¹
¹福島県立医科大学 医学部 生体機能研究部門
- SY6-04 Mouse model for research on an aberrant dopamine transmission
 笹岡 俊邦¹、小林 聡子¹、勝木 邦子¹、勝木 元也¹
¹自然科学研究機構 基礎生物学研究所
- SY6-05 Tetrahydrobiopterin-depleted mice as a model for malignant hyperphenylalaninemia and dopa-responsive dystonia
 一瀬 千穂¹、浦野 扶美²、下村 敦司³、佐藤 崇²、池本 和久¹、白石 弘章¹、
 千田 隆夫³、一瀬 宏²、野村 隆英¹
¹藤田保健衛生大学 医学部 薬理学、²東京工業大学 大学院 生命理工学研究科
 分子生命科学、³藤田保健衛生大学 医学部 第一解剖学

14:30 ~ 17:00 C会場

- SY7-01 ~ SY7-05 統合失調症の分子病態
 Molecular approach to investigate schizophrenia
 座長：西川 徹(東京医科歯科大学大学院)
 那波 宏之(新潟大学脳研究所)
- SY7-01 Functional analysis of new DISC1 binding protein, DBZ
 松崎 伸介^{1,2}、片山 泰一³、遠山 正彌^{1,2}
¹大阪大学大学院 医学系研究科 神経機能形態学、²21世紀COEプログラム、³浜松医科大学第一解剖学教室

Sep 29 (Thu) Symposium

- SY7-02 Dysbindin and pathogenesis of schizophrenia
橋本 亮太¹
¹ 国立精神・神経センター 神経研究所 疾病研究第三部
- SY7-03 Neurotrophic activity of EGF and IL-1 on dopaminergic neurons and later cognitive abnormalities
那波 宏之¹、岩倉百合子¹、水野 誠¹、津田 法子¹、鄭 英君¹、渡部雄一郎²、染矢 俊幸²
¹ 新潟大学 脳研究所 分子神経生物学、² 新潟大学大学院医歯学総合研究科精神医学分野
- SY7-04 Diverse CNR/Protocadherin-a family and Fyn-tyrosine kinase for Schizophrenia
八木 健^{1,2,3}、服部功太郎^{1,2,3}
¹ 大阪大学 生命機能研究科、² 科学技術振興機構 CREST、³ 国立精神神経センター
- SY7-05 Developmentally regulated psychotomimetic-inducible genes: Implications for the pathophysiology of schizophrenia
西川 徹¹
¹ 東京医科歯科大学 大学院 精神行動医科学分野

14:30 ~ 17:00 D会場

SY8-01 ~ SY8-05 精神神経疾患の新展開

New scopes for looking into neuropsychiatric disease

座 長：池中 一裕(生理学研究所)

吉良 潤一(九州大学大学院医学研究院)

- SY8-01 Molecular targeted therapy for polyglutamine disease
祖父江 元¹
¹ 名古屋大学 大学院医学系研究科 神経内科
- SY8-02 Molecular neuropathology of multiple system atrophy
貫名 信行¹
¹ 理研脳科学総合研究センター構造神経病理研究チーム
- SY8-03 Arrested oligodendrocyte development in a demyelinating disease model
池中 一裕¹
¹ 自然科学研究機構 生理学研究所 分子神経生理研究部門
- SY8-04 Pathogenesis of intracellular amyloid β -protein 42: A novel therapeutic target in Alzheimer's disease
大八木保政¹
¹ 九州大学 大学院医学研究院 脳神経病研究施設 神経内科
- SY8-05 Mechanism of axonal damage in axonal Guillain-Barré syndrome after *Campylobacter* infection
吉良 潤一¹
¹ 九州大学 大学院医学研究院 脳神経病研究施設 神経内科

Sep 30 (Fri) Symposium

9:00 ~ 11:30 C会場

SY9-01 ~ SY9-04 疼痛関連分子研究の最前線

The front-line research on pain-related molecules

座長：井上 和秀(九州大学大学院薬学研究院)

吉村 恵(九州大学大学院医学研究院)

SY9-01 TRP channels and Nociception

富永 真琴^{1,2}

¹自然科学研究機構 岡崎統合バイオサイエンスセンター 細胞生理部門、²総合研究大学院大学生理科学専攻

SY9-02 Lysophosphatidic acid involved in the initiation of neuropathic pain

植田 弘師¹

¹長崎大学大学院医歯薬学総合研究科分子薬理学分野

SY9-03 Acid-sensing ion channel 3 (ASIC3) is capable of transducing the tissue acidification caused by myocardial ischemia into pain.

八木 淳一¹、マックレスキー エドウィン²

¹杏林大学 医学部 統合生理学、²オレゴンヘルスサイエンス大学 ヴォラム研究所

SY9-04 Role of spinal microglia in the pathogenesis of neuropathic pain

津田 誠¹、井上 和秀¹

¹九州大学 薬学研究院 薬効解析学分野

9:00 ~ 11:30 D会場

SY10-01 ~ SY10-05 神経突起形成の分子機構

Molecular mechanism of neurite formation

座長：中山 敬一(九州大学生体防御医学研究所)

貝淵 弘三(名古屋大学大学院医学系研究科)

SY10-01 Neuronal polarity and axon formation

貝淵 弘三¹

¹名古屋大学大学院 医学系研究科 神経情報薬理学講座

SY10-02 Protrudin induces process formation by promoting membrane transport

中山 敬一¹、白根 道子¹

¹九州大学 生体防御医学研究所 分子発現制御学分野

SY10-03 Contact-dependent regulation of process arborization of neurons and glia by DNER-Notch signaling

見学美根子¹、永樂 元次¹、金 清華¹

¹理化学研究所 脳科学総合研究センター 神経細胞極性研究チーム

SY10-04 Role of Calcium-Regulated Local Protein Synthesis Within Nerve Growth Cones

竹居光太郎^{1,2}、五嶋 良郎^{1,2}

¹横浜市立大学大学院 医学研究科 分子薬理神経生物学教室、²科学技術振興機構 CREST

SY10-05 Signaling mechanisms of axon guidance molecules, semaphorins

根岸 学¹、生沼 泉¹、加藤 裕教¹

¹京都大学大学院 生命科学研究科 生体システム学分野

一般演題（ミニシンポジウム） プログラム

	28日(水) 8:45～11:45	
	前 半	後 半
Neurotransmitters, channels and receptors	B会場 MS1-01～06	
Diversity of cellular signaling systems		B会場 MS2-01～06
Neuron-glia interaction	C会場 MS3-01～07	
Neuronal death and rebirth		C会場 MS4-01～05
Neuronal differentiation and development I	D会場 MS5-01～06	
Neuronal differentiation and development II		D会場 MS6-01～06
Molecular pathology of dementia and ischemia	E会場 MS7-01～05	
Molecular basis of neuropsychiatric disorder		E会場 MS8-01～07

Sep 28 (Wed) Mini-Symposium

◆◆◆ ミニシンポジウムー Mini-Symposium ◆◆◆

8:45 ~ 10:15 B会場

MS1-01 ~ MS1-06 Neurotransmitters, channels and receptors

座長：熊倉鴻之助（上智大学生命科学研究所）

高坂 新一（国立精神神経センター神経研究所）

- MS1-01 Expression and function of KCNQ channels in microglia
王 冰¹、パナシュ ウルリケ²、波田野佳子¹、青木 俊助³、
ケテンマン ヘルマート²、和田 圭司³、野田 百美¹
¹九州大学 大学院 薬学府 病態生理学分野、²Department of Cellular
Neurosciences, Max-Delbrück Center for Molecular Medicine, D-13092 Berlin, Germany、
³国立精神神経センター
- MS1-02 Structural insight of ifenprodil recognition by NR2B amino terminal domain of
NMDA receptor
Chian-Ming Low¹、Fui-Mee Ng¹
¹Department of Pharmacology, Faculty of Medicine, National University of Singapore
- MS1-03 Shank3 mediates interaction of PSD-95 and GluR1 AMPA receptor
内野 茂夫¹、和田 英則¹、中村 泰子¹、内山 孝由¹、堤 も絵¹、平澤 孝枝¹、
高坂 新一¹
¹国立精神神経センター 神経研究所 代謝研究部
- MS1-04 Effects of a glial toxin fluorocitrate on extracellular D-serine contents in the
medial prefrontal cortex of the rat
兼松宗太郎¹、石井 澄和¹、海野 麻未¹、山本 直樹¹、原 諭吉²、西川 徹¹
¹東京医科歯科大学 大学院 歯学総合研究科、²東京医科歯科大学 大学院 保健
衛生学研究科
- MS1-05 Effects of MK-801 on the gene expression of serine racemase and D-amino acid
oxidase and on the D-serine levels in rat brain
橋本 篤司¹、吉川 正信¹、安藤 英祐²、矢野 広²、松本 英夫²、川口 充³、
岡 哲雄¹
¹東海大学 医学部 臨床薬理学、²東海大学 医学部 精神科学、³東京歯科大学
薬理学
- MS1-06 Inhibition of nicotinic acetylcholine receptors by dehydroepiandrosterone and its
sulfate ester in adrenal chromaffin cells and in *Xenopus* oocytes
工藤 賢三¹、立川 英一¹、近藤ゆき子¹、水間 謙三¹、平 英一¹
¹岩手医科大学 医学部 薬理学講座

10:15 ~ 11:45 B会場

MS2-01 ~ MS2-06 Diversity of cellular signaling systems

座長：米田 幸雄（金沢大学薬学部薬物学）

山本 秀幸（熊本大学大学院医学薬学研究部）

- MS2-01 ApolipoproteinA-I increases association of cytosolic cholesterol with
microtubules in rat astrocytes
伊藤 仁一¹、長安 祐子¹、ケイロラ アリレザ¹、横山 信治¹
¹名古屋市立大学大学院 医学研究科 代謝細胞生化学 I

Sep 28 (Wed) Mini-Symposium

- MS2-02 Feeding behavior of NPY-Y1 knock out mice
仁木 剛史¹、椎谷 友博¹、山口 剛¹、浦山 勝裕¹、三富 明夫¹、長谷川歩未¹、樋口 宗史¹
¹新潟大学大学院 医歯学総合研究科 薬理学分野
- MS2-03 Neuronal differentiation is promoted by arginine methylation of RNA-binding proteins
Graef Isabella¹、Haggarty Stephen²、Wang Fan³、Crabtree Gerald¹、宮田 信吾^{1,2}、森 泰丈^{1,2}、藤原 達司^{1,2}、種子田 艶^{1,2}、奥田 洋明^{1,2}、西村 将彦^{1,2}、遠山 正彌^{1,2}
¹大阪大学大学院 医学系研究科 神経機能形態学講座、²21世紀COEプログラム
- MS2-04 Regulation of Ca²⁺/calmodulin-dependent protein kinase I β 2 by the sequential autophosphorylation mechanism.
平井 志保¹、内藤 康仁¹、佐々木泰治¹
¹北里大学 薬学部 薬学科
- MS2-05 Regulation of intracellular localization of Cyclin-dependent kinase 5 (Cdk5) activators p35 and p39 by myristoylation
浅田 明子¹、合田 正貴²、林 宣宏²、山田 真理¹、斉藤 太郎¹、久永 眞市¹
¹首都大学東京 都市教養学部 理工系 生命科学コース、²藤田保健衛生大学 総合医科学研究所 医高分子部門
- MS2-06 The FcR γ / Fyn signaling cascade is critical in brain during cuprizone-induced demyelination and myelination
清和 千佳¹、田中嘉代子²、酒井 梨沙¹、梶田 真澄²、阿相 皓晃¹
¹東京都老人総合研究所、²埼玉医科大学

8:45 ~ 10:30 C会場

MS3-01 ~ MS3-07 Neuron-glia interaction

座長：野田 百美（九州大学大学院薬学研究院）
丹羽 正美（長崎大学医学部薬理学第1）

- MS3-01 Changes in expression of neurotrophic factors by nicotine in cultured astrocytes
及川 弘崇¹、中道 範隆¹、加藤 俊介¹、米田 幸雄¹
¹金沢大学 大学院 自然科学研究科 薬物学研究室
- MS3-02 PGE2 modulates the hippocampal neuron loss induced by kainic acid
竹宮 孝子^{1,2}、松村 潔³、前原 通代⁴、植松 智⁵、鈴木 香子²、杉浦 弘子²、審良 静男⁵、山形 要人²
¹東京女子医大 医学部 第一生理、²東京都神経研 神経薬理、³大阪工業大学 情報科学、⁴東京女子医大 中央検査部、⁵大阪大学 微研 自然免疫
- MS3-03 Activity-dependent interaction between axons and astrocytes promotes CNS myelination
石橋 智子¹、Philip R Lee¹、R. Douglas Fields¹
¹米国立衛生研究所
- MS3-04 Sema4D implicated in NGF-dependent neurite outgrowth
高原 瑞恵¹、稲垣 忍¹
¹大阪大学大学院 医学系研究科 保健学専攻

Sep 28 (Wed) Mini-Symposium

- MS3-05 Glia-to-vascular communication mediated by extracellular ATP
小泉 修一¹、藤下加代子¹、井上 和秀²
¹国立衛研 薬理、²九州大学大学院 薬学研究院 薬効解析学
- MS3-06 Tissue distribution and functional analysis for contactin associated protein 4 (Caspr4) in central nervous system
二川 俊隆¹、大磯 茂¹、三浦 岳彦¹、宝来佐和子²、渡邊 和忠³、武田 泰生¹、山田 勝士¹
¹鹿児島大学 大学院医歯学総合研究科 生体機能制御学講座 薬物動態制御学分野、²東京農工大学 大学院連合農学研究科 資源環境学、³長岡技術科学大学 生物エネルギー工学
- MS3-07 Cystatin F mRNA expression in spontaneous chronic late-onset demyelination animal model
馬 堅妹^{1,2}、田中 謙二¹、池中 一裕¹
¹自然科学研究機構 生理研究所 分子生理研究部門、²大連医科大学 解剖学教室

10:30 ~ 11:45 C会場

MS4-01 ~ MS4-05 Neuronal death and rebirth

座 長：木山 博資（大阪市立大学大学院医学研究科）
和中 明生（奈良県立医科大学解剖学第二）

- MS4-01 Altered bHLH gene expression in cortical cells by A β and its role in cell death
内田 洋子¹、五味不二也¹
¹東京都老人総合研究所 老年病ゲノムチーム
- MS4-02 Multiple candidate genes analysis identifies α -synuclein as a susceptibility gene for sporadic Parkinson's disease
水田依久子¹、佐竹 渉¹、岡 晃²、猪子 英俊²、山本 光利³、服部 信孝⁴、村田 美穂⁵、戸田 達史^{1,6}
¹大阪大学大学院 医学系研究科 臨床遺伝学、²東海大学 分子生命科学、³香川県立中央病院 神経内科、⁴順天堂大学 脳神経内科、⁵国立精神・神経センター 武蔵病院 神経内科、⁶科学技術振興機構 戦略的創造研究推進事業（CREST）、
- MS4-03 Selegiline potentiates effects of donepezil on cognitive impairment induced by amyloid beta (25-35)
恒川 浩子^{1,2}、野田 幸裕^{1,3}、王 大勇¹、毛利 彰宏¹、鍋島 俊隆¹
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藤本製薬株式会社 創薬研究所、³名城大学 薬学部 医薬連携実習部門 病態解析学
- MS4-04 The role of galectins during goldfish optic nerve regeneration
胡桃沢智子^{1,2}、永島 幹子^{1,2}、馬渡 一浩¹、加藤 聖²
¹金沢大院 医 保健学、²金沢大院 医 脳情報分子
- MS4-05 Effects of CICR on interleukin-1 β -associated adenosine releases in mouse hippocampus
朱 剛^{1,2}、岡田 元宏²、吉田 淑子^{2,3}、森 文秋¹、若林 孝一¹、兼子 直²
¹弘前大学 医学部 附属脳神経血管病態研究施設 分子病態部門、²弘前大学 医学部 神経精神医学講座、³シバ医理科 神経科学分子生物研究所

Sep 28 (Wed) Mini-Symposium

8:45 ~ 10:15 D会場

MS5-01 ~ MS5-06 Neuronal differentiation and development I

座長：高松 研（東邦大学医学部生理）
吉川 和明（大阪大学蛋白質研究所）

- MS5-01 Impaired development of sensory neurons in mice lacking paternal *necdin* gene
細川 明里¹、桑子賢一郎¹、西村伊三男¹、吉川 和明¹
¹大阪大学 蛋白質研究所 神経発生制御研究室
- MS5-02 BDNF influences the decision of the neuronal laminar fate during development of the mouse cerebral cortex through precocious neurogenesis.
福光 秀文¹、大塚 正成¹、古川 昭栄¹
¹岐阜薬科大学 薬学部 分子生物学教室
- MS5-03 4-Methylcatechol facilitates survival of cultured neural stem cells via enhanced expression of heme oxygenase-1 without changing their differentiation fate
古川 美子¹、浦野 友美¹、南村 美里¹、古川 昭栄¹
¹岐阜薬科大学 分子生物学
- MS5-04 The *Drosophila* retin gene is required for proper development of photoreceptors
Hyunjoo Kim¹、Eunju Kim¹、Jeyoun Jang¹、Jaeseung Yoon¹、Kwanghee Baek¹
¹Graduate School of Biotechnology, Kyung Hee University
- MS5-05 Activation of the wnt/ β -catenin pathway promotes proliferation of neural progenitor cells in the adult mouse subventricular zone
安達 一英^{1,2,3}、坂口 昌徳³、山下 徹³、藤田 裕子³、後藤由季子⁴、
アルヴァレスブイラ アルトロ⁵、河瀬 斌¹、岡野 栄之³、澤本 和延^{1,2}
¹慶應義塾大学 医学部 脳神経外科、²慶應義塾大学 医学部 ブリヂストン神経発生・再生学寄付講座、³慶應義塾大学 医学部 生理学教室、⁴東京大学 分子細胞生物学研究所、⁵カリフォルニア大学 サンフランシスコ校 脳神経外科
- MS5-06 Different labeling methods delineate different cell classes and migratory paths of the early postnatal subventricular zone progenitors
鈴木 諭¹、柳原 豊史¹、関 善弘¹、馬渡 真也¹、山本 緑¹、岩城 徹¹
¹九州大学大学院医学研究院神経病理

10:15 ~ 11:45 D会場

MS6-01 ~ MS6-06 Neuronal differentiation and development II

座長：田中 英明（熊本大学医学部神経分化学）
佐藤 真（福井大学医学部形態機能医科学講座）

- MS6-01 Wnt-3a promotes both neural progenitor proliferation and neuronal differentiation during hippocampal development.
鹿川 哲史¹、吉永 豊¹、清水 健史¹、井上 俊洋¹、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
- MS6-02 Neurogenesis in the adult mouse striatum after cerebral ischemia
二宮充喜子^{1,2,3,5}、山下 徹^{1,2,4,5}、砂堀 毅彦^{1,2,5}、坂口 昌徳^{1,2,5}、阿部 康二⁴、
荒木 信夫³、岡野 栄之^{2,5}、澤本 和延^{1,2,5}
¹慶應義塾大学 医学部 ブリヂストン神経発生・再生学寄付講座、²慶應義塾大学 医学部 生理学教室、³埼玉医科大学 医学部 内科部門 神経内科、⁴岡山大学大学院 医歯学総合研究科 神経病態内科学、⁵JST, CREST

Sep 28 (Wed) Mini-Symposium

- MS6-03 Roles of Disrupted-In-Schizophrenia-1 in the later stage of hippocampal neuron
坪井 大輔¹、田谷真一郎²、篠田 友靖²、匹田 貴夫²、黒田 摂子²、貝淵 弘三²
¹名古屋大学大学院 理学研究科 生命理学専攻 生体応答論講座、²名古屋大学大学院 医学系研究科 細胞情報医学専攻 神経情報薬理学講座
- MS6-04 RGMa inhibition promotes axonal growth and recovery after spinal cord injury
羽田 克彦¹、藤谷 昌司¹、山下 俊英¹
¹千葉大学 大学院医学研究院 神経生物学
- SY6-05 Fate and origin of multipolar cells during the cortical plate development
田畑 秀典¹、宮田 卓樹²、仲嶋 一範^{1,3}
¹慶應義塾大学 医学部 解剖学教室、²名古屋大学 大学院医学研究科 機能形態学講座 細胞生物学、³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
- SY6-06 IQGAP3, a novel effector of Rac1 and Cdc42, regulates neurite outgrowth through actin cytoskeletal reorganization
王 淑杰¹、渡辺 崇¹、則竹 淳¹、佐藤 和正¹、吉村 武¹、深田 正紀²、貝淵 弘三¹
¹名古屋大学大学院 医学系研究科 神経情報薬理学講座、²国立長寿医療センター研究所 遺伝子蛋白質解析室

8:45 ~ 10:00 E会場

MS7-01 ~ MS7-05 Molecular pathology of dementia and ischemia

座 長：柳澤 勝彦（長寿医療研究センター）

井林 雪郎（九州大学大学院医学研究院）

- MS7-01 Visualization of newly deposited tau in neurofibrillary tangles and neuropil threads
宮坂 知宏^{1,2}、渡邊 淳³、斉藤 祐子⁴、村山 繁雄⁴、マン デビッド⁵、山崎 峰雄⁶、レイビッド リブカ⁷、森島 真帆¹、長嶋 和郎²、井原 康夫¹
¹東京大学 医学系研究科 神経病理、²北海道大学医学部分子細胞病理学、³国立長寿医療センター、⁴東京都老人総合研究所 老化臨床神経科学研究グループ、⁵マンチェスター大学、⁶日本医科大学第2内科、⁷オランダブレインバンク
- MS7-02 The role of Caspase-4 in endoplasmic reticulum stress-induced apoptosis of familial Alzheimer's disease
行岡 太志¹、松崎 伸介¹、小山 佳久¹、遠山 正彌¹
¹大阪大学大学院 医学系研究科 神経機能形態学
- MS7-03 Neurotoxic function of induced microsomal prostaglandin E₂ synthase-1 in cerebral ischemia.
太田 梓¹、松尾 由理¹、植松 智²、審良 静男²、佐々木泰治¹
¹北里大学 薬学部 薬理学、²大阪大学 微生物病研究所 自然免疫学
- MS7-04 Attenuation of focal cerebral ischemic injury in transgenic mice overexpressing PAF-acetylhydrolase II (PAF-AH(II)) in neurons
梅村 公子¹、平島 豊¹、遠藤 俊郎¹、河野 望²、井上 貴雄²、青木 淳賢²、新井 洋由²、木内 博之³、小田 正哉³、石井 陽子⁴、加藤 一郎^{5,6}、平賀 紘一⁶
¹富山医科薬科大学 医学部 脳神経外科、²東京大学 大学院 薬学系研究科 衛生化学教室、³秋田大学 医学部 脳神経外科、⁴富山医科薬科大学 医学部 病理学講座、⁵富山医科薬科大学 21世紀COEプログラム、⁶富山医科薬科大学 医学部 生化学講座

Sep 28 (Wed) Mini-Symposium

- MS7-05 Hydrogen sulfide is the mediator of cysteine neurotoxicity in cerebral ischemia
Qu Kun¹, C.P.L.H. Chen³, B Halliwell², P.K. Moore¹, P.T.-H. Wong¹
¹Departments of Pharmacology and ²Biochemistry, ³Faculty of Medicine, National University of Singapore, 18 Medical Drive, Kent Ridge, Singapore 117597; and Department of Neurology

10:00 ~ 11:45 E会場

MS8-01 ~ MS8-07 Molecular basis of neuropsychiatric disorder

座長：大森 哲郎（徳島大学精神医学分野）
山田 茂人（佐賀大学医学部精神医学）

- MS8-01 Role of Phosphorylation Dependent Ubiquitination of BMAL1 in Mammalian Circadian Clock
田丸 輝也¹、磯島 康史²、高松 研¹
¹東邦大・医・第2生理、²大阪大学 蛋白質研究所蛋白質高次機能研究学部門 体内環境統合蛋白質研究室
- MS8-02 A Vibrissae-Related Pattern of Immunoreactive Parvalbumin and L1 in SI Cortex of Neuropsin- Deficient Mouse
イスラム モハマド シャイフル¹、石川 保幸¹、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 細胞構造学講座
- MS8-03 Aripiprazole's agonist and antagonist properties at human dopamine D2L and D2S receptors
田鳥 祥宏¹、三輪 貴志¹、菊地 哲朗¹
¹大塚製薬株式会社 探索第二研究所
- MS8-04 Altered pericentrin 2 (PCNT2) expression in Bipolar Disorder
ピライ アニータ¹、中村 和彦¹、山田 和男²、岩山 佳美²、豊田 倫子²、武井 教使¹、三辺 義雄¹、鈴木 勝昭¹、関根 吉統¹、岩田 泰秀¹、三好 耕³、本田 章子³、馬場 孝輔³、片山 泰一³、遠山 正彌³、吉川 武男²、森 則夫¹
¹浜松医科大学 医学部 精神神経医学講座、²理化学研究所 脳科学総合研究センター 分子精神科学研究チーム、³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講座 プロセッシング機能形態分野
- MS8-05 Mood stabilizing drugs enhance adult neurogenesis by Notch signaling activation in neural stem cells.
東 幹人¹、池中 一裕¹、等 誠司¹
¹総合研究大学院大学 生命科学科 生理科学専攻
- MS8-06 δ FosB determines resistance to excitotoxicity induced by kainic acid.
本田(大西) 陽子¹、大西 克典¹、高瀬敬一郎²、石橋 仁³、江藤 圭⁴、梶谷 康介¹、作見 邦彦¹、後藤 純信⁵、野田 百美⁴、重藤 寛史²、中別府雄作¹
¹九州大学 生体防御医学研究所 脳機能制御学分野、²九州大学 大学院 医学研究院 脳神経病研究施設 神経内科、³九州大学 大学院 医学研究院 細胞システム生理、⁴九州大学 薬学研究院 医療薬科学部門 生命薬学講座、⁵国際医療福祉大学 リハビリテーション学部 作業療学科
- MS8-07 Vlg1 mutant mice showed high susceptibility to audiogenic seizure
八木 秀司¹、高村 佳弘^{1,2}、赤城 好男²、吉田 和典³、佐藤 真^{1,4}
¹福井大学 医学部 形態機能医科学講座 組織細胞形態学・神経科学領域、²福井大学 医学部 感覚運動医学講座 眼科学、³福井大学 医学部 形態機能医科学講座 心理学領域、⁴SORST, JST

一般演題（ポスター発表） プログラム

	F 会 場	
	28日(水)	29日(木)
細胞接着因子	P1-001～005	
再生、移植	P1-006～009	
可塑性	P1-010～012	
プログラム細胞死	P1-013～021	
本能・情動・行動	P1-022	
感覚系・運動系	P1-023～024	
睡眠、生体リズム	P1-025～026	
学習、記憶	P1-027～028	
神経内分泌	P1-029	
自律神経系	P1-030	
老化	P1-031	
脳血流、代謝	P1-032～034	
イメージング	P1-035～036	
疾患モデル	P1-037～045	
発育、発達障害	P1-046～049	
変性疾患	P1-050～063, 116	
精神疾患	P1-064～081	
虚血	P1-082～085	
外傷	P1-086～088	
認知症、アルツハイマー病	P1-089～098	
薬物依存、精神薬理	P1-099～109	
中毒症	P1-110～111	
脳腫瘍	P1-112	
てんかん	P1-113～115	
イオンチャンネル、興奮膜		P2-001～005
神経伝達物質、修飾物質		P2-006～015
受容体、輸送体		P2-016～023
シナプス		P2-024～027
情報伝達、変換、修飾		P2-028～040
軸索輸送、細胞運動、細胞骨格		P2-041～045
ニューロン、グリア		P2-046～062
ミエリン		P2-063～070
神経免疫		P2-071～073
パターン形成		P2-074～075
細胞分化		P2-076～099
突起伸展、回路網形成		P2-100～109
栄養因子		P2-110～119

Sep 28 (Wed) Poster Session

F会場

掲示時間 9:00 ~ 17:00
 討論 / 奇数番号 13:00 ~ 13:45
 偶数番号 13:45 ~ 14:30

◆◆◆ ポスターセッションー Poster Session ◆◆◆

細胞接着因子

- P1-001 Gicerin paticipates in the neurite outgrowth from PC12 cells induced by NGF.
 平 英一¹、小浜 恵子¹、工藤 賢三¹、近藤ゆき子¹、水間 謙三¹、立川 英一¹
¹岩手医科大学 医学部 薬理学
- P1-002 Specific localization of tetraspanin protein CD9 in mouse dorsal horn
 高橋由香里¹、星 登美子¹、石橋 智子¹、山口 宜秀¹、馬場 広子¹
¹東京薬科大学 薬学部 機能形態学教室
- P1-003 Immunohistochemical analysis of neural cell recognition molecule NB-2 in the rat brain
 豊島 学¹、武田 泰生²、霜田 靖¹、渡邊 和忠¹
¹長岡技術科学大学 生物系 神経機能工学、²鹿児島大学大学院 医歯学総合研究科
- P1-004 Immunohistochemical detection of neural cell recognition molecule NB-3 in the rat brain
 桜井 都衣¹、武田 泰生²、霜田 靖¹、渡邊 和忠¹
¹長岡技術科学大学 生物系 神経機能工学、²鹿児島大学大学院 医歯学総合研究科
- P1-005 Spatiotemporal expression of a novel member of immunoglobulin superfamily, mKirre, in the mouse brain
 森川 吉博¹、久岡 朋子¹、北村 俊雄²、仙波恵美子¹
¹和歌山県立医科大学 医学部 第二解剖、²東京大学医科学研究所 先端医療研究センター 細胞療法分野

再生、移植

- P1-006 Role of Retinoids in Goldfish Retina during Optic Nerve Regeneration
 櫻井 裕之^{1,2}、馬渡 一浩¹、松川 通²、杉谷 加代¹、加藤 聖²
¹金沢大院 医 保健学、²金沢大院 医 脳情報分子
- P1-007 IGF-I accelerates axonal regeneration in the goldfish retina after optic nerve injury through PI3K/Akt system
 村山 大育¹、郡山 恵樹¹、本間 啓子¹、加藤 聖¹
¹金沢大院 医 医科学
- P1-008 TRANSPLANTATION OF CRYOPRESERVED HUMAN BONE MARROW-DERIVED MULTIPOTENT ADULT PROGENITOR CELLS FOR NEONATAL HYPOXIC-ISCHEMIC INJURY
 松川 則之^{1,2}、安原 隆雄²、David C Hess²、James E Carroll²、Cesario V Borlongan²
¹名古屋市立大学 医学部 神経内科、²ジョージア医科大学 医学部 神経内科
- P1-009 Implication of DNA methyltransferase in EAAC1/EAAT3 expression in response to nerve injury
 奥山 範子¹、桐生・瀬尾寿美子¹、田嶋 正二²、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大阪大学 蛋白質研究所

Sep 28 (Wed) Poster Session

F 会場

掲示時間 9:00 ~ 17:00
 討論 / 奇数番号 13:00 ~ 13:45
 偶数番号 13:45 ~ 14:30

可 塑 性

- P1-010 Neuropsin modulates the conversion of nmda-LTP to compound-LTP
 石川 保幸¹、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 細胞構造学講座
- P1-011 Gene expression analysis associated with Long-lasting synaptogenesis after repetitive exposures to glutamate in hippocampal slice cultures.
 河合 克宏¹、富永 (吉野) 恵子²、谷口 直子²、田代 朋子¹、小倉 明彦²
¹青山学院大学大学院 理工学研究科、²大阪大学大学院 生命機能研究科
- P1-012 Expression of hippocampal neuropsin (KLK8) mRNA is regulated by steroid hormones
 原田 暁子¹、石川 保幸¹、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 細胞構造学講座

プログラム細胞死

- P1-013 Peripheral lipopolysaccharide injection induces apoptosis in the murine olfactory bulb and rostral migratory stream
 森 啓至¹、金子 葉子¹、中島 昭¹、永津 郁子²、太田 明¹
¹藤田保健衛生大学 医学部 生理学、²藤田保健衛生大学 医学部 解剖
- P1-014 ER stress response in dendrites of primary neurons
 村上 智彦^{1,2}、柳田 寛太¹、今泉 和則¹
¹宮崎大学 医学部 解剖学 分子細胞生物学分野、²奈良先端科学技術大学院 バイオサイエンス研究科 細胞構造
- P1-015 Functional changes following sustained exposure to glutamate at a low concentration in cultured neurons derived from discrete rat brain regions
 神戸 悠輝¹、中道 範隆¹、石岡 佑吉¹、米田 幸雄¹
¹金沢大学 大学院 自然科学研究科 薬物学研究室
- P1-016 Involvement of double strand RNA-dependent protein kinase (PKR) on endoplasmic reticulum stress-induced cell death in rat retinal ganglion cells
 嶋澤 雅光¹、原 英彰¹
¹岐阜薬科大学 生体機能分子学講座
- P1-017 Attenuation of apoptosis by glucocorticoid modulatory element-binding protein 1 via specific binding to procaspases
 上原 孝¹、鶴間 一寛¹、守本 亘孝²、原 英彰²、野村 靖幸¹
¹北海道大学 薬学部 薬理学、²岐阜薬科大学 生体機能分子学講座
- P1-018 Intracellular signaling mechanism of sustained nitric oxide (NO) exposure-induced apoptosis in PC12 cells
 山本 敏文¹、山本 秀子²
¹横浜市立大学 国際総合科学研究科 バイオ科学専攻、²東京都精神医学総合研究所 分子精神医学

Sep 28 (Wed) Poster Session

F会場

掲示時間 9:00 ~ 17:00
 討論 / 奇数番号 13:00 ~ 13:45
 偶数番号 13:45 ~ 14:30

- P1-019 Relationship of polyglutamine-expanded GFP expression to ER stress in PC12 cells
 中山 均¹、下家 浩二²、永井 義隆³、磯崎 稔¹、佐藤 広康¹、吉栖 正典¹、池内 俊彦²
¹奈良県立医科大学 薬理学教室、²関西大学 工学部 神経生物学研究室、³大阪大学大学院医学系 遺伝医学 臨床遺伝学
- P1-020 Differential function and localization of two splice variants of caspase-3 binding protein 2
 渡辺 崇¹、武笠 毅¹、野中 隆²、長谷川成人²、額田 敏秀¹
¹東京都精神医学総合研究所 神経情報伝達研究チーム、²東京都精神医学総合研究所 分子神経生物学研究チーム
- P1-021 Depletion of intracellular Ca²⁺ store itself may be a major factor in thapsigargin-induced ER stress and apoptosis in PC12 cells.
 門司 晃¹、吉田 一郎¹、田代謙一郎¹、橋岡 禎征¹、神庭 重信¹
¹九州大学大学院 医学研究院 精神病態医学

本能・情動・行動

- P1-022 The efferent projection of the "running neurons" located in the ventromedial nucleus of the hypothalamus: The neural structure supporting hyper-running behavior
 関 忍¹、坂内 慎¹、稲川健太郎¹、高橋 迪雄¹
¹味の素株式会社 健康基盤研究所

感覚系・運動系

- P1-023 Activation of cytosolic phospholipase A₂ in the dorsal root ganglion of neuropathic pain rats.
 長谷川茂雄¹、津田 誠¹、井上 和秀¹
¹九州大学大学院 薬学府 薬効解析学分野
- P1-024 Changes in transcription factors in mouse cochlea after intense noise exposure
 長嶋 玲子¹、荻田喜代一¹
¹接南大 薬 薬理

睡眠、生体リズム

- P1-025 Abnormalities in non-visual photoreception in mice lacking PACAP
 川口ちひろ¹、畑中 道賢¹、磯島 康史²、新谷 紀人¹、橋本 均¹、永井 克也²、馬場 明道¹
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
- P1-026 Combination of the two ROR response elements in the *Bmal1* promoter confers robustness to the mouse *Bmal1* oscillation
 池田 正明^{1,2}、徐 海源^{1,2}、楊 芳^{1,2}、熊谷 恵^{1,2}、林 隆司^{1,2}、山田 栄一³、中島 芳浩⁴、近江谷克裕⁴、野村 正彦¹
¹埼玉医大・生理、²埼玉医大・ゲノム医学研究センター・分子時計プロジェクト、³埼玉医大・精神医学、⁴産総研・セルエンジニアリング

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F 会場

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 偶数番号 13:45 ~ 14:30

学習、記憶

- P1-027 Epac-specific cAMP analogue induces GluR1 and NR2B degradation via calpain activation in adult hippocampus
 松崎 秀夫¹、ピーター オラウソン²、ドリュウ キラリー²、ジェーン テイラー²、
 アンガス ネアーン²、森 則夫³
¹浜松医科大学 医学部、²エール大学医学部 精神医学、³浜松医科大学 精神神経
 医学
- P1-028 Activation of microglia leads to deficit of learning and memory in rat
 渋谷 俊臣¹、田中佐知子¹、大滝 博和²、塩田 清二²、沼澤 聡¹、吉田 武美¹、
¹昭和大学 薬学部 臨床毒性学教室、²昭和大学 医学部 第一解剖学教室

神経内分泌

- P1-029 Effect of leptin on BDNF expression in the hypothalamus
 小森 忠祐¹、森川 吉博¹、仙波恵美子¹
¹和歌山県立医科大学 医学部 第二解剖

自律神経系

- P1-030 Autonomic receptor-mediated histamine H₁ receptor gene expression
 福井 裕行¹、三好 勝洋¹、藤本 勝巳²、堀尾 修平¹
¹徳島大学 大学院ヘルスバイオサイエンス研究部 分子薬物学分野、²広島大学 大
 学院医歯薬総合研究科 探索医科学講座

老 化

- P1-031 Subcellular localization of SIRT1(Sir2 α), an NAD-dependent histone
 deacetylase, in the brain -SIRT1(Sir2 α) shuttles between the cytosol and the
 nucleus-
 堀尾 嘉幸¹、丹野 雅也¹、坂本 淳¹
¹札幌医科大学 医学部 薬理学講座

脳血流、代謝

- P1-032 Working hypothesis on the central nervous system fatigue
 渡辺 恭良¹、田中 雅彰¹、尾内 康臣²、水野 敬¹、岡田 知久³、山本 茂幸¹、
 田島 世貴¹、笹部 哲也¹、齋藤 大輔³、田邊 宏樹³、塚田 秀夫⁴、尾上 浩隆⁵、
 定藤 規弘³、倉恒 弘彦⁶
¹大阪市立大学 大学院 医学研究科、²先端医療技術センター、³生理学研究所 大
 脳皮質機能部門、⁴浜松ホトニクス 中央研究所、⁵東京都神経科学総合研究所、⁶関
 西福祉科学大学 健康科学科

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- P1-033 Amino acids as candidates for objective biomarkers and anti-fatigue substances in physical, mental and complex fatigue
 水野 敬¹、野崎 聡¹、山口 浩二^{1,2}、水間 広¹、田中 雅彰¹、
 笹部 哲也^{1,3}、安宅 鈴香¹、杉野 友啓⁴、白井 智子⁴、梶本 佳孝⁴、
 倉恒 弘彦^{2,5}、西田 泰⁶、梶本 修身^{4,7}、渡辺 恭良¹
¹大阪市立大学 大学院医学研究科 システム神経科学、²大阪大学 大学院医学系研究科 分子病態内科学（血液・腫瘍内科）、³大阪大学 大学院歯学系研究科 顎口腔病因病態制御学講座（第一口腔外科）、⁴（株）総合医科学研究所、⁵関西福祉科学大学 健康福祉学部 健康科学科、⁶内閣府警察庁科学警察研究所 交通部 交通安全研究室、⁷大阪外国語大学保健管理センター
- P1-034 Change in amino acid metabolism in the rat brain inhibited axonal flow by colchicine
 渡辺 光代¹、中臺 武人¹、金松 知幸¹
¹創価大学工学部生物工学科

イメージング

- P1-035 A dynamic change of trace element distribution in rat basophilic leukemia cells (2H3) after antigen stimulation measured by in-air micro-PIXE
 櫻井 映子^{1,4}、水摩 恵子^{2,4}、安部 繁^{2,4}、猪俣 一正^{2,4}、酒井 卓郎³、
 佐藤 隆博³、神谷 富裕³、山崎 浩道^{2,4}、石井 慶造^{2,4}、谷内 一彦^{1,4}
¹東北大学 大学院医学系研究科、²東北大学 大学院工学研究科、³日本原子力研究所 高崎研究所、⁴21世紀COEプログラム
- P1-036 Visualization of active translation using molecular interaction formed at the translation termination.
 森 泰丈¹、宮田 信吾¹、藤原 達司¹、遠山 正彌¹
¹大阪大学大学院 医学系研究科 神経機能形態学講座

疾患モデル

- P1-037 Analysis for functional interaction between alfa-synuclein and UCH-L1 proteins in vivo.
 安田 徹¹、仁平 友子¹、和田圭一郎¹、和田 圭司²、水野 美邦¹、望月 秀樹¹
¹順天堂大学 医学部 脳神経内科、²国立精神神経センター 神経研 疾病研究第四部
- P1-038 Behavioral and microarray analysis of knock-in mouse which express only δ FosB from *fosBs* gene
 大西 克典¹、作見 邦彦¹、山崎 勝久¹、本田（大西）陽子¹、三浦 智史¹、
 富永 洋平¹、中別府雄作¹
¹九州大学 生体防御医学研究所 脳機能制御学分野
- P1-039 Increase of AMPA receptor glutamate receptor 1 subunit and B-cell receptor associated protein 31 gene expression in hippocampus of fatigued mice
 鎌倉 昌樹¹、玉置 啓祐²、榊 利之¹、米田 幸雄²
¹富山県立大学 工学部 生物工学研究センター、²金沢大学大学院 自然科学研究科 薬物学

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- P1-040 Neurotoxicities of local anesthetics on bovine adrenal chromaffin cells at clinical use concentrations
水間 謙三¹、立川 英一¹、工藤 賢三¹、近藤 ゆき子¹、平 英一¹
¹岩手医科大学 医学部 薬理学
- P1-041 Transgenic mice expressing mutant G392E human neuroserpin show neuronal dysfunction with aggregate formation in neurons
高澤 久美¹、高澤 啓¹、加藤 一郎^{1,3}、石井 陽子²、笹原 正清²、平賀 紘一¹
¹富山医科薬科大学 医学部 生化学、²富山医科薬科大学 医学部 病理学 2、³富山医科薬科大学 21 世紀 COE プログラム
- P1-042 Influence of chronic variable stress to electric sensitization of the acoustic startle response in rats.
金井 重人¹、朝倉 幹雄¹、田中 大輔¹、菱沼 拓児¹、藤井佐知子¹、五十嵐潤子²、長島 秀明¹、貴家 康男¹、御園生篤志¹、長田 賢一¹、金子 律子²
¹聖マリアンナ医科大学 医学部 神経精神科学教室、²聖マリアンナ医科大学 医学部 解剖学教室
- P1-043 Neonatal Isolation and Environmental Enrichment in an Animal model of PTSD: Effects on Conditioned and Unconditioned Fear after Stress.
土岐 茂¹、森信 繁¹、今中 章弘¹、山脇 成人¹
¹広島大学大学院 精神神経医科学
- P1-044 Effects of SNAP-25 mutation at PKC-dependent phosphorylation site on development and the behavior of aged mice
佐藤 拓¹、鈴木 映二¹、山森 早織²、東 貞宏³、片岡 正和⁴、横山 正宗¹、渡辺 滋⁵、宮岡 等¹、高橋 正身²
¹北里大学 医学部 精神科、²北里大学 医学部 代謝・蛋白学、³北里大学 医学部 実験動物学、⁴信州大学 工学部、⁵北里大学 医学部 生物物理系
- P1-045 The effect of repeated MK-801 on the c-Jun in the rat frontal cortex
Myoung Suk Seo², Won Je Jeon², Se Hyun Kim¹, Yeni Kim³, Ung Gu Kang¹, Yong Sik Kim¹
¹Department of Psychiatry and Behavioral Science and Institute of Human Behavioral Medicine, Seoul National University College of Medicine、²Clinical Research Institute, Seoul National University Hospital、³Department of Biochemistry, Seoul National University College of Medicine

発育、発達障害

- P1-046 Possible Involvement of Serotonergic System in Stress Response Mechanisms in Rat Brain Development
松本真知子¹、今野幸太郎¹、富樫 広子²、山口 拓¹、吉岡 充弘¹
¹北海道大学院・医学部・神経薬理、²北海道医療大学・薬学部・病態生理学

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- P1-047 Characterization of anxiolytic-like behaviors in adult rats experienced with early postnatal stress
 山口 拓¹、富樫 広子^{1,2}、樋口かさね³、今野幸太郎¹、白川 哲夫⁴、
 松本真知子¹、吉岡 充弘¹
¹北海道大学 大学院 医学研究科 神経薬理学分野、²北海道医療大学薬学部病態生
 理学教室、³北海道大学大学院歯学研究科口腔機能学講座、⁴北海道大学病院高次口腔
 医療センター障害者歯科治療部門
- P1-048 DNA microarray analyses of thyroid hormone-dependent gene expression in the
 developing mouse cerebellum: identification of metabotropic and NMDA-type
 glutamate receptor genes as highly dependent genes
 高橋 理貴¹、根岸 隆之¹、今村 誠¹、近藤 恭光²、田代 英夫²、田代 朋子¹
¹青山学院大学大学院 理工学研究科、²理化学研究所 田代分子計測工学研究室
- P1-049 Enriched Environment enhances Neuropsin mRNA in the hippocampus and
 amygdala
 林 利充¹、小林 寛和¹、石川 保幸¹、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 細胞構造学講座

変性疾患

- P1-050 A possible role of parkin and ubiquitin carboxy-terminal hydrolase L1 in
 neurotransmission; potentiation of P2X receptor channels
 野田 百美¹、真子 好正¹、佐藤あゆみ¹、西川 香里²、天野 大樹^{1,2}、
 青木公三子²、和田恵津子²、小坂 仁^{2,3}、節家理恵子^{1,2}、櫻井省花子^{1,2}、
 王 玉来²、青木 俊介^{2,4}、和田 圭司²、
¹九州大学 大学院 薬学研究院 病態生理学分野、²国立精神・神経センター 神経
 研究所 疾病研究第4部、³科学技術振興機構、さきがけ、⁴新エネルギー・産業技術
 総合開発機構
- P1-051 Chemical compound, BIX, protects cells from neuronal death induced by ER
 stress via induction of ER molecular chaperone.
 金本 聡自^{1,2}、工藤 喬³、今泉 和則²
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 細胞構造学講座、²宮崎大
 学 医学部 解剖学講座 分子細胞生物学講座、³大阪大学大学院 医学系研究科
 精神医学教室
- P1-052 Histologic analysis of mutant SOD1 aggregation in ER and large hyaline
 inclusions induced by ER stress
 小山 佳久¹、山岸 寛²、片山 泰一³、加藤 昌昭⁴、青木 正志⁴、糸山 泰人⁴、
 加藤 信介⁵、遠山 正彌¹
¹大阪大学 大学院医学系研究科 神経機能形態学講座、²Department of Molecular
 Neurobiology, Max-Planck-Institute of Neurobiology、³浜松医科大学 解剖学講座、
⁴東北大学 医学部 神経内科、⁵鳥取大学 医学部 脳研病理

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- P1-053 Autophagy is activated during ERstress via the ER-residenttransmembrane kinase IRE1
 緒方麻衣子^{1,2}、Stefan J Marciniak³、浦野 文彦⁴、水島 昇⁵、David Ron³、今泉 和則²
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 細胞構造学教室、²宮崎大学 医学部 解剖学講座 分子細胞生物学分野、³Skirball Institute of Biomolecular Medicine and the Departments of Cell Biology, Medicine and Pharmacology, New York University School of Medicine, New York, USA、⁴Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, USA、⁵東京都臨床医学総合研究所、代謝制御研究部門
- P1-054 Characterization of chorein whose dysfunctions cause Chorea-acanthocytosis
 倉野 裕¹、中村 雅之¹、水野恵三子¹、市場 美緒¹、上野 修一²、佐野 輝¹
¹鹿児島大学 大学院 歯学部総合研究科 社会行動医学講座 精神機能病学、²徳島大学大学院 ヘルスバイオサイエンス研究部 神経情報医学部門 情報統合医学講座 精神医学
- P1-055 Spinocerebellar degeneration caused protein, aprataxin, is a 3'-5' exonuclease
 他田 正義¹、高橋 哲哉¹、五十嵐修一^{1,2}、伊達 英俊³、小山 哲秀¹、志賀 篤¹、高野 弘基¹、小宅 睦郎¹、辻 省次³、西澤 正豊¹、小野寺 理²
¹新潟大学脳研究所神経内科、²新潟大学脳研究所 生命科学リソース研究センター脳疾患リソース解析部門 分子神経疾患資源解析学分野、³東京大学大学院医学系研究科 神経内科
- P1-056 An NF - kappaB inhibitor attenuates A53T alpha-synuclein-caused cell death in an inducible cell model
 田中 有史¹、森田 幸孝¹、スミス ウォンリ²、エンゲレンダー シモン⁵、寺田 整司¹、大谷 恭平¹、氏家 寛¹、黒田 重利¹、クリストファー ロス^{2,3,4}、¹岡山大学 歯薬学総合研究科 精神病態学、²ジョーンズホプキンス大学 医学部 精神科 神経生物学、³ジョーンズホプキンス大学 医学部 神経内科、⁴ジョーンズホプキンス大学 医学部 神経科学、⁵テクニオンーイスラエル工科大学
- P1-057 ALTERED CHOLESTEROL METABOLISM IN NIEMANN-PICK TYPE C1 MOUSE BRAINS INDUCES MITOCHONDRIAL DYSFUNCTIONS
 道川 誠¹、于 文新¹、キョウ 建生¹、高 美姫¹、柳澤 勝彦¹
¹国立長寿医療センター 研究所 アルツハイマー病研究部
- P1-058 Transplantation of tyrosinase cDNA-transfected hepatocytes into the striatum of hemi-parkinsonian model
 浅沼 幹人¹、宮崎 育子¹、Francisco J Diaz-Corrales¹、難波 正義²、小川 紀雄¹
¹岡山大学大学院歯薬学総合研究科 神経情報学、²新見公立短期大学
- P1-059 Visualization of soluble Polyglutamine dimer in Living cell
 高橋 俊昭¹、菊池 信矢²、小野寺 理³、西澤 正豊²
¹新潟大学 医学部 保健学科、²新潟大学脳研究所神経内科、³新潟大学脳研究所生命科学リソースセンター

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- P1-060 ALS2CL, a novel ALS2 homologous protein, interacts with ALS2: A possible functional modulator for ALS2
 鈴木一字都宮恭子¹、秦野 伸二²、大友 麻子¹、國田 竜太³、水村 光³、
 将口一宮田 淳子¹、柳澤 佳子³、須賀恵津子³、池田 穰衛¹
¹東海大学 総合医学研究所 分子神経科学部門、²東海大学 医学部 基礎医学系
 分子生命科学、³科技団 SORST
- P1-061 Lack of a BMP antagonist, Tsukushi (TSK), causes retinal degeneration in young adult mice
 栗山 正¹、太田 訓正¹、清成 寛²、澤井 元³、相澤 真一²、田中 英明¹
¹熊本大学 大学院医学薬学研究部 神経分化学分野、²理化学研究所 発生・再生科学総合研究センター、³大阪大学 大学院医学部 情報伝達医学専攻情報生理学
- P1-062 Age-related severity of dopaminergic neurodegeneration to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity causes motor dysfunction in C57BL/6 mice
 大橋 聡¹、森 厚詞¹、栗原 直樹¹、光本 泰秀²、中井 正三¹
¹大塚製薬 探索第二研究所、²北陸大学 薬学部 代替医療薬学教室
- P1-063 MCC-257, orally active neurotrophin enhancer, attenuates thermal hypoalgesia and protects cutaneous innervation in hyperglycemic mice
 柿木 文平¹、関本 澄人¹、大上 哲也¹、瀬島 樹子¹、山上 圭司¹
¹三菱ウェルファーマ株式会社 創薬第一研究所

精神疾患

- P1-064 DISC1 transports Grb2 in kinesin-1 dependent manner
 篠田 友靖¹、田谷真一郎¹、貝淵 弘三¹
¹名古屋大学大学院 医学系研究科 神経情報薬理学講座
- P1-065 Chronic treatment with SSRIs desensitizes both 5-HT_{2A} and 5-HT_{2C} receptor function
 山内 美紀¹、宮良 孝子¹、松島 哲弥¹、舘林 智子¹、横山 史和¹、小野沢 要¹、
 吉田 晶子¹、今西泰一郎¹
¹明治製菓株式会社 創薬研究部門
- P1-066 Changes of Neural Cell Adhesion Molecule Fragments in Patients' Sera of Schizophrenia
 吉田 敏¹、田中 陽子²、嶋田 裕美¹、上田 浩¹、浅井 邦彦²
¹岐阜大学 工学部 生命工学科、²浅井病院
- P1-067 Differential effects of typical and atypical antipsychotics on abnormal behaviors in mice lacking PACAP
 新谷 紀人¹、田中 一裕¹、嶋田 健¹、中島 美貴¹、川口ちひろ¹、山本亜希子¹、
 橋本 均¹、馬場 明道¹
¹大阪大学大学院 薬学研究科 神経薬理学分野

Sep 28 (Wed) Poster Session

F 会場

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 討論 / 奇数番号 13:00 ~ 13:45
 偶数番号 13:45 ~ 14:30

- P1-068 Double-stranded RNA injection in early pregnancy causes behavioral changes in the offspring
 牧之段 学¹、辰巳 晃子²、眞部 孝幸²、下田 重郎³、磯 博行³、芳野 浩樹¹、木内 邦明¹、山内 崇平¹、岸本 年史¹、和中 明生²
¹奈良県立医科大学 医学部 精神科、²奈良県立医科大学 医学部 第2解剖学、³兵庫医科大学 医学部 行動学研究室
- P1-069 Isolation rearing-induced increase in exploratory activity in mouse staircase test
 高橋 恵子¹、吾郷由希夫²、伊藤 壯一¹、馬場 明道²、松田 敏夫¹
¹大阪大学大学院 薬学研究科 複合薬物動態学分野、²大阪大学大学院 薬学研究科 神経薬理学分野
- P1-070 Methamphetamine treatment further deteriorates cognitive dysfunction in socially isolated mice: A useful mouse model of schizophrenia
 谷内 一彦¹、賈 飛勇¹、代 紅梅¹、加藤 元久¹、櫻井 映子¹
¹東北大学大学院医学系研究科機能薬理学分野
- P1-071 Effects of menstrual cycle on mRNA expression of *FKBP5* and *5HTT* in leukocytes of normal female.
 木内佐和子¹、伊賀 淳一¹、上野 修一¹、山内 健¹、沼田 周助¹、宋 鴻偉¹、田吉 純子¹、葉久 真理²、竹内美恵子²、安井 敏之³、苛原 稔³、森田 恭子⁴、六反 一仁⁴、大森 哲郎¹
¹徳島大学 大学院 ヘルスバイオサイエンス研究部 神経情報医学部門 情報統合医学講座 精神医学分野、²徳島大学 医学部 保健学科 看護学専攻 母性・小児看護学講座、³徳島大学 大学院 ヘルスバイオサイエンス研究部 発達予防医歯学部門 発生発達医学講座 女性医学分野、⁴徳島大学 大学院 ヘルスバイオサイエンス研究部 プロテオミクス医科学部門 生体制御医学講座 ストレス制御医学分野
- P1-072 The reconstruction mechanisms of neural network by antidepressants and mood stabilizers
 今井 智之¹、鶴飼 渉¹、石井 貴男¹、黒澤 茂樹¹、吉永 敏弘¹、齋藤 諭¹、橋本 恵理¹、池田 官司¹、齋藤 利和¹
¹札幌医科大学 医学部 神経精神医学講座
- P1-073 The role of the interaction of *DISC1* / *KENDRIN* in the nervous system
 清水 尚子¹、松崎 伸介¹、服部 剛志¹、三好 耕²、遠山 正彌¹
¹大阪大学大学院 医学系研究科 神経機能形態学、²岡山大学大学院 医歯学総合研究所 神経情報学
- P1-074 Increased serum soluble L-selectin levels in unmedicated schizophrenia
 岩田 泰秀¹、和久田智久¹、渡部 崇¹、土手 基慶¹、森 則夫¹
¹浜松医科大学 医学部 精神神経医学講座
- P1-075 The role of the interaction of dysbindin, one of schizophrenia susceptibility genes, and transcription factors in neurons.
 奥田 洋明^{1,2}、宮田 信吾^{1,2}、松崎 伸介^{1,2}、熊本奈都子^{1,2}、遠山 正彌^{1,2}、
¹大阪大学大学院 医学系研究科 神経機能形態学講座、²21世紀 COE プログラム

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- P1-076 Analysis of interaction between Snapin and Dysbindin, one of schizophrenia susceptibility genes
 熊本奈都子¹、松崎 伸介¹、山口 淳²、遠山 正彌¹
¹大阪大学 大学院 医学系研究科 神経機能形態学講座、²バック研究所
- P1-077 Screening for genes involved in major depressive disorder using chronically stressed mice
 渡邊 佳奈¹、井上 浄¹、袁 華¹、青木 美和¹、窪田 杏子¹、新野 直樹¹、遠山 正彌¹
¹大阪大学 大学院 医学系研究科 神経機能形態学講座
- P1-078 Gene expression profile of adult mouse hippocampus after chronic treatment of water-immersion plus restraint stress
 青木 美和¹、井上 浄¹、渡邊 佳奈¹、窪田 杏子¹
¹大阪大学 大学院 医学系研究科 神経機能形態学講座
- P1-079 Association analysis of adenosine A1, A2A, dopamine D1, and D2 receptor genes with schizophrenia in the Japanese population.
 後藤 玲央¹、光安 博志^{1,2}、前田 直子¹、小林 祐樹¹、川寄 弘詔¹、神庭 重信¹
¹九州大学大学院医学研究院精神病態医学分野、²松尾病院
- P1-080 ONO-2333Ms, a novel CRF1 receptor antagonist: anxiolytic and antidepressant-like effects
 鏡石 佳史¹、岸 昭宏¹、吉田 真幸¹、勝又 清至²、勝部 伸夫²、立石 成人³、鎌中 喜久¹
¹小野薬品工業株式会社 創薬第三研究所、²小野薬品工業株式会社 福井安全性研究所、³小野薬品工業株式会社 研究本部
- P1-081 Association analysis of human cAMP-GEF II gene polymorphisms with Japanese schizophrenia patients
 光安 博志^{1,2}、小林 祐樹^{1,3}、後藤 玲央¹、前田 直子⁴、川寄 弘詔¹、神庭 重信¹
¹九州大学大学院医学研究院精神病態医学分野、²松尾病院、³理化学研究所脳科学総合研究センター 行動遺伝学チーム、⁴東京都立松沢病院

虚 血

- P1-082 Induction of microsomal prostaglandin E₂ synthase-1 in rat brain after cerebral ischemia.
 松尾 由理¹、深田 哲也¹、佐々木泰治¹
¹北里大学 薬学部 薬理学
- P1-083 Pathological significance of a constitutively active calcineurin generated by calpain activation in mouse brain ischemia.
 塩田 倫史¹、福永 浩司¹
¹東北大学大学院 薬学研究科 薬理学分野

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- P1-084 17 β -estradiol regulate expression of glutamate transporters after transient ischemic insult in gerbil hippocampus
加藤 寿章¹、藤田 公和²、日高 聡²、柴山 健三³、今田 英己²、芳本 信子²、永田 豊²、宮地 栄一²
¹藤田保健衛生大学短期大学 臨床検査学、²藤田保健衛生大学 医学部 第二生理学、³藤田保健衛生大学 衛生学部 成人看護学
- P1-085 Nitric oxide production during microsphere embolism accounts for blood-brain barrier disruption in rat brain
韓 峰¹、白倉 尚¹、白崎 康文²、福永 浩司¹
¹東北大学 薬学研究科 薬理学分野、²第一製薬

外 傷

- P1-086 Neuropsin promotes oligodendroglial cell death, demyelination and axonal degeneration after injury to the spinal cord
吉田 成孝¹、寺山 隆司¹、板東 良雄¹
¹旭川医科大学 解剖学第一
- P1-087 4-methylcatechol improves locomotor function damaged after spinal cord injury via enhancement of neurotrophic factor synthesis.
大野 仁志¹、福光 秀文¹、古川 昭栄¹
¹岐阜薬科大学 分子生物学教室
- P1-088 Expression of myelencephalon-specific protease(MSP) in cryogenic injury model of rat brain
岡 雄一¹、浅井 清文²、青山 峰芳²、打田 淳¹、藤田 政隆³、多田 豊曠²、片野 広之¹、間瀬 光人¹、山田 和雄¹
¹名古屋市立大学大学院医学研究科 神経機能回復学分野、²名古屋市立大学大学院医学研究科 分子神経生物学分野、³理化学研究所脳科学総合研究センター

認知症、アルツハイマー病

- P1-089 Vitamin A exhibits potent anti-amyloidogenic and fibril-destabilizing effects in vitro
小野賢二郎¹、吉池 裕二²、高島 明彦²、長谷川一浩³、内木 宏延³、山田 正仁¹
¹金沢大学大学院 医学系研究科 脳老化・神経病態学、²理化学研究所アルツハイマー病研究チーム、³福井大学 医学部 分子病理学
- P1-090 Syntaxin5 interacts specifically with presenilin holoproteins and affects processing of β APP in neuronal cells
須賀 圭¹、齋藤 綾子¹、富山 貴美²、森 啓²、赤川 公朗¹
¹杏林大学 医学部 細胞生理、²大阪市立大学 医学部 脳神経科学
- P1-091 The S3 cleavage site of Notch-1 by presenilin/ γ -secretase has a diversity.
田上 真次¹、大河内正康¹、福森 亮雄¹、姜 経緯¹、伊藤 尚弘¹、武田 雅俊¹
¹大阪大学大学院 医学系研究科 精神医学教室

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- P1-092 Assembly of hereditary variant amyloid β -protein in the presence of gangliosides
 山本 直樹^{1,2}、平林 義雄³、甘利 雅邦⁴、山口 晴保⁵、ガリーナ ロマノフ⁶、
 ウィリアム ノストランド⁶、柳澤 勝彦¹
¹国立長寿医療センター アルツハイマー病、²日本学術振興会、³理化学研究所・脳研、⁴老年病研究所附属病院、⁵群馬大、⁶ストニー・ブルック大
- P1-093 Deficiency in presenilin-1 and -2 alters overall glycosylation of membrane proteins in fibroblasts: protein specific up or down regulated maturation by presenilin 1 and 2
 鄒 鶴^{1,2}、白石 博久¹、高 美姫¹、キョウ 建生¹、于 文新¹、
 駒野 宏人¹、柳澤 勝彦¹、道川 誠¹
¹国立長寿医療センター研究所 アルツハイマー病研究部、²日本学術振興会
- P1-094 A mechanism underlying apolipoprotein E-isoform -specific induction of lipid efflux from neurons
 道川 誠¹、キョウ 建生¹、斎藤 博幸²、鄒 鶴¹、于 文新¹、
 高 美姫¹、ルンドー カッツ ジセル³、フィリップ ミシエル³、柳澤 勝彦¹
¹国立長寿医療センター研究所・アルツハイマー病研究部、²神戸薬科大学、³ペンシルバニア大学医学部
- P1-095 Donepezil and galantamine differently regulate nicotinic acetylcholine and NMDA receptor functions in rat cortical neurons
 森口 茂樹¹、檜橋 敏夫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ノースウエスタン大学 医学部 分子薬理
- P1-096 Characterization of γ -secretase complex reconstituted by truncated presenilin (PS) fragments
 丸谷 寿裕¹、白石 博久²、王 華芹³、荒木 亘⁴、西村 正樹³、柳澤 勝彦¹、
 駒野 宏人¹
¹国立長寿医療センター アルツハイマー病研究部、²南カリフォルニア大学 ケックメディカルスクール、³滋賀医科大学 分子神経センター 脳疾患基礎、⁴国立精神センター 神研
- P1-097 Phosphatidylserine-liposomes inhibit microglial production of neurotoxic molecules
 橋岡 禎征^{1,2}、韓 連熙³、加藤 隆弘¹、門司 晃¹、内海 英雄³、澤田 誠⁴、
 神庭 重信¹、中西 博²
¹九州大学大学院 医学研究院 精神病態医学、²九州大学大学院 歯学研究院 加齢口腔科学、³九州大学大学院 薬学研究院 機能分子解析学、⁴名古屋大学 環境医学研究所 脳生命科学分野
- P1-098 Decrease in GTP-sensitive high affinity agonist binding of muscarinic acetylcholine receptors in autopsied brains of dementia with Lewy bodies and Alzheimer disease
 塩崎 一昌¹
¹横浜市立大学 医学部 精神医学

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薬物依存、精神薬理

- P1-099 A possibility of Leu-Ile as a novel therapeutic agent for morphine-induced dependence
丹羽 美苗¹、新田 淳美¹、山田裕一郎¹、柴田 陽子¹、斉藤 邦明²、清島 満²、LIYA SHEN³、野田 幸裕^{1,4}、鍋島 俊隆¹
¹名古屋大学大学院 医学系研究科 医療薬学・附属病院薬剤部、²岐阜大学大学院 医学研究科・病態情報解析医学、³Lab. of Cellular Carcinogenesis and Tumor Promotion Center for Cancer Research, NCI, Bethesda, USA、⁴名城大学 薬 医薬連携実習部門・病態解析学
- P1-100 Mechanism of protective effect of non-steroidal anti-inflammatory drugs on methamphetamine-induced neurotoxicity
宮崎 育子¹、辻 武史¹、浅沼 幹人¹、Francisco J Diaz-Corrales¹、三好 耕¹、小川 紀雄¹
¹岡山大学大学院医歯薬学総合研究科 神経情報学
- P1-101 A role for tissue plasminogen activator/plasmin system in nicotine dependence
伊藤 美奈¹、永井 拓¹、亀井 浩行¹、橋本 和樹¹、田熊 一敏¹、鍋島 俊隆²、山田 清文¹
¹金沢大学大学院 自然科学研究科 病院薬学、²名古屋大学大学院 医学系研究科 医療薬学・附属病院薬剤部
- P1-102 Antidepressants increase glial cell line-derived neurotrophic factor (GDNF) expression through mitogen-activated protein kinase (MAPK) activation in rat C6 glioma cells.
久岡 一恵¹、土岡 麻美^{1,2}、前田奈津子¹、竹林 実¹
¹(独) 国立病院機構 呉医療センター 臨床研究部、²広島大院 医歯薬学総合 薬効解析科学
- P1-103 Effects of serotonin receptor ligands on cocaine-induced behavioral sensitization in mice
吾郷由希夫¹、林 藍子²、中村 茂生²、馬場 明道¹、松田 敏夫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 薬学研究科 複合薬物動態学分野
- P1-104 Effects of serotonin receptor ligands on methamphetamine-induced sensitization of prefrontal serotonin release in mice.
中村 茂生¹、吾郷由希夫²、宇田 美里¹、馬場 明道²、松田 敏夫¹
¹大阪大学大学院 薬学研究科 複合薬物動態学分野、²大阪大学大学院 薬学研究科 神経薬理学分野
- P1-105 Effect of 5-HT_{1B} agonist on escalated aggression and prefrontal cortex serotonin in mice
坂内 慎^{1,2}、フィッシュ エリック²、サラ ファクシドモ²、クラウス ミチェック²、¹味の素株式会社 健康基盤研究所、²タフツ大学 心理学部

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- P1-106 Effects of AMPA on clozapine-induced dopamine and noradrenaline release in rat medial prefrontal cortex: implications for neurocognitive effects of atypical antipsychotic drugs
 梶畑 俊雄¹、中原 辰雄^{1,2}、長尾奈穂子¹、黒木 俊秀¹、橋本喜次郎²、平野 誠²、神庭 重信¹
¹九州大学大学院医学研究院精神病態医学、²肥前精神医療センター
- P1-107 Potent blockade of dopamine D2 receptors inhibits clozapine-induced dopamine release in rat medial prefrontal cortex
 長尾奈穂子¹、中原 辰雄^{1,2}、黒木 俊秀¹、梶畑 俊雄¹、橋本喜次郎²、平野 誠²、神庭 重信¹
¹九州大学大学院 医学研究院 精神病態医学、²肥前精神医療センター
- P1-108 Effects of therapeutic-relevant concentration of carbamazepine on CICR
 吉田 淑子^{1,2}、岡田 元宏¹、朱 剛^{1,3}、兼子 直¹
¹弘前大学 医学部 神経精神医学講座、²シバタ医理科 神経科学分子生物研究所、³弘前大学 医学部 附属脳神経血管病態研究施設 分子病態部門
- P1-109 Effects of SKF-38393, a selective dopamine D1 receptor agonist on expression of d-amphetamine induced behavior and expression of the immediate early gene Arc in the prefrontal cortex of rats
 毛呂 裕臣¹、井田 逸朗¹、大嶋 明彦¹、桜井 規子¹、志原 伸幸²、堀川 幸男²、三國 雅彦¹
¹群馬大学大学院 医学系研究科 脳神経精神行動学、²群馬大学 生体調節研究所 調節機構部門 遺伝情報分野

中毒症

- P1-110 Mechanism of tributyltin neurotoxicity in cultured cortical neurons
 中津 祐介¹、古武弥一郎¹、駒坂 和哉¹、太田 茂¹
¹広島大学大学院 医歯薬学総合研究科
- P1-111 Involvement of dopaminergic system in δ 9-tetrahydrocannabinol-induced psychosis-related behavior in mice
 永井 宏¹、江頭 信昭²、佐野 和憲²、緒方 歩²、水木 愛²、三島 健一²、岩崎 克典²、西村 良二¹、藤原 道弘²
¹福岡大学 医学部 精神医学教室、²福岡大学 薬学部 臨床疾患薬理学教室

脳腫瘍

- P1-112 Interaction between cancer cells and microglia in brain metastasis of lung cancer
 清家 稔博¹、藤田 慶大¹、城戸 瑞穂²、田中 輝男²、井口 東郎³、野田 百美¹
¹九州大学大学院 薬学府 病態生理学分野、²九州大学大学院 歯学部 硬組織構造解析講座、³九州がんセンター 臨床研究部 腫瘍動態研究室

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てんかん

- P1-113 Accumulation of oxidative damage in nucleic acids of brain following kainic acid-induced excitotoxicity is suppressed by MTH1, an oxidized purine nucleoside triphosphatase
梶谷 康介¹、山口 浩雄¹、作見 邦彦¹、大野みずき¹、古市 正人²、中別府雄作¹
¹九州大学 医学部 生体防御医学研究所 脳機能制御学、²九州大学 医学部 アイソトープ総合センター
- P1-114 Characterization of seizures induced by direct injection of kainic acid into amygdala in different mouse strains
春日井基文¹、赤池 浩一¹、今村 真一²、松久保秀幸¹、田中 滋也³、佐野 輝¹、
¹鹿児島大学大学院 医歯学総合研究科 精神機能病学、²鹿児島大学大学院 医歯学総合研究科 脳神経病態制御外科学、³田中脳神経外科クリニック
- P1-115 Involvement of neuropsin in hippocampal neuronal degeneration
山崎 浩誠¹、石川 保幸¹、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

変性疾患

- P1-116 Alexander disease model mice
田中 謙二¹、竹林 浩秀¹、池中 一裕¹
¹自然科学研究機構 生理学研究所 分子神経生理部門

Sep 29 (Thu) Poster Session

F会場

掲示時間 9:00 ~ 17:00
 討論 / 奇数番号 13:00 ~ 13:45
 偶数番号 13:45 ~ 14:30

イオンチャネル、興奮膜

- P2-001 Novel acyclic cyclophanes inhibit *N*-methyl-D-aspartate receptors expressed in *Xenopus* oocytes
 益子 崇¹、長岡 裕樹¹、三宅 宗晴¹、目鳥 幸一¹、木澤 靖夫¹、草間 貞¹
¹ 日本大学 薬学部
- P2-002 Expressions of acid-sensing ion channel-1a (ASIC1a) and ASIC1b in mouse spiral ganglion neurons
 鵜川 真也¹、石田 雄介¹、島田 昌一¹
¹ 名古屋市立大学 大学院医学研究科 分子形態学
- P2-003 PICK1 is localized in intracellular membrane components containing immature GluR2 subunit in rat brain
 板倉 誠¹、山森 早織¹、高橋 正身¹
¹ 北里大学 医学部 代謝・蛋白学
- P2-004 Intracellular localization of stargazin-like protein, γ -8
 山森 早織¹、板倉 誠¹、稲村美穂子²、高橋 正身¹
¹ 北里大学 医学部 代謝・蛋白学、² 北里大学病院 麻酔科
- P2-005 Tricyclic antidepressant desipramine induces glutamate release from presynaptic nerve terminals
 江藤 圭^{1,2}、梶原三紗子^{1,2}、野田 百美¹、石橋 仁²
¹ 九州大学 大学院 薬学府 病態生理学分野、² 九州大学 医学研究院 分子機能生理

神経伝達物質、修飾物質

- P2-006 N-terminus of human tyrosine hydroxylase type 1 affects the stability in mammalian cells
 中島 昭¹、林 宣宏²、金子 葉子¹、森 啓至¹、江草 悠美¹、永津 俊治³、太田 明¹
¹ 藤田保健衛生大学 医学部 第1生理学、² 藤田保健衛生大学 総合医科学研究所 医高分子学、³ 藤田保健衛生大学 医学部 薬理学
- P2-007 Peptidergic system is correlated with the neurotoxicity in (+) MK-801-treated schizophrenic model rat brain: suppressive effect of neuroleptics
 アリフ モハンマド¹、アハマド マヒウディン¹、隈部有希子¹、星野 玄¹、知久馬敏幸²、加藤 武¹
¹ 横浜市立大学大学院 総合理学研究科、² 昭和薬科大学 薬品分析化学部門
- P2-008 A single exocytotic event in digitonin-permeabilized adrenergic chromaffin cells
 笹川 展幸¹、村山 典恵¹、熊倉鴻之助¹
¹ 上智大学 生命科学研究科 神経化学部門

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- P2-009 Effects of pyrethroids on the hippocampal release of glutamate and GABA in freely moving rats
小林 晴男¹、Hossain Muhammad Mubarak²、鈴木 忠彦¹、佐藤 至¹、
武脇 義³、鈴木 幸一⁴、立川 英一²
¹岩手大学 農学部 獣医学科、²岩手医科大学 医学部 薬理学講座、³岐阜大学
応用生物科学部 応用生物科学科 獣医学講座、⁴岩手大学 農学部 農業生命科学
科
- P2-010 Characterization of Recombinant Tryptophan Hydroxylase Isoform 2
小川慎太郎¹、浦野 扶美¹、一瀬 宏¹
¹東京工業大学 生命理工学研究科 分子生命科学専攻
- P2-011 Inhibition of the exocytotic release of glutamate from rat cerebellar granule cells by nitric oxide
津々木博康¹、居原 秀¹、幸田 知子²、原 正之¹、小崎 俊司²
¹大阪府立大学院 理学系研究科 生物科学専攻、²大阪府立大学院 生命環境科学研究科 獣医学専攻
- P2-012 Effects of reward stimulation during recall of conditioned fear stress on amygdalic dopamine and serotonin levels
横山 正宗¹、鈴木 映二¹、佐藤 拓¹、渡辺 滋²、宮岡 等¹
¹北里大学 医学部 精神科、²北里大学 医学部 生物物理系
- P2-013 Plasma Nitrate Levels in Deficit were lower than Non-Deficit Forms of Schizophrenia
鈴木 映二¹、横山 正宗¹、佐藤 拓¹、渡辺 滋²、中木 敏夫³、中村 誠⁴、
浅井 昌弘⁵、宮岡 等¹
¹北里大学 医学部 精神科、²北里大学 医学部 生物物理系、³帝京大学 医学部
薬理学教室、⁴慶應義塾大学 医学部 精神神経科学教室、⁵財団法人井之頭病院
- P2-014 Neuropeptides from scorpion venom
Chai Siaw Ching¹., Siew Phui Yee¹., Armugam A¹., Jeyaseelan K¹.
¹Dept. of Biochemistry and Biological Sciences National University of Singapore
- P2-015 Effect of hydrogen sulphide on intracellular calcium in neuronal cells: direct evidence of H₂S as a new neuromodulator
Lee Shiau Wei¹., Ye-Shi Hu¹., Jin-Song Bian¹
¹Dept. of Pharmacology, Faculty of Medicine, National University of Singapore

受容体、輸送体

- P2-016 Methamphetamine-induced changes of μ -opioid receptors: a candidate of biochemical marker
山本 秀子¹、亀ヶ谷悦子¹、今井 一英²、高松 幸雄¹、笠井 慎也¹、
山本 敏文^{1,3}、萩野 洋子¹、五十子将史¹、佐藤 彬¹、曾良 一郎^{1,4}、
古閑比佐志^{2,5}、池田 和隆¹
¹東京都精神医学総合研究所、²千葉県産業振興センター、³横浜市立大学大学院、⁴東北大学大学院、⁵かずさ DNA 研究所

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- P2-017 M₅muscarinic acetylcholine receptors and cerebrovascular abnormalities
 山田 真久¹、北村 尚士¹、樋口 真人²、松葉由紀夫²、西道 隆臣²、山田 一之³、
 高島 明彦⁴、WESS JURGEN⁵、野口 孝則⁶
¹理化学研究所 脳科学総合研究センター 山田研究ユニット、²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、³理化学研究所 脳科学総合研究セ
 ンター リサーチリソースセンター、⁴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、⁵Laboratory of Bioorganic Chemistry, NIDDK、⁶神戸学院
 大学栄養学部
- P2-018 Critical role of R155 in the second intracellular loop in melanin-concentrating
 hormone receptor
 斎藤祐見子¹、手塚 満恵¹、斎藤 静司²、土居 洋文²、丸山 敬¹
¹埼玉医科大学 薬理学、²セレスターレキシコサイエンス
- P2-019 Selective and high affinity interaction of N, N-diisopropyl-5-methoxytryptamine,
 Foxy methoxy, with rat serotonin transporter heterologously expressed in COS
 cells
 十川 千春¹、大山 和美²、十川 紀夫¹、田川 淳平³、藤野 敦子³、浅沼 幹人⁴、
 船田 正彦⁵、小野寺憲治¹、北山 滋雄¹
¹岡山大学 大学院 医歯薬学総合研究科 歯科薬理、²岡山大学 歯学部 R I 実験
 施設、³岡山大学歯学部、⁴岡山大学 大学院 医歯薬学総合研究科 神経情報、⁵国
 立精神・神経センター 薬物依存研究部
- P2-020 Dopamine D₂-like receptor-mediated [³⁵S]GTPγS binding in rat striatal
 membranes: Effects of dopaminergic antagonists
 小田垣雄二¹、豊嶋 良一¹
¹埼玉医科大学 精神医学講座
- P2-021 Transport of adenosine and uridine in primary cultured rat cortical neurons and
 astrocytes
 長井 克仁¹、松永 良子¹、山路麻須美¹、長澤 一樹¹、藤本 貞毅¹
¹京都薬大 衛生化学
- P2-022 Cell-based assay systems for high-throughput screening of drug candidates
 acting on human G protein coupled receptors (GPCRs)
 Bookyung Ko¹、Sungryul Yu¹、Jeong Soo Park²、Jaeseung Yoon¹、Kwanghee Baek¹
¹Graduate School of Biotechnology, Kyung Hee University、²PanGen Biotech Inc.,
 Seongnam City, Korea
- P2-023 Identification functional P2 receptor subtypes expressed in three human cell
 lines with a Cytosensor Microphysiometer
 浦江 隆次¹、柴田あずみ¹、田中 孝典¹、入江 伸¹、岩田 仲生²、尾崎 紀夫³、
 岡田三津子¹
¹医療法人相生会九州臨床薬理クリニック臨床薬理研究部門分子神経遺伝学研究室、
²藤田保健衛生大学医学部精神科、³名古屋大学大学院医学系研究科細胞情報医学専攻
 脳神経病態制御学講座 精神医学分野

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シナプス

- P2-024 Downregulation of drebrin-A expression suppresses morphological maturation of dendritic spines and synaptic targeting of NMDA receptors in developing hippocampal neurons
高橋 秀人¹、白尾 智明¹
¹群馬大学 医学系研究科 高次細胞機能学
- P2-025 Increase of SNARE-binding affinity of synaphin/complexin by phosphorylation
車多 厚志^{1,2}、西須 英雄³、小谷 昌司²、阿部 輝雄³
¹新潟大学 脳研究所 生命科学リソース研究センター、²新潟大学 理学部 生物学科、³新潟大学 脳研究所 細胞神経生物学
- P2-026 Gene transfer methods for neurons in organotypic hippocampal slice culture
安田 新¹、鈴木 香子¹、竹宮 孝子¹、杉浦 弘子¹、山形 要人¹
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
- P2-027 Kspot, a novel ubiquitin ligase, may control synapse formation
多田 敬典^{1,2}、岡野ジェイムス洋尚^{1,2}、松本 雅記^{2,3}、中山 敬一^{2,3}、鹿島 晴雄⁴、岡野 栄之^{1,2}
¹慶應大 医 生理学、²科技団・CREST、³九州大 生医研 分子発現制御学、⁴慶應大 医 精神神経科学

情報伝達、変換、修飾

- P2-028 Involvement of Rho/Rhotekin pathway in the development of neural polarity
伊東 秀記¹、岩本 郁子¹、森下 理香¹、浅野 富子¹、永田 浩一¹
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
- P2-029 Identification and characterization of β CaM kinase II promoter binding protein
落合 祥啓¹、益本 修治¹、桜田 巧¹、吉村 好之¹、山内 卓¹
¹徳島大学大学院 薬科学教育部
- P2-030 Phosphorylation of synapsin I by Ca^{2+} /calmodulin-dependent protein kinase II in hypothalamic GT1-7 neurons
山本 秀幸¹、平上ゆかり¹、川原 正博²、佐々木泰治³
¹熊本大学大学院 医学薬学研究部 細胞情報薬理学分野、²九州保健福祉大学 薬学部薬学科 分析学講座、³北里大学 薬学部 薬理学教室
- P2-031 Leucine enhances p70S6K signals in cortical neurons.
石塚 佑太¹、那波 宏之¹、武井 延之¹
¹新潟大学 脳研究所 分子神経生物学分野
- P2-032 Activation of latent cyclin-dependent kinase 5 (Cdk5)-p35 complexes by membrane dissociation
朱 英善¹、斉藤 太郎¹、浅田 明子¹、久永 真市¹
¹東京都立大学 理学研究科 生物科学

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- P2-033 The signal cascade stimulated by the neural activity-regulated adhesion molecule Arcadlin.
 杉浦 弘子¹、安田 新¹、岡村 航²、鈴木 香子¹、竹宮 孝子¹、田中 秀和²、三木 直正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大阪大学大学院 医学部 情報薬理
- P2-034 Possible induction of hypoglycemic neuronal death by reduction of phospholipase C- β 1 and- γ 1
 角田 大智¹、長澤 一樹¹、一見 恭子¹、川北 豊¹、長井 克仁¹、藤本 貞毅¹
¹京都薬科大学 薬学研究科 薬学専攻
- P2-035 Characterization of the dimerization mechanism of ROCKII
 宮本 宗周¹、内藤 康仁¹、佐々木泰治¹
¹北里大学 薬学部 薬学科
- P2-036 Cdk5/p39 is a labile complex dissociated by detergent with a comparable kinase activity with Cdk5/p35
 久永 眞市¹、山田 真理¹、佐藤 裕¹、関川 明生¹、浜住 由子¹、浅田 明子¹、斎藤 太郎¹
¹首都大学東京 都市教養学部 理工系 生命科学コース
- P2-037 Structural Insights into Eph/ephrinB-Mediated Reverse Signaling Network
 Jianxing Song¹、Xiaoyuan Ran、Minfen Li¹、Jingxian Liu¹
¹Departments of Biochemistry and Biological Sciences National University of Singapore
- P2-038 Role of C-terminus of PKC γ in tissue-specific translocation and regulation
 Yeong Sui Sum¹、Tan Bee Jen¹、Duan Wei¹
¹Department of Biochemistry, Faculty of Medicine, National University of Singapore
- P2-039 Differential expression of the GTP cyclohydrolase I gene by two promoters in *Drosophila melanogaster*
 Jaegoo Byun¹、Jaeseung Yoon¹、Kwanghee Baek
¹Graduate School of Biotechnology, Kyung Hee University
- P2-040 Functions of protein phosphorylations in Drosophila photoreceptors
 Sunji Lee¹、Eunsung Lee¹、Hyunjoo Kim¹、Jeyoun Jang¹、Eunju Kim¹、Kwanghee Baek¹、Jaeseung Yoon¹
¹Graduate School of Biotechnology, Kyung Hee University

軸索輸送、細胞運動、細胞骨格

- P2-041 Involvement of P2X₄ receptor in ATP-induced chemotaxis of microglia
 大澤 圭子¹、入野 康宏¹、中村 泰子¹、赤澤 智宏¹、井上 和秀²、高坂 新一¹
¹国立精神・神経センター 神経研究所 代謝研究部、²九州大学大学院・薬学研究院 薬効解析学分野
- P2-042 ER membrane binding domain of kinectin
 豊島 至¹、阿部エリカ¹、大川 聡¹、菅原 正伯¹、渡辺 純夫¹
¹秋田大学 医学部 第一内科

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- P2-043 Roles of Lasp-family protein and Fascin in actin bundle formation and elongation in filopodia at neuronal growth cone
 宮本 茂昭¹、中川 裕之¹、寺崎 朝子²、大橋 一世²
¹九州工業大学 情報工学部 生命情報工学科、²千葉大学 理学部 生物学科
- P2-044 Different contribution of N-shc and Sck adaptor proteins to reorganization of actin cytoskeleton
 秋野 公造¹、今泉 敏史¹、大神 和子¹、山口 陽子¹、森 望¹
¹長崎大学 医学部 解剖学第一
- P2-045 Search for the proteins which interact with N-terminal 126 amino acids of MAP1B: The new site of tubulin interaction
 五味不二也¹、内田 洋子¹
¹東京都老人総合研究所 老年病ゲノムグループ

ニューロン、グリア

- P2-046 Molecular and functional characterization of a Na⁺-independent choline transporter in rat astrocytes
 稲津 正人¹、武田 弘志¹、松宮 輝彦¹
¹東京医科大学 薬理学
- P2-047 Neuronal expressions and molecular properties of brain acyl-CoA hydrolase isoforms
 高木 充弘¹、大友 隆之¹、野水 基義¹、山田 純司¹
¹東京薬科大学 薬学部 病態生化学
- P2-048 Effects of activation by LPS on glutamine transporter expressed in cultured cortical astrocytes
 小椋 正人¹、木村 仁美¹、高野 桂¹、中道 範隆¹、米田 幸雄¹
¹金沢大学大学院 自然科学研究科
- P2-049 Serotonin-induced excitotoxicity in rat motoneurons.
 宮崎 真¹、濱野 史子¹、富松 直子¹、金井 文彦¹、小俣 政男¹、荒川 義弘¹
¹東京大学 医学部 附属病院 臨床試験部
- P2-050 NMDA-induced MCP-1 production is mediated by the activation of ERK and JNK MAP kinases and PI3 kinase in the organotypic cortico-striatal slice culture
 片山 貴博¹、金子 周司²、佐藤 公道³、南 雅文¹
¹北海道大学大学院 薬学研究科 薬理学分野、²京都大学大学院 薬学研究科 生体機能解析学分野、³奈良先端科学技術大学院大学
- P2-051 Regulation of neuronal differentiation by NMDA signals in neural progenitor cells in vitro
 米山 雅紀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
- P2-052 BK-induced migration of microglia
 井福 正隆¹、王 冰¹、野田 百美¹
¹九州大学 大学院 薬学研究院 医療薬科学専攻 生命薬学講座 病態生理学分野

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- P2-053 Regulation of mitochondrial gene expression by glutamate signals in cultured cortical neurons of mice
 杉山 千絵¹、中谷 有希¹、折田 将成¹、荻田喜代一¹
¹摂南大学 薬学部 薬理学
- P2-054 The first report: Effect of hippocampal cholinergic neurostimulating peptide precursor protein (HCNP-pp) over-expression in immature PC12 cells
 高田 幸児¹、松川 則之¹、中澤 秀嘉¹、山脇 健盛¹、小鹿 幸生¹
¹名古屋市立大学大学院 医学研究科 神経病態学
- P2-055 Roles for p21^{Cip1/WAF1} during oligodendrocyte development
 谷内 孝次^{1,2}、田中 啓之^{1,2}、遠山 正彌^{1,2}
¹大阪大学 医学部 神経機能形態学、²21世紀COEプログラム
- P2-056 The requirement of NF κ B in p38 MAP kinase activation linked to the induction of TNF α in LPS-stimulated microglia
 中嶋 一行¹、松下 雄一¹、上杉 美幸¹、遠山 陽子¹、高坂 新一²、栗原 正¹
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
- P2-057 Increased neurogenesis by lysophosphatidic acid in neurosphere culture system
 福岡 伸之¹、森山隆太郎¹
¹近畿大学理工学部生命科学科
- P2-058 A new splice variant of neuroglycan C, a CNS-specific transmembrane chondroitin sulfate proteoglycan
 青野 幸子¹、時田 義人¹、平野佳奈子¹、黒田 喜幸¹、中西 圭子¹、伊田みちる¹、松井ふみ子¹、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
- P2-059 Fc receptor-positive oligodendrocyte precursor cells in multiple sclerosis brain: A novel therapeutic target
 中原 仁¹、相磯 貞和¹
¹慶應義塾大学 医学部 解剖学教室
- P2-060 Analysis of synthesis and uptake of lactate in primary neuronal and astrocytic culture cells using ¹³C-NMR spectroscopy
 小山 晶子¹、中嶋 一行¹、中臺 武人¹、金松 知幸¹
¹創価大学 工学部 生物工学科
- P2-061 *Phgdh* hypomorphic mice serve as an animal model of human genetic serine deficiency
 古屋 茂樹^{1,2}、吉田 一之^{2,4}、境 和久³、篠田 陽子²、東 徳洋⁵、端川 勉³、平林 義雄²
¹九州大学 バイオアーキテクチャーセンター 生物機能デザイン分野、²理化学研究所 脳科学総合研究センター 平林研究ユニット、³理化学研究所 脳科学総合研究センター 神経構築技術開発チーム、⁴宇都宮大学 ベンチャービジネスラボラトリー、⁵宇都宮大学 農学部 生物生産科学科
- P2-062 The role of GFAP positive cells in the intestinal villi
 常松健一郎¹、中原 仁²、丹・竹内 京子²、相磯 貞和²
¹慶應義塾大学医学部小児科学教室、²慶應義塾大学医学部解剖学教室

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ミエリン

- P2-063 Structure and activity of brain 2',3'-cyclic-nucleotide 3'-phosphodiesterase
栗原 正¹、吉原 千草¹
¹創価大学 工学部 生命情報工学科
- P2-064 The function of phospho-MBP in developing mouse brain.
酒井 梨紗^{1,2,3}、小見山貴継¹、清和 千佳¹、須川 誠¹、入江 祥史²、
石毛 敦²、渡辺 賢治²、小島 周二³、阿相 皓晃¹
¹東京都老人総合研究所 グリア細胞研究グループ、²慶応義塾大学 医学部 漢方医学講座、³東京理科大学 薬学部 放射線生命化学研究室
- P2-065 The changes of paranodal proteins in the PNS of the cerebroside sulfotransferase-deficient mice
星 登美子^{1,2}、山口 宜秀²、馬場 広子²
¹東京薬科大学 生命科学研究科 脳神経機能学研究室、²東京薬科大学 薬学部 機能形態学教室
- P2-066 Conduction properties of corpus callosum in mice in vivo.
板東 良雄¹、高草木 薫²、柏柳 誠²、吉田 成孝¹
¹旭川医科大学 医学部 解剖学第一講座、²旭川医科大学 医学部 生理学第二講座
- P2-067 Expression of Annexin 2 in murine peripheral nervous system
林 明子¹、中島圭慧子¹、鈴木 彩佳¹、星 登美子¹、山岸 克将¹、山口 宜秀¹、
馬場 広子¹
¹東京薬科大学 薬学部 機能形態
- P2-068 Myelin protein mapping using 16-BAC/SDS-PAGE
山口 宜秀¹、馬場 広子¹
¹東京薬科大学 薬学部 機能形態学教室
- P2-069 Effects of neonatal exposure to tributyltin on expression of glycoconjugates in the rat brain
小嶋 久子¹、中村 和生¹、峰田 理恵¹、桑田 正広²、菅野 幸子³、玉井 洋一⁴
¹北里大学 医学部 代謝蛋白学、²八戸大学、³宮崎県立看護大、⁴こころ クリニック
- P2-070 Hydrogen sulphide regulates calcium homeostasis in BV-2 microglial cells
Ye-Shi Hu¹、Lee Shiao Wei¹、Jin-Song Bian¹
¹Dept. of Pharmacology, Faculty of Medicine, National University of Singapore

神経免疫

- P2-071 The possible regulatory mechanism of proinflammatory cytokine expression in murine locus coeruleus
金子 葉子¹、森 啓至¹、中島 昭¹、永津 郁子²、太田 明¹
¹藤田保健衛生大学 医学部 生理学 1、²藤田保健衛生大学 医学部 解剖学 2
- P2-072 Manifestation of myasthenic weakness by autoantibodies against MuSK
重本 和宏¹、久保 幸穂²、羽藤 直人³、山田 啓之³、松田 正司⁴、丸山 直記²
¹愛媛大学 医学部 環境社会医学、²東京都老人総合研究所、加齢臓器障害研究グループ、³愛媛大学 医学部 耳鼻咽喉科、⁴愛媛大学 医学部 統合生命科学講座

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- P2-073 Microarray analysis of chemokines and chemokine receptors induced by lipopolysaccharide in rat microglia
 鈴木 俊二¹、菅野 素子¹、横山 彰子¹、高橋 寿明¹、今井 嘉紀¹、田中 潤也¹、
¹愛媛大学 医学部 分子細胞生命科学講座 分子細胞生理学分野

パターン形成

- P2-074 A new system for the three-dimensional visualization of tangential migration in the developing mouse forebrain
 四津 真人¹、田畑 秀典¹、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
- P2-075 Analysis of Reelin-Dab1 signal transduction system in layer formation of cerebral neocortex using RNAi
 本田 岳夫¹、田畑 秀典^{1,2}、仲嶋 一範¹
¹慶應義塾大学 医学部 解剖学、²科学技術振興機構 戦略的創造研究推進事業

細胞分化

- P2-076 Necdin represses cdc2 gene expression via E2F1 and prevents neuronal apoptosis
 栗田 光将¹、吉川 和明¹
¹大阪大学大学院 理学研究科 蛋白質研究所 神経発生制御研究室
- P2-077 Mammalian Müller glial cells can be converted to a neuronal lineage
 久保田 享¹、中島 欽一²、西田 幸二¹、田野 保雄¹
¹大阪大学大学院 医学系研究科 臓器制御医学、²奈良先端科学技術大学院大学 分子神経分化制御学
- P2-078 Differentiation of neural progenitor cells into smooth muscle cells induced by TGF- β and agonists of G protein-coupled receptors
 浅野 富子¹、森下 理香¹、永田 浩一¹、伊東 秀記¹、上田 浩²、篠原 春夫³
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岐阜大学 工学部、³東海学園大学 人間健康学部
- P2-079 Molecular mechanism of cholinergic differentiation by L3/Lhx8 in murine ES cells
 眞部 孝幸¹
¹奈良県立医科大学 医学部 第二解剖
- P2-080 Necdin promotes GABAergic neuron differentiation through ternary complex formation with MAGE-D1 and Dlx
 桑島 孝明¹、吉川 和明¹
¹大阪大学 蛋白質研究所 神経発生制御
- P2-081 Neuroprotective effect of acetylcholine esterase inhibitor on young neurons generated in the adult mouse olfactory bulb and hippocampus
 金子奈穂子^{1,2,3}、岡野 栄之³、澤本 和延^{1,3}
¹慶應義塾大学 医学部 プリダストン神経発生・再生学寄附講座、²山梨大学 大学院 医学工学総合教育部、³慶應義塾大学 医学部 生理学教室

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- P2-082 Induction of ectopic oligodendrocyte precursors in fetal cerebral cortex by intraventricular injection of FGF-2
成瀬 雅衣^{1,2}、宮田 卓樹³、等 誠司^{1,2}、池中 一裕^{1,2}、BANSAL RASHMI⁴
¹総合研究大学院大学 生命科学研究科、²自然科学研究機構 生理学研究所、³名古屋大学 医学部、⁴University of Connecticut Medical School
- P2-083 17 β -estradiol-induced differentiation and intracellular signal pathway in rat neural stem cells
岡田 牧子¹、古川 美子¹、古川 昭栄¹
¹岐阜薬科大学 薬学研究科 分子生物学教室
- P2-084 Translational repression mediated neural RNA-binding protein Musashi
今井 貴雄¹、河原 裕憲¹、小澤 洋子²、芝田 晋介¹、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 眼科学教室
- P2-085 Mash1 affects cell fates in the postnatal rat cerebellum
山本 緑¹、鈴木 諭¹、岩城 徹¹
¹九州大学 大学院 医学研究院 神経病理
- P2-086 Effects of nicotine on neurogenesis and plasticity in the hippocampus.
鬼頭 昭三¹、北川麻衣子¹、卯之原美恵¹、山下 和泉¹、山本 由香¹、木村 泰大¹、新郷 明子¹
¹兵庫大 健康科学部 脳科研
- P2-087 RNAi analysis of Drosophila MAGE in the nervous system
迫田 順哉¹、西村伊三男¹、吉川 和明¹
¹大阪大学大学院 理学研究科 生物科学専攻
- P2-088 RNA-binding protein Hu regulates proliferation and differentiation in Mammalian nervous system
岡野ジェイムス洋尚^{1,2}、矢野 真人^{1,2}、赤松 和土³、五十嵐真奈^{1,2}、岡野 栄之^{1,2}
¹慶應義塾大学 医学部 生理学教室、²CREST、³トロント大学 カナダ
- P2-089 Abnormal development of enteric neural crest cells in the nerve growth factor receptor, p75, knockout mice
星 雅人¹、赤澤 智宏¹、高坂 新一¹
¹国立精神神経センター 神経研究所 代謝研究部
- P2-090 Gene expression during unidirectional differentiation of mouse embryonic stem cells into neurons
祭 友昭^{1,2}、大津 昌弘¹、百木 智子¹、中山 孝³、原田 基裕⁴、鈴木 豊⁵、近藤 靖⁵、笠井 久隆^{1,6}、井上 順雄¹
¹首都大学東京 健康福祉学部 神経再生科学研究室、²東京慈恵会医科大学 整形外科科学教室、³横浜市立大学 医学部 生化学、⁴青山学院大学 理工学研究科、⁵田辺製薬 先端医学研究所、⁶工学院大学 応用化学研究科
- P2-091 Analysis of DNA double-strand break repair proteins during *in vitro* neural differentiation
川端 昌弘¹、川端 晃幸²
¹岡山大学 大学院 医歯薬学総合研究科 薬理学分野、²岡山理科大学 理学部 医工学

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- P2-092 Functional Analysis of a Novel Neuron-Specific Protein Family, BRINP
 石井美奈子¹、森 卓哉²、小林三和子¹、松岡 一郎^{1,2}
¹北海道大学 創成科学共同研究機構 流動部門 生命系、²北海道大学 大学院 薬学研究科
- P2-093 Astrocyte differentiation of the EGF-responsive proliferating cells in early postnatal mouse cerebellum
 岡野一内田 孝幸¹、加藤 隆二¹、石崎 泰樹¹
¹群馬大学大学院 医学系研究科 分子細胞機能
- P2-094 The lineage tracing of Olig2 expressing cells in the cryo-injured adult CNS
 辰巳 晃子¹、竹林 浩秀²、眞部 孝幸¹、池中 一裕²、和中 明生¹
¹奈良県立医科大学 医学部 第2解剖学、²自然科学研究機構・生理学研究所・分子神経生理研究部門
- P2-095 Fibroblast growth factor 2 maintains neural stem cells in an undifferentiated state and promotes their proliferation via the glycogen synthase kinase 3 β inactivation
 清水 健史¹、鹿川 哲史¹、井上 俊洋¹、吉永 豊¹、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
- P2-096 The role of TROY in the development of the nervous system
 久岡 朋子¹、森川 吉博¹、小森 忠祐¹、北村 俊雄²、仙波恵美子¹
¹和歌山県立医科大学 医学部 第二解剖、²東京大学 医科学研究所 先端医療研究センター 細胞療法分野
- P2-097 PACAP-induced PACAP mRNA expression and neuronal differentiation in neural precursor cells
 廣瀬 恵^{1,2}、橋本 均¹、嶋田 健¹、中西 恵己¹、新谷 紀人¹、伊賀 純子¹、荒川 尚久¹、馬場 明道¹
¹大阪大学大学院 薬学研究科 神経薬理学分野、²日本学術振興会特別研究員
- P2-098 A role of CARM1 in neuronal differentiation.
 藤原 達司¹、楚 東嶺¹、小山 佳久¹、森 泰丈¹、遠山 正彌¹
¹大阪大学大学院医学研究科ポストゲノム疾患解析学講座
- P2-099 Filamin A-interacting protein (FILIP) deficiency results in increased Filamin A expression and decreased proliferation in the ventricular zone during neocortex development
 Mohammad Tariqur Rahman¹、Soichi Morikubo^{1,2}、Hideshi Yagi¹、Takashi Nagano¹、Masaru Okabe¹、Makoto Sato^{1,4}
¹Division of Cell Biology and Neuroscience, Department of Morphological and Physiological Sciences、²Division of Ophthalmology, Department of Sensory and Locomotor Medicine, Faculty of Medical Sciences, University of Fukui, Matsuoka, Fukui 910-1193, Japan、³Genome Information Research Center, Osaka University, Yamadaoka 3-1, Suita, Osaka 565-0871, Japan、⁴Solution Oriented Research for Science and Technology, Japan Science and Technology Corporation, Kawaguchi, Saitama 332-0012, Japan

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突起伸展、回路網形成

- P2-100 Dendritic morphogenesis of cerebellar Purkinje cells through extension and retraction: time-lapse analysis and involvement of calcium/calmodulin-dependent protein kinase II and neuronal activity
田中 正彦¹、柳川右千夫^{2,3}、小幡 邦彦⁴、丸野内 隼¹
¹藤田保健衛生大 総医研 応用細胞学、²群馬大院 医 遺伝発達行動学、³科学技術振興機構 SORST、⁴理研 脳センター
- P2-101 PR#1, a monoclonal antibody raised against the detergent insoluble membrane / lipid rafts from PC12 cells, promotes neurite outgrowth of PC12 cells.
山崎 泰広^{1,2}、長塚 靖子³、大島恵理子³、鈴木 康夫²、平林 義雄³、端川 勉¹
¹理化学研究所 脳科学総合研究センター 神経構築、²静岡県立大学 薬学部 生化学教室、³理化学研究所 脳科学総合研究センター 神経回路メカニズム
- P2-102 Restoration from neurodegenerative changes by withanoside IV and by its active metabolite, sominone
久保山友晴¹、東田 千尋²、小松かつ子^{1,3}
¹富山医科薬科大学 和漢薬研究所 生薬資源科学分野、²富山医科薬科大学 和漢薬研究所 薬効解析センター、³21世紀 COE プログラム 富山医科薬科大学
- P2-103 Ras regulates neuronal polarity via the PI3-kinase/Akt/GSK-3 β /CRMP-2 pathway.
吉村 武¹、貝淵 弘三¹
¹名古屋大学大学院 医学系研究科 神経情報薬理学講座
- P2-104 Developmental gene expression of Ca²⁺/calmodulin-dependent protein kinase I in mouse brain and its involvement of dendritic extension in hippocampal neurons.
鎌田 暁史¹、阪上 洋行²、福永 浩司¹、近藤 尚武²
¹東北大学大学院 薬学研究科 薬理学分野、²東北大学大学院 医学系研究科 細胞生物学講座 細胞組織学分野
- P2-105 Dorsally derived netrin-1 controls axonal patterning of primary sensory axons in the developing spinal cord
渡辺 啓介^{1,2}、玉巻 伸章^{3,4}、古田 貴寛⁴、Susan L. Ackerman⁵、池中 一裕^{1,2}、小野 勝彦^{1,2}
¹生理研 分子神経生理、²総研大 生命科学、³熊本大院 医薬 脳回路構造学、⁴京都大院 医 高次脳形態学、⁵The Jackson Lab., Bar Harbor, ME, USA
- P2-106 Metabolite 1 of protopanaxadiol-type saponins, an axonal regenerative factor, stimulates teneurin-2 linked by PI3-kinase cascade
中西 類子¹、東田 千尋¹、橋本 斎²、小松かつ子^{2,3}、横澤 隆子¹
¹富山医科薬科大学 和漢薬研究所 民族薬物研究センター 薬効解析分野、²富山医科薬科大学 和漢薬研究所 生薬資源科学分野、³富山医科薬科大学 21世紀 COE プログラム
- P2-107 Analysis of the mechanism of Reelin-induced tyrosine phosphorylation of Dab1
久保健一郎¹、御子柴克彦²、仲嶋 一範^{1,3}
¹慶応義塾大学医学部解剖学教室、²東京大学医科学研究所脳神経発生・分化分野、³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

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- P2-108 Phosphorylation of GSK-3 β in neurite outgrowth from PC12D cells
 神 絵里香¹、佐野 護¹
¹京都府立医科大学 大学院 医学研究科 病態分子薬理学
- P2-109 DNA microarray analysis of activity-dependent gene expression in cultured rat cortical cells
 北村 主税¹、近藤 恭光²、田代 英夫²、田代 朋子¹
¹青山学院大学 理工学部 化学・生命科学科、²理化学研究所本所 分子計測工学研究室

栄養因子

- P2-110 Effects of an eight hour phase advance of the light-dark cycle on neurotrophin levels in various brain regions of rats
 仙波りつ子¹、続木 雅子¹、中川 千玲¹、一坂 吏志²、畠 義郎³
¹愛知県コロニー・研究所、²鳥取大・医・生命・神経生物、³鳥取大院・医・機能再生・生体高次機能
- P2-111 Adenoviral gene transfer of hepatocyte growth factor (HGF) prevents death of injured adult motoneurons after peripheral nerve avulsion
 渡部 和彦¹、林 祐一¹、川添 陽子¹、坂本 剛¹、宮沢 大介²、船越 洋²、中村 敏一²
¹東京都神経科学総合研究所 分子神経病理、²大阪大学大学院 医学系研究科 組織再生医学講座分子組織再生分野
- P2-112 Neuroprotective Effect of Pigment Epithelium-Derived Factor (PEDF)-Expressing Adenoviral Vector in the Quinolinic Acid Rat Model of Huntington Disease
 佐柳 友規^{1,2}、矢部 武士^{1,2,3}、山田 陽城^{1,2,3}
¹北里大学 北里生命科学研究所、²北里大学 大学院 感染制御科学府、³北里研究所 東洋医学総合研究所
- P2-113 BDNF sustains high level of proliferation rate of cultured mouse neural stem/progenitor cells when applied to them with FGF-2 in combination.
 坂井 美香¹、福光 秀文¹、古川 昭栄¹
¹岐阜薬科大学 分子生物学教室
- P2-114 Neurotrophic effects of genipin: Neuroprotective actions on ER stress in Neuro2a cells
 山崎眞津美¹、千葉 賢三¹
¹北陸大学 薬学部 生化学
- P2-115 Neurotrophic effects of genipin: Neuroprotective actions through nitric oxide synthase activation on oxidative stress in Neuro2a cells
 千葉 賢三¹、山崎眞津美¹、佐藤 敬子¹
¹北陸大学 薬学部 生化学
- P2-116 Differential Distributions of Epidermal Growth Factor Family and Phosphorylated-ErbB1 in adult Rat Brain
 朴 英善¹、小見 笑子¹、岩倉百合子¹、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

Sep 29 (Thu) Poster Session

F 会場

揭示時間 9:00 ~ 17:00
 討論 / 奇数番号 13:00 ~ 13:45
 偶数番号 13:45 ~ 14:30

- P2-117 Neuroprotective effects of isoflavones as selective estrogen receptor modulators.
 新郷 明子¹、山下 和泉¹、卯之原美恵¹、北川麻衣子¹、山本 由香¹、木村 泰大¹、
 鬼頭 昭三¹
¹兵庫大 健康科学部 脳科研
- P2-118 NGF prevents 2-deoxy-D-glucose-induced apoptosis via PI3-K signaling pathway in PC12 cells
 下家 浩二¹、山本 優子¹、岸 宗一郎¹、笹谷 晴恵¹、内海 孝宏¹、嶋村 勇一¹、
 新家 一男²、池内 俊彦¹
¹関西大学 工学部 神経生物学研究室、²東京大学 分子細胞生物学研究所
- P2-119 Behavioral abnormalities of the transgenic mice over-expressing HB-EGF
 穴戸 裕二¹、田中 隆之¹、朴 英善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、²愛媛大学 医学部 分子細胞生命科学 生
 化学・分子遺伝学

Sep 28 (Wed) Luncheon Seminar

◆◇◆ ランチョンセミナーー Luncheon Seminar ◇◇◆

12:00 ~ 13:00 B会場

LS-1 グラクソ・スミスクライン(株)、吉富薬品(株) 共催

座長：渡邊 義文（山口大学医学部高次神経科学（神経精神医学））

自殺予防から見た臨床精神薬理

Suicide prevention and clinical psychopharmacology

張 賢徳

帝京大学医学部附属溝口病院精神神経科

12:00 ~ 13:00 C会場

LS-2 ヤンセンファーマ(株) 共催

座長：鍋島 俊隆（名古屋大学医学部附属病院薬剤部）

アルツハイマー病とニコチン性受容体

Alzheimer's disease and nicotinic acetylcholine receptors

下濱 俊

京都大学大学院医学研究科脳病態生理学講座臨床神経学

Sep 29 (Thu) Luncheon Seminar

12:00 ~ 13:00 B会場

LS-3 大塚製薬㈱ 共催

座長：加藤 進昌（東京大学大学院医学系研究科精神医学分野）

統合失調症治療の現状と方向性

Current state and future direction in the treatment of schizophrenia

尾崎 紀夫

名古屋大学大学院医学系研究科精神医学分野

12:00 ~ 13:00 C会場

LS-4 旭化成ファーマ㈱、ヤンセンファーマ㈱ 共催

座長：小澤 寛樹（長崎大学大学院医歯薬学総合研究科
病態解析制御学講座精神病態制御学）

ミルナシプランの治療反応性予測

Prediction of Antidepressant Response to Milnacipran

吉田 契造

名古屋大学大学院医学系研究科精神医学分野

12:00 ~ 13:00 D会場

LS-5 日本イーライリリー㈱ 共催

座長：小山 司（北海道大学大学院医学研究科脳科学専攻神経機能学講座
精神医学分野）

精神科領域における個別化薬物治療の可能性－薬理遺伝学からみた統合失調症治療－

Personalized pharmacotherapy in psychiatric field –Pharmacogenetics in schizophrenia treatment–

兼子 直

弘前大学医学部神経精神医学講座

発表抄録集

特別講演

招待講演

ISNシンポジウム

理事会企画オープンシンポジウム

躁うつ病の薬理生化学的研究懇談会
合同シンポジウム

日本精神行動遺伝学会
合同シンポジウム

シンポジウム

一般演題プログラム
(ミニシンポジウム、ポスター)

PL-01 Activation of the higher brain function by endogenous satiety substances increased during food intake

Yutaka Oomura¹

¹Dept. of Integrative Physiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

The 2.5mM glucose concentration in CSF becomes twice during food intake. Responding to this increase, ependymal cells in the III cerebral ventricle release acidic FGF in CSF and the brain. Released aFGF first suppresses food intake by inhibition of lateral hypothalamic feeding neurons. Secondly, aFGF activates hippocampal CA1 neurons, thus facilitates spatial learning and memory. Then aFGF activates the hypothalamo-pituitary-adrenal axis, and the efferent sympathetic outflow. The phagocytosis in macrophages is also enhanced by aFGF thus body immune action is facilitated.

The glucose increase itself acts as the satiation, inhibiting lateral hypothalamic neurons and facilitating ventromedial satiety neurons. Then glucose activates hippocampal CA1 neurons, thus facilitates spatial learning and memory. This facilitation is caused by presynaptic increases in transmitter release and phosphorylation of synapsin I, and postsynaptic increases in response to NMDA and phosphorylation of GluR I, PKC, CaMKII, ERK, and MARKS.

These evidences indicate that food intake is necessary not only for keeping body homeostasis but also for reforming the higher brain function.

PL-02 The molecular basis of monogamy

Larry J. Young¹

¹Dept. of Psychiatry and Behavioral Sciences, Center for Behavioral Neuroscience, Emory University, Atlanta, USA

Studies in monogamous rodents are shedding light into the neurobiological and molecular mechanisms that regulate complex social behaviors, including social bonding. Comparative studies in monogamous prairie voles and promiscuous montane and meadow voles suggest that the neuropeptides oxytocin and vasopressin play critical roles in pair bonding. Furthermore, species differences in the expression pattern of the oxytocin and vasopressin receptor genes appear to underlie the species differences in these social behaviors. Monogamous species have high levels of receptor expression in the nucleus accumbens and ventral pallidum, while non-monogamous species do not. Blocking these receptor populations with antagonists prevents pair bond formation. These brain regions are involved in reward and reinforcement, suggesting that pair bond formation involves peptidergic modulation of the mesolimbic reward system. Over expressing the vasopressin receptor in the ventral pallidum of non-monogamous species using viral vector gene transfer results in the expression of pair bonds. The species differences in vasopressin receptor expression in the brain are associated with an expansion in a repetitive element in the 5' flanking region of the prairie vole vasopressin receptor gene. Furthermore, individual variation in the length of the microsatellite in prairie voles determines both the expression levels of the vasopressin receptor in the brain, as well as social behavioral phenotype. The human vasopressin receptor also has repetitive microsatellite sequences in the 5' flanking regions, and these sequences are highly polymorphic, and one of these microsatellites has been associated with autism. Interestingly the chimpanzee vasopressin receptor gene lacks this microsatellite. These studies have important implications for the evolution of social behaviors, and potentially for variation in human social behaviors, including psychopathologies characterized by disruptions in social behavior.

PL-03 Catecholamine research: Present, past, and future

Toshiharu Nagatsu¹¹Dept. of Pharmacology, Fujita Health University, School of Medicine; and Dept. of Brain Life Science, Nagoya University, Research Institute of Environmental Medicine, Nagoya, Japan

The catecholamines dopamine, noradrenaline (norepinephrine), and adrenaline (epinephrine) are neurotransmitters in the central and peripheral nervous systems, and hormones in the periphery. Adrenaline is the hormone first crystallized from the adrenal medulla by Abel and Takamine around 1900. Noradrenaline was discovered as the neurotransmitter in the sympathetic nerves (von Euler, 1946). Dopamine was discovered as the neurotransmitter in the brain (Carlsson, 1958). Catecholamines are synthesized in catecholaminergic cells from tyrosine by tyrosine 3-monooxygenase (tyrosine hydroxylase) and aromatic L-amino acid decarboxylase via dopa to dopamine, then by dopamine beta-monooxygenase (dopamine beta-hydroxylase) to noradrenaline, and finally by noradrenaline N-methyltransferase (phenylethanolamine N-methyltransferase) to adrenaline. Catecholamines are stored in and released from synaptic vesicles in catecholamine neurons. Catecholamines released from catecholamine neurons transmit chemical information to the target cells through catecholamine receptors, i.e., adrenergic α -1, -2, β -1, -2, -3, and dopaminergic D1-D5 receptors. The signals of catecholamines as neurotransmitters are terminated by reuptake into presynaptic catecholamine neurons (Axelrod, 1960) by plasma membrane catecholamine transporters, and catecholamines are again stored in synaptic vesicles by vesicular monoamine transporters. Catecholamines are also inactivated by monoamine oxidase, catechol O-methyltransferase, and phenol sulfotransferase. In postsynaptic cells, the mechanism and various factors of the signal transduction have been elucidated, i.e., cyclic AMP, Ca, G proteins, DARPP-32 (dopamine and cyclic AMP-regulated phosphoprotein of 32 kDa) (Greengard, 1984), and protein kinases such as protein kinase A, protein kinase C, and Ca/calmodulin-dependent protein kinase, and protein phosphatases. Structures of molecules related to catecholamines, such as enzymes, transporters, receptors, signal transducers, and the mechanism of regulation and expression of the genes were elucidated by 2000. The *in vivo* dynamics of catecholamine neurotransmission have been examined by molecular imaging such as positron emission tomography. Catecholamines participate in a wide range of physiological and pathological mechanisms: metabolic regulations, stress responses, behaviors, neurological, psychiatric, endocrine, and cardiovascular diseases. Genetically engineered mice of catecholamine-related genes are valuable for producing models of neuropsychiatric diseases such as Parkinson disease. In the brain, catecholamines as well as acetylcholine, serotonin, histamine, adenosine, ATP, and various neuropeptides play important roles with glutamic acid and gamma-aminobutyric acid in the neuronal networks. The mesocortical dopamine neurons projecting from the ventral tegmental area to the nucleus accumbens and prefrontal cortex regulate emotion, memory, reward, or motivation, and may be closely related to mental diseases. Catecholamine neurotransmitters in the brain would be important both in elucidating the molecular mechanism of and in developing new drugs against neuropsychiatric disorders.

PL-04 Temporal and spatial regulation by CaM kinase II

Howard Schulman¹¹Dept. of Neurobiology, Stanford University School of Medicine and PPD Biomarker Discovery Sciences, Stanford, USA

Ca^{2+} /calmodulin (CaM)-dependent protein kinase (CaMKII) is a ubiquitous mediator of Ca^{2+} -linked signalling that phosphorylates and regulates many substrates involved in synaptic plasticity, electrical excitability, neurotransmitter synthesis, and gene expression. How does nature achieve specificity in signaling with such a broad specificity kinase? In fact, the multimeric structure and autophosphorylation of CaMKII enable temporal and spatial regulation of the kinase that increases specificity of signal transduction. CaMKII can: (i) be activated in a Ca^{2+} -spike frequency-dependent manner; (ii) achieve a long-term active state independent of its initial Ca^{2+} /CaM activators; (iii) undergo a 'switch-like' activation; and (iv) and translocate to certain anchoring proteins that facilitate phosphorylation of membrane proteins which is crucial for certain forms of learning and memory.

Autophosphorylation is ultrasensitive to Ca^{2+} (hill coefficient (n_H) = 5.5) and becomes even more switch-like and shifts to higher Ca^{2+} in the presence of protein phosphatase 1 (n_H = 8.6). In neurons and in heart activated kinase translocates and anchors to the NMDA receptor and L channel, respectively, ultimately leading to enhanced Ca^{2+} fluxes. Interaction with the NR2B subunit of the NMDA receptor produces autonomous activity without autophosphorylation that becomes more persistent with longer stimulation. Translocation to the membrane compartment is critical for effective phosphorylation. CaMKII action leads to facilitation or potentiation of Ca^{2+} influx in both cardiac myocytes and neurons that has both physiological and pathophysiological consequences.

IL-01 Molecular Asymmetry of hippocampal circuitry

Isao Ito¹

¹Dept. of Biology, Graduate School of Sciences, Kyushu University, Fukuoka, Japan

Asymmetrical hemispheric specialization is a fundamental concept of brain science and has been described mainly in higher-order functions of the brain. Recently we have found that synaptic distribution of NMDA receptor GluR ϵ 2 (NR2B) subunits in mouse hippocampus is asymmetrical between the left and right, and between the apical and basal dendrites of single neurons. These asymmetrical allocations of ϵ 2 subunits differentiate the properties of NMDA receptors and synaptic plasticity between the left and right hippocampus. Our findings show asymmetries involved in a basic structure and function of simple neuronal network.

Hippocampal CA1 pyramidal neurons receive major excitatory inputs from Schaffer collateral (sch) fibers from ipsilateral CA3 pyramidal neurons and commissural (com) fibers from contralateral CA3 pyramidal neurons. To characterize the NMDA receptors selectively in the sch-CA1 synapses, we have developed a method by which com fibers are denervated in live mice. Surprisingly, NMDA-EPSCs recorded in hippocampal slices prepared from the com fiber-denervated mice showed asymmetrical sensitivities to the ϵ 2 subunit-selective antagonist Ro 25-6981 between the left and right hippocampus, and between the apical and basal dendrites of individual neurons. NMDA-EPSCs in the com-CA3 synapses, examined in naive mice, showed opposite asymmetry in Ro 25-6981 sensitivities to those in the sch-CA1 synapses. The difference in the properties of NMDA receptors was reflected in distinct properties of LTPs in the left and right hippocampus. Western blot analyses of PSD proteins purified from the com fiber-denervated mice hippocampi revealed that the functional asymmetries of hippocampal synapses can be explained by the asymmetrical allocation of ϵ 2 subunits to these synapses.

Our findings indicate that the ϵ 2 subunit can be a key molecule to explore the unsettled problems in the field of brain asymmetry and suggest that the brain can involve asymmetries at each level of its structural hierarchy, namely neuron, synapse, neuronal network and left/right hemispheres of the brain.

IL-02 Biology in the prion infections: From BSE to variant Creutzfeldt-Jakob disease

Tetsuyuki Kitamoto¹

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Prion is a newly established infectious agent to get infectivity by the structural change of prion protein. There is no infectivity in normal type prion protein (PrP^C), and there is getting the infectivity in the abnormal conformation (PrP^{Sc}). Therefore, the conversion of prion protein from PrP^C to PrP^{Sc} is the most important research in this field.

Then, for this conversion, what kind of approaches has been done? It is a genome study that was done in a beginning. If the gene variation could explain this conversion, there does not need to be such an easy thing. The genome studies revealed followings; familial prion diseases occurring by the mutation of prion protein, and normal Val or Met polymorphisms at codon 129 influencing a clinicopathological phenotype of prion diseases. The next approach was done in the field of the protein chemistry. We could differentiate the molecular weights of protease-resistant PrP into type 1 (21KDa) or type 2 (19KDa). This typing can classify only two kinds of prions in itself. However, a classification of six kinds of prion disease became possible when we mixed it with the codon 129 Val/Met polymorphism; MM1, MV1, VV1, MM2, MV2, or VV2. Interestingly, a distinct PrP^{Sc} type has a distinct prion infectivity.

Unfortunately, three-dimensional conformation of PrP^{Sc} does not become clear. In addition, even if three-dimensional conformation of one PrP^{Sc} becomes clear, I have to say that the prion diseases have various clinicopathological phenotypes, and infectivity of prions also shows variations. Today, I will present the biology of the prion infection and will show the new concept about the folding memory of PrP^{Sc}.

ISN-01 Dizocilpine (MK-801) induced phosphorylations of the GSK-3 β and ERK signal pathway

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¹Dept. of Psychiatry and Behavioral Science and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul, Korea

Dizocilpine (MK-801) is a non-competitive NMDA receptor antagonist, which induces psychotomimetic behavioral changes in animals. And ERK and GSK-3 β have been suggested to play important roles in pathogenesis of psychotic disorder and action mechanism of psychotropic agents. We investigated phosphorylations of ERK and GSK-3 β associated molecules in rat brain after MK-801 treatment. Single administration of MK-801 induces acute changes in phosphorylations of Akt-GSK-3 β -CREB and Ser338-c-Raf-MEK-ERK in different fashion according to MK-801 dosage in rat frontal cortex. After injecting low dose of MK-801 (0.25-1mg/kg), rats showed increased motility and Akt-GSK-3 β -CREB phosphorylations were increased accordingly, while Ser338-c-Raf-MEK-ERK phosphorylations were reduced. At 2mg/kg, rats motility started to decrease and Akt-GSK-3 β -CREB phosphorylations also decreased, while Ser338-c-Raf-MEK-ERK phosphorylations increased. After injecting high dose of MK-801 (4-8mg/kg), phosphorylations of these molecules were all decreased, and rats showed hypomotility and ataxia. In contrast, after repetitive treatment of MK-801 (5x and 10x), phosphorylations of these two pathways were all increased in rat frontal cortex 24hr after last administration. And these changes were not different among repeated treatment of 0.5, 1 and 2mg/kg MK-801, and Ser338-c-Raf phosphorylation was not affected. Taken together, MK-801 induces changes in phosphorylations of GSK-3 β and ERK associated signaling pathways in relation with behavioral changes, and these changes may be implicated in the psychotomimetic behavioral changes induced by MK-801.

ISN-02 The molecular and cellular basis of non-dopamine systems in addiction

Wei Hao¹

¹Mental Health Institute, Central South University, Changsha, China

The subject of drug addiction is multifaceted and many aspects of it are controversial. Progress has been achieved a great deal in the understanding of the causes of addiction. A major hypothesis has suggested that the neurotransmitter dopamine might play a central role in the molecular mechanisms of rewards and some addiction. This neural substrate is, of course, the mesotelen-cephalic dopamine system, and especially dopamine projections to the nucleus accumbens and accumbens-related circuitry (often called the mesolimbic or mesocorticolimbic dopamine system). However, there are growing evidences showing that dopamine systems may play less important role as we thought, especially in chronic states of addiction. For example, it is well established that dopamine systems are activated not only by positive stimuli, but by aversive, painful and stressful stimuli and events; dopamine antagonists, such as haloperidol, fail to reduce amphetamine-induced ratings of pleasure or euphoria; and blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of 'high'. The author will introduce the researches conducted by his team on neurobiological mechanisms of morphine addiction in the non-dopamine systems of morphine dependent rats, by focusing the NMDA system, and endogenous opioid system, to try show drug-induced adaptations in these systems and related specific behavioral features of addiction.

ISN-03 Ethnicity, culture and pharmacogenetics

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Despite the existence of huge inter-individual and cross-ethnic variations in response to psychotropics and other medications, the practice of pharmacotherapy (including psychopharmacotherapy) has been largely "one size fits all," leaving drug choice and dosing decisions mostly to trial and error. Compounding this, the importance of ethnicity and culture in determining the metabolism and disposition of medications (pharmacokinetics) and their interactions with therapeutic targets (pharmacodynamics) has become increasingly evident. Genes controlling the expression of drug metabolizing enzymes as well as the function of brain are highly polymorphic, and the pattern and distribution of these polymorphisms are typically divergent across ethnic groups. To the extent that these genetic patterns determine drug response, ethnic variations in these genetic dispositions will lead to differential responses in the clinical setting. In addition, the expression of these genes is significantly influenced by environmental factors including diet as well as exposure to natural products (e.g., herbs and tobacco). Superimposed on these biological influences, culturally determined beliefs and behavioral patterns also profoundly influence patients' expectations of treatment response, adherence, as well as interactions with clinicians. It is expected that pharmacogenomic methods will be developed for routine clinical use in the near future, such that the results derived from such tests will be used to inform clinicians regarding the choice of medications, dosing strategies as well as risks for different side effects in ways that are individually tailored and ethnically relevant.

ISN-04 The association of gene expression in anxiety, depression and suicide

Tan Chay Hoon¹, Zhu YZ¹, Sherrin T¹, Tang YM², Lau G²

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Suicide is a complex behavior. Studies of suicide subjects have found that an increased number of stressful life events occur in the months preceding the self-destructive act. Stress is a precursor to anxiety, depression and suicide. Clinical studies suggest a genetic component in these psychiatric disorders. Neurotransmitter, neuropeptides and neuro-modulators involved have been identified and characterized. Alterations in cholecystokininB (CCKB) and corticotropin-releasing hormone (CRH) gene expression have been reported to be significantly different in the brains of suicide subjects as compared to controls. In this study, we report CCKB and CRH gene expressions between suicide completers [mean age 37.2 ± 12 years] and matched control subjects [mean age 37.6 ± 11.9 years]. CCKB and CRH1 gene expression are higher in the cerebellum, cingulate gyrus and pre-frontal cortex of suicide completers when compared to their age and gender matched controls. However, there is a significant down-regulation of CRF2 mRNA expression in the cerebellum and cingulate gyrus. CRF1 and CRF2 gene expressions are expressed in opposite directions matching the inverse functional relationship of the subtypes: CRH1 is anxiogenic and CRF2 mediates central anxiolytic properties. The findings in this study implicate a role for CCKB and CRH in suicide. Further studies are required to characterize the relationship between CCKB and CRH in suicide and stress-related disorders.

ISN-05 Ginseng enhances contextual fear conditioning and neurogenesis in rats

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Panax Ginseng is a commonly used galenical known to have an enhancing effect on learning, especially for aged rodent. Neurogenesis in the hippocampus has been shown to be necessary for hippocampus/amygdala-dependent learning tasks. To investigate the role of Ginseng in neurogenesis and learning of rats, we administered both Ginseng and BrdU for five consecutive days. One day after the last Ginseng and BrdU co-administration, contextual fear conditioning (CFC) was conducted. Ginseng in a dose-dependent manner increased the %freezing time and the number of BrdU-positive cells in the dentate gyrus of rats that received CFC. On the other hand, Ginseng increased the number of BrdU-positive cells in the dentate gyrus in a dose-dependent manner. Further, we administered one dose of BrdU after Ginseng treatment for five consecutive days, and the number of BrdU-positive cells did not increase significantly. However, when one dose of BrdU was given 1 day before the following five consecutive days of Ginseng treatment, the number of BrdU-positive cells markedly increased in the hippocampus. Therefore, it is likely that Ginseng enhances not proliferation but survival of newly generated neurons in the hippocampus. Thus, an increase in CFC-related neurogenesis may be one mechanism of Ginseng's properties to enhance learning ability.

OS-01 Neurological disorder and AP complex-mediated post-Golgi membrane traffic

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Proper localization of proteins to appropriate organelles in a cell is prerequisite for normal cellular functions. Its breakdown sometimes leads to pathological conditions not only for the cells, but also for multicellular organisms. Membrane traffic mediates the localization of proteins to the organelles in secretory and endocytic pathways. Among them, clathrin-coated vesicles (CCV) regulate the membrane traffic in the post-Golgi network. The AP complex, a major coat component of the clathrin-coated vesicle, plays a role in formation of CCV as well as cargo selection. There are six structurally related AP complexes in mammals; four of them are ubiquitously expressed, whereas two others are cell-type specific. The neuron-specific AP-3B has been suggested to be involved in de novo formation of synaptic vesicles from endosomes, although its role in individual organism remains unknown. To answer this question, we established a mouse line deficient in μ 3B, a subunit of AP-3B, using gene knockout (KO) technique. Interestingly, it turned out that μ 3B-KO mice suffered from epileptic seizure. Subsequent analyses revealed that synapses, especially of inhibitory neurons, were abnormal morphologically, that the release of inhibitory neurotransmitter GABA was impaired, and that the amount of VGAT, a GABA transporter, on synaptic vesicles was decreased, in μ 3B-KO mice. Electrophysiological analyses further indicated that the neuroexcitability in hippocampus enhanced in μ 3B-KO mice compared to wild-type mice. These observations suggest that insufficient release of GABA because of abnormal structure and function of synaptic vesicles leads to the excessive neuroexcitability and neurotransmission, which ultimately results in epileptic seizure in μ 3B-KO mice.

OS-03 Deficiency of lysosomal proteases and disorders of neuronal and microglia I functions

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It has been long believed that the primary function of cathepsins is to degrade proteins by bulk proteolysis in lysosomes and that cathepsins compensate for each other because of their overlapped substrate specificities. However, recent results from cathepsins gene knockouts have revealed that an imbalance of cathepsins causes disorders of neuronal and microglial functions in the central nervous system (CNS). In hippocampal and cortical interneurons, cathepsin D-deficiency induced a progressive lysosomal degradation of GAD65/67, GABA biosynthetic enzymes. The degradation of GAD65/67 may be responsible for an impairment of GABAergic transmission and a manifestation of generalized seizure of cathepsin D-deficient mice. Furthermore, cathepsin D-deficient microglia may induce secondary neuronal death by secretion of reactive oxygen species. On the other hand, cathepsin S-deficient microglia failed to spread on the neuronal surface injured motoneurons possibly due to inability for extracellularly degrading perineuronal nets that surrounding the surface of neurons. This may limit the function of microglia to regenerate injured axons. Cathepsins are now recognized to have more complex functions than simply being garbage disposers, and their imbalance may provoke CNS disorders through impairment of neuronal and microglial functions. Recently, we have found that intra-arterially injected microglia prepared from wild-type animals could cross the blood-brain barrier to accumulate in the pathological regions of cathepsin D-deficient mice. These infiltrated exogenous microglia may compensate the deficient enzyme to restore CNS disorders.

OS-02 Deficiency of autophagy and the pathogenesis of neurodegenerative disorders

Eiki Kominami¹

¹Juntendo University School of Medicine, Tokyo, Japan

Autophagy is a membrane trafficking mechanism that delivers cytoplasmic constituents into the lysosome/vacuole for bulk protein degradation. This mechanism is involved in the preservation of nutrient under starvation condition, as well as the normal turnover of cytoplasmic component. Aberrant autophagy has been reported in several neurodegenerative disorders, hepatitis and myopathies. Among the many Atg genes that regulate autophagy, Atg7, which encodes an E1-like enzyme common for the Atg8 (alias LC3)- and Atg12-conjugation systems, is a critical gene for autophagosome formation in eukaryotic cells. We generated conditional-knockout mice of Atg7, which is common E1 enzyme for ATG-systems. Atg7 was essential for ATG-conjugation systems and autophagosome formation, amino acids supply in neonates and starvation-induced bulk degradation of proteins and organelles in mice. Furthermore, Atg7-deficiency led to multiple cellular abnormalities, such as appearance of concentric membranous structure and deformed mitochondria, and accumulation of ubiquitin-positive aggregates. Our results indicate the important role of autophagy in the quality control of proteins and organelles in quiescent cells in addition to starvation response and thus, the impairment of autophagy may be linked to the pathogenesis of many neurodegenerative disorders with ubiquitin-inclusion. To investigate the pathological roles in mammal, we generated brain-specific knockout-mice of Atg7. In this conference, we will discuss the molecular mechanism of accumulation of ubiquitin-positive aggregates in autophagy deficient cells.

OS-04 The role of mitochondrial dysfunction in selective degeneration of dopamine neurons in Parkinson disease

Wakako Maruyama¹

¹Department of Geriatric Medicine, National Center for Geriatrics and Gerontology

In Parkinson disease (PD), selective cell death of nigro-striatal dopamine neurons and accumulation of modified and unfolded protein to make inclusion bodies are characteristic pathologic feature. The pathogenesis in PD is considered to be due to mitochondrial dysfunction, oxidative stress, and the impairment of ubiquitin-proteasome system (UPS). These factors interact each other, and in an animal model of PD prepared with a complex I inhibitor, rotenone, selective loss of dopaminergic neurons and inclusion bodies were detected. Mitochondria play a key role in this process, by decreased energy synthesis, generation of reactive oxygen species (ROS) and activation of apoptotic signaling. In addition to mitochondrial oxidative phosphorylation, oxidation of dopamine by monoamine oxidase and its autooxidation generate ROS in dopamine neurons. Especially non-enzymatic oxidation of dopamine produces superoxide, and also quinone and semiquinone, which produce neuromelanin (NM) by polymerization. NM accumulates in nigral dopamine neurons according to aging. The effects of NM isolated from human brain were examined on the mitochondria and the UPS system. It was found that NM increases ROS production through release of iron, insults mitochondrial function, and inhibits the ubiquitin-26S proteasome system. Mitochondrial dysfunction reduces the proteasome activity directly by oxidative modification of composing proteins, and indirectly by inhibition of 20S proteasome by binding of oxidatively modified proteins to the catalytic site further. These results suggest that mitochondrial dysfunction may determine the selective vulnerability of dopamine neurons in PD.

OS-05 Diversity of endoplasmic reticulum stress response

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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-termed stresses in the ER result in apoptotic cell death. 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). Cell fates after ER stress are regulated by the balance of both apoptosis and the UPR signaling. 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 cyclic AMP responsive element and ER stress responsive element, 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. In this symposium, in addition to the analysis of novel ER stress sensor, OASIS, our recent work regarding the autophagy activated by ER stress will be showed. Disturbance of autophagy rendered cells vulnerable to ER stress, suggesting that autophagy plays important roles in cell survival after ER stress.

JS1-01 The Effects of Antipsychotics on Neurogenesis and survival

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The atypical antipsychotics have superior therapeutic efficacy to treat not only positive symptoms but negative symptoms and cognitive dysfunctions with much lower potentials of side effects, although the key mechanism of these therapeutic potentials have not yet clarified. As the important pathophysiology of schizophrenia, brain morphological change has been emerged and discussed, and abnormality of neurogenesis has been considered as the key mechanism of brain neural network change as well as the decrease of neuronal survival. In the present study, we examined the influences of typical and atypical antipsychotics on the proliferation, migration and differentiation activity of rat embryonic neural stem cells (NSCs), and survival potential of neurons. In the mitochondrial and ER stressed conditioned, atypical antipsychotics have indicated the protective effect on neuronal damage in the assay of MTT. In those conditioned, promotional effects of neuronal differentiation were also found by atypical antipsychotics, in evaluation of counting MAP2 positive cells and ELISA. In addition, we attempted to investigate the intracellular signaling change in the NSCs and neurons. We found that different regulations of Akt and ERK signaling by typical and atypical antipsychotics were contributed to their different cellular functions. Moreover, the addition of antidepressant to the treatment of atypical antipsychotic increased neuronal differentiation of NSCs, but not changed protective effect of neurons. These results may suggest that the different potential on neurogenesis and neuronal survival function are the key mechanism of different clinical response of these psychotropic drugs, and alteration of trophic factor signaling is a important action of these drugs.

JS1-02 Stress vulnerability of the hippocampus in developing rat brain.

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Hippocampus has been intensively focused for recent two decades in the field of neuropsychopharmacology because it is highly stress-vulnerable brain region while at the same time it has potent electrophysiological, chemical, and anatomical neural plasticities. In the present study, we first examined effects of acute single footshock and/or 2-wk behavioral stress to developing 4-6wk aged rats for atrophy in hippocampal sub-regions and performed an immunohistochemical detection of BrdU incorporation in the subgranular zone (SGZ). Next, we measured XBP1 mRNA spliced/unspliced ratio in the rat hippocampus by RT-PCR method as a possible marker of intracellular unfolded protein response phenomenon in order to elucidate mechanisms that could be positively activated by behavioral stress loading. Statistically significant volume atrophy by 2-wk stress was observed in the hippocampal CA3 and granule cell layer, although no significant change of brain hemisphere volume was detected. The counts of BrdU incorporated cells in the SGZ detected significant and equivalent decrease of the number by both acute and chronic stress group compared to the control group, and no synergic sensitization or subsensitization were observed by the combination of chronic and acute treatment. For detection of XBP1 splicing, we first measured the spliced/unspliced mRNA ratio in the hippocampus and evaluated the change of the ratio by an application of endoplasmic reticulum Ca-ATPase inhibitor, thapsigargin (TPG), directly into the hippocampus. We found abundant existence of spliced XBP1 transcript also in the control vehicle treated hippocampus and significantly increased XBP1 splicing at 3 days after TPG injection. The change of XBP1 splicing by stress paradigms will be presented at the meeting.

JS1-03 Human Interferon-alpha suppressed cell proliferation through interleukin-1 production in adult rat dentate gyrus

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Therapeutic use of human interferon-alpha (hIFN- α), a cytokine derived from leukocyte, is known to cause various neuropsychiatric side effects. Especially depression occurs in 30-45% of patients, which frequently interrupts the treatment. hIFN- α treated animals have also been reported to show depression like behaviors, however, mechanisms underlying depression caused by hIFN- α are left to be defined. Recently, decrease in neurogenesis in the dentate gyrus has been considered as a possible neuropathological mechanism of depression. Various cytokines including several inflammatory cytokines are known to modulate neurogenesis, therefore, we investigated the effect of subchronic treatment of hIFN- α (5000-50000IU/kg/day) on neurogenesis in adult rat DG. The doses correspond to clinical doses, and have been also demonstrated to induce depressive behavior without reducing voluntary activity. hIFN- α , one week after the treatment, decreased BrdU-labeled proliferating cells in DG, while it did not affect cell differentiation into mature granule cells. With hIFN- α treatment, activated interleukin-1beta (IL-1 β), a major proinflammatory cytokine, increased in hippocampus. Co-administration of IL-1 receptor antagonist completely blocked the hIFN- α -induced suppression of cell proliferation in DG. Thus, our results demonstrated that hIFN- α suppressed cell proliferation, in which IL-1 β signal plays an essential role. Decrease of cell proliferation caused by hIFN- α induced IL-1 β may in part responsible to hIFN- α induced depression.

JS1-04 Mechanisms of action of antidepressants from the viewpoint of adult hippocampal neurogenesis

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Proliferation and maturation of neurons has been demonstrated to occur in the hippocampus of adult brain. These newborn neurons are suggested to play a role in several important neuronal functions including memory and response to novelty. Studies using magnetic resonance imaging have reported hippocampus volume is reduced in patients with depression. Recent studies from laboratories demonstrated that exposure to stress down-regulated and chronic administration of an antidepressant up-regulated neurogenesis in adult hippocampus. Moreover, we indicated the cAMP signal transduction cascade contributed to increased neurogenesis and the maturation of newborn cells. Taken together, these findings suggested the implication of hippocampal neurogenesis in antidepressant action. In the symposium, I would like to present the effect of lithium augmentation therapy to the hippocampal neurogenesis as well.

JS1-05 Expression of neurotrophic factor by antidepressant via mitogen-activated protein kinase (MAPK) activation

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Recent morphological studies provide evidence for glial reduction in particular brain areas in mood disorders. Thus, glial and neuronal remodeling such as expression of trophic factors may be involved in therapeutic action of antidepressants. Glial cell line-derived neurotrophic factor (GDNF), originally purified from a rat glioma cell line supernatant as a potent trophic factor, has been reported to have important roles in high-ordered brain function. In our clinical study, GDNF levels in whole blood in patients with mood disorders were significantly lower than those in healthy subjects, supporting a possible involvement of GDNF in mood disorders. In vitro study, we found that sub-chronic treatment with antidepressant increased both of GDNF mRNA and GDNF release in rat astrocyte and C6 glioma cells. These were completely and selectively inhibited by MAPK- extracellular signal-related kinase (ERK) kinase inhibitors. We also found acute activation (within five minutes) of MAPKs including not only ERK but also p38 MAPK and c-Jun N-terminal protein kinase by antidepressant. The extent of acute ERK activation and GDNF release by antidepressant was strongly correlated to each other, suggesting a key factor of ERK activation on GDNF expression by antidepressants. Although serotonin (5-HT), as well as antidepressant, induces both of acute ERK activation and GDNF expression in C6 cells, the antidepressant-induced action is independent of 5-HT, because the cells do not express 5-HT by themselves. These data suggest a possible existence of monoamine-independent target of antidepressant for GDNF expression. We are currently investigating the novel target of antidepressant-induced ERK activation, which seems to be related to the remodeling of neuronal and glial network.

JS1-07 The neurochemical mechanism of action of the anxiolytic effect of selective serotonin reuptake inhibitor: its effect on the amygdala

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Selective serotonin reuptake inhibitors (SSRIs) have wide indications for the treatment of various anxiety disorders, including panic disorder, generalized anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder and social anxiety disorder in addition to depression. Until recently, no animal model has been available for screening the anxiolytic effect of SSRIs and studying its mechanism of action. We have investigated the relationship between serotonin neurotransmission and anxiety using conditioned fear stress (CFS), an animal model of anxiety. CFS increased serotonin neurotransmission in the medial prefrontal cortex and amygdala. In behavioral pharmacological studies, SSRIs, serotonin_{1A} agonists and monoamine oxidase inhibitors, which are assumed to facilitate serotonin neurotransmission, decreased conditioned freezing, an index of anxiety or fear, in CFS. In vivo microdialysis studies showed that serotonin neurotransmission in the medial prefrontal cortex increased after recovered from the freezing behavior. Microinjection of SSRI to the basolateral nucleus of the amygdala reduced conditioned freezing, indicating that the amygdala is one of target brain sites of anxiolytic action of SSRIs. Furthermore, CFS-induced c-Fos expression in the basolateral nucleus of the amygdala was reduced by SSRI pretreatment. Taken together, recent studies suggest that the anxiolytic effect of a selective serotonin reuptake inhibitor in conditioned fear is mediated by its effect on the amygdala, and support the hypothesis of serotonin function in anxiety by which facilitation of serotonin neurotransmission decreases anxiety in agreement with the clinical evidence.

JS1-06 Neuron-Glial interaction as a novel target system for antidepressant

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Although antidepressants have been used clinically for more than 50 years, no consensus has been reached concerning their precise molecular mechanism of action. Pharmacogenomics is a powerful tool that can be used to identify genes affected by antidepressants or by other effective therapeutic manipulations, i.e., chronic lithium treatment, repeated ECT and rTMS. Using differential cloning strategy, we have previously identified several cDNA fragments as antidepressant related genes. Some of these genes are expressed in glial cells in the brain. Neuron-Glial interaction may play a critical role in the effects of antidepressant as a novel target. Defining the roles of these genes in drug-induced neural plasticity is likely to transform the course of research on the biological basis of mood disorders. Novel biological approaches beyond the monoamine hypothesis are expected to evoke paradigm shifts in the future of depression research. Here, we introduce some of the new candidate molecules and molecular systems in antidepressant research.

JS1-08 Regulation of TH activity in rat locus coeruleus after chronic variable stress

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The tyrosine hydroxylase (TH) containing neurons in the nucleus locus coeruleus (LC) is known to receive both an excitatory corticotropin-releasing hormone (CRH) and an inhibitory GABA neural inputs in the pericellular dendritic zone (peri-LC). The CRH and norepinephrine (NE) play roles in modulating the stress response. We previously found a decrease of the basal level of CRH immunoreactivity (-ir) in the paraventricular nucleus of rats treated with chronic variable stress (CVS) for 14 days. Furthermore a novel stressor augmented the CRH response after CVS. In the present study we examined the influence of CVS on the TH-ir and glutamic acid decarboxylase (GAD)-ir of LC. TH-ir was significantly decreased in LC after CVS, and footshock-induced reactivity in TH-ir was increased in LC after CVS. Concurrent clomipramine or fluvoxamine treatment prevented both the CVS-induced sensitization and the delayed hypoactivity of the TH, suggesting that an increase in a serotonin availability contributes to the normalization of both hypoactivity and sensitization of LC-NE neurons modified under stressful situation. GAD-ir was significantly increased in peri-LC by a single footshock and a slight but significant increase was continued after CVS while the footshock-induced GAD-ir increase in peri-LC was attenuated after CVS. Moreover, we investigated the influence of the CRH receptor antagonist, α -h-CRH (i.c.v.) on the CVS-induced activation of the TH-ir in the LC. The α -h-CRH i.c.v. diminished the enhanced-TH reactivity by novel stressor after CVS. Our results suggest that stress-induced activation of the LC-TH response might be regulated by GABA input in peri-LC, and also the CRH input from central nucleus of amygdala and/or the bed nucleus of stria terminalis might regulate the TH reactivity.

JS1-09 Effects of Haloperidol, Lithium, Imipramine and Diazepam on Amygdalic Nitrate Levels

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Nitric oxide (NO) has been studied in relation to the etiologies of various psychiatric diseases, including mood disorders, schizophrenia, and anxiety disorders. However, little is known about whether clinically available psychotropic drugs affect the NO system in the brain.

This study was designed to examine whether intraperitoneally injected psychotropics change NO levels in the rat amygdala, which is an important area for emotional and affective disorders.

We determined levels of NO₂- and NO₃-, final oxidation products of NO measurable in-vivo, using an in-vivo brain microdialysis method. The psychotropics tested in this study were haloperidol (antipsychotic agent; 1.0 mg/kg), lithium chloride (mood stabilizer; 50 mg/kg), imipramine (anti-depressant; 20 mg/kg), and diazepam (anxiolytic; 0.5 mg/kg). This study was approved by the Kitasato University School of Medicine Animal Experiments and Ethics Committee.

Between 60 and 90 min after Li administration, NO₃- levels were significantly lower than those of control animals ($p < 0.05$). Between 20 and 60 min after IMP administration, NO₃- levels were significantly higher than those of controls ($p < 0.05$). From 120 min after haloperidol administration onward, NO₃- levels were significantly higher than those of control rats ($p < 0.05$).

These observations suggest that lithium and imipramine acutely induce opposite effects on NO-related systems in the amygdala. Therefore, there might be a relationship between the amounts of NO produced in the amygdala and mood states.

Haloperidol induced a long-lasting excitatory effect on the NO-system. There is a possibility of effect being involved in the antipsychotic actions of haloperidol. The anxiolytic effect of diazepam dose not, however, involve the NO-system.

JS1-10 THE long-term lithium treatment increased GAP-43 mRNA by bHLH transcription factor in rat brain

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Lithium is a mood stabilizer used in treatment of bipolar disorders. We reported that GAP-43 protein was induced after 4-5 weeks lithium treatment. We examined the GAP-43 mRNA expression after long-term treatment with lithium in the rat brain. GAP-43 mRNA also increased in rat cerebral cortex after 4-5 weeks treatment with lithium. We detected the E-box binding protein to the GAP-43 promoter by gel shift assay. MATH-2 antibody inhibited the E-box binding protein to bind the GAP-43 promoter in gel shift assay. Therefore, it was recognized that E-box binding protein was MATH-2. MATH-2 increased the activity about 2.5 times compared with control in luciferase assay, and MATH-2 regulated GAP-43 gene expression than the other transcription factors. MATH-2 protein level increased about 4 times after 5 weeks lithium treatment. We considered that MATH-2 induced increase of GAP-43 RNA and GAP-43 protein level after lithium treatment. 5 weeks lithium treatment increased in the MATH-2 protein level about 4 times by immunoblot. Long-term lithium treatment translocated MATH-2 to nucleolus and nuclear membrane by immunohistochemistry. GAP-43 is known to play an important role in the releasing process for several neurotransmitters (ACh, 5-HT and DA). It was considered that the long-term lithium treatment regulated GAP-43 and release of neurotransmitters by MATH-2.

JS2-01 Clinical pharmacogenetics in the treatment of schizophrenia

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Numerous investigations on metabolic enzymes, cytochrome P450 (CYP) have been conducted since 1990. In the psychiatric field, the focus has been on CYP2D6, which is a major enzyme involved in metabolism of antidepressants and antipsychotics. Poor metabolizers (deficit metabolizers) for CYP2D6 represent 7% among Caucasians, while they account for less than 1% of Asian. The frequency of mutated allele for CYP2D6*10, which leads the decrease in CYP2D6 activity, is 40% in Asian. It has been reported that steady-state plasma concentration of haloperidol in subjects with mutated alleles for CYP2D6 is significantly higher than that in subjects without mutated alleles. At the same time, steady-state plasma concentration of risperidone differs between CYP2D6 genotypes. In addition, several studies suggest that better efficacy or higher scores of side effects are observed in the subjects with mutated alleles for CYP2D6. Recently receptor polymorphism has become a concern and association between clinical response and polymorphism of dopamine and serotonin has been reported. In the dopamine D2, subjects with -141C Ins allele in -141C Ins/Del polymorphism and subjects with A1 allele in Taq 1A have a better response to dopamine antagonists. Association between Ser allele and typical antipsychotics and between Gly allele and atypical antipsychotics has been investigated. There are still no data indicating significant association between dopamine D4 and clinical response to antipsychotics. Clinical pharmacogenetical studies from both a pharmacokinetical point and a pharmacodynamical point of views are required in order to introduce and practice the individualized medicine in psychiatric field easily.

JS2-03 Gene expression analysis of mitochondria-related genes in bipolar disorder using DNA microarray

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Accumulating evidence suggests mitochondrial dysfunction in bipolar disorder. Analyses of mitochondria-related genes using a DNA microarray showed significantly increased *LARS2* (mitochondrial leucyl-tRNA synthetase) in the postmortem prefrontal cortices of patients with bipolar disorder provided by the Stanley Foundation Brain Collection. *LARS2* is a nuclear gene encoding the enzyme catalyzing the aminoacylation of mitochondrial tRNA^{Leu}. A well-studied mitochondrial DNA point mutation 3243A>G in the region of tRNA^{Leu} (UUR), related with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), is known to decrease the efficiency of aminoacylation of tRNA^{Leu}. We found that *LARS2* was upregulated in the transmitochondrial cybrids carrying 3243A>G. Thus, we postulated that upregulation of *LARS2* is a hallmark of 3243A>G mutation. We examined the 3243A>G mutation in these brains using the PNA (peptide nucleic acid)-clamped PCR-RFLP method. The 3243A>G was detected in the postmortem brains of two patients with bipolar disorder and one with schizophrenia. These patients also showed higher levels of the mutation in their liver and significantly higher gene expression of *LARS2* compared with other subjects. These results suggest that the accumulation of 3243A>G mutation in the brain has a pathophysiological role in bipolar disorder and probably in schizophrenia.

JS2-02 Genome-wide affected sibpair linkage analysis of schizophrenia in the Japanese Families

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The Japanese Schizophrenia Sib-pair Linkage Group (JSSLG), a multi-site collaborative study group, was established to create a national resource for genetic studies of schizophrenia in 1997. The main purpose of the group is to determine if there are common genes that contribute to the susceptibility for schizophrenia in the Japanese population by affected sibpair analysis. First-stage genome-wide scan was carried out by genotyping 417 short-tandem repeat (STR) markers in 338 individuals from 130 families with 148 affected sibpairs identified at 16 sites nationwide in Japan. Multipoint nonparametric linkage analysis resulted in no loci in the initial screen fulfilled the criteria for significant or suggestive evidence for linkage. Susceptibility genes with λ s of 3 and 2 were excluded from 98% and 70% of the genome, respectively. The second-stage scan was carried out by genotyping 5,861 SNPs of the Illumina's SNP-based linkage panel IV in 602 individuals from 236 families with 267 affected sibpairs identified at 27 sites. The panel have 0.64 cM of the average genetic distance between uniquely mapped SNPs and an average minor allele frequency (MAF) was 29% in the JSSLG families. The rate of Mendelian inconsistency or impossible recombination identified by the MERLIN program was 0.027% in the families with parents indicating approximate genotyping error rate of less than 0.1%. The information content was increased from 57% in the first screening to 71% at the point of the markers. Significant and suggestive evidence for linkage was obtained at several regions, though they were estimated with λ s < 1.4. JSSLG linkage data will serve to evaluate genomic contributions to susceptibility to schizophrenia in the Japanese population.

JS2-04 Genome-wide linkage and association studies of schizophrenia

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Schizophrenia is a devastating neuropsychiatric disorder with a multifactorial background. To search for schizophrenia susceptibility loci, we are taking three genetic approaches as follows, I) Genome-wide linkage study: The Japanese Schizophrenia Sib-pair Linkage Group (JSSLG) carried out a first-stage genome-wide scan by genotyping 417 STR markers of 338 individuals from 130 families. No evidence for linkage was obtained. However 10 chromosomes had at least one region with a nominal p value < 0.05. We selected the region of chromosome 5 for the association study because of supportive observations of the previous linkage studies, and found significant association of 2 genes with schizophrenia. II) Genome-wide association study: We started the case-control study using 25,000 STR markers distributed across the entire genome. To overcome the type I error due to multiple comparison tests, we planned three sequential steps of screening using the independent sample set each. To date the first pooled sample set has been genotyped for 10,078 markers. Significant associations were found for 864 markers with the disease. The first screening with remaining markers and the second screening using the markers survived after the first one are on the way. III) Locus-wide association study: Since the glutamatergic dysfunction hypothesis was proposed for the pathogenesis of schizophrenia, we have been conducting a systematic study of associations of glutamate receptor genes and glutamate transporter genes with schizophrenia. To increase the statistical power of the studies, we selected a number of common SNPs to cover the entire gene region with linkage disequilibrium. We found associations of *GRIN2D*, *GRIA4*, *GRM3*, *GRM8* and *SLC1A2* with schizophrenia.

JS2-05 Molecular Genetical Approach to Neuropsychiatric Diseases from single gene diseases

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Most psychiatric disorders are thought to be etiologically multifactorial and have challenged researchers to define the genes and mechanisms that contribute to the complex diseases. Psychiatric disorders are diagnosed as clinical entities, and symptoms range widely and show variety of courses even in a single clinical entity such as schizophrenia. Thinking of this variety, there is an interesting and definite fact that patients with apparently identical genotypes can have many different clinical conditions in single gene diseases. 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 disease-responsive gene, CHAC or VPS13A. Although ChAc had been recognized as an autosomal recessive hereditary disease, several reports were suggestive of autosomal dominant inheritance. Variety of disease-responsive mutations in ChAc patients have been reported, but only a single heterozygous mutation was found in some patients. A Japanese autosomal dominant ChAc-family with a single heterozygous mutation in the VPS13A gene in the affected members was also reported. Recently we found a ChAc-family in which 4 out of 5 family members possessing the mutation heterozygously showed mild but obvious symptoms related to ChAc. Then we hypothesize the presence of modifier genes and try to identify them using human samples and gene-targeted model mouse.

SY1-01 Effects of homocysteine on amyloid β -protein generation

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The characteristic pathological feature of the brains of individuals with Alzheimer's disease (AD) is the deposition of the amyloid β -protein (A β). Interestingly, it is strongly suggested that hyperhomocysteinemia is a risk factor for AD. However, the molecular basis underlying the association of elevated homocysteine level with an increased risk for AD is unclear. Recently, we have identified Herp as an enhancer of A β generation (Sai et al., J. Biol. Chem. 277:12915, 2002), although it was identified as a homocysteine-induced protein (Kokame et al., J. Biol. Chem. 276:32846, 2000). Previously, we showed that the overexpression of Herp in the cells enhances presenilin (PS)-mediated A β generation, possibly through the binding of Herp to PS. This suggests that the up-regulation of Herp by a high homocysteine level contributes to A β accumulation. Thus, to determine whether homocysteine level affects A β generation, we investigated the effect of the homocysteine treatment of cells on A β generation. We found that the treatment of cells with a high homocysteine level caused a reduction in A β generation, probably due to the toxic effect of homocysteine, which was accompanied by Herp induction. In addition, the treatment of cells with a high homocysteine level changed the ratio of the levels of A β 42 versus A β 40. Taken together with our previous results showing that Herp mainly enhances A β 40 generation, it is suggested that a high homocysteine level affects the ratio of A β 42 generation compared with that of A β 40 generation through Herp upregulation. In this symposium, we will discuss the possible pathogenic roles of homocysteine in AD, including its role in A β generation.

SY1-03 Cholesterol and Alzheimer's disease: Apolipoprotein E-mediated cholesterol metabolism in the central nervous system

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Apolipoprotein E (apoE) alleles are associated with development of Alzheimer's disease (AD), with the ϵ 4 allele increasing and the ϵ 2 allele decreasing risk for developing AD. ApoE is the major apolipoprotein that modulates cholesterol transport in the central nervous system. Importantly, there is an isoform dependence to apoE-mediated lipid efflux with apoE2 being the most effective and apoE4 being the most ineffective. We have defined the dependence of lipid efflux on apoE polymorphism in neuronal culture system using the various engineered forms of apoE to elucidate the mechanisms underlying apoE-mediated lipid efflux from neurons. The importance of altered cholesterol metabolism in AD development has been suggested by epidemiological studies. Biological studies have shown amyloid β -protein (A β) secretion being modulated by cellular cholesterol level. However other lines of evidence show controversial results. In addition to the role of cholesterol in A β generation, different interactions of cholesterol with A β and its role in AD pathogenesis have been shown, that is, A β affects cholesterol dynamics in neurons, and altered cholesterol metabolism in turn leads to neurodegeneration with abnormally phosphorylated tau (tauopathy). In this review, the reciprocal interactions between cholesterol and A β , and the role of cholesterol in tauopathy are discussed. The isoform-specific involvement of apoE in this cascade, in which high-density lipoprotein (HDL)-like particles are generated and supplied to neurons to maintain cholesterol homeostasis, is also discussed.

SY1-05 Mitochondrial genome polymorphisms associated with longevity or Alzheimer's disease

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Human life span in ancient history was much shorter than that at the present time. Therefore it is reasonable to speculate that certain mitochondrial single nucleotide polymorphisms (mtSNPs) that predispose one toward susceptibility to adult- or elderly-onset diseases, such as Parkinson's disease and Alzheimer's disease, have never been a target for natural selection in the past. To examine these hypotheses, we have constructed a mtSNP database (http://www.giib.or.jp/mtsn/index_e.shtml) by sequencing the entire mitochondrial genomes from 672 subjects: 96 in each of 7 groups, i.e., centenarians, young obese or non-obese subjects, diabetic patients with or without major vascular involvement, patients with Parkinson's disease, and those with Alzheimer's disease (Genome Res 14: 1832, 2004). A mtSNP, 199T-C in the major noncoding region, was detected in 8 of the 96 patients with Alzheimer's disease, whereas this substitution was detected in 20 of the 96 centenarians. This 199T-C transition associated with longevity was detected in various haplogroups. Another mtSNP, 13651A-G (NDS: Thr439Ala), was not detected in 96 patients with Alzheimer's disease, whereas this substitution was detected in 5 of the 96 centenarians. This 13651A-G transition represents haplogroup D4a. Two synonymous mtSNPs, 5147G-A and 5417G-A in the ND2 gene, were detected in 9-10 of the 96 patients with Alzheimer's disease, whereas these substitutions were detected in 2 of the 96 centenarians. The 5147G-A and 5417G-A transitions predisposing to Alzheimer's disease represent haplogroup N9b. These results suggest that these distinct mtSNPs contribute to susceptibility to Alzheimer's disease. Present data point out necessity of large-scale case control studies and functional analysis of mitochondria.

SY1-02 How do omega-3 fatty acids effect Alzheimer's disease

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Epidemiological studies have suggested that diet may play a role in Alzheimer's disease (AD). Fruits, vegetables, fish, and vitamin C, vitamin E, α - β -carotene, B vitamins, folate, and n-3 polyunsaturated fatty acid (PUFA) are protective factors. In contrast, excess intake of total caloric, fat, saturated fatty acids, and hydrogenated fatty acids are risk factors of AD. So, a high antioxidant, low saturated fat/low caloric diet pattern is recommended at present for prevention of AD.

n-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are rich in marine products and n-6 PUFA linoleic acid and arachidonic acid (AA) are rich in animal fat. Increased intake of fish is associated with reduced risk of AD. n-3 PUFA levels are lower in serum and brains of AD patients. n-3 PUFA may exert their effects through several mechanisms including decrease in oxidative stress, decrease in cardiovascular risk factors, (hypertension, diabetes mellitus, insulin resistance, hyperlipidemia), anti-thrombotic, anti-arrhythmic, or anti-inflammatory, or direct effects on neuronal cell membrane fluidity.

Though, effects of ω -3 PUFA on Alzheimer pathogenesis, particularly on amyloidosis (amyloid β protein; A β) are unknown, recent studies have shown supplementation of n-3 PUFA in the diet restored behavioral deficits and learning activity in APPsw (Tg2576) transgenic mouse. Plaque burden was significantly reduced in these animals. A deficiency of DHA affects neurotransmission, membrane-bound enzyme and ion channel activities, gene expression, intensity of inflammation, and synaptic plasticity. It is also suggested changes in physico-chemical properties of membrane fluidity by the deficiency of DHA may alter enzyme activities of α and γ secretase of APP.

SY1-04 Anti-amyloidogenic effects of polyphenols: implications for the prevention and therapeutics of Alzheimer's disease

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Alzheimer's disease (AD) is characterized by deposition of amyloid β -peptide (A β) in the brain. Epidemiological studies have suggested protective effects of wine-related and other polyphenols on AD. We examined the effects of wine-related polyphenols (myricetin, morin, quercetin, kaempferol, (+)-catechin and (-)-epicatechin), curcumin, rosmarinic acid, and polymeric polyphenol, tannic acid, on the formation, extension, and destabilization of β -amyloid fibrils (fA β) at pH 7.5 at 37 °C *in vitro*, using fluorescence spectroscopy with thioflavin T and electron microscopy. All examined polyphenols dose-dependently inhibited formation of fA β from fresh A β (1-40) and A β (1-42), as well as their extension. Moreover, these polyphenols dose-dependently destabilized preformed fA β s. The overall activity of the molecules examined was in the order of: tannic acid > myricetin = morin = quercetin = curcumin = rosmarinic acid > kaempferol > (+)-catechin = (-)-epicatechin. In cell culture experiments, myricetin-treated fA β were suggested to be less toxic than intact fA β , as demonstrated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. Although the exact structure-activity relationships for the anti-amyloidogenic effects of the polyphenols are still unclear, polyphenols could be key molecules for the development of preventives and therapeutics for AD.

SY2-01 Do-it-all or simply single minded? The role of Zic genes in neural development

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The Zic family genes encode nuclear zinc-finger proteins located in developing nervous system. Recent studies of human, mouse, frog, fish and ascidian Zic homologues have provided evidence that Zic genes are involved in neural development at various developmental stages. They control the initial phase in which ectoderm differentiates into neuroectoderm, and may act as a bridge between secreted neural tissue induction signals and the basic-helix-loop-helix class of neurogenesis-inducing transcriptional regulatory factors. Loss-of-function mutation analyses with different Zic gene subtypes have shown that the Zic family of genes controls the process of neurulation. Mutations result in neural tube defects, which are seen at different rostrocaudal levels, depending on which particular Zic gene subtype has been affected. The development of holoprosencephaly, forebrain anomalies, and cerebellar dysgenesis, indicates that region-specific morphogenesis of the CNS is also controlled by Zic genes. In addition, Zic can control retinal axon guidance at optic chiasm, which is essential for the establishment of binocular function. The underlying molecular actions of Zic gene products that allow them to act as developmental controllers are main targets of our current research. Recent molecular characterization revealed that Zic proteins are able to enhance gene expression of many developmentally critical genes such as Wnts, CyclinD1 and Notch. Zic proteins can physically and functionally interact with Gli proteins, raising a possibility that Zic can modulate the hedgehog-signaling pathway. Further identification and characterization of the Zic binding proteins may be important for the comprehensive understanding of the Zic-mediated developmental processes.

SY2-02 A role of PTF1a, a bHLH transcription factor, in neuronal subtype specification

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The molecular machinery governing glutamatergic-GABAergic neuronal subtype specification is unclear. We would like to introduce a novel cerebellar mutant, *cerebelless*, which lacks the entire cerebellar cortex in adults. The primary defect of the mutant brains was a specific inhibition of GABAergic neuron production from the cerebellar ventricular zone (VZ), resulting in secondary and complete loss of external germinal layer, pontine and olivary nuclei during development. We identified the responsible gene, *Ptf1a*, whose expression was lost in the cerebellar VZ but maintained in the pancreas in *cerebelless*. Lineage tracing revealed two types of neural precursors exist in the cerebellar VZ: *Ptf1a*-expressing and non-expressing precursors, which generate GABAergic and glutamatergic neurons, respectively. Introduction of *Ptf1a* into glutamatergic neuron precursors in the dorsal telencephalon generated GABAergic neurons with representative morphological and migratory features. Our results suggest that *Ptf1a* is involved in driving neural precursors to differentiate into GABAergic neurons in the cerebellum.

SY2-04 Regulation of brain functions by δ FosB, a naturally occurring truncated form of FosB

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Jun and Fos proteins play important roles as components of an AP-1 complex, to regulate the transcription of genes involved in various neuronal responses in brain. Among the four members of fos family genes, only the *fosB* gene forms two mature mRNAs, *fosB* and Δ *fosB* by alternative splicing, each of which encodes FosB and Δ FosB, respectively. Δ FosB lacks the C-terminal 101 amino acid region of FosB with strong transactivating domains. FosB and Δ FosB form heterodimers with each Jun protein, thereby stimulating the DNA binding activities. FosB and Δ FosB can either upregulate or downregulate the expression of subsets of genes in an antagonistic manner. A basal expression of *fosB* is detected in some neurons scattered throughout the brain cortex, and in the hippocampus. The *fosB* expression is rapidly and transiently induced in brain in response to various stimuli, while chronic stimulation of brain dramatically and selectively increases the level of Δ FosB in the brain. It has been reported that *fosB*-null and Δ FosB transgenic mice both exhibit increased sensitivity to the rewarding and locomotor-stimulant effects of cocaine, thus puzzling us how FosB and Δ FosB regulate brain functions. To distinguish functions of FosB and Δ FosB in brain, we established a mutant mouse line expressing only Δ FosB from the endogenous *fosB* gene, and *fosB*-null mice lacking both FosB and Δ FosB expression. We found that mice expressing only Δ FosB exhibit a hyperactive phenotype judging from locomotor analysis as well as behavioral analyses in the open field and elevated plus maze, while *fosB*-null mice exhibit a hypoactive phenotype in comparison to the wild type. Furthermore, we found that the mice expressing only Δ FosB but not *fosB*-null mice exhibit an increased resistance to excitotoxicity in brain.

SY2-03 Using Chemical Probes to Dissect the Calcineurin/NFAT Pathway Signaling in Neural Development

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The proper wiring of the mammalian nervous system relies on the nerve growth cone to respond to guidance cues. For these guidance cues to be effective in the complex and dynamic field of embryonic morphogenetic signals, the immediate turning events must be coupled with more elaborate responses in the nucleus. While the membrane proximal signaling pathways are beginning to be understood, relatively little information is available about the propagation of these signals to the nucleus, the integration of multiple concomitantly active signaling pathways and their downstream transcriptional programs, which affect axonal extension and guidance decisions. We have recently found that NFATc family of transcription factors function in the control of neuronal morphogenesis by conveying netrin and neurotrophin signals to the nucleus, leading to the direct activation of genes essential for neurite outgrowth. We are using a combination of classical genetics and chemical genetics to identify the targets of the calcineurin/NFAT pathway targets that control axon extension in the developing embryo.

SY2-05 Regulation of memory formation by transcription factor CREB

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Memory consolidation requires new gene expression. Previous genetic studies have shown that the loss of function of transcription factor CREB leads to an impairment of memory consolidation, indicating that CREB is an essential molecule for this process. These findings raise the possibility that the gain of function of CREB leads to enhancement of memory consolidation. To examine this hypothesis, we have generated transgenic mice up-regulating CREB activity using CREB Y134F mutant, which is more sensitive to CREB kinases than wild type CREB (MCB, 20, 4320-, 2000). Our in vitro studies using Fluorescence Resonance Energy Transfer (FRET) indicated that weak activation of CREB kinases is enough to induce an interaction of transcription coactivator CBP with this mutant CREB, resulting in activation of CREB-mediated transcription. We generated transgenic mice overexpressing this mutant in forebrain under the control of α -CaMKII promoter. These mutant mice showed the up-regulation of expression of CREB target genes, indicating this active CREB mutant is functional in vivo. In contextual fear conditioning, mutant mice showed normal 30min memory but enhanced 24hrs memory, suggesting that these mutant mice show the enhancement of memory consolidation. Consistent with this, these mutant mice also shows significantly better performance in Morris water maze. Furthermore, aged mutant mice did not show an impairment of long-term fear memory, suggesting that up-regulation of CREB activity rescues an impairment of memory consolidation with aging. From these findings, we concluded that up-regulation of CREB activity leads to enhancement of memory consolidation. CREB, especially, CREB-CBP interaction might function as a molecular switch to determine strength of memory.

SY3-01 The physiological mechanisms behind psychosomatic disease

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Using mouse models, our research group has recently been investigating the physiological mechanisms underlying the psychosomatic aspects of diseases such as asthma, insulin-dependent diabetes, chronic rheumatoid arthritis, and hepatitis. In these basic experiments, we employed social disruption stress, social isolation stress, and communication box-induced psychological stress as psychosocial stress paradigms. Interestingly, psychological stress at a young age exacerbated the airway inflammation of adult ovalbumin (OVA)-sensitized animals, with the number of mononuclear cells and eosinophils and the IL-5 levels in the bronchoalveolar lavage being significantly elevated in a stress group compared with a control group. Furthermore, this stress-induced exacerbation of airway inflammation was completely inhibited by prior-treatment with RU-486, a glucocorticoid antagonist, before stress-exposure. Together with the present finding that the serum OVA-specific IgE levels failed to diverge in comparison of the control and stress groups, these results indicate that a transient activation of the hypothalamic-pituitary-adrenal (HPA) axis at a young age is related to the local inflammatory response of adult asthma. In a hepatitis model of NKT cell-dependent apoptosis, both electric foot-shock stress and social disruption stress aggravated liver injury via an elevation of the number of liver NKT cells and the expression of Fas on hepatocytes. Such stress-induced changes in the liver were found to be dependent on activation of the HPA axis. Presented in detail are our newly observed findings based on mouse models of several diseases.

SY3-02 Stress responses and depression under the influence of environmental chemicals

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The central nervous system is highly sensitive to environmental chemicals especially during the critical period of brain development. Intrauterine exposure to diethylstilbestrol, a synthetic estrogenic compound, has been shown to increase the incidence of depression and anxiety in human patients. Similar phenomena have been found in rats receiving intrauterine exposure to bisphenol A (BPA), a typical endocrine disrupter. Prenatal exposure to BPA increased immobility time (an index of depressive behavior) in the forced swimming test and avoidance responses to odors of predators in the odor avoidance test. Perinatal exposure to low dose of endocrine disrupters, such as BPA, diethylhexyl phthalate (DEHP) and tributyltin (TBT) impaired sexual differentiation of open field behavior and passive avoidance learning. In the open field test, control female rats were more active and explored more frequently than male controls. In the passive avoidance test, control male rats learned better than females. All treated groups did not show the sexual dimorphism. The sex difference in the volume of the locus coeruleus LC (female > male) was also abolished in all treated groups. Furthermore, sexual differentiation of neuronal odor responses and expression of estrogen receptors in the medial amygdala were impaired by BPA. In contrast to the endocrine disrupters, exposure to plant-derived environmental chemicals such as green odor reduced stress responses such as swimming-induced fatigue-like responses, aggressive responses to the intruder and activation of hypothalamo-pituitary-adrenal axis. These findings suggest that the artificial and natural environmental chemicals have diverse but opposite effects on higher brain functions including emotional control and stress managements.

SY3-03 Neonatal isolation induces susceptibility to learned helplessness, an animal model of depression, in adulthood rats

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Adverse childhood experience may induce the vulnerability to stress later in life, resulting in an increased risk for the development of stress-related disorders, such as depression. However, the mechanism of the stress vulnerability remains to be unknown. We have investigated the influence of neonatal isolation (NI) on the susceptibility to learned helplessness (LH), an animal model of depression in rats. Pups were individually isolated from the mother, nest and siblings for 1 h/day from postnatal days 2 - 9. In adulthood, we measured the number of escape failures and the escape latency 24 hours after exposure to a 40 min session of 0.8mA inescapable shock. Our behavioral analyses revealed that the population of learned helplessness in NI rats was markedly higher than that in non-isolated rats. Without inescapable shock, learned helplessness was induced in neither NI nor non-isolated rats. These findings suggest that isolated experience in neonatal period may alter profound long-term behavioral reactivity to stress later in life. In addition, we investigated to identify genes involved in the molecular mechanism underlying the susceptibility to learned helplessness found in NI rats, using a cDNA microarray technique. Based on the results of the cDNA microarray followed by real-time quantitative PCR analysis, the hippocampal levels of LIMK-1 and GABA-B receptor 2 mRNA in the LH rats subjected to NI are significantly lower than those in non-LH rats without NI. Furthermore, NI alone significantly decreases the levels of LIMK-1 mRNA, not GABA-B receptor 2. These findings suggest that long-term reduction in hippocampal LIMK-1 mRNA expression may be involved in the susceptibility to LH in the NI rats.

SY3-05 Novel candidate genes for stress responses in the brain

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The capacity of response to stressor is one of the most basic and important mechanisms in mammals. The dysfunction of molecular cascades and neural systems of the stress response may be involved in the pathophysiology of psychiatric disorders such as depression and stress-related disorders. We investigated the effects of pharmacological stressors (FG 7142 and yohimbine) and immobilization stress on gene expression in the cerebral cortex of mice. The DNA microarray experiment revealed novel candidate genes for stress responses in the neocortex of adult mice one hour after treatment with FG 7142 (20 mg/kg, i.p.), a partial inverse agonist of benzodiazepine sites within the GABA_A receptor complex. The upregulations of the candidate genes were confirmed by a quantitative real-time RT-PCR method. Moreover, there were statistically significant elevations in mRNAs of three genes (BTG2, CCN1 and Adamts1) in the cortex after immobilization stress (one hour). The injection of yohimbine (5mg/kg, i.p.; an antagonist of α -2-adrenergic receptors) produced significantly elevated mRNAs of BTG2 and CCN1 in the brain area. In addition, the increasing effects of FG 7142 on the mRNA levels of BTG2, CCN1 and Adamts1 were completely reversed by co-administrations of flumazenil, an antagonist of benzodiazepine receptors. In the experiment of in situ hybridization, the FG 7142-induced BTG2 gene expression was also demonstrated in the brain. Consequently, the present study provided a new insight into the molecular basis of stress responses in the brain. The stress-responsive genes could be involved in the pathophysiology of the stress-related psychiatric disorders.

SY4-02 Accelerated demethylation in an astrocyte specific gene promoter mediated by Notch-signaling

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Neurons and astrocytes are generated from common neural precursor cells, but astrocyte differentiation normally occurs during the late stage of brain development. We have previously reported that GFAP-positive astrocyte differentiation is dependent on the transcriptional activity of STAT3. A CpG dinucleotide in the STAT3 recognition sequence within the GFAP gene promoter is highly methylated at midgestation which becomes demethylated as the brain develops, enabling STAT3 to induce GFAP expression. This demethylation correlates closely with the onset of astrocyte differentiation. Thus, it is conceivable that the epigenetic modification such as DNA methylation of cell type-specific gene promoter controls the switch from neurogenesis to astrocytogenesis in the developing telencephalon. Notch is a pluripotent transmembrane protein, which is participated in the various types of biological processes. Here we report that the activation of Notch-signaling causes precocious cytokine-induced astrocyte differentiation of neural precursors at midgestation. Furthermore, the activated Notch-signaling accelerate demethylation of specific CpG sites including STAT3 binding element in the GFAP gene promoter. Inhibition of Notch-signaling prevented both the differentiation of GFAP-positive astrocytes and demethylation of GFAP gene promoter in the neural precursors. These data suggest that Notch-signaling is involved in the change of DNA methylation status that regulates the fate specification of neural precursors in the fetal brain.

SY3-04 Molecular pathophysiology of bipolar disorder

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Among depressive disorders, some subtypes are especially refractory to conventional treatment. Such disorders include vascular depression, depression with personality disorders, and bipolar spectrum disorders. Because it is reported that nearly half of young patients with severe depression will later develop bipolar disorder, its neurobiological study will also contribute to the development of new treatment for refractory depression. Although stress is an important trigger of first episode of bipolar disorder, patients gradually become vulnerable to stress, and the interval to the next episode shortens with relapse. This suggests that bipolar disorder is somehow a disorder of neuroplasticity. While it is generally accepted that genetic factors contribute to the onset of bipolar disorder, its neurobiological basis is still enigmatic. Recently, neuroprotective effects of mood stabilizers have drawn attention. We have been focusing on mitochondrial dysfunction in bipolar disorder based on findings of disordered brain energy metabolism detected by phosphorus-31 magnetic resonance spectroscopy, comorbidity of mood disorders with mitochondrial disorders, and associations with mutations or polymorphisms of mitochondrial DNA (mtDNA). Mitochondria play important roles intracellular calcium signaling and neuroplasticity. We have been analyzing mtDNA in bipolar disorder and reported association of mtDNA 10398 polymorphism, 3644 mutation, and 3243 mutation with bipolar disorder. Gene expression analysis of the postmortem brains also supported mitochondrial dysfunction in bipolar disorder. Altered neuronal plasticity or cell viability due to mitochondrial dysfunction is suggested to be one of risk factors for bipolar disorder.

SY4-01 Expression and function of Oct-3/4 in neural stem/progenitor cells

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Oct-3/4, a member of the POU transcription factor family was discovered in 1990 by three independent research groups including ours, as a transcription factor that functions specifically in undifferentiated state of embryonic carcinoma cells. In vivo, Oct-3/4 is expressed in inner cellular mass (ICM), suggesting its critical role in differentiation of embryonic stem (ES) cells. It is now generally accepted that differentiation of ES cells is triggered by minor increase or decrease of the Oct-3/4 expression level. The target of Oct-3/4 seems to include Sox-2 and Nanog. On the other hand, the questions remain unclear whether Oct-3/4 exists in tissue stem cells and how Oct-3/4 regulates differentiation of tissue stem cells. Here, we show that Oct-3/4 is expressed in neurosphere composed of neural stem/progenitor (NS) cells and that increase and decrease of Oct-3/4 influence the cell fate. Oct-3/4 down-regulation accelerates neuronal differentiation of NS cells whilst its sustained expression prevents neuronal differentiation. Transplantation of neurospheres pretreated by adenovirus vectors of Oct-3/4 into the adult rat brain shows down-regulation of Oct-3/4 promotes differentiation of NS cells in vivo. Our findings suggest that Oct-3/4 might be one of the essential regulators of NS cell differentiation and that the modulation of Oct-3/4 could be a useful tool in clinical application of NS cells for neurological disorders.

SY4-03 Hormonal regulation of neural stem cells

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SY4-04 Fate regulation of neural precursor cells in the embryonic mouse neocortex

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Cortical neural precursor cells (NPCs) sequentially undergo expansion, neurogenic and gliogenic phases during development, although the underlying mechanisms are poorly understood. Recent studies have identified a number of extrinsic factors that regulate the fate of NPCs. We have recently shown that Wnt signaling induces neuronal differentiation of NPCs in an instructive manner. Importantly, Wnt signaling does so in late embryonic stage (neurogenic phase) of NPCs but not in early embryonic stage (expansion phase) or in perinatal stage (gliogenic phase) of NPCs. In early embryonic stage, Wnt signaling promotes proliferation of NPCs. In this symposium, I will discuss possible mechanisms that might account for this stage-dependent response. Likewise, STAT3-activating ligands induce astrocytic differentiation in late (gliogenic phase) but not in early (expansion and neurogenic phases) NPCs. These stage-dependent responses of NPCs might play a central role in determining the timing of differentiation and the size of final population of each differentiated cell type.

SY5-01 Expression and functional significance of Ca²⁺/calmodulin-dependent protein kinase I in neuronal differentiation

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Multifunctional Ca²⁺/calmodulin-dependent protein kinases (CaMKs), including CaMKs I, II and IV, regulate a variety of neuronal functions at downstream of various receptors for neurotransmitters such as glutamate, dopamine and serotonin. These signaling pathways are tightly related to neuronal development and mental disorders such as schizophrenia and bipolar disorder. In this symposium, we will focus on the expression and functional significance of CaMKI in neuronal development. *In situ* hybridization histochemistry was performed to examine the expression of CaMKIs in developing mouse brain. The four isoforms of CaMKIs were found to exhibit distinct spatiotemporal expression during neuronal development. CaMKIs α and β 2 mRNAs were expressed abundantly in the embryonic brain and spinal cord. CaMKI γ exhibited restricted expression to particular brain regions such as the ventromedial hypothalamic nucleus, amygdaloid nucleus, cerebral cortex and hippocampus throughout the development. The expression of CaMKI δ mRNA appeared after birth and progressively increased particularly in the hippocampus with a peak during early postnatal development. Next, to examine the roles of CaMKI in dendritic development, we transfected a kinase-dead mutant of CaMKI δ and CaMKIV into the primary hippocampal neurons. The expression of a kinase-dead mutant of CaMKI δ led to a significant decrease in average dendritic length without any effects on the number of dendrites. In contrast, the expression of a kinase-dead mutant of nuclear-targeted CaMKIV had a significant effect on the number of dendrites but not average dendritic length. These findings suggest that CaMKI may be involved in different steps from CaMKIV during the dendritic development of hippocampal neurons.

SY5-03 Dopamine receptor signaling through CaM kinase II and calcineurin, and psychiatric disorders

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Dopamine D2 receptors (D2R) exists as two alternatively spliced isoforms, which differ in the insertion of 29 amino acids in the third cytoplasmic loop, termed D2SR and D2LR. Evidences using D2LR-null mice suggested that a preferential involvement of D2LR in postsynaptic responses such as D1/D2 agonist-induced increased locomotor activity and haloperidol-induced catalepsy (Usiello A et al., 2000). We here found novel D2R signaling through CaM kinase II (CaMKII) and calcineurin using D2LR-transfected NG108-15 cells. We also documented a pronounced increase in NF- κ B activation through extracellular signal-regulated kinase (ERK) and calcineurin activities. Calcium imaging with fluo-3 revealed that quinpirole, a D2R agonist, increased the intracellular Ca²⁺, which was blocked by sulpiride and pertussis toxin in D2LR-transfected NG108-15 cells. The quinpirole-induced CaMKII activation was associated with an increased BDNF expression in NG108-15 cells. Although ERK activation was involved in quinpirole-induced NF- κ B activation in both D2SR and D2LR signalings, calcineurin activation contributed to the NF- κ B activation only in D2LR signaling. Dopamine-induced up-regulation of NF- κ B was also evident in the prefrontal region of mice treated with risperidone, which is known to cause DA release in the prefrontal cortex. We also defined preferential expression of CaMKII δ and γ isoforms in the substantia nigra DA neurons. The DA neurons highly expressed BDNF. Since BDNF and NF- κ B-dependent transcription have pivotal roles in neuronal survival, BDNF expression and NF- κ B activation through D2 receptors provide novel strategies for treatment of the psychiatric disorders. Y. Takeuchi and K. Fukunaga. J. Neurochem. 90: 155-163, 2004.

SY4-05 Molecular mechanisms underlying the maintenance of neural stem cells in the adult brain

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Neural stem cells exist not only in developing mammalian brains but also in adult brains and provide new neurons in specific regions such as the olfactory bulb and the dentate gyrus of the hippocampus throughout lifespan. While the size of neural stem cell pool in the adult brain is strictly regulated, mechanisms underlying the maintenance and differentiation of adult neural stem cells remain largely unknown. Notch signaling is shown to play significant roles to keep neural stem cells undifferentiated and the activation of this signaling expands neural stem cell pool. The number of neural stem cells in the adult brain could be altered by several factors and psychiatric stress conditions might be one of those factors. We have utilized mouse stress models and investigated kinetics of adult neural stem cells in the subventricular zone. The number of neural stem cells in the subventricular zone decreased after exposure to stress. We have also examined effects of drugs that are used to treat patients with mood disorders on the neural stem cell. Treatment with antidepressants reverted the effects of stress and increased the size of neural stem cell pool. Interestingly, mood stabilizing drugs, which are used to treat bipolar disorder patients, showed similar effects on the neural stem cell pool but through distinct mechanisms from antidepressants. Mood stabilizers at therapeutic concentrations activated Notch signaling in the neural stem cell. Molecular mechanisms that maintain or alter the size of neural stem cell pool in the adult brain will be discussed.

SY5-02 The role of Ca²⁺/calmodulin-dependent protein kinase II in neuronal activity and seizure

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Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) is highly enriched in the central nervous system and proposed to play important roles in various neuronal functions including the regulation of neuronal activity. However, which protein function is responsible for such regulation, i.e., its protein kinase activity, calmodulin-binding capacity or multimeric structure and/or interaction with other proteins, remains to be determined yet. To clarify specifically the role of its protein kinase activity, we engineered knock-in mice with the inactivated α subunit of CaMKII by replacing Lys-42 with Arg-42. CaMKII activity was reduced by 60% in forebrain homogenate from homozygous mutants compared to wild type littermates, while CaMKII α protein level was unchanged. The birth rates of homozygous mutants, heterozygotes and wild type littermates followed the Mendelian distributions. The spontaneous death rate of homozygotes by the age of 6 months was higher than those of heterozygotes and wild type littermates. Spontaneous seizure was sporadically observed in homozygotes and heterozygotes, but rarely in wild type controls. When pentylenetetrazole was injected into mice, homozygotes manifested severer seizure than wild type controls, indicating increased susceptibility to seizure in homozygous mutants. Cytochrome oxidase staining showed decreased neuronal activity in certain areas of limbic structure in homozygous mutants compared to wild type controls, suggesting changes in emotional behaviors. These results indicate that protein kinase activity of CaMKII is important for maintaining basic and normal neuronal activity *in vivo*.

SY5-04 Visualization of synaptic Ca²⁺/calmodulin-dependent protein kinase II activity in living neurons

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Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) is highly enriched in excitatory synapses in the central nervous system and critically involved in synaptic plasticity, learning, and memory. However, the precise temporal and spatial regulation of CaMKII activity in living cells has not been well described, because of a lack of specific methods. In order to optically monitor this activation processes, we designed a fusion protein named Camui, an entire CaMKII protein flanked with cyan- and yellow fluorescent proteins. We designed Camui to detect any conformation change associated with activation processes using fluorescence resonance energy transfer (FRET). Since FRET efficiency depends on the distance and angle between two fluorophores, a conformation change accompanied by CaMKII activation will change FRET efficiency. Using the purified Camui protein, Ca²⁺ application induced a FRET efficiency change and autophosphorylation in parallel. In non-neuronal cells, raising the intracellular Ca²⁺ concentration changed FRET efficiency, indicating that Camui can be used to measure CaMKII activity. In hippocampal cultured neurons, we could detect the CaMKII activation in dendritic spines using Camui. In combination with two-photon microscopy, we demonstrate that Camui can be used to observe temporal and spatial regulation of CaMKII activity in living neurons.

SY5-05 Calcium/calmodulin signaling and psychiatric disorders

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We have been conducting a comprehensive behavioral test battery on genetically engineered mice to identify the behavioral significance of the genes expressed in the brain. Recently, we subjected mice lacking calcineurin (=CN), a calcium/calmodulin protein phosphatase, to the test battery. The mutant mice showed severe working memory deficit, increased locomotor activity, decreased social interaction, and impairments in prepulse inhibition and latent inhibition. The abnormalities of CN mutant mice were strikingly similar to those described for schizophrenic patients (Zeng et al, 2001; Miyakawa et al., 2003). Consistent with these findings, human genetics studies in a large sample of affected families detected significant association of the PPP3CC gene, which encodes the calcineurin gamma catalytic subunit, with the disease (Gerber et al., 2003). To further identify the signaling pathways or the neuronal functions responsible for the behavioral phenotype of CN mutant mice, we are now conducting the behavioral test battery on various strains of mutant mice bearing mutations in the genes of the molecules related to calcineurin functions/signaling pathways. Some of the preliminary results obtained in this project will be presented and discussed.

SY6-02 An endocrine activin regulates anxiety-related behavior and postnatal neurogenesis

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Activin, a member of transforming growth factor- β superfamily, is an endocrine that regulates differentiation and proliferation of a wide variety of cells. We previously showed that the expression of activin β A is regulated by neuronal activity, and that activin regulates spine morphology and synaptic plasticity in the hippocampus. In this symposium we show novel roles for activin in the higher order brain function. We generated forebrain-specific activin- and follistatin (which antagonizes the activin signal)-transgenic mice, ACM and FSM, respectively, to investigate roles that activin plays in behavior of living animals. Behavioral analyses revealed that FSM showed a decreased general locomotor activity and enhanced anxiety, while ACM showed a hyperactive behavior and reduced anxiety. Importantly, the postnatal neurogenesis in the subgranular zone of the hippocampus in FSM was significantly decreased. Thus, activin plays an important role in the postnatal neurogenesis. These results suggest that decrease in the postnatal neurogenesis that is caused by activin inhibition affects an anxiety-related behavior in adulthood. Taken together, ACM and FSM mice would be useful animal models of mood disorder.

SY6-04 Mouse model for research on an aberrant dopamine transmission

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Dopaminergic system is considered to be involved in locomotor control, emotional behavior, reward, motivation and thought process. A dysfunction of dopaminergic system is probably involved in psychiatric diseases like schizophrenia. So far five subtypes of dopamine receptors (D1R-D5R) are identified and classified into two groups, D1-like (D1R, D5R) and D2-like (D2R, D3R, D4R) receptors on the basis of the gene structure and the pharmacological and intracellular signaling properties. Our research purpose is to clarify biological meaning of dopaminergic system using genetically engineered mice. We generated knockout (KO) mice lacking each of five dopamine receptors and multiple KO mice lacking more than one dopamine receptor simultaneously. We focus on D1R and D2R, major subtypes of D1-like and D2-like receptors, respectively, which are most widely and abundantly expressed. Although the D1R/D2R double KO (DKO) mice were born normally and showed suckling behavior, the D1R/D2R DKO mice exhibited rapid decrease in locomotion and no initiation of feeding around weaning period, and eventually died with emaciation by the third postnatal week. These findings suggest that dopaminergic system is involved in neural development in the area which are implicated in the regulation of locomotion and feeding. To examine involvement of dopaminergic system in neural development we generated mutant mice in which dopaminergic transmission can be shut off at a time point of interest. We utilized tetracycline controllable expression system and generated transgenic mice harboring conditional D1R expression on the D1R/D2R DKO background. We will present findings of the mice by molecular biological, morphological and behavioral analyses.

SY6-01 Genetic analysis of schizophrenia-related trait in mice

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Deficits in prepulse inhibition (PPI) have been reported in schizophrenics and their relatives suggesting that it may represent an endophenotype for schizophrenia. PPI is one of the few behavioral measures that can be examined by the same paradigm in both rodents and humans. Based on the assumption that genes controlling PPI should overlap with those for schizophrenia susceptibility, we have performed QTL analysis using mice. We first tested several inbred strains for their intrinsic PPI, and found that C57BL/6N (B6) mice showed the highest percentage of PPI and the C3H/HeN (C3) strain displayed the lowest. Then, we prepared 1000 F2 mice from B6 and C3 progenitor strains, scored their PPI and genotyped them using 80 genome-wide microsatellite markers. Further, we have performed fine-mapping of each significant QTL to select candidate genes from those regions.

SY6-03 Noradrenaline transmission and memory retrieval deficits

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Noradrenaline (NA) transmission is considered to be involved in attention, cognition, memory, mood, and sleep through modulation of synaptic excitability and plasticity. Accumulating evidence suggests that alterations in the central NA system may be associated with the pathology of some neuropsychiatric diseases, such as depression, anxiety, and posttraumatic stress disease. However, little is known about the neural mechanism underlying the pathogenesis of these diseases caused by altered NA transmission. The present study shows that the mutation of the gene encoding tyrosine hydroxylase (TH) in mice impairs long-term memory requiring the association of events because of the reduced NA metabolism. The memory deficit in the TH mutants is restored by pharmacological stimulation of NA activity before the test, suggesting that this impairment is characterized at least by the deficit in retrieval of reconsolidated memory. The deficit in the mutants is also restored by intra-amygdala stimulation through α 1- or β -adrenergic receptors. In addition, intra-amygdala NA stimulation in the wild type animals increases their susceptibility to recall reconsolidated memory. Moreover, the retrieval of reconsolidated memory is dependent on the NA system originating from the locus coeruleus. These findings indicate that the locus coeruleus-amygdala NA system, primarily through α 1- and β -adrenergic receptors, plays an important role in improving the retrieval of reconsolidated memory trace. The altered NA transmission in the amygdala may affect a process of emotional memory and be implicated in the pathological state of certain neuropsychiatric diseases.

SY6-05 Tetrahydrobiopterin-depleted mice as a model for malignant hyperphenylalaninemia and dopa-responsive dystonia

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Tetrahydrobiopterin (BH4) is an essential cofactor for tyrosine hydroxylase (TH), tryptophan hydroxylase, phenylalanine hydroxylase as well as nitric oxide synthase. Genetic defects in the enzymes for BH4-biosynthesis were causative for malignant hyperphenylalaninemia and dopa-responsive dystonia (DRD). We established mice unable to synthesize BH4 (*Pts*^{-/-}) by disruption of 6-pyruvoyltetrahydropterin synthase (PTPS) gene. *Pts*^{-/-} mice died shortly after birth, and the amount of TH protein in nerve terminals is dependent on the intracellular concentration of BH4. Then, we rescued *Pts*^{-/-} mice by transgenic introduction of human PTPS cDNA under the control of human dopamine- β -hydroxylase promoter (*DPS*). Plasma phenylalanine concentration of *DPS*-rescued (*Pts*^{-/-}, *DPS*) mice was 37 times higher than that of wild type, and was decreased by administration of BH4. Human PTPS was expressed efficiently in the adrenomedullary cells and noradrenergic region in the brain, but only in a small number of the dopaminergic neurons of the ventral tegmental area and substantia nigra. Dopamine level of the *DPS*-rescued mice was restored to 52 % of the wild type in the midbrain, whereas 21% in the striatum. TH immunoreactivity in the lateral region of the caudate-putamen was weak compared with that in the medial region and the nucleus accumbens. We concluded that dopaminergic nerve terminals projecting to the lateral region of the striatum are the most sensitive to BH4 insufficiency. Biochemical and pathological changes in *DPS*-rescued mice were similar to those in human malignant hyperphenylalaninemia and DRD.

SY7-01 Functional analysis of new DISC1 binding protein, DBZ

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Schizophrenia is a devastating psychiatric disorder with a lifetime prevalence of about 1 % worldwide, which commonly leads to a chronic course. The underlying mechanism still remains unknown, however several lines of studies have revealed that schizophrenia is a multifactorial disorder influenced by genetic, neurodevelopmental, and social factors. *DISC1* was identified as a potential susceptibility gene for schizophrenia due to its disruption by a balanced (1;11) (q42;q14) translocation, co-segregating with major psychiatric diseases in a large Scottish family (schizophrenia, bipolar affective disorder and recurrent major depression). To determine the function of *DISC1* in the brain, we previously performed a yeast two-hybrid screen on a human brain cDNA library and found three binding partners, FEZ1, DBZ, and KENDRIN. On the other hand, PACAP (-/-) mice display remarkable behavioral changes and PAC1-deficient mice also have altered emotional behavior and two related patients with a partial trisomy 18p, which leads to the overexpression of PACAP, suffer from severe mental retardation. These results indicate that aberrant regulation of PACAP expression could result in variable phenotypes including cognitive and psychomotor functions in human. In this presentation, we show that *DISC1* interacts with the novel zinc finger protein DBZ via PACAP stimulation and some results of physiological functional analysis of *DISC1*/DBZ interaction. Our results will help the elucidation of pathophysiological role of *DISC1* and a better understanding of the general etiology of schizophrenia.

SY7-03 Neurotrophic activity of EGF and IL-1 on dopaminergic neurons and later cognitive abnormalities

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Maternal stress, viral infection, and obstetric complication induce the production of inflammatory cytokines in amniotic fluid and embryonic/neonatal tissues. Some cytokines mediate inflammatory processes and also exert a strong neurotrophic activity on midbrain dopaminergic neurons. Therefore, these cytokines are implicated in schizophrenia and Parkinson's disease, both in which dopaminergic dysfunction is hypothesized. In agreement, abnormal signals of EGF/Erbb1 and IL-1/IL-1RA are detected in the brain of patients. Here we show that peripheral cytokine activities in immature animals influences later behavioral/cognitive development and dopaminergic metabolism, depending on cytokine species administered. EGF, IL-1, IL-2, IL-6, interferon-gamma, TNF or LIF was subcutaneously administered to rat pups. These cytokines appeared to penetrate the developing BBB. During juvenile stages, neonatal interferon-gamma decreased motor activity whereas IL-2 increased motor activity. After adolescence, IL-1, EGF- and LIF-treated rats developed cognitive/behavioral abnormalities in startle response, prepulse inhibition, social interaction, and/or working memory, although their learning ability of IL-1- and EGF-treated rats was normal. IL-1- and EGF-treated animals also displayed neuropathologic alterations including brain weight loss and abnormal dopamine turnover without apparent neurodegeneration. These animal experiments illustrate that, during development, inflammatory cytokine activities in the periphery can perturb dopaminergic development and induce future psychobehavioral and/or cognitive impairments.

SY7-05 Developmentally regulated psychotomimetic-inducible genes: Implications for the pathophysiology of schizophrenia

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The onset of schizophrenia typically occurs after puberty and psychotomimetic ability of dopamine agonists and NMDA receptor antagonists appears to be age-dependent and to come out after a critical period in both humans and experimental animals. These observations suggest that schizophrenia and related psychoses could be associated with maturation of a specific neuronal system that might consist of certain molecules with differential responses to those schizophrenomimetic drugs including methamphetamine (MAP: a indirect dopamine agonist) and phencyclidine (PCP: a NMDA antagonist) across the critical period. On the basis of this hypothesis, as a candidate for a schizophrenia-related molecule, we have identified a developmentally regulated MAP- or PCP-inducible gene, *mrt1* (MAP responsive transcript 1) or *prt1* (PCP responsive transcript 1), respectively, that encodes a synaptic PDZ- and/or PX-domain containing protein from the neocortex. The late-developing, cocaine-cross reactive, D1-antagonist sensitive and long-lasting nature of MAP-induced changes in *mrt1b* variant expression seems to resemble those of stimulant-induced behavioral sensitization, a model of the onset and relapse of schizophrenia. The fact that expressional alterations of *prt1* in the neocortex following PCP injection has been found to be haloperidol-insensitive and mimicked by dizocilpine, but not MAP, indicates the involvement of *prt1* in the susceptibility to antipsychotic-resistant (non-dopaminergic) symptoms of schizophrenia such as negative symptoms.

SY7-02 Dysbindin and pathogenesis of schizophrenia

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Genetic variation in dysbindin (*DTNBP1*: dystrobrevin binding protein 1) has recently been shown to be associated with schizophrenia. The dysbindin gene is located at chromosome 6p22.3, one of the most promising susceptibility loci in schizophrenia linkage studies. We attempted to replicate this association in a Japanese sample of 670 patients with schizophrenia and 588 controls. We found a nominally significant association with schizophrenia for four single nucleotide polymorphisms and stronger evidence for association in a multi-marker haplotype analysis ($p=0.00028$). We then explored functions of dysbindin protein in primary cortical neuronal culture. Overexpression of dysbindin induced the expression of two pre-synaptic proteins, SNAP25 and synapsin I, and increased extracellular basal glutamate levels and release of glutamate evoked by high potassium. Conversely, knockdown of endogenous dysbindin protein by small interfering RNA (siRNA) resulted in the reduction of pre-synaptic protein expression and glutamate release, suggesting that dysbindin might influence exocytotic glutamate release via up-regulation of the molecules in pre-synaptic machinery. The overexpression of dysbindin increased phosphorylation of Akt protein and protected cortical neurons against neuronal death due to serum deprivation and these effects were blocked by LY294002, a phosphatidylinositol 3-kinase (PI3-kinase) inhibitor. siRNA-mediated silencing of dysbindin protein diminished Akt phosphorylation and facilitated neuronal death induced by serum deprivation, suggesting that dysbindin promotes neuronal viability through PI3-kinase-Akt signaling. Genetic variants associated with impairments of these functions of dysbindin could play an important role in the pathogenesis of schizophrenia.

SY7-04 Diverse CNR/Protocadherin-a family and Fyn-tyrosine kinase for Schizophrenia

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Schizophrenia is a common psychiatric disorder that affects about one percent of the population. Family, twin, and adoption studies have shown that heredity plays an important role in the etiology of schizophrenia. CNR/Protocadherin-a (CNR/Pcdh-a) family is diverse cadherin related molecules in the brain, which has firstly isolated as Fyn-tyrosine-kinase binding molecules. The human CNR/Protocadherin-a genes are clustered on chromosome 5q31. Fyn kinase is located on 6q21 and participates in brain development and neurotransmission by phosphorylating NMDA receptor. Their genomic regions 5q31 and 6q21-22 are susceptible loci for schizophrenia. To explore CNR/Pcdh-a and Fyn abnormality in schizophrenia, we characterized coding single nucleotide polymorphisms (SNPs) in CNR/Pcdh-a and analyzed Fyn expression in schizophrenia patients. In this symposium, I would like to introduce our recent findings for molecular function of CNR/Pcdh-a and Fyn in the brain and suggest candidates of molecular cascades for risk of schizophrenia.

SY8-01 Molecular targeted therapy for polyglutamine disease

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Spinal and bulbar muscular atrophy (SBMA) is a late-onset lower motor neuron disease affecting only males. 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. This type of mutation also causes a variety of hereditary neurodegenerative diseases including Huntington disease, several forms of spinocerebellar ataxia, and dentatorubral and pallidolysian atrophy (DRPLA). 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. Surgical 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 striking deterioration of symptoms by testosterone administration. Leuprorelin, 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. However, flutamide, an androgen antagonist promoting nuclear translocation of AR, yielded no therapeutic effect. The ligand thus appears to be the key molecule in the pathogenesis as well as the main therapeutic target of SBMA. We are now conducting a randomized, double-blind, placebo-controlled study of leuprorelin for SBMA. Over-expression of a molecular chaperone HSP70, which renatures misfolded mutant AR, ameliorates neuromuscular phenotypes of the Tg by reducing nuclear-localized mutant AR. HSP70 appears to enhance the degradation of mutant AR via ubiquitin-proteasome pathway. motor

SY8-02 Molecular neuropathology of multiple system atrophy

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Multiple system atrophy (MSA) is a disease entity, which includes different diseases such as olivopontocerebellar atrophy, striatonigral degeneration and Shy-Drager syndrome depending on their phenotype. Its pathological feature is glial cytoplasmic inclusion (GCI) in oligodendroglial cells. Biochemical analysis revealed that GCI is composed of alpha synuclein, which also accumulates as Lewy body in Parkinson disease. Regarding the function of alpha synuclein, we studied on the interaction of alpha synuclein with MAP kinase pathway and revealed that alpha synuclein affects the MAPK pathway and accelerates cell death and also reported alpha synuclein degradation by serine protease neurosin. We have also established the transgenic mouse with alpha synuclein in oligodendrocyte. In this talk I will present those works and review the recent studies on MSA.

SY8-04 Pathogenesis of intracellular amyloid β -protein 42: A novel therapeutic target in Alzheimer's disease

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Major therapeutic strategies of Alzheimer's disease (AD) are to inhibit amyloid β -protein (A β) aggregation and promote extracellular A β removal, because extracellular A β neurotoxicity is thought to cause neurodegeneration. A β vaccination and inhibitors of A β aggregation are thus being developed. While, it has recently been suggested that intracellular A β is even more important than extracellular A β in AD pathogenesis. Because, i) the pathogenic A β species, A β 42, is accumulating in the neurons much earlier than extracellular accumulation; ii) intracellular A β 42 causes neuronal apoptosis at far lower levels than extracellular A β 42; and iii) neuronal loss but not plaque numbers correlates well with dementia in AD. Recently, we have reported that intracellularly accumulating A β 42 directly activates p53 promoter leading to p53 mRNA overexpression and apoptosis in vitro. Moreover, Swedish mutant amyloid precursor protein (APP)-transgenic mice (Tg2576) and familial AD mutant presenilin (PS) 1-transgenic mice showed the degenerating neurons to be both A β 42- and p53-positive, and A β 42/p53/TUNEL-positive neurons were also found in AD brain. Intracellularly accumulating A β 42 is also reported to induce mitochondrial dysfunction and synaptic pathology. Thus, cytosolic A β 42 accumulating neurons may be at high risk for degeneration through p53-dependent apoptosis and mitochondrial/synaptic dysfunction, and inhibition of A β 42 accumulation in cytosol may attenuate neuronal loss and progression of AD. Since cytosolic A β 42 may be degraded by proteasome, activation of proteasome may decrease the cytosolic A β 42 levels. Accordingly, we have established a system to search for drugs that promote intracellular A β degradation, developing novel approaches for the cure of AD.

SY9-01 TRP channels and Nociception

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Noxious thermal, mechanical, or chemical stimuli evoke pain through excitation of the peripheral terminals called nociceptor, and many kinds of ionotropic and metabotropic receptors are involved in this process. Capsaicin receptor TRPV1 is a nociceptor-specific ion channel that serves as the molecular target of capsaicin. TRPV1 can be activated not only by capsaicin but also by noxious heat (with a thermal threshold $>43^{\circ}\text{C}$) or protons (acidification), all of which are known to cause pain in vivo. Studies using TRPV1-deficient mice have shown that TRPV1 is essential for selective modalities of pain sensation and for thermal hyperalgesia. One mechanism underlying inflammatory pain which is initiated by tissue damage/inflammation and characterized by hypersensitivity is sensitization of TRPV1. In addition to TRPV1, there are five thermosensitive ion channels in mammals, all of which belong to the TRP (transient receptor potential) super family. These include TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1. These channels exhibit distinct thermal activation thresholds ($>52^{\circ}\text{C}$ for TRPV2, $>34\text{--}38^{\circ}\text{C}$ for TRPV3, $>27\text{--}35^{\circ}\text{C}$ for TRPV4, $<25\text{--}28^{\circ}\text{C}$ for TRPM8 and $<17^{\circ}\text{C}$ for TRPA1) and are expressed in primary sensory neurons as well as other tissues. Some of the thermosensitive TRP channels are likely to be involved in thermal nociception, since their activation thresholds are within the noxious range of temperatures. TRPA1 co-expressed with TRPV1 in small diameter DRG neurons is especially thought to be involved in nociception because it is reported to be activated by allyl isothiocyanate and cinnamaldehyde.

SY8-03 Arrested oligodendrocyte development in a demyelinating disease model

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Demyelinating diseases are characterized by the degeneration/degradation of myelin membrane, resulting in an inefficient conduction along the axons and ultimately conduction block. However, degeneration/degradation of the myelin membrane is initially accompanied with remyelination by the oligodendrocyte precursor cells (OPCs) present in the brain. During this initial phase there are no apparent symptoms. Later at a certain point of disease progression remyelination is severely affected, resulting in generation of naked axons and conduction block. It is critical to understand how this inhibition of remyelination occurs. In this study we searched for any pathological signs appearing before apparent demyelination in the mouse model for demyelination. This mouse model is a transgenic (tg) animal harboring two extra copies of the myelin proteolipid protein (PLP) gene. They form complete myelin until 2 months of age, after which myelin degeneration starts, which is accompanied by remyelination. However, by 8 months most of the axons become naked with little sign of remyelination. We demonstrated that inefficient remyelination is not caused by the deprivation of OPCs expressing Olig1, Olig2, and Sox10. Furthermore, premyelinating oligodendrocyte was even present, suggesting that oligodendrocytes cannot form intact myelin sheath due to a change in microenvironment. Thus, extrinsic mechanisms may contribute to the defect in remyelination. During demyelination, microglial cells and astrocytes become activated, and the environment may become inhibitory for oligodendrocyte to form intact myelin.

SY8-05 Mechanism of axonal damage in axonal Guillain-Barré syndrome after *Campylobacter* infection

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Campylobacter jejuni (*C.jejuni*) enteritis is frequently associated with an axonal variant of Guillain-Barré syndrome (GBS), in which the mechanism of axonal damage remains unknown. We found that antibodies against *C. jejuni* DNA binding protein from starved cells (C-Dps) in sera were significantly more common in *C. jejuni*-related GBS patients than healthy controls and patients with other neurological diseases or *C. jejuni* enteritis. C-Dps was shown to specifically bind to sulfatide, and its binding to the cell surface of nerve growth factor-differentiated PC12 cells dose-dependently induced leakage of lactate dehydrogenase, but not in a Schwann cell line, S16. C-Dps injected to the rat sciatic nerves densely bound to the node of Ranvier, and induced paranodal demyelination and unclustering of sodium channels at the nodes, which corresponded to a significant decrease in the amplitude of compound muscle action potentials. Thus, direct neurotoxic effects of C-Dps may contribute to axonal damage in *C. jejuni*-related GBS.

SY9-02 Lysophosphatidic acid involved in the initiation of neuropathic pain

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Following partial sciatic nerve ligation (PSNL), sustained chronic pain called neuropathic pain (NP) is induced. NP is well characterized by abnormal pain such as hyperalgesia, and allodynia, which causes burning pain even by the tactile stimuli in human. However, little is known of molecular basis of mechanisms underlying such abnormal pain. From the background information that many diseases with demyelination are accompanied with NP, we have focused on various molecules possibly involved in injury-induced demyelination in relation to the mechanisms underlying NP. We finally identified lysophosphatidic acid (LPA) as an initiator of neuropathic pain by use of LPA1 receptor knock-out mice. This abnormal pain was reproduced by a single injection (i.t.) of LPA. Both PSNL and LPA injection caused demyelination at the dorsal root and various gene expressions in dorsal root ganglion (DRG), and all of them were abolished in LPA1 KO-mice. Unique findings are that nociceptive responses through C-fibers (substance P neurons) are lost in such NP models. This finding was supported by anatomical studies showing the loss of substance P-like immunoreactivity in DRG and spinal dorsal horn in such models. LPA-induced demyelination was also confirmed by SEM and TEM observation using co-cultured and ex vivo myelinated DRG neurons. In such studies we observed LPA-induced sproutings and retraction in demyelinating A-fibers and C-fibers, respectively. These findings may underlie the reorganization of primary afferent innervation observed in NP.

SY9-03 Acid-sensing ion channel 3 (ASIC3) is capable of transducing the tissue acidification caused by myocardial ischemia into pain.

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Chest pain that patients with coronary artery disease often experience (angina pectoris) is caused by myocardial ischemia. Acid sensing ion channel 3 (ASIC3), which is highly expressed on the cardiac afferents and most sensitive to pH drops among the ASIC family, has been proposed to transduce the acidification caused by myocardial ischemia into electrical signals leading to nociception. However, this proposal requires that ASIC3 has certain kinetic properties to detect the acidification, because occlusion of a coronary artery for several minutes decreases myocardial tissue pH to just around 7.0 or 6.7 at the lowest. Furthermore, ASIC3 channels desensitize rapidly, whereas the chest pain is persistent. Here, we report that the ASIC3 channels do indeed produce a sustained current within the critical range of extracellular pH between 7.4 and 6.7, which originates from the so-called "window current" caused by overlap of the activation and inactivation curves of ASIC3. Lactate, an anaerobic metabolite, enhanced the sustained current at pH 7.2 and 7.1, but not at pH 7.0-6.8, probably due to its ability to chelate extracellular divalent ions. The pH dependency of the sustained current in cardiac afferent neurons differs from that in the homomeric ASIC3 channels, but it could be explained by co-existence of homomeric ASIC3 and heteromeric ASIC3-containing channels in the sensory neurons. These data indicate that ASIC3 would play a central role in mediating the lactic acidosis of myocardial ischemia into pain.

SY10-01 Neuronal polarity and axon formation

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Neurons are one of the most highly polarized cells, comprised of two structurally and functionally distinct parts, axon and dendrites. However, it remains largely unknown how neuronal polarity is established. We previously showed that collapsin response mediator protein-2 (CRMP-2) is enriched in growing axon of cultured hippocampal neurons. The overexpression of CRMP-2 induces the formation of multiple axons, whereas truncated fragment of CRMP-2 or knockdown of CRMP-2 by RNAi inhibits the formation of the primary axon. Thus, CRMP-2 appears to play a crucial role in the determination of axon/dendrite fate and axon elongation. We have recently found that CRMP-2 interacts with tubulin dimers to promote microtubule-assembly for axon growth, and that CRMP-2 binds to Sra-1, an effector of Rac1 to regulate WAVE-dependent reorganization of actin filaments. CRMP-2 links kinesin-1 to tubulin dimers and Sra-1, and participates in the kinesin-1-dependent transport of tubulin dimers and the Sra-1/WAVE complex to developing axons. We have also found that the PAR-6/PAR-3 complex and the Akt/GSK-3 β pathway are involved in neuronal polarization downstream of PI3-kinase. The PAR-6/PAR-3 complex mediates the Cdc42-induced Rac1 activation through direct interaction with STEF/Tiam1 (Rac GEF) for axon growth. GSK-3 β phosphorylates CRMP-2 and inactivates its tubulin-binding activity. Akt appears to phosphorylate GSK-3 β and inactivates its kinase activity, thereby increasing non-phosphorylated active CRMP-2 which promotes axon growth. This time, we summarize and discuss functions of these polarity molecules in regulation of neuronal polarity and cytoskeleton.

SY10-03 Contact-dependent regulation of process arborization of neurons and glia by DNER-Notch signaling

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During CNS development, neurons and glia exchange signals through cell-cell interactions and reciprocally control morphological and biochemical differentiation in stepwise processes. Notch signaling is one of the most important mediators of such cell-cell interaction; it has been implicated in fate determination of neural stem cells, astrocyte differentiation and dendritic arborization of neurons. We have recently identified DNER (Delta/Notch-like EGF-related Receptor) as a novel Notch ligand that is specifically expressed in dendrites of CNS neurons. In the developing cerebellum, DNER is strongly expressed in Purkinje cell dendrites, which are tightly associated with radial fibers of Bergmann glia expressing Notch. DNER induces radial fiber formation of Bergmann glia through activating Deltex-dependent Notch signaling. I would like to discuss DNER-Notch signaling during contact-dependent regulation of process arborization of neurons and glia in the CNS.

SY9-04 Role of spinal microglia in the pathogenesis of neuropathic pain

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Neuropathic pain is a common and severely disabling state that affects millions of people worldwide. This type of pain may be experienced after nerve injury or from diseases that affect peripheral nerve function. While the dominant theme in research on neuropathic pain has been to understand the roles of neurons in the peripheral nervous system and the dorsal horn, there is a rapidly growing body of evidence indicating that glia, especially microglia, in the spinal cord are activated following nerve injury. However, until recently it remained an open question whether activated microglia play a causal role in neuropathic pain behaviors. Here we will present recent evidence that activated spinal microglia are the cause and key cellular intermediaries in the pathogenesis of neuropathic pain. In activated microglia, P2X₄ receptor, a ligand-gated cation channel activated by ATP, is a required molecular mediator. P2X₄ receptors (P2X₄Rs) in the spinal cord are upregulated exclusively in activated microglia after nerve injury. Blocking P2X₄Rs pharmacologically or reducing P2X₄R expression molecularly leads to a reversal of nerve injury-induced neuropathic pain. We will also show recent findings that fibronectin, an extracellular matrix protein, causes an increase in the expression of P2X₄Rs in microglia and that an increase in the fibronectin expression in the dorsal horn was observed in neuropathic rats. Understanding of how P2X₄Rs are expressed and activated in spinal microglia following nerve injury may lead to new strategies that may aid in the management of neuropathic pain.

SY10-02 Protrudin induces process formation by promoting membrane transport

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The increase in cell surface area that accompanies neurite outgrowth requires a supply of membrane components at the tips of the projections, but the underlying mechanisms of such membrane transport are unclear. We have now identified a key molecule in this process: protrudin. This protein is most abundant in neurons and in other cell types that extend projections. Whereas protrudin is localized to the endoplasmic reticulum and plasma membrane of resting cells, it moves to the tips of processes via the trans-Golgi network during process formation. Forced expression of protrudin induced process formation in neuronal and nonneuronal cells, whereas inhibition of protrudin function resulted in suppression of neurite outgrowth. The atypical FYVE domain of protrudin preferentially interacts with phosphatidylinositol 5-phosphate, and this interaction is necessary for neurite extension. Protrudin also associates with Rab11 and the t-SNARE protein SNAP-25. These results suggest that, through its interaction with phosphatidylinositol 5-phosphate, protrudin functions as a tethering effector for the Rab-SNARE system during vesicle fusion with the plasma membrane.

SY10-04 Role of Calcium-Regulated Local Protein Synthesis Within Nerve Growth Cones

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The local mRNA translation has been recently shown to play an important role in developing axons and/or dendrites in response to external signals. Nerve growth cones are known to contain many kinds of mRNA, however, direct evidence of growth cone local protein synthesis has not shown yet due to technical problem and its regulatory mechanisms is unclear. Since the regulation of the intracellular calcium is required for proper neurite extension, we focused on the role of eukaryotic elongation factor-2 (eEF2), a protein translational factor known to be regulated by calcium signaling. Immunocytochemistry revealed high expression of dephosphorylated eEF2 in the extending growth cones of cultured DRG neurons. When calcium influx by KCl or ATP stimulus caused neurite to retract temporarily, the phosphorylation of eEF2 was transiently increased within growth cones. These raised a possibility that local protein synthesis via eEF2 in the growth cone may be involved in neurite extension mechanisms, since dephosphorylated eEF2 promotes protein translation. To determine the functional significance of growth cone eEF2 in the neurite extension mechanisms, we employed a chromophore-assisted laser inactivation (CALI), a method of acute and localized protein inactivation. CALI of eEF2 in growth cone resulted in growth arrest of neurite. These findings provide the first direct evidence for an important role of growth cone eEF2 in the regulation of neurite extension.

SY10-05 Signaling mechanisms of axon guidance molecules, semaphorins

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Axon guidance represents a key stage in the formation of neuronal network. Axons are guided by a variety of guidance factors, such as semaphorins, ephrins and netrin. Plexins are cell surface receptors for semaphorin molecules, and their interaction governs axon guidance. We have found that the Sema4D receptor Plexin-B1 directly stimulates the intrinsic GTPase activity of R-Ras that has been implicated in promoting cell adhesion and neurite outgrowth. This activity required the interaction of Plexin-B1 with Rnd1, a member of Rho family GTPases. Down-regulation of R-Ras activity by the Plexin-B1-Rnd1 complex was essential for the Sema4D-induced growth cone collapse in hippocampal neurons. Thus, Plexin-B1 mediates Sema4D-induced repulsive axon guidance signaling by acting as a GAP for R-Ras. Expression of R-Ras GAP activity of Plexin-B1 requires Rnd1 interaction and Sema4D binding. Cytoplasmic domain of Plexin-B1 has two separated GAP domains, C1 and C2. C1 and C2 domains interacted each other, and Rnd1 disrupts this interaction. On the other hand, Sema4D induced clustering of Rnd1-bound Plexin-B1. Thus, Rnd1 opens the two R-Ras GAP domains of Plexin-B1, and Sema4D-induced receptor clustering stimulates R-Ras GAP activity and neurite remodeling in hippocampal neurons. We conclude that Plexins mediate semaphorin-induced repulsive signaling by novel activation mechanism of R-Ras GAP.

一般演題（ミニシンポジウム） プログラム

	28日(水) 8:45～11:45	
	前 半	後 半
Neurotransmitters, channels and receptors	B会場 MS1-01～06	
Diversity of cellular signaling systems		B会場 MS2-01～06
Neuron-glia interaction	C会場 MS3-01～07	
Neuronal death and rebirth		C会場 MS4-01～05
Neuronal differentiation and development I	D会場 MS5-01～06	
Neuronal differentiation and development II		D会場 MS6-01～06
Molecular pathology of dementia and ischemia	E会場 MS7-01～05	
Molecular basis of neuropsychiatric disorder		E会場 MS8-01～07

MS1-01 Expression and function of KCNQ channels in microglia

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In the brain, neurons were shown to express various KCNQ subtypes except KCNQ4 by single cell RT-PCR and immunocytochemistry (Brown et al., 2002). However, whether glial cells express KCNQ channels is not yet known. Among glial cells, microglial cells were reported to have HERG-like channel that is known to contribute to a slow component of M-type potassium current. Therefore, we have performed electrophysiological characterization as well as quantitative RT-PCR of M-like channel components in rat primary cultured microglia. Quantitative RT-PCR analyses showed that microglia possess KCNQ5 and KCNQ3 abundantly but express very low level of KCNQ1, KCNQ2, and KCNQ4. The electrophysiological analyses showed that outward currents activated by application of step pulses from holding potential of -60 mV to between -80 and +40 mV were dose-dependently inhibited by linopirdine, a KCNQ channel blocker. On the contrary, a KCNQ channel opener, retigabine, increased the amplitude of outward currents both in cultured microglia and acutely dissociated microglia in slice preparation. The microglia activated by either LPS or high [K⁺]_o and glutamate (1 mM) were more susceptible to linopirdine and retigabine. Immunocytochemical staining showed that KCNQ5 channels were translocated to membrane in the LPS-activated microglia. The expression of TNF- α in microglia was increased by high [K⁺]_o and glutamate but was attenuated by the addition of 10 μ M retigabine. These results indicate that KCNQ channels in microglia are more functional in pathological condition and may contribute to neuroprotective effects of microglia.

MS1-03 Shank3 mediates interaction of PSD-95 and GluR1 AMPA receptor

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PSD-95 is a major scaffolding protein of the postsynaptic density and plays important roles in neuronal development and plasticity. Previous studies showed that overexpression of PSD-95 in hippocampal neurons enhanced postsynaptic clustering of AMPA receptors and maturation of glutamatergic synapses. Since PSD-95 fails to directly interact with AMPA receptors, it has been proposed that the anchoring molecules would exist between PSD-95 and AMPA receptors. In this study, we searched for these molecules by yeast two-hybrid screening system and obtained Shank3/ProSAP2 from mouse brain cDNA library. Shank3 is a multidomain protein containing ankyrin repeats, an SH3 domain, a PDZ domain, a long proline-rich region, and a sterile alpha motif. By using an extract prepared from cortical neurons, we demonstrated that the SH3-PDZ domain of Shank3 directly interacted with PSD-95 and with GluR1 subunit of AMPA receptors. In addition, mutational analyses revealed that GluR1 bound to the PDZ domain of Shank3 via its C-terminal PDZ binding motif. To investigate the expression of Shank3 in cortical neurons, we raised anti-Shank3 antibody and immunostained cortical neurons. The pattern of Shank3 immunoreactivity was strikingly punctate, mainly seen in the spines, and closely matched with those of PSD-95. These findings indicate that Shank3 is colocalized with PSD-95 in the same spines. Furthermore, when Shank3 and GluR1 were overexpressed in cortical neurons, they formed complex in the spines. Together with the biochemical interaction of Shank3 with PSD-95 and GluR1, these results suggest that Shank3 is important molecule to associate PSD-95 with AMPA receptors in excitatory synapse.

MS1-05 Effects of MK-801 on the gene expression of serine racemase and D-amino acid oxidase and on the D-serine levels in rat brain

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We have evaluated the acute effects of increasing doses of MK-801 (0.2-1.6 mg/kg) on the gene expression of serine racemase and D-amino acid oxidase (DAO) in discrete brain areas of rats. We have also investigated the effects of the chronic MK-801 administration on the gene expression of serine racemase and DAO and on the D-serine levels. The acute administration of MK-801 produced a dose-dependent and drastic elevation in the gene expression of serine racemase in most parts of the brain. In contrast, the acute administration of MK-801 (0.8 and 1.6 mg/kg) caused a drastic decline in the expression of DAO mRNA in all the brain areas, whereas a slight but significant increase in the expression of DAO mRNA was observed in the pons-medulla after the administration of MK-801 (0.4 mg/kg). Following the chronic administration of MK-801 (0.4 mg/kg), the gene expression of serine racemase was significantly increased in almost all brain areas, whereas no significant changes were found in the level of DAO mRNA in most parts of the brain. In addition, the chronic administration produced a slight but significant increase in the concentrations of D-serine in the cortex and striatum. These present findings suggest that the upregulation of serine racemase and the elevation of the D-serine level after the MK-801 administration could reflect a compensation response of the serine racemase to antagonism of the NMDA receptors by MK-801 and that serine racemase and DAO could play an important role in the regulation of NMDA receptors via the D-serine metabolism.

MS1-02 Structural insight of ifenprodil recognition by NR2B amino terminal domain of NMDA receptor

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NMDA receptors are involved in mediating excitatory synaptic transmissions in the brain and have been implicated in numerous neurological disorders. The proximal amino terminal domains (ATDs) of NMDA receptor constitute many modulatory binding sites that some may serve as potential drug targets. There is little biochemical and structural data on the ATDs of NMDA receptors as it is difficult to produce the functional proteins. An optimized method was established in our laboratory to reconstitute the insoluble recombinant ATD of NMDA receptor NR2B subunit (ATD2B) through productive refolding of 6xHis-ATD2B protein from inclusion bodies. Circular dichroism (CD) and dynamic light scattering characterizations revealed that the solubilized and refolded 6xHis-ATD2B adopted well-defined secondary structures and monodispersity. More significantly, the soluble 6xHis-ATD2B could specifically bind its putative ligands to saturation. These ligands bound to 6xHis-ATD2B with dissociation constants (K_D) that were within the range of the IC₅₀ values determined electrophysiologically. Mutating critical amino acids contributing to ifenprodil binding (D101A, I150A, F176A and D101A/F176A) reduced 6xHis-ATD2B K_Ds as compared to wild type 6xHis-ATD2B (2.3 to 5.5-fold). D101A/F176A double mutant showed greater reduction in affinity (10.4-fold). D113, which was not a molecular determinant of ifenprodil binding, had little effect on the K_D when mutated (0.8-fold compared to wild-type). Taken together, we provided strong evidences that our refolded protein existed in a conformation capable of binding its putative ligands. This is the first report on a functional recombinant ATD2B with a characterized K_D. Support by NMRC/0581/2001 CML.

Keywords: NMDA, RECEPTOR, SUBUNIT, AMINO ACID, BINDING

MS1-04 Effects of a glial toxin fluorocitrate on extracellular D-serine contents in the medial prefrontal cortex of the rat

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D-Serine is known to act as an endogenous co-agonist of the NMDA type glutamate receptor in the mammalian brain. To understand the molecular and cellular basis of regulation of D-serine signal, we have examined in the rat the possible participation of glial cells in the extracellular release of D-serine with fluorocitrate (FC), which is a selective and reversible glial toxin, using an in vivo microdialysis technique. Straight-shaped cellulose dialysis tubing was implanted into the medial prefrontal cortex (mPFC). Amino acids were quantified by high-performance liquid chromatography with fluorometric detection. Intra-mPFC infusion of FC via the dialysis tubing markedly reduced the extracellular concentration of L-glutamine to 20% of the control. This result is consistent with the previous report and supports the inhibition of the glial function. The FC infusion also decreased the prefrontal extracellular levels of D-serine by 20-30%, but increased those of glycine and taurine. The differential effects of FC on the extracellular contents of various amino acids in the mPFC appears to deny the possibility that the FC-induced decrease in the extracellular D-serine concentration is due to a non specific phenomenon. Moreover, the FC infusion into the mPFC caused behavioral changes including sniffing and head bobbing. Together with the observations that D-serine-like immunoreactivity is found in the glial cells and that depolarization stimuli fails to produce an increase in the extracellular release of D-serine, the present findings suggest that some glial cells in the mPFC may be involved in the control of the extracellular concentrations of D-serine and in the behavioral expression.

MS1-06 Inhibition of nicotinic acetylcholine receptors by dehydroepiandrosterone and its sulfate ester in adrenal chromaffin cells and in *Xenopus* oocytes

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Steroids are known to be synthesized in the brain as well as in peripheral steroidogenic glands. These brain-derived steroids are termed neurosteroids. Recent research revealed that neurosteroids modulate neural excitability through interaction with neurotransmitter receptors and ion channels via a rapid mechanism. Dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are abundant neuroactive neurosteroids. Physiological roles of these steroids in the brain have not been still clarified. To evaluate whether these steroids modulate nicotinic receptor-mediated responses, the short-term effects of the steroids on acetylcholine (ACh)-induced catecholamine (CA) secretion were investigated using cultured bovine adrenal chromaffin cells as a model of a catecholaminergic neuron. Furthermore, the effects of these steroids on neuronal ACh receptors ($\alpha 3\beta 4$, $\alpha 4\beta 2$, $\alpha 7$) expressed in *Xenopus* oocytes were examined by voltage clamp recordings. Our results were as follow. 1) DHEA and DHEAS concentration-dependently inhibited CA secretion from the chromaffin cells evoked by ACh. The inhibitory effect of DHEA on the CA inhibition was stronger than that of DHEAS. 2) DHEA at higher concentrations inhibited K⁺ (56 mM)-evoked CA secretion, but DHEAS did not affect it. 3) These steroids inhibited ACh-induced Na⁺ influx similar to the CA inhibition. 4) DHEA and DHEAS reduced the ACh-induced inward currents on all of the expressed neuronal ACh receptors in a concentration-dependent manner. These results suggest that DHEA and DHEAS inhibit the ACh-induced CA secretion mainly due to the blockade of nicotinic ACh receptor. Our results further indicate that these steroids may modulate neuronal nicotinic receptor-mediated responses, thereby regulating neural excitability in the brain.

MS2-01 Apolipoprotein A-I increases association of cytosolic cholesterol with microtubules in rat astrocytes

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Apolipoprotein (apo) A-I stimulates translocation of caveolin-1, protein kinase C α and newly synthesized cholesterol to the cytosolic lipid-protein particle (CLPP) fraction in the cytosol of rat astrocytes (J. Biol. Chem., 277, 7929-7935, 2002, J. Biol. Chem., 277, 44709-44714, 2002 and J. Lipid Res., 45, 2269-2276, 2004). In this work, we investigated the interaction of CLPP-related proteins such as caveolin-1 and protein kinase C α or CLPP-related lipids with cytoskeletons in order to understand intracellular cholesterol trafficking. Paclitaxel (taxol), a drug to fix microtubules, suppressed partly apoA-I-mediated release of lipids such as cholesterol, sphingomyelin and phosphatidylcholine in rat astrocytes, suggesting that the microtubules regulate the intracellular cholesterol trafficking to link to assembly of cellular lipids to apoA-I-HDL. The association of cytosolic lipids, caveolin-1 and protein kinase C α with the reconstituted microtubule-like filaments (rMT) was increased much more in the cytosol prepared from rat astrocytes stimulated with apoA-I for 5 min than that from the cells without apoA-I stimulation. The increase of this association by apoA-I was suppressed by scaffolding domain-peptide of caveolin-1. Under the condition to depolymerize microtubules, the binding of cytosolic caveolin-1 with protein kinase C α or α -tubulin was enhanced in the cytosol fraction of the cells stimulated with apoA-I for 5 min. These findings suggest that apoA-I upregulates the association of CLPP and microtubules through cytosolic caveolin-1 to induce apoA-I-mediated cholesterol release.

MS2-03 Neuronal differentiation is promoted by arginine methylation of RNA-binding proteins

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Protein methylation is a common post-translational modification that can potentially regulate signal transduction pathways in a similar manner as protein phosphorylation. However, phosphorylation has mainly been researched in signal transduction so far. The nervous system has long been recognized to be sensitive to levels of methylation, as diets poor in folate and vitamin B12 required for AdoMet production cause demyelination, but the physiological relevance of this modification remains unknown. Moreover, recent study of Cimato et al (J. Cell. Biol. 138, 1089-1103, 1997) have implied that protein methylation could mediate neurite outgrowth of PC12 cells by nerve growth factor (NGF), but the molecular mechanism remains unknown. 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. Recent progress in the identification of PRMTs (protein arginine N-methyltransferase) provides a clue for analyzing physiological roles of protein arginine methylation. And, many RNA-binding proteins, which are abundant in brain, exist RGG and/or RXR motifs which are methylated arginine residues. So, we hypothesize that translational control is affected by PRMTs catalyzed methylation of RNA-binding proteins and arginine methylation is one of the regulatory factors of signal transduction during neurite outgrowth. In this study, to clarify the mechanism for PRMTs regulated neurite outgrowth, we used methyl-thioadenosine (MTA, a methylation inhibitor) and GFP-fusion RGG repeat protein. And we examined effects of arginine methylation in RNA-binding proteins for signal transduction and mRNA stabilities during neurite outgrowth.

MS2-05 Regulation of intracellular localization of Cyclin-dependent kinase 5 (Cdk5) activators p35 and p39 by myristoylation

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Cdk5 is a Pro-directed Ser/Thr kinase. Mice lacking Cdk5 exhibit a disrupted cortical lamination pattern, suggesting that Cdk5 is involved in the neuronal migration in the developing mouse brain. Cdk5 has also been implicated in the pathological degeneration of neurons. These mean the regulation of Cdk5 activity is important for whole life. Cdk5 is activated by association with a neuron-specific activator p35 or p39. According to the expression pattern in the brain and phenotypes of mice lacking respective genes, they are supposed to have different functions. Moreover, p35 and p39 double KO mouse showed the same phenotype as Cdk5 KO mouse, indicating that their functions are complementary. Their amino acid sequence homology is 57% with a high similarity at the Cdk5 binding C-terminal region and the N-myristoyl consensus sequence at the N-terminal. It is not clear what difference between p35 and p39 determines their distinct function. Intracellular localization is important for Cdk5 activities and would be a key issue for understanding the functional differences between them. We were interested in the myristoylation signal as a factor to determine it. The expression constructs of p35 and p39 for both wild type and G2A mutant (Gly-to-Ala mutation at the second amino acid) with myc-tag at the C-terminal site were generated and transfected into COS-7 cells. [H3]myristic acid incorporation and cellular localization were examined. Myristoylation was occurred only in wild type p35 and p39 but not in G2A mutants. Immunofluorescent microscopy showed the G2A mutants of p35 and p39 have the tendency to translocate into nuclei with a different manner. These results suggest the presence of the different intracellular localization mechanism between p35 and p39.

MS2-02 Feeding behavior of NPY-Y1 knock out mice

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NPY is a potent agent for feeding. Besides NPY, many orexigenic neuropeptides, such as AgRP, and anorexigenic neuropeptides, such as α -MSH, a POMC gene product, also participate in central regulation of feeding. At least 6 NPY receptor subtypes (Y1-6) have been identified in mice. Y1 and Y5 receptors are involved in positive feeding regulation in hypothalamus. To clarify the role of Y1 receptor on feeding, feeding behavior of Y1-KO mice and gene expression of feeding-related neuropeptides were studied. Body weight and food intake were measured and brains were dissected to perform RT-PCR. From 4 to 40 weeks old, body weight of both male and female Y1-KO mice was increased twice as much as that of wild type. From 40 weeks old, body weight of male Y1-KO mice did not increase to be the same level of the wild type. In contrast, body weight of female Y1-KO mice was kept higher until 69 weeks. Food intake was higher in male Y1-KO mice from 4 to 40 weeks old and was within the normal range at the older age. In female Y1-KO, food intake was not changed except for that at 17 weeks old. Because NPY is an orexigenic peptide, gene expression of other orexigenic/anorexigenic peptides might change in Y1-KO mouse hypothalamus. To test this hypothesis, we evaluated gene expression of those peptides by RT-PCR. POMC mRNA expression was decreased in male Y1-KO mouse hypothalamus but not other peptide mRNA such as AgRP. Because α -MSH, a melanocortin receptor agonist, which is derived from POMC protein, can decrease the feeding behavior, increase in body weight in Y1-KO mice was partly due to augmented feeding, which resulted from diminished expression of POMC gene.

MS2-04 Regulation of Ca²⁺/calmodulin-dependent protein kinase I β 2 by the sequential autophosphorylation mechanism

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Ca²⁺/calmodulin-dependent protein kinase (CaMK) is known to mediate signals associated with elevation of intracellular Ca²⁺. CaMKI β 2 belongs to a family of CaMKI (α , β 1, β 2, γ) which is used to fully activate via phosphorylation by an upstream CaMKI kinase (CaMKK). We have already demonstrated about CaMKI β 2 specific inactivation mechanism which is Ca²⁺/CaM independent phosphorylation within calmodulin binding domain (Thr304). Autophosphorylation of Thr304 prevents Ca²⁺/CaM complex from binding to CaMKI β 2, and decrease its activity. Here we report the identification novel phosphorylation sites of CaMKI β 2. CaMKI β 2 was phosphorylated at Thr171 located in the activation loop by CaMKK like CaMKI α , then CaMKI β 2 appears to be maximal activity in vitro. Replacement of Thr171 with Ala or Asp prevented phosphorylation and activation by CaMKK and the latter replacement also led to partial activation even in the absence of CaMKK. The phosphorylation at Thr171 occurred in response to a Ca²⁺ ionophore, ionomycin, within 1 min in CaMKI β 2 transfected cells. Thr304 was phosphorylated at a slower rate and the phosphorylation occurred after 5 min from stimulation. CaMKI β 2 activated by CaMKK lost most of its activity with incubation in the absence of Ca²⁺ while the enzyme which was not phosphorylated at Thr171 decreased much milder. The activity of the mutant with substitution of Thr304 to Ala partially decreased in the same condition. These indicate that CaMKI β 2 has additional phosphorylation site as well as Thr304 to inhibit the activity following activation. These results suggest that this auto-regulatory mechanism ensure the rapid activation and inactivation of CaMKI β 2 in response to intracellular Ca²⁺ level.

MS2-06 The FcR γ / Fyn signaling cascade is critical in brain during cuprizone-induced demyelination and myelination

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Inclusion of cuprizone (bis-cyclohexanone oxaldihydrazone) in the diet of mice produces a massive demyelination, when cuprizone was removed from the diet, remyelination was initiated. Previously we have shown that signaling via FcR γ induces the Fyn-MBP cascade for myelogenesis. To elucidate whether FcR γ and Fyn signaling cascade are also involved in the process of demyelination and remyelination, we used FcR γ /Fyn doubly deficient mice, and mice were fed a diet containing 0.2% cuprizone for 3 weeks or 5 weeks, and then a normal diet for 2 weeks. Firstly, we examined total and phosphorylated MBP expression, because MBP is the major phosphoprotein of central nervous system myelin. After 3 weeks of exposure to cuprizone, phosphorylated MBP is remarkably decreased in normal control mice and after 7 weeks of recovery in normal diet, phosphorylation of MBP levels were near the normal. However, phosphorylated MBP components did not change in the mutant mice. In addition, after the recovery, the phosphorylation of MBPs were still profoundly depressed. These results suggest that MBP phosphorylation may be involved in the process of demyelination and / or remyelination.

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MS3-01 Changes in expression of neurotrophic factors by nicotine in cultured astrocytes

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This study was aimed at investigation of mechanisms underlying signaling mediated by nicotinic acetylcholine receptors (nAChRs) in cultured rat neocortical astrocytes. nAChRs are composed of heteromeric assemblies of at least eight alpha subunits ($\alpha 2$ - $\alpha 9$) and three beta subunits ($\beta 2$ - $\beta 4$), while $\alpha 8$ subunit is absent from mammals. Cortical astrocytes were incubated with fluo-3 AM for determination of intracellular free Ca^{2+} on fluorescence image analysis. Astrocytes were exposed to nicotine at different concentration from 10 to 1,000 μ M, followed by determination of the number of cells with high fluorescent intensity 2 min later. The exposure to nicotine led to an increase in the number of cells with high fluorescence intensity in cortical astrocytes. This increase by nicotine was significantly prevented by the addition of the $\alpha 4\beta 2$ heteromeric subtype specific antagonist dihydro- β -erythroidine and the $\alpha 7$ homomeric subtype specific antagonist methyllycaconitine, respectively. Cortical neural preparations were exposed to nicotine for 8 h, followed by further exposure to hydrogen peroxide at 100 μ M for 6 h and subsequent determination of cell survivability on MTT colorimetric assays. The prior exposure to nicotine significantly attenuated cell death induced by subsequent hydrogen peroxide in cortical neural preparations. Cortical astrocytes were exposed to nicotine at different concentrations up to 1,000 μ M for 8 h, followed by detection of mRNA for different neurotrophic factors on RT-PCR. The exposure to nicotine induced a marked increase in expression of various neurotrophic factor mRNA in cultured cortical astrocytes. These results suggest that nAChRs may be functionally expressed by rat neocortical astrocytes to induce expression of different neurotrophic factors.

MS3-03 Activity-dependent interaction between axons and astrocytes promotes CNS myelination

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Previous work from our lab has demonstrated that activity-dependent release of ATP and adenosine from premyelinated axons activates purinergic receptors on myelinating glia and regulates their development and myelination in response to action potential firing. Here we report a new mechanism of activity-dependent regulation of myelination mediated by astrocytes. Release of ATP from premyelinating axons firing action potentials causes release of the cytokine LIF, which acts on oligodendrocytes at the premyelinating stage to promote differentiation and increase myelination. Measurements of conditioned medium show that LIF is released from astrocytes in culture in response to ATP receptor activation. Release of LIF from astrocytes grown on DRG axons was also induced by stimulating action potential firing with electrical pulses, and LIF release was inhibited by electrical stimulation in the presence of apyrase, an enzyme that rapidly degrades extracellular ATP. Levels of LIF mRNA were increased in astrocytes stimulated with ATP receptor agonists or grown on axons stimulated to fire action potentials. This process occurred only after oligodendrocyte progenitor cells (OPCs) have matured to the O1 positive stage. ATP treatment of O1 positive OPCs in co-culture with DRG neurons increased the number of MOG positive oligodendrocytes 7 days after ATP treatment, and increased the number of MOG positive myelin profiles counted after 14-21 days. These results involve astrocytes in the activity-dependent regulation of myelination, and provides an explanation for the unexpected myelin deficits reported in GFAP deficient mice and LIF deficient mice.

MS3-05 Glia-to-vascular communication mediated by extracellular ATP

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Recent accumulating evidence show that glial cells especially astrocytes have active roles to modulate synaptic transmission. They respond to various neurotransmitters or mechanical stimuli, and release various diffusible molecules that function as the astrocyte-to-astrocyte and also the astrocyte-to-neuron mediators. We previously showed that astrocytes release ATP in response to various stimuli and form intercellular Ca^{2+} wave that even invaded into adjacent neurons, resulted in dynamic regulation of synaptic transmission. Astrocytes surround not only synapses but also vascular walls using astrocytic endfeet. In this study, we show that the extracellular ATP-dependent Ca^{2+} wave also travels into astrocytic endfeet where P2Y2 receptors are present. P2 receptors are also present in vascular walls including brain pericytes and vascular smooth muscle cells, and activation of these P2 receptors could modulate vascular tones. We demonstrate that astrocytes regulate vascular function via (1) a dynamic communication by extracellular ATP and (2) through a molecule(s) that is upregulated by P2Y2 receptor-mediated signals in astrocytic endfeet.

MS3-02 PGE2 modulates the hippocampal neuron loss induced by kainic acid

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Neurons and astrocytes form intimate networks in the brain. In responding to neuronal activity, astrocytes release glutamate, leading to increases in neuronal Ca^{2+} levels. Prostaglandin (PG) E₂ has been implicated in the Ca^{2+} -dependent glutamate release in astrocytes, suggesting that PGE₂ is important in the neuron-astrocyte signalling pathway. In neurological diseases, including epileptic seizures, this signalling pathway may be accelerated, leading to increases in neuronal Ca^{2+} levels and neuronal cell death. Here we investigated the source and the effect of PGE₂ on neuron-astrocyte signalling in vivo using hippocampal microinjection of kainic acid (KA). Following the microinjection of KA, the concentration of hippocampal PGE₂ showed a delayed continuous elevation. We also observed CA3 pyramidal neurons were completely lost in the ipsilateral side. As cyclooxygenase-2 (COX-2) selective inhibitor, NS398 completely blocked the elevation of PGE₂ and decreased neuron loss significantly, the delayed neurotoxicity may be mediated by a sustained increase of PGE₂ that was produced by COX-2. Then, we investigated the expression and regulation of PGE₂ synthase, mPGES-1, in the brain. mPGES-1 was induced by KA in vascular endothelial cells, but not in either neurons or astrocytes. Using mPGES-1 knockout mice (mPGES-1^{-/-}), we are currently studying whether mPGES-1 is involved in the regulation of in vivo astrocyte-neuron signalling.

MS3-04 Sema4D implicated in NGF-dependent neurite outgrowth

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Semaphorins were primarily found as repulsive molecules that retract growing axons. However, these also functions as attractive factors to grow axons depending on neuron types or developmental stages. For example, we previously found that Sema4D stimulated axonal outgrowth of embryonic dorsal root ganglion (DRG) neurons in stead of retraction. Sema4D (S4D) acted as an attractive cues in a nerve growth factor (NGF)-dependent manner in these neurons, since antibody to NGF blocked its action. In this study we investigate whether S4D itself activates NGF receptor, TrkA or it stimulates NGF-triggered activation of TrkA, by using HEK 293T cells transfected with trkA and/or plexinB1. We found that S4D accelerated NGF-induced activation of TrkA when cells were transfected with trkA and plexinB1, but did not when cells were transfected with trkA alone. Furthermore, we found that PlexinB1 is associated with TrkA, but not TrkB, suggesting that S4D could enhance NGF-signaling, but not BDNF signaling. Since S4D activates RhoA small GTPase via PlexinB1 and PDZ-containing RhoGEF (Hirokawa et al., 2002), however it is not clear how Sema4D-plexinB1 signaling associate with NGF-TrkA signaling. We will further investigate whether TrkA associating with plexinB1 is involved in neurite outgrowing action of S4D in relating to Rho small GTPase family in the DRG neurons.

MS3-06 Tissue distribution and functional analysis for contactin associated protein 4 (Caspr4) in central nervous system

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Contactin associated protein 4 (Caspr 4) is a member of the Caspr family that contains five molecules so far identified in mammals. Among these molecules, Caspr 1 and Caspr 2 have been well characterized as key molecules that are functionally related to the formations of paranodal and juxtaparanodal junctions of both central and peripheral myelin, respectively. In contrast with them, the roles of Caspr 3, 4 and 5 have not been well characterized yet. In this study, we focused on Caspr 4, and tried to characterize its tissue distribution and molecular interactions especially in the intracellular region. To characterize the aspect of its expression, we generated a polyclonal antibody against human Caspr4, and we found that Caspr4 was dominantly expressed in the central nervous system. The expression level was up-regulated after birth and kept in high level in adult. Moreover, Caspr 4 was subcellularly localized in synaptosome, Golgi, ER and plasma membrane. In the previous study, we screened human adult brain cDNA library to identify the molecules that interact with Caspr 4 intracellular domain by using Yeast two-hybrid system, and we found that Ligand of Numb protein X2 (Lnx2) was a candidate which functionally interacted with PDZ binding motif of Caspr 4. Lnx2 contains a Ring finger domain, four PDZ domains and the class II PDZ binding motif at the C-terminal portion. According to the results from GST-pull down assay, we found that the intracellular region of Caspr 4 bound to either one of four PDZ domains of Lnx2. We have been currently performing the immunocytochemical and molecular biological analyses to investigate their functional interactions on the mechanisms of cell signal transduction.

MS3-07 Cystatin F mRNA expression in spontaneous chronic late-onset demyelination animal model

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Cystatin F is a type cystatin that has been discovered recently, and is one of the endogenous papain-like cathepsin inhibitors which have high affinity with cathepsin L. In normal tissue cystatin F mRNA expression was found in lymphoid organs, such as thymus, spleen, and lymph nodes. In pathological conditions, its expression was detected in some kinds of tumor cells. Till now, however, there are no reports about the expression of cystatin F in the central nervous system. In our laboratory, by the cDNA microarray analysis, about 6 folds higher expression of cystatin F mRNA was found in the brain of spontaneous chronic late-onset demyelination disease animal model produced by overexpression of the proteolipid protein gene. By *in situ* hybridization study, the expression of cystatin F was detected in the white matter of model mice, but not in the wild type mice. By further detailed study, we found that cystatin F is mainly expressed in microglial cells, which have been found to be activated according to the previous studies, not in astrocytes or oligodendrocytes. In other demyelination disease animal models, like jimpy or shiverer mice, no expression of cystatin F was found in the brain by *in situ* hybridization method. Thus, the expression of cystatin F mRNA may be the feature of demyelinating diseases and involved in the demyelinating process through the activated microglial cells.

MS4-02 Multiple candidate genes analysis identifies α -synuclein as a susceptibility gene for sporadic Parkinson's disease

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Parkinson's disease (PD), one of most common human neurodegenerative diseases, is characterized by loss of dopaminergic neurons in substantia nigra of midbrain. PD is a complex disorder, with multiple genetic and environmental factors influencing disease risk. To identify causative genes for sporadic PD, we performed case-control association studies of 267 single nucleotide polymorphisms (SNPs) in 122 candidate genes. Of the 267 SNPs tested, rs7684318 in α -synuclein (*SNCA*), a major component of Lewy bodies (pathological hallmark of PD), showed the strongest association with PD ($p=5.0 \times 10^{-10}$). Linkage disequilibrium (LD) analysis by using 29 SNPs in the 430 kb region around rs7684318 revealed that the entire *SNCA* gene is in a single LD block ($D' > 0.9$) spanning about 120 kb. Within this LD block, six SNPs including rs7684318 were in a tight LD group ($r^2 > 0.85$) and most strongly associated with PD ($p=2.0 \times 10^{-9}$ – 1.7×10^{-11}). Haplotype association analysis did not show lower p-values than a single SNP. Allele C of rs7684318 was positively associated with PD, more strongly in recessive model than in dominant model. Real-time RT-PCR analysis in relation to rs7684318 genotypes showed that *SNCA* expression level tended to be lower in CC than in CT and TT in lymphoblastoid cells and brain. These demonstrate that *SNCA* is a definite susceptibility gene for sporadic PD and suggest that low expression of *SNCA* also has a relation to etiology of the disease.

MS4-04 The role of galectins during goldfish optic nerve regeneration

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The mammalian central nervous system (CNS) neurons fail to regenerate after lesions, whereas the lesions of fish CNS neurons are followed by successful recovery. We have investigated this recovery mechanism of goldfish optic nerve as a model system of CNS regeneration.

Galectin is a β -galactoside binding lectin and it is identified at least 14 subfamilies. The molecule is expressed by neural and nonneural cells intracellularly (cytoplasm and nucleus) as well as extracellularly (plasma membrane and extracellular space). Recently, galectin-1 has been shown to promote axonal elongation in peripheral nervous system, however, it is unclear whether galectins implicate in the CNS regeneration. Therefore, we studied effects of galectins on axonal regeneration after goldfish optic nerve transection. We cultured goldfish retinal explants in L-15 medium and added recombinant galectin-1 (oxidized form) into the medium for 5 days. The goldfish optic nerves had been injured 5 days previously. Compared with control retinal explants which were not treated with recombinant galectin-1, the neurite outgrowth was enhanced by recombinant galectin-1. We further investigated immunohistochemical localization of galectin-1 in goldfish retina. Positive immunoreactivity of galectin-1 in the retina was seen in the ganglion cells and inner nuclear layer during optic nerve regeneration. Thus, galectin-1 seems to involve in some roles for the optic nerve regeneration process. We are now in progress to isolate a cDNA fragment for goldfish galectin-1, and to further investigate the levels of galectin-1 mRNA and cellular localization of galectin-1 mRNA after optic nerve transection.

MS4-01 Altered bHLH gene expression in cortical cells by A β and its role in cell death

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Neurogenesis is enhanced in AD or a mutant APP transgenic mouse hippocampus. However, A β action on neural stem cells has been controversial: impairing vs. promoting neuronal differentiation of cultured neural stem cells. Mash1 is a bHLH factor, which is involved in initiating neurogenesis. Up-regulation of Mash1 has been documented in adult hippocampus after ischemia or in status epilepticus, however, its regulation in AD has not known yet. Here we have demonstrated the up-regulation of Mash1 and down-regulation of Olig2 in cerebral cortical cultures treated with A β . Mash1 was expressed in nestin-positive immature cells but was rarely expressed in postmitotic neurons in the cerebral cortical culture. Majority of Mash1-positive cells in the cortical culture co-expressed Olig2. A β increased in the proportion of Olig2-negative/mash1+ cells, which are not labeled with the cell markers of neurons, astrocytes or oligodendrocytes. These results indicate that A β 1-42 may alter the gene expression of Mash1 and Olig2 in immature cells, possibly neural stem cells. Misexpression of Mash1 in neurosphere cells enhanced neural differentiation in the presence of EGF/FGF2, but it accelerated cell death in the absence of EGF/FGF2. The growth factor deprivation altered the expression of bHLH factors in neurosphere cells: the up-regulation of Mash1 and the down-regulation of Olig2. This mimics the alteration of Mash1 and Olig2 expressions in immature cells in A β -treated cortical cultures, suggesting that A β may alter the bHLH gene expression in neural stem cells to undergo cell death.

MS4-03 Selegiline potentiates effects of donepezil on cognitive impairment induced by amyloid beta (25-35)

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Selegiline, which is an irreversible inhibitor of monoamine oxidase B and is used as the therapeutic drug in Parkinson's disease, has been demonstrated to have potential cognitive-improving effects on Alzheimer's disease (AD) under the treatment with a cholinesterase inhibitor (ChE-I), donepezil. To confirm such clinical events, in this study, we investigated whether the co-administration of donepezil with selegiline showed the synergistic cognitive-improving effects in an animal model of AD. Either donepezil (0.1 mg/kg) or selegiline (3 mg/kg) improved the cognitive deficits induced by intracerebroventricular injection of amyloid beta (25-35) (A β) in the Y-maze and conditioned-fear learning, whereas selegiline (3 mg/kg), but not donepezil (0.1 mg/kg), improved the deficit of the novel-object recognition task in A β -treated mice. Co-administration of donepezil (0.05 mg/kg) with selegiline (1 mg/kg), significantly improved the deficits in those tests at the non-effective dose by themselves, indicating synergistic cognitive-improving effects. Such improved effects were antagonized by pretreatment with scopolamine, a muscarinic receptor antagonist, or haloperidol, a dopamine receptor antagonist. Furthermore, co-administration of donepezil (0.05 mg/kg) with selegiline (1 mg/kg) significantly recovered the decreased level of total glutathione in the frontal cortex, and the level of oxidized glutathione was not changed by any treatments. These results suggest that 1) selegiline can potentiate the effect of donepezil to ameliorate the cognitive deficits in AD, 2) such synergistic effect is mediated through both cholinergic and dopaminergic systems, and 3) selegiline in combination with donepezil can protect neurons in the frontal cortex from oxidative stress elicited by A β .

MS4-05 Effects of CICR on interleukin-1 β -associated adenosine releases in mouse hippocampus

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Interleukin-1 β (IL-1 β) and adenosine, which are respective peptide and nonpeptide neuromodulators, play an important role in both excitatory and inhibitory neurotransmission. Especially, these neuromodulators contribute to neuroprotection and neurodegeneration in the CNS. To clarify the possible mechanisms of controversial actions of these neuromodulators, we determined the effects of Ca²⁺-induced Ca²⁺-releasing system (CICR) on IL-1 β -induced adenosine release in hippocampus using *in vitro* mini-slice method. Both basal and K⁺-evoked adenosine releases were increased by 3.5 ng/ml IL-1 β , while those releases were decreased by inhibitors of CICRs, including inositol 1,4,5-trisphosphate receptor (IP3R) and ryanodine receptor (RyR). The stimulatory effect of IL-1 β on basal adenosine release was reduced by removal of extracellular Ca²⁺ and IP3R inhibitor, but was not affected by RyR inhibitor. The stimulatory effect of IL-1 β on K⁺-evoked adenosine release was reduced by RyR inhibitor, whereas neither removal of extracellular Ca²⁺ nor IP3R inhibitor affected. Intraneuronal Ca²⁺ mobilization regulates various neuronal processes; however, overload response of Ca²⁺ mobilization prevents neuronal processes and leads to neuronal damage. It has been demonstrated that IL-1 β increases intracellular Ca²⁺ level dose-dependently through activation of both Ca²⁺ influx and CICR. In addition, adenosine is widely accepted to be an inhibitory and excitatory neuromodulator via adenosine A1 and A2 receptors, respectively. Therefore, the present results suggest that the potent effect of IL-1 β to adenosine release might contribute to the neuroprotective action of IL-1 β , whereas, IL-1 β -induced neurodegeneration might be due to the overload response of Ca²⁺ mobilization induced by IL-1 β .

MS5-01 Impaired development of sensory neurons in mice lacking paternal neccdin gene

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Necdin is expressed in terminally differentiated neurons and acts as a signaling protein that suppresses both mitosis and apoptosis. The human neccdin gene (NDN) located in chromosome 15q11-q13 is maternally imprinted, paternally transcribed, and not expressed in Prader-Willi syndrome (PWS), a human genomic imprinting-associated neurodevelopmental disorder. Although neccdin deficient mice display several abnormal phenotypes, little is known about molecular mechanisms leading to neurodevelopmental defects. We have previously reported that neccdin is involved in the maturation of nerve growth factor (NGF)-dependent sensory neurons in the dorsal root ganglia (DRG). In this study, we analyzed the development of DRG neurons in mutant mice deficient in the paternal neccdin gene. Mouse embryos defective in the paternal neccdin allele displayed absent neccdin expression in DRG, in which the TrkA receptor tyrosine kinase and the p75 neurotrophin receptor are expressed in a normal fashion. Neccdin was coexpressed with the NGF receptors TrkA receptor tyrosine kinase and p75 neurotrophin receptor in subpopulations of DRG neurons. Neccdin null DRG had an increased number of apoptotic neurons at embryonic day 12.5. Furthermore, neccdin null DRG had a reduced density of substance P-containing neurons which require NGF for their survival and development. Behavioral analyses of thermal sensation showed that neccdin null mice at postnatal stages had significantly high tolerance to heat-induced pain, which is often observed in individuals with PWS. These results suggest that paternally expressed neccdin promotes the survival of NGF-dependent neurons by enhancing TrkA signal pathway and plays an important role in sensory neuron development.

MS5-03 4-Methylcatechol facilitates survival of cultured neural stem cells via enhanced expression of heme oxygenase-1 without changing their differentiation fate

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4-Methylcatechol (4MC) was initially found as a stimulator of neurotrophin synthesis in various cultured cells. Further studies revealed that 4MC directly activates MAPK/ERK and Trks, high-affinity neurotrophin receptor family, and maintains neuronal survival without mediation of neurotrophin actions in rat cortical neurons, suggesting direct neurotrophic actions of 4MC. Chronic injection into rats elicited nerve sprouting from the transected sciatic nerve, and suppressed peripheral neuropathies accompanied by diabetes or acrylamide toxicity. These suggest that 4MC behaves like a neurotrophic molecule in vivo and in vitro. As the effects on neuronal differentiation have not been examined, the actions of 4MC on neural stem cells (NSCs) cultured from 15-day-old rat embryos were investigated. Cells grown in neurospheres were dissociated and plated on culture vessels coated with poly-L-ornithine, and cultured for another 3 days in the presence of FGF-2. After several days following a short time treatment with 4MC in the absence of FGF-2, RT-PCR, immunoblot and immunohistochemical analysis revealed that 4MC treatment did not induce neuronal or glial differentiation of the cells. A few hours after the exposure to 4MC, RT-PCR and immunoblot analysis showed that the expression of heme oxygenase (HO)-1 mRNA and protein were markedly enhanced. Hydrogen peroxide-treatment caused a substantial level of cell death of the NSCs, but pretreatment with 4MC antagonized against the effect. These results may present a merit of 4MC as a therapeutic drug for neuronal disorders, because it supports survival of NSCs and related cells without changing their differentiation fate.

MS5-05 Activation of the wnt/ β -catenin pathway promotes proliferation of neural progenitor cells in the adult mouse subventricular zone

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The subventricular zone (SVZ) of the lateral ventricle in the adult mammalian brain contains various types of precursor cells with distinct function and morphology. Type B astrocytes act as neural stem cells that generate rapidly proliferating transit-amplifying precursor cells (type C cells) and then differentiate into migrating neuroblasts (type A cells). Previous studies indicate that wnt/ β -catenin signaling pathway is involved in the control of proliferation or neuronal differentiation of neural progenitor cells in the embryonic brain. Here, we studied the role of the wnt/ β -catenin signaling in the adult mouse SVZ. Nuclear accumulation of β -catenin was observed in a small population of SVZ cells in the normal adult brain. Administration of an inhibitor for GSK-3 β increased the number of SVZ cells that contain detectable amount of nuclear β -catenin and the number of proliferating type C cells. Retrovirus-mediated expression of a stabilized β -catenin also promoted proliferation of type C cells and inhibited their differentiation into the type A cells. These results suggest that β -catenin can induce proliferation of type C cells in the adult mouse SVZ.

MS5-02 BDNF influences the decision of the neuronal laminar fate during development of the mouse cerebral cortex through precocious neurogenesis.

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The cerebral cortex is organized into six neuronal layers, each of which contains neurons with similar morphology, function, gene/molecular expression, and axonal projection. The neurons peculiar to each layer are generated sequentially in the ventricular zone (VZ) of the dorsal telencephalon at embryonic stages, migrate to the cortical plate (CP) and occupy final position there. The earlier-born neurons come to lie in the deeper layer and the later-born ones in the more superficial layer. Although many molecules involved in the migration and/or positioning have identified, mechanisms for generation of layer-specific neurons are poorly understood. To test a possibility that brain-derived neurotrophic factor (BDNF) is involved in the laminar formation, we examined effects of BDNF protein or anti-BDNF antibody that neutralizes BDNF activity on the behavior and property of neural progenitor cells after injection into the ventricular space of 13.5-day-old embryonic mice. The cells were labeled with bromodeoxyuridine (BrdU) or transfected with green fluorescent protein (GFP) expression vector before analyses. BDNF altered the position and gene expression of BrdU-labeled and/or GFP-expressing neurons for layer IV to those of the neurons of layer V-VI. Further, BDNF could act on neural progenitors only when they were around S-phase of cell cycle, and hasten their interkinetic migration in the VZ followed by accelerated timing of neurogenesis of their daughter cells. Moreover, anti-BDNF antibody altered the migration to upper layer, opposite direction caused by BDNF itself. These results strongly suggested that BDNF is a factor involved in the decision mechanisms of the neuronal laminar fate of the cerebral cortex during development.

MS5-04 The *Drosophila* retinin gene is required for proper development of photoreceptors

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To identify the genes functioning in visual phototransduction and visual system development in *Drosophila melanogaster*, we performed 2-dimensional electrophoresis/MALDI-ToF analysis for wild type and *eya* (eyes absent) mutant head protein extracts. We identified over 40 protein spots from this analysis, that are present only in wild type heads not in *eya* mutant heads. Among these protein spots, three abundant protein spots with molecular weight of about 20 kDa and with different isoelectric points were all turned out to correspond to the *Drosophila* retinin protein, the protein discovered about twenty years ago but with no known functions elucidated so far. Western analysis using anti-phosphothreonine antibody showed that these three protein spots are the differently phosphorylated forms of retinin. Northern analysis using retinin cDNA as probe showed that the gene is expressed only in the eyes of *Drosophila*. We isolated the knockout mutants for the retinin gene by using RNAi and found that the retinin protein is required for the proper development of *Drosophila* photoreceptor cells. [Supported by the Neurobiology Research Program from the Korean Ministry of Science and Technology]

MS5-06 Different labeling methods delineate different cell classes and migratory paths of the early postnatal subventricular zone progenitors

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The early postnatal subventricular zone (SVZ) generates either glia or olfactory interneurons. By retroviral labeling of the SVZ progenitors, we have previously observed two migration patterns: (1) progenitors migrated radially into the overlying white matter and cortex, but only at the level of viral injection; these gave rise to astrocytes and oligodendrocytes, (2) progenitors migrated in a bidirectional, rostrocaudal pattern along the entire extent of the SVZ; these cells migrated into the olfactory bulb (OB) and developed into interneurons, but they did not turn to migrate radially out of the SVZ until they reached the OB. To determine broader cell classes of the early postnatal SVZ progenitors and their migratory paths, we injected PKH26 lipophilic dye either in the posterior SVZ (pSVZ) or the lateral ventricle (LV) of neonatal rats, immunohistochemically characterized the labeled cells, and compared the labeling pattern with that obtained by retroviral injection. We found that LV injection of PKH26 labeled glial progenitors migrating radially out of the SVZ along the entire rostrocaudal extent of the SVZ including the rostral migratory stream (RMS) and OB, while pSVZ injection of PKH26 or retrovirus never labeled cells migrating radially out of the RMS proximal to the OB. We assume the glial progenitors migrating radially out of the RMS were labeled by the dye having reached the RMS through the rostral extent of the ventricle. Using multiple labeling techniques and comparing the results would lead us to further understanding of the complex cell migration patterns in the developing brain.

MS6-01 Wnt-3a promotes both neural progenitor proliferation and neuronal differentiation during hippocampal development.

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Wnt family proteins are secreted glycoproteins that consist of at least 19 members in mouse. Among them, Wnt-3a is markedly expressed in the developing hippocampus. A function of Wnt-3a was demonstrated to be essential for hippocampal formation, since a targeted disruption of the mouse Wnt-3a gene caused ablation of hippocampus (Lee et al., 2000: Development 127, 457-467). In spite of this severe defect appeared in the mutants, the direct role of Wnt-3a on hippocampal cell development has yet to be elucidated. Thus, we study whether Wnt-3a is involved in the proliferation of hippocampal progenitors, differentiation of hippocampal neurons, or their survival. The primary cultures were prepared from E15 mouse hippocampus, and treated with or without recombinant Wnt-3a for 4 days. Wnt-3a induced a 1.4-fold increase in the number of total cells. The number of Tuj1-positive neurons was also increased to 1.4-fold by Wnt-3a. Thus, Wnt-3a-stimulated hippocampal progenitors showed two distinct phenotypes, elevated cell proliferation and neuronal differentiation. These data raise two possibilities of Wnt-3a action: (1) Wnt-3a promotes cell divisions of hippocampal progenitor cells, but does not inhibit their neuronal differentiation like the other mitogens for neural progenitors (FGF2 etc.). This idea is consistent with our observation that there is no significant difference in the percentage of Tuj1-positive neurons between Wnt3a-treated and non-treated cultures. (2) There are two distinct populations of neural progenitors that show different responses to Wnt-3a stimulation: proliferation and differentiation. These hypotheses are currently challenged by a series of BrdU incorporation assays with various timings of BrdU application.

MS6-03 Roles of Disrupted-In-Schizophrenia-1 in the later stage of hippocampal neuron

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Disrupted-In-Schizophrenia 1 (DISC1) is a candidate gene for schizophrenia as susceptibility factor. DISC1 is reported to interact with NUDEL, FEZ1, ATF4/5, and so on. However, the function of DISC1 remains to be clarified. To understand roles of DISC1, we here identified Pur- α , hnRNP-U and RACK1 as DISC1-interacting molecules. Recent studies indicate that Pur- α , hnRNP-U and RACK1 are components of messenger ribonucleo-protein (mRNP) complex. We found that DISC1 formed a complex with Pur- α , hnRNP-U and RACK1 *in vitro*. DISC1 was co-localized with Pur- α and mRNP complex in dendrites and dendritic spine of cultured hippocampal neurons. These results indicate that DISC1 forms a complex with mRNP complex including Pur- α , hnRNP-U and RACK1 in dendrites. To determine physiological roles of DISC1 in neuronal morphologies, we performed the knockdown of DISC1 using RNA interference. In DISC1-depleted neurons distributions of mRNA granules and RACK1, which is component of mRNP complex, did not change. These results suggest that DISC1 is not essential for determination of mRNP complex distribution. The role of DISC1 in neuronal morphologies and functions will be discussed.

MS6-05 Fate and origin of multipolar cells during the cortical plate development

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During the development of mammalian cerebral cortex, majority of the cortical plate neurons are generated in the ventricular zone (VZ) facing the lateral ventricle and then migrate toward the pial surface passing through the subventricular zone (SVZ), intermediate zone (IZ), and developing cortical plate (CP). Three distinct migration modes are known for this radial migration. Locomotion is the best known migration mode, in which neurons migrate using the radial fibers as the scaffold. In somal translocation, neurons retract their processes reaching the pial surface to elevate the cell body. Third migration mode is multipolar migration, which we previously reported (J Neurosci, 23, 9996-10001(2003)). The cells using this mode were frequently found in the SVZ/IZ, and were observed to move toward the cortical plate very slowly with frequent changes in the direction and rate of their migration. We also observed that the multipolar cells transformed into locomotion cells and then entered the CP. These observations suggest that the cortical plate neurons migrate via multiple phases rather than using only one mode chosen. However, how frequently the migrating neurons from the VZ take multipolar migration mode *in vivo*, and how the multipolar cells are generated have not been fully described. To chase the cohort which finished the terminal cell division at the particular period in the VZ, we applied bromodeoxyuridine and iododeoxyuridine sequentially into the mouse which had been introduced with a GFP-expressing vector using *in utero* electroporation system. We also observed several patterns of the generation of the multipolar migration cells in slice cultures. The origin and fate of multipolar cells will be discussed.

MS6-02 Neurogenesis in the adult mouse striatum after cerebral ischemia

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Previous studies indicate that cerebral ischemia induces proliferation of neural progenitor cells followed by a partial regeneration of neurons in the damaged brain tissue. In our mouse model of transient middle cerebral artery occlusion (MCAO), the number of proliferating cells in the subventricular zone (SVZ) significantly increased at 14 days after MCAO, followed by appearance of Doublecortin-positive neuroblasts in the ischemic striatum. Cell lineage analyses using a Cre-LoxP system suggest that some of these neuroblasts were born in the SVZ, and then migrated into the damaged striatum. In addition, we found a number of Mash1-positive cells in the ischemic striatum, which probably correspond to the Type C transit amplifying precursors that are supposed to be immotile. Intrastriatal infusion of Noggin increased the number of neuroblasts in the striatum, while EGF decreased it. These results suggest a possibility that the ischemic striatum as well as the SVZ contain neural progenitor cells that contribute to neuronal regeneration.

MS6-04 RGMA inhibition promotes axonal growth and recovery after spinal cord injury

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Repulsive guidance molecule (RGM) is a recently identified protein implicated in both axonal guidance and neural tube closure. Here we report RGMA as a potent inhibitor of axon regeneration in the adult central nervous system (CNS). RGMA inhibits mammalian CNS neurite outgrowth by a mechanism dependent on activation of the Rho/Rho-kinase pathway. RGMA expression is found in oligodendrocytes, myelinated fibers, and neurons in adult rat spinal cord, and is induced around the injury site following spinal cord injury. We developed an antibody to RGMA, which efficiently blocks the effect of RGMA *in vitro*. Intrathecal administration of the antibody to rats with thoracic spinal cord hemisection results in significant axon growth of the corticospinal tract, and improves functional recovery. Thus, RGMA plays an important role in limiting axonal regeneration after CNS injury, and the RGMA antibody offers a possible therapeutic agent in clinical conditions characterized by a failure of CNS regeneration.

MS6-06 IQGAP3, a novel effector of Rac1 and Cdc42, regulates neurite outgrowth through actin cytoskeletal reorganization

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Rac1 and Cdc42, members of Rho family GTPases, play critical roles in diverse cellular processes such as axon guidance and neuronal morphogenesis. They exert the physiological functions through the reorganization of cytoskeleton and adhesion molecules in the concert with their effectors. Here, we identified IQGAP3, closely related to other IQGAPs, as a novel effector of Rac1 and Cdc42. We found that IQGAP3 is predominantly expressed in brain and directly binds to actin filaments through its calponin homology domain. In cultured hippocampal neurons, IQGAP3 accumulated at the proximal region of axon and the tips of dendrites. We also found that the depletion of IQGAP3 inhibits neurite outgrowth and axonogenesis. Furthermore, IQGAP3 was indispensable for the Rac1/Cdc42-induced neurite elongation and branching in PC12 cells. These results indicate that IQGAP3 regulates neurite elongation and axonogenesis through the regulation of actin filaments downstream of Rac1 and Cdc42.

MS7-01 Visualization of newly deposited tau in neurofibrillary tangles and neuropil threads

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Neurofibrillary tangles (NFTs) and neuropil threads (NTs), the major hallmark of Alzheimer's disease (AD), are composed of the microtubule-associated protein tau that has undergone posttranslational modifications, including deamidation and isomerization on asparaginyl or aspartyl residues. Because such modifications represent protein aging, we generated two antibodies, TM4, specific for Asp-387 of tau, and iD387, specific for isoAsp-387 of tau, to investigate the evolution of NFTs and NTs. On western blots of Sarkosyl-insoluble fractions, TM4 strongly labeled paired helical filament-tau (PHF-tau), while iD387 preferentially labeled PHF-smear. Thus, it is reasonable to postulate that TM4-labeled tau (unmodified tau species) represents more recent deposition, and iD387-labeled tau (modified tau species) represents earlier deposition. Unexpectedly, TM4 even immunostained highly evolved NFTs, suggesting that deposition of newly produced tau continues until neuronal death. iD387 labeled the whole profile of NFTs up to distal dendritic branches, whereas TM4-staining was localized to particular portions of NFTs in proximal dendrites and neuronal perikarya. In NTs, TM4 preferentially labeled the outer portion, whereas iD387 intensely labeled the core portion. Based on TM4-positive NFT counts and total NFT counts, we speculate that NFTs in the human hippocampus are produced at a constant rate irrespective of the disease stage.

MS7-03 Neurotoxic function of induced microsomal prostaglandin E₂ synthase-1 in cerebral ischemia.

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The production of prostaglandin E₂ (PGE₂) is known to be observed in the ischemic brain regions, however, the induction and roles of microsomal PGE₂ synthase (mPGES)-1, an inducible terminal enzyme for PGE₂, in the brain after ischemia have not been identified yet. In cerebral cortex of rat brain after transient ischemia, we have demonstrated the coordinate inductions of mPGES-1 and COX-2 in microglia and endothelial cells (Yuri Ikeda-Matsuo et al. in this meeting). In this study, to clarify the roles of mPGES-1 induction observed in cerebral cortex in PGE₂ production and pathology of brain ischemia, male and female mPGES-1 knockout (KO) and wild-type (WT) mice were subjected to 2-hr of right middle cerebral artery occlusion and reperfusion. The mPGES-1 induction was observed in cerebral cortex of WT mice, but not in KO mice, 24 hr after transient ischemia. The induction of COX-2 and constitutive expression of mPGES-2, cPGES, and COX-1 were similar between the cortex of WT and KO mice. The ischemia-induced PGE₂ production observed in the cortex of WT mice was completely abolished in KO mice. Furthermore, using TTC staining, Tunnel staining and immunostaining for cleaved (activated) caspase-3 of brain slices 24 hr after ischemia, we found that ischemia-induced edema, infarction, apoptotic cell death and caspase-3 activation were all reduced in KO mice compared to WT mice. Finally, the behavioral neurological dysfunctions observed after ischemia in WT mice were significantly improved in KO mice. These results suggest that PGE₂ production though induction of mPGES-1 after transient ischemia is one of the most possible candidates contributing to expansion of the ischemic brain damage.

MS7-05 Hydrogen sulfide is the mediator of cysteine neurotoxicity in cerebral ischemia

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Elevated plasma homocysteine is linked to increased risk of acute stroke. Homocysteine may be converted to cysteine via an intermediate cystathionine. Cysteine is known to cause neuronal cell death and it has been reported to be elevated in brain ischemia, but little is known about the effects of cysteine in stroke and the mechanism of its neurotoxicity. Cerebral ischemia was studied in a rat stroke model created by permanent occlusion of the middle cerebral artery (MCAO). The resultant infarct volume was measured 24 h after occlusion. Administration of cysteine (10mmol/kg) significantly increased the infarct volume after MCAO. This increase was abolished by concomitant administration of either propargylglycine (PAG, an irreversible inhibitor of cystathionine γ -lyase (CSE)) or aminooxyacetic acid (AOAA, an inhibitor of cystathionine β -synthase (CBS)), inhibitors that prevent the formation of H₂S from cysteine. In addition, administration of sodium hydrosulphide (NaHS, an H₂S donor) mimicked the effects of cysteine but the NaHS-induced increase in infarct volume was not affected by PAG and AOAA. In contrast, the effects of both cysteine and NaHS were abolished by the administration of MK-801 (an NMDA receptor channel blocker). Administration of PAG alone, but not AOAA, significantly decreased the baseline level of MCAO-induced infarct volume. No changes were observed in the cortical mRNA expression of CBS and CSE after MCAO. The present results strongly suggest that the effects of cysteine occurred via the production of H₂S, which appears to be a mediator that contributes to ischemic damage after MCAO. Inhibition of H₂S synthesis may be a novel approach to stroke therapy.

MS7-02 The role of Caspase-4 in endoplasmic reticulum stress-induced apoptosis of familial Alzheimer's disease

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Missense mutations in the human presenilin-1 (PS1) gene, which is found on chromosome 14, cause early-onset familial Alzheimer's disease (FAD). We reported that mutations in PS1 affect the unfolded-protein response (UPR) by disturbed function of IRE1, which is the proximal sensor of conditions in the ER lumen and cause an increase in vulnerability to apoptosis induced by various cell stresses. And more, FAD-linked PS1 variants alter proteolytic processing of the amyloid precursor protein and cause an increase in vulnerability to apoptosis induced by various cell stresses and PS1 mutations also lead to decreased expression of GRP78/Bip, a molecular chaperone, present in the ER, that can enable protein folding. These results show that mutations in PS1 may increase vulnerability to ER stress by altering the UPR signalling pathway. On the other hand, although caspase-12 has been implicated in ER stress-induced apoptosis and amyloid-beta-induced apoptosis in rodents, it was controversial whether similar mechanisms operate in humans. Human caspase-4 was cloned as the most homologous gene to mouse caspase-12, in agreement with the fact that both molecules belong to the caspase-1/ICE subfamily within the caspase family. Then we confirmed that human caspase-4 is localized to the ER membrane and that is cleaved when cells are treated with ER stress-inducing reagents, but not with other apoptotic reagents. Thus, caspase-4 can function as an ER stress-specific caspase in humans, and may be involved in pathogenesis of AD. In this study, we investigate whether PS1 mutations effects on the cleavage of caspase4 and the cell death of

MS7-04 Attenuation of focal cerebral ischemic injury in transgenic mice overexpressing PAF-acetylhydrolase II (PAF-AH(II)) in neurons

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BACK GROUND AND PURPOSE: Reactive oxygen species (ROS) are produced in many physiological and pathological conditions including cerebral ischemia. ROS oxidize unsaturated fatty acyl chains in membrane phospholipids to produce toxic phospholipid hydroperoxides and a variety of oxidized phospholipids, both of which can cause cell damages and ultimately induce apoptosis. Platelet-activating factor (PAF)-acetylhydrolase isoform II (PAF-AH (II)) has the ability to hydrolyze short chain phospholipids and oxidized fragments of polyunsaturated fatty acids. Overexpression of PAF-AH (II) in Chinese hamster ovary-K1 cells suppressed oxidative stress-induced cell death. In the present study, we generated transgenic mice overexpressing PAF-AH (II) in neurons and examined neuroprotective effects of this enzyme in focal cerebral ischemic injury. METHODS and RESULTS: (1) We generated four independent lines of transgenic mice overexpressing the human PAF-AH (II) cDNA under the control of the mouse Thy 1.2 promoter. (2) Immunohistochemistry using anti-human PAF-AH (II) antibody revealed cytosolic stainings in neurons throughout the transgenic mouse brain. (3) Western blot and enzymic analyses confirmed overexpression of PAF-AH (II) in the transgenic mouse brain. (4) Male mice were subjected to 60 minutes of transient middle cerebral artery occlusion by a suture method. Infarct sizes after reperfusion for 24 hours, which were estimated by triphenyltetrazolium chloride (TTC)-staining mouse brains, were dramatically decreased in the transgenic mice compared with wild-type mice. CONCLUSION: Our data suggest that human PAF-AH (II) has the strong neuroprotective effects against ischemic injury.

MS8-01 Role of Phosphorylation Dependent Ubiquitination of BMAL1 in Mammalian Circadian Clock

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The molecular clockwork that causes the fundamental feedback loops to stably oscillate with a ~24 hr-periodicity remains unclear. Fibroblasts treated with serum-shock and dexamethazone (Dex) were used generally as the cellular clock model. Previous results suggest that BMAL1 in the clock-synchronized fibroblasts is turned over after functioning as a transcriptional driver. Here, we demonstrated that BMAL1 underwent proteolysis via ubiquitin (Ub)-proteasome pathway both in clock functioning (wild type) and non-functioning (CRY-/-) fibroblasts that expressed stably over-expressed Flag-Ub. The Ub-conjugation of BMAL1 was clearly suppressed by ERKs pathway inhibitors. Furthermore, Ubiquitin-proteasome and ERK pathway inhibitors clearly affected on Dex-induced circadian gene expression rhythms, which were monitored with rhythm-reporting system using fibroblasts stably expressing Per2- and BMAL1-luciferase. From these findings, we propose that turn over of BMAL1 protein via Ub-proteasome pathway, which is partially dependent on circadian regulated ERKs phosphorylation, is important in the stably oscillating clockwork in mammalian cells.

MS8-02 A Vibrissae-Related Pattern of Immunoreactive Parvalbumin and L1 in SI Cortex of Neuropilin- Deficient Mouse

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Our previous studies showed that the cell adhesion molecule L1 and its regulatory protease, neuropilin (NP), are involved in activity-dependent and neural injury-related cellular responses. It is known that the calcium-binding protein parvalbumin (PV) is highly responsive to several plasticity events including long term potentiation (LTP), kindling epileptogenesis, and post developmental neurogenesis induced by enriched environments. Thus, PV expression may be an appropriate marker to study the developmental plasticity of vibrissae-related cortical patterns. Since the relationship between L1 and NP in the developing cortex is still unknown, we examined PV-like and L1-like immunoreactivities (ir) in the vibrissal representation (the barrel) within the primary somatosensory cortex (SI) using NP^{-/-} and age-matched NP^{+/+} mice. PV-ir was localized to a prominent vibrissae-like array of patches in layer IV, consisting of dense terminal-like PV-ir and labeled interneurons of the SI cerebral cortex as shown by previous studies. On the other hand, L1-ir was condensed in the axon terminals in layer V and barrel septa of layer IV in the SI. NP-knockout mice displayed a lower density of PV-ir in the barrel area, but a less profound change in L1-ir in the same region. Further analysis was performed using mice kept in enriched environments to study activity-dependent changes of the PV-ir and L1-ir in the developing cerebral cortex.

MS8-04 Altered pericentrin 2 (PCNT2) expression in Bipolar Disorder

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Pericentrin 2 (PCNT2), a centrosomal protein, has been found to be an interacting partner of DISC1 (disrupted-in-schizophrenia 1) protein. DISC1 gene is considered as a potential candidate gene for major psychiatric disorders. Recently, it has been found that the DISC1 protein lacks functional motifs; hence, it has been hypothesized that a signaling cascade involving several molecules interacting with DISC1, rather than the DISC1 molecule itself, may explain the pathophysiology of several psychiatric disorders. PCNT2 is pivotal to microtubule organization and assembly of mitotic spindle apparatus. PCNT2 gene is located on chromosome 21q22.3, which is a bipolar disorder (BD) susceptibility region. In the present study, we examined the possibility of disease-related aberrant mRNA levels of PCNT2 in the postmortem brain samples (Stanley Foundation) of schizophrenia (n = 32), BD (n = 34) and control (n = 33). A significant difference in PCNT2 expression was observed between BD and control (Mann-Whitney U test; $p = 0.029$); PCNT2 expression in BD samples was found to be significantly higher than that in control. We also examined the differential expression of PCNT2 in the lymphocyte samples (Japanese) of schizophrenia (n = 26), BD (n = 21), and control (n = 59). An elevated expression of PCNT2 was observed in BD, compared to control ($p = 0.015$). In a case-control study of Japanese subjects, we investigated the association of PCNT2 allelic variants with BD (285 BD and 287 age- and gender-matched control), by analyzing 20 SNPs evenly distributed throughout the 121.6 kb gene; 2 SNPs showed a tendency for association with BD. Results from gene expression analysis and association study lead to the same conclusion that, PCNT2 may be a candidate gene for BD.

MS8-06 δ FosB determines resistance to excitotoxicity induced by kainic acid

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Expression of Jun and Fos proteins which form AP-1 transcription factor complex, are rapidly and transiently induced in neurons by various stimuli to the brain. It has been shown that kainic acid, an agonist for subsets of glutamate receptors, induces c-Fos and c-Jun expression in hippocampus, and that mice lacking c-Fos exhibit an increased sensitivity while mice defect in phosphorylation of c-Jun exhibit an increased resistance to the excitotoxicity induced by kainic acid. We have shown that expression of *fosB* gene, a member of *fos* family, is also induced in hippocampus by kainic acid. *fosB* gene produces FosB and Δ FosB by alternative splicing of its transcript. Δ FosB lacks the C-terminal 101 amino acid region of FosB which contains strong transactivating domains. FosB and Δ FosB can either upregulate or downregulate the expression of subsets of genes in an antagonistic manner. To investigate how FosB and δ FosB are involved in the excitotoxicity induced by kainic acid, we examined *fosB*-null mice lacking both FosB and δ FosB expression and *fosB^{Δd}* mice which express only δ FosB from the endogenous *fosB* gene. *fosB^{Δd}* mice express an increased level of δ FosB in hippocampus, and exhibited a decreased susceptibility to seizure induced by kainic acid, while *fosB*-null mice exhibited a slightly increased susceptibility, in comparison to C57BL/6 wild type mice or heterozygous mice. To clarify the molecular basis for altered responses of these mice to the excitotoxicity induced by kainic acid, we are now performing analyses of gene- and protein-expression profiles in their brains, as well as electrophysiological analyses.

MS8-03 Aripiprazole's agonist and antagonist properties at human dopamine D2L and D2S receptors

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Aripiprazole is the first clinically approved atypical antipsychotic agent having dopamine D2 receptor partial agonist activities. To evaluate aripiprazole's agonist and antagonist properties, we established a Chinese hamster ovary cell line expressing high and low densities of the long and short isoforms of human dopamine D2 receptors, then compared its properties with OPC-4392, (-)-3-PPP, and terguride (other partial agonists) using forskolin-stimulated cAMP accumulation as an index. In cells expressing high receptor densities, all partial agonists predominantly behaved as agonists. However, in cells expressing low receptor densities, the partial agonists showed significantly lower maximal effects than dopamine. Aripiprazole showed the lowest intrinsic activities. In addition, all compounds blocked the action of dopamine with a maximum effect equal to that of each compound alone. Aripiprazole's low intrinsic activities may account for the clinical finding that, unlike the other partial agonists, it is substantially active against both positive and negative symptoms of schizophrenia.

MS8-05 Mood stabilizing drugs enhance adult neurogenesis by Notch signaling activation in neural stem cells

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Bipolar disorder, characterized by recurrent fluctuations in mood, is a major mental health problem. Mood stabilizing drugs, lithium, valproic acid and carbamazepine, are commonly used to treat bipolar disorder and help control manic and depressive mood into normal condition. A multitude of studies has shown variety of biochemical and biological effects of mood stabilizers. However, most of the studies, if not all, used these drugs at higher concentrations than used to treat bipolar disorder patients. Therefore, shared molecular mechanisms and the effects in the brain underlying the therapeutic action of mood stabilizers are largely unknown. Here, we describe that lithium at the therapeutic concentrations increases the number of neural stem cells, whereas higher doses of lithium decrease the neural stem cell number, in the adult brain. The effect of mood stabilizing drugs to enhance self-renewal ability of neural stem cells is also evident in vitro by a colony-forming neurosphere assay. Treatment of neural stem cells with mood stabilizing drugs at the therapeutically relevant concentrations in the cerebrospinal fluid increases number of neurospheres via activation of the Notch signaling pathway. Mood stabilizers upregulate target genes of Notch signaling, *Hes1* and *Hes5*, in the neurospheres, but have little effect on either glycogen synthase kinase-3 β -mediated or inositol pathway signaling. We suggest that a common pharmacological effect of the mood stabilizing drugs is to enhance neurogenesis in the adult brain by activating Notch signaling in the neural stem cells.

MS8-07 *Vlgr1* mutant mice showed high susceptibility to audiogenic seizure

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Susceptibility to audiogenic seizures, that are reflex seizures provoked by loud noise, can be induced in rodents by acoustic priming (exposing animals to strong auditory stimuli at an early developmental stage). Some strains of mice and rats are susceptible to audiogenic seizures without priming, and they have been used as good experimental models with which to study epilepsies. Here we identified *Vlgr1d* and *Vlgr1e*, novel alternatively spliced variants of *Vlgr1b/MGRL1*. *Vlgr1* (*Vlgr1b*, *Vlgr1d* and *Vlgr1e*) mRNA is expressed predominantly in the neuroepithelium of the developing mouse brain. Knockout mice lacking exons 2-4 of *Vlgr1* were susceptible to audiogenic seizures without priming, although there were not apparent histological abnormalities in their brain. Ninety-five % of these knockout mice exhibited wild running, a feature typical of the preconvulsive phase of audiogenic seizures triggered by loud noise (11 kHz, 105 dB), and 68% exhibited tonic convulsions at 3 weeks after birth. To elucidate the influence of genetic background in the susceptibility of audiogenic seizures, we backcrossed the *Vlgr1* knockout mice to C57BL/6J mice that are known to be highly resistant to audiogenic seizures. C57BL/6J-backcrossed *Vlgr1* knockout mice were surely susceptible to audiogenic seizures. Our monogenic mice, which have a unique genetic background, serve as a useful tool for further studies on seizures. We are now studying about responses of *Vlgr1* knockout mice to antiepileptic agents. Details will be discussed at the meeting.

一般演題（ポスター発表） プログラム

	F 会 場	
	28日(水)	29日(木)
細胞接着因子	P1-001～005	
再生、移植	P1-006～009	
可塑性	P1-010～012	
プログラム細胞死	P1-013～021	
本能・情動・行動	P1-022	
感覚系・運動系	P1-023～024	
睡眠、生体リズム	P1-025～026	
学習、記憶	P1-027～028	
神経内分泌	P1-029	
自律神経系	P1-030	
老化	P1-031	
脳血流、代謝	P1-032～034	
イメージング	P1-035～036	
疾患モデル	P1-037～045	
発育、発達障害	P1-046～049	
変性疾患	P1-050～063, 116	
精神疾患	P1-064～081	
虚血	P1-082～085	
外傷	P1-086～088	
認知症、アルツハイマー病	P1-089～098	
薬物依存、精神薬理	P1-099～109	
中毒症	P1-110～111	
脳腫瘍	P1-112	
てんかん	P1-113～115	
イオンチャンネル、興奮膜		P2-001～005
神経伝達物質、修飾物質		P2-006～015
受容体、輸送体		P2-016～023
シナプス		P2-024～027
情報伝達、変換、修飾		P2-028～040
軸索輸送、細胞運動、細胞骨格		P2-041～045
ニューロン、グリア		P2-046～062
ミエリン		P2-063～070
神経免疫		P2-071～073
パターン形成		P2-074～075
細胞分化		P2-076～099
突起伸展、回路網形成		P2-100～109
栄養因子		P2-110～119

P1-001 Gicerin participates in the neurite outgrowth from PC12 cells induced by NGF

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Gicerin/CD146 is a cell adhesion molecule, which belongs to the immunoglobulin superfamily. We have reported that it has a homophilic binding activity, which participates in the neurite extension from embryonic neurons. To elucidate how gicerin is involved in the neurite extension mechanism, we employed PC12 cells, which expresses gicerin/CD146. PC12 cells are well characterized cell and extend neurites by NGF. We examined whether if gicerin/CD146 is involved in the neurite extension induced by NGF. PC12 cells extend longer neurites by nerve growth factor (NGF) on gicerin substrate than on without gicerin substrate, which indicates that gicerin participates in neurite extension by NGF. We also found that the expression of gicerin in PC12 cells is induced by NGF by transcription level. Over-expression of gicerin also promotes neurite extension by gicerin-gicerin homophilic interaction. These finding suggested that increase of gicerin expression by NGF promotes the gicerin-gicerin homophilic interaction resulting in the neurite extension.

P1-003 Immunohistochemical analysis of neural cell recognition molecule NB-2 in the rat brain

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Neural cell recognition molecules play important roles in cell migration, neurite outgrowth, synaptogenesis and myelination during development of the nervous system. NB-2 that we isolated and identified is a neural cell recognition molecule belonging to contactin subgroup of the immunoglobulin superfamily. We reported previously that NB-2 expression is prominent in the auditory system including cochlear nucleus (CN), superior olivary complex (SOC) and inferior colliculus (IC), using X-gal staining of NB-2(+/-) mice in which NB-2 gene is replaced with LacZ gene and immunostaining of the rat brain using anti-NB-2 polyclonal antibody. In addition, NB-2 knockout mice exhibit impaired neural function in the auditory system. These observations indicate that NB-2 plays important roles in the auditory system. Here we report the detailed analysis of the NB-2 expression pattern in rat brain using anti-NB-2 monoclonal antibody that we produced recently.

Immunohistochemical analysis of the rat brain using the antibody showed that NB-2 was strongly expressed in the CN, SOC, lateral lemniscus (LL), IC, medial geniculate nuclei (MGN), and the auditory area. In the central auditory pathway, auditory signal is first transfer to CN, subsequently to SOC, LL, IC and MGN, and finally reaches to the auditory area of cerebral cortex. Thus, NB-2 was expressed in all brain regions of the auditory pathway. In addition, substantia nigra (SN), caudate putamen (CPu) and fibers extending from SN to CPu were stained with NB-2 antibody. CPu receives input from SN and thereby regulates somatic movement. These suggest that NB-2 may play roles in the basal ganglia motor loop as well as in the auditory system.

P1-005 Spatiotemporal expression of a novel member of immunoglobulin superfamily, mKirre, in the mouse brain

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Immunoglobulin superfamily (IgSF) proteins are well known to play critical roles during the development of the nervous system. Previously, we have reported that a member of IgSF, mKirre (mammalian homolog of the *Drosophila kirre*), is expressed in bone marrow stromal cells and the brain. However, little is known about the localization and function of mKirre in the brain. In the present study, to investigate the expression pattern of mKirre gene, we performed in situ hybridization histochemistry in the developing and adult mouse brain. At embryonic day (E) 11.5, we observed mKirre mRNA in the differentiating zones of various regions, such as the caudate-putamen, the geniculate body, the thalamus, the amygdala, and the brainstem, where its gene expression persisted to the adult though the expression levels were much less prominent. After birth, we observed high expression of mKirre mRNA in the glomerular and mitral cell layer of the olfactory bulb, the cortical plate of the neocortex, the cochlear nucleus, and the molecular and granule cell layers of the cerebellum. At postnatal day (PN) 7, the expression of mKirre mRNA was first observed in the dentate gyrus of the hippocampus. The expression pattern of mKirre mRNA in the adult brain was the same as that in the brain at PN7 except for its gene expression in piriform cortex of the adult brain. From the spatiotemporal expression pattern of mKirre mRNA, mKirre may play important roles in later developmental processes of neurons, especially the synapse formation.

P1-002 Specific localization of tetraspanin protein CD9 in mouse dorsal horn

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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 as microdomains 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. Recently, we found the characteristic accumulation of CD9 in mouse dorsal horn Lamiae I and II. Since C and A δ fibers form synapses in these regions, CD9 may have some function on pain sensation. To know the functional role of CD9, localization and relationship of this protein and various pain-related receptors were examined. First, double immunostaining was performed by the combination of anti-CD9 antibody and various cell-type as well as synapse specific markers, suggesting that it is located in the neuronal processes. Distribution of the capsaicin receptor, transient receptor potential vanilloid subfamily 1 (TRPV1) was well correlated with that of CD9 in the spinal dorsal horn. Furthermore, these proteins also colocalized in DRG neurons, spinal trigeminal nucleus and free nerve endings in the skin, all of which were related to pain sensation. However the distribution of TRPV1 in spinal dorsal horn was not affected in CD9 KO mice, indicating that CD9 is not necessary for the specific localization of this receptor. Since CD9 is known to modulate functions of the various receptors, it may act as one of modulators for pain sensation.

P1-004 Immunohistochemical detection of neural cell recognition molecule NB-3 in the rat brain

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NB-3, a member of contactin subgroup of the immunoglobulin superfamily, is markedly expressed in the central nervous system during the postnatal days when myelination and synaptic maturation occur. In our previous study, X-gal staining of NB-3 (+/-) mice in which NB-3 gene was replaced with Lac Z gene indicated that the expression is increased in the mouse cerebellum during adulthood. Behavioral tests for motor function demonstrated that mice deficient for NB-3 are impaired in motor coordination. In this study, we produced monoclonal antibody against NB-3 in mouse and investigated detailed localization of NB-3.

Immunostaining of the rat brain at postnatal days 7 and 14 showed that NB-3 was localized in the layer V and layer II/III of the cerebral cortex and the accessory olfactory bulb. This result was consistent with our previous results obtained from Lac Z staining of the NB-3 (+/-) mouse brain at postnatal day 14. NB-3 was localized to the cell surface of cell body and nerve fibers in the layer V and layer II/III of the cerebral cortex. NB-3 positive signals were also detected around the glomeruli of the olfactory bulb and the Purkinje cells of all lobules in the cerebellum at postnatal day 14. In addition to these regions, the straight fibers extending from the Purkinje cell layer to the surface of the molecular layer were immunostained in 3 month-old rats. Moreover, cells with astrocyte-like morphology were stained in the corpus callosum and the granular cell layer of the cerebellum. These results suggested that NB-3 is expressed not only in neurons but also in glial cells. We are now trying to specify the types of NB-3-expressing cells.

P1-006 Role of Retinoids in Goldfish Retina during Optic Nerve Regeneration

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Retinoic acid is synthesized from retinal via retinol and is catalyzed by retinaldehyde dehydrogenase (RALDH). Retinoic acid is also well known as one of the transcription factor. Role of retinoic acid in the retina during optic nerve regeneration is unclear. We previously reported that a retinol-binding protein in the goldfish retina increased after optic nerve injury. Therefore, we investigate in the present study whether or not neurite outgrowth was affected by retinoic acid and whether or not expression of RALDH mRNA was affected after optic nerve injury.

To examine the effect of retinoic acid on neurite outgrowth, we conducted retinal explant culture system. Retinoic acid induced an enhancement of neurite outgrowth as compared to the control. We next isolated cDNA fragments for RALDH with probe of PCR product amplified by primer constructed from zebrafish sequence. We obtained 834 bp fragment of goldfish RALDH cDNA. By using this cDNA probe, RT-PCR was conducted in the goldfish retinal samples following optic nerve injury. We made digoxigenin (DIG)-labeled RNA probes for RALDH. We examined localization of RALDH mRNA in the retina by in situ hybridization with this RNA probe.

Level of RALDH mRNA increased at 5 days and peaked at 10 days and then gradually decreased and returned to the control value by 40 days after axotomy. A faint expression of RALDH mRNA was detected mainly in the ganglion cells of the control retina. The level of RALDH mRNA was increased in the ganglion cells 10 days after optic nerve transection. These results strongly indicate that retinoic acid triggers neurite outgrowth from retinal ganglion cells after optic nerve injury in accompanying with the RALDH activation.

P1-007 IGF-I accelerates axonal regeneration in the goldfish retina after optic nerve injury through PI3K/Akt system

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The rat retinal ganglion cells (RGCs) fail to regenerate after optic nerve injury. On the contrary, the fish RGCs can survive and reinnervate their axons to the tectum after injury. We compared a difference of survival and death signals in both the species. In rat retina, Western blot analysis revealed that phospho-Akt (p-Akt) and phospho-Bad (p-Bad) were decreased 2-3 days, whereas Bax was increased 4-fold 6-8 days after optic nerve injury. In goldfish retina, p-Akt and p-Bad were increased 3-5 days and an anti-apoptotic Bcl-2 was increased 10-20 days after optic nerve injury. In the axotomized goldfish retina, IGF-I phosphorylated the Akt earlier (3-5 days) and higher (3-fold) than that in the intact retina. Furthermore, an inhibitor of phosphatidylinositol 3-kinase (PI3K), wortmannin dose-dependently suppressed neurite outgrowth from goldfish retinal explants in culture. Next, we performed an immunohistochemical analysis using anti IGF-I antibody. In goldfish, the levels of IGF-I were increased at the ganglion cells and inner nuclear layer (INL) by 3-5 days after optic nerve injury. In contrast, the levels of IGF-I in rat were decreased at the RGCs and INL by 3 days. In rat retinal explant culture, neurite outgrowth was enhanced by IGF-I and inhibited by wortmannin. These results suggest that IGF-I/Akt system is one of the most important signaling molecule for survival and neurite outgrowth of RGCs after optic nerve injury.

P1-009 Implication of DNA methyltransferase in EAAC1/EAAT3 expression in response to nerve injury

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The injured motor neurons of mice progressively died over several weeks, while those of rats could survive and regenerate. We have demonstrated that the expression of a neuronal glutamate transporter, EAAC1, was a critical factor for determining the fate; the expression of EAAC1 was down-regulated in injured motoneurons of mice, while up-regulated in those of rats. Therefore it is intriguing to reveal a possible mechanism underlying the down regulation of EAAC1 expression in mouse. Several lines of studies demonstrated that DNA methylation is a potent mechanism for suppressing gene expression in various kinds of cells including neurons. Since the genomic sequence around the translational start site of EAAC1 encodes CpG islands, which are preferential targets of DNA methyltransferase (Dnmt), it is likely that DNA methylation is involved in the transcriptional repression of EAAC1. From this aspect, we examined an implication of Dnmt in nerve injured motor neurons, and identified that mRNA for Dnmt1, which is essential for maintaining DNA methylation after DNA replication, was up-regulated in nerve injured motor neurons of mice whereas those in rats did not. Immunohistochemical analysis also revealed that Dnmt1 protein was accumulated in nuclei of injured neurons of mice, but not in those of rats. Furthermore, in vitro study showed that EAAC1 mRNA was increased in 5-aza-2'-deoxycytidine treated-neuronal PC12 cells. Although it is not clear about detailed mechanism how Dnmt1 suppresses the expression of EAAC1, the present data suggests that Dnmt1 contributes to the transcriptional repression of EAAC1 in injured motor neurons of mice.

P1-011 Gene expression analysis associated with Long-lasting synaptogenesis after repetitive exposures to glutamate in hippocampal slice cultures

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We have previously shown that repetitive exposures to glutamate (100 μ M, 3min, 3 times at 24h intervals) induced a long-lasting synaptic enhancement accompanied by synaptogenesis in rat hippocampal slice cultures. To get clues for molecular mechanisms underlying this phenomenon, we analyzed the time course of gene expression changes between 4h and 12d after the repetitive stimulation using our original oligoDNA microarray "Synptoarray". "Synptoarray" contains probes for 500 genes selected for their likely involvement in the construction and function of synapses, and has been shown to be capable of detecting $\pm 20\%$ changes in gene expression. Messenger RNAs extracted from the stimulated and the mock-stimulated control cultures were reverse-transcribed, amplified, labeled with Cy3 or Cy5, and compared by competitive hybridization. The results demonstrated that major differences in gene expression following the repetitive stimulation took place between 24h and 96h after the 3rd stimulation. Genes for regulatory proteins of the actin-cytoskeleton as well as for synaptic scaffold proteins were the major components of the differentially expressed genes, indicating the dynamic changes in the structural reorganization of the synapse following repetitive exposures to glutamate.

P1-008 TRANSPLANTATION OF CRYOPRESERVED HUMAN BONE MARROW-DERIVED MULTIPOTENT ADULT PROGENITOR CELLS FOR NEONATAL HYPOXIC-ISCHEMIC INJURY

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Stem cell therapy, via stimulation of endogenous stem cells or transplantation of exogenous stem cells, has targeted neurogenic sites for brain protection and repair. Based on its neurogenic and neurotrophic factor-secreting features, especially during the postnatal period, the hippocampus stands as an appealing target for stem cell therapy. In this study, we investigated the efficacy of intrahippocampal transplantation of Multipotent Adult Progenitor Cells (MAPCs), which are pluripotent progenitor cells with the ability to differentiate into a neuronal lineage. Seven-day old SD rats were initially subjected to unilateral hypoxic-ischemic (HI) injury, subsequently exposure to hypoxic environment. At day 7 after HI injury, animals received stereotaxic hippocampal injections of vehicle or MAPCs derived either from SD rats (syngeneic) or Fisher rats (allogeneic). Behavioral tests were conducted on post-transplantation days 7 and 14 using the EBST and the rotarod. MAPC transplanted animals exhibited reduced motor asymmetry and longer time spent on the rotarod than vehicle. Both syngeneic and allogeneic MAPC transplanted injured animals did not significantly differ in their behavioral improvements at both test periods. Immunohistochemical evaluations of graft survival after behavioral testing at day 14 post-transplantation revealed that syngeneic and allogeneic transplanted MAPCs survived in the hippocampal region. These results demonstrate that transplantation of MAPCs ameliorated motor deficits associated with HI injury. The similar degree of behavioral recovery produced by syngeneic and allogeneic MAPC grafts indicates that allogeneic transplantation is a feasible and efficacious cell replacement strategy that could be considered for clinical use.

P1-010 Neuropsin modulates the conversion of nmda-LTP to compound-LTP

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LTP in the hippocampus is one form of synaptic plasticity and is thought to be a cellular mechanism underlying learning and memory. In which LTP has been studied most extensively, at least two forms of LTP coexist in hippocampal area CA1 (nmda-LTP, compound-LTP), but its physiological mechanism remains to be established. Previously, we have shown that neuropsin (NP), a secreted-type serine protease, modulated LTP in CA1. However, how do NP play a role in plasticity, it is not clarified. We report here, what kind of mechanism involved in LTP modulation by NP. First, to examine whether nmda-LTP modulate by NP, which was perfused for 10 min before short theta burst stimulation (s-TBS), which normally enhances only the nmda-LTP, but not compound-LTP. Moreover, we found that there was a severe impairment in compound-LTP induced by 1-TBS in hippocampal slices derived from the NP-/- mice. We present several evidences indicating that activation of NP is important for the shift from nmda-LTP to compound-LTP via L-type VDCCs. We have identified NP as an endogenous extracellular enzyme system that is capable of converting nmda-LTP to compound-LTP.

P1-012 Expression of hippocampal neuropsin (KLK8) mRNA is regulated by steroid hormones

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The limbic areas express abundantly steroid hormone receptors, and respond to adrenal and gonadal steroid hormones which influence hippocampal plasticity, i.e. synaptic remodeling, long-term potentiation, and stress-related memory. Recently, a number of steroid hormone-sensitive proteases of the kallikrein (KLK)-like family have been cloned. Neuropsin (NP, or KLK8), one of the kallikrein family serine protease, is expressed specifically in the limbic system and plays an important role in hippocampal plasticity. Therefore, it is assumed that NP is involved in steroid-dependent plasticity. To test the hypothesis, we first examined whether these steroid hormones regulate NP mRNA expression using semi-quantitative assay of primary cultures of hippocampal neurons and in situ hybridization histochemistry in vivo. In estradiol treatment, expression of NP mRNA was up-regulated at each concentration that we tested. In contrast, expression of NP mRNA was increased by low concentration (5 nM) of corticosterone but unchanged by high concentration (500 nM). We further analyzed by in situ hybridization histochemistry and found that NP mRNA was decreased in CA1 subfield of hippocampus 2 hours after subcutaneous injection of corticosterone in adrenalectomized male mice and increased 2 hours after injection of estradiol in CA3 subfield of ovariectomized female mice. These results strongly suggest that expression of NP receives hormonal regulation by steroids a region-specific and with steroid type-dependent manner.

P1-013 Peripheral lipopolysaccharide injection induces apoptosis in the murine olfactory bulb and rostral migratory stream

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Olfactory bulb (OB) is one of the few structures in adult mammalian CNS in which there is a continuous supply of newly generated neurons in subventricular zone. Therefore, the balance between the supply of new cells and apoptosis in OB probably determines olfactory function. In this study, the effect of the propagation of innate immune reaction triggered by peripheral lipopolysaccharide (LPS) on OB of C3H/HeN mice was examined, because LPS-induced tumor necrosis factor (TNF)- α is known to trigger the apoptotic cascade mediated by TNF/TNF receptor pathway. Within 0.5 h after the intraperitoneal injection of 50 μ g LPS, the rectal temperature significantly decreased and mRNA expression levels in OB of the genes encoding TNF- α was significantly enhanced in the LPS-injected mice. Double immunofluorescence microscopy confirmed that almost all TNF- α -immunopositive cells in OB of the LPS-injected mice were in the subependymal zone and that they overlapped with those immunostained with antibody against glial fibrillary acidic protein, but not with the one against F4/80, an antigenic marker of microglia. The number of TUNEL-positive cells exclusively identified in granule cell layer was significantly increased in LPS-injected mice sacrificed at 24 h after the injection. These results suggest that peripheral LPS injection may cause a disequilibrium between the supply and the disappearance of the cells in OB, which may lead to olfactory dysfunction.

P1-015 Functional changes following sustained exposure to glutamate at a low concentration in cultured neurons derived from discrete rat brain regions

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Although the excitatory neurotransmitter glutamate (Glu) is ubiquitously distributed in the mammalian central nervous system, Glu could elicit different actions on the functionality and integrity of discrete brain structures in a particular situation. In this study, we have attempted to elucidate mechanisms underlying signaling processes of Glu in cultured neurons derived from discrete brain structures. Rat neocortical, striatal and hippocampal neurons were individually cultured for 9 days *in vitro* in either the presence or absence of Glu at 50 μ M, followed by washing and exposure to Glu at different concentrations for 1 h. Cellular viability was then determined 48 h later on MTT assays. The transient exposure to Glu significantly decreased the number of living cells in a concentration-dependent manner at a concentration range of 1 to 1,000 μ M in hippocampal neurons irrespective of the presence of Glu in culture medium, but did not markedly affect cell survivability in striatal neurons cultured in the presence of 50 μ M Glu. Immunoblotting analysis revealed that culturing with Glu at 50 μ M led to a significant decrease in endogenous levels of NR2A, NR2B and NR2C, but not NR1, subunits in striatal neurons without markedly affecting those in neocortical and hippocampal neurons. On semi-quantitative RT-PCR analysis, however, no significant alterations were seen in mRNA expression of those subunits in neocortical, hippocampal and striatal neurons cultured in the presence of 50 μ M Glu. These data suggest that prior sustained exposure to Glu at a low concentration would result in subsequent tolerance to the excitotoxicity of Glu through a mechanism related to downregulation of NR2 subunits at the posttranscriptional level in cultured rat striatal neurons.

P1-017 Attenuation of apoptosis by glucocorticoid modulatory element-binding protein 1 via specific binding to procaspases

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Caspases are divided into two classes. The initiator caspase, which includes caspase-8, and -9, possess a long prodomain, while the effector caspase, which includes caspase-3 and -7, possess a short one. More recently, we demonstrated that glucocorticoid modulatory element-binding protein 1 (GMEB1) can interact with prodomain of procaspase-2. We found that this molecule inhibits the autoproteolytic activation of procaspase-2 by oligomerization on a chemical compound-dependent system. Here we show that GMEB1 is capable of binding to not only procaspase-2 but also procaspase-8 and -9. GMEB1 attenuated the Fas-mediated activation of caspases and consequent apoptosis. To directly assess the function of endogenous GMEB1, we knocked down its expression in SH-SY5Y cells by siRNA technique. Interestingly, siRNA-mediated gene silencing of GMEB1 in cells dramatically accelerated to induce apoptosis in response to hypoxic stress. Furthermore, we attempted to elucidate the role of GMEB1 on a model of focal ischemia with neuro-specific GMEB1 transgenic mice. Cerebral infarcts and brain swelling induced by middle cerebral artery (MCA) occlusion in GMEB1 transgenic mice were significantly smaller than those in wild-type mice. These results suggested that GMEB1 is an endogenous caspase-regulating protein that selectively binds to initiator procaspases.

P1-014 ER stress response in dendrites of primary neurons

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When unfolded or misfolded proteins accumulate in the ER (so called ER stress), the unfolded protein response (UPR) signals are transmitted from the ER to nucleus and cytoplasm. The induction of UPR-target genes facilitates correct folding of unfolded proteins in order to protect cells from ER stress. In contrast, excessive or long-termed stresses in the ER result in apoptotic cell death. Cell fate after ER stress is regulated by the balance of both apoptosis and the UPR signaling. Recently, ER stress has been reported to be linked to neuronal death in various neurodegenerative diseases. However, it remains unclear whether ER stress and its stress response indeed occur in the patient brains. It is important to image the ER stress in the patient brains in order to demonstrate the relationship between ER stress and neuronal death in neurodegenerative diseases. Neurons have the ER not only in the soma and but also in the dendrites unlike in the case of non-neuronal cells, but it is unclear whether ER stress and UPR occur in the dendrites. In this study, we examined localization of ER stress sensors, IRE1, PERK, ATF6, in primary neurons. All of these sensors localized in the ER of soma and dendrites, indicating the possibility that dendrites could respond to ER stress. Moreover, we also show the UPR signaling in dendrites of primary neurons.

P1-016 Involvement of double strand RNA-dependent protein kinase (PKR) on endoplasmic reticulum stress-induced cell death in rat retinal ganglion cells

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In this study, we examined whether activation of a double strand RNA-dependent protein kinase (PKR) participates in neuronal cell death induced by endoplasmic reticulum (ER) stress in cultured retinal ganglion cells (RGC-5, a rat ganglion cell line transformed with E1A virus). Retinal damage was induced by tunicamycin (a protein glycosylation inhibitor), and cell viability was measured by Hoechst 33342 and YO-PRO-1 or propidium iodide double stainings, or resazurin reduction assay. When cultured RGC-5 cells were incubated with tunicamycin at the concentration between 1 and 4 μ g/ml for up to 24 hrs, a number of cells underwent cell death in concentration- and time-dependent dependent manners. An imidazolo-oxindole derivative that acts as ATP-binding site directed inhibitor of PKR (a PKR inhibitor) at 0.1 to 1 μ M concentration-dependently inhibited the tunicamycin-induced cell death. Treatment with tunicamycin increased in ER stress-related proteins such as GRP78/BiP, ATF-4 and GADD153/CHOP. A PKR inhibitor concentration-dependently inhibited the increase of CHOP induced by tunicamycin but not BiP protein production. These results indicate that inhibition of PKR activation shows a neuroprotective effect against ER stress-induced retinal damage and PKR activation on the ER stress-induced cell death may be involved in the underlying mechanism.

P1-018 Intracellular signaling mechanism of sustained nitric oxide (NO) exposure-induced apoptosis in PC12 cells

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Nitric oxide (NO) is a short-lived, highly reactive gaseous radical that is synthesized in many mammalian tissues and which has a role in both physiological and pathological functions. We have shown previously that prolonged exposure to an NO donor, NOR3, even at low concentrations induced cell death in PC12 cells. We also reported the early increase in mitochondrial H₂O₂ production during NOR3 exposure and these events were accompanied by strong inhibition of cytochrome c oxidase activity. In the present study, we have examined the activation of PKC, protein tyrosine kinase and mitogen-activated protein kinase (MAPK) cascades in PC12 cells. An NO donor, NOR3 induced cell death even at low concentrations. These NOR3-induced cell death were suppressed by SB203580 (a specific inhibitor of p38 MAPK), calphostin c (a PKC inhibitor), and genistein (a protein tyrosine kinase inhibitor), but not by PD98059 (a MEK inhibitor) and SP600125 (a JNK inhibitor). Furthermore, exposure of PC12 cells to NOR3 resulted in an increased p38 MAPK phosphorylation, but not p42/p44 MAPK (ERK1/2) and c-Jun NH2-terminal kinase (JNK). Time-course studies showed that p38MAPK activation was observed from 2 h to at least 6 h after exposure to NOR3. These activations were suppressed by SB203580, calphostin c and genistein. These findings suggest that cell death induced sustained exposure to NO at physiologically low concentrations is mediated by the activation of upstream kinases, PKC and protein tyrosine kinase, and the specific activation of p38MAPK cascade.

P1-019 Relationship of polyglutamine-expanded GFP expression to ER stress in PC12 cells

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Expansion of polyglutamine repeats has been shown to cause a number of neurodegenerative disorders. To investigate the effects of polyglutamine expression on neuronal cells, we constructed PC12 cells expressing expanded poly Qn (n=19 or 81) under the control of the Tet-OffTM system. The CAG repeats of the Qn-green fluorescent protein vector were inserted into the pEYFP-N1 vector (CLONTECH) to construct the polyglutamine-YFP (Qn-YFP) expression plasmids. The stably transfected PC12 were maintained in DMEM medium with 5% FCS and 5% HS containing 100 μ g/ml hygromycin, 500 ng/ml blasticidin S, 10 ng/ml doxycycline (Dox). By western blot analysis with anti-GFP antibody, we confirmed that the removal of Dox induced the expression of 19Q and 81Q GFP. In particular, 2 days after Dox removal, the aggregate formation of the 81Q but not 19Q was significantly detected by the existence of high molecular weight proteins in a stacking gel. Expression of 81Q induced apoptotic cell death. The removal of Dox induced phosphorylation of eIF2 α only in 81Q-expressing cells, whereas no significant change in protein levels of GRP78/Bip was found in both 81Q- and 19Q-expressing cells. This result suggests the down-regulation of protein synthesis in 81Q-expressing cells. Ubiquitination of 81Q GFP is now under investigation.

P1-021 Depletion of intracellular Ca²⁺ store itself may be a major factor in thapsigargin-induced ER stress and apoptosis in PC12 cells

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The mechanisms of intracellular calcium store depletion and store-related Ca²⁺ dysregulation in relation to apoptotic cell death in PC12 cells were investigated at physiological temperature with a leak-resistant fluorescent indicator dye Fura-PE3 by a cooled CCD imaging analysis system. Electron microscopic observation has shown thapsigargin-induced apoptosis in PC12 cells. Thorough starvation of stored Ca²⁺ by BAPTA/AM (50 μ M), or La³⁺ (100 μ M) enhanced while dantrolene (100 μ M) attenuated the TG-induced apoptosis by preventing a calcium release from internal stores. The immunoblotting analysis revealed an enhanced expression of GRP78, the hallmark of endoplasmic reticulum (ER) stress when cells were treated by TG along with BAPTA/AM. These results indicate that depletion of intracellular Ca²⁺ stores itself induces the ER stress and apoptosis in PC12 cells without involvement of capacitative calcium entry or sustained [Ca²⁺] elevation.

P1-023 Activation of cytosolic phospholipase A₂ in the dorsal root ganglion of neuropathic pain rats

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Cytosolic phospholipase A₂ (cPLA₂) hydrolyzes phospholipids containing arachidonic acid, which in turn is metabolized to prostaglandins by the cyclooxygenase pathway and to leukotrienes by the 5-lipoxygenase pathway, both of which play important roles in pain signaling. Full activation of cPLA₂ requires Ca²⁺ binding to an N-terminal C2 domain and phosphorylation on serine residues. The aim of the present study was to examine changes in the level of cPLA₂ phosphorylation in sensory neurons of spinal nerve-injured rats, a model for neuropathic pathological pain. We carried out immunohistochemical analyses using an antibody for the Ser⁵⁰⁵ phosphorylated active form of cPLA₂ (p-cPLA₂) and found that the level of p-cPLA₂ immunofluorescence in the ipsilateral dorsal root ganglion (DRG) was markedly increased after nerve injury. Almost all of p-cPLA₂-positive cells were also immunostained with MAP2 (a neuronal marker), but not with GFAP (an astrocyte marker), indicating that the phosphorylation of cPLA₂ in the DRG is restricted to neurons. We also found that there were many DRG neurons showing intense immunofluorescence of p-cPLA₂ in the vicinity of their plasma membranes, indicating a translocation of cPLA₂. The number of neurons with the translocation was increased as early as day 3 and the peak was observed on day 14, the time course of which matched emergence of the tactile allodynia, a pain response to innocuous mechanical stimulus. These results indicate that peripheral nerve injury induces an activation of cPLA₂ in DRG neurons and suggest that cPLA₂ may have a role in the pathophysiology of neuropathic pain.

P1-020 Differential function and localization of two splice variants of caspase-3 binding protein 2

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Caspase-3 plays a critical role in the process of apoptosis. To clarify this mechanism in neurons, we have purified novel caspase-3 binding proteins (C3BPs) from rat brain using a caspase-3 affinity chromatography. One of C3BPs (C3BP2) is supposed to have two alternative splice variants: long (C3BP2-L) and short forms (C3BP2-S). These two splice variants were expressed for each in mammalian cultured cells together with an active-form of caspase-3 (Csp). Csp showed caspase-3 activities and induced cell apoptosis, both of which were further enhanced by C3BP2-S, or inversely suppressed by C3BP2-L. Moreover, immunofluorescent imaging showed that both C3BP2-S and C3BP2-L were located to endosomal membranes, in which C3BP2-S was also present in the cytoplasm with a reticular distribution. These results indicate that caspase-3 is inversely regulated by two splice variants of C3BP2 which are differentially localized in the cytoplasm.

P1-022 The efferent projection of the "running neurons" located in the ventromedial nucleus of the hypothalamus: The neural structure supporting hyper-running behavior

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It has been reported that stimulating the ventromedial part of the ventromedial nucleus of the hypothalamus (vmVMH) induces hyper-running behavior in the rat. Unilateral microinjection of kainic acid into the VMH of the rat exclusively elicited stereotypical running behavior associated with autonomous nervous activities that support running behavior such as elevations of blood pressure and heart rates. Bilateral lesions made by ibotenic acid in the VMH decreased spontaneous wheel running activity. However, the characterization of the vmVMH neurons involved in the running activity (= running neurons) has not been elucidated. The objective of this study is to investigate the efferent projections from the vmVMH. To stimulate the VMH, kainic acid was microinjected into the rat VMH unilaterally under the urethane-anesthetized condition. The brain was removed 90 min after microinjection and c-Fos immunoreactive signals were detected. The c-Fos signal was used as a marker of the direct and indirect projection sites of the VMH. Consequently, to elucidate primary projection sites from the vmVMH, the anterograde axonal tracer, biotinylated dextran amine (BDA) was microinjected iontophoretically into the vmVMH. Double labeling immunocytochemistry was performed to detect tracers and some of the neurotransmitters simultaneously. c-Fos immunoreactivities and BDA signals were detected in the periaqueductal gray (PAG) and cuneiform nucleus (CnF). These parts are known as the mesencephalic locomotor region (MLR). Vesicular glutamate transporter signals were immunocytochemically detected at the BDA positive synaptic terminals in the PAG. These results indicate that the vmVMH neurons (running neurons) have the direct glutamatergic projection to the MLR that involves in spontaneous running.

P1-024 Changes in transcription factors in mouse cochlea after intense noise exposure

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Sensorineural hearing loss can be caused by a variety of insults, including acoustic trauma, exposure to ototoxic drugs, infections or aging. There is compelling evidence that reactive oxygen species (ROS) are formed in the cochlea during acoustic overstimulation. The formation of ROS may trigger a variety of intracellular events, including lipid peroxidation expression of transcription factors, and transcriptional activation of genes. Several distinct transcription factors are known to participate in stress-induced apoptotic pathways in neuronal cells. These include activator protein-1 (AP-1), nuclear factor kappa B (NF κ B), and antioxidant-response element (ARE) binding proteins. In this study, we investigated the changes in transcription factors in the cochlea in response to acoustic overstimulation. Nuclear extracts were prepared from the cochlear at various time points after intense noise exposure (4 kHz octave band, 125 dB, 5 h), and then subjected to electrophoretic mobility shift assay to determine DNA binding activity of transcription factors, such as AP-1, NF κ B, ARE binding protein and cyclic AMP response element binding protein (CREB). AP-1 DNA binding was markedly increased 2 to 12 h after the noise exposure, with a peak at 2 h after exposure. In addition to AP-1, DNA binding of CREB and NF κ B was increased immediately after exposure. However, ARE binding was not significantly affected by exposure. Supershift analysis revealed that JunD and FosB of Fos/Jun family proteins participate to enhancement of AP-1 DNA binding induced by noise exposure and that p65 of NF κ B components was involved in NF κ B DNA binding at 2 h after exposure. Taken together, both of AP-1 and NF κ B may function as molecules for stress response in the cochlea after intense noise exposure.

P1-025 Abnormalities in non-visual photoreception in mice lacking PACAP

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PACAP is a member of secretin/glucagon family neuropeptides and expressed in a small subset of retinal ganglion cells constituting the retino-hypothalamic tract, a monosynaptic pathway from the retina to the suprachiasmatic nucleus (SCN). In the previous study, we showed possible roles of PACAP in light-induced phase shift of the locomotor activity rhythm, and light-induced gene expressions in the SCN. The light-responsive functions lacking to form vision are defined as non-visual photoreception (NVP), including the photoentrainment of the circadian clock, suppression of activity by light, and pupillary light reflex. The involvement of PACAP in NVP has not been well understood. To clarify the possible functions of PACAP in NVP, we investigated light-induced phase delay of locomotor activity rhythm, light-induced suppression of locomotor activity, and pupillary light reflex in PACAP-knockout mice (PACAP^{-/-}).

In PACAP^{-/-}, the magnitude of phase delay due to relatively bright light (100 lx or 600 lx, white light, 5 min), but not dim light (20 lx) at CT15 significantly reduced compared with those in wild-type mice. Unlike phase delay, all three intensities of light (20, 100 or 600 lx, white light, 60 min) at ZT13 failed to induce an acute suppression of activity in PACAP^{-/-}. On the contrary, PACAP^{-/-} showed a normal pupillary reflex to these three intensities of light (1 min, wavelengths 460-490 nm). The present results suggest that PACAP is implicated in NVP functions, especially in the photoentrainment of the circadian clock and acute regulation of locomotor activity by light.

P1-027 Epac-specific cAMP analogue induces GluR1 and NR2B degradation via calpain activation in adult hippocampus

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Recent studies have identified Epac (exchange protein directly activated by cAMP) as a target for cAMP. Epac is a cAMP-regulated GTP exchange factor that appears to be involved in the activation of Rap1 but not to be directly involved in the regulation of the PKA-Ras-ERK pathway. In studies of the function of Epac in rodent brain, we have found that infusion of the Epac specific cAMP analogue, 8-pCPT-2-O-Me-cAMP (8-CPT) into hippocampus blocked contextual fear learning (see accompanying poster by Olausson et al). Here, we examined potential biochemical mechanisms that might be involved in the effects of Epac activation on learning and memory (see also accompanying poster by Kiraly et al). Hippocampal sections were prepared from male C57BL/6 mice (8 weeks old) and immediately incubated for 1 h without or with 8-CPT in fresh artificial cerebrospinal fluid (ACSF, oxygenated Krebs-HCO₃ buffer) at 30°C. Protein levels were detected by immunoblotting using various antibodies. (1) In a dose-dependent manner, 8-CPT treatment decreased levels of GluR1, NR2B and C-Jun but not GluR2. (2) Other cAMP analogues such as 8-Br-cAMP, Sp-cAMPs and Rp-cAMPs had no effect. (3) The effect of 8-CPT was dependent on Ca²⁺ and was blocked in Ca²⁺-free conditions. (4) An inhibitor of calpain, but not inhibitors of cathepsin or caspase, blocked the effect of 8-CPT. These results suggest that Epac-activation by 8-CPT induces GluR1, NR2B and C-Jun degradation via calpain activation in hippocampus. Further studies are underway to examine the mechanism of regulation of calpain, and whether calpain plays a role in the Epac-mediated regulation of learning.

P1-029 Effect of leptin on BDNF expression in the hypothalamus

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It has been reported that brain-derived neurotrophic factor (BDNF) regulates feeding behavior and energy expenditure. Although BDNF is highly expressed in the hypothalamus, the regulatory mechanisms of BDNF expression in the hypothalamus remain unclear. In the present study, we investigated the effect of leptin, an important regulator for food intake in the hypothalamus, on the expression of BDNF in the hypothalamus. Intravenous administration of leptin induces the expression of BDNF mRNA in the ventromedial hypothalamic nucleus (VMH). In situ hybridization combined with immunohistochemistry revealed that BDNF mRNA was detected in phosphorylated signal transducer and activator of transcription 3-positive neurons in the VMH, suggesting that leptin regulates BDNF expression directly in the VMH neurons. In addition to BDNF mRNA, BDNF protein is highly expressed in the VMH of leptin-treated mice. In addition, BDNF-immunoreactive fibers were abundant in the dorsomedial hypothalamus (DMH) of leptin-treated mice. To study the anatomical relationship between BDNF-immunoreactive fibers and TrkB-immunoreactive neurons in the DMH, we performed double-immunofluorescence method using antibodies against BDNF and TrkB. Many close appositions were observed between BDNF-immunoreactive fibers and TrkB-immunoreactive neurons in the DMH of leptin-treated mice. These results suggest that leptin regulates food intake partly through BDNF-TrkB signaling in the DMH. 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 (13204074) and a Research Grant on Priority Areas from Wakayama Medical University.

P1-026 Combination of the two ROR response elements in the *Bmal1* promoter confers robustness to the mouse *Bmal1* oscillation

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Transcriptional regulation of clock genes appears essential for generating circadian oscillations. Recent studies have provided evidence that ROR response element (ROR-RE)-binding proteins, which include Rev-Erb α and Rev-Erb β , as well as ROR α , β , and γ , are expressed in-phase in the suprachiasmatic nucleus (SCN) and interact with ROR-REs in the *Bmal1* promoter to regulate *Bmal1* circadian expression. The precise mechanism by which these ROR-RE-binding proteins regulate the *Bmal1* gene has not been elucidated. In this study, we found that ROR α was the most potent enhancer of *Bmal1* promoter activity among ROR-RE-binding proteins and that ROR α -induced enhancement of *Bmal1* transcription was decreased markedly by the single deletion of two ROR-REs in the proximal *Bmal1* promoter, using a luciferase reporter assay. Real-time monitoring of the *Bmal1* promoter showed that a deletion of the upstream ROR-RE abolished the circadian expression of the *Bmal1* reporter. In addition, the *Bmal1* promoter with a deletion of the downstream ROR-RE oscillated with damped amplitude of reporter activity. These observations indicate that the two proximal ROR-REs differentially contribute to the circadian expression of the *Bmal1* gene and a combination of the two ROR-REs mediates the robustness of the *Bmal1* oscillation, amplifying its amplitude via the transactivation of ROR α .

P1-028 Activation of microglia leads to deficit of learning and memory in rat

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Activation of microglia in the brain leads to the development of neurodegenerative disease such as Alzheimer's disease. Activated microglia releases inflammatory cytokines such as interleukin beta (IL-1 β) and tumor necrosis factor alpha (TNF α) that contribute to neurodegeneration. Interactions between neuronal and glial cells during the development of neurodegeneration remain to be clarified. We have designed the animal model of neuronal inflammation in order to study the contribution of microglial activation. And then we determined whether inflammation causes neurodegenerative and functional change in neuronal cells.

Lipopolysaccharide (LPS) was injected into rat hippocampus CA1 region daily for 5 days in order to produce chronic inflammatory conditions. LPS injection for 5 days caused learning deficit in rats when examined by a passive avoidance test. Using immunohistochemical study, expression of IL-1 β was noted in LPS injection and co-localized with anti CD11b antibody (marker of microglia and macrophage), but not with GFAP antibody (marker of astrocyte). GFAP positive cells in LPS-treated rats were existed greatly than that in PBS-treated rats. Hippocampal sections were performed to TUNEL and HE staining to determine neuronal cell death. We failed to detect signs of apoptotic and necrotic cell death. These results suggest that activation of microglia by chronic LPS treatment results in the functional change of neurons without obviously neuronal cell death.

P1-030 Autonomic receptor-mediated histamine H₁ receptor gene expression

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[Aim] Regulation of allergy symptoms by autonomic nerve is clinically noticed. We observed up-regulation of histamine H₁ receptors (H₁Rs) in nasal mucosa of allergy model rats. The stimulation of H₁Rs induces increase in H₁R gene expression. In the present study autonomic receptor-mediated H₁R gene expression was examined. [Methods] U373-M3 cells and U373- β 2 cells expressing recombinant M₃ muscarinic receptors and recombinant β 2 adrenergic receptors, respectively, besides naturally existing H₁Rs were used. H₁R mRNA was determined by real-time PCR. Promoter activity of H₁Rs was performed by luciferase reporter assay. H₁Rs were determined by [³H] mepyramine binding assay. H₁R mediated signaling was assessed by determining IP₃ accumulated after H₁R stimulation. [Results] Muscarinic stimulation induced time- and dose-dependent increase in H₁R in U373-M3 cells. This up-regulation was inhibited by a protein kinase C inhibitor. H₁R signaling was also increased in up-regulated cells. Muscarinic stimulation even induced increase in H₁R mRNA. H₁R mRNA stability was unchanged but H₁R promoter activity was increased in up-regulated cells. Adrenergic stimulation induced down-regulation of H₁Rs in U-373(2) cells. A protein kinase A inhibitor reversed this down-regulation. Both H₁R mRNA stability and H₁R promoter activity were decreased in down-regulated cells. [Discussion] Parasympathetic stimulation induced up-regulation of H₁Rs by increased gene expression. In contrast, sympathetic stimulation induced down-regulation of H₁Rs by both decreased gene expression and decreased stability of mRNA. Protein kinase C and protein kinase A were involved in up- and down-regulation respectively. The present results demonstrate the regulation of H₁R gene expression by autonomic nerve.

P1-031 Subcellular localization of SIRT1(Sir2 α), an NAD-dependent histone deacetylase, in the brain -SIRT1(Sir2 α) shuttles between the cytosol and the nucleus-

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Sir2 (silent information regulator 2) is an NAD-dependent deacetylase that is broadly conserved from bacteria to humans. Sir2 is implicated in the regulation of aging, because its increased expression extends the lifespan of yeast and nematodes. Mammalian SIRT1 (Sir2 α) is a member of the Sir2 family. Recently, SIRT1 was shown to interact with various transcription factors, such as p53, forkhead transcription factors (FOXOs), and MyoD, and to participate in stress tolerance, differentiation, and development. We found that SIRT1 is dominantly expressed in the cytosol of some subsets of neurons in adult mouse brain. On the other hand, ependymal cells of adult brain and neural stem cells from fetal brain expressed SIRT1 in the nucleus and the cytosol. To investigate the difference of subcellular localization, we constructed various deletion clones and point-mutated SIRT1 tagged with GFP, and examined subcellular localization of wild and mutant clones. We identified two nuclear localization signals (NLS) and also two nuclear export signals (NES) in the amino acid sequence of SIRT1. We confirmed the function of NLSs and NESs in SIRT1 by a cell fusion technique (heterokaryon formation). L929 cells were fused with COS7 cells which was transfected with SIRT1-GFP in the presence of polyethylene glycol. The resultant heterokaryons showed that nuclei of L929 cells expressed SIRT1-GFP. Furthermore, treatment with leptomycin B, a specific inhibitor of Crm1 dependent nuclear export, inhibited nuclear export of SIRT1. These data indicate that SIRT1 is a nucleocytoplasmic shuttling protein. The subcellular localization of SIRT1 affects its function and may be regulated by some intracellular or extracellular signals.

P1-033 Amino acids as candidates for objective biomarkers and anti-fatigue substances in physical, mental and complex fatigue

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Much attention has been paid to the molecular and neural mechanisms of fatigue. However, the mechanisms have not yet been elucidated, mainly because the objective biomarkers of fatigue have not yet been established. To establish such objective biomarkers for different types of fatigue, we investigated levels of various substances including general metabolites, neurosteroids, endocrine hormones, and amino acids after a relaxed control state and physical, mental or complex fatigue session for 4 or 8 hours by using an ergometer cycle (physical load), Advanced Trail Making Test, Japanese KANA pick-up test and mirror drawing test (mental load), and a driving simulator (complex load) in healthy volunteers. As a result, we found that some of plasma amino acid levels were significantly decreased after these fatigue sessions as compared with those after the relaxed session. Amino acids could be used as biomarkers for quantification of extent of fatigue and development of anti-fatigue substances in different types of fatigue.

P1-035 A dynamic change of trace element distribution in rat basophilic leukaemia cells (2H3) after antigen stimulation measured by in-air micro-PIXE

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The micro-particle induced X-ray emission (PIXE) method can measure the density of metals in a micro range. In this study, the elemental content of RBL-2H3 cells before and after exposure to antigen stimulation was determined by in-air micro-PIXE. The aggregation of IgE receptors of RBL-2H3 cells initiates the increase of intracellular calcium concentration, and finally causes histamine release. The 2H3 cells were cultured in Eagle's minimum essential medium (MEM) with 15 % of fetal bovine serum in a flask in an atmosphere of 0.5 % of CO₂ in air. The 2H3 cells were seeded on 5 μ m Mylar film (5 $\times$ 10⁵ cells/ film) in a culture dish and were incubated overnight. Cultured 2H3 cells on the film in a culture dish were sensitized with 0.5 μ g/ml of monoclonal IgE. The 2H3 cells were stimulated with 20 ng/ml of DNP-HAS as an antigen for 30 min. Released histamine in the supernatants was measured by HPLC-fluorometry. The cells were washed 7 times with THAM-HCl buffer, and were subjected to freeze-drying after rapidly freezing. As phosphorus is a constituent element of a nucleus and a membrane of a cell, the contour lines from element distribution of phosphorus reflect structure of a cell. The various element distributions of cells were markedly changed after stimulation. Sodium and magnesium accumulated into cells and potassium leaked out through the cells after stimulation. It could be observed that calcium was also increased. The element distribution of sulfur was varied by antigen stimulation, suggesting that sulfur, a constituent of heparin, was released by degranulation. This is the first report to demonstrate the dynamic changes of elements after the cell stimulation within a cell. The micro-PIXE method is useful to determine the elemental distribution within a cell.

P1-032 Working hypothesis on the central nervous system fatigue

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To understand the mechanism of central nervous system (CNS) fatigue, positron emission tomography (PET) imaging in humans during mental task revealed that the orbitofrontal cortex (Brodmann's area 11) and inferior frontal cortex (BA10) are activated in well correlation with the extent of fatigue sensation (Visual Analogue Scale). In the chronic fatigue syndrome (CFS) patients who suffered from intolerable fatigue sensation prolonged longer than 6 months and were diagnosed by CDC criteria (Fukuda et al., 1994), we demonstrated the reduction of serotonin transporter in the rostral sector of anterior cingulate and of acetyl-L-carnitine uptake in the vicinity of the anterior cingulate and dorsolateral prefrontal cortex (BA9/46d). More recently, we found the volume reduction of prefrontal cortices in the patients. We further investigated the responsiveness of the brain in CFS patients and in control subjects by using fMRI. While the subjects were conducting a fatigue-inducing continual visual search task, the responsiveness of the auditory cortices to transient noise reduction of short duration was measured in the same trial-frame. During the fatigue-inducing period, the extent of the activation of brain regions related to visual search decreased in both groups. However, the time window of the activation was almost the same between the CFS patients and control subjects. Although the responsiveness of the auditory cortices during the fatigue-inducing period was not changed in the control subjects, it was attenuated during the fatigue-inducing period in the CFS patients. Taken together, the working hypothesis on the CNS fatigue could be illustrated.

P1-034 Change in amino acid metabolism in the rat brain inhibited axonal flow by colchicine

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We examined the effect of colchicine, inhibitor of axonal flow, on amino acid metabolism in the rat brain. Adult male SD rats weighing 300-350 g were injected intraventricularly with colchicine (150 μ g). Colchicine group) or saline (Control group). The rats were injected with [1-¹³C] glucose intravenously (1 g/kg) 48 hours after the ventricular injection of colchicine and these rats were sacrificed by exposure to microwaves for 1.2 sec at 4.8 kW 40 min after the glucose injection. The brains were removed and amino acid fractions were extracted. The ¹³C incorporation into the cerebral amino acid from [1-¹³C] glucose was measured by ¹³C-NMR spectroscopy and the concentrations of cerebral amino acid were measured by HPLC. The ¹³C incorporation into glutamine and glutamate were decreased by 50 %, however the glutamine concentrations were increased 1.55 fold and the glutamate concentrations were not changed 40 min after the injection of [1-¹³C] glucose in the cerebra of the colchicine group, compared to those values in the control group. It is well known that glutamine is synthesized in the astrocyte from neuronal glutamate, and this glutamine then traffics to the neuron from the astrocyte. These data suggest that the rate of glycolysis and the turnover rate of glutamate-glutamine/neuron-astrocyte cycle are decreased, and that the influx of glutamine from blood to brain occurs by neuronal insult induced by colchicine.

P1-036 Visualization of active translation using molecular interaction formed at the translation termination

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We attempt to visualize ongoing translation by detecting an intermolecular reaction at the point of translation termination, using fluorescence resonance energy transfer (FRET). We transiently express a pair of FRET probes and an mRNA which was tagged with MS2 binding site (MS2-BD) just downstream of its terminator codon. The expressed mRNA were tethered by one of the tripartite FRET probe which comprises of a Upf1, an MS2 protein and YFP. When the translating ribosome recognizes the terminator codon on the MS2-BD-tagged mRNA, the other FRET probe which encodes eukaryotic release factor 3 (eRF3) fused with CFP is integrated into the termination complex. If an interaction between Upf1 and eRF3 increases, this reaction can be detected as FRET. We show the result by applying this system to COS7 cell and PC12 cells and demonstrate that this can reflect a real-time imaging of translation level from the specific mRNA, beta-actin.

P1-037 Analysis for functional interaction between alfa-synuclein and UCH-L1 proteins in vivo

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To elucidate the molecular pathway involved in the degeneration of dopaminergic neurons in Parkinson's disease (PD), a functional interaction between alfa-synuclein (aS) and UCH-L1 proteins was investigated in vivo. The type-1 recombinant adeno-associated virus (rAAV1) carrying human aS cDNA (rAAV1-aS) was stereotactically injected to substantia nigra of the 3- or 12-month-old transgenic (Tg) mice that overexpress human UCH-L1 possessing PD-linked Ile93Met mutation. The non-Tg littermates were used as a control. One month after the rAAV1-aS injection, exogenous aS was accumulated in nigral cell bodies and striatal fibers. Almost all of the aS-positive cells were also immunopositive for Ser129-phosphorylated aS. Nigral cells of UCH-L1-Tg mice were found to be more vulnerable to aS accumulation than that of control littermates, while striatal dopamine concentration was not significantly decreased in these mice. We are now examining for the presence of intraneuronal inclusions and the molecular pathway involved in nigral cell loss seen in UCH-L1-Tg mice.

P1-039 Increase of AMPA receptor glutamate receptor 1 subunit and B-cell receptor associated protein 31 gene expression in hippocampus of fatigued mice

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Central fatigue is the symptom most likely to disrupt the mental and physical activities and to cause various disabilities. The basic mechanism of fatigue still remains unclear. In this study, we have searched for genes expressed in murine hippocampus after fatigue on differential display screening to elucidate the mechanisms underlying fatigue. Transforming growth factor-beta, a contributing factor to fatigue, has been shown to be expressed in the dentate gyrus of hippocampus in exhausted mice. Therefore, we considered that the causal factors of fatigue might be present in hippocampus. Mice were forced to swim in an adjustable-current water pool, and the maximum swimming time (endurance) until fatigue was measured three times. The gene expression was compared in hippocampus between mice with equal swimming capacity. We found that the genes of GluR1 subunit of AMPA receptors and B-cell receptor-associated protein 31 (Bap31) that acts as a transport molecule in the secretory pathway or as a mediator of apoptosis, were upregulated in exhausted mice. Increases of gene expression of GluR1 and Bap31 in mice with fatigue were confirmed by Northern blot and real time-PCR analyses. On the other hand, no significant difference was observed in gene expression of AMPA receptor subunits other than GluR1 between fatigued and sedentary mice. These results suggest that fatigues would at least in part involve a compositional change in AMPA receptors through increased expression of GluR1 subunit as well as upregulation of Bap31 gene in murine hippocampus.

P1-041 Transgenic mice expressing mutant G392E human neuroserpin show neuronal dysfunction with aggregate formation in neurons

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BACKGROUND and PURPOSE: Neuroserpin is a member of the serine protease inhibitor (serpin) superfamily and is expressed in neurons of the developing and adult brain. Familial encephalopathy with neuroserpin inclusion bodies (FENIB), an autosomal dementia, has been recently reported. FENIB is diagnosed by inclusions of mutant neuroserpin proteins (S49P, S52R, H338R, and G392E) in neurons. A human neuroserpin cDNA encoding most severely disruptive mutation, G392E, was expressed under the control of the mouse Thy-1.2 promoter in mice, to determine whether the mutant protein would accumulate in neurons, causing neurodegeneration. **RESULT:** (1) Immunohistochemistry using an anti-human neuroserpin antibody detected deposits each with various sizes in neurons throughout the transgenic mouse brain. (2) Western blot analyses confirmed age-dependent accumulation of the mutant neuroserpin in cerebrum, brain stem, spinal cord but not in cerebellum. (3) Homozygous transgenic mice were more susceptible to seizures induced by kainate administration than wild-type mice. **CONCLUSION:** The histological, biochemical, and physiological features of homozygous G392E transgenic mice could imitate those of human FENIB, indicating that this transgenic mouse strain is useful for the study of the pathogenesis and potential therapies of the disease.

P1-038 Behavioral and microarray analysis of knock-in mouse which express only δ FosB from *fosB* gene

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fosB gene, a member of *fos* family encoding subunits of AP-1 transcription factor complex, produces FosB and Δ FosB by alternative splicing of its transcript. Δ FosB lacks the C-terminal 101 amino acid region of FosB which contains strong transacting domains. FosB and Δ FosB can either upregulate or downregulate the expression of subsets of genes in an antagonistic manner. The *fosB* expression is rapidly and transiently induced in brain in response to various stimuli, while chronic stimulation of brain selectively and continuously increases the level of Δ FosB in specific regions of the brain. It has been reported that *fosB*-null and Δ FosB transgenic mice both exhibit increased sensitivity to the rewarding and locomotor-stimulant effects of cocaine, thus puzzling us how FosB and Δ FosB regulate such behavior or brain function. To distinguish functions of FosB and Δ FosB in brain, we established a *fosB*-null mouse lacking both FosB and Δ FosB expression and a point mutation-knock-in (*fosB*^{td}) mouse which expresses only Δ FosB from the endogenous *fosB* gene. In *fosB*^{td} mice, an increased level of Δ FosB expression was observed in the specific regions of brain where authentic *fosB* gene is expressed, in comparison to the wild type. We found that *fosB*^{td} mice exhibit a hyperactive phenotype while *fosB*-null mice exhibit a hypoactive phenotype. Furthermore, *fosB*^{td} mice, and to a lesser extent *fosB*-null mice exhibited an increased exploring behavior in the open field. On the elevated plus maze, we found that *fosB*^{td} mice stay longer in the open arms while *fosB*-null mice stay shorter in the open arms, in comparison to the wild type. To clarify the molecular basis for the altered behaviors in these mice, we are now analyzing gene- and protein-expression profiles in their brains.

P1-040 Neurotoxicities of local anesthetics on bovine adrenal chromaffin cells at clinical use concentrations

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Recent reports on a permanent neurologic injury have generated concern about the potential neurotoxicity of lidocaine. Bovine adrenal chromaffin cells, which are originated from a neural crest and are regarded as autonomic ganglions, secrete catecholamines(CAs) via a stimulation of nAChRs. It is well known that local anesthetics block cation channels, and inhibit the acetylcholine-evoked Ca²⁺ influx into the cells and CA secretion from the cells at low concentrations. However, the effects of the local anesthetics at clinical (higher) concentrations on the chromaffin cells are obscure. In this study, we investigated the effects of local anesthetics on CA secretion at the doses clinically used, and also on lactate dehydrogenase(LDH) and aspartate aminotransferase(AST) release from the bovine adrenal chromaffin cells. Dibucaine(Dibu), tetracaine(Tetra), bupivacaine(Bupiva), lidocaine(Lido), ropivacaine(Ropiva), pivalacaine(Mepiva) procaine(pro), prilocaine(Prilo) and etidocaine(Etido) secreted CAs from the cells in a concentration-dependent manner, but the effects of Dibu, Tetra, Bupiva and Lido were greater than those of the other. On the other hand, Dibu, Tetra and Lido increased both of AST and LDH from the cells at higher concentrations. These results suggest that Dibu, Tetra and Lido at the clinical doses permeabilize the cell membranes and cause damage to the bovine adrenal chromaffin cells.

P1-042 Influence of chronic variable stress to electric sensitization of the acoustic startle response in rats

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The acoustic startle response (ASR) is a short latency reflex elicited by a sudden and intense acoustic stimulus. The ASR amplitude can be enhanced by an aversive stimuli such as a footshock. The activity of the corticotropin-releasing hormone (CRH) neurons that project to the nucleus reticularis pontis caudalis (PnC) from the central nucleus of amygdala (CeA) directly play an important role in enhancement of ASR. We previously found a decrease in the CRH immunoreactivity of CeA 24 hours (h) after the last stress of chronic variable stress (CVS) for 13 days whereas the CRH immunoreactive response was augmented by a footshock. In the present study, we examined the influence of the footshock on the ASR of rats exposed to CVS for 14 days and discussed the amygdaloid CRH involved in the variable footshock response of ASR after CVS. Male Wistar rats were used. Rats were treated with CVS for 13 days according to the procedure of Roth and Katz (1981). The ASRs were measured 24 h after CVS 13 days (CVS-14d), immediately after mild footshock (0.6mA, 2s, 5 times) following CVS (CVS + FS), and 24 h after footshock (24 h after CVS + FS). The handling rats for 13 days served as a control animal. A mild footshock had no significant influence on the ASR amplitude of control rats. The ASR amplitude was not changed in CVS rats (CVS-14d). A mild footshock significantly augmented the ASR of CVS rats (CVS + FS). This ASR augmentation disappeared 24 h later (24h after CVS + FS). These results demonstrated that the enhancement of ASR by footshock after CVS may be attributed to sensitization of the CRH neuronal reactivity in CeA.

P1-043 Neonatal Isolation and Environmental Enrichment in an Animal model of PTSD: Effects on Conditioned and Unconditioned Fear after Stress

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Background: Since exposure to extremely stressful events can lead to PTSD in only 20-30% of victims, some vulnerable factors are involved in the development of PTSD. Human studies suggest early adversity increases the vulnerability to stress and consequently induces PTSD. Investigating molecular basis of the stress vulnerability, we made a stress vulnerable model due to rearing environment in an animal model of PTSD. **Methods:** Neonatal isolation (NI) and environmental enrichment (EE) were used to study the effects of rearing environment. Litters were subjected to NI or were non-handled. Additionally, half of each group was housed under enrichment or normal conditions. Later in adulthood, those rats were exposed to single prolonged stress (SPS), an animal model of PTSD. After a week, contextual fear and avoidant behavior were examined. **Results:** Contextual fear in the SPS-exposed rats subjected to NI were significantly higher than that in those without NI. While NI alone increased only avoidant behavior, SPS alone independently produced enhanced contextual fear, and avoidant behavior. EE significantly ameliorated the contextual fear in the SPS-exposed rats subjected to NI. Interestingly, EE alone decreased avoidant behavior, but enhanced stress-induced avoidance. **Conclusions:** Based on these findings, the experience of SPS enhanced aversive learning often seen in PTSD in rats subjected to NI. Therefore, it is conceivable that the neonatal isolation may aggravate the stress susceptibility. Whereas EE ameliorated conditioned fear, it enhanced stress-induced avoidant behavior in the rats subjected to NI. These results suggest that neonatal isolation and environmental enrichment produce complex effects on the defensive system in rats.

P1-045 The effect of repeated MK-801 on the c-Jun in the rat frontal cortex

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c-Jun is a component of transcription factor AP-1, which binds and activates transcription at TRE/AP-1 element and plays critical roles in neuronal apoptosis, regeneration and protection. We observed the amount and phosphorylation of molecules associated with c-Jun in rat frontal cortex after repetitive injection of MK-801, which antagonizes NMDA receptor selectively and induces psychotomimetic behavioral changes in rodents. Rats were given daily intraperitoneal injection of MK-801 (0.5, 1 and 2 mg/kg) for 1, 5 and 10 days. And the changes in signaling proteins were examined 24hr after the last injection of MK-801. In the rat frontal cortex, repeated injection (5X and 10X) of MK-801 significantly decreased amount of c-jun, but not Jun B and Jun D, in rat frontal cortex. And phosphorylation of Ser-73-c-Jun was also decreased. Three different dosage of MK-801 (0.5, 1 and 2 mg/kg) induced same pattern of changes in c-Jun. However, single injection of MK-801 did not induce changes in amount and phosphorylation of c-jun. The amount of JNK and phosphorylation of Thr-183/Tyr-185-JNK, one of the upstream of c-Jun, was not affected by repetitive MK-801 treatment. And amount of c-Fos, another component of AP-1, was not changed after repeated injection of MK-801. Taken together, repeated treatment of MK-801 (0.5-2 mg/kg) decreased amount and phosphorylation of c-jun. Therefore, c-Jun may be one of the signaling molecule related to the neuronal and behavioral changes induced by MK-801.

P1-047 Characterization of anxiolytic-like behaviors in adult rats experienced with early postnatal stress

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We investigated behavioral expression and neurochemical responses to the emotional stimuli in the adulthood with traumatic events during periadolescence.

Rat pups were subjected to electrical foot-shock (FS) for 5 days on the day 14 (2WFS) or 21 (3WFS) after birth. The behavioral analysis was explored using elevated plus-maze and contextual fear conditioning paradigms at the 10 week-old of age. Non-stressed rats were subjected as a littermate control. Serum corticosterone levels were determined as a measure of HPA-axis activity. Expression of c-Fos proteins was immunohistochemically determined as a functional marker of cellular response.

In the elevated plus-maze test, rats experienced with early postnatal stress significantly increased time spent in the open arm. However, this anxiolytic-like behavior was markedly observed in 3WFS rats, as compared with 2WFS rats. Conversely, in the contextual fear conditioning test, the freezing behavior significantly decreased in 2WFS, but not 3WFS rats. In 2WFS rats, conditioned fear stress exerted the attenuated response of corticosterone and the decreased c-Fos-immunoreactive cells in the dorsal raphe nucleus.

Taken together, these findings suggest that traumatic events during periadolescence produce the anxiolytic-like behaviors, indicating changes in anxiety susceptibility. This behavioral vulnerability could be associated with the exaggerated neurochemical responses to the emotional stimuli, with a critical developmental period.

P1-044 Effects of SNAP-25 mutation at PKC-dependent phosphorylation site on development and the behavior of aged mice

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SNAP-25 is a protein essential for neurotransmitter release from presynaptic nerve terminals. SNAP-25 is phosphorylated by protein kinase C at Ser¹⁸⁷, and this phosphorylation is believed to play important roles in the regulation of synaptic functions. To ascertain the physiological importance of this phosphorylation, we generated a mutant mouse substituting Ser¹⁸⁷ of SNAP-25 with Ala using "knock-in" technology. Previously, we showed young (10 to 15 weeks old) homozygous mutant mice to exhibit various abnormal behaviors. In the present study, we examined the behaviors of aged mice, i.e. those of more than one year old. The body weights of wild type mice increased rapidly after birth up to 10 weeks, increasing gradually thereafter. In striking contrast, the increases in body weights of the homozygous mice stopped around 15 weeks after birth, and the average weights of aged (60 to 73 weeks old) male and female homozygous mice were only 60 and 67 % of those wild type mice, respectively. In an open field test, most of the aged wild type mice explored the entire area, though some showed thigmotaxis. The rate of locomotion did not change throughout the test period and was not variable among trials. In contrast, all of the aged homozygous mice showed abnormal behaviors such as strong thigmotaxis, hyperlocomotion or freezing-like behavior. Even during the period of hyperlocomotor activity, the homozygous mice often stopped moving for several minutes. Since the open field is considered to be a stressful environment, the older SNAP-25 knock-in mice might be more susceptible to stress than the younger animals. Taken together, these results indicate that phosphorylation of SNAP-25 at Ser¹⁸⁷ continues to exert effects on growth and behavior in adulthood.

P1-046 Possible Involvement of Serotonergic System in Stress Response Mechanisms in Rat Brain Development

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Recent study focuses on the characteristics of the serotonin (5-HT) receptors in the forebrain during development period, however, few studies have addressed whether early postnatal stress affects the 5-HTergic mechanism underlying regulation of emotional stress in adult. The aim of the present study was to assess whether traumatic events during the early postnatal stage would differently affect the rat brain development, focusing on the 5-HTergic function. Rats received aversive stimuli foot shock (FS) at the postnatal period of the second week (2W-FS), but not the third (3W-FS), markedly reduced fear-related freezing behavior during exposure to conditioned fear stress (CFS), at the postadolescent period (10-12 weeks old). This anxiolytic-like behavior observed in 2W-FS was similar to that in rats having electrolytic lesion of either median raphe nuclei (MRN) or dorsal raphe nuclei (DRN), which are two major sources of 5-HTergic projection to the forebrain. On the other hand, 3W-FS significantly increased percentage of time spent on open arms compared to non-FS control, estimated by unconditioned fear stress, elevated plus maze test (EPM). The anxiolytic effects observed in 3W-FS are mimicked by electrolytic lesion of MRN, but not DRN. These data suggest that aversive stress exposed at the second and/or the third week is attributable to the 5-HTergic system underlying regulation of emotional stress on the postnatal development of the brain. In other words, the critical period of neural circuit development appears to exist in the 5-HTergic response to fear stimuli, which may be implicated in the lifelong susceptibility to emotional stress.

P1-048 DNA microarray analyses of thyroid hormone-dependent gene expression in the developing mouse cerebellum: identification of metabotropic and NMDA-type glutamate receptor genes as highly dependent genes

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Thyroid hormone (TH) is indispensable for growth and differentiation of many organs including the brain which is particularly vulnerable to its deficiency. To identify TH-regulated genes, we analyzed gene expression changes during postnatal cerebellar development using two types of DNA microarrays; a commercially available high-density array and an original oligoDNA microarray "Synaptarray" focused mainly on genes involved in synaptogenesis. Using the Synaptarray, developmental gene expression was compared between control and experimentally hypothyroid mice which have been exposed *in utero* to anti-thyroid drug methimazole (2-mercapto-1-methylimidazole; MMI 0.025%) from the embryonic day 15. The results demonstrated a massive difference in gene expression at postnatal day (PND) 15 as expected from morphological studies. In addition, a significant difference was detected already at PND4 when morphological differences are minimal. We thus carried out a large scale screening for TH-responsive genes using high-density arrays at PND4 by comparing normal control, hypothyroid, and hypothyroid receiving daily T4 injection after birth. They were compared by competitive hybridization in two pairs, hypothyroid vs. control and hypothyroid with T4 addition vs. hypothyroid. Genes which were both down-regulated by hypothyroidism in the former pair and up-regulated by T4 replacement in the latter pair were considered as TH-responsive. Many transcription factors, translation initiation factors, neurotransmitter receptors, and ion channels were detected as TH-responsive. Among these, various subunits of glutamate receptors of NMDA-type (NMDAR) and metabotropic type (mGluR) were confirmed further by real-time PCR to be strongly dependent on TH during development.

P1-049 Enriched Environment enhances Neuropilin mRNA in the hippocampus and amygdala

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Neuropilin, limbic serine protease, exhibited an activity-dependent change by modifying the synaptic adhesion molecule L1, which was localized to the asymmetric synapse in the mouse hippocampus. Environmental enrichment is known to induce neural development and plasticity change in the hippocampus and amygdala of rodent and is an effective method to study long-lasting morphological and behavioral effects by neural activity. However, it is not yet known how enriched environment stimulate neural self organization with the activity-dependent. One presumed system for organization of developing neural networks is provided by interaction of cell adhesion molecules (CAM) and their proteolytic regulation. Therefore, the aim of this work is to examine whether enriched environment might induce changes the protease-CAM system in the hippocampus and amygdala complex. By *in situ* hybridization, neuropilin mRNA was up-regulated in the hippocampus and amygdala when brains of enriched and normal pups were compared. Moreover, the density of L1 mRNA was increased in the hippocampus and amygdala in the enriched group. These results suggest that the protease-CAM system of limbic brain is participate in activity-dependent synaptic modulation in the postnatal developing brain.

P1-051 Chemical compound, BIX, protects cells from neuronal death induced by ER stress via induction of ER molecular chaperone

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The endoplasmic reticulum (ER) is an organelle in which secretory and transmembrane proteins are made and processed. When unfolded and misfolded proteins accumulate in the ER, so-called in ER stress condition, the cell invokes responses to remove these defective proteins. This regulatory system in response to ER stress is termed the unfolded protein response (UPR). The UPR is composed of translational attenuation, induction of ER molecular chaperones and degradation of unfolded proteins. Recently, it has been reported that ER stress is involved in neural cell death in neurodegenerative disorders. In fact, accumulation of unfolded proteins is observed in neurodegenerative disorders, for example, Alzheimer's disease, Parkinson's disease and so on.

In this study, we investigated the possibility of therapeutic agent for neurodegenerative disease. We performed the screening the compounds and picked up the agent which induced the expression of ER molecular chaperone, GRP78/BiP. Surprisingly, this agent, named BIX, did not cause ER stress despite upregulation of GRP78/BiP. Additionally, pretreatment for SK-N-SH neuroblastoma cells with BIX reduced the cell death by thapsigargin or tunicamycin, the agents that caused ER stress. These results suggest that abundant GRP78/BiP proteins prevent the neural cell death induced from ER stress, and that BIX may be useful for the treatment of neurodegenerative diseases.

P1-053 Autophagy is activated during ER stress via the ER-resident transmembrane kinase IRE1

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The endoplasmic reticulum (ER) is susceptible to various stresses that provoke the accumulation of unfolded proteins in the ER (ER stress). Eukaryotic cells deal with accumulation of unfolded proteins in the ER by the unfolded protein response, involving the induction of molecular chaperones, translational attenuation and ER-associated degradation, to prevent cell death. The ER stress has been reported to be involved in neuronal death in many neurodegenerative disorders. Recently, autophagy, a regulated process that is activated for bulk removal of cellular proteins and organelles, has also been observed in neuropathologically affected neurons. Here, we found that the autophagy system is activated as a novel signaling pathway in response to ER stress. In IRE1 α -deficient cells, the autophagy induced by ER stress was inhibited, indicating that IRE1 α is essential for autophagy activation after ER stress. Disturbance of autophagy rendered cells vulnerable to ER stress, suggesting that autophagy plays important roles in cell survival after ER stress.

P1-050 A possible role of parkin and ubiquitin carboxy-terminal hydrolase L1 in neurotransmission; potentiation of P2X receptor channels

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Loss of ubiquitin carboxy-terminal hydrolase L1 (UCH L1) function causes dying-back type of axonal degeneration, and loss of parkin function causes an autosomal recessive juvenile-onset form of Parkinson's disease. UCH L1 works not only as a de-ubiquitinating isozyme but also as an ubiquitin ligase or an ubiquitin carrier protein. Parkin is an E3 ubiquitin ligase. Both enzymes work in the ubiquitin-proteasome system, but their function in neuronal cells and neurotransmission remains elusive. Here, we show that overexpression of UCH L1 or parkin potentiated adenosine triphosphate (ATP)-induced membrane currents. ATP-induced inward currents were measured in mock-, UCH L1-, or parkin-transfected PC12 Tet-Off cells under the conventional whole-cell patch clamp configuration. The amplitude of ATP-induced currents was significantly greater in UCH L1- or parkin-transfected cells. Mutant (C90S)-UCH L1 which lacks hydrolase activity also had potentiating effect on P2X receptors, suggesting that increased level of mono-ubiquitin but not hydrolase activity play an important role. In contrast, mutated parkin (T415N) did not produce potentiating effect, suggesting that ubiquitin ligase activity is important. Immunocytochemical study showed no increase in the number of P2X receptors. The increased currents were attenuated by inhibition of cAMP-dependent protein kinase (PKA). In addition, ATP-induced currents were likely modified via dopamine and cyclic AMP-regulated phosphoprotein that is regulated not only by PKA but also by phosphatases and cyclin-dependent protein kinase 5. Our finding provides the first evidence for a relationship between UCH L1/parkin and a neurotransmitter receptor, suggesting that UCH L1 and parkin may play an important role in synaptic activity.

P1-052 Histologic analysis of mutant SOD1 aggregation in ER and large hyaline inclusions induced by ER stress

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The aggregates of mutant Cu/Zn superoxide dismutase 1 (SOD1), such as neuronal Lewy body-like hyaline inclusions (LBHIs) and astrocytic hyaline inclusions (Ast-HIs), are known as a morphological hallmark of mutant SOD1-linked familial amyotrophic lateral sclerosis (FALS). However, the mechanisms by which mutant SOD1 forms aggregates in FALS remain unclear. We investigated the accumulation of SOD1 in the endoplasmic reticulum (ER) under ER stress by exposing to tunicamycin and thapsigargin in SK-N-SH neuroblastoma cells that expressed mutant L84V SOD1. Tunicamycin and thapsigargin induced mutant SOD1 aggregation, but not topoisomerase. The aggregated mutant SOD1 was clearly ubiquitinated and localized to ER. A distribution of ER was dramatically changed after ER stress exposure, suggesting that aggregates of mutant SOD1 deteriorate ER functions. Furthermore, large hyaline inclusions compatible with LBHIs are generated by tunicamycin treatment. Ultrastructurally, these inclusions consisted of approximately 15-25 nm granule-coated fibrils and granular material, with the fibrils are representing the morphological hallmark of mutant SOD1-linked FALS. These findings suggest that ER stress promotes the aggregation of mutant SOD1 and is involved in the development of neuronal LBHIs.

P1-054 Characterization of chorein whose dysfunctions cause Chorea-acanthocytosis

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Chorea-acanthocytosis (ChAc) is an autosomal recessive neurodegenerative disorder. Clinically, ChAc shows Huntington's disease-like neuropsychiatric symptoms and erythrocyte acanthocytosis. The mutations of VSP13A, encoding a large protein called chorein, cause ChAc. Recently, a ChAc-model mouse introducing #60-61 exons-deletion corresponding to a human disease mutation was produced. Anti-chorein polyclonal antibody was generated with an antigen, synthetic oligopeptide corresponding to the amino acid sequence of the middle part of human chorein. In the present study, we have characterized the chorein in human and mouse erythrocytes and the mouse brain by the antibody. The expression levels of chorein in mouse brain regions were identified by immunoblot analysis. Erythrocyte samples of ChAc patients and healthy controls were used for immunoblot analysis to compare the difference of the chorein expression. Immunohistological and immuno-electron microscopical observation was performed for localization of chorein. We found chorein is expressed ubiquitously in mouse brain and is localized underneath plasma membrane in erythrocyte. Chorein showed little expression in the targeted model mouse and in ChAc patients erythrocyte whose mutations lead to produce truncated proteins, which could be theoretically detected by the antibody. Thus this antibody should be useful for both diagnosis of ChAc and investigation for chorein. These results suggest that chorein may have important roles in the brain and be present as a structural protein in erythrocyte.

P1-055 Spinocerebellar degeneration caused protein, aprataxin, is a 3'-5' exonuclease

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Purpose: To elucidate the physiological function of aprataxin (APTX). **Background:** APTX is a causative gene for early-onset ataxia with ocular motor apraxia and hypobuminaemia (EAOH/AOA1), an autosomal recessive disorder of spinocerebellar degeneration. APTX binds to X-ray repair cross-complementing group 1 protein, which is the scaffold protein for base excision repair (BER) machinery in single strand DNA break repair (SSBR). The lymphoblastoid cells of EAOH/AOA1 patients were sensitive to agents, which cause single strand break. These findings support the idea that APTX might take an important role in SSBR system. However, physiological function of APTX is unclear. **Materials & Methods:** His-tagged human full length aprataxin was expressed using baculovirus expression system and was purified by metal affinity beads followed by fractionation with gel filtration chromatography. Double or single strand DNA substrates were incubated with that recombinant protein at 37°C for 0-90 minutes. The products, which were labeled by fluorescein, were analyzed by electrophoresis in a denaturing 20% polyacrylamide gel and visualized by Typhoon 9400 Variable Mode Imager. The undigested oligonucleotide was analyzed using ImageQuant software. **Results:** APTX has bidirectional exonuclease activity. 3'-5' exonucleases often preferentially excise a mismatched DNA terminus to enhance fidelity of DNA synthesis. However, the APTX 3'-5' exonuclease equally excise matched and mismatched DNA termini. **Conclusions:** We showed that the full length human APTX is a bidirectional exonuclease and could not confirm that the APTX 3'-5' exonuclease contribute to increase the fidelity of DNA synthesis. Therefore, it would act to remove the blocked 3'-end interfering with the DNA synthesis in SSBR system.

P1-057 ALTERED CHOLESTEROL METABOLISM IN NIEMANN-PICK TYPE C1 MOUSE BRAINS INDUCES MITOCHONDRIAL DYSFUNCTIONS

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Niemann-Pick type C1 (NPC1) disease is an autosomal recessive disorder characterized by progressive neurodegeneration including ataxia, dystonia, seizures, and dementia. The responsible gene, NPC1 gene, for causing NPC1 disease has been identified and it has been shown that cholesterol trafficking is impaired due to the lack of NPC1 expression in cells from the patients with NPC1 disease and model mice of NPC1 disease. However, the molecular mechanism responsible for neuronal dysfunction in brains of patients with NPC1 disease still remains unknown. This study demonstrates the mechanism, by which altered cholesterol metabolism in mitochondria induced neurodegeneration in NPC1 mice (Yu et al, J Biol Chem, 2005). We found that the amount of cholesterol within mitochondria membranes is significantly elevated in NPC1 mouse brains and neural cells. In addition, the mitochondrial membrane potential, the activity of ATP synthase, and henceforth the level of ATP are markedly decreased in NPC1 mouse brains and neurons. Importantly, reducing the level of cholesterol within mitochondrial membranes using methyl-β-cyclodextrin can restore the activity of ATP synthase, and the concomitant treatment with methyl-β-cyclodextrin and cholesterol restored ATP synthase activity down to the control level. Finally, NPC1 neurons show an impaired neurite outgrowth, which can be rescued by exogenous ATP. These results suggest that mitochondrial dysfunctions and subsequent ATP deficiency, which are induced by altered cholesterol metabolism in mitochondria, may be responsible for neuronal impairment in NPC1 disease.

P1-059 Visualization of soluble Polyglutamine dimer in Living cell

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[Background & Purpose]: Polyglutamine diseases are inherited neurodegenerative disease with intranuclear aggregate formation caused by the expansion of a homopolymeric glutamine stretch in various genes. Recent works revealed that the aggregate showed protective activity against expanded polyglutamine cytotoxicity. Therefore one of the hypotheses is the dimer or oligomer formation of expanded polyglutamine stretch might cause the cell dysfunction. To clarify this possibility, it is important to visualize the dimer or oligomer formation in living cell. **[Materials & Methods]:** We generated fusion proteins of monomeric-YFP(mYFP) or monomeric-CFP(mCFP) and polyglutamine stretch. We cotransfected COS7 or SH-SY5Y with these in several different combinations. If two fluorescent proteins are close enough to produce fluorescence resonance energy transfer(FRET), we will detect them by fluorescence confocal microscopy(CSU10). **[Results & Discussion]:** FRET was only observed in combination with mCFP-poly(Q)/mYFP-poly(Q) or poly(Q)-mCFP/poly(Q)-mYFP. The number of the cells which showed FRET increased in length dependent manner(Q12-9.5%, Q36-24.2%, Q56-27.2%, Q80-36.7%). By construct, in combination with mCFP-poly(Q)/poly(Q)-mYFP or poly(Q)-mCFP/mYFP-poly(Q), we did not find any FRET. This result indicated that polyglutamine stretch made dimer in a parallel manner, not an anti-parallel manner in living cell. Furthermore, the intensity of FRET increased in length dependent manner(Q12-0.77, Q36-0.82, Q56-0.90, Q80-0.91). It suggested that the stability of dimer formation increased by length dependent manner. This new technique to visualize the soluble dimer or oligomer of expanded polyglutamine in living cell will tell us a new aspect of pathogenesis of expanded polyglutamine stretch.

P1-056 An NF-κappaB inhibitor attenuates A53T alpha-synuclein-caused cell death in an inducible cell model

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Parkinson disease (PD) is a common progressive neurodegenerative disorder. Mutations in the alpha-synuclein gene cause autosomal dominant familial PD. We have created inducible PC12 cell lines harboring wild-type and A53T alpha-synuclein using the tet-off gene expression regulatory system.

In induced conditions, cells expressing A53T alpha-synuclein showed cytoplasmic aggregates which were positive for alpha-synuclein and ubiquitin. Expression of A53T alpha-synuclein significantly increased apoptotic cell death. Because it has been reported that NFκappaB may be involved in neural cell death, we studied the NFκappaB pathway in our cell model. We observed NFκappaB immunoreactivity in nuclei in cells expressing A53T alpha-synuclein. We also detected cytoplasmic aggregates stained for IκappaB after induction of A53T alpha-synuclein.

In a pathological study, we found nuclei with increased immunoreactivity of NF-κappaB, and Lewy bodies stained for IκappaB in PD patient brains. To further analyze the involvement of the NF-κappaB pathway, we evaluated cell death in the presence of an NF-κappaB inhibitor. We found that cell death caused by A53T alpha-synuclein was attenuated by the inhibitor. Our data suggest that the NF-κappaB pathway is involved in cell death caused by A53T alpha-synuclein, and that the pathway may be a potential target for PD therapeutics.

P1-058 Transplantation of tyrosinase cDNA-transfected hepatocytes 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 also dopamine. Previous studies showed a therapeutic potency of tyrosinase that may complement tyrosine hydroxylase when dopaminergic neurons are degenerated and may normalize L-DOPA-induced abnormal dopamine turnover. Furthermore, we previously reported that intrastriatal transplantation of tyrosinase-producing cells of melanoma or melanocytes markedly and long-lastingly ameliorated apomorphine-induced contralateral rotation behavior in hemi-parkinsonian models. To investigate the possible effects of non-melanogenic cells transfected with tyrosinase gene, we performed intrastriatal transplantation of human hepatocyte HLE cells transfected with tyrosinase cDNA into hemi-parkinsonian mice lesioned by 6-OHDA. In the transplanted group with tyrosinase cDNA-transfected HLE cells that constitutively produce L-DOPA, the apomorphine-induced rotation behavior was markedly ameliorated at 7 days up to 2 months after the transplantation. Taken together with our previous studies showing therapeutic effects of melanogenic cell transplantation, the present results suggest a therapeutic potency of tyrosinase-expressing cells for the parkinsonian when striatal dopamine is depleted.

P1-060 ALS2CL, a novel ALS2 homologous protein, interacts with ALS2: A possible functional modulator for ALS2

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The loss-of-functional mutations in the *ALS2* gene account for a number of recessive motor neuron diseases including amyotrophic lateral sclerosis, primary lateral sclerosis, and hereditary spastic paraplegia. The causative gene product, ALS2/alsin, mediates the activation of Rab5 GTPase via its guanine nucleotide exchanging reaction (Rab5GEF activity), thereby inducing striking enlargement of endosomes in the cells. In addition, ALS2 forms a homophilic oligomer, which is crucial for the ALS2-associated Rab5GEF activity and endosome dynamics. Recently, we have reported a novel ALS2 homologous gene, ALS2 C-terminal like (*ALS2CL*), and demonstrated that its gene product, ALS2CL, exhibited a specific but a relatively weak Rab5GEF activity with strong Rab5-binding properties. Here, to gain further insights into the molecular function of ALS2CL, we analyzed the molecular interaction between ALS2CL and ALS2, as well as the subcellular distribution of ALS2CL and ALS2. Yeast two-hybrid assay and co-immunoprecipitation demonstrated that ALS2CL directly interacted with ALS2. Furthermore, overexpression of ALS2CL suppressed the ALS2-mediated enlargement of endosomes in HeLa cells. These results imply that ALS2CL is a novel ALS2 binding protein and may function as a modulator in the ALS2-mediated membrane trafficking *in vivo*. Currently, the molecular basis of the ALS2CL-mediated modulation of endosome dynamics is being studied.

P1-061 Lack of a BMP antagonist, Tsukushi (TSK), causes retinal degeneration in young adult mice

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We have identified a novel secreted factor, Tsukushi, from chick lens cDNA library. In previous studies, Tsukushi functions as a BMP antagonist in chick axis formation in cooperation with chordin (Ohta et al., Dev. Cell vol.7, 2004)

We tried further investigations into these early developmental events using TSK knockout mice. However, they did not show any apparent developmental disorders. In chick and frog, TSK gene is expressed in ciliary marginal zone, which is a potential source of the adult retinal stem cells in mouse. We raised a polyclonal antibody against mouse TSK (M-TSK), and analyzed M-TSK protein distribution. M-TSK protein was observed in developing retina, and its distribution moved from inner to outer retinal layer. We analyzed aged mouse retina, and found that the retina of TSK depleted mice showed retinal degeneration, especially photoreceptor cell missing. To investigate why the retinal degeneration happened, we analyzed knockout mouse retina by immunohistochemistry or ERG recording from postnatal day 0 to 3 months old. As the results, TSK knockout mice showed a variety of phenotypes, and were divided into early and late cell death groups: Early cell death shows severe outer nuclear layer (ONL) loss until P21. The apoptosis is observed in the inner nuclear layer (INL) and ONL. Active caspase-3 staining (apoptosis) overlapped with horizontal cell marker in INL. At P14 mouse, M-TSK was observed in horizontal cells. Thus, earlier phenotype may be due to depletion of M-TSK expression in horizontal cell. Late cell death was indicated by the gradual loss of a-wave of ERG, and the retinal cell death was seen from 7 weeks. Now we are analyzing retinal cell death by primary culture.

P1-063 MCC-257, orally active neurotrophin enhancer, attenuates thermal hypoalgesia and protects cutaneous innervation in hyperglycemic mice

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To determine whether MCC-257, a novel neurotrophin enhancing agent, could ameliorate thermal hypoalgesia and cutaneous innervations, we examined behavioral responses to thermal stimuli, substance P (SP) levels and numbers of nerve fibers in plantar skins between control hyperglycemic *+Lepr^{db}/+Lepr^{db}* mice and MCC-257-treated ones. Hyperglycemic animals were once daily treated with vehicle or MCC-257 at doses of 3 mg/kg p.o. and 10 mg/kg p.o. for 7 weeks. Thermal nociceptive responses were examined using the hot plate apparatus at the beginning and the end of the treatment. After 7 weeks of treatment, plantar skins were excised and processed for substance P measurement by enzyme-linked immunosorbent assay with SP antibody and the immunohistochemistry with PGP 9.5 (pan-neuronal marker) antibody. Thermal nociceptive responses in hyperglycemic mice were significantly delayed compared with that of normoglycemic mice (*m⁺/+Lepr^{db}*) both at the beginning and the end of the treatment. MCC-257 treatment significantly improved thermal hypoalgesia at the dose of 10 mg/kg. SP levels in plantar skins was declined in vehicle-treated diabetic mice compared with that of normoglycemic mice, whereas MCC-257 treatment significantly attenuated its decline as compared with that of vehicle-treated mice. In addition, immunohistochemical assessment of plantar skins for PGP 9.5-positive nerve fibers also demonstrated that cutaneous innervations in vehicle-treated diabetic mice were significantly reduced and MCC-257 diminished its reduction. These results suggest that MCC-257 has beneficial effects on sensory impairments caused by diabetic mellitus and is a promising drug candidate for diabetic neuropathy.

P1-065 Chronic treatment with SSRIs desensitizes both 5-HT_{2A} and 5-HT_{2C} receptor function

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Chronic treatment with selective serotonin reuptake inhibitors (SSRIs) produces persistent increases in 5-HT in the synaptic cleft and may lead to the desensitization of post-synaptic 5-HT receptors through the continuous stimulation of receptors. In the present study, we investigated whether the chronic administration of fluvoxamine and paroxetine could desensitize 5-HT_{2A} and 5-HT_{2C} receptors using m-chlorophenylpiperazine (mCPP) to evaluate 5-HT receptor sensitivity in rats. Acute treatment with fluvoxamine or paroxetine reduced spontaneous locomotion, as observed with the administration of mCPP. These effects were completely reversed by treatment with a selective 5-HT_{2C} receptor antagonist, SB 242084. On the other hand, the mCPP-induced increase in the serum concentration of corticosterone was not blocked by SB242084 but was blocked by the 5-HT_{2A} antagonist, ketanserin. Chronic treatment with fluvoxamine or paroxetine attenuated mCPP-induced hypolocomotion and the increase in the serum corticosterone, while they had no effects on these parameters in control rats. Also, chronic treatment with these drugs had no effects on the mCPP concentration in the rat brain. These results suggest that the function of both 5-HT_{2A} and 5-HT_{2C} receptors is desensitized by chronic treatment with either fluvoxamine or paroxetine as a consequence of prolonged exposure to elevated levels of 5-HT. The desensitization of 5-HT_{2A} and 5-HT_{2C} receptor function might contribute to the therapeutic mechanism of action of SSRIs in the treatment of depression and anxiety disorders.

P1-062 Age-related severity of dopaminergic neurodegeneration to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity causes motor dysfunction in C57BL/6 mice

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This study examined the influence of aging on dopaminergic neuronal degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication in view of various perspectives. Young (10 weeks) and older (14-15 months) C57BL/6 mice were treated with 1 or 2 injections of MPTP (20 mg/kg at 2h intervals). At 3 days after MPTP treatment, although no mortality was seen in young mice, the survival rates in older mice were 100% and 72% in 1 and 2 injections, respectively. Extensive dopaminergic cell loss was found in the striatum and substantia nigra of older mice, but not young mice given MPTP, with marked decreases in striatal dopamine (DA) levels. Furthermore, we found a behavioral change in the tail suspension test (TST) associated with the extent of decreases in striatal DA levels in older mice under our experimental condition. Additionally, monoamine oxidase-B (MAO-B) activity in striatal tissue homogenate was enhanced by advancing age, whereas the normal aging process did not affect mitochondrial membrane potential in striatal synaptosomes and ATP production rate in striatal tissue homogenate. These results clearly present age-related vulnerability to MPTP neurotoxicity in C57BL/6 mice, and indicate that the increase in MAO-B activity in normal aging process may be involved in the high sensitivity to MPTP intoxication. This study also supports our previous report showing that there is a threshold level of the decrement in striatal DA content producing behavioral change in the TST using MPTP-treated mouse model of PD.

P1-064 DISC1 transports Grb2 in kinesin-1 dependent manner

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Disrupted-In-Schizophrenia-1 (DISC1) was identified at the breakpoint of a chromosomal translocation associated with schizophrenia in a large Scottish family. The physiological functions of DISC1, however, were not well understood. Here, we identified Grb2 as a novel DISC1-interacting molecule by affinity column chromatography. Grb2 is composed of one SH2 domain flanked by two SH3 domains. N-terminal SH3 domain of Grb2 directly recognized the C-terminal region of DISC1. We also identified kinesin-1 as a DISC1-interacting molecule. We then investigated whether DISC1 was involved in Grb2 transport or localization. In cultured hippocampal neuron, both DISC1 and Grb2 accumulated in distal part of axon. Knockdown of DISC1 by RNA-interference resulted in Grb2 delocalization. Moreover, functional blocking of kinesin-1 resulted in mislocalizations of both DISC1 and Grb2 from growth cone. These results suggest that DISC1 transports Grb2, in kinesin-1 dependent manner.

P1-066 Changes of Neural Cell Adhesion Molecule Fragments in Patients' Sera of Schizophrenia

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The neural cell adhesion molecule (NCAM) plays important roles in neural migration, synaptogenesis, and CNS development. Change of NCAM fragments in CSF of schizophrenic patients was reported previously¹ and we aimed to detect circulating NCAM fragments in the serum and differences between schizophrenic patients and healthy controls. Samples were obtained from 11 chronic schizophrenic patients and 9 healthy controls. All patients were diagnosed according to DSM-IV criteria and received consistent doses of typical or atypical antipsychotic medication. NCAM fragments in sera, after removal of albumin and globulin, were measured by Western blotting technique with the monoclonal antibody (5A5) against sialylated NCAM. NCAM immunoreactive bands were detected primarily at 180kDa, 140kDa, 120kDa, 75kDa, 68kDa and 52kDa in human serum. Samples from patients and controls showed similar qualitative patterns of bands. However, schizophrenic patients showed increases at the 180kDa, 140kDa, 120kDa and 68kDa bands but decreases at the 75kDa and 52kDa bands compared to healthy controls. The band intensity ratio ([68kDa]/[75kDa]) was substantially elevated in schizophrenic patients. For healthy controls, the [68kDa]/[75kDa] ratio was positively correlated with ages. The antibody (H300) self-assembled monolayer on a tiny gold plate could trap NCAM from serum. We detected a change of NCAM molecular structure by Fourier transform infrared spectroscopy-attenuated total reflectance system, suggesting increase of sialic acid bound to NCAM in the schizophrenic patient serum compared to controls. In conclusion, the increase of NCAM fragments in schizophrenic patients suggests elevated membrane turnover or abnormalities in the regulation of proteolysis of NCAM. ¹Exp Neurol. 29-46 (2001).

P1-067 Differential effects of typical and atypical antipsychotics on abnormal behaviors in mice lacking PACAP

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PACAP is a neuropeptide widely distributed in the nervous system and implicated in neurotransmission, neural plasticity, and neurotrophic actions. We have recently demonstrated that mice lacking PACAP (PACAP^{-/-}) exhibit multiple abnormal behaviors, including hyperactive and preservative jumping behaviors in an open-field test (OFT), prolonged immobility time resulted from reduced swimming behavior in a forced-swim test (FST), and object working memory impairments in an object recognition test (ORT). These behavioral changes related to psychiatric or cognitive abnormalities are commonly observed in the animal models for schizophrenia, such as rodents treated with amphetamine or phencyclidine. Here we examined the effects of typical (haloperidol) and atypical (risperidone) antipsychotics on these abnormal behaviors in PACAP^{-/-} mice. Both haloperidol (0.02-0.2 mg/kg, i.p.) and risperidone (0.05-0.3 mg/kg, i.p.) dose-dependently ameliorated the hyperkinetic behavior in OFT in PACAP^{-/-} mice. In PACAP^{-/-} mice, risperidone (0.1 mg/kg) also ameliorated the prolonged immobility in FST and working memory impairments in ORT, however, haloperidol (0.02 mg/kg) showed no effects. These results suggest that dopamine D2 and serotonin 2 pathways are differentially involved in the mechanisms underlying the abnormal behaviors in PACAP^{-/-} mice, and that PACAP^{-/-} mice might be one of a relevant animal model for schizophrenia.

P1-069 Isolation rearing-induced increase in exploratory activity in mouse staircase test

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We have previously shown that social isolation induces locomotor hyperactivity, aggressive behavior and deficits of prepulse inhibition of the acoustic startle response in mice (Sakae et al., Eur J Pharmacol 2001; Ago et al., J Neurochem 2002). However, little is known about the effect of isolation rearing on anxiety-related behavior in mice. In this study, we examined the effect of isolation rearing on the behavior in mouse staircase test, an animal model of anxiety. Male ddY mice (3 weeks old) were either housed in groups of 5-6/cage or isolated for more than 6 weeks before the experiments. The staircase test consisted of placing an experimentally naive mouse in an enclosed staircase with five steps (2.5 × 10 × 7.5 cm). The apparatus was 45 cm in length, with one end 12 cm and the other 25 cm in height. The number of steps climbed, indices of exploratory and locomotor activity, and the number of rearing, indices of the anxiety and emotionality, in a 3-min period were measured. We first examined the effects of diazepam, a classical benzodiazepine anxiolytic, and methamphetamine, a potent psychostimulant, on the behavior of group-reared mice in the staircase test. Diazepam increased the number of steps climbed to the top step of the staircase, but did not affect the number of rearing. On the other hand, methamphetamine increased the number of steps climbed to the second step and decreased the number of rearing, reflecting the locomotor stimulant effect of methamphetamine. Isolation-reared mice showed the increased numbers of steps climbed to the top step and of rearing in the staircase test. These findings suggest that isolation-rearing increases anxiety and exploratory activities in mice.

P1-071 Effects of menstrual cycle on mRNA expression of FKBP5 and 5HTT in leukocytes of normal female

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Menstruation-related-psychological symptoms are often seen in women of reproductive age. The mechanism is still unknown yet but both hypothalamic-pituitary-adrenal axis and serotonergic system may be involved under this hormonal cycle related symptoms. We chose two candidate genes: One is *FKBP5* gene, which codes FKBP51 (FK506-binding protein) induced by glucocorticoids and reported to be related to the antidepressant effect. Another is *SLC6A4* gene coding serotonin transporter (5HTT), a direct target protein of Selective Serotonin Reuptake Inhibitors (SSRIs). We hypothesized that measurement of *FKBP5* or *5-HTT* mRNA levels in peripheral leukocytes may work as markers for the psychological changes across the menstrual cycle. 37 young female subjects were included in this study. Basal body temperature with menstrual memory scale was measured everyday and Hospital Anxiety and Depressive Scales (HADS) with blood hormone measurements were done in each phase of one menstrual cycle (menstrual, follicular and luteal phase). *FKBP5* and *5-HTT* mRNA levels in peripheral leukocytes were determined with quantitative real-time PCR method. Only twelve subjects had normal menstrual cycles during this study. In these twelve women, HADS scores failed to show a consistent difference among the menstrual cycle phases. *FKBP5* mRNA expression was significantly lower in the follicular phase compared with the other phases, but there was no expressional difference in *5-HTT* mRNA levels among the phases. Our results suggest that mRNA levels of *FKBP5* but not those of *5-HTT* are influenced by the menstrual cycle. Further studies are necessary with patients of menstruation-related disorders.

P1-068 Double-stranded RNA injection in early pregnancy causes behavioral changes in the offspring

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Epidemic of influenza infection is known to be a risk for schizophrenia, partly due to maternal infection and subsequent higher incidence of schizophrenic offspring. Recent studies demonstrated that influenza infection in pregnant mice resulted in marked behavioral changes including deficits in prepulse inhibition in the offspring, rendering this system an animal model of schizophrenia. In the present study, we first reproduce above phenomenon by injecting intraperitoneally double-stranded RNA (poly I-C) into pregnant mice (embryonic day 9.5). Double-stranded RNA mimics viral infection by eliciting immune responses. Pups born from the injected mothers were raised to 8 or 10 weeks old and their behaviors were tested. Compared to control mice (born from saline-treated mothers), the mice showed statistically significant deficits in prepulse inhibition, one of the hallmarks of schizophrenia. They also showed abnormal fear-conditioning tasks. To elucidate mechanisms underlying the behavioral changes, morphological and neurochemical features of the experimental and control mice are now under investigation.

P1-070 Methamphetamine treatment further deteriorates cognitive dysfunction in socially isolated mice: A useful mouse model of schizophrenia

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Previous studies suggest that exposure to stress is a trigger to drug abuse and also related to susceptibility of schizophrenia. The effects of methamphetamine (METH) on the social isolation stress-caused impairment of learning and memory have not been studied until now. The aim of this study was to investigate the effects of METH on social isolation stress-caused cognitive impairment in a battery of tasks including startle response, acoustic fear conditioning and the Morris water maze tests. ICR mice were divided into three groups after weaning: socially-housed mice, socially-isolated mice, and social isolated mice treated with METH. Four weeks after isolated and grouped rearing, the mice in social isolated plus METH group were injected daily with 1 mg/kg METH for seven days. After one-week rest, the startle responses were examined 20 min following the final injection of METH. One week after completing behavioral experiments, GFAP expression in the brain sections was examined immunohistochemically. Repeated injections of METH further enhanced the disruption of PPI and deteriorated the cognitive dysfunction in acoustic fear conditioning and Morris water maze tests in socially isolated mice. Social isolation stress increased the GFAP expression in regions of frontal cortex, hippocampus CA3 and amygdala. METH treatment further enhanced the GFAP expression in sub-regions of hippocampus CA2, CA3 and CA4. These findings demonstrate that METH significantly enhances social isolation-induced sensorimotor impairment, cognitive dysfunction and GFAP expression in the mouse brain. Social isolation with and without METH treatment is a useful mouse model of positive and negative symptoms of schizophrenia in order to examine the efficacy of the therapy.

P1-072 The reconstruction mechanisms of neural network by antidepressants and mood stabilizers

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It has been emerged that the neurogenesis in hippocampus is changed by the stresses and treatments of antidepressants and mood stabilizers, and the fact considered that the abnormality of neurogenesis causes neuropsychiatric diseases included mood disorders. In the previous study, we examined the influences of antidepressants and mood stabilizers on the functional activity changes of Neural Stem Cells (NSCs) especially by exposure of endoplasmic reticulum (ER) stress, and evaluated the alteration of ER protein expressions. Furthermore, we tried to analyze the in vivo mechanisms of stimulation of neural network reconstruction, using NSCs transplantation system in the experimental model of psychiatric disease. In the analysis using NSCs from rat embryonic cultures, we obtained suppressive effects of antidepressants, fluoxetine, paroxetine and amitriptyline on the ER stress induced inhibition of NSCs differentiation to neurons. In the western blotting analysis, the expression of ER stress protein, GRP78, was changed by these drugs treatment on NSCs. In vivo evaluation of NSCs function changes, we intravenously transplanted NSCs, marked by the fluorescent cell marker CFDA SE, into the chronic alcohol treatment rat model, which is known to have brain damages including decrease of neurogenesis in hippocampus. We detected the accumulation of transplanted cells in subventricular zone and distribution in dentate gyrus of hippocampus in the slices of alcohol treatment rat brain. These results suggest that the potential of neurogenesis promotion may relate to their clinical effectiveness, and the alterations of ER protein expression play an important role in the action of antidepressants and mood disorders for their maintenance effects of neural network.

P1-073 The role of the interaction of DISC1 / KENDRIN in the nervous system

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Disrupted-in-Schizophrenia (DISC1) was identified as a novel gene disrupted by a (1:1)(q42.1;q14.3) translocation that segregated with major mental disorders in a Scottish family. In order to clarify how DISC1 causes susceptibility to schizophrenia and other psychiatric diseases, we have identified possible partners that interact with the DISC1 protein by the yeast two-hybrid system. One of the binding partners of DISC1 is KENDRIN/pericentrin-B, a giant protein known to localize specifically to the centrosome. Recent study indicates that DISC1 localizes to the centrosome by binding to KENDRIN and that the deletion of the kendrin-binding region of DISC1 disrupted the centrosome localization. It suggests that DISC1 works with KENDRIN at the centrosome. However, the implication of DISC1 interaction with KENDRIN/pericentrin-B remains unclear. On the other hand, KENDRIN/pericentrin-B has been reported to anchor the γ -tubulin complex to the centrosome and to play a role in microtubule nucleation and organization in animal cells. So, some kinds of DISC1 mutation or a truncated form of DISC1 lacking the C-terminus downstream of the translocation breakpoint containing the KENDRIN-binding region might affect the microtubule-nucleating activity of the centrosome. Therefore, we examined the endogenous interaction between DISC1 and KENDRIN/pericentrin-B in the nervous system to understand the roles of KENDRIN/pericentrin-B in neuronal circuit formation. These analyses might suggest the pathophysiological roles of DISC1 and KENDRIN/pericentrin-B.

P1-075 The role of the interaction of dysbindin, one of schizophrenia susceptibility genes, and transcription factors in neurons

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Schizophrenia is a common, debilitating psychiatric disorder for which treatment is empirical and unsatisfactory. Intense efforts to identify etiological factors have been launched in order to facilitate rational therapy. Genetic factors are known to be important in the etiology of schizophrenia up to now. So, recent genomic-wide linkage studies have revealed several susceptibility genes for schizophrenia, including dysbindin (DTNBP1: dystrobrevin binding protein 1) at 6p22.3. Furthermore, it comes to be known recently that abnormal development of the brain is implicated in the etiology and/or pathology of various psychiatric diseases, including schizophrenia. And there is reported that environmental factors greatly influence the brain developing. So environmental factors are important as well as genetic factors onset of schizophrenia. The above-mentioned suggest the possibility that environmental factors are able to influence gene expression patterns that are regulated by chromatin remodeling and/or transcription factors interaction during nerve developmental period. And it is one of the possibilities that such transcriptional regulation abnormalities induce schizophrenia. Therefore, to investigate the relationship between the abnormality of transcriptional regulation during nerve developmental period and appearance of schizophrenia, we screened the interaction partners of dysbindin by using yeast two-hybrid system. From the result, we found the interaction of dysbindin and several transcriptional factors, and further checked the interactions of them in mammalian cells, HEK 293. And now, to elucidate the target genes of the transcriptional factors, we screen the gene by the DNA microarray analysis.

P1-077 Screening for genes involved in major depressive disorder using chronically stressed mice

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Repeated stressful events are known to be closely related to the onset of depression. To investigate the molecular mechanisms involved in depression, we examined genes that were differentially expressed in the brains of unstressed and chronically stressed mice. Chronic stress was induced by water-immersion and restraint (2hrs/day, for 3 weeks). These chronically stressed mice exhibited depressive behavior upon the tail-suspension test and a decreased number of adult neural stem cells in the hippocampus. Basal glucocorticoid concentration is upregulated in the blood of stressed mice which is observed in the patients of depression. The microarray technique was used to analyze the gene expression profiles of the medial prefrontal cortex of the chronically stressed and unstressed mice. Results were confirmed by quantitative RT-PCR analysis and in situ hybridization. Several genes showed consistently altered expression in the brains of stressed mice compared to unstressed mice. Especially one of the candidate genes, CSRG1 (chronic stress related gene 1) mRNA was upregulated in the oligodendrocytes in the corpus callosum of the prefrontal cortex. Detailed analyses of these genes will contribute towards understanding the mechanisms underlying the dysfunction of the medial prefrontal cortex in depression.

P1-074 Increased serum soluble L-selectin levels in unmedicated schizophrenia

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Background: Numerous studies have linked schizophrenia with altered immune function. The selectin family of adhesion molecules plays a prominent role in the immune/inflammatory responses. To further study inflammatory processes in schizophrenia, we determined serum levels of selectins in patients with schizophrenia. Additionally, we also investigated selectins in patients with major depression, since the result in the illness may be helpful to identify specificity of that in schizophrenia. Methods: We used 25 patients with schizophrenia and 18 patients with major depression. All patients are either medication-naïve (first onset) or medication-free for at least 6 months. They were compared to the 36 healthy subjects. Serum sP-selectin, sE-selectin and sL-selectin were determined with enzyme-linked immunosorbent assay method. Results: Serum L-selectin levels in schizophrenia was increased significantly compared to controls ($p=0.003$) and major depression ($p=0.007$), whereas there are no significant differences between depression and controls. No significant differences were in the serum levels of sE-selectin and sP-selectin among three groups. Conclusions: The serum sL-selectin elevation observed in the schizophrenic patients may be specific to the illness and be involved in the pathogenesis of the illness.

P1-076 Analysis of interaction between Snapin and Dysbindin, one of schizophrenia susceptibility genes

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Dysbindin at chromosome 6p22.3 has been reported as one of the most promising susceptibility genes for schizophrenia in many linkage studies. DYSBINDIN was initially identified as the interacting protein with dystrobrevin, the dystrophin-related protein, which is expressed in brains and muscles. So DYSBINDIN was initially expected to be associated with the dystrophin glycoprotein complex found at post synaptic sites in brains. However, DYSBINDIN was found in part in axon terminals of glutamatergic pathways in brains. It was reported that there was a significant reduction of DYSBINDIN in the terminal fields of glutamatergic connections of the hippocampus in schizophrenia cases compared to controls and that the reduction of presynaptic DYSBINDIN was independent of dystrobrevin and the dystrophin glycoprotein complex. Additionally, it has recently reported that DYSBINDIN might influence exocytotic glutamate release and neural viability. These results are compatible with the hypoglutamatergic hypothesis of schizophrenia and suggest that DYSBINDIN might play an important role in the pathogenesis of schizophrenia. To gain additional insights into the role of DYSBINDIN in brains, we performed a yeast two hybrid screening for DYSBINDIN binding partners using brain cDNA library and found some interactors. One of the binding partner is SNAPIN, which was initially identified as a SNAP25 binding protein. SNAPIN was reported to enhance the interaction with SNARE complex in a phosphorylation dependent manner, but the role of this protein in SNARE mediated fusion is still under discussion. Here, we report the distribution and functional analysis of SNAPIN and discuss about the capability of SNAPIN on the neurotransmitter release through the interaction with DYSBINDIN.

P1-078 Gene expression profile of adult mouse hippocampus after chronic treatment of water-immersion plus restraint stress

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So far a particular gene could not explain how depressive disorders are lead. A number of environmental factors as well as genetic ones are thought to contribute to stress-mediated neuronal pathological processes causing depression. Chronic stress, which is known to be closely related to the onset of depression, raises reduction of the adult neurogenesis in the dentate gyrus and decrease of the hippocampal volume in the rodent brain. We hypothesized exhaustive gene profile of stress-affected hippocampus would elucidate genes which plays a major role in the hippocampal morphological change in response to stress. To better understand the molecular mechanisms involved in stress-induced neural circuit remodeling and architectural changes of hippocampus, we compared gene expression in dentate gyrus of unstressed and chronically stressed mice. Chronic stress was treated 12 weeks old male c57/BL6J mice by water-immersion plus restraint. Applied DNA microarray technology, we successfully obtained genes that are up- or down-regulated more than 1.5 fold. All of these genes were frequently observed with real time RT-PCR and in situ hybridization analysis in dentate gyrus. To further address depression related gene, we investigated the effect of fluoxetine, a serotonin selective reuptake inhibitor and inducing neurogenesis in hippocampus with block to stress effect, on the stress-induced genes expression changes in dentate gyrus. We report Hcsrg1 (Hippocampal chronic stress related gene 1), that is down regulated in response to chronic stress but does not show significant expression level change in fluoxetine treated mouse with or without chronic stress

P1-079 Association analysis of adenosine A1, A2A, dopamine D1, and D2 receptor genes with schizophrenia in the Japanese population

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Antipsychotic agents used for the treatment of schizophrenia affect dopamine D2 receptor (DRD2) mediated neurotransmissions, suggesting that dopaminergic dysfunction plays an important role in the pathophysiology of schizophrenia. It is known that SCH23390, a selective dopamine D1 receptor (DRD1) antagonist, inhibited PCP-induced schizophrenia-like behaviors. It is also reported that adenosine neurotransmitter system has functional interaction with dopaminergic neurotransmission. Therefore, it is possible to hypothesize that the functions of adenosine A1 and A2A receptors (ADORA1 and ADORA2A) could be some part of the pathophysiological mechanisms of schizophrenia. To clarify the relationship between four receptors and schizophrenia, the polymorphisms (SNPs) of these four receptor genes were analyzed in both schizophrenia patients and normal controls.

Total 29 fragments for genotyping experiments were amplified by PCR from each subject consisting of the schizophrenia patients (n=100) and normal controls (n=100). Primers were designed based on the positions of SNPs based on the database of JSNP. Using the amplified DNA fragments, all the subjects were genotyped with 27 SNPs and 2 deletions in ADORA1 gene, 4 SNPs in ADORA2A gene, 1 SNP in DRD1 gene, and 18 SNPs in DRD2 gene. Based on the results, genotyping and allele frequencies were calculated. Association analysis of each polymorphism was performed between schizophrenia patients and normal individuals. So far, no significant difference was identified. Haplotype prediction, linkage disequilibrium calculation, and multi-variate statistical analysis are now being carried out. All subjects were given informed consent before blood collection strictly based on the ethical regulations of Kyushu University.

P1-081 Association analysis of human cAMP-GEFII gene polymorphisms with Japanese schizophrenia patients

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We have previously reported novel genes of second-messenger regulated Rap1-GEF (guanine nucleotide exchange factor) gene family whose GEF activities are positively regulated by the binding of second-messenger molecules such as cAMP, calcium and diacylglycerol (DAG), indicating that three major second messengers transduce their signals to target molecules different from protein kinases. A part of this gene family includes cAMP-GEFI and cAMP-GEFII, CalDAG-GEFI and CalDAG-GEFII. Both cAMP-GEFI and cAMP-GEFII have binding domains for cAMP as well as GEF domains. Since antipsychotics have antagonistic actions for dopamine receptors regulating intracellular cAMP concentrations in central nervous system, cAMP-GEFs can be good candidates for molecular studies of schizophrenia. In order to investigate the contribution of cAMP-GEFII to the pathophysiological mechanisms of schizophrenia, we carried out a genetic analysis of single nucleotide polymorphisms (SNPs) of the cAMP-GEFII gene. Information of a total 21 SNPs was collected based on the databases of both dbSNP and JSNP and our genotyping experiments, which included 3 coding SNPs and 17 intron SNPs and one regulatory SNP. We found two novel non-synonymous ones. We genotyped 96 schizophrenic patients and 112 healthy controls with the 21 SNPs by direct sequencing method. The results of haplotype prediction, linkage disequilibrium calculation, and multi-variate statistical analysis are now being analyzed. Although there was slightly different distribution of the regulatory SNP between schizophrenia and controls, no statistical significant association was found. All subjects were given informed consent based on the ethical regulations of Kyushu University.

P1-083 Pathological significance of a constitutively active calcineurin generated by calpain activation in mouse brain ischemia

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In the brain ischemia, excessive increases in intracellular Ca²⁺ levels may cause delayed neuronal death, by activating various Ca²⁺-dependent enzymes. Among Ca²⁺-dependent enzymes, calcineurin (CaN) is particularly interested as a mediator of neuronal apoptosis, because FK-506 and cyclosporin A, specific CaN inhibitors prevent neuronal death following ischemia. CaN, Ca²⁺/calmodulin-dependent protein phosphatase, is composed of A and B subunits with 60 kDa and 19 kDa, respectively. Calpain, a Ca²⁺-dependent cysteine protease, in vitro converts it to constitutively active forms with 45 or 48 kDa by cleaving out the auto-inhibitory domain in the A subunit. However, little is known about mechanism and temporal profile of generation of active CaN in vivo during ischemia. We here documented generation of constitutively active CaN by limited proteolysis by calpain during brain ischemia in the mouse middle cerebral artery occlusion (MCAO) model. We also established assay system to measure the constitutively active CaN activity, which is independent with Ca²⁺/calmodulin. The generation of constitutively active CaN was peaked 2 hours after ischemia. We also confirmed increased Ca²⁺-independent CaN activities with a similar temporal profile. Furthermore, we found that the constitutively active CaN induced translocation of NFAT (nuclear factor of activated T-cells) into the nuclei in the hippocampal CA1 pyramidal neurons following after ischemia. Taken together, calpain-mediated proteolysis of CaN converts it a constitutively active form in the brain ischemia and in turn upregulates NFAT-induced transcription followed by neuronal apoptosis.

P1-080 ONO-2333Ms, a novel CRF1 receptor antagonist: anxiolytic and antidepressant-like effects

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We evaluated the anxiolytic and antidepressant-like effects of ONO-2333Ms, a novel corticotropin-releasing factor type 1 (CRF1) receptor antagonist, using male rats.

In the experiments using swim-stressed rats, elevated plus maze test was performed after the stress exposure. Both the number of entries and time spent in the open arms were significantly decreased in the vehicle-treated swim-stressed rats compared with the vehicle-treated non-stressed rats, indicating that anxiety was augmented by the stress. ONO-2333Ms significantly ameliorated the decreases in both indexes compared with the vehicle-treated swim-stressed group, suggesting that ONO-2333Ms would elicit anxiolytic-like effects under stressful conditions where endogenous CRF activity is stimulated. In the learned helplessness test, one-week repeated oral administrations of ONO-2333Ms or imipramine HCl significantly inhibited the increase of escape failures induced by inescapable foot shocks. Moreover, single oral administration of ONO-2333Ms but not imipramine HCl inhibited the increase of escape failures as well.

In olfactory bulbectomized (OB) rats, one-week repeated oral administrations of ONO-2333Ms significantly reduced the hyperemotionality scores on post-administration day 1 and 7, respectively. ONO-2333Ms also significantly suppressed the scores on pre-administration day 7, indicating that the antidepressant-like effects of ONO-2333Ms were persistent. In addition, on post-administration day 8, ONO-2333Ms indicated ameliorative effects against the anxiety-like behavior in the elevated plus-maze. These results suggest that ONO-2333Ms possesses not only anxiolytic but also antidepressant-like properties and may elicit a rapid or similar onset of action compared with the current marketed antidepressants.

P1-082 Induction of microsomal prostaglandin E₂ synthase-1 in rat brain after cerebral ischemia

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The increased production of prostaglandin E₂ (PGE₂) observed in the ischemic brain region has been demonstrated to contribute to development of ischemic lesion, however, the mechanisms underlying the ischemic PGE₂ production is poorly understood. Microsomal prostaglandin E₂ synthase (mPGES)-1 is an inducible protein recently shown to be an important enzyme in inflammatory prostaglandin E₂ (PGE₂) production in some peripheral inflammatory lesions. We have previously demonstrated that induction of mPGES-1 in rat and mice microglia contributes to lipopolysaccharide-induced production of PGE₂. In this study, to investigate the serial changes of mPGES-1 expression in the brain after cerebral ischemia, male Sprague-Dawley rats were subjected to 2-hr of right middle cerebral artery occlusion and reperfusion. The induction of mRNA and protein of mPGES-1, but not cPGES, mPGES-2 and COX-1, were observed to be co-induced with those of COX-2, in the cerebral cortex 6 hr and 24 hr after reperfusion, respectively. The increased PGE₂ production was also observed in the cortex. The expression of mPGES-1 protein was peaked at 3 days after reperfusion, while that of COX-2 was peaked at 24 hr after reperfusion. To determine the cells which expressed mPGES-1 after cerebral ischemia, the brain slices were double-immunostained with mPGES-1 and cell-type specific marker protein antibodies. The mPGES-1-positive cells observed in the cortex of ischemic site were also positive for CD11b and von Willebrand factor, a marker for microglia and endothelial cells, respectively, as well as for COX-2. These results suggest that the coordinate inductions of mPGES-1 and COX-2 in microglia and endothelial cells are involved in ischemic PGE₂ production.

P1-084 17β-estradiol regulate expression of glutamate transporters after transient ischemic insult in gerbil hippocampus

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After transient ischemia/recirculation treatment, delayed neuronal death in gerbil hippocampus CA1 area occurs by excessive release of glutamate from abnormally stimulated synaptic terminals into extracellular (EC) space around neurons. High affinity Na⁺-dependent glutamate transporters maintain the glutamate concentration in EC space at low level by taking the excitatory neurotransmitter into glia or neurons. Dysfunction of the transporters induces neuronal damage by accumulating cytotoxic glutamate in EC space to trigger neuronal degeneration.

Application of transient ischemia to Mongolian Gerbil brain produces selective neuronal death several days after the insult. Molecular mechanisms of delayed neuronal death remain elusive. Intraperitoneal (i.p.) injection of 17β-estradiol (17β-ED) to the treated animal is possible to induce protective effects against ischemia-induced neuronal death. We measured amount of three glutamate transporters: GLAST, GLT-1, and EAAC1, in hippocampal regions by Western blotting analysis. Daily intraperitoneal (i.p.) administration of 17β-ED to the animal after ischemic attack induced significant recovery of these three glutamate transporters in protein level. These results suggest that 17β-ED can protect progression of neuronal death caused by ischemia through conserving the glutamate transporter systems in the brain.

P1-085 Nitric oxide production during microsphere embolism accounts for blood-brain barrier disruption in rat brain

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Microsphere embolism (ME)-induced permanent ischemia in rat leads to brain edema and in turn neuronal injuries. Detrimental effects of NO and peroxynitrite (ONOO⁻) are documented in brain ischemia/reperfusion (I/R)-induced injury. However, whether NO production involves in ME-induced blood-brain barrier (BBB) disruption have not been evaluated. We recently introduced a novel calmodulin antagonist, DY-9760e, having powerful neuroprotective effects on ischemic brain damage. Since DY-9760e preferentially inhibits Ca²⁺/calmodulin-dependent nitric oxide synthase (NOS) in vivo and in vitro, we here assessed whether inhibition of NO production is involved in cytoprotective effects of vascular endothelial cells in rat ME model. ME was induced by injecting 1000 microspheres (50 μ m in diameter) into left internal carotid artery. We then measured NO production by microdialysis method and protein tyrosine nitration by immunoblotting in the ipsilateral forebrain. Consistent with our previous observation in gerbil I/R model, DY-9760e completely inhibited NO production immediately after and 24 or 48 hours after ME. Unlike gerbil I/R model, protein tyrosine nitration was markedly increased 6-48 hours after ME. When BBB disruption was assessed by extravasation of Evans blue (EB) dye, the content of EB dye significantly increased in the ipsilateral brain following ME. The BBB disruption is closely associated with increased protein tyrosine nitration in brain microvessels. DY-9760e treatment reduced the increased BBB permeability to EB in the ME brain. Taken together, NO production and protein tyrosine nitration underlie the BBB disruption and inhibition of the detrimental effects of NO by DY-9760e contribute to its neuroprotective effects in the ME-induced brain damage.

P1-087 4-methylcatechol improves locomotor function damaged after spinal cord injury via enhancement of neurotrophic factor synthesis

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Several strategies have been employed to minimize tissue damage and to enhance axonal growth and regeneration after injury to the central nervous system (CNS). The failure of axonal regeneration after CNS injury is thought to result in part from the molecules inhibitory for axonal growth, the lack of neurotrophic factors, and/or inflammatory reactions. Although the delivery of protein and viral vector-mediated gene transfer of neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are effective for regeneration of the spinal cord injury, there are a number of methodological drawbacks. In this study, we tested the effects of 4-methylcatechol (4MC), a nonadrenergic compound that stimulates neurotrophin synthesis such as NGF and BDNF. Left side of the adult Wistar rat spinal cord was hemitranssected at the 8th thoracic vertebra. Then, 4MC dissolved in PBS was injected intraperitoneally (150 μ g/kg weight) every 12 or 24 hr for 14 days. Locomotor function of the left hind limb was evaluated according to Basso, Beattie and Bresnahan rating scale. For RT-PCR analysis, the regions just rostral or caudal to the injury site of the spinal cord (1 mm length each) were collected time-dependently, and their total RNAs were used. Locomotor function was significantly improved in the animals with 4MC administration. Furthermore, both BDNF and FGF-2 mRNA expressions were significantly enhanced around the injury site between 12 or 18 hrs after 4MC injection. Taking into account our previous finding that exogenous FGF-2 conspicuously improved the locomotor function damaged after spinal cord injury, present results suggest that 4MC stimulates nerve regeneration of the injured spinal cord partly via enhancement of FGF-2 and/or BDNF synthesis.

P1-089 Vitamin A exhibits potent anti-amyloidogenic and fibrildestabilizing effects in vitro

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Cerebral deposition of amyloid β -peptide (A β) in the brain is an invariant feature of Alzheimer's disease (AD). Plasma or cerebrospinal fluid concentrations of antioxidant vitamins and carotenoids, such as vitamins A, C, E and β -carotene, have been reported to be lower in AD patients, and these vitamins clinically have been demonstrated to slow the progression of dementia. In this study, we used fluorescence spectroscopy with thioflavin T and electron microscopy to examine the effects of vitamin A (retinol, retinal, and retinoic acid), β -carotene, and vitamins B2, B6, C and E on the formation, extension, and destabilization of β -amyloid fibrils (fA β) in vitro. Among them, vitamin A and β -carotene dose-dependently inhibited formation of fA β from fresh A β , as well as their extension. Moreover, they dose-dependently destabilized preformed fA β s. The overall activity of the molecules examined was in the order of: retinol = retinal > β -carotene > retinoic acid. Although the exact mechanisms are still unclear, vitamin A and β -carotene could be key molecules for the prevention and therapy of AD.

P1-086 Neuropilin promotes oligodendroglial cell death, demyelination and axonal degeneration after injury to the spinal cord

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Previous studies indicated that the expression of neuropilin, a serine protease, was induced in mature oligodendrocytes after injury to the central nervous system (CNS). To explore the role of neuropilin after spinal cord injury (SCI), we have examined behavioral performances and the expression of histopathological markers in wild-type (WT) and neuropilin-deficient (neuropilin^{-/-}) mice after crush injury. In situ hybridization revealed that neuropilin mRNA expression was induced in the spinal cord white matter from WT mice after crush SCI, peaking at day 4. In WT mice, SCI resulted in the initial hindlimb impairments followed by a gradual recovery over 14 days. Equivalent crush SCI to neuropilin^{-/-} mice also caused the initial impairments of hindlimb function followed by a gradual recovery, but the recovery at day 10 and 14 in neuropilin^{-/-} mice was significantly improved compared to WT mice. Neuropilin^{-/-} mice also showed attenuated demyelination, oligodendroglial death, and axonal damage after SCI. Although axonal degeneration in the corticospinal tract was obvious caudal to the lesion site in both strains of mice after SCI, the number of surviving nerve fibers caudal to the lesion was significantly larger in neuropilin^{-/-} mice than WT mice. These observations suggest that neuropilin is involved in the pathogenesis of SCI mediated by demyelination, oligodendroglial death, and axonal degeneration.

P1-088 Expression of myelencephalon-specific protease(MSP) in cryogenic injury model of rat brain

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[Purpose] An understanding of the mechanisms of demyelination in injury to the central nervous system (CNS) is important in any therapeutic approach to CNS insult. Several proteases have been shown to degrade myelin protein. The myelencephalon-specific protease (MSP) is expressed in mainly in the brain and spinal cord of rats. Its function and alteration have not yet been clarified. In the study, we examined the gene and protein expression of MSP after cryogenic brain injury, and investigated the regional distribution of MSP expression in the CNS during the evolution of this injury. [Method] A burr-hole was made at the parietal bone of rats, and then cortical lesions were produced with a liquid nitrogen-cooled metal rod. Rats were sacrificed at 6, 12, 24, and 48 h and at 5, 7, and 14 days after cryogenic injury (CI) ($n = 5$ for each period). We examined the expression of MSP after CI using *in situ* hybridization, immunohistochemistry, and Western blotting. [Results] Analysis of MSP mRNA by *in situ* hybridization revealed a higher level of expression around the cryogenic area than on the contralateral side from 2 - 7 days after CI, with peak expression occurring 7 days after CI. Immunohistochemical analysis demonstrated expression of MSP protein at 1 day after CI, in the same region in which MSP mRNA was observed, with peak expression again at 7 days after CI, in the area around the lesion. Double immunohistochemical labeling revealed that MSP was expressed mainly in oligodendrocytes. [Conclusions] These results suggest that expression of MSP may be related to the turnover of myelin-associated proteins after CI. The regulation of active MSP may be important in the physiological or pathological changes involved in demyelination and remyelination.

P1-090 Syntaxin5 interacts specifically with presenilin holoproteins and affects processing of β APP in neuronal cells

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The specific roles of syntaxin 5 (Syx5) in the interaction with presenilin (PS) and the accumulation of β -amyloid precursor protein (β APP), as well as the secretion of β -amyloid peptide (A β peptide) were examined in NG108-15 cells. Syx5, which localizes from the endoplasmic reticulum (ER) to the Golgi, bound to PS holoproteins, while the other Syxs studied did not. Among familial Alzheimer's disease (FAD)-linked PS mutants, PS1 Δ E9, which lacks the endoproteolytic cleavage site, showed markedly decreased binding to Syx5. The interaction domains in Syx5 were mapped to the transmembrane region and to the cytoplasmic region containing the α -helical domains, which are distinct from the H3 (SNARE motif). Among all of the Syxs examined, only overexpression of Syx5 resulted in the accumulation of β APP in the ER to *cis*-Golgi compartment, an attenuation of the amount of the C-terminal fragment (APP-CTF) of β APP, and a reduction in the secretion of A β peptides. Furthermore, co-expression of Syx5 with C99 resulted in an increase in APP-CTF and suppressed A β secretion. Taken together, these results indicate that Syx5 may play a specific role in the modulation of processing and/or trafficking of FAD-related proteins in neuronal cells by interaction with PS holoproteins in the early secretory compartment of neuronal cells.

P1-091 The S3 cleavage site of Notch-1 by presenilin/ γ -secretase has a diversity

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Notch proteins are transmembrane receptors required for a variety of signaling events throughout development and in adulthood. Upon binding of ligands, notch receptors undergo ectodomain shedding (S2 cleavage). The resultant C-terminal product, NEXT (Notch extracellular truncation), undergoes intramembraneous proteolysis by presenilin (PS)/ γ -secretase (S3 cleavage), releasing NICD (Notch intracellular cytoplasmic domain) which is moved to the nucleus and directly involved in activating target genes. This canonical notch pathway is known as regulated intramembraneous proteolysis. B APP is another substrate for PS/ γ -secretase, which has at least two cleavage sites. Γ 40 cleavage occurs in near the middle of transmembrane domain, releasing Alzheimer's disease associated amyloid beta (A β), while Γ 49 cleavage liberates AICD (B APP intracellular cytoplasmic domain); a putative transcriptional modifier. It is noteworthy that both the cleavage sites have a diversity. Recently, we have found that Notch-1 is cleaved by PS/ γ -secretase at another site (S4 cleavage) releasing Notch-1 A B-like fragment (NB). The S4 site corresponds to Γ 40 site of B APP, and importantly, it also has a diversity. Moreover, the cleavage precision of S4, Γ 40, and Γ 49 is affected by familial AD associated PS mutants. FAD associated B APP mutants and subcellular localization can also affect Γ 40, and Γ 49 cleavage, respectively. S3 cleavage is essential in NICD generation, but so far, there has been no report concerning the diversity. In this study, we first show that S3 site indeed has a diversity like S4, Γ 40, and Γ 49 sites. Next, we examined whether subcellular localization or a Notch-1 mutant would affect S3 cleavage precision with cell-free PS/ γ -secretase assay.

P1-093 Deficiency in presenilin-1 and -2 alters overall glycosylation of membrane proteins in fibroblasts: protein specific up or down regulated maturation by presenilin 1 and 2

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The mutations of presenilins (PS1 and PS2) account for more than 70% of early-onset familial Alzheimer's disease (AD). Presenilins are considered to be the catalytic subunits of the γ -secretase complex and to play an important role in protein processing. Here we report that PS-regulated maturation of membrane proteins has a highly protein-specific manner. We found an enhanced cell surface-binding of ricinus communis (RCA120) and an attenuated binding of peanut agglutinin (PNA) in PS1- and PS2-null cells, similar results were found in cell lysate blotting with HRP-lectins. The maturation of nicastrin was suppressed in the PS-1 and -2 double knockout cells, whereas, surprisingly, the maturation of many other transmembrane proteins, such as integrin β 1, integrin α 3, TGF β receptor II, EGFR and FGFR1 were enhanced in the PS deficient cells. These results suggest that PS has dual functions in the maturation of membrane proteins, that is, the protein-specific promotion or inhibition of its glycosylation.

P1-095 Donepezil and galantamine differently regulate nicotinic acetylcholine and NMDA receptor functions in rat cortical neurons

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Alzheimer's disease is a progressive neurodegenerative disorder with cognitive dysfunction. Decrease in nicotinic acetylcholine (nACh) and NMDA receptors are found in Alzheimer's disease, possibly contributing to memory deficits. Galantamine and donepezil, potent cholinesterase inhibitors, are known to rescue Alzheimer's disease patients. We here characterized regulation of nACh (α 4 β 2-type) and NMDA channel functions by these drugs with whole-cell patch clamp techniques using cultured rat cortical neurons. Galantamine at 1 μ M potentiates the nACh-induced currents to 130% of the control, but donepezil at 100 nM and 10 μ M had no effect on the ACh-induced currents. Both multipolar and bipolar-type neurons responded to NMDA in a dose-dependent manner. Galantamine potentiates the NMDA-induced currents in multipolar-type neurons to 130% of the control, showing bell-shaped dose-response relationships at range of 100 nM to 10 μ M. The maximal potentiation of NMDA currents was obtained at 1 μ M. However, galantamine did not affect NMDA-induced currents in bipolar-type neurons. In multipolar type neurons, donepezil at 1 to 10 μ M inhibited NMDA currents to 80% of the control, but potentiated to 140-250% of the control at 30 to 100 μ M. On the other hand, donepezil (1 nM to 100 μ M) potentiated the NMDA-induced currents up to 200% of the control in bipolar-type neurons. AMPA- and kainate-induced currents were not affected by 1 μ M galantamine or 10 μ M donepezil. Taken together with nACh receptors, the modulation of NMDA receptor activity by galantamine and donepezil is deemed to be partially responsible for improvement of cognition, learning and memory in Alzheimer's disease patients.

P1-092 Assembly of hereditary variant amyloid β -protein in the presence of gangliosides

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A fundamental question regarding the development of Alzheimer's disease and cerebral amyloid angiopathy is how amyloid β -protein (A β) assembles and deposits in the brain. Here we show that hereditary variant Dutch- and Italian-type A β s rapidly assemble in the presence of GM3 ganglioside (GM3) whereas the Flemish-type A β rapidly assembles in the presence of GD3 ganglioside (GD3). Notably, cerebrovascular smooth muscle cells, which compose the cerebral vessel wall at which the Dutch- and Italian-type A β s deposit, exclusively express GM3. In contrast, GD3 is upregulated in the co-culture of endothelial cells and astrocytes, which forms the cerebrovascular basement membrane, the site of Flemish-type A β deposition. Taken together with our previous findings that the Arctic-type A β rapidly assembles in the presence of GM1 ganglioside, which is likely to be the responsible ganglioside for A β deposition in brain parenchyma, our present results suggest that regional A β assembly and deposition is preferentially induced by the local gangliosides in the brain.

P1-094 A mechanism underlying apolipoprotein E-isoform - specific induction of lipid efflux from neurons

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Apolipoprotein E (apoE) alleles are associated with development of Alzheimer's disease (AD), with the ϵ 4 allele increasing and the ϵ 2 allele decreasing risk for developing AD. ApoE is the major apolipoprotein and modulates cholesterol transport in the central nervous system. We have found that apoE induces lipid efflux from astrocytes and neurons and there is an isoform dependence to this effect with apoE2 being the most effective and apoE4 being the most ineffective (Michikawa et al., J. Neurochem, 2000). We also have found that apoE3 has greater ability to generate HDL particle and thus can supply more cholesterol to neurons than apoE4 (Gong et al., J Biol Chem, 2002). However, the mechanism underlying apoE-isoform dependency in lipid efflux remains unclear. Here we have defined the dependence of lipid efflux on apoE polymorphism in neuronal culture system using various engineered forms of apoE to elucidate the mechanisms underlying apoE-mediated lipid efflux from neurons. We found that lower level of cholesterol efflux mediated by apoE4 was recovered by mutant apoE4 (E225A). Since mutant apoE4 (E225A) lacks domain interaction between N-terminus and C-terminus and thus its structure is similar to that of apoE3, these results indicate that the presence or absence of domain interaction can explain the different ability between apoE3 and apoE4 in lipid efflux. The increased level of cholesterol release mediated by apoE3 was reduced to a level of apoE4 by inhibition of apoE to associate with ABCA1. These results suggest that domain interaction and subsequent loss of association with ABCA1 in apoE4 results in decreased level of lipid efflux.

P1-096 Characterization of γ -secretase complex reconstituted by truncated presenilin (PS) fragments

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Amyloid β -protein (A β) is generated from APP by sequential proteolytic cleavages catalyzed by β - and γ -secretase. Mutations in presenilin genes cause early onset familial Alzheimer's disease. Recent accumulating evidence showed that the presenilin (PS) complex, including PS, nicastrin (NCT), APH-1 and PEN-2, is essential for γ -secretase activity involved in intramembraneous cleavages of APP. However, it remains unclear how these three PS cofactors activate γ -secretase. To gain deep insights into the mechanism underlying the formation of the active γ -secretase complex, we reconstituted γ -secretase activity in PS-null cells by the coexpression of C-terminal truncated PS1 (PS1 Δ C) and the PS1 C-terminal short fragment, because the successful reconstitution of γ -secretase activity in PS-null cells by truncated PS fragments would allow us to identify the PS domain involved in the formation of active γ -secretase complex. Using this reconstitution system, we found that the exogenous expression of the PS1 C-terminal short fragment with NCT and APH-1 completely rescued a defect of the γ -secretase activity of PS1 Δ C in PS-null cells, which was accompanied by a rescue of a defect in the assembly of PS1 Δ C with NCT and APH-1. The characterization of this reconstituted PS complex revealed that both TM8 and the PS1 C-terminal seven-amino-acid-residue tail are involved in the formation of the active γ -secretase complex via the assembly of PS1 with NCT and APH-1.

P1-097 Phosphatidylserine-liposomes inhibit microglial production of neurotoxic molecules

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Microglial cells activated by A β (amyloid- β) peptide have been reported to injure neurons by releasing neurotoxic molecules such as TNF- α (tumor necrosis factor- α), NO (nitric oxide) and reactive oxygen species. On the other hand, it has been shown that phagocytes that have engulfed apoptotic cells actively suppress the inflammatory responses by releasing anti-inflammatory mediators such as interleukin-10 and prostaglandin E2. Thus it is tempting to speculate that activated microglia may change from pro-inflammatory to anti-inflammatory after phagocytosis of apoptotic cells. In this study, we have attempted to elucidate effects of PS(phosphatidylserine)-liposomes, as mimic apoptotic cells, on the inflammatory response of microglial activation induced by A β . Pretreatment of PS-liposomes significantly inhibited the release of both TNF- α and NO from rat primary microglia activated by A β combined with IFN- γ (interferon- γ). PS-liposomes also reduced the expression of mRNA encoding TNF- α in A β /IFN- γ -activated microglia. Furthermore, pretreatment of PS liposomes substantially decreased the generation of superoxide radicals associated with 6-3 microglia which is activated by lipopolysaccharide combined with PMA(phorbol 12-myristate 13-acetate) in ESR(electron spin resonance spectra) using DEPMPO(5-diethoxyphosphoryl-5-methyl-1-pyrroline-N-oxide), a spin trap reagent. These results strongly suggest that PS-liposomes inhibit inflammatory responses of activated microglia.

P1-099 A possibility of Leu-Ile as a novel therapeutic agent for morphine-induced dependence

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TNF- α and GDNF have neuroprotective effects on the drug dependence. However, TNF- α triggers the induction of some cytokines in periphery tissues and GDNF cannot pass through the BBB. Therefore, they cannot be therapeutic agents for the drug dependence. We investigated whether 1) Leu-Ile can induce TNF- α and 2) the effects of Leu-Ile on morphine (MOR)-induced dependence are attributable to the induction of GDNF synthesis. Leu-Ile and/or MOR increased TNF- α and GDNF in the neuronal cells. Leu-Ile blocked the acquisition of MOR-induced place preference (PP) and development of sensitization of locomotion (SL) in wild-type mice. Interestingly, Leu-Ile attenuated PP and SL even after development. TNF- α knockout and GDNF heterozygous mice showed enhanced responses to MOR-induced PP compared with wild-type mice. Inhibitory effect of Leu-Ile on MOR-induced PP was not observed in TNF- α knockout and GDNF heterozygous mice. Leu-Ile significantly inhibited the increase of the extracellular dopamine levels induced by the repeated MOR treatment in the nucleus accumbens of wild-type mice. These results suggest that Leu-Ile inhibits MOR-induced dependence via the induction of TNF- α and GDNF, and the inhibitory effects on MOR dependence is attributed to attenuation of MOR-induced increase in extracellular dopamine levels. Leu-Ile could be a novel treatment agent for MOR-induced dependence.

P1-101 A role for tissue plasminogen activator/plasmin system in nicotine dependence

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Tissue plasminogen activator (tPA), a serine protease, catalyzes conversion of plasminogen to plasmin. We have previously demonstrated that the tPA/plasmin system participates in the rewarding effect of morphine by regulating dopamine (DA) release in the nucleus accumbens (NAc) (PNAS 101, 3650-3655, 2004). In the present study, we investigated the role of tPA/plasmin system in nicotine dependence. ICR and C57BL/6J (wild-type and tPA^{-/-}) mice were used. Extracellular DA levels in the NAc of mice were measured using an *in vivo* microdialysis. The rewarding effect of nicotine was evaluated by a conditioned place preference test. *In vivo* microdialysis revealed that nicotine-induced DA release was markedly diminished in tPA^{-/-} mice, whereas basal DA levels in the NAc were not different between wild-type and tPA^{-/-} mice. Microinjections of either exogenous tPA or plasmin into the NAc significantly increased nicotine-induced DA release in tPA^{-/-} mice. In ICR mice, microinjections of either tPA or plasmin significantly potentiated nicotine-induced DA release without affecting basal DA levels. In contrast, plasminogen activator inhibitor-1 reduced nicotine-induced DA release in a dose-dependent manner. Furthermore, the nicotine-induced conditioned place preference was significantly reduced in tPA^{-/-} mice. Our findings suggest that tPA/plasmin system is involved in the modulation of nicotine-induced DA release in the NAc, and plays a crucial role in nicotine dependence.

P1-098 Decrease in GTP-sensitive high affinity agonist binding of muscarinic acetylcholine receptors in autopsied brains of dementia with Lewy bodies and Alzheimer disease

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To determine changes in signal transduction from the muscarinic acetylcholine receptor (mAChR) to G protein in brain tissue of dementia with Lewy bodies (DLB) and Alzheimer disease (AD), we investigated GTP-sensitive agonist high affinity binding, which is considered an index of the formation of the mAChR-G protein complex. Brain tissue was obtained at necropsy from 8 patients with DLB, 9 patients with Alzheimer disease and 7 patients as controls. Membrane fractions were prepared from frontal and temporal cerebral tissues. Displacement curves of [³H]L-quinuclidinyl benzilate (QNB) binding by carbamylcholine were analyzed by the nonlinear least-squares methods. The proportion of and affinity for the agonist in GTP-sensitive agonist high affinity binding were estimated. The percentages GTP-sensitive agonist high affinity bindings were significantly decreased in DLB ($P < 0.01$) and Alzheimer disease ($P < 0.05$) only in the frontal lobe. There were no significant differences in the temporal lobe. The ratio of agonist affinity (K_d value of low affinity component / K_d value of high affinity component) did not significantly differ among groups in either the frontal lobe or temporal lobe. The concentration of mAChR-G protein complex is considered reduced in the frontal lobe of brains with DLB and Alzheimer disease. Therefore, signal transduction from mAChR to G protein was disturbed in the frontal lobe in these diseases.

P1-100 Mechanism of protective effect of non-steroidal anti-inflammatory drugs on methamphetamine-induced neurotoxicity

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Methamphetamine (METH), a well-known drug of abuse, produces acute damage to striatal nerve terminal of dopamine neurons. We have previously showed that METH-induced neurotoxicity in mouse brain is attenuated by some non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ibuprofen, ketoprofen and indomethacin, but not aspirin. Recently, attention has focused on anti-inflammatory drugs, which activate peroxisome proliferator-activated receptors (PPAR), in particular the PPARgamma isoform, whose ligands include some NSAIDs. To clarify the mechanism of protective effect of NSAIDs on METH-induced neurotoxicity, we examined the expression of PPARgamma, cyclooxygenase-1 (COX-1) and COX-2 in the striatum of mice treated with METH. Male BALB/c mice (9 weeks old) received repeated METH injection (4 mg/kg x4, i.p. with 2 h-interval). Mice were also subcutaneously administered with ibuprofen (20 mg/kg x4) or aspirin (100 mg/kg x4) 30 min prior to each METH injection. Three days after the last METH injection, expression of PPARgamma, COX-1 and COX-2 were examined by immunohistochemistry. Expression of PPARgamma was reduced in the striatum of METH-injected mice, and only ibuprofen blocked the reduction of PPARgamma, but not aspirin. METH treatment increased expression of COX-1 and COX-2, and reduced with both ibuprofen and aspirin. These results suggest that the protective effect of ibuprofen against METH-induced neurotoxicity is based on its property as PPARgamma agonist, but not on its COX-inhibitory property.

P1-102 Antidepressants increase glial cell line-derived neurotrophic factor (GDNF) expression through mitogen-activated protein kinase (MAPK) activation in rat C6 glioma cells

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Recent postmortem and imaging studies provide evidence for glial reduction in different brain areas in mood disorders. Thus, glial plasticity such as a modulation of neurotrophic factors, especially GDNF, may be involved in therapeutic action of antidepressants. We previously demonstrated that sub-chronic treatment with amitriptyline, a tricyclic antidepressant, significantly increased both of GDNF mRNA and GDNF release in C6 cells, and these were completely inhibited by MAPK-extracellular signal-related kinase (ERK) kinase (MEK) inhibitors (U0126 and PD98059). Here, we found that acute treatment (five minutes) with amitriptyline increased ERK activity. The amitriptyline-induced ERK activation reached at maximum level within five minutes, and returned to around basal level within one hour. The acute ERK activation by amitriptyline was in dose-dependent manner with 23.2 μ M of EC₅₀. The acute treatment with amitriptyline activated not only ERK but also p38 MAPK and c-Jun N-terminal protein kinase (JNK). However, the amitriptyline-induced GDNF release was not inhibited by p38 MAPK inhibitors (PD169316 and SB203580) or JNK inhibitors (SP600125 and D-JNKI1). Furthermore, different classes of antidepressants increased acute ERK activity, but non-antidepressant psychotropic drugs did not. The extent of acute ERK activation and GDNF release was significantly correlated to each other in individual antidepressants. Taken together with our results, the acute activation of ERK is critical for GDNF release caused by antidepressants. To investigate the mechanism of antidepressant-induced ERK activation may contribute to find a novel target of antidepressants for reconstruction of neuronal and glial network.

P1-103 Effects of serotonin receptor ligands on cocaine-induced behavioral sensitization in mice

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Repeated administration of methamphetamine (METH) or cocaine causes a long-lasting augmented locomotor response, which is called behavioral sensitization. We have recently shown that osemozotan (previously called MKC-242), a selective serotonin (5-HT)_{1A} receptor agonist, and ritanserin, a 5-HT₂ receptor antagonist, inhibited METH-induced behavioral sensitization in mice. The present study examined the effects of 5-HT receptor ligands in cocaine-induced behavioral sensitization. To induce the sensitization, male 4 weeks-old ddY mice were administered repeatedly with cocaine at 15 mg/kg for 7 days (day 1 to day 7), and challenged with cocaine at 15 mg/kg after the withdrawal for 7 or 14 days (day 15 or 22). For the effect of the drugs on the expression, the ligands were injected 30 min before cocaine challenge (day 15). For the effect of the drugs on the development, the ligands were co-administered daily with cocaine for 7 days (from day 1 to day 7). For the effect of the drugs on the maintenance, the ligands were treated daily for 7 days after the repeated treatment with cocaine (from day 8 to day 14). Cocaine-pretreated mice showed increased locomotor response to cocaine challenge after the withdrawal for 7 and 14 days. Osemozotan and ritanserin inhibited the expression and development of repeated cocaine-induced behavioral sensitization in dose-dependent manner. On the other hand, azasetron, a 5-HT₃ receptor antagonist, attenuated only the development of the sensitization. All 5-HT receptor ligands used here did not affect the maintenance of the sensitization. These results suggest that 5-HT system plays a role in cocaine-induced behavioral sensitization in a different way from METH sensitization.

P1-105 Effect of 5-HT_{1B} agonist on escalated aggression and prefrontal cortex serotonin in mice

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5-HT_{1B} receptor agonists modulate locomotion, satiety and male sexual behavior. In mice, they are also effective anti-aggressive agents and can attenuate several forms of heightened aggression, including alcohol-, social instigation-, and frustration-heightened aggression. The objective of this study was to investigate the effect of 5-HT_{1B} receptor agonist, CP-94,253 on schedule-heightened aggression and on 5-HT release in the prefrontal cortex (PFC). Male CFW mice were housed as residents and performed a nose-poke response on a fixed interval schedule 10 min (FI10) that was reinforced by the opportunity to briefly confront an intruder (12 sec). CP-94,253 (0-10mg/kg, IP) was given 30 min before an operant task that was reinforced by a 5-min aggressive encounter. To antagonize this effect, the 5-HT_{1B/1D} antagonist, GR 127935 (10mg/kg, IP) was administered 30 min before CP-94,253 injection. 5-HT release in the PFC was measured by *in vivo* microdialysis following CP-94,253 (10mg/kg, IP). The results confirm that mice maintained on a FI10 schedule accelerated their rate of responding towards the end of the interval, and doubled their rate of aggression. CP-94,253 dose-dependently decreased response rate, index of curvature and the frequency of bites. All decreases except response rate were antagonized by GR 127935. In aggression naive mice, CP-94,253 decreased extracellular 5-HT levels by approximately 30 % in the PFC. This decline began 10 min after injection and persisted for 100 min. These results suggest that a systemic injection of CP-94,253 decreases endogenous 5-HT in the PFC, and reduces schedule-heightened aggressive behavior via activation of the 5-HT_{1B} receptor.

P1-107 Potent blockade of dopamine D2 receptors inhibits clozapine-induced dopamine release in rat medial prefrontal cortex

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Atypical antipsychotic drugs such as clozapine have been postulated to improve negative and neurocognitive symptoms of schizophrenia by ameliorating prefrontal dopaminergic neurotransmission possibly through the antagonism of 5-HT_{2A} and dopamine (DA)-D₂ receptors. To elucidate the role of prefrontal D₂ receptors in atypical antipsychotic action, we examined the effect of the selective D₂ receptor antagonists on clozapine-induced release of DA and noradrenaline (NA) in rat medial prefrontal cortex (mPFC) using *in vivo* microdialysis. Reverse microdialysis of clozapine into the mPFC increased basal extracellular DA and NA levels in a concentration-dependent manner. Co-perfusion with sulpiride, a selective D₂ receptor antagonist devoid of 5-HT_{2A} receptor affinity, significantly attenuated clozapine-induced DA release in the mPFC. Raclopride, a potent D₂ receptor antagonist, also significantly inhibited the effect of clozapine on mPFC DA release. When perfused alone, sulpiride had no effect on basal extracellular DA and NA levels in the mPFC. Neither sulpiride nor raclopride affect the clozapine-induced increase in extracellular NA levels. These results suggest that the modest occupancy of D₂ receptors in the mPFC may be required to enhance mPFC DA release, whereas the more potent occupancy of D₂ receptors may inhibit mPFC DA release. This assumption may be consistent with the receptor binding profile of clozapine, a potent 5-HT_{2A} antagonist with weak D₂ receptor affinity, which may contribute to the greater ability to enhance prefrontal DA neurotransmission. Moreover, this finding may have clinical implications for limitation of augmentation therapy of clozapine with the potent D₂ antagonist antipsychotics for refractory schizophrenia.

P1-104 Effects of serotonin receptor ligands on methamphetamine-induced sensitization of prefrontal serotonin release in mice

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Repeated administration of psychostimulants elicits a progressive enhancement of locomotor activity known as behavioral sensitization. We have recently shown that osemozotan (previously called MKC-242), a selective serotonin (5-HT)_{1A} receptor agonist, and ritanserin, a 5-HT_{2A/2C} receptor antagonist, inhibited methamphetamine (METH)-induced locomotor sensitization in mice. To clarify the neurochemical mechanisms underlying METH-induced behavioral sensitization, the present study examined, using *in vivo* microdialysis technique, the effect of repeated administration of METH on the release of 5-HT, dopamine (DA) and noradrenaline (NA), in the prefrontal cortex and striatum of mice. To induce the sensitization, 4 weeks old male ddY mice were administered repeatedly with METH at 1 mg/kg for 7 days, and challenged with METH at 1 mg/kg after drug withdrawal for 7 days. For the effects of the drugs on the expression, the ligands were injected 30 min before a challenge dose of METH. For the effects of drugs on the maintenance, the ligands were treated daily for 7 days after repeated treatment with METH. The basal extracellular 5-HT, DA and NA levels in the prefrontal cortex and striatum did not differ significantly between saline- and METH-pretreated mice. Repeated METH enhanced METH challenge-stimulated release of 5-HT, but not DA and NA, in the prefrontal cortex. The increased response of 5-HT release was not observed in the striatum. Osemozotan and ritanserin reversed METH-induced increase in prefrontal 5-HT release in the expression and maintenance of the sensitization. These results suggest that 5-HT system including 5-HT_{1A} and 5-HT_{2A/2C} receptors in the prefrontal cortex plays a key role in METH-induced behavioral sensitization in mice.

P1-106 Effects of AMPA on clozapine-induced dopamine and noradrenaline release in rat medial prefrontal cortex: implications for neurocognitive effects of atypical antipsychotic drugs

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Atypical antipsychotic drugs such as clozapine and olanzapine have been postulated to improve neurocognitive symptoms of schizophrenia by modulating prefrontal glutamatergic and dopaminergic neurotransmission. Functional interactions of these drugs with mGluR receptors are well demonstrated, whereas little is known about their effect on the AMPA/kinate receptors. To elucidate the interaction between atypical antipsychotics and AMPA/kinate receptors, we investigated the effect of AMPA on clozapine-induced release of dopamine (DA) and noradrenaline (NA) in rat medial prefrontal cortex (mPFC) using *in vivo* microdialysis. Reverse microdialysis of clozapine into the mPFC increased extracellular DA and NA levels up to over three times of predrug basal levels. Co-perfusion with (±)AMPA significantly potentiated the clozapine-induced DA and NA release in the mPFC in a concentration-dependent manner. When perfused alone, AMPA slightly increased basal DA levels but had no effect on basal NA levels in the mPFC. AMPA produced a similar potentiation of the effect of olanzapine, but not haloperidol, on DA and NA release. The competitive inhibitor of AMPA/kinate receptors CNQX partially attenuated the ability of AMPA to enhance clozapine-induced DA and NA release, while the non-competitive inhibitor (±)SYM2206 completely abolished the effect of AMPA. Although AMPA/kinate receptors are rapidly desensitized following receptor activation, the atypical antipsychotic clozapine and olanzapine may prevent the desensitization of AMPA receptors. Such a prolonged depolarization of AMPA receptors may facilitate glutamatergic as well as catecholaminergic neurotransmission in the mPFC. This mechanism of action of atypical antipsychotic drugs may be the basis for their neurocognitive effects.

P1-108 Effects of therapeutic-relevant concentration of carbamazepine on CICR

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To clarify the antiepileptic and mood stabilizing actions of carbamazepine (CBZ), this study determined the effects of CBZ on gene expression associated with Ca²⁺-induced Ca²⁺-releasing system (CICR) and CICR-associated monoamine exocytosis mechanism using real-time PCR and microdialysis, respectively. Chronic administration of therapeutically-relevant dose of CBZ reduced the mRNA expression of sodium/myo-inositol cotransporter (SMIT), wolfframin (Wfs1), inositol 1,4,5-trisphosphate receptor (Itp) and ryanodine receptor (Ryr). Both basal and Ca²⁺-evoked monoamine releases, which were regulated by Itp predominantly and Ryr weakly, were increased by perfusion with therapeutically-relevant concentration of CBZ. Contrary, the K⁺-evoked release, which was regulated by Ryr predominantly and Itp weakly, was reduced by therapeutically-relevant concentration of CBZ. The stimulatory effects of CBZ on basal and Ca²⁺-evoked releases were reduced by pre-treatment with Itp antagonist, whereas the stimulatory effects of Itp agonist were enhanced by pre-treatment with CBZ. The pre-treatment with CBZ did not affect the stimulatory effect of Itp agonist on K⁺-evoked release. These results suggest that CBZ enhances CICR-associated monoamine exocytosis mechanism via indirect activation of both Itp and Ryr. This indirect activation of CICR induced by therapeutically-relevant concentration of CBZ may induce down-regulation of gene expression associated with CICR. The combination between indirect activation of CICR and down-regulation of CICR-associated intraneuronal Ca²⁺ signalling induced by chronic administration of CBZ, at least partially, is involved in the mechanism of antiepileptic or mood stabilizing actions of CBZ.

P1-109 Effects of SKF-38393, a selective dopamine D1 receptor agonist on expression of d-amphetamine induced behavior and expression of the immediate early gene Arc in the prefrontal cortex of rats

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Repeated administration of psychostimulants produces peculiar phenomenon "behavioral sensitization" which gradually develops over time and remains for a long time once established in rodents. In this study we have investigated if dopamine D1 agonist can reverse, or not the behavioral sensitization by repeated administration of d-amphetamine(AMP) and assessed the effects of treatments on the expressions of Arc and some receptor or its binding protein genes in rats. Rats were pretreated with 6 AMP injections. Following a 14-day withdrawal period, six groups of rats were treated either with SKF-38393(SKF; a selective D1 agonist), SCH-23390 (SCH; a selective D1 antagonist), YM-09151-2 (YM; a selective D2 antagonist), SKF+SCH, SKF+YM or physiological saline once daily for five days. 3 days or 4 weeks after the end of the reversal treatment, all subjects were once again challenged with AMP. The other groups of rats which received AMP with or without SKF were decapitated at 1h after the indicated treatment and the cortex was removed quickly. We subsequently measured the mRNA levels of Arc, Calcitonin, Gsk3b, metabotropic glutamate receptor 1, D1 and D2 receptor, using the quantified RT-PCR with TaqMan system. Behavioral sensitization have established in all groups. In SKF treated group stereotyped behavior significantly decreased. D-amphetamine administration significantly increased the expression of arc mRNA. SKF administration also increased the expression of arc mRNA significantly compared with Saline treated group. These findings suggest that dopamine D1 agonist promote the expression of plasticity-related genes and supports the view that the mechanisms of this treatment may involve a neuroplasticity as well as behavioral sensitization.

P1-111 Involvement of dopaminergic system in δ -9-tetrahydrocannabinol-induced psychosis-related behavior in mice

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In human, cannabis abuse often could precipitate a psychotic state called "cannabinoid psychosis", with hallucinations, delusions and emotional liability, resembling schizophrenia. Schizophrenia has long been associated with abnormalities in information processing and attention mechanisms. In an attempt to better understand the mechanisms underlying the pathophysiology of schizophrenia, sensorimotor information gating processes have received much attention. One well-established method for evaluating sensory filtering is the paradigm of prepulse inhibition (PPI), which is the reduction of the startle reflex by implementation of a weak intensity prepulse immediately before the startle stimulus. The disruption of PPI in schizophrenic patients has been well described in several studies. In the present study, we examined the effect of Δ -9-tetrahydrocannabinol (THC), the major psychoactive component of cannabis, on PPI of startle reflex in mice. THC (10 mg/kg, i.p.) impaired the PPI concomitant with the decrease of the startle response. SR141716 (10 mg/kg, i.p.), a CB1 cannabinoid receptor antagonist, reversed the THC-induced PPI deficits and decrease in startle reactivity. These findings suggest that THC induces these psychosis-related behaviors through direct actions via CB1 cannabinoid receptors. Similarly, haloperidol (0.3 mg/kg, i.p.) and risperidone (0.1 mg/kg, i.p.), antipsychotics, improved the PPI deficits concomitant with a decrease in the startle response. Moreover, THC (10mg/kg, i.p.), which impairs the PPI deficits, significantly increased dopamine release in the nucleus accumbens, and its increase were reversed by SR141716 (10 mg/kg, i.p.). These results suggested the involvement of the dopaminergic system in the THC-induced psychosis-related behavior.

P1-113 Accumulation of oxidative damage in nucleic acids of brain following kainic acid-induced excitotoxicity is suppressed by MTH1, an oxidized purine nucleoside triphosphatase

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Neuronal excitotoxicity, especially during ischemia-induced neuronal death, is believed to involve cellular damage caused by free radicals generated through multiple mechanisms. However, it is not clear yet whether the excessive excitation of neurons itself causes such oxidative damage in brain. In the present study, we examined accumulation of 8-oxoguanine (8-oxoG), an oxidized form of guanine, in mouse brain after systemic administration of kainic acid, an analog of glutamate. An increased accumulation of 8-oxoG in cellular DNA and RNA was evident in CA3 field of hippocampus from 6 to 24 h after the administration of kainic acid, following severe seizure. Laser scanning confocal microscopy revealed that 8-oxoG accumulates in both cytoplasm and nuclei of CA3 pyramidal neurons, astrocytes and microglia. The systemic administration of kainic acid caused a delayed and prolonged increase of MTH1 expression, which can protect cells from oxidative damage by hydrolyzing oxidized purine nucleoside triphosphatase such as 8-oxo-dGTP or 2-OH-dATP, in the hippocampus. In order to examine whether MTH1 can protect neurons from the excitotoxicity, NeuN-immunoreactivity of CA3 pyramidal neurons in hippocampus was compared between MTH1-null and wild-type mice after the systemic administration of kainic acid. Number of NeuN-positive neurons was apparently decreased in both mice 7 days after the administration, and there was no significant difference between MTH1-null and wild-type mice. However, we found that 8-oxoG accumulates more significantly in the CA3 field of MTH1-null mice in comparison to the wild type, thus suggesting that MTH1 hydrolyzes oxidized purine nucleotides to avoid cellular damage resulting from their accumulation in the hippocampus induced by the excitotoxicity.

P1-110 Mechanism of tributyltin neurotoxicity in cultured cortical neurons

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Tributyltin chloride (TBT) has been used in a variety of industrial products, but TBT represents an environmental and health hazard. Although it has been reported that TBT displays toxicity in rat neonatal brain and rat hippocampal slice cultures, the mechanism of neurotoxicity has been elucidated little. In this study, neurotoxicity of TBT was investigated in cultured rat cortical neurons. TBT induced cell death in time- and dose-dependent manners. We examined the involvement of glutamate in TBT neurotoxicity because glutamate plays important roles in various types of neuronal cell death. Glutamate release was induced by TBT and application of glutamate receptor antagonists, MK-801 and CNQX reduced TBT neurotoxicity. These results suggest that released glutamate and consequent activation of glutamate receptors are involved in TBT neurotoxicity. Therefore we investigated whether some factors, which are believed to be concerned in glutamate excitotoxicity, are also involved in TBT neurotoxicity. The cell death caused by TBT was also reduced by α -tocopherol (a membrane-permeable antioxidant), SB202190 (p38 mitogen-activated protein kinase inhibitor) and U-0126 (an extracellular signal-regulated protein kinase inhibitor). Additionally, we inspected the involvement of caspase-3. TBT activated caspase-3 in cortical neurons, but caspase-3 inhibitor did not protect from TBT toxicity and its activity was not decreased by glutamate receptor antagonists. These results indicate that glutamate toxicity caused by TBT is caspase-independent.

P1-112 Interaction between cancer cells and microglia in brain metastasis of lung cancer

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Incidence of brain metastasis has been increasing in the recent years due to the prolonged survival period of cancer patients. However, the molecular mechanism responsible for brain metastasis is poorly understood to date. To elucidate this, we established an animal model for brain metastasis using human lung cancer-derived cells (HARA-B). HARA-B cells (2×10^5 cells/0.1 ml PBS) were injected into the left cardiac ventricle of nude mice. Brain metastases were determined histologically 4-5 weeks after the inoculation of the cells. Brain metastases were found in the whole brain, and the number of the metastatic lesions was the highest in the cerebellum and midbrain. Accumulation of microglia was noted around the metastatic lesions in the brain. We performed the co-culture experiment with HARA-B cells and microglia to examine interaction between both cells. A growth rate of HARA-B cells was reduced in this co-culture with microglia. We also confirmed the inhibitory effect of the conditioned medium of microglia on the growth rate of HARA-B cells. These results suggest that microglia might have a role to prevent the growth of cancer cells metastasized to the brain. Further studies are under investigation to identify cytokines which is responsible for growth inhibition of cancer cells.

P1-114 Characterization of seizures induced by direct injection of kainic acid into amygdala in different mouse strains

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Previous studies described that mice in different strains show different seizure susceptibility to systemic administration of kainic acid (KA). However, limbic seizures induced by direct KA-microinjection into amygdala have not been accomplished. In the present study, we succeeded in inducing seizures by microinjecting KA into amygdala in mice. Each six mice per strain (C57BL/6 and FVB/N) underwent implantation of electrodes in the left amygdala (LA) and the left sensorimotor cortex (LCx). Stainless cannula was also inserted into the LA for KA injection. All animals received KA injection into the LA (0.5 μ g). On electroencephalograms, multiple spike discharges initially appeared in the LA within 10-20 min after KA injection and mouth and facial movements were observed. At 20-60 min after KA injection, the seizure discharge propagated to the LCx. Within 60-90 min after KA injection the amplitude of the multiple spike discharges increased, which spread to the LCx, and head nodding, forelimb clonus, rearing and falling, and generalized tonic clonic seizures were observed in both strains. The amplitude of spikes in the LCx of FVB/N was statistically greater than that of C57BL/6 at 48 hours after KA injection. Histological studies with morphometric analysis of the neuronal density of CA3 revealed that neuronal death was significantly severer in FVB/N than in C57BL/6. In the KA-induced amygdala-seizure, FVB/N showed more sensitive susceptibility to seizure compared to C57BL/6.

P1-115 Involvement of neuropsin in hippocampal neuronal degeneration

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The extracellular proteases are involved in a variety of processes including plasticity and degeneration. Neuropsin (NP) is an extracellular serine protease, which is expressed most abundantly in the neurons of the limbic system. The mRNA expression is up-regulated after excitotoxic injury by intrahippocampal injection of kainic acid (KA). The result implies that NP relates excitotoxin-induced injury and/or protection mechanism against brain damage. However, little is known about mechanical involvement of extracellular proteolysis in the neural degeneration and regeneration. In this study, we intraperitoneally administered epileptogenic dose of KA and observed the extent of neuronal degeneration of NP knock-out (KO) mice in comparison with that of wild-type mice (WT). Neuronal cell death was not induced in NP KO mice, while it was excessive in WT mice 24hr after KA administration. The activity of MMP9, which is known to increase after KA administration and promote the neuronal cell death, was more rapidly disappeared in NP KO mice than that of WT mice. These results suggest that the proteolytic activities of NP and MMP9 mediate neuronal degeneration in the hippocampus.

P2-001 Novel acyclic cyclophanes inhibit N-methyl-D-aspartate receptors expressed in *Xenopus* oocytes

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Purpose: As excitotoxicity has been implicated in a variety of neuropathological conditions, understanding the pathways involved in this type of cell death is of critical importance to the future clinical treatment of many diseases induced by excitotoxicity. In order to make the compound that have inhibitory effects on NMDA receptors, we synthesized four acyclic cyclophanes, TGCn, ACCn, DNCn and TsDCn, and measured the effects of these compounds on NMDA receptor. **Methods:** Macroscopic currents were recorded with a two-electrode voltage clamp using a Dual Electrode Voltage Clamp Amplifier CEZ-1250. To study the effects of acyclic cyclophanes on recombinant NMDA receptors expressed in *Xenopus* oocytes, macroscopic currents were measured in the presence of 10 μ M glutamate and glycine. **Results and Conclusions:** All acyclic cyclophanes were found to inhibit macroscopic currents at heteromeric NR1/NR2A receptor at -70 mV. To determine the subunit-specificity of inhibition by TGCn, ACCn, DNCn and TsDCn, we compared their effects on NR1/NR2 receptors containing different NR2 subunit: NR2A, NR2B, NR2C and NR2D. The degree of inhibition by these compounds was in the order NR2A > NR2B > NR2C = NR2D except for TGCn and 10 μ M TGCn did not inhibit to NR1/NR2B, NR1/NR2C and NR1/NR2D. We measured dose-dependency of the inhibition by DNCn and TsDCn to NR1/NR2A receptors at -70 mV. The IC₅₀ values for DNCn and TsDCn to NR1/NR2A receptors were 0.35 μ M and 0.23 μ M and the inhibition by these compounds showed voltage-dependency. These results indicate that the inhibition by these compounds may directly act on the pore of NMDA receptor, as open channel blocker. This work was supported by The Sasakawa Scientific Research Grant from The Japan Science Society

P2-003 PICK1 is localized in intracellular membrane components containing immature GluR2 subunit in rat brain

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PDZ domain binds to various receptors, transporters, ion channels and kinases through the interaction with the C-termini of these proteins. PICK1 (Protein interacting with C kinase 1) contains a single PDZ domain and binds to GluR2 subunit of AMPA receptor. PICK1 has been suggested to be involved in the regulation of GluR2 receptor number in plasma membrane since the overexpression of PICK1 accelerated the endocytosis of GluR2 in hippocampal neurons. In order to study the regulatory mechanism GluR2 trafficking by PICK1, we isolated PICK1-bound intracellular vesicles from rat brain. In subcellular fractionation of rat brain homogenate, PICK1 was found to be enriched in the light-density microsomal fraction (LDM), and PICK1-bound vesicles purified from the LDM by using antibody-conjugated magnetic beads contained GluR2 subunit. To characterize the sugar chains of GluR2 receptor, we treated these vesicles with either endoglycosidase H (Endo H) or peptide:N-glycosidase F (PNGase F) and found that the most of GluR2 in PICK1-bound vesicles was Endo H-sensitive. Furthermore, a large part of GluR2 subunit coimmunoprecipitated with PICK1 was also Endo H-sensitive. All of these results suggest that PICK1 is mainly associated with immature GluR2 subunit in endoplasmic reticulum, and play some regulatory roles in AMPA receptor trafficking in the proximal secretory pathway (ER to medial-Golgi).

P1-116 Alexander disease model mice

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Alexander disease is caused by heterozygous mutation in glial fibrillary acidic protein (GFAP). The pathological hallmark is the presence of astrocytic GFAP aggregation called Rosenthal fibers (RF). To understand the pathophysiology of Alexander disease and utilize those results to the understanding of normal function of astrocytes in vivo, we have established transgenic mice that express human GFAP R239H mutant under the control of mouse GFAP promoter. Immunohistochemistry using human GFAP specific antibody, SMI21, showed that this immunoreactivity was present only in S100 beta positive astrocytes and ependymal cells. Some astrocytes possessed the aggregations with SMI immunoreactivity that was co-labeled by small heat shock protein, alpha B crystalline and HSP25. Contrary to the case of human, transgenic mice showed no abnormality of myelin formation and structure. To examine whether the presence of human GFAP aggregation altered brain functions, we challenged kainic acid administration to transgenic and wild type mice and studied the susceptibility of convulsion and the vulnerability of hippocampal cell damage. Transgenic mice were more susceptible to systemic administration of kainic acid (20 mg/kg) than wild type mice as revealed by the number of mice showing tonic-clonic convulsion: 8 out of 11 for transgenic mice and 2 out of 14 for wild type mice. Transgenic mice were more vulnerable to excitotoxicity of kainic acid as revealed by the appearance of Fluoro Jade positive dying hippocampal neurons after 24 hours administration. We concluded that Alexander disease model mice compromised the protective function against kainic acid excitotoxicity.

P2-002 Expressions of acid-sensing ion channel-1a (ASIC1a) and ASIC1b in mouse spiral ganglion neurons

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ASIC channels (ASICs) are neuronal proton-gated cation channels, all of which are subunits that associate as homomers or heteromers to constitute functional complexes, and are expressed in mammalian central and peripheral nervous systems. As previously described, ASIC2 and ASIC3 are expressed in spiral ganglion neurons in the mouse cochlea, contributing to amiloride-sensitive acid-evoked responses in the ganglion neurons. ASIC2 or ASIC3 gene-disrupted mice showed substantial impairments in their auditory brainstem evoked responses (ABRs), indicating that both ASIC2 and ASIC3 channels are essential for the auditory transduction. We investigated the expression of ASIC1 genes - ASIC1a and its N-terminal splice variant ASIC1b - in mouse cochlea. *In situ* hybridization experiments revealed that ASIC1a transcripts and ASIC1b transcripts were expressed moderately and intensely in the spiral ganglia, respectively. We generated an anti-ASIC1 antibody by immunizing rabbits, performed Western blot analyses, and confirmed the expressions of both ASIC1a and ASIC1b channels in mouse cochlea extracts at the protein level. Subsequent immunohistochemical studies showed the expressions of both channels in the ganglia, which is in good agreement with our *in situ* hybridization results. To clarify the functional roles of both channels in the auditory system, we prepared ASIC1 gene-disrupted mice, and are currently examining their ABRs. In this meeting, we'll show the results of the examinations and discuss the contributions of the ASIC1 channels to the mouse auditory system.

P2-004 Intracellular localization of stargazin-like protein, γ -8

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Stargazin/ γ -2 and γ -8 are the member of TARPs (transmembrane AMPA receptor regulatory proteins) and play important roles in AMPA receptor trafficking and clustering into postsynaptic plasma membrane. Recent studies also show that TARPs may also act as positive modulators of AMPA receptor ion channel function. Previously we showed that stargazin/ γ -2 and γ -8 were localized in distinct component of postsynaptic membrane and were regulated by different types of kinases and phosphatases, suggesting that stargazin/ γ -2 and γ -8 may play different roles in synapse. Recently we discovered that γ -8 was reserved in intracellular membrane components with mature GluR2. The γ -8-containing vesicles were apparently distinguishable from endoplasmic reticulum. Immunoelectron microscopy revealed that γ -8 was localized to intracellular membrane components in dendrites. AMPA receptor and β -tubulin were coimmunoprecipitated by anti- γ -8 antibody. GST fusion protein pull-down assay demonstrated that cytoplasmic C-terminal region of γ -8 interacted with β -tubulin. These results suggest that γ -8 plays important roles in the vesicular trafficking of AMPA receptor through the binding to microtubules in adult rat brain. When PC12 cells were transfected with stargazin/ γ -2 and γ -8, the expressed γ -8 was localized in intracellular membrane components, whereas the expressed stargazin/ γ -2 was localized in plasma membrane. These results suggested γ -8 played role in the trafficking of matured AMPA receptor in cytoplasm in tubulin-dependent mechanism.

P2-005 Tricyclic antidepressant desipramine induces glutamate release from presynaptic nerve terminals

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The effects of antidepressant drugs on spontaneous excitatory postsynaptic currents (EPSCs) were investigated in the mechanically dissociated rat locus coeruleus (LC) neurons which had their presynaptic nerve terminals attached. The membrane currents were recorded by the whole-cell patch-clamp technique. Desipramine, a tricyclic antidepressant, reversibly and concentration-dependently increased the frequency of spontaneous EPSCs, but did not alter their amplitude distribution. The inhibitors of high-voltage-activated Ca^{2+} channels failed to block the facilitatory action of desipramine, while they inhibited the high K^{+} -induced facilitation of spontaneous EPSC frequency. The desipramine action was also observed in the absence of extracellular Ca^{2+} . Pretreatment of thapsigargin in Ca^{2+} -free solution fully inhibited the desipramine action, thus suggesting the involvement of Ca^{2+} release from intracellular Ca^{2+} stores at glutamatergic presynaptic nerve terminals. Imipramine and nortriptyline, other tricyclic antidepressants, and amoxapine, mianserin and fluoxetine, non-tricyclic antidepressants, also increased the EPSC frequency, while tranlycypromine, an inhibitor of monoamine oxidase, did not increase the glutamate release. The present results indicate that modulation of spontaneous glutamatergic transmission by tricyclic- and non-tricyclic-antidepressant drugs may regulate the excitability of LC neurons.

P2-007 Peptidergic system is correlated with the neurotoxicity in (+) MK-801-treated schizophrenic model rat brain: suppressive effect of neuroleptics

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Noncompetitive NMDA receptor antagonist dizocilpine ((+)-MK-801) produces neurotoxicity and schizophrenic symptoms where the role of peptidergic system is not well understood. We examined the changes of neuropeptides, cholecystokinin (CCK) and somatostatin (SS) as well as their neuropeptide-degrading enzymes, prolyl oligopeptidase (POP) and thimet oligopeptidase (EP 24.15), and glial marker proteins, GFAP and CD11b, in the PC/RSC, frontal cortex, and hippocampus of a MK-801-induced schizophrenic model rat brain. Since atypical neuroleptic clozapine but not typical neuroleptic haloperidol prevents the MK-801-induced negative schizophrenic symptom, we examined the pretreated effects of the neuroleptics on the neuropeptidergic system. SS mRNA and peptide levels significantly decreased in the PC/RSC and hippocampus but not in the frontal cortex 3 days after 0.5 mg/kg MK-801 treatment. CCK mRNA and peptide levels significantly decreased in all of the brain regions examined, and POP and EP 24.15 increased in the PC/RSC. Pretreatment with clozapine but not haloperidol completely recovered the changes in these neuropeptides and peptidases. Immunohistochemical study of GFAP and CD11b showed that immunoreactive glial cells increased in the PC/RSC after the MK-801 treatment and were suppressed by the pretreatment with clozapine. These data suggest that changes of neuropeptides and their peptidases are correlated with the changes of glial cells, and may have role in the control of negative schizophrenia symptoms.

P2-009 Effects of pyrethroids on the hippocampal release of glutamate and GABA in freely moving rats

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We have been studying effects of pyrethroids, allethrin (type I), cyhalothrin (type II) and deltamethrin (type II), on the mechanism of brain neurotransmission. In the present study, we studied changes in the hippocampal release of glutamate (Glu) and GABA after the exposure of the pyrethroids. A microdialysis probe was implanted into the left hippocampus of male SD rats. Glu and GABA were detected by HPLC with ECD. Rats were treated i.p. with pyrethroids or the same volume of vehicle. The extracellular level of Glu was increased by 10 and 20 mg/kg allethrin to about 175 and 150% of baseline with a peak time of 60 min and decreased to 50% at 60 mg/kg up to 3 hrs after injection. Cyhalothrin 10, 20 and 60 mg/kg inhibited the release of Glu to 60, 50 and 30%, respectively, with a peak time of 40-60 min after injection. Deltamethrin 10 and 20 mg/kg increased the efflux of Glu to 190% with a peak time of 40 min and 60 mg/kg i.p. increased it to 275% and remained at a steady level up to 3 hrs. On the contrary, the extracellular level of GABA was decreased by 10 and 20 mg/kg allethrin to 50% of baseline and increased to 250% by 60 mg/kg with a peak time of 90 min after injection. Cyhalothrin 10, 20 and 60 mg/kg stimulated GABA release to 130, 210 and 300%, respectively with a peak time of 40-90 min. Deltamethrin 10, 20 and 60 mg/kg inhibited GABA release to 75, 55 and 40%, respectively with a peak time 60-90 min. Local infusion of 1 μM tetrodotoxin with Ringer's solution through the dialysis probe completely prevented the effects of allethrin, cyhalothrin and deltamethrin, but incompletely the effects of deltamethrin at 60 mg/kg on Glu and GABA release. Above results suggest that these pyrethroids are able to alter the release of Glu in opposite direction than GABA release.

P2-006 N-terminus of human tyrosine hydroxylase type 1 affects the stability in mammalian cells

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Wild-type human tyrosine hydroxylase type 1 (hTH1) and 4 mutants (del-52, the first 52 amino acid residues deleted; del-157, the first 157 amino acid residues deleted; RR-EE, Arg³⁷-Arg³⁸ replaced by Glu³⁷-Glu³⁸; and S40D, Ser⁴⁰ replaced by Asp⁴⁰) were expressed in AtT-20 mouse neuroendocrine cells. The amounts of dopamine that accumulated in AtT-20 cells expressing these hTH1 phenotypes were in the following order: del-52 = del-157 = RR-EE > S40D > wild-type. The quantitative real-time PCR method did not detect any difference among the expression levels of the mRNA encoding wild-type hTH1 and those encoding the N-terminus-deleted mutants. The assay on the degradation rate of hTH1 revealed that the N-terminus-deleted hTH1 mutants were much more stable than wild-type. Computer-assisted analysis of the spatial configuration of hTH1 identified 5 newly recognized PEST motifs, one of which was located in the N-terminus sequence of Met¹-Lys¹² and predicted that deletion of the N-terminus region would alter the secondary structure within the catalytic domain. We report that the high stability of the N-terminus-deleted hTH1 mutants can be generated by the loss of a PEST motif in their N-termini and the structural change in the catalytic domain.

P2-008 A single exocytotic event in digitonin-permeabilized adrenergic chromaffin cells

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Calcium-induced catecholamine release from digitonin-permeabilized chromaffin cells seems to consist of at least two distinct steps: MgATP-dependent priming of release and Ca^{2+} -triggered ATP-independent release from the primed vesicles. The initial Ca^{2+} -induced release for 1-2 min reflects ATP-independent release from the primed vesicles, and the release thereafter is sustained by the release from the ATP-dependent newly primed vesicles. To characterize a single exocytotic event from the different components, spike parameters (rise time, middle width and area) and spike shape were analyzed. Bovine chromaffin cells cultured onto collagen coated glass-base dish were washed with PBS(-) and incubate with Ca-EGTA cytosolic buffer. Single-cell amperometric recording was performed under an inverted microscope at 25 $^{\circ}\text{C}$, and released catecholamines were monitored with a carbon fiber microelectrode (5 μm diameter). Exposure of digitonin (20 μM , 20 sec)-permeabilized cells to Ca^{2+} (10 μM) with or without MgATP (5 mM) evoked a train of events with the frequency of 211 ± 34 and 162 ± 27 (number of spike/5 min, n=5), respectively. We observed distinctive kinetics in the events. The values of rise time and middle width in the presence of MgATP were approx. 30% greater than those observed in the absence of MgATP. These results suggest that the rate of catecholamine release from the newly primed vesicles is slower than the release from primed vesicles.

P2-010 Characterization of Recombinant Tryptophan Hydroxylase Isoform 2

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Tryptophan hydroxylase (TPH) catalyzes the rate limiting step of serotonin biosynthesis. Recently, a brain specific isoform of TPH (TPH2) was discovered (Walther *et al.*, Science 2003). Since serotonin plays a central role as a neurotransmitter in the brain, it is important to investigate the regulatory mechanism of the TPH2 activity *in vitro*.

Human TPH2 cDNA was cloned by RT-PCR from human brain mRNA, and expressed in *E. coli* as a maltose-binding protein (MBP) fused form. MBP-hTPH2 protein was purified by amylose-resin affinity column chromatography and by size-exclusion chromatography. MBP-fused human tyrosine hydroxylase type 1 (MBP-hTH1) was also expressed and purified similarly, and we compared the characteristics of these two enzymes.

First, the effects of divalent cations were examined, since hTPH2 also requires Fe^{2+} ion for the catalytic reaction, as same as other aromatic amino acid hydroxylases. We found that the hTPH2 activity was increased in the presence of Cu^{2+} . Addition of Co^{2+} , Mn^{2+} , or Ca^{2+} to the incubation mixture inhibited the TPH2 activity, while addition of Mg^{2+} or Zn^{2+} showed no inhibitory effect. The inactivation with Ca^{2+} was not observed in MBP-hTH1. Second, the inhibitory effects of L-phenylalanine against MBP-hTPH2 and MBP-hTH1 were investigated, because L-Phe could be a poor substrate to the both enzymes. Phenylalanine inhibited the MBP-hTH1 activity stronger than the MBP-hTPH2 at concentrations below 600 μM .

These results indicated that divalent metal cations differently affect the activity of MBP-hTPH2, and the reactivity to metal ions were different between MBP-hTPH2 and MBP-hTH1.

P2-011 Inhibition of the exocytotic release of glutamate from rat cerebellar granule cells by nitric oxide

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[Purpose] Nitric oxide (NO) modulates the release of various neurotransmitters, some of which are thought to be involved in neuronal plasticity. However, the molecular mechanism by which NO modulates the exocytotic release of neurotransmitters remains controversial. Previously, we reported that NO inhibited the exocytotic release of glutamate from rat cerebellar granule cells (CGCs). In order to determine this mechanism, the effects of NO on the exocytotic release of glutamate were investigated using a NO-related reagents and Ca²⁺ channel blockers. [Methods] CGCs were isolated from 7-8 days old Wistar rats and the cells were treated with high-K⁺ or Ca²⁺ ionophore to induce glutamate release, following incubation with various reagents. The contents of the released glutamate were determined by HPLC. Intracellular Ca²⁺ concentration in CGCs was measured by the fluorescent Ca²⁺ dye, Fluo-3 AM. [Results & discussion] Treatment with NO-related reagents revealed that NO inhibited the K⁺-evoked glutamate release. BoNT/B attenuated the enhancement of glutamate release caused by NO synthase (NOS) inhibition, indicating that NO acts on the K⁺-evoked exocytotic pathway. cGMP related reagents did not affect the K⁺-evoked glutamate release. Ca²⁺ ionophore-induced release of glutamate were not affected by NO-related reagents, suggesting that NO inhibits Ca²⁺ entry into cells. Monitoring of intracellular Ca²⁺ showed that NO inhibited K⁺-evoked changes in intracellular Ca²⁺ concentration. These results suggest that NO inhibits exocytotic release of glutamate via inhibition of voltage-dependent Ca²⁺ channels. To determine which Ca²⁺ channel subtypes are inhibited by NO, further studies including the effect of NO on inhibition by Ca²⁺ channel blockers are in progress.

P2-013 Plasma Nitrate Levels in Deficit were lower than Non-Deficit Forms of Schizophrenia

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As evidence supporting the relationship between NO and central nervous system function continues to accumulate, evidence of a relationship between NO and schizophrenia has also been reported. Previous findings suggest that there is excess NO production in schizophrenic brains. On the other hand, Strauss et al. proposed that positive and negative symptoms in schizophrenia be scrutinized separately. Carpenter and his colleagues termed the subtype of schizophrenia, which is characterized by primary negative symptoms, as "deficit syndrome". The purpose of this study was to test whether nitric oxide production levels differ between deficit and non-deficit forms of schizophrenia. To address the question, we investigated plasma nitrate levels, an index of in vivo nitric oxide production, in deficit syndrome patients (n = 11), non-deficit syndrome patients (n = 14), and healthy controls (n = 12). This study was carried out in accordance with the Declaration of Helsinki and the study design was approved by the Ethics Committee of the Department of Neuropsychiatry, Keio University. Informed consent was obtained from each patient upon provision of a thorough explanation of the procedures. Plasma nitrate levels were measured with a combination of high-performance liquid chromatography and the Griess reaction. The plasma nitrate levels of deficit syndrome patients were significantly lower than those of non-deficit syndrome patients (p < 0.05). These results suggest that a decline in nitric oxide production may be involved in primary negative symptoms.

P2-015 Effect of hydrogen sulphide on intracellular calcium in neuronal cells: direct evidence of H₂S as a new neuromodulator

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H₂S has been positioned as a new neuromodulator. To investigate the role of H₂S in the neuronal activity, we observed its effect on intracellular calcium ([Ca²⁺]_i) in both SH-SY5Y neuroblastoma cells and primary cultured rat neurons. We found that direct application of different concentrations of NaHS (10⁻⁵-10⁻³ M), a donor for H₂S, had no significant effect on [Ca²⁺]_i in these cells. However, inhibition of H₂S generating enzyme, cystathionine β-synthase (CBS), with aminooxyacetate (AOAA) significantly decreased [Ca²⁺]_i, suggesting that endogenous H₂S plays an important role in regulation of neuronal function. To examine whether stimulation of neuroreceptors with different neurotransmitters could alter the action of H₂S, we observed the effect of H₂S after pretreatment with GABA, dopamine or 5-hydroxytryptamine (5-HT). It was found that H₂S was able to increase [Ca²⁺]_i 10 min after application of dopamine or GABA, which themselves alone had no effect on [Ca²⁺]_i. NaHS also increased [Ca²⁺]_i after pretreatment with 5-HT, which itself induced a transient [Ca²⁺]_i elevation. Taken together, our findings suggest that H₂S may modulate neuronal activity through interaction with various neurotransmitters. Our results provide direct evidence that H₂S is a new neuromodulator.

P2-012 Effects of reward stimulation during recall of conditioned fear stress on amygdalic dopamine and serotonin levels

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Conditioned fear, which is acquired by experimental animals when a tone (conditioned stimulus; CS) is combined with an electrical foot shock (unconditioned stimulus; US), is regarded as an animal model of anxiety disorders. Difficulty eliminating acquired conditioned fear stress (CFS) has been taken as an explanation for the treatment-resistance of anxiety disorders. We hypothesized that reward stimulation, which is involved in intracranial self-stimulation, changes the memory of conditioned fear. The purpose of this study was to test whether reward stimulation during recall of conditioned fear changes extracellular levels of dopamine and serotonin in the amygdala, using brain microdialysis methods. This study was approved by the Kitasato University School of Medicine Animal Experiments and Ethics Committee. Eight-week old male Sprague Dawley rats were placed in a conditioning chamber, and at the end of a 30 s exposure to a tone (CS), the animals were exposed to 1 s inescapable electrical foot shock (US). Sham group animals were exposed to the tone without the electrical foot shock. On Day 2, the medial forebrain bundle (MFB) - stimulated animals, which were implanted with electrodes in the MFB, were subjected to tones with electrically rewarding brain stimulations. The control group animals received tones only. On day 2, serotonin levels of both the MFB - stimulated and the control group were increased by CFS in comparison with the sham group. In contrast, the control, but not the MFB - stimulated, group showed elevated dopamine. These findings suggested that reward stimulation during recall of conditioned fear suppresses the activation of dopamine neurons but not that of serotonin neurons in the amygdala.

P2-014 Neuropeptides from scorpion venom

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Scorpion venoms are a rich source of bioactive peptides. Accumulated data have demonstrated that scorpion neurotoxins affect the ion permeability of excitable cells by specific interaction with calcium, potassium, sodium, and chloride ion channels. Detailed knowledge about the biological properties of the venom of the Chinese scorpion, *Buthus martensi* Karsch (BmK), has been mainly limited to neurotoxic components present in the venom of this species. BmK has also been used in traditional Chinese medicine to treat epilepsy, anti-hyperalgesic and reversal effects on circulation failure. Our global gene expression analysis on the effect of the low molecular weight proteins (10kDa to 2kDa; BmKII) from this scorpion venom, on human neuroblastoma cells showed that genes involved in neurogenesis, angiogenesis as well as ion channel functions pathways have been modulated. The alpha-toxins from the venom were found to be the main components responsible for the effects. Alpha-toxins have been known to bind to sodium channels to cause prolonged channel inactivation. This study postulates that alpha-toxin may also be exploited to bring about neurogenesis and angiogenesis.

P2-016 Methamphetamine-induced changes of μ-opioid receptors: a candidate of biochemical marker

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Repeated amphetamine administration results in behavioral sensitization that remains during long periods of withdrawal. Perpetuation of behavioral sensitization related to abuse and/or relapse may be associated with stable changes in gene expression. To explore the participated genes, in the present study, we used a newly developed cDNA array system comprising mouse KIAA (mKIAA) cDNA clones. We examined the changes in gene expression levels 24 h or 21 days (long-term withdrawal period) after chronic methamphetamine (MAP; 2 mg/kg, i.p., daily) treatment for 2 weeks. During the long-term withdrawal, mice were daily treated with saline or fluoxetine (20 mg/kg, i.p.). mRNAs were purified from pooled hippocampus or frontal cortex of 20 mice per group. ³²P-labeled DNA probes were synthesized from the mRNAs as templates and hybridized with cDNA array containing approximately 1700 mKIAA clones. MAP-induced changes (more than 30 %) in gene expression were found in hundreds of clones 24 h after chronic MAP administration. After long-term withdrawal, stable changes remained in several clones. In the hippocampus and the frontal cortex, expressions of some genes related to opioid receptors were remarkably changed. Of interest, in the frontal cortex of mice with long-term withdrawal period, μ-opioid receptor gene and protein expressions were markedly low. The decrease in gene expression of μ-opioid receptor was partially suppressed by subchronic fluoxetine treatment. By contrast, in the hippocampus, several gene expressions including μ-opioid receptors were increased after only short-term withdrawal. These results suggest that μ-opioid receptor in the frontal cortex and/or in the hippocampus might be involved in the relapse after long-term withdrawal period.

P2-017 M₅ muscarinic acetylcholine receptors and cerebrovascular abnormalities

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A considerable body of evidence indicates that disturbances in the central muscarinic acetylcholine (ACh) receptor system play a role in several pathophysiological conditions, including Alzheimer's and Parkinson's disease, depression, schizophrenia, and epilepsy. It has been hypothesized that impairments in cerebrovascular function involving, among other mechanisms, vascular muscarinic cholinergic pathways may play a role in the progress of Alzheimer's dementia. The M₅ muscarinic ACh receptor (M₅R) has been shown to play a crucial role in mediating ACh-dependent dilation of cerebral blood vessels. Last year, we reported that M₅R^{-/-} mice displayed cerebrovascular insufficiency due to lack of autoregulation of cerebral blood flow (CBF) and significantly reduced CBF in cortex and hippocampus. Pyramidal neurons from M₅R^{-/-} mice showed an increase in spine loss and dendritic atrophy in cortex and hippocampus. Here we show that male M₅R^{-/-} mice displayed constitutive cerebrovascular constriction in cerebral arteries using magnetic resonance angiography in vivo. Hippocampus-dependent spatial and non-spatial memory was also impaired in male M₅R^{-/-} mice. Our findings suggest that impaired M₅R signaling may play a role in the pathophysiology of cerebrovascular deficits.

P2-019 Selective and high affinity interaction of N, N-diisopropyl-5-methoxytryptamine, Foxy methoxy, with rat serotonin transporter heterologously expressed in COS cells

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N, N-diisopropyl-5-methoxytryptamine (5MeO-DIPT), so called Foxy methoxy, is known as a designer hallucinogenic tryptamine derivative widely used, and has been classified under controlled substance recently. Precise mechanism of its action in the central nervous system is not known yet, and there is no experimental data about the effect on the monoamine neurotransmitter transporters. We aimed to clarify the actions of 5MeO-DIPT on the transporters for dopamine (DAT), norepinephrine (NET) and serotonin (SERT). Each rat transporter was transiently expressed in COS-7 cells, and uptake assay was performed using radio-labeled substrate for each transporter. 5MeO-DIPT specifically inhibited [³H]serotonin uptake by the SERT-expressing cells in a high affinity manner at concentrations similar to those of cocaine. Potency of 5MeO-DIPT in inhibiting DAT and NET was 1-2 order weaker than SERT, and 5MeO-DIPT had no effect on rat GABA transporter, GAT-1, in concentrations up to 1mM. Furthermore, 5MeO-DIPT did not stimulate the reverse transport of preloaded [³H]serotonin through SERT as well as cocaine, while methamphetamine stimulated it. These results suggest that 5MeO-DIPT functions as a selective SERT inhibitor, underlying its serotonergic action and toxicity.

P2-021 Transport of adenosine and uridine in primary cultured rat cortical neurons and astrocytes

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In the brain, the endogenous adenine and uracil nucleotides are an important role in neurotransmission and preservation of genetic information, but the brain lacks the de novo biosynthesis pathway of nucleotide. Therefore, supply of adenosine and uridine, a precursor for the corresponding nucleotide synthesis by salvage pathway, to neurons and astrocytes is physiologically essential. In this study, we examined transport mechanisms of adenosine and uridine in primary cultured rat cortical neurons and astrocytes. Expression of NT isoform was analyzed by reverse transcription-PCR. In the transport assay, the cells were incubated with [³H]nucleoside in appropriate buffer, and then the reaction was terminated by adding excess volume of ice-cold buffer. The mRNAs for ENT1, ENT2 and CNT2 were detected in neurons and astrocytes. [³H]Adenosine and [³H]uridine were time-, temperature- and concentration-dependently taken up into neurons and astrocytes, and the transport activities by neurons were greater than those by astrocytes. The uptakes of [³H]adenosine and [³H]uridine by neurons and astrocytes partially required the Na⁺ (20-30%), and were significantly reduced by almost nucleosides used in this study, irrespective of existence of Na⁺. Nano molar concentrations of nitrobenzylmercaptopyrine riboside (NBMPR) had no or little effect on Na⁺-independent uptakes of [³H]adenosine and [³H]uridine by neurons and astrocytes, although the uptakes were completely inhibited by adding 50-100 μ M NBMPR. Therefore, ENT1, ENT2 and CNT2 are expressed in neurons and astrocytes, and transports of adenosine and uridine in the cells is predominantly contributed to ENT2. These findings may provide a new insight as to the development of therapies for neurodegenerative disorders.

P2-018 Critical role of R155 in the second intracellular loop in melanin-concentrating hormone receptor

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Melanin-concentrating hormone (MCH) receptor 1 (MCH1R) is a class A G protein-coupled receptor (GPCR). The MCH system has been linked to a variety of physiological functions, especially for the regulation of feeding and energy metabolism. We recently reported the importance of a dibasic motif in the membrane-proximal C-terminal region for MCH1R function. Here, we reveal that an Arg residue in intracellular loop 2 of MCH1R plays a critical role in receptor function. We analyzed the roles of two distinct motifs, BBXXB and BXBB (where B is a basic residue and X is a nonbasic residue), located in the three intracellular loops of MCH1R. Triple-substitution mutants of intracellular loops 1 and 3 could still activate calcium mobilization, while mutations in intracellular loop 2 led to a complete loss of induction of signal transduction without changing the high-affinity K_d value. By analyzing a series of single-point mutants, a mutation of Arg155 in intracellular loop 2 was found to be responsible for the signaling mediated by MCH. A sequence alignment search revealed that the Arg in MCH1R was evolutionally conserved from mammals to zebrafish. We further discuss the significance of the positions corresponding to Arg155 in some other GPCRs and interpret a possible explanation for the role of Arg155 by accessible surface area analysis and generating a theoretical three-dimensional structure of the rat MCH1R using homology modeling.

P2-020 Dopamine D₂-like receptor-mediated [³⁵S]GTP γ S binding in rat striatal membranes: Effects of dopaminergic antagonists

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Functional coupling between some receptors and G proteins is detectable by agonist-induced [³⁵S]GTP γ S binding in mammalian brain membranes, in particular when it is derived from G_{i/o} subtype. We have reported that dopamine stimulates [³⁵S]GTP γ S binding in rat striatal membranes and this effect is mimicked by several dopamine D₂-like receptor agonists, but not by D₁-like agonists, indicating the involvement of dopamine D₂-like receptor subtypes. In the present study, the effects of several dopamine receptor antagonists on dopamine-stimulated [³⁵S]GTP γ S binding in rat striatal membranes were investigated. The increase in specific [³⁵S]GTP γ S binding induced by 30 μ M dopamine was potently inhibited by (+)-butaclamol, but not by (-)-butaclamol, indicative of the stereospecificity. Dopamine-stimulated [³⁵S]GTP γ S binding was also inhibited potently by the dopamine D₂-like receptor antagonists such as domperidone, haloperidol, and S(-)-sulpiride, but not by the selective dopamine D₁-like receptor antagonist R(+)-SCH23390. Interestingly, dopamine-stimulated [³⁵S]GTP γ S binding was inhibited by S(-)-raclopride in a biphasic manner. The high-affinity site of 60-70 % was displaced by nanomolar concentrations of S(-)-raclopride, whereas remaining 30-40 % of the binding was displaceable only at micromolar range. Spiperone inhibited the binding also in a biphasic manner. These results indicate that dopamine-stimulated [³⁵S]GTP γ S binding in rat striatal membranes is mediated mainly through dopamine D₂-like receptors, but also through some unknown receptors other than dopamine D₂-like receptors, to which S(-)-raclopride and spiperone show low affinity.

P2-022 Cell-based assay systems for high-throughput screening of drug candidates acting on human G protein coupled receptors (GPCRs)

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We have recently developed an efficient animal cell expression system that confers position-independent expression of the recombinant genes (J. Biotechnol. 107, 95-105.), and applied this system for developing the cell-based assay systems for high-throughput screening of drug candidates acting on human GPCRs. Two well-known GPCRs, the human dopamine D₂ receptor and muscarinic acetylcholine receptor type 2, were chosen to demonstrate the expression system is suitable for expression of GPCRs. The stable CHO (Chinese hamster ovary) cell line expressing the human dopamine D₂ receptor or muscarinic acetylcholine receptor type 2 was developed after the selection with increasing concentrations of methotrexate. We characterized the cell lines developed for ligand-binding affinity and receptor-mediated inhibition of adenyl cyclase. In case of human dopamine D₂ receptor-expressing CHO cell line, the saturation analysis of receptors' binding to dopamine revealed that K_d and B_{max} values are about 0.45 $\pm$ 0.13 nM and 1.42 $\pm$ 0.13 pmol/mg protein, respectively. The cell lines showed the proper response to dopamine by decreasing the cytoplasmic cAMP level (EC₅₀: 0.85 $\pm$ 0.025 nM). In case of human muscarinic acetylcholine receptor type 2-expressing CHO cell line, the saturation analysis of receptor binding to acetylcholine, revealed that K_d and B_{max} values are about 0.50 $\pm$ 0.12 nM and 1.61 $\pm$ 0.13 pmol/mg protein, respectively. The cell lines showed the proper response to acetylcholine by decreasing the cytoplasmic cAMP levels (EC₅₀: 0.92 $\pm$ 0.021 nM). Our data suggest that the two GPCR proteins expressed are functional in CHO cells. [Supported by the BK21 research grants from Korean Ministry of Education & Human Resources Development]

P2-023 Identification of functional P2 receptor subtypes expressed in three human cell lines with a Cytosensor Microphysiometer

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The extrusion of protons is considered to be a general parameter of the activation of many kinds of membrane or intracellular molecules, such as receptors, ion channels and enzymes. A Cytosensor Microphysiometer is a device that measures changes in the extracellular acidification rate. Classification of P2 receptors expressed in various mammalian cells has been performed by the differences of Ca²⁺ signaling caused by ATP analogues among P2 receptor subtypes. In the present study, we attempted to identify P2 receptor subtypes expressed in three human cell lines, HEK293 cells, glioma cells and NT-2 cells by the differences in proton signaling among P2 receptor subtypes using the Cytosensor Microphysiometer. In HEK293 cells, ATP caused rapid extracellular acidification followed by slow extracellular alkalization. Only extracellular acidification was observed in human glioma cells. Based on the selectivity for various P2 receptor agonists, rapid extracellular acidification appears to be involved in P2Y1 and P2Y2 receptor subtypes in HEK293 cells. It is likely that an additional P2 receptor subtype, which is involved in extracellular alkalization, expresses functionally in HEK293 cells. We now examine whether P2 receptors in human NT-2 cells may cause extracellular alkalization.

P2-025 Increase of SNARE-binding affinity of synaphin/complexin by phosphorylation

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It is now established that SNARE proteins (syntaxin, SNAP-25 and VAMP) mediate synaptic vesicle exocytosis. Four-helix bundle structure consisting of these three proteins is assumed to be critical for synaptic vesicle fusion with the presynaptic membrane. The cytosolic protein synaphin/complexin preferentially binds to the ternary complex of the above SNARE proteins and facilitates synaptic vesicle exocytosis. Its importance in neurotransmitter release was clearly demonstrated by phenotype of knockout mouse, and block of release by a partial sequence peptide injected into the nerve terminal. However, its mechanism of action remains unsolved. In this study, we have examined the effects of phosphorylation of the protein on its interactions with the SNARE complexes. Synaphin contains one potential site (Ser-115) for phosphorylation by casein kinase II (CKII). This residue is not involved in SNARE binding, because a mutant protein in which this residue was replaced by alanine (S115A) exhibited SNARE binding similar to that of the wild type protein. Wild type synaphin was phosphorylated by CKII in vitro, and incubated with the Triton X-100 extract of rat brain membranes. Bound SNARE proteins were detected by immunoblotting. Phosphorylated synaphin showed significantly increased affinity toward SNAREs compared with non-phosphorylated synaphin. S115A-synaphin treated with CKII did not show any increase in SNARE binding affinity, suggesting that phosphorylation of Ser-115 is important for the observed increase of SNARE binding affinity. These findings raise a possibility that synaphin phosphorylation by CKII may regulate its activity in vivo.

P2-027 Kspot, a novel ubiquitin ligase, may control synapse formation

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Ubiquitin-Proteasome system (UPS) of protein degradation has a crucial role in regulating synaptic structure and function. By controlling the stability, activity and localization of target proteins, this versatile regulatory system can shape the pattern, activity and plasticity of synaptic connections. Recently many neurodegenerative disorders have been thought to be caused by accumulation of harmful proteins in the CNS because of malfunction of UPS. We identified a novel ubiquitin ligase (E3), Kspot as a target molecule of high titer autoantibody produced in a serum of a patient with stomach cancer, associated with psychiatric symptoms including severe depression, involution and amnesia. Kspot is strongly and exclusively expressed in the mammalian nervous system and is highly conserved throughout species. In this study we demonstrated that Kspot interacts with Skp1 and Cul1 as E3 and mediated ubiquitination of cellular proteins. Moreover we have identified Kspot binding proteins by biochemical purification. More recently Kspot homologue, FSN-1, was reported to control presynaptic differentiation in *C. elegans*. We predict that Kspot may have a similar function as that of FSN-1 and the analysis of Kspot function may also explain the pathophysiology of certain type of psychiatric disorders associated with malignancy.

P2-024 Downregulation of drebrin-A expression suppresses morphological maturation of dendritic spines and synaptic targeting of NMDA receptors in developing hippocampal neurons

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Drebrin is a major F-actin binding protein in the brain. We have recently demonstrated that synaptic clustering of drebrin governs synaptic targeting of PSD-95. In the present study, we examined whether inhibition of drebrin clustering alters morphological maturation of spines and synaptic targeting of NMDA receptors (NMDAR) in cultured hippocampal neurons. Upregulation of drebrin A (neuron specific isoform) occurs after 7 days in vitro (DIV). Suppression of the drebrin A-upregulation by antisense treatment from 12 DIV to 14 DIV inhibited not only synaptic clustering of drebrin but also the morphological maturation and maintenance of dendritic spines. The spine width in antisense-treated neurons was significantly less than that in control neurons, although the spine length was not different. The antisense treatment decreased spine density to 50% of control. Immunocytochemistry showed that suppression of drebrin A-upregulation attenuated synaptic clustering of NR1. In middle density cultures under the conditions of spontaneous activity, antisense-treated neurons had smaller number of NR1 clusters than control neurons (about 75% of control). In low density cultures, synaptic clustering of NR1 was much enhanced under the conditions of activity blockade by NMDAR antagonist APV. Notably, in this condition, the antisense treatment strongly inhibited synaptic clustering of NR1 (about 40% of control). These results indicated that drebrin clustering play a pivotal role in activity-dependent synaptic trafficking of NMDAR. Further, it is known that activity-dependent synaptic localization of NMDAR depends on their subunit composition. Therefore, it is interesting to examine whether synaptic clustering of drebrin regulates synaptic targeting of NMDAR in a subunit-specific manner.

P2-026 Gene transfer methods for neurons in organotypic hippocampal slice culture

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Experimental studies of neuronal genes are contingent upon the ability to transfect neurons with DNA constructs designed to probe their function. Although electroporation is an established method for transferring macromolecules into both prokaryotic and eukaryotic cells, its application to neurons in intact tissues has been relatively limited. We improved the gene transfer system into neurons in organotypic slice cultures by using a transfection reagent for electroporation. Plasmids were dissolved in Tris-EDTA (TE) or a transfection reagent (TR). A pair of electrodes was held in place by a frame across the slice, and square pulses were applied by using a pulse generator. After transfection, hippocampal slices were fixed and mounted on a glass slide. GFP expressing neurons were imaged with a laser scanning microscope. EGFP expressing slices allowed clear visualization of the morphologies of neurons by using either TE or TR. Next, we tested whether this electroporation technique is useful for functional analysis of candidate genes. Here, we focused on *arcadin*, a neuronal cell adhesion molecule. The fluorescence of *arcadin*-EGFP was detected in neurons when plasmids were dissolved in TR. We are currently co-expressing YFP and CFP-constructs of neuronal genes in neurons to analyze the assembly of these two molecules by using fluorescence resonance energy transfer (FRET). This method will allow the characterization of gene function in neurons and development of therapeutic constructs in the future.

P2-028 Involvement of Rho/Rhotekin pathway in the development of neural polarity

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The mutations of the genes involved in Rho GTPase regulation and signaling have been found in patients suffering from various neuropsychiatric disorders. Rhotekin has been identified as an effector of small GTPase Rho but its function is almost unknown. To clarify the physiological function of Rhotekin, we performed yeast two-hybrid screen of human heart cDNA library with Rhotekin as bait and identified PIST (PDZ domain protein interacting specifically with TC10) as a binding partner. The interaction of Rhotekin with PIST was confirmed by co-sedimentation and immunoprecipitation assays. The binding was inhibited by activated versions of Rho proteins. The C-terminal SPV motif of Rhotekin exhibited binding to the PDZ domain of PIST. Based on the western blot analyses with a specific antibody, PIST was most likely to consist of at least three splicing variants, of which expression levels were different in rat brain of various developmental stages. Immunofluorescence analyses revealed the partial co-localization of PIST and Rhotekin at synapse of rat primary hippocampal neuron. Since there are some structural similarities between synaptic junction of neuron and adherens junction of epithelial cell, we also determined the distribution of Rhotekin and PIST in an epithelial cell line, Madine Darby Canine Kidney (MDCK) cells. Rhotekin and PIST were found at the Golgi-apparatus in growing fibroblast-like MDCK cells while they were observed at regions of cell-cell contact in fully polarized cells. Moreover, PIST and Rhotekin were recruited to the cell-cell contact sites upon initiation of calcium-dependent cell-cell adhesion. These results suggest that Rhotekin and PIST may play roles in the development and/or maintenance of neural and epithelial polarity.

P2-029 Identification and characterization of β CaM kinase II promoter binding protein

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Although Ca²⁺/calmodulin-dependent protein kinase II (CaM kinase II) is an ubiquitous multifunctional Ser/Thr kinase, it is of particular importance in the central nervous system (CNS). While little is known about their unique physiological roles or substrate specificity, several studies have described discrete expression patterns for each of the CaM kinase II isoforms. The gene for the α and β isoforms is expressed almost exclusively in the nervous system. Previously, we analyzed the promoter activity of the α and β gene using neuroblastomas, as well as non-neuronal cell lines, and neuronal cell type-specific promoter activity was found in the 5'-upstream region. In the present study, to understand the neuronal cell type-specific expression of CaM kinase II, we investigated binding proteins that specifically activated the promoter of β CaM kinase II gene. The protein that bound the promoter sequence was found in rat brain nuclear extract by electrophoretic mobility shift assay. Then, we purified the promoter binding protein using DEAE-cellulose, ammonium sulfate fractionation, gel filtration, and polyacrylamide gel electrophoresis. The binding protein has molecular mass of about 150 kDa. To investigate the effect of the binding protein on the promoter activity, the cDNA was prepared by RT-PCR from poly(A)⁺RNA of cerebellum. The cDNA was expressed with a luciferase reporter gene containing a neuronal cell type-specific promoter of β CaM kinase II in neuronal cells. The promoter activity of β CaM kinase II was enhanced in neuronal cells by the binding protein. These results indicated that the binding protein was one of the proteins regulating promoter activity of β CaM kinase II.

P2-031 Leucine enhances p70S6K signals in cortical neurons

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Recent studies strongly suggest that several biochemical signaling cascades couple neurotransmitter and neurotrophin receptors to translational regulatory factors in protein synthesis-dependent forms of synaptic plasticity and memory. We have reported that brain-derived neurotrophic factor enhanced the translation machinery in a mammalian target of rapamycin (mTOR)-dependent manner. We examine the another molecules which stimulate neuronal translation. In proliferating cells, the branched-chain amino acids (BCAAs) have the unique ability to initiate signal transduction pathways that modulate protein synthesis through the activation of the translation initiation. Thus, the biochemical action of BCAAs on translational machinery was investigated in CNS neurons. Among the amino acids tested, leucine showed the most potent effect. The addition of leucine induced phosphorylation of p70S6K together with the increase of its kinase activity in cortical neurons. Leucine also induced the phosphorylation of ribosomal protein S6, a substrate of p70S6K. These processes were all inhibited by the treatment with rapamycin, a specific inhibitor of mTOR. Therefore, leucine regulates p70S6K activity in a mTOR-dependent manner and possibly controls basal translation in neurons.

P2-033 The signal cascade stimulated by the neural activity-regulated adhesion molecule Arcadlin

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Arcadlin is rapidly and transiently induced in hippocampal neurons by synaptic activity. The extracellular (EC) domain of Arcadlin consists of six cadherin repeats, and its cytoplasmic region interacts with TAO2 kinase that is the most upstream kinase of p38 MAP kinase signaling pathway. We previously reported the homophilic interaction between EC domains of Arcadlin induced p38 MAPK phosphorylation and an internalization of Arcadlin protein in HEK293T cells.

In this study, we tried to clarify the target protein phosphorylated by p38 MAPK. As we observed an activated p38 MAPK was distributed close to the plasma membrane, we assumed that p38 MAPK might phosphorylate TAO2 kinase, which then induces Arcadlin internalization. We found that GST-TAO2 fusion protein was phosphorylated by an immunoprecipitated p38 MAPK in vitro. We further determined one of the amino acids phosphorylated by p38 MAPK was in the C-terminal region of TAO2. Then, we changed this serine residue to alanine, and expressed the mutated TAO2 and arcadlin in HEK293T cells. An addition of Arcadlin EC domain protein induced a phosphorylation of p38 MAPK, but not an endocytosis of Arcadlin in mutant TAO2-expressing cells. These results suggest that a homophilic interaction between Arcadlin ECs induces an activation of p38 MAPK, which in turn phosphorylates the C-terminal region of TAO2, resulting in an endocytosis of Arcadlin and TAO2. We are currently studying the effect of this mutation on the functional interaction between Arcadlin and TAO2 using fluorescence resonance energy transfer (FRET).

P2-030 Phosphorylation of synapsin I by Ca²⁺/calmodulin-dependent protein kinase II in hypothalamic GT1-7 neurons

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There is substantial evidence that Ca²⁺/calmodulin-dependent protein kinase II (CaM kinase II) is involved in glutamate release from neurons via phosphorylation of synapsin I. However, it is not clear at present whether or not CaM kinase II is involved in release of neuropeptides in brain. Gonadotropin-releasing hormone (GnRH) is released from hypothalamic neurons to stimulate pituitary gonadotropin secretion and to exert autocrine effects on the GnRH release. In the present study, we identified CaM kinase II and synapsin I in hypothalamic GnRH-releasing neurons (GT1-7 cells). Immunoblot analysis indicated that CaM kinase II and synapsin I were expressed in the cells and that a major isoform of CaM kinase II was δ 2. Treatment of the cells with GnRH increased phosphorylation of synapsin I at serines 566 and 603, which are major *in vitro* phosphorylation sites by CaM kinase II. The phosphorylation of synapsin I was increased in the cells which were stably transfected with CaM kinase II cDNA. Immunostaining of the cells indicated that CaM kinase II and synapsin I were localized in neuronal soma but not in neurites. These results may suggest that phosphorylation of synapsin I by CaM kinase II is involved in GnRH-induced GnRH release in hypothalamic neurons.

P2-032 Activation of latent cyclin-dependent kinase 5 (Cdk5)-p35 complexes by membrane dissociation

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Cyclin-dependent kinase 5 (Cdk5) is a Ser/Thr kinase of increasingly recognized importance in a large number of fields, ranging from neuronal migration to synaptic plasticity and neurodegeneration. However, little is known about its mechanism of activation beyond its requirement for binding to p35 or p39. We have examined membrane interactions as one method of regulating the Cdk5-p35 complex. The kinase activity of Cdk5-p35 is low when it is bound to membranes. The Cdk5-p35 found in rat brain extract associates with membranes in two ways. Approximately 75% of complexes associate with membranes via ionic interactions only, and the remaining 25% associate with membranes via ionic interactions together with lipidic interactions. Solubilization with detergent or high-salt solution activates Cdk5-p35 several fold, and this activation is reversible. Therefore, membrane interactions represent a novel mechanism for the regulation of Cdk5-p35 kinase activity.

P2-034 Possible induction of hypoglycemic neuronal death by reduction of phospholipase C- β 1 and - γ 1

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Severe hypoglycemia causes neuronal loss, but the detailed mechanism of hypoglycemic neuronal death remains unclear, though the excessive activation of poly(ADP-ribose)polymerase-1 (PARP-1) is involved in the death. Recently, phospholipase C (PLC)- β 1 and - γ 1 have been reported to protect neurons from oxidative stress, and to play an important role in neuronal survival and death. We also showed that the overstimulation of NMDA receptor results in the reduction of protein level of PLC- β 1 and - γ 1, following neuronal death. In this study, we investigated the mechanism of hypoglycemic neurotoxicity, focusing on PLC- β 1 and - γ 1, using primary cultured rat cortical neurons. Expression level of protein was assessed by western blot analysis and immunofluorescence. Neuronal viability was assessed by MTT method. Glucose deprivation caused significant neuronal death in a time-dependent manner, and induced the accumulations of poly(ADP-ribose) (PAR) and nitrotyrosine, a metabolite by PARP-1 and an oxidative stress maker, respectively. The almost of glucose deprivation-induced neuronal death and accumulation of nitrotyrosine were suppressed by MK-801, a NMDA receptor antagonist, confirmed that the stimulation of NMDA receptor was involved. However, 3-aminobenzamide, an inhibitor of PARP-1, had no effect on the accumulation of nitrotyrosine, although the inhibitor prevented the increase of PAR. Furthermore, the reduction of expression level of PLC- β 1 and - γ 1 by glucose deprivation was observed in neurons. Thus, it was indicated that glucose deprivation caused the enhancement of vulnerability against oxidative stress through the reductions of PLC- β 1 and - γ 1, in addition to excessive activation of PARP-1.

P2-035 Characterization of the dimerization mechanism of ROCKII

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The small GTPase RhoA is intracellular signaling molecule that regulates the rearrangement of cytoskeleton. One of the most important downstream targets of activated RhoA is the Rho-associated coiled-coil-containing protein kinase (ROCK), which is known to the existence of isoforms, ROCKI and ROCKII. ROCKI is ubiquitously expressed except in the brain and muscle, whereas ROCKII is expressed in the brain. This indicates the importance of the Rho/ROCKII signaling pathway in the central nervous system. ROCK consists of N-terminal catalytic domain, coiled-coil region that contain the Rho binding motif, and pleckstrin homology (PH) domain. The C-terminal region negatively regulates its kinase activity, and GTP-bound Rho interaction between Rho binding domain generally results in disruption of this intramolecular inhibition. Recently it has been demonstrated the ROCKI has oligomerization state that play a crucial role in not the ROCK activity but the substrate binding of ROCK. The amino acid segments from 47-78 and 379-415 are shown to be necessary to maintain the dimeric ROCKI structure. However, the enzymatic properties and regulatory region of ROCKII is not determined. In this study, to examine the regulatory mechanism of ROCKII, recombinant ROCKII was expressed and purified with baculovirus/Sf9 system or from E.coli. When treated with the cross-linking reagent, the full length ROCKII migrated as dimer in SDS-PAGE, while the enzyme from E.coli were monomer. And the latter exhibited much less activity than the former. Furthermore to define the necessary segments or the amino acids of maintaining the dimeric structure of ROCKII, the various truncated ROCKII mutants were expressed with baculovirus/Sf9 system. The dimer formations and activities of the mutants were analyzed.

P2-037 Structural Insights into Eph/ephrinB-Mediated Reverse Signaling Network

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Signal transduction through receptor tyrosine kinases plays an essential role in the development of multicellular organisms. The Eph receptor tyrosine kinases and their ligand ephrins have been implicated to function at the interface between pattern formation and morphogenesis, a critical step for neural development and vascular morphogenesis. Eph receptors and ephrins transmit signals bidirectionally ("forward" or "reverse"). In other words, the same Eph and ephrin proteins can either send or receive signals, all depending on the developmental context. Recently, Eph/ephrinB-mediated signaling networks have been found to be involved in learning and memory formation, neuronal regeneration, pain processing, and tumorigenesis. In this regard, the cytoplasmic domain of ephrinB plays a pivotal role in initiating reverse signaling networks which regulate neuronal and cancer development by interacting with a series of intracellular protein partners. One research focus in my laboratory is to gain structural insight as well as to design mimetic targeting the ephrinB-mediated reverse signaling network by use of NMR spectroscopy and other biochemical & biophysical methods. In the current report we will present: 1) Determination of the NMR structure and dynamics of the functional ephrinB subdomain. 2) Molecular mechanism by which Tyr-phosphorylation abolished the well-packed ephrinB -hairpin structure but initiated the binding of the ephrinB cytoplasmic domain to the Nck2 SH2 domain. 3) Determination of the NMR structure of the Nck2 SH2 domain and insights into the structural basis for the diverse binding with phosphorylated ephrinBs. 4) Possible cross-communication with other signaling network.

P2-039 Differential expression of the GTP cyclohydrolase I gene by two promoters in *Drosophila melanogaster*

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GTP cyclohydrolase I (GTP CHI) is the enzyme which catalyzes the rate-limiting step in the biosynthesis pathway of tetrahydrobiopterin (BH4), which function as a cofactor in the various redox reaction. It has been known that two kinds of differentially spliced transcripts for GTP CHI are produced from two promoters, head-specific promoter and constitutive promoter. We have analyzed the 5'-flanking region of the two promoters for *Drosophila* GTP CHI gene. From the transient transfection experiment, we found the minimal 5'-flanking region of the head-specific promoter and constitutive promoter required for the efficient expression of GTP CHI are located between -96 ~ +31, and -77 ~ +35, respectively. We have also cloned and sequenced the promoter region of GTP CHI gene in *Drosophila virilis*. From the comparison of the promoter sequences of the GTP CHI gene in two species, we find the conserved sequences, which may be important for the GTP CHI gene expression in *Drosophila melanogaster*. The transgenic fly was constructed using the head-specific or constitutive GTP CHI promoter-lacZ fusion plasmid to analyze their differential expression during fly development in vivo. The head-specific promoter is active in the late pupae and adult, while the constitutive promoter is highly active in embry stage. [Supported by the Neurobiology Research Program from the Korean Ministry of Science and Technology]

P2-036 Cdk5/p39 is a labile complex dissociated by detergent with a comparable kinase activity with Cdk5/p35

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Cyclin-dependent kinase 5 (Cdk5) is a Pro-directed Ser/Thr kinase playing important roles in various neuronal activities including neuronal migration during brain development, synaptic activity and neuronal cell death. Cdk5 is activated by association with a neuron-specific activator, p35 or its isoform p39. In contrast to Cdk5/p35, which kinase activity has been studied well, little is known about Cdk5/p39. We investigated the stability and kinase activity of Cdk5p39, comparing to Cdk5-p35. Kinase active Cdk5/p39 was not isolated from rat brain extracts or the extract of HEK293 cell expressing Cdk5 and p39 by immunoprecipitation under conditions where active Cdk5/p35 could be prepared. p39 dissociated from Cdk5 in the presence of detergent, indicated that p39 has a lower binding affinity for Cdk5 than p35. We developed the method for purification of Cdk5/p35 from the extract of Sf9 cells infected with baculovirus encoding Cdk5 and p39. Purified Cdk5/p39 showed the similar substrate specificity to Cdk5/p35 but the opposite sensitivity to detergent. Cdk5/p39 was inactivated by Triton X-100, while Cdk5/p35 was activated. Using an N-terminal-truncation fragment of p35 and p39, whose amino acid sequences are different from each other, we studied a role of the N-terminal domain on the stability of the complexes. However, the N-terminal deletion did not change the stability, as well as substrate specificity, of respective Cdk5s. These results provide a method to study Cdk5/p39 in future and suggest that Cdk5/p39 activity is regulated in neurons by reversible complex formation, different from Cdk5/p35 that is regulated by synthesis and degradation of p35.

P2-038 Role of C-terminus of PKC γ in tissue-specific translocation and regulation

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Protein kinase C (PKC) is a phospholipids dependent serine/threonine protein kinase with 10 isozymes that are divided into three subfamilies based on their sequence homology and sensitivity to activators. They play important roles in various cellular signaling transductions, including the regulation of synaptic plasticity and memory, neurotransmitter release and Pb-induced neuronal toxicity. Despite its ubiquitous expression in various tissues, the central nervous system contains several unique PKCs, particularly the γ -subspecies of PKC (PKC γ) that only present in the central nervous system. We investigated the role of highly variable V5 domain of PKC γ in TPA-mediated translocation. Deletion mutants of PKC γ that have various length of the V5 domain were constructed and their catalytic activity was analyzed. The PKC γ - Δ 680 mutant that has the hydrophobic motif and turn motif intact could not be activated by TPA or protamine sulphate and displayed aberrant membrane translocation pattern when stimulated with TPA. The implication of our findings in the treatment of disorders in the central nervous system will be discussed.

P2-040 Functions of protein phosphorylations in *Drosophila* photoreceptors

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The functions of transient receptor potential (TRP) calcium ion channel, the major plasma membrane calcium channel in *Drosophila* photoreceptor, have been known to be regulated by phosphorylation. A growing body of evidence suggests that there are more than one protein kinase C (PKC) functioning in *Drosophila* visual system. However, inactivation of no afterpotential C (INAC) PKC is the only one so far identified to function in *Drosophila* visual system. We have identified a new PKC functioning in *Drosophila* visual system. We isolated two P-element insertion lines for this gene and found that one of these are homozygous lethal while the other is homozygous viable. The lethal line turned out to have a P-element insertion in exon region and the viable line had P-element insertion in intron region of the gene. Electoretinogram (ERG) analysis of the viable line showed weak TRP mutant phenotype, suggesting that the TRP calcium channel is not functioning properly in this mutant. Northern analysis showed about four times less expression in the mutant than in the wild type. Precise excision of the P-element from this mutant reverts the mutant phenotypes back to wild type. We also knocked out the functions of mitochondria in the photoreceptors for providing the anoxia conditions and found that the flies in anoxia conditions have similar phenotypes to those of the mutants with P-element insertion in PKC gene. Supported by the Neurobiology Research Program from the Korean Ministry of Science and Technology.

P2-041 Involvement of P2X₄ receptor in ATP-induced chemotaxis of microglia

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Extracellular ATP is known to regulate physiological functions of microglia through various types of ATP receptors which consist of ionotropic P2X receptors (P2XRs) and G-protein coupled P2Y receptors (P2YRs). We have previously shown that ATP induced membrane ruffling and chemotaxis of microglia and suggested that these effects were mediated by P2Y₁₂R. We report here that P2X₄R is also involved in ATP-induced chemotaxis of microglia.

To determine whether phosphatidylinositol 3-kinase (PI3K) pathway participates in the regulation of ATP-induced microglial chemotaxis, we examined the effect of PI3K inhibitors, wortmannin and LY294002, on ATP-stimulated microglia using Dunn chemotaxis chamber. PI3K inhibitors prevented the chemotaxis. Phosphorylation of Akt, which is known to be a downstream target of PI3K pathway, was increased by ATP stimulation in a time-dependent manner. The Akt phosphorylation was reduced by chelating extracellular calcium. These results indicate that activation of PI3K pathway is important for ATP-induced microglial chemotaxis and suggest a possibility that ionotropic P2XR may regulate the microglial chemotaxis by affecting PI3K pathway. Therefore, we examined the effect of P2XRs antagonists on ATP-induced microglial chemotaxis. P2X₁-4Rs antagonist TNP-ATP had inhibitory effect, while both P2X₁, 2, 3, 5, 7Rs antagonist PPADS and P2X₇R antagonist BBG had no effect. We constructed expression plasmids of short hairpin RNA specific for P2X₄R gene (shP2X₄) and examined the chemotaxis of microglia transduced with shP2X₄ by using lentivirus system. Suppression of P2X₄R expression reduced the chemotaxis of the microglia. These results strongly suggest that ATP-induced microglial chemotaxis is mediated by P2X₄R in addition to P2Y₁₂R.

P2-043 Roles of Lasp-family protein and Fascin in actin bundle formation and elongation in filopodia at neuronal growth cone

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Neuronal cells extend the growth cones forming lamellipodia and filopodia in response to the external guidance factors. The reorganization of actin cytoskeleton is thought to supply the mechanical forces to extend these protrusions in the same manner as motile cells, but the detailed molecular mechanism is still unclear. We have studied the molecular mechanisms that mediate the transfer of cell signals to the actin cytoskeleton, implicating the roles of WAVES. Next, we aimed to explore the molecular mechanisms of actin bundle formation and its elongation in filopodia. We induced the growth cones in NG108 cell lines and analyzed the molecular mechanisms of actin bundle formation and elongation in filopodia. We found a novel Lasp-family protein, Lasp-1 and Lasp-2(LIM and SH3 protein 1,2) localized to the actin bundle in filopodia similar to fascin. To clarify their roles, these proteins were tagged with fluorescent proteins for live cell observation. After photobleaching the growth cone co-expressing fluorescent proteins tagged with actin and fascin, the fluorescence from actin was recovered from the tips in the filopodium and lamellipodium, on the contrary, that from fascin gradually recovered to the anterograde direction on the same actin filament in bundle. Both Lasp family proteins showed similar behavior to fascin. These results indicate that fascin and Lasp family proteins interact with actin filaments by non-covalent bond and would stabilize them on the process of elongation, following the actin filament polymerization initiated by the tip complex.

P2-045 Search for the proteins which interact with N-terminal 126 amino acids of MAP1B: The new site of tubulin interaction

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Previously we reported overexpression of MAP1B containing N-terminal 126 amino acids promoted neuronal death. To reveal the mechanism of MAP1B N-terminal induced neuronal death, we searched for the proteins that interact with N-terminal of MAP1B by two-hybrid system. Alpha-tubulin was found to interact with MAP1B N-terminal and their *in vitro* interaction was proved with pull-down assay. The interaction of tubulin and MAP1B N-terminal has not yet been reported. β -tubulin was also found to interact with MAP1B N-terminal, but interaction of β III tubulin and MAP1B N-terminal was very weak. To investigate the effect of MAP1B containing N-terminal and lacking N-terminal, they were transfected in COS7 cells. There were much proportion of round formed cells in N-terminal containing MAP1B transfected than in N-terminal lacking MAP1B transfected. There might be some interference in interaction between MAP1B and tubulin in cells express more MAP1B containing N-terminal.

P2-042 ER membrane binding domain of kinectin

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Background: Kinectin had been found as kinesin binding protein on endoplasmic reticulum (ER). Membrane insertion portion was identified in the end of N-terminus but specific localization domain was obscure and was thought to require the half of the molecule. We reported that initial 40 amino acid of kinectin is enough for distributing on ER in this meeting of the last year. **Methods:** We newly cloned a full length kinectin from human brain. Truncated constructs of N-terminus region were made connecting with green fluorescence protein (GFP) to visualize in Cos7 cells. **Results:** 7-31 amino acids (7-31kinectin-GFP) were enough for localize on ER in reticular pattern, whereas 7-25kinectin-GFP, 1-25 kinectin-GFP distributed evenly in the cytoplasm. The reticular pattern was identical with ER marker but vague with Golgi marker (Clontech). Inversion of the direction of 7-31kinectin-GFP was attempted by the change of GFP from N type to C type, resulted in that most of 7-31kinectin-GFP did not distribute on ER with some exception. **Conclusion:** Membrane binding of kinectin requires amino acid number 7-31 to localize on ER in the proper direction.

P2-044 Different contribution of N-shc and Sck adaptor proteins to reorganization of actin cytoskeleton

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Shc is an adaptor protein which plays key roles in phosphotyrosine signal transduction pathways. N-Shc/ShcC and Sck/ShcB, both of which are mainly expressed in nervous system, are recently discovered homologues of Shc protein. Although their different tissue expression profiles were impressive, specific features of adaptor functions of two closely-related Shc homologues remain largely unknown. Shc appears to contribute to integrin MAPK activation and to organize cytoskeletal rearrangement in response to extracellular matrix. In this study, we examined functional differences among Shc family members as regulator/modulators of cytoskeleton of N-shc/Sck-transfected NG108-15 cells and human Mesenchymal Stem Cells (hMSCs). Electron-microscopic analysis and phalloidin staining showed the different morphological changes of actin cytoskeleton of both cultured cells. Especially in NG108-15 cells, Sck enhanced lamellipodium formation with filopodia with statistical significance compared with enhancement by Shc or N-shc. Next, we established and show the characterization of mesenchymal stem cells derived from the mice lacking either SCK or N-shc.

P2-046 Molecular and functional characterization of a Na⁺-independent choline transporter in rat astrocytes

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In this study, we examined the molecular and functional characterization of choline uptake into cultured rat cortical astrocytes. Choline uptake into astrocytes showed little dependence on extracellular Na⁺. Na⁺-independent choline uptake was saturable, and mediated by a single transport system with an apparent Michaelis-Menten constant of 35.7 μ M and a maximal velocity of 49.1 pmol/mg protein/min. Choline uptake was significantly decreased by acidification of the extracellular medium and by membrane depolarization. Na⁺-independent choline uptake was inhibited by unlabeled choline, acetylcholine and the choline analogue hemicholinium-3. The prototypical organic cation TEA and other n-tetraalkylammonium compound such as TBA and THA inhibited Na⁺-independent choline uptake. Various organic cations also interacted with the Na⁺-independent choline transport system. Corticosterone and 17 β -estradiol, known inhibitors of organic cation transporter 3 (OCT3), did not cause any significant inhibition. RT-PCR demonstrated that astrocytes expressed low levels of OCT1, OCT2 and OCT3 mRNA, but the functional characteristics of choline uptake are very different from the known properties of these OCTs. The high-affinity Na⁺-dependent choline transporter CHT1 is not expressed in astrocytes as evidenced by RT-PCR. Furthermore, mRNA for choline transporter-like protein 1 (CTL1) and its splice variants CTL1a and CTL1b was expressed in rat astrocytes, and the inhibition of CTL1 expression by RNA interference completely inhibited Na⁺-independent choline uptake. We conclude that rat astrocytes express an intermediate-affinity Na⁺-independent choline transport system. This system seems to occur through a CTL1 and is responsible for the uptake of choline and organic cations in these cells.

P2-047 Neuronal expressions and molecular properties of brain acyl-CoA hydrolase isoforms

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Acyl-CoAs are not only primary substrates for fatty acid degradation and lipid synthesis, but also proposed to affect various cellular mechanisms and functions, including ion fluxes, membrane trafficking, and gene expression. Long-chain acyl-CoAs were also reported to play a role in synaptic vesicle formation and long-term potentiation in the hippocampus. Thus, any factors affecting the acyl-CoAs levels would impact cellular functions. A brain long-chain acyl-CoA hydrolase (BACH) is widely distributed in the brain and mainly responsible for catalytic activity in the tissue. Here we report the expressions and molecular properties of two BACH isoforms, 43- and 50-kDa BACHs, in the mouse brain. Primer extension analysis showed that the 43- and 50-kDa BACHs are generated from distinct mRNA transcribed by alternative use of transcription start sites on the BACH gene. The molecular properties of 43- and 50-kDa BACHs were almost the same in palmitoyl-CoA hydrolyzing activity, protein stability, and cellular distribution into cytosol. The level of 43-kDa BACH expression in the mouse brain during development was higher than that of 50-kDa BACH, suggesting that 43-kDa BACH is a major BACH species in the mouse brain. Immunoblotting showed that the change in 43-kDa BACH expression during brain development corresponded to that of the palmitoyl-CoA hydrolyzing activity and microtubule-associated protein 2 (MAP2) expression. In addition, immunohistochemistry showed that cells expressing BACHs almost coincided with cells committed to the neuronal lineage, which expressed MAP2, but not nestin. Therefore, BACHs, particularly 43-kDa BACH, may play some roles associated with neuronal mechanisms and functions regulated by intracellular acyl-CoAs.

P2-049 Serotonin-induced excitotoxicity in rat motoneurons

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Amotrophic lateral sclerosis (ALS) is a progressive, fatal disease caused by selective degeneration of motoneurons. The pathogenesis of ALS has not been fully clarified but an involvement of glutamate excitotoxicity and oxidation/nitration-mediated damage has been suggested. The development of the drugs that prevent these toxic mechanisms has not been so far succeeded. Riluzole, titled as a glutamate release inhibitor, is the only drug approved for ALS. However, its effect is quite marginal. Serotonin (5HT) neurons and glutamate neurons are physiologically known excitatory input for spinal motoneurons, but little is known about the involvement of 5HT in the pathogenesis of ALS. Therefore, we tested the 5HT excitotoxicity using the pure culture of rat motoneurons. The toxicities were evaluated by the survival rate after 3 days in culture. 5HT showed toxicity dose-dependently with the EC₅₀ of 50 μ M. The toxicity was comparable to that of glutamate or even more. Both a 5-HT_{1A} selective antagonist NAN-190 and a 5-HT_{2A} selective antagonist MDL-11939 could block the toxicity of 5HT, suggesting the both receptors are involved in the toxicity. These findings suggest that serotonin might be involved in the pathogenesis of ALS, and 5-HT_{1A} antagonists or 5-HT_{2A} antagonists may be useful for the treatment of ALS.

P2-051 Regulation of neuronal differentiation by NMDA signals in neural progenitor cells in vitro

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In this study, we have evaluated the regulation of proliferation and differentiation through activation of N-methyl-D-aspartate (NMDA) receptors in neural progenitor cells prepared from neocortex of 18-day-old embryonic rats. After cerebral cortex being treated with enzyme solution for 1 h, cells were collected from lower layer obtained in 45% percoll density gradient centrifugation, and subsequently cultured in DMEM/F12 medium containing bFGF for 12 days in vitro (DIV) with a half-medium change every 2 days. In vitro culture of progenitor cells resulted in the formation of round spheres with immunoreactive to nestin, but not that to MAP-2 and GFAP, within 12 DIV in the presence of bFGF. Removal of bFGF induced marked expression of both MAP-2 and GFAP in the cells cultured on 18 DIV. An RT-PCR analysis revealed constitutive expression of glutamate receptor subunits in progenitor cells cultured for 0 and 12 DIV. On fluorescence image analysis for determination of intracellular free Ca²⁺ ions, a brief exposure to NMDA markedly increased the fluorescence intensity in neurospheres cultured for 2 to 6 DIV, but not in those cultured for 8 to 12 DIV. A similarly potent increase was seen in the fluorescence intensity after brief exposure to NMDA in the cells differentiated by removal of bFGF. The increase by NMDA was invariably prevented by MK-801. Moreover, sustained exposure (10 days from 2 to 12 DIV) to NMDA led to not only profound inhibition of the formation of neurospheres on 12 DIV, but also to facilitation of differentiation of neurospheres in the absence of bFGF. These results suggest that NMDA signals may play crucial roles for commitment of neural progenitor cells to neurons.

P2-048 Effects of activation by LPS on glutamine transporter expressed in cultured cortical astrocytes

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In the mammalian central nervous system, the excitatory amino acid neurotransmitter glutamate is supposed to be recycled through the glutamine (Gln)/glutamate cycle that involves different transporters including excitatory amino acid transporters, vesicular glutamate transporters and Gln transporter (GlnT) belonging to the system A transporter family. In addition to this prevailing scheme, we have previously shown possible functional expression of GlnT by cultured rat neocortical astrocytes. In this study, we have attempted to elucidate effects of activation by lipopolysaccharide (LPS), which is one of bacterial endotoxins often used for stimulation of microglia as well as astrocytes, on GlnT expressed in cultured neocortical astrocytes. Cultured astrocytes from neocortex were exposed to LPS at different concentrations from 0.001 to 10 μ g/mL for 24 h. The exposure to LPS significantly induced NO₂ accumulation in culture medium in a concentration-dependent manner when determined by the fluorescent assay using a DAN reagent. Semi-quantitative RT-PCR analysis revealed that the exposure to LPS at 10 μ g/mL for 24 h significantly decreased the expression of mRNA for GlnT but not for the other system A transporter ATA2. This decrease was seen in cultured astrocytes exposed to LPS for longer than 12 h but not in cultured neurons from neocortex. Moreover, the exposure to LPS significantly decreased the expression of GlnT mRNA with a concomitant decrease in the accumulation of [³H]Gln in a concentration-dependent manner at a concentration range of higher than 1 μ g/mL, without affecting cell viability, in cultured astrocytes. These results suggest that activation by LPS may negatively modulate the expression and function of GlnT in cultured neocortical astrocytes.

P2-050 NMDA-induced MCP-1 production is mediated by the activation of ERK and JNK MAP kinases and PI3 kinase in the organotypic cortico-striatal slice culture

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Monocyte chemoattractant protein-1 (MCP-1, CCL2) is a well-defined CC chemokine implicated in the pathophysiology of various brain injuries such as cerebral ischemia, multiple sclerosis and AIDS dementia. Using organotypic cortico-striatal slice cultures, we previously demonstrated that NMDA- or ATP γ S-treatment induced MCP-1 production mainly in astrocytes, and that ERK and JNK positively regulated ATP γ S-induced MCP-1 production, while p38 MAP kinase suppresses it. In this study, we investigated the effects of various protein kinase inhibitors on NMDA-induced MCP-1 production in cortico-striatal slice cultures. Slice cultures were prepared from postnatal day 2-3 Wistar rats and cultured for 10-11 days. First, we checked the effects of various kinase inhibitors on NMDA-evoked cell injury using propidium iodide fluorescent dye. All of the kinase inhibitors used in this study had no effects on the cell injury. Next, the effects of the kinase inhibitors on NMDA-induced MCP-1 production were examined using ELISA. MEK inhibitor PD98059 and JNK inhibitor SP600125 significantly suppressed MCP-1 production induced by NMDA as in the case of the induction by ATP γ S. In addition, PI3 kinase inhibitor LY294002 also inhibited NMDA-induced MCP-1 production. These results indicate that NMDA-induced MCP-1 production is mediated by the activation of ERK and JNK MAP kinases and PI3 kinase.

P2-052 BK-induced migration of microglia

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Bradykinin (BK) is produced and acts at the site of injury and inflammation not only in periphery but also in the brain. Previously, we reported that BK receptor mRNAs were expressed in microglia and BK induced Ca²⁺-dependent K⁺ currents. However, their cellular function was not much known yet and also the distinction of B₁ and B₂ receptors was not elucidated. In the present study, we tested whether BK induces migration of microglia, because migration of microglia towards damaged tissue plays an important role in regeneration under pathological condition in the central nervous system. Furthermore, we investigated which type of BK receptor was involved and the mechanism of BK-induced migration was compared to that induced by ATP. Microglial cells were isolated from the mixed cultures of cerebrocortical cells from postnatal day 3 Wistar rats. Migration of microglia was monitored with time lapse video microscopy. Images were acquired in 1-min intervals for 1 hour and stored on a computer and analyzed. In the presence of 300nM BK, the total distance of microglial migration for 1 hours was increased 2-fold. Charybdotoxin (CTX, 0.1 μ M), a blocker of large conductance Ca²⁺-activated K⁺ channels, completely inhibited BK-induced microglial migration. Similarly, BK-induced migration was markedly inhibited by B₁ antagonist. However, B₂ antagonist did not affect the BK-induced migration. BK-induced migration of microglia was not affected by pretreatment with pertussis toxin (PTX) for 12 hr, while ATP-induced migration was significantly inhibited by PTX. These results suggest that activation of large conductance Ca²⁺-activated K⁺ channel was essential for BK-induced migration of microglia and B₁ but not B₂ receptor was involved in the BK-induced migration of microglia.

P2-053 Regulation of mitochondrial gene expression by glutamate signals in cultured cortical neurons of mice

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Glutamate receptor activation is well known to cause an increase in intracellular Ca^{2+} and mitochondrial depolarization. Mitochondrial injury is induced by a decline in the mitochondrial RNA transcripts, protein synthesis, and mitochondrial function as well as by mitochondrial DNA damage. In this study, we evaluated effects of glutamate exposure on expression of mitochondrial mRNA (mtRNA) and activity of mitochondrial respiratory chain (MRC) in primary cultured cortical neurons of mice. Cerebral cortex was dissected in 15 days-old fetal mouse to obtain neural cells. Cells were cultured under a medium containing 10% FCS for 6 days, followed by further culture under serum-free medium for 6 days. Cultured cortical neurons (12 DIV) obtained were exposed to glutamate for 15 min at concentrations of 1 to 500 μM . After being washed, cells were incubated for 1, 2, 4, 6, 12 and 24 h, to assess viability, expression of mRNA and activity of MRC. Cell viability was significantly reduced 24 h after glutamate exposure at the concentrations of above 10 μM . Glutamate exposure markedly decreased MRC complex I (rotenone-sensitive NADH dehydrogenase) activity 2 h later, with sustained decrease at least until 24 h. In addition, northern blot analysis revealed that glutamate was effective in inducing a decrease in the level of NADH-ubiquinone oxidoreductase subunits (ND1 and ND6) mRNA 6 h after exposure. These results suggest that glutamate signals negatively regulate mitochondrial gene expression in primary cultured cortical neurons. Glutamate-induced decrease in expression of mitochondrial gene may be involved in sustained mitochondrial dysfunction to induce neuronal death.

P2-055 Roles for p21^{Cip1/WAF1} during oligodendrocyte development

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p21 and p27 are Cip/Kip family members of cell cycle-dependent kinase inhibitors. Both of them have very important functions during the oligodendrocyte differentiation process. It has been reported that they have non-overlapping functions during the differentiation of oligodendrocytes. p27^{-/-} oligodendrocytes cannot withdraw from the cell cycle in an appropriate manner. p21^{-/-} oligodendrocytes can efficiently exit the cell cycle but cannot differentiate properly. Recently it has been also reported that p21 is strongly induced during FGF-induced dedifferentiation phase. It is the interesting point that p21 has some roles both in differentiation and in dedifferentiation phases. We focused on the roles of p21 in developmental process of oligodendrocytes.

P2-057 Increased neurogenesis by lysophosphatidic acid in neurosphere culture system

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Lysophosphatidic acid (LPA) is an intercellular lipid mediator that exerts diverse cellular effects through cell surface LPA receptors (Lpa1 to Lpa4). Expression of Lpa1 in a neuroepithelial cell layer of the embryonic cerebral cortex has suggested that LPA signaling plays an important role in cortical development. Recent studies have revealed that LPA influences neuroepithelial cell morphologies and stimulates final mitosis, possibly leading to malformation of the mouse cerebral cortex. Here we examine the mechanisms by which LPA affects neurogenesis using a neurosphere culture system, widely employed in neurodevelopment studies. Neurospheres were generated by cultivating single cortical cells derived from embryonic day 13 mice for 5 days in the presence of basic fibroblast growth factor, but without fetal calf serum. When LPA was added at 1 μM during culture, a marked reduction in neurosphere diameter and a 50% decrease in total cell number were observed. These effects of LPA were accompanied by increased cell death, but not decreased cell proliferation. When plated on Cell-tak-coated coverslips and cultured for further 4 days, neurosphere-derived single cells differentiated into microtubule-associated protein (MAP) 2-positive neurons (49% of total cells) and myelin basic protein (MBP)-positive oligodendroglia (24% of total cells). On the other hand, LPA-treated neurospheres produced 69% neurons and 12% oligodendroglia. Consistent with these data, oligolineage (platelet-derived growth factor receptor a positive) cell populations were decreased in LPA-treated neurospheres. These findings suggested that LPA enhanced neurogenesis and repressed gliogenesis.

P2-054 The first report: Effect of hippocampal cholinergic neurostimulating peptide precursor protein (HCNP-pp) over-expression in immature PC12 cells

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HCNP-pp is a unique multifunctional protein. It is not only the precursor of HCNP, but also the protein itself interacts with several molecules, such as MAP kinase cascade (Raf-1), GRK-2, serine proteases, phosphatidylethanolamine and ATP, suggesting to involve in the neuronal growth and memory formation. However, roles of function of HCNP-pp in neuronal cells are not fully understood. Previously, we have demonstrated that retroviral vector mediated increased expression of HCNP-pp in the embryonic brain resulted the hippocampal malformation accompanied with neuronal cell loss and decreases in the level of activated Erk. In this experiment, we obtained a stable PC12 cell line which was reconstructed by using Complete Control® inducible mammalian expression system (Stratagene, USA), and investigated the cell fate after HCNP-pp over-expression by adding ponasterone A (Pon A). Immature PC12 cells showed increases of HCNP-pp expression in a time dependent manner following Pon A administration to the culture medium. However, morphology of the cells was not significantly changed. These results suggest that the role of function of HCNP-pp varies from immature PC12 cells from mouse developing hippocampal cells in vivo.

P2-056 The requirement of NF κ B in p38 MAP kinase activation linked to the induction of TNF α in LPS-stimulated microglia

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Microglia induce a cytotoxic cytokine, tumor necrosis factor alpha (TNF α), in many pathological conditions of the brain. However, the molecular mechanism of the induction has not been accurately understood. In this study, we examined the association of nuclear factor kappa B (NF κ B) activation with the p38 mitogen-activated protein kinase (p38)-dependent TNF α induction in lipopolysaccharide (LPS)-stimulated microglia. Microglia were prepared according to the method described previously. When the effect of NF κ B inhibitor (SN50) or p38 inhibitor (SB203580) was examined, the microglia were pretreated with the inhibitor for 1 h prior to the addition of LPS. The amount of TNF α secreted to the medium, the activation of NF κ B and the activation of p38 were detected by immunoblotting. LPS-induced TNF α production was found to be suppressed by the pretreatment with a specific NF κ B inhibitor similar to the effect of p38 inhibitor. Since the activation of NF κ B was suggested to be linked to the induction of TNF α , the requirement of NF κ B was examined at the step of MAP kinase activation in LPS-stimulated microglia. The inhibitor experiments revealed that the activation of p38 is suppressed by the treatment with NF κ B inhibitor, but NF κ B activation (I κ B degradation and translocation of p65) was not affected by the treatment with p38 inhibitor. These results suggest that NF κ B activation is necessary to the activation of p38 which is required for the induction of TNF α in LPS-stimulated microglia.

P2-058 A new splice variant of neuroglycan C, a CNS-specific transmembrane chondroitin sulfate proteoglycan

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Neuroglycan C (NGC) is a membrane-spanning chondroitin sulfate proteoglycan that is predominantly expressed in the brain. We have reported that three transcripts for NGC splice variants (NGC-I, -II, and -III) exist in the human brain. In the present work, we discovered a new transcript for another splice variant, NGC-IV, in primary cultured neurons derived from the rat hippocampus, but not in primary cultured glial cells. RT-PCR experiments showed that the transcript for NGC-IV also existed in the human hippocampus. The NGC-IV cDNA comprised four exons (1, 2, 3, and 6) of the NGC gene, and the deduced NGC-IV protein had the shortest cytoplasmic domain among four splice variants. To confirm whether NGC-IV is expressed as a protein in the brain, we made an antibody against the oligopeptide specific to NGC-IV. We could demonstrate by Western blotting that NGC-IV was really expressed in the rat hippocampus. These results indicate that NGC-IV is expressed in some neuronal cells in the hippocampus, and suggest that it plays some roles there.

P2-059 Fc receptor-positive oligodendrocyte precursor cells in multiple sclerosis brain: A novel therapeutic target

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Multiple sclerosis (MS) is a demyelinating disease of central nervous system (CNS) affecting more than one million people worldwide leading to severe disabilities and decreased quality of life. Clinical strategy to recover the lost neural functions, or to remyelinate the axons remains to be developed. Recently to our surprises, it has become evident that oligodendrocyte precursor cells (OPCs) are preserved in MS lesions, even in chronic cases. These findings raised a possibility that it is not the lack of proper cells but rather the lack of differentiation stimuli that may hinder from remyelination in MS lesions. We have previously demonstrated that immunoglobulin Fc receptors, particularly the common γ chain of them (FcR γ), is the key molecule that promote differentiation of mouse OPCs into myelinating oligodendrocytes both *in vitro* and *in vivo* (Nakahara *et al.*, Dev. Cell (2003)). Although an application of this finding to MS therapy may be expected, expression of FcR γ in human OPCs in MS brains remained uncertain. In this study, we provide evidences that FcR γ is expressed in preserved OPCs in human MS lesions. Our findings indicate that FcR γ would serve as a future therapeutic target for an effective remyelinating therapy. Also, a possible existence of "microglia-like OPCs" is discussed.

P2-061 *Phgdh* hypomorphic mice serve as an animal model of human genetic serine deficiency

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3-Phosphoglycerate dehydrogenase (*Phgdh*), an enzyme catalyzing the first step of L-serine biosynthesis, is expressed predominantly by Radial glia/astrocytic lineage in rodent brain. A null mutation of *Phgdh* leads to mid-gestation embryonic lethality associated with severe neurodevelopmental defects (Yoshida *et al.*, 2004). To investigate the role of *Phgdh*-dependent glial L-serine biosynthesis in later stages of neural development, we generate hypomorphic *Phgdh* mice that express only ~10% of normal *Phgdh* mRNA and protein, resulting in decreased free serine levels that is ~30% of normal. Histological examinations reveal that neonatal mutant brain exhibits mild congenital microcephaly accompanied by swollen ventricles and hypoplasia of the cerebral cortex, hippocampus and cerebellum. Most notably, there are clear defects in the formation of subcortical axon tracts, corpus callosum and anterior commissure. These developmental defects recapitulate abnormalities of patients with human serine deficiency (de Koning *et al.*, 2003). Thus, the *Phgdh* hypomorphic mutant is an excellent animal model to investigate a role of glial L-serine biosynthesis in neuronal circuit formation and to define the neuropathology seen in human serine deficiency.

P2-063 Structure and activity of brain 2',3'-cyclic-nucleotide 3'-phosphodiesterase

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2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNP) is known as a useful marker for oligodendrocytes in the central nervous system. When bovine CNP is solubilized by elastase, 236 amino-acid residue fragment (elastase CNP) with full enzyme activity is released (Kurihara *et al.*, 1987 J. Biol. Chem. 262, 3256-3261). In the previous study, we prepared the recombinant protein corresponding to human elastase CNP and used for the X-ray crystallographic analysis (Sakamoto *et al.*, 2005 J. Mol. Biol. 346, 789-800). In the present study, we prepared the 13-14 residue shorter recombinant proteins and compared their enzyme activity with that of the original recombinant human elastase CNP. DNA fragments were synthesized by PCR, cloned, and connected to pGEX-6P-1. The fused proteins were expressed in *E. coli* BL21(DE), and CNP fragments were then released by PreScission Protease. Whereas the protein 13-residue shorter from the N-terminus had enzyme activity comparable with that of the original human elastase CNP, the protein 14-residue shorter from the C-terminus had remarkably lower enzyme activity. Therefore, the N-terminal 13 residues do not seem essential and the C-terminal 14 residues seem essential for enzyme activity of human elastase CNP.

P2-060 Analysis of synthesis and uptake of lactate in primary neuronal and astrocytic culture cells using ¹³C-NMR spectroscopy

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In recent years, research of metabolic trafficking between neurons and astrocytes is advanced. In astrocytes surrounding capillaries, glucose is processed by glycolysis, resulting in the release of lactate as an energy substrate for neurons. To determine the lactate metabolism in the brain, we investigated the synthesis and uptake of lactate in primary neuronal and astrocytic culture using ¹³C-NMR spectroscopy. Neurons and astrocytes were incubated with DMEM (glucose free) for 12 hrs, then incubated for an additional 4 hrs after [1, 6-¹³C] glucose or [3-¹³C] lactate was added to the medium. NMR measurement of the medium demonstrated that neuronal and astrocytic consumption of glucose was 0.312 ± 0.073 and 1.924 ± 0.189 μ mole/mg-protein/h (n=3), and astrocytic consumption of lactate was 4.31 and 0.43 μ mole/mg-protein/h (n=2), respectively. When astrocytes were incubated for 4 hrs with medium obtained from neuronal culture (for 12hrs) and [1, 6-¹³C] glucose, the [3-¹³C] lactate synthesis in astrocytes increased more than that in normal medium (1.41 times). When neuron cells were incubated for 4 hrs with medium obtained from astrocytic culture (for 12hrs) and [1, 6-¹³C] glucose, the [3-¹³C] lactate synthesis in neurons were almost the same as that in normal medium (1.05 times). That effect of neuronal medium on enhancement of [3-¹³C] lactate synthesis in astrocyte were decreased (20%) by heat treatment (10min, 70-80^o C) of neuronal medium. The findings indicate that lactate may be used as an energy substrate rather than glucose for primary neuronal culture and that neuronal cells may release a factor other than glutamate that accelerate astrocytic lactate synthesis.

P2-062 The role of GFAP positive cells in the intestinal villi

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Enteric nervous system (ENS) is a unique neural construction containing reflex pathways capable of functioning independently of central control. The number of intestinal neurons is so many as spinal ones, and the neural circuits cover the whole gastrointestinal tract. In this system, enteric glial cells (EGCs), a numerous ENS components, support neurons. They are star shaped GFAP positive population and more closely resemble astroglia of CNS than other peripheral glia. EGCs are also related to inflammation and blood regulation in the gastrointestinal, but many aspects of their function is not well understood. Especially in the intestinal mucosal layer, even the existence of EGCs has never been discussed, although abundant neural fibers, mucosal plexus and immune cells are in the villi. To investigate the existence of EGCs in the villi, we examined the distribution pattern of GFAP positive cells in the mice ileum by immunohistochemistry. We found GFAP positive cells are in the shaft of the villi and extend their fibers to the tip. Interestingly their fibers seem to build up a network with each other along with the capillary. To examine what this construction means and how the neural fibers interact with these cells, we analyzed the expression of intestinal neural marker GAP-43. This marker is a Ca binding phospho protein expressed in the neural regeneration. Surprisingly almost all the GFAP positive cells express GAP-43. These results suggest that GFAP positive cells in the villi may be involved in physiological role of neural regeneration.

P2-064 The function of phospho-MBP in developing mouse brain

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Myelin basic protein (MBP) is the major phosphoprotein of central nervous system myelin. Although the function of phospho-MBP in myelin has not yet been elucidated, phosphorylated MBP components are reduced in demyelinating diseases. To elucidate the function of phospho-MBP in brain, at first, we developed antibodies that specifically recognize the MBP phosphorylated at a individual site. We have carried out immunoblot analysis by using anti-phospho-MBP specific antibody on the myeline fraction isolated from 20months old mouse brain and demyelinating brain exposed the copper chelator, cuprizone in the diet. Phosphorylating MBP decreased greatly both in aged brain and cuprizone-induced demyelinating brain compared with total MBP. These results suggest that phosphorylation state of MBPs are likely to be associated with demyelination and remyelination.

P2-065 The changes of paranodal proteins in the PNS of the cerebroside sulfotransferase-deficient mice

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The cerebroside sulfotransferase (CST)-deficient mice lack sulfatide, which is a major glycolipid in myelin. The mutant CNS shows the disruption of paranodal junctions (PJ), whereas compact myelin is well preserved. In addition, Na⁺ channel clusters in the node of Ranvier become elongated and K⁺ channel clusters move their locations from juxtaparanode to paranodal regions. Both channel clusters disappear with age in the mutant CNS. In contrast, disappearance of channel clusters is not prominent in the mutant PNS, suggesting that the loss of myelin sulfatide may influence differently between the CNS and PNS axons. To determine the role of sulfatide on the formation of PJ in the PNS, the distributions of paranodal proteins, Caspr and neurofascin 155 (NF155) in the CST-deficient mice were examined. As results, about half of the nodal regions represented by Na⁺ channel clusters were still associated with Caspr clusters in the CST-deficient PNS whereas only a few paranodal regions contained Caspr clusters in the CNS. The lengths of these remaining clusters in the PNS were significantly shorter and were colocalized with NF155, suggesting that PJ may be partially formed in these regions. From double immunostaining of anti-Caspr and anti-Kv1.2 antibodies, short Caspr clusters were located in the flanking regions of the nodes, while Kv1.2 clusters were in the rest of paranodal regions. Thus, aberrant distributions of Caspr, NF155 and Kv1.2 in the CST-deficient PNS suggested that sulfatide may not be necessary to form junction between outermost paranodal myelin loops and axolemma in the PNS.

P2-067 Expression of Annexin 2 in murine peripheral nervous system

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Annexin 2 (AX2) is a family of calcium-, actin- and phospholipid-binding proteins implicated in a number of intracellular functions such as signal transduction, membrane trafficking and mRNA transport, likewise the regulation of membrane/cytoskeleton contacts and extracellular functions. Annexin expression in the central nervous system (CNS) is upregulated in some pathological conditions, and this protein is essential for survival of neurons as well as glial cells in brain culture. However, expression and specific localization of this protein in the PNS is still uncertain. In the present study we examined distribution of AX2 in PNS. By western blot analysis, the amount of AX2 was higher in the sciatic nerve (SN) homogenate than those in spinal cord homogenate. Immunohistochemical analysis showed characteristic distribution of AX2 around the node of Ranvier and Schmidt-Lanterman incisures, which were considered to be a route for transport of ions and metabolites between cytoplasmic myelin layers. The same distribution of AX2 was observed in SNs from both wild-type and cerebroside sulfotransferase knockout mice, in which paranodal axo-glial junction was disrupted. It suggests that AX2 are not affected by presence of a paranodal junction, even though this protein is present close to the junctional region. From its characteristic distribution as well as the molecular feature, AX2 may be important for maintaining normal myelin function in the PNS.

P2-069 Effects of neonatal exposure to tributyltin on expression of glycoconjugates in the rat brain

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Tributyltin (TBT) is an environmental pollutant, and the accumulation in the aquatic food chain is serious problems for the Japanese that take fishes and mollusks as staple foods. We previously found that brain myelin enzyme (2', 3'-cyclicnucleotide 3'-phosphodiesterase, CNP) activities in neonatal TBT exposed rats were significantly decreased compared with those of control groups. The expression of mRNAs of major myelin proteins, CNP, proteolipid protein (PLP), myelin basic protein (MBP), and myelin-associated glycoprotein (MAG), were analysed by Real-Time PCR. Enhancement of the gene expression of MAG, MBP, and CNP were observed in the TBT-exposed rat in juvenile stage. These results showed that neonatal exposure to TBT affected to the myelination, even in the relatively low level exposure. MAG, a member of the Siglec family of sialic acid-binding lectins, binds to sialoglycoconjugates on axons, is known as one of growth-inhibitory proteins of myelin membranes. In this study, we investigated the expression of mRNAs of Nogo-A, Nogo receptor (NgR), and CMP-sialic acid: lactosylceramide sialyltransferase (ST, GM3 synthase). Nogo-A is also growth-inhibitory molecule, and MAG and Nogo bind to the same neuronal receptor, NgR. Rat pups were given TBT by a single injection on the day of birth at a dose of 60 nmol/kg-1, and brains of pups were collected on 21, 35, and 49 days of age. Total RNA was extracted from brain cerebrum, and mRNA level was quantified by Real-Time PCR. The mRNA expression level of Nogo-A in the TBT-exposed brain was higher than that of control brain, but level of ST was not different. These data suggest that TBT affects expression of myelin proteins, but not for glycoconjugates in myelin membranes.

P2-066 Conduction properties of corpus callosum in mice in vivo

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Transgenic and knockout mice have been used to investigate the molecular mechanisms of demyelinating diseases. However, less attention has been given to elucidate how demyelination is involved in the dysfunction of nerve conduction. We established an experimental system to measure the electrophysiological properties of nerve conduction of cortical neurons between the left and right cerebral hemispheres (callosal connection) in mice. Using ketamine-Xylazine (100 and 10 mg/kg, i.p.) anesthesia, stimulating and recording electrodes were placed in the right and left sensorimotor cortices with a distance of 3.0-3.5 mm. Electrical stimulation (less than 200 μ A, 1Hz) applied to the right cortex evoked antidromic responses of left cortical neurons with a latency of 9.79 ± 2.16 ms (Mean $\pm$ S.D.). This experimental system may contribute to the understanding the pathophysiological mechanisms of demyelinating animal models.

P2-068 Myelin protein mapping using 16-BAC/SDS-PAGE

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Myelin is a unique structure that consist of multiple membrane layers. Since myelin has crucial roles in the CNS and PNS, the loss or damage of myelin results serious neurological diseases and inflammatory demyelinating disease. The analysis of proteins in damaged myelin is required to clarify the mechanism of dysmyelination and demyelination. In the present study, a proteomic analysis of the myelin was undertaken to obtain a better understanding of myelin biology. At first, we applied standard two-dimensional electrophoresis (isoelectric focusing: IEF and SDS-PAGE) to analyze myelin proteins. This 2D analysis provided high resolution of soluble and pI 4-9 proteins. However, most of myelin proteins were highly basic and compacted at the basic edge of the 2D gel. In addition, even when the gel with pH 6-11 gradient was used, the pH gradient was not sufficiently extended to separate highly basic proteins. Therefore, an alternative 2D electrophoresis using the cationic detergent, benzyl hexadecylammonium chloride (16-BAC) to solubilize proteins was adapted for the analytical separation of myelin proteins. The myelin proteins were identified by western blotting and mass spectrometry. This 16-BAC/SDS-PAGE method improved separation, resolution and identification of the myelin proteins. We concluded that the combination analysis of IEF/SDS-PAGE and 16-BAC/SDS-PAGE is required for the analysis of myelin proteins, and that this procedure may be useful for the comparative analysis of myelin fractions from wild and dysmyelinating model mutant mouse.

P2-070 Hydrogen sulphide regulates calcium homeostasis in BV-2 microglial cells

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Hydrogen sulphide (H₂S), which is produced endogenously from L-cysteine in mammalian tissues, has been suggested to function as a neuromodulator in the brain. However, the role of H₂S in microglial cells is unclear. In this study, the effect of exogenous and endogenous H₂S on intracellular calcium homeostasis was investigated using BV-2 microglial cells. Sodium hydrosulphide (NaHS), a H₂S donor, caused a concentration-dependent (0.1-0.5 mM) increase in intracellular calcium concentration ([Ca²⁺]_i). This effect was significantly attenuated in the presence of a calcium free extracellular solution, Gd³⁺ (100 μ M), a non-selective Ca²⁺ channel blocker or thapsigargin (1 μ M), an inhibitor of the sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase. These observations suggest that the increase in [Ca²⁺]_i in response to H₂S involves both calcium influx across the plasma membrane and calcium release from intracellular stores. Using RT-PCR, two H₂S producing enzymes, cystathionine β -synthase (CBS) and cystathionine γ -lyase (CSE), were found to be expressed in BV-2 microglial cells. Inhibition of either enzyme with amino-oxyacetate (a CBS inhibitor), β -cyano-L-alanine, D,L-propargylglycine (two CSE inhibitors) significantly decreased [Ca²⁺]_i, suggesting that endogenous H₂S may have a positive tonic influence on [Ca²⁺]_i homeostasis in BV-2 microglial cells. These findings support the possibility that H₂S may serve as a neuromodulator to facilitate signaling between neurons and microglial cells.

P2-071 The possible regulatory mechanism of proinflammatory cytokine expression in murine locus coeruleus

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Cytokines and catecholamines are known to constitute a significant portion of the regulatory neuroimmune networks involved in maintaining homeostasis in the central nervous system (CNS). Although we have already reported the increase of norepinephrine (NE) turnover and the upregulation of proinflammatory cytokines within the locus coeruleus after the intraperitoneal injection of lipopolysaccharide (LPS), the relationship between these increase remains unclear. In order to clarify it, we examined the effect of NE on the expression level of proinflammatory cytokines in the primary cultured microglia. Microglia, which are one of the major cell types that produce proinflammatory cytokines in the CNS, were isolated from mouse neonate brains. Simultaneous incubation of microglia with LPS and NE reduced the mRNA and protein levels of TNF- α . These data support the hypothesis that NE negatively regulates the expression of proinflammatory cytokine expression, which contributes to the observed anti-inflammatory properties of NE. By contrast, the simultaneous stimulation enhanced the expression of IL-1 β at both mRNA and intracellular protein levels. Interestingly increased IL-1 β protein was not produced to the culture media. The investigation to elucidate the regulatory mechanism of cytokine expression in the cells is currently in progress in our laboratory.

P2-073 Microarray analysis of chemokines and chemokine receptors induced by lipopolysaccharide in rat microglia

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Chemokines and their receptors play important roles in activation, migration, localization and differentiation of immune effector cells. We have investigated the expression of chemokines and their receptors expressed in rat microglia (MG) using cDNA microarray technique. In this study, we introduce the profile of chemokines and their receptors gene expression induced by lipopolysaccharide (LPS) in MG. When MG were isolated from primary mixed glial cultures (MGC) prepared from newborn rats and incubated with LPS for 24 h, upregulation of CXCL7, CXCL15, and SDF-2 and downregulation of CCL25, CCL28, and CX3CR1 were detected in response to LPS. When MGC were treated with LPS for 24 h, MG changed their expression more divergently than that of isolated MG, as increasing CCL2, CCL3, CCL4, CXCL1, CXCL2 and CXCR5 expression and decreasing CCL25, CCR3 and CX3CR1 expression. These results suggested that the microenvironment surrounding MG, for example the glial network, is an important factor for the expressional regulation of chemokines and their receptors in MG. Treatment of MG in the MGC with LPS for 2 h increased the expression of 13 chemokines and 16 chemokine receptors. Interestingly, upregulation of CCL28, CCR1 and CCR10 expression in MG was detected 0.5 h post treatment of MGC with LPS, suggesting that acute and transient production of chemokines and their receptors in LPS-stimulated MG might be required at the early immune responses. Taken together, these evidences indicated that the divergent expression of chemokines and their receptors in MG might mediate a series of immune reactions induced by microglial activation.

P2-075 Analysis of Reelin-Dab1 signal transduction system in layer formation of cerebral neocortex using RNAi

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Formation of highly organized neocortical structure depends on the correct placement of the appropriate number and types of neurons. Reelin is a large glycoprotein secreted by neurons in the developing brain, particularly Cajal-Retzius cells in the cortical marginal zone. Disruption of the *reeler* gene causes neuroanatomical abnormalities such as a defect in the preplate splitting and inverted cortical lamination. Dab1 is a cytoplasmic adaptor protein and interacts with at least two Reelin receptors, VLDLR and ApoER2, through the N-terminal phosphotyrosine-binding (PTB) domain. The absence of Dab1 causes an almost exact neuroanatomical phenocopy of the *reeler* (*reeler* mutant mice). Although numerous attempts have been made to study the function of Reelin-Dab1 signaling, it remains to be elucidated what effect Reelin-Dab1 signaling would have on the migrating neurons. Since the positioning of neurons in the brain is totally disturbed in these mutant mice, we encounter difficulties in distinguishing whether the defect is cell-autonomous or a secondary effect by the cells' surroundings (non-cell-autonomous). For this reason, Hammond et al. constructed Dab1 (+/+) <--> Dab1 (-/-) chimera, and showed Dab1 functioned cell-autonomously with respect to radial migration. However, the question of what occurs in Dab1-lacking neurons remains unanswered in their study. We therefore examined the features of Dab1-knockdown neurons, in particular their morphology, by introducing a plasmid vector expressing siRNA (small interfering RNA) against *dab1* into migrating neurons using *in utero* electroporation. How the migrating neurons are altered in this loss-of-function experiment *in vivo* will be discussed.

P2-072 Manifestation of myasthenic weakness by autoantibodies against MuSK

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Myasthenia gravis (MG) is an antibody-mediated autoimmune disease in which the nicotinic acetylcholine receptor (AChR) at neuromuscular junctions (NMJ) is the major autoantigen. AChR-specific antibodies are detected in 90% of non-immunosuppressed patients with generalized MG. Hoch et al. found a novel antigen, muscle-specific kinase (MuSK), in 2/3 of patients with generalized MG who were lacking detectable AChR autoantibodies (seronegative MG). Recent studies showed that the frequency of MuSK antibodies in patients of seronegative MG patients varied from 4 to 50 %. The pathogenic mechanisms of MG caused by AChR antibodies are well delineated, but MuSK autoantibodies have not been shown to be pathogenic. There have not been reports of inducing MG by immunization of animals with purified MuSK proteins. Here we demonstrated the first evidence that MuSK antigen caused myasthenic weakness in animals. Our results *in vivo* showed that MuSK requires the maintenance of the synapses not only for the formation, and the interference of the roles by MuSK antibodies caused myasthenic weakness. We are currently studying the synaptic structures conjunction with the junctional AChRs, and this model system would provide new knowledge of the molecular pathogenesis of MG and MuSK functions in mature NMJ.

P2-074 A new system for the three-dimensional visualization of tangential migration in the developing mouse forebrain

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The cerebral cortex contains two major classes of neurons, the glutamatergic projection neurons and the gamma-aminobutyric acid (GABA)ergic interneurons. In the developing cerebral cortex, the projection neurons arise in the pallial ventricular zone and migrate radially toward the pial surface, whereas most interneurons are known to derive from the subpallial telencephalon and migrate tangentially into the pallium in mice. While the tangential migration of cortical interneurons from the subpallium to the pallium has been well studied in slice cultures, migratory profile of the tangential migration in three dimensions remains largely unknown. To clarify the three-dimensional migration profile of interneurons, we developed a new technique involving focal electroporation into a small portion of the telencephalic hemisphere. Using this technique, in combination with whole-mount telencephalic hemisphere cultures, we were able to transfect and label a population of interneurons derived from a small, defined portion of the telencephalic hemisphere, and visualize their migration in three dimensions. Focal electroporation also allows us to perform overexpression or loss-of-function experiments using any molecules related to interneuron migration. Migratory profile of interneurons derived from each small part of the ganglionic eminence will be discussed.

P2-076 Necdin represses cdc2 gene expression via E2F1 and prevents neuronal apoptosis

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Necdin is a growth suppressor expressed predominantly in terminally differentiated neurons. Necdin has been implicated in the pathogenesis of Prader-Willi syndrome, a human neurodevelopmental disorder associated with genomic imprinting. Necdin interacts with the transcription factor E2F1 and represses E2F1-dependent transcription of various genes. However, detailed mechanisms underlying E2F1-dependent transcriptional repression by necdin remain largely unknown. In the present study, we investigated the necdin-induced transcriptional repression of the *cdc2* gene which is one of the E2F-regulated genes and involved in the control of cell cycle progression and apoptosis. Necdin repressed E2F1-dependent *cdc2* promoter activity in undifferentiated embryonal carcinoma P19 cells which differentiate into postmitotic neurons by retinoic acid treatment. Chromatin immunoprecipitation analysis revealed that necdin repressed E2F1-dependent transcriptional activation of the *cdc2* promoter through its interaction with E2F1. Furthermore, necdin formed a complex with E2F1 at the *cdc2* promoter during retinoic acid-induced neuronal differentiation of P19 cells. We then examined whether necdin regulates apoptosis in postmitotic neurons through the E2F1-*cdc2* system. In necdin-deficient cerebellar granule neurons, apoptosis induced by deprivation of membrane depolarization was significantly augmented. Under these conditions, the E2F1-*cdc2* system in the granule neurons was activated. These results suggest that necdin represses *cdc2* gene expression through the complex formation with E2F1 to prevent neuronal apoptosis.

P2-077 Mammalian Müller glial cells can be converted to a neuronal lineage

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Purpose: It was reported recently that mammalian Müller glial cells can become retinal progenitor cells and differentiate into neurons *in vivo* when stimulated by an intravitreal injection of N-methyl-D-aspartate. We investigated if rat Müller glial cells can be converted to neurons *in vitro*.

Methods: Primary Müller glial cells were isolated from the retinas of Long-Evans rats (postnatal day 12-16). The cells were cultured in the presence of serum. After a week, they were replated into nonadhesive dishes to form aggregate spheres, cultured for 4 days, transferred to chamber slides coated with ornithine and laminin, and cultured another 7 days in a differentiation medium. They then were stained with anti- β -tubulin III antibody (Tuj-1).

Results: The rat Müller glial cells successfully formed aggregate spheres (Müllerspheres) and expressed nestin, a retinal progenitor marker. They were converted to neurons and expressed β -tubulin III, the neuronal marker.

Conclusion: Mammalian Müller glial cells can be converted into a neuronal lineage *in vitro* under appropriate conditions. These cells could be a source of neuronal cells and used in regenerative medicine to treat degenerative retinal diseases.

P2-079 Molecular mechanism of cholinergic differentiation by L3/Lhx8 in murine ES cells

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The Lim homeobox family of transcription factors is involved in many processes during the development of the mammalian central nervous system. L3, also called Lhx8 (L3/Lhx8), is a member of the Lim homeobox gene family and is selectively expressed in the medial ganglionic eminence (MGE). Our previous study demonstrated that L3/Lhx8-null mice specifically lacked cholinergic neurons in the basal forebrain. Furthermore, we demonstrated that L3/Lhx8 depletion in N2a cells led to suppression of cholinergic marker expression without any apparent decrease in the number of cholinergic marker-positive cells. Intriguingly, GABAergic marker expression and the number of cells with the GABAergic phenotype were dramatically increased in differentiating L3/Lhx8-knockdown N2a cells. These results suggested the possibility that L3/Lhx8 is involved in the determination of transmitter phenotypes (GABAergic or cholinergic cell fate) in a population of neurons during basal forebrain development. In the present study, we report the effects of siRNA against the L3/Lhx8 messenger RNA (mRNA) on retinoic acid (RA)-induced neural differentiation in murine ES cells. Furthermore, we also examined that the expression patterns of L3/Lhx8 mRNA underlying these RA-induced differentiation processes in ES cells.

P2-081 Neuroprotective effect of acetylcholine esterase inhibitor on young neurons generated in the adult mouse olfactory bulb and hippocampus

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Neurogenesis continues in the two regions in the adult mammalian brain - the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG), and the subventricular zone (SVZ) of the lateral ventricle in which neural stem cells generate olfactory bulb (OB) interneurons. Acetylcholine (ACh) plays an important role in memory formation, which has been suggested to be partially dependent on neurogenesis in DG. Although previous studies have reported that ACh affects neurogenesis in the adult DG and OB, the function of the cholinergic input on the adult neural progenitor cells is largely unknown. In this study, we observed direct synaptic contacts of cholinergic fibers onto the immature neurons in OB and DG. Distribution of acetylcholine receptor in these brain regions was studied using fluorescence-conjugated alpha-bungarotoxin, a specific ligand to nicotinic acetylcholine receptor subunit. Binding of alpha-bungarotoxin was detectable on the immature postmitotic neurons but not on the proliferating cells. To examine the function of ACh in neurogenesis, we used donepezil, a potent and selective acetylcholine esterase inhibitor that has been proved to improve cognitive impairment in Alzheimer's disease. Adult mice were injected 0.5 - 2.0mg/weight (kg)/day of donepezil once a day for one to four weeks, and dividing cells were labeled with BrdU either pre- or post- donepezil treatment. The results indicated that donepezil significantly enhanced survival, but not proliferation, of the newly generated neurons in SGZ and SVZ. Taken together, these results suggest that cholinergic input promotes survival of newly generated neurons in the adult OB and DG.

P2-078 Differentiation of neural progenitor cells into smooth muscle cells induced by TGF- β and agonists of G protein-coupled receptors

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Neural progenitor cells isolated from the embryonic cerebral cortex are well known to differentiate into neurons and glial cells, but recent reports have demonstrated differentiation into smooth muscle cells (SMCs) under the influence of fetal bovine serum. Here we report that agonists for G protein-coupled receptors, including endothelin, lysophosphatidic acid and carbachol, effectively promote this SMC differentiation in the presence of transforming growth factor- β (TGF- β). Incubation of neural progenitor cells with agonists for G protein-coupled receptors or TGF- β alone significantly induced the expression of a SMC marker protein, α -smooth muscle actin, and their combination resulted in incremental increase. Stimulation with the combination of both agonists increased the numbers of large, flat cells with thick actin fibers and also induced expression of other SMC marker proteins. SMC differentiation proved highly dependent on extracellular matrix elements, such as fibronectin and laminin. An inhibitor of Rho kinase, Y-27632, strongly blocked the expression of α -smooth muscle actin induced by G protein-coupled receptor agonists, while exerting only weak effects on TGF- β induced expression. Consistently, endothelin and lysophosphatidic acid significantly activated RhoA but TGF- β did not. Transfection of constitutively active mutants of G α 12, G α 13 and RhoA induced expression of α -smooth muscle actin in unstimulated cells, but those of G α 12 and G α 11 and G β γ were without effects. These results suggest that G protein and TGF- β signaling pathways cooperatively promote SMC differentiation of neural progenitor cells in RhoA/Rho kinase-dependent and -independent manners.

P2-080 Necdin promotes GABAergic neuron differentiation through ternary complex formation with MAGE-D1 and Dlx

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The potent growth suppressor necdin is expressed predominantly in postmitotic neurons. Necdin shows a moderate homology to MAGE (melanoma antigen) family proteins, all of which contain a large homology domain (MHD). A necdin homologous protein, MAGE-D1 (also termed NRAGE or Dlxin-1) interacts with Dlx/Msx homeodomain proteins via a specific domain distinct from the MHD. The Dlx proteins play pivotal roles in GABAergic neuron differentiation in developing mouse forebrain. Thus, we examined the modulatory effects of necdin on GABAergic neuron differentiation through its interactions with MAGE-D1 and Dlx. We first analyzed the expression of necdin in developing telencephalon of E13.5 mice by immunohistochemistry. The majority of necdin-positive cells in developing forebrain were consistent with the cells expressing MAGE-D1 and the GABAergic neuron markers GAD65/67 and calbindin-D28k. Co-immunoprecipitation analysis revealed that a ternary complex of necdin, MAGE-D1, and Dlx2 (or Dlx5) was formed in HEK293A cells. The combination of necdin and MAGE-D1 facilitated Dlx2-dependent activation of the Wnt-1 promoter carrying a Dlx binding site. We next examined the effects of necdin and MAGE-D1 on the differentiation of forebrain GABAergic neurons using cultured slices to which cloned genes were introduced by electroporation. Overexpression of necdin and MAGE-D1 increased the number of GABAergic neurons expressing GAD65/67 and calbindin-D28k in the ganglionic eminence, in which endogenous Dlx protein level is high. In necdin-deficient mice, expression of calbindin-D28k was markedly reduced during forebrain development. These results suggest that necdin regulates the differentiation of forebrain GABAergic neurons by forming the ternary complex with MAGE-D1 and Dlx.

P2-082 Induction of ectopic oligodendrocyte precursors in fetal cerebral cortex by intraventricular injection of FGF-2

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The mammalian CNS develops from self-renewing stem cells that generate neurons, astrocytes, and oligodendrocytes, which is regulated by various extrinsic signals. During development, oligodendrocyte precursors originate from the ventral, but not the dorsal part of the brain, and this process is regulated by Shh. Shh patterns the ventral region by controlling the expression of transcription factors including the basic helix-loop-helix gene *Olig2*. *Olig2* has been shown to be deeply related to the oligodendrocyte generation. Thus, it has been thought that neural stem/progenitor cells in the dorsal ventricular zone of forebrain do not generate oligodendrocytes *in vivo*.

It was reported that fibroblast growth factor-2 (FGF-2) induced oligodendrocytes differentiation from neural precursor cells *in vitro*. However, the effects of FGF-2 in oligodendrocytes generation *in vivo* were largely unknown. In this study, we studied the role of FGF-2 in promoting the generation of oligodendrocytes *in vivo*. To directly test this, we used *in utero* microinjection technique, and injected FGF-2 into the lateral ventricles of mouse fetal telencephalon. We found that a single injection of FGF-2 at E13.5 resulted in ectopic expression of *Olig2* and *PDGFR α* genes in dorsal ventricular zone of the cortex and that a ventral marker gene, *Dlx2*, was detected in the dorsal neural progenitor cells at E15.5. These results demonstrated that FGF-2 ventralized dorsal neural progenitor cells *in vivo*, and induced ectopic oligodendrocyte precursors in the embryonic brain. We suggested that the fate of dorsal neural progenitor cells can be changed by alternating FGF-2 expression *in vivo*.

P2-083 17 β -estradiol-induced differentiation and intracellular signal pathway in rat neural stem cells

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Estrogens participate to regulate development processes of central nervous system, whereas their influences on neural stem cells (NSCs) have not yet well defined. Although it has long been thought that estrogens act on cells through intracellular estrogen receptors, ER α and ER β , recent observations suggest estrogen actions via novel membrane-initiated mechanisms. In this study, the effects of 17 β -estradiol (E2) on differentiation and phosphorylation of cellular molecules in cultured rat NSCs were examined. Cells were prepared from embryonic rat brain (telencephalon at embryonic day 15) and cultured in the presence of FGF-2. Cells grown in neurospheres were dissociated and plated on culture vessels coated with poly-L-ornithine, and cultured for another 3 days in the presence of FGF-2. For treatment with E2, medium was changed to that containing various concentration of E2 but not FGF-2. E2 rapidly activated signal transduction molecules of NSCs such as MAPK, Akt and CREB, which was not prevented when the cells were pretreated with an ER antagonist ICI182,780. These observations suggest that E2 activates not only intracellular but also extracellular signaling pathways. RT-PCR and immunohistochemical analysis revealed that exposure of the cells to E2 for a few days induced the expression of myelin basic protein (MBP) but not microtubule-associated protein (MAP2) or glial fibrillary acidic protein (GFAP), suggesting that E2 regulates the differentiation of NSCs to oligodendrocytes.

P2-085 Mash1 affects cell fates in the postnatal rat cerebellum

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It has been reported that dividing progenitors in the white matter (WM) of the early postnatal rat cerebellum give rise to a variety of glia and neurons, including astrocytes, Bergmann glia, oligodendrocytes and interneurons (1). However, it remains unclear when and where the postnatal cerebellar progenitors make cell fate decisions. The role of basic helix-loop-helix (bHLH) transcription factors during the postnatal developing cerebellum has not yet been fully addressed. Mash1, a bHLH factor, is known to be an important proneural gene in the embryonic central nervous system. It has been recently demonstrated that this gene is also required for the specification of neurons and oligodendrocytes in the postnatal SVZ (2). To investigate the role of Mash1 in the postnatal cerebellum, we transduced Mash1-GFP fusion gene in vivo into the progenitors in the deep cerebellar WM of postnatal day 3/4 rats using a retrovirus vector. The morphology and location of the infected cells were analyzed at 27/28 days postinjection in comparison with the results obtained with control retrovirus vector expressing GFP alone. By control retroviral injection, we observed many GFP-labeled cells differentiating into neurons, astrocytes and oligodendrocytes in the internal granule and molecular layers or the WM across a couple of folia. In contrast, the large majority of cells misexpressing Mash1 appeared to be immature and more cells with migratory morphology remained in the WM. The data indicate that Mash1, when misexpressed, is capable of interfering the cell fate decision in the postnatal cerebellar WM. Ref. (1) Zhang L, et al. J. Comp. Neurol., 370:536-550, 1996. (2) Parras MC, et al. EMBO J., 23:4495-4505, 2004.

P2-087 RNAi analysis of Drosophila MAGE in the nervous system

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Necdin, a mitotic suppressor expressed in postmitotic neurons, is implicated in their survival and differentiation. Necdin shows a moderate homology to the melanoma antigen gene (MAGE) family proteins. Since human and mouse genomes contain >30 MAGE family members, outcomes of loss-of-function analyses of necdin may be complicated due to the redundancy of mammalian MAGE genes. In contrast, *Drosophila melanogaster* has only a single necdin-homologous gene (dMAGE). Therefore the *Drosophila* system may provide a useful tool to elucidate the original function of MAGE family. We have previously found that dMAGE is specifically expressed in postmitotic neurons including photoreceptors and mushroom body neurons, which are derived from postembryonic neurogenesis. In contrast, dMAGE is expressed in neuroblasts, but not in neurons during embryogenesis. In this study, we generated the transgenic fly in which inverted repeat of the dMAGE cDNA induces RNAi-mediated gene silencing. The GAL4/UAS system was adopted to introduce this transgene in a cell-type specific manner. We first confirmed an about 90% reduction of the dMAGE endogenous expression by RT-PCR and Western blotting. When dMAGE expression was downregulated under the control of the sevenless-GAL4 driver, photoreceptors underwent apoptosis, which was detected by double labeling for DNA fragmentation and activated caspase-3. Furthermore, knockdown of dMAGE expression in mushroom body neurons using the OK107-GAL4 driver resulted in morphological deformities of the mushroom bodies. These findings suggest that dMAGE is the important gene for the development and survival of *Drosophila* neurons.

P2-084 Translational repression mediated neural RNA-binding protein Musashi

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Musashi is an evolutionarily conserved family of RNA-binding proteins that is preferentially expressed in the nervous system (Reviewed by Okano et al., *J. Cell Sci.* 115, 2002). The first member of the Musashi family was identified in *Drosophila*. This protein plays an essential role in regulating the asymmetric cell division of ectodermal precursor cells known as sensory organ precursor cells through the translational regulation of target mRNA (Nakamura et al., *Neuron* 13, 1994; Okabe, Imai et al. *Nature* 411, 2001). Its mammalian homologue, Musashi-1, is a neural RNA-binding protein that is strongly expressed in fetal and adult neural stem cells (NSCs). Mammalian Musashi-1 augments Notch signaling through the translational repression of its target mRNA, m-Numb, thereby contributing to the self-renewal of NSCs (Imai et al. *Mol. Cell Biol.* 21, 2001). Musashi1 protein was also shown to be present in the translational machinery using sucrose gradient centrifugation analysis. Recently, we demonstrated that Musashi1 bound directly to a molecule that interacts with both a translation initiation factor and mRNA as well as Musashi-target mRNA(s), thereby repressing the target gene(s) of Musashi at the translational level. And we also found that this Musashi-mediated translational repression is likely to be modified by phosphorylation.

P2-086 Effects of nicotine on neurogenesis and plasticity in the hippocampus

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NCAM, a member of the Ig superfamily expressed on the surface of most neural cells, is involved in cell-cell interactions during brain development, synaptic plasticity, and regeneration.

In our previous studies, we showed that nicotine administration induced expression of IGF-1 mRNA in the rat hippocampus and cerebral cortex and concluded that at least a part of nicotine's beneficial effects on hippocampal and cortical neurons were due to increased IGF-1 mRNA expressions. Nevertheless, the situation may be somewhat different as far as nicotine's effects on the neuronal progenitor cell, which is still on the way of differentiation are concerned.

To clarify this problem, nicotine was intraperitoneally injected into four week-old Wistar strain rats in several doses followed by successive injections of BrdU for the next four days. Then rats were sacrificed and vertical sections of the hippocampus formation were offered for double immunohistochemical staining of BrdU/PSA-NCAM, BrdU/NeuN or BrdU/GFAP. As the results, numbers of both BrdU(+)/PSA-NCAM(+) cells and BrdU(+)/NeuN(+) cells were much decreased nicotine-dose dependently. On the other hand, as much as 1mg/kg was needed for nicotine to exert its effect on the number of BrdU(+)/GFAP(+) cells. These results reveal that nicotine inhibits neurogenesis and plasticity in the hippocampus of adult rats. It is concluded that nicotine has two-sided effects on neurons, beneficial positive effects on matured neurons and negative effects on developing neurons.

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P2-088 RNA-binding protein Hu regulates proliferation and differentiation in Mammalian nervous system

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Hu family is a group of neuronal RNA-binding proteins that have been shown to induce neuronal differentiation when overexpressed in immature neural progenitor cells. Hu proteins have been shown to enhance the stabilization and/or translation of target mRNAs, such as p21 (CIP1), by binding to AU-rich elements in untranslated regions (UTRs). Recently, we show that Hu induces p21 expression, cell cycle arrest, and neuronal differentiation in mouse neuroblastoma N1E-115 cells. To reveal molecular mechanisms of Hu functions, we isolated several Hu-interacting proteins including hnRNP K. hnRNP K was also shown to bind CU-rich sequences in p21 mRNA 3'UTR and repress its translation in both non-neuronal and neuronal cells. By using RNAi, we also showed that the Hu-p21 pathway contributes to the regulation of neurite outgrowth and proliferation in N1E-115 cells, and this pathway is antagonized by hnRNP K. These results suggest that functionally antagonistic two RNA binding proteins, Hu and hnRNP K, control the timing of the switch from proliferation to neuronal differentiation through the post-transcriptional regulation of p21 mRNA. Furthermore, to address in vivo functions of Hu proteins, we generated HuD deficient mice. These mice exhibited a transient impaired cranial nerve development-phenotype at an early embryonic stage. Adult HuD^{-/-} mice exhibited an abnormal hindlimb reflex and poor rotarod performance. Neural stem/progenitor cells in HuD^{-/-} mice exhibited increased self-renewal capacity and decreased differentiation ability toward neurons, suggesting that HuD is required for cell cycle exit of proliferating neural stem/progenitor cells and differentiation of neuronal cells in vivo.

P2-089 Abnormal development of enteric neural crest cells in the nerve growth factor receptor, p75, knockout mice

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The nerve growth factor receptor, p75, is expressed in all early migrating neural crest cells. p75 knockout mice show the reduction in the number of sympathetic and sensory neurons, suggesting that p75 might have certain roles in the development and differentiation of neural crest cells, although its functions are remained unclear. To explore whether p75 has some possible roles on the early migrating neural crest cells, we further analyzed the early development of neural crest cells in p75 knockout mice. At embryonic day 10.5 (E10.5), whole gut *in situ* hybridization analyses revealed that the area of RET distribution in p75 knockout mice is narrower than littermate wild type. Whole mount immunohistochemistry for neurofilament also showed the reduction in the number of enteric neurons in p75 knockout mice at E10.5. Moreover, the number of phox2b-positive enteric neural crest cells in p75 knockout mice was 22% less than that of littermate wild type at E10.5. However, we could detect neither the significant decrease of BrdU-positive cells nor the increase of TUNEL-positive cells in the enteric neural crest cells. Although the function of p75 in the development of neural crest cells still remains unclear, these results indicate that p75 has some certain roles during the early development and differentiation of neural crest cells.

P2-091 Analysis of DNA double-strand break repair proteins during *in vitro* neural differentiation

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DNA double-strand breaks (DSBs) can be introduced by various sources including radiation, chemicals and endonucleases, and cause cell death or cancer if unrepaired. DSBs are repaired in two pathways. One repair system is the nonhomologous end joining (NHEJ) and the other is the homologous recombination repair (HRR). Recently knockout mice of genes involved in NHEJ and HRR were analyzed in detail. Phenotypes of mice deficient in Ku70/80, XRCC4 or DNA ligase IV resemble qualitatively each other, high sensitivity to ionizing radiation, premature senescence, inability to rejoin both coding and recombination signal sequence ends during V(D)J recombination, and growth defects including massive neuronal death. Among HRR gene defects, only XRCC2-deficient mice showed insufficiency of neural development and RAD51-, RAD51L1-, RAD51L2-, RAD51L3- and XRCC3-deficient mice were all lethal in early embryonic stage except DMC1 specific to germ cells. In this study, we investigated expression of Xrcc4 and DNA ligase IV during *in vitro* neurogenesis using mouse P19 embryonal teratocarcinoma cell line. Analysis of time course of Xrcc4 protein expression demonstrated the protein transiently increased after neural induction treatment, suggesting the protein is involved in early stage of neurogenesis. The *in vitro* neural differentiation model may be useful in elucidating a role of Xrcc4 in neural development.

P2-093 Astrocyte differentiation of the EGF-responsive proliferating cells in early postnatal mouse cerebellum

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Cerebella from early postnatal mice were digested with papain, and the dissociated cells were fractionated by a discontinuous Percoll gradient. The small cell fraction was comprised mainly of granule cell precursors, while the large cell fraction contained the cells expressing glial fibrillary acidic protein (GFAP) very weakly. When the cells in the large cell fraction were cultured in the presence of epidermal growth factor (EGF), the number of these GFAP-weakly-positive cells increased extensively. Most of these cells also expressed nestin, a marker for neural stem cells, and brain lipid binding protein. We found the basic helix-loop-helix transcription factor OLIG2, which has been shown to be required for oligodendrocyte and motor neuron development, was localized mainly in the nucleus of these cells in the presence of EGF. When EGF was removed, most of the cells stopped proliferating and lost nestin expression. When ciliary neurotrophic factor (CNTF) was given to these cells, OLIG2 disappeared from the nucleus and the cells began stronger GFAP expression. In the presence of Leptomycin B, a specific inhibitor of CRM1-dependent nuclear export, CNTF did not induce disappearance of OLIG2 from the nucleus or the increase in the number of GFAP-positive cells. These results suggest that the export of OLIG2 from the nucleus is important for CNTF-induced astrocyte differentiation of these cells.

P2-090 Gene expression during unidirectional differentiation of mouse embryonic stem cells into neurons

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We have developed a Neural Stem Sphere (NSS) method, which can produce a large number of neurons from mouse and primate embryonic stem (ES) cells (Neurosci. Res., 46, 241-249, 2003). The NSS method consists two stages: In stage 1, cultured in astrocyte-conditioned medium (ACM) under free-floating conditions, within 4 days, colonies of undifferentiated mouse ES cells give rise to NSSs with a periphery of neural stem cells. In stage 2, culturing the NSSs on an adhesive substrate in ACM promotes neurogenesis. In the present study, we analyzed gene expression during culture of mouse ES cells by quantitative real-time RT-PCR. Expression of Oct-4, a marker of ES cells, in the colonies of ES cells was down-regulated during culture in stage 1 and became very low in NSSs at day 4. In contrast, expression of Sox1, a neuroectodermal marker, became marked from day 2 in stage 1, and nestin, a neural stem cell marker, from day 3. Expression of the neuronal marker MAP2 became distinct at day 4 in stage 1. Cells in NSSs differentiated into neurons in stage 2 and expression of MAP2 increased. However, expression of the astroglial marker GFAP and the oligodendroglial marker MBP did not increase in stage 2. Interestingly, expression of the early mesodermal gene marker brachyury, the primitive endodermal marker GATA4 or the epidermal marker cytokeratin-17 was low and did not significantly increase throughout culture. These results demonstrate that the colonies of ES cells give rise to NSSs, instead forming embryoid bodies, and that ES cells unidirectionally differentiate into neurons via neuroectoderm and neural stem cells but form neither endodermal nor mesodermal cells. This work was partly supported by Selective Research Fund of Tokyo Metropolitan Universities.

P2-092 Functional Analysis of a Novel Neuron-Specific Protein Family, BRINP

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We have previously reported that Bone morphogenetic protein (BMP) and retinoic acid (RA) play important roles in the neurogenesis of the PNS. Subsequently, we identified a novel protein which is induced synergistically by BMP2 and RA in these neurons. Thus, BRINP1 (BMP/RA-inducible neural specific protein-1) is a prototype member of a novel protein family which includes BRINP2 and BRINP3. Three BRINP family proteins are specifically expressed in the nervous system in complementary as well as in alternating manners. Flow cytometric analysis revealed that over-expressed BRINPs suppress the cell cycle progression in several cell types. We also found that aberrant high activity of NRSF, a transcription factor that controls nonneuronal suppression of neuronal genes leads to tumorigenesis of neuronal progenitor cells concomitantly with suppression of BRINP1. These findings suggest that BRINPs play important roles in the cell cycle arrest of terminally differentiated neuronal cells. BRINPs are unique proteins in that they possess no conserved motif except for a signal peptide and a coiled-coil domain. In the present study, we examined the structural requirements for the BRINPs to exert their functions. Our results indicated that BRINPs require the signal peptide for their glycosylation and appropriate targeting to unidentified mesh-like subcellular architecture in proliferating cells with both neural and nonneural origin, although lack of signal peptide did not affect the cell cycle suppression. Further characterization of functional domains of BRINPs and their interaction with other proteins will be discussed.

P2-094 The lineage tracing of Olig2 expressing cells in the cryo-injured adult CNS

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Our previous study with double labeling of BrdU and cell markers suggested that a number of astrocytes were differentiated from resident oligodendrocyte progenitor (OPCs)-like cells in the injured adult brain (Neurochem. Int. vol.46, 2005). To directly trace the lineages of the OPCs, we employed double transgenic mice that express tamoxifen-sensitive *CreER* under the control of the *Olig2* promoter together with ROSA-EGFP reporter. We found that GFP positive cells appeared around the injured region. These GFP(+) cells that also had Olig2-immunoreactivity in their nuclei could be divided into two populations; One was O1-positive population and another was nestin expressing cells. Double labeling with cell markers revealed that some of the nestin-positive cells co-expressed GFAP. None of the GFP-positive cells was Tuj-1-positive. These results suggested that dormant OPCs *in vivo* took heterogeneous fates in response to injury.

P2-095 Fibroblast growth factor 2 maintains neural stem cells in an undifferentiated state and promotes their proliferation via the glycogen synthase kinase 3 β inactivation

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Co-ordination of cell cycle exit and differentiation commitment is an essential program for neural development. Although FGF2 is known to maintain neural stem cells in an undifferentiated state and promote their proliferation, the molecular basis for these FGF2 effects has yet to be elucidated. Here, we report that FGF2 signaling inhibits kinase activity of glycogen synthase kinase 3 β (GSK3 β) in the neuroepithelial cell culture. Inactivation of GSK3 β increased β -catenin protein level in the nucleus and subsequently induced the expression of Cyclin D1, a cell cycle regulator, to promote cell cycle progression. PI3 kinase inhibitor LY294002 impaired the effects of FGF2 on both GSK3 β phosphorylation and Cyclin D1 expression, suggesting that these FGF2 effects were dependent on the activation of PI3 kinase-Akt pathway. FGF2 signaling through PI3 kinase-Akt-GSK3 β pathway also potentiated the promoter activities of Hes1 and Hes5, which are Notch target genes involved in the maintenance of undifferentiated neural stem cell phenotype. β -catenin stabilization was sufficient for the Hes promoter activation by FGF2. We propose that GSK3 β is a dual functional molecule that couples cell cycle regulation and differentiation commitment of neural stem cells in the presence of FGF2.

P2-097 PACAP-induced PACAP mRNA expression and neuronal differentiation in neural precursor cells

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PACAP has been suggested to be involved in the development of the embryonic nervous system. Previously, we showed that PACAP acts as an autocrine or paracrine regulatory factor in PACAP gene expression in PC12 cells, and that mRNAs for PACAP, VIP, and their receptors were expressed in neural stem cell-enriched cultures derived from in vitro neuronal culture model of embryonic stem (ES) cell differentiation. In this study, we examined the effects of PACAP on the PACAP gene expression, as well as the ability to self-renew (expansive cellular proliferation) and neural differentiation in cortical precursor cells and ES-cell-derived neural precursor cells. PACAP mRNA was induced by PACAP (100 nM) in neural cells differentiated from ES cells within 4 h after stimulation and returned to basal levels at 8 h. PACAP reduced the number of secondary neurospheres and increased the number of cells positive for the neuronal marker MAP2. PACAP did not influence the number of cells positive for neural stem cell marker nestin, astrocyte marker GFAP, and oligodendrocyte marker CNPase. To further study whether brief exposures to PACAP induce neuronal differentiation from neural precursor cells, we examined the effects of PACAP exposure for 0.5 to 24 h on neural precursor cells. In monolayer culture of cortical precursor cells, PACAP exposure for 3 h was sufficient for neuronal differentiation. In ES-cell-derived neural precursor cells, PACAP induced neuronal differentiation as well. These results suggest that PACAP signaling elicits an increase in its own expression in an autocrine manner, and that PACAP does not induce the self-renewal but instead induces early neuronal differentiation in neural precursor cells.

P2-099 Filamin A-interacting protein (FILIP) deficiency results in increased Filamin A expression and decreased proliferation in the ventricular zone during neocortex development

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Previously, we have reported that the gene expression of Filamin A-interacting protein (FILIP) is restricted to the ventricular zone (VZ) in the developing neocortex and regulates the start of radial migration therein [Nagano et al., Nat Cell Biol. 2002]. Using RNAi technology, we have confirmed that Filamin A, expression of which in VZ is controlled by FILIP, determines the polarity-dependent migration in VZ [Nagano et al., J Neurosci. 2004]. These observations prompted us to generate FILIP knockout (KO) mouse to study the effect of FILIP deficiency during neocortex development. To disrupt the functional expression of FILIP gene we have replaced its largest exon with a *LacZ* and *PGK-Neo* cassette. As expected, we have observed that Filamin A expression at postnatal day 0 is increased in VZ and reduced in upper cortical plate (CP) in KO than that in wild type littermates (WT). A decreased proliferation was observed at embryonic day (E) 17.5 in KO than that in WT but remains similar both in WT and KO at earlier stages (E14.5 and E16.5), where the day of confirmation of vaginal plug is designated as E0.5. Distribution and number of tangentially migrating neuronal subtypes e.g. GABA⁺ and Calretinin⁺ neurons remains similar both in WT and KO. All together, these results fit to a major phenotype observed in KO where columnar organization of CP neurons is disrupted. To study any behavioral or functional disorder due to such malformation of neocortical development, FILIP-KO mouse therefore will be a valuable animal model.

P2-096 The role of TROY in the development of the nervous system

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Neural stem cells are present in both the embryonic and the adult mouse forebrain. Although the majority of neuroepithelial cells in early embryonic development have the properties of stem cells, these cells are restricted to the subventricular zone (SVZ) lining to the lateral ventricle within the postnatal and adult CNS. TROY is a member of the tumor necrosis factor receptor superfamily, and our previous report showed that TROY mRNA is expressed in the germinal regions of embryonic and adult CNS. In this study, we demonstrated that TROY protein is also expressed in neuroepithelial cells and postnatal SVZ. Double-immunofluorescent staining revealed that TROY was expressed in nestin-positive neuroepithelial cells and radial glial cells, but not in MAP2-positive differentiating neurons during embryonic stages. TROY-expressing cells in the postnatal SVZ were positive for Musashi-1 and negative for polysialic acid-neural cell adhesion molecule, indicating that TROY is expressed in uncommitted or glial precursor cells, but not in neuronal precursor cells. In addition, TROY was expressed in astroglial lineage cells in the postnatal CNS.

In vitro studies showed that overexpression of TROY in PC12 cells inhibited NGF-induced neuronal differentiation. Taken together, TROY is expressed in the undifferentiated neuroepithelial cells, radial glial cells, and glial lineage cells, which may be a default lineages, and may be involved in maintaining a default state by repressing neuronal differentiation during CNS development.

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P2-098 A role of CARM1 in neuronal differentiation

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The coactivator-associated arginine methyltransferase (CARM1/PRMT4) is an enzyme that catalyzes the formation of asymmetric N,N-dimethylarginine residues. Many CARM1 substrates possess nucleic acid binding properties (PABP1, HuR, SmB, and Histone H3), but others can remodel chromatin (p300/CBP). CARM1 plays a key role in hormone-induced gene activation and define cofactor methylation and is broadly expressed. However, there had been no information concerning roles of CARM1 in neuronal differentiation. Previous study showed that CARM1 stable PC12 cell line become apoptotic following NGF stimulation (Wei Xu et al, science 294, 2507 2001). Our previous study indicated suppression of CARM1 promotes neuronal differentiation of PC12 cells. These results suggest that CARM1 might be a negative regulator of neuronal differentiation. To test this hypothesis, we analyzed CARM1 expression during development of mouse brain by using western blotting and immunohistochemistry. CARM1 was strongly expressed in embryo, but its expression was dramatically decreased in postnatal. This expression pattern was corresponding to nestin, which is marker of neural stem cells. These data suggest that CARM1 might be a negative regulator of neuronal differentiation in vivo and required for keeping proliferation of neural stem cells. Furthermore, to examine this hypothesis, we suppressed endogenous CARM1 expression in neural stem cells. In this presentation, we will show a role of CARM1 in neuronal differentiation.

P2-100 Dendritic morphogenesis of cerebellar Purkinje cells through extension and retraction: time-lapse analysis and involvement of calcium/calmodulin-dependent protein kinase II and neuronal activity

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Cerebellar Purkinje cells have the most elaborate dendritic trees among the neurons in the CNS. To investigate dynamical aspects of dendritic morphogenesis of Purkinje cells, we performed a time-lapse analysis of cerebellar cell cultures derived from glutamate decarboxylase 67-green fluorescent protein knockin mice. Purkinje cells extended several primary dendrites during the culture for 25 days. Time lapse analysis started from 10 days in vitro (DIV) revealed that not only extension but also retraction of primary dendrites occurred during this process. Interestingly, the retraction of primary dendrites occurred most frequently between 10-15 DIV concomitantly with the occurrence of extension of the other primary dendrites in a cell. Analysis of morphological characteristics of the retracted primary dendrites revealed that the shortest primary dendrites tended to retract. Furthermore, treatment with an inhibitor of calcium/calmodulin-dependent protein kinase (CaMK) II reduced the number of primary dendrites specifically during 5-15 DIV, which is the period of the occurrence of active extension and retraction. Blockade of both non-NMDA and metabotropic glutamate receptors also reduced the number of primary dendrites during the same period. These findings suggest that the final morphology of Purkinje cells is achieved not only through extension but also through partial retraction of their dendrites and that CaMKII and neuronal activity are involved in this dendritic morphogenesis.

P2-101 PR#1, a monoclonal antibody raised against the detergent insoluble membrane / lipid rafts from PC12 cells, promotes neurite outgrowth of PC12 cells

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Glycosphingolipids (GSLs) and cholesterol are known to form lipid microdomains, often called lipid rafts. By extensive studies on lipid raft microdomains, the knowledge of their characteristics and cellular functions has been rapidly accumulating. In this study, we focused on the functional significance of lipid rafts with respect to neural differentiation. To examine this event, we prepared the detergent insoluble membrane (DIM) by sucrose density gradient centrifugation of Tx-100 lysates from PC12 cells, immunized them to mouse, and selected monoclonal antibodies (MAbs) which can induce neurite outgrowth. The first screening was performed using enzyme-linked immunosorbent assay (ELISA) with culture supernatants on the wells immobilized by DIM fractions. Among them, 42 wells were positive. Next, we checked if these MAbs could induce neurite outgrowth in PC12 cells, and obtained one MAb, termed PR#1, with such activities. TLC/immunostaining assay with glycolipids extracted from PC12 cells exhibited a number of immunoreactive bands of PR#1. These glycolipids were resistant to alkali hydrolysis and found to contain an oligosaccharide composed of fucose, glucose and galactose by GC-MS analysis. Thus the antigen for MAb PR#1 was considered to be fucose-containing GSLs. We are now trying to analyze the mechanism of neurite outgrowth induced by PR#1 through the fucoglycosphingolipid-enriched microdomains.

P2-103 Ras regulates neuronal polarity via the PI3-kinase/Akt/GSK-3 β /CRMP-2 pathway

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The neuron is one of the most highly polarized cells known and is comprised of two structurally and functionally distinct parts, an axon and dendrites. In cultured hippocampal neurons, neurons extend several minor processes during the first 12-24 h after plating. Then, one of the processes begins to extend rapidly to form an axon, resulting in the morphological polarization of the neuron. The remaining processes result in the morphological features of dendrites. We previously showed that collapsin response mediator protein-2 (CRMP-2) is critical for specifying axon/dendrite fate, possibly by promoting neurite elongation via microtubule assembly. In addition, we reported that glycogen synthase kinase-3 β (GSK-3 β) phosphorylates CRMP-2 at Thr-514, inactivates the CRMP-2 activity, and participates in neuronal polarization through CRMP-2. It has been shown that Ras regulates the PI3-kinase/Akt/GSK-3 β pathway and MAPK cascade. Here, we found that Ras was involved in neuronal polarization. The expression of the constitutively active form of Ras, PI3-kinase or Akt induced the formation of multiple axons in hippocampal neurons. Inhibition of PI3-kinase suppressed Ras-induced the formation of multiple axons. These results suggest that Ras regulates neuronal polarity through the PI3-kinase/Akt/GSK-3 β /CRMP-2 pathway.

P2-105 Dorsally derived netrin-1 controls axonal patterning of primary sensory axons in the developing spinal cord

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Netrin-1 is a long-range diffusible factor expressed in the ventral midline of the developing neural tube and has chemoattractive or chemorepulsive effects on growing axons. Netrin-1 is also expressed in the dorsal spinal cord. However, roles of this dorsally derived netrin-1 remain totally unknown. Here we show that dorsally derived netrin-1 controls the correct guidance of primary sensory axons. During development, DRG axons grow into the dorsolateral margin of the spinal cord, and the projections into the dorsal horn occurs after a waiting period of a few days. Netrin-1 was transiently expressed in the dorsal horn of the cord during middle phase of the waiting period, and the absence of netrin-1 resulted in aberrant invasion of sensory axons, including both cutaneous and proprioceptive afferents, into the dorsal horn. Netrin-1 derived from the dorsal spinal cord, but not the floor plate was involved in the correct projections of sensory axons. Furthermore, netrin-1 suppressed axon outgrowth from DRG in vitro. DRG neurons expressed netrin-1 receptor unc5c and unc5a, but not Dcc. Unc5c^{com} mutant mice showed aberrant projections of the axons, which were partially similar to the defect as observed in netrin-1 mutants, whereas the aberrant invasion was not observed in Dcc mutants at the same stage. Therefore, the inhibitory effect of netrin-1 on DRG axons is mediated by Unc5h family receptors, but not by Dcc. These results demonstrate that netrin-1 in the dorsal spinal cord acts as an inhibitory cue and elaborates the waiting period for primary sensory axons

P2-102 Restoration from neurodegenerative changes by withanoside IV and by its active metabolite, sominone

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We have been developing anti-dementia drugs based on reconstructing neuronal networks in damaged brain, and found that withanoside IV (a constituent of Ashwagandha; root of *Withania somnifera*) induced neurite outgrowth in neuroblastoma cells and cultured rat cortical neurons. In this study, it was clarified that oral administration of withanoside IV (10 μ mol/kg/day, 13 days) improved memory deficit in A β (25-35)-injected mice (i.e.v., 25 nmol). Immunostaining for phosphorylated NF-H (axonal marker), MAP2 (dendritic marker) and synaptophysin (synaptic marker) showed that decreases in axons, dendrites and synapses in brains of A β (25-35)-injected mice were recovered by withanoside IV administration. Sominone, an aglycone of withanoside IV, was detected from the serum of mice from 3 h after oral administration of withanoside IV, whereas withanoside IV itself could not be detected. Against atrophy of neurites induced by A β (25-35) in cultured rat cortical neurons, sominone (1 μ M) administration induced axonal and dendritic regeneration, and synaptic reconstruction. In addition, an experiment of FM1-43 release showed that treatment with sominone enhanced exocytosis potency from synaptic sites. These results suggest that withanoside IV is metabolized into sominone after oral administration, and sominone may be a active principle for reconstruction and re-functioning of neuronal networks. To identify the signal pathway of sominone, an antagonist of estrogen receptor and inhibitors of protein kinases were used against sominone-induced neurite outgrowth. The effect of sominone was specifically inhibited by LY294002 (3 μ M, PI3-kinase inhibitor).

P2-104 Developmental gene expression of Ca²⁺/calmodulin-dependent protein kinase I in mouse brain and its involvement of dendritic extension in hippocampal neurons

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Multifunctional Ca²⁺/calmodulin-dependent protein kinases, including CaMKI, CaMKII and CaMKIV, are highly expressed in brain and play important roles for various neuronal functions including neurite growth. In this study, we examined the gene expression of four isoforms of CaMKI in developing mouse brain by *in situ* hybridization histochemistry. During the development, CaMKI α and β 2 showed prominent expression throughout brain and spinal cord. CaMKI γ showed highly restricted expression to particular brain regions such as the ventromedial hypothalamic nucleus, amygdaloid nucleus, cerebral cortex and hippocampus. On the other hand, CaMKI δ showed a prominent expression in the hippocampal pyramidal cell layer and progressive increase in its expression during the postnatal development. By quantitative RT-PCR, the expression of CaMKI δ in hippocampus was gradually increased from postnatal day 5 (P5) to P21, and persistent until adult. Then, we overexpressed the kinase-dead mutants of CaMKI and CaMKIV in primary hippocampal neurons. The overexpression of a kinase-dead mutant of CaMKI δ reduced the average dendritic length without any significant changes in the number of dendrites. In contrast, the overexpression of a kinase-dead mutant of nuclear-targeted CaMKIV resulted in decreased number of dendrites without any effects on the average dendritic length. These results suggest that CaMKI δ and CaMKIV are involved in regulation of dendritic extension and initiation of dendrite, respectively, in hippocampal neurons. Our findings provide the evidence for the differential roles of CaMKI and CaMKIV in dendritic growth.

P2-106 Metabolite 1 of protopanaxadiol-type saponins, an axonal regenerative factor, stimulates teneurin-2 linked by PI3-kinase cascade

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We previously showed that 20-O- β -D-glucopyranosyl-20(S)-protopanaxadiol (M1), a metabolite of protopanaxadiol-type Ginseng saponins by intestinal bacteria, had axonal extension activity in degenerated neurons, and improved memory disorder and synaptic loss induces by an active fragment of amyloid β A β (25-35). It is unknown how M1 shows these effects in neurons. To clarify the signal transduction mechanism of M1-induced axonal extension, phosphorylated proteins by M1 stimulation were identified since most of cellular signal pathways are regulated by phosphorylation / dephosphorylation. The combination of immunoprecipitation and MALDI-TOF-MS revealed that teneurin-2 and mPar3 were specifically phosphorylated by M1 stimulation. mPar3 is known as an axonal specifying molecule and to be regulated by PI3-kinase. On the other hand, putative structure of teneurin-2 is a transmembrane protein. Although teneurin-2 is speculated to act as a homophilic adhesive protein, we supposed another scenario which the membrane-spanning protein played a role as signaling molecule like growth factor receptors. Therefore, the involvements of teneurin-2 and PI3-kinase in the M1 signal was studied. siRNA for teneurin-2 was transfected in rat cortical neurons. In the teneurin-2-deficient neurons, M1-induced axonal extension and PI3-kinase activation were significantly inhibited. In addition, treatment with PI3-kinase inhibitor also reduced M1-induced axonal extension. These results suggest that M1 induces axonal outgrowth through the teneurin-2-PI3-kinase cascade.

P2-107 Analysis of the mechanism of Reelin-induced tyrosine phosphorylation of Dab1

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During mammalian brain development, the precise patterns of neuronal alignment are controlled by an extracellular matrix protein, Reelin, which is secreted from Cajal-Retzius neurons in the marginal zone of the neocortex. When Reelin binds to its receptors, tyrosine phosphorylation of the intracellular adaptor protein Disabled 1 (Dab1) is induced. Although the molecular cascade of Reelin signaling is being uncovered, the mechanism of tyrosine phosphorylation of Dab1 remains unclear, because these receptors do not contain tyrosine kinase domains. In this study, we show that 1) Reelin induces tyrosine phosphorylation of Dab1 depending on Src family PTKs. 2) Reelin induces subcellular translocation of Dab1. We present a model of the mechanism of Reelin-induced efficient tyrosine phosphorylation of Dab1. In addition, we investigated the biological role of Reelin-Dab1 signaling cascade by using the *in utero* gene transfer system.

P2-109 DNA microarray analysis of activity-dependent gene expression in cultured rat cortical cells

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Activity-dependent genes are key factors for the establishment of the neural network and for neural plasticity. In the present study, we surveyed for such genes by analyzing gene expression in the presence of tetrodotoxin (TTX) and during recovery after TTX removal using our original oligoDNA microarray "Synaptarray". Cerebral cortical cells from E18 rat embryos were cultured for 14 days to ensure synaptogenesis, then treated with 1 μ M TTX for 2 days. After TTX removal, cells were further cultured for up to 2 days without TTX. Cell viability estimated by LDH leakage was not affected by TTX while synaptic density estimated by Synapsin I immunoreactivity decreased to 80% of untreated control after 2 days in TTX. From cells at the end of 2 day-exposure to TTX (0h) as well as at 5h (5h), 1day (1d) and 2 days (2d) after TTX removal, total RNA was extracted, reverse-transcribed, and amplified to yield cRNA. After labeling with Cy3 or Cy5, cRNA samples were compared by competitive hybridization in the following 3 pairs; 5h/0h, 1day/0h, and 2days/0h. A large proportion of genes involved in exocytosis and regulation of actin dynamics were up-regulated gradually after TTX removal, while those involved in cell cycle control, apoptosis, and stress response did not show significant changes. Among the up-regulated genes, Munc13-1, Synaptophysin, LIMK1, MRCK, and Rho A as well as the growth factors, BDNF and FGF8, were the earliest responding genes. In contrast, only a limited proportion of postsynaptic protein genes including neurotransmitter receptors was up-regulated at later than 1day. Recovery of neuronal activity thus initially induces recovery of neurotransmitter release and actin dynamics, which will re-establish the function of the post-synaptic structure.

P2-111 Adenoviral gene transfer of hepatocyte growth factor (HGF) prevents death of injured adult motoneurons after peripheral nerve avulsion

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Hepatocyte growth factor (HGF) exerts strong neurotrophic activities on motoneurons both *in vitro* and *in vivo*. We examined survival-promoting effects of an adenoviral vector encoding human HGF (AxCaHGF) on injured adult rat motoneurons after peripheral nerve avulsion. The production of HGF in COS1 cells infected with AxCaHGF and its bioactivity was checked by immunofluorescence, ELISA, western blot and MDCK cell scatter assay. The facial nerve or the seventh cervical segment (C7) ventral and dorsal roots of 3 month-old Fischer 344 male rats were then avulsed and removed from the stylomastoid or vertebral foramen, respectively, and AxCaHGF or PBS was inoculated in the lesioned foramen. The AxCaHGF treatment significantly prevented the loss of injured facial motoneurons (58.8 $\pm$ 5.9% survival at 4weeks) and C7 ventral motoneurons (75.4 $\pm$ 4.4% survival at 4weeks) after avulsion as compared to the treatment with PBS (30.2 $\pm$ 6.7% survival of facial motoneurons and 44.6 $\pm$ 9.3% survival of C7 motoneurons at 4weeks). The AxCaHGF treatment ameliorated choline acetyltransferase immunoreactivity in the injured motoneurons after avulsion. These results indicate that HGF may prevent the degeneration of motoneurons in adult humans with motoneuron injury and motor neuron diseases.

P2-108 Phosphorylation of GSK-3 β in neurite outgrowth from PC12D cells

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Glycogen synthase kinase 3 (GSK-3) is identified as a negative regulator of glycogen synthase, and more recently implicated in a wide range of signaling pathway, including the outgrowth of neurites, the activation of GSK-3 β by NGF through TrkA has been shown to stimulate axon elongation in various neuronal cells. While other studies suggested the inactive form of GSK-3 β is required at the leading edge of neuronal growth cones. A subline of PC12 cells, PC12D cells, extends neurites within several hours in response not only to NGF but also to dbcAMP and staurosporine. Then, changes in phosphorylation of GSK-3 β were studied in relation to the outgrowth of neurites in PC12D cells in immunofluorescence and immunoblotting experiments. Immunoblotting studies revealed that amount of GSK-3 was not changed in relation to the neurite growth by various agents. The phosphorylation of activating site of GSK3 β (T-216) was found to be increased in NGF-treated cells but not in dbcAMP or staurosporine-treated cells. The phosphorylation of inhibitory site of GSK3 β (S-9) was decreased in staurosporine-treated cells but was not clearly changed in NGF- and dbcAMP-treated cells. The outgrowth of neurites by these agents was all inhibited by GSK inhibitor (VIII). But wortmannin inhibited neurite growth in only NGF-treated cells. The inactivated GSK-3 β (S-9) was observed in the leading edge of growth cones in colocalization with actin in the neurites elicited various agents. These results suggest that PI3-K pathway involving both Akt and GSK-3 β appeared to be important for neurite extension in response to NGF, while dbcAMP and staurosporine dependent neurite growth might be induced in other way. Nevertheless, inactive form of GSK3 β (S-9) may play a role in leading edges of growth cones.

P2-110 Effects of an eight hour phase advance of the light-dark cycle on neurotrophin levels in various brain regions of rats

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During the postnatal development, circadian clock generates rhythms and synchronizes them to the environment. The entrainment of intrinsic rhythm to environmental one is important to form the sleep-awake rhythm. If the rhythm is not formed, the postnatal development of brain is shown to be disturbed, resulting in expression of autism-like behaviors. Brain-derived neurotrophic factor (BDNF) is known to be one of the factors forming circadian rhythms. Therefore we first examined circadian changes in BDNF levels in selected brain regions from 10-week-old male rats. In the hippocampus, BDNF showed maximal levels at circadian times (CT) 6 and 14 while, in the neocortex and cerebellum, the levels were the highest during CT2 - CT6. Then we investigated effects of an eight-hour phase advance of the light-dark cycle (LD) on neurotrophin levels in various brain regions from adult male rats. Brain regions were dissected from rats under the normal cycle at CT3.5 (group A) and CT11.5 (B) one day before advance of the cycle. Moreover, brain regions were dissected at the same time as in group A on the first day (C) after starting the advance of the LD cycle and on 7 days (D). Among four neurotrophins, most remarkable changes were observed in levels of BDNF in the entorhinal cortex including the piriform and amygdaloid nuclear complex. Eight-hour phase advance significantly elevated BDNF levels in group C, but not in groups B and D as compared to group A. Recently, the damage of amygdaloid nuclear complex is most convincing for etiology of autism. Thus, changes in BDNF levels in the region should be noted.

P2-112 Neuroprotective Effect of Pigment Epithelium-Derived Factor (PEDF)-Expressing Adenoviral Vector in the Quinolinic Acid Rat Model of Huntington Disease

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Pigment epithelium-derived factor (PEDF) is a 50kDa glycoprotein and a member of the serine protease inhibitor (SERPIN) gene family. It is a potent and broadly acting neurotrophic factor that protects various types of cultured neurons against glutamate excitotoxicity and induced-apoptosis. However, the *in vivo* neuroprotective effects of PEDF in the central nervous system (CNS) have not been fully analyzed. To investigate whether PEDF acts as a neurotrophic factor *in vivo*, we analyzed the effects of adenovirus-mediated transfer of PEDF gene in the model rats of Huntington disease (HD). Adenoviruses encoding PEDF (Ad.PEDF), beta-galactosidase (Ad.LacZ), or sham were stereotactically injected into the striatum of rats. One week after treatment, the rats were unilaterally lesioned through the intrastriatal injection of 100 nmol of quinolinic acid (QA). The rats receiving QA showed ipsilateral rotations by the stimulation of apomorphine. A significant reduction of apomorphine-induced rotations was observed in Ad.PEDF pretreated rats. Immunohistochemical analysis revealed that Ad.PEDF pretreatment significantly increased NeuN- and DARPP-32-positive neurons in the striatum one week after lesion compared to control. Furthermore, RT-PCR analysis showed that the intrastriatal expression of pro-inflammatory genes such as TNF α , IL-1 β and MIP1 α mRNA was significantly reduced one day after lesion in Ad.PEDF pretreated rats. The present results suggest that adenoviral delivery of PEDF may be useful tool for the treatment of neurodegenerative disorders such as HD.

P2-113 BDNF sustains high level of proliferation rate of cultured mouse neural stem/progenitor cells when applied to them with FGF-2 in combination

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Neural stem cells (NSCs), which exist in developing or adult nervous systems, proliferate and differentiate into neurons, astrocytes or oligodendrocytes. There is increasing interest in NSCs and neural progenitor cells (NPCs) for therapeutic applications. Transplantation of cultured NSCs/NPCs into a host brain may be one of the promising treatments for neurodegenerative diseases and brain injuries. However, as aging progresses in the NSCs/NPCs by long-term culture with repetitive passages, abilities for proliferation and neuronal differentiation are declined. Therefore, in this study, effects of brain-derived neurotrophic factor (BDNF) on NSCs/NPCs were examined, because BDNF increased neurons that differentiated from NSCs/NPCs. NSCs/NPCs were isolated from mouse telencephalon at embryonic day 14, cultured in the defined medium supplemented with or without FGF-2 (10 ng/ml) and/or BDNF (100 ng/ml), and passaged every 3 days. Three groups of cultures were differently maintained as follows: D0F group, with FGF-2 for all period; D0B group, with both FGF-2 and BDNF for all period; D4B group, with FGF-2 alone for the first 4 days and with FGF-2 and BDNF in combination for subsequent period. The cell number was increased 3-times and 5-times of the beginning in D0F and D0B groups 10 days after cell plating, respectively. Further, the proliferation rate of D0B, but not that of D4B, was always higher than that of D0F, demonstrating that BDNF is active on facilitating proliferation of NSCs/NPCs when used from the beginning with FGF-2 in combination. Taken into account our previous observations that BDNF facilitates neuronal fate of cultured NSCs/NPCs, it is suggested that BDNF effectively maintains the abilities of not only proliferation but also neuronal differentiation.

P2-115 Neurotrophic effects of genipin: Neuroprotective actions through nitric oxide synthase activation on oxidative stress in Neuro2a cells

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We have reported that a herbal iridoid compound, genipin, has neurotogenic activity in PC12h and Neuro2a cells through activation of nitric oxide synthase (NOS). It has been suggested that NOS has antioxidant role and scavenging role for free radicals, to protect cells against oxidative stress. In this study, we examined whether genipin has protective effects on 6-hydroxydopamine (6-OHDA)-induced cytotoxicity, as a model of oxidative stress. The toxicity was evaluated by MTT reduction assay and LDH release assay. 6-OHDA induced cytotoxicity dose-dependently (0-20 μ M) in Neuro2a cells, and the toxicity was enhanced by several NOS inhibitors (L-NAME: 0.5 mM, ETPI: 0.5 μ M, 1400W: 0.5 μ M). The observed potentiation by L-NAME of 6-OHDA-induced toxicity was significantly suppressed by NO donor (SNAP), not completely but significant. Therefore, in Neuro2a cells, intrinsic NO might act as a protective factor on 6-OHDA-induced cytotoxicity under resting state. Genipin prevented 6-OHDA-induced cytotoxicity in a dose-dependent manner (0-10 μ M). Furthermore 50 μ M genipin increased intracellular NO release monitored with NO sensitive fluorescent probe (DAF-2DA) in Neuro2a cells. Thus our data suggest that NOS possesses the protective effect for the oxidative stress, such as 6-OHDA treatment, under resting state, and genipin has neuroprotective effects through activation of NOS as well as the neurotogenic activity.

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P2-117 Neuroprotective effects of isoflavones as selective estrogen receptor modulators

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Phytoestrogens are plant constituents with a phenol structure, contained in a variety of edible plants and considered nature's SERMs (selective estrogen receptor modulators). Among the most common phytoestrogens, isoflavones and isoflavone glycosides are heterocyclic phenols closely related to estrogenic steroids in their structures.

In this study, we examined estrogen-like or antiestrogenic actions of isoflavones in the cerebral cortex and hippocampus on the basis of our previous data that estradiol induces IGF-1 mRNA expression, up-regulate estrogen receptors and facilitate ERE binding in these brain areas of rats. Used materials were ovariectomized and non-ovariectomized 4 week-old Wistar strain female rats. Each of rats was further divided into the following three groups. Group A: rats fed with phytoestrogen-free control diet, Group B: rats fed with diet with soy bean-derived estrogen and Group C: rats fed with control diet combined with chronic intraperitoneal injections of minimum dose of -estradiol. After feeding, rats were sacrificed to remove the cerebral cortex and hippocampus. Expressions of mRNAs of IGF-1, estrogen receptors α and β , and ERE binding were analysed by real time PCR assay and gel shift assay, respectively.

As the results, it was revealed that isoflavones increased mRNA expressions of IGF-1 and estrogen receptors in both ovariectomized and non-ovariectomized rats. Differences between estrogen receptor and in responses to isoflavones were analysed. On the other hand, isoflavone feeding increased ERE binding as much as chronic injections of estrogen did in the ovariectomized rats. The detailed mechanism of these results is left for further experiments. Support Contributed By: Kampo Science Foundation, Japan.

P2-114 Neurotrophic effects of genipin: Neuroprotective actions on ER stress in Neuro2a cells

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We have demonstrated previously that genipin, a natural iridoid compound, induces neuronal differentiation through NO-cGMP-PKG pathway in PC12h and Neuro2a cells. It is widely known that 6-hydroxydopamine (6-OHDA) induces oxidative stress and that oxidative stress causes endoplasmic reticulum (ER) stress. In this study, we investigated whether genipin exerts protective effect, as another neurotrophic effect, on ER stress-induced cell death using 6-OHDA in Neuro2a cells. Treatment with 6-OHDA (0-20 μ M) for 24 h significantly reduced MTT reduction activity in a concentration-dependent manner. Furthermore, 6-OHDA (20 μ M) markedly increased the level of GRP78, one of ER stress-response proteins, suggesting that 6-OHDA induces cell death accompanied with ER stress in Neuro2a cells. Genipin (2.5-10 μ M) significantly prevented both 6-OHDA-induced cell death and expression of GRP78 protein in these cells. We tested protective effect of genipin on A23187-induced cell death as a more certain model of ER stress. A23187, a calcium ionophore, is widely used as an ER stress inducer. Genipin (4-20 μ M) significantly prevented cell death in Neuro2a cells treated with the inducer (1 μ M) for 4 h in a concentration-dependent manner. We have previously suggested that genipin directly binds to and activates neuronal NO synthase. We tested effects of NO and its downstream product, cGMP, on 6-OHDA-induced GRP78 expression. Both an NO donor and a cGMP analog depressed the increased GRP78 protein. These findings suggest that genipin shows protective effect on ER stress-induced cell death with involvement of NO and cGMP in Neuro2a cells. This work was supported by MEXT. FRONTIER(2005-2009).

P2-116 Differential Distributions of Epidermal Growth Factor Family and Phosphorylated ErbB1 in adult Rat Brain

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Epidermal growth factor (EGF) and structurally related peptides such as transforming growth factor alpha (TGF α) and heparin-binding EGF-like growth factor (HB-EGF) are ligands for ErbB1 receptor and play crucial roles in central nervous system (CNS), such as proliferation, survival and cell fate regulation. Using two-site enzyme immunoassays (EIAs), we measured protein levels of EGF, TGF α and HB-EGF in adult rat brain, and compared with their mRNA expressions as well as with phosphorylation levels of their receptors (ErbB1). There were significant variances in brain distributions of each ErbB1 ligand. Among ErbB1 ligands, the content of HB-EGF protein are higher than those of TGF α and EGF in adult rat brain regions. The distributions of ErbB1 ligands failed to match those of mRNA or ErbB1 phosphorylation levels. In parallel, there are significant basal phosphorylation of ErbB1, with the largest activation in the midbrain. These observations suggest that the activation of brain ErbB1 involves post-translational regulation of multiple EGF family members in a region-specific manner.

P2-118 NGF prevents 2-deoxy-D-glucose-induced apoptosis via PI3-K signaling pathway in PC12 cells

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Nerve growth factor (NGF), one of the neurotrophic factors mainly acting in the peripheral nervous system (PNS), prevents apoptosis which is induced by various stimulants. We present that NGF suppressed 2-deoxy-D-glucose (2DG)-induced apoptosis in PC12 cells. An analysis using LY294002 (LY), a specific inhibitor of phosphatidylinositol 3-kinase (PI3-K), revealed that NGF prevented this apoptosis via the PI3-K signaling pathway. We found that the number of Hoechst 33482-positive cells was increased by the treatment of LY in the presence of 2DG plus NGF. We also found that 2DG transiently increased the expression of GRP78, and NGF increased the expression of GRP78. Interestingly, the expression of GRP78 was decreased by addition of LY. These results suggest that NGF prevents 2DG-triggered ER stress-mediated apoptosis via the PI3-K signaling pathway in PC12 cells. The physiological importance of the expression of GRP78 is under investigation.

P2-119 Behavioral abnormalities of the transgenic mice over-expressing HB-EGF

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Members in the epidermal growth factor (EGF) family bind to ErbB receptors (ErbB1-4) and produce mitotic and trophic action on various types of CNS cells. In rats, abnormal EGF receptor (ErbB1) stimulation given during limited neonatal stages leads to the severe and persistent behavioral dysfunctions. Heparin-binding EGF-like growth factor (HB-EGF), a member of the EGF family, shows neurotrophic actions on CNS neurons, such as survival of dopaminergic neurons, neuroprotective effect against seizure and ischemia. To study the physiological roles of HB-EGF in the brain, we have generated the transgenic mice that over-expresses HB-EGF gene in the forebrain regions. mRNA coding human preproHB-EGF was expressed under α -CaMK II promoter. HB-EGF transgenic mice exhibited behavioral abnormalities in locomotor activity in adulthood. Gross learning ability of the transgenic mice appeared to be normal as revealed by fear conditioning test. In neurochemical aspects, there were significant changes in levels of dopamine and their metabolites in the striatum, and in norepinephrine levels in the frontal cortex at the adult stage. These results suggest that ErbB/HB-EGF signal regulates brain function and behavior through the alterations of monoamine metabolism in the brain.

◆◆◆ 人名索引 ◆◆◆

氏名	演題番号	氏名	演題番号	氏名	演題番号	氏名	演題番号
A		浅井 清文	P1-088	D		福永 浩司	SY5-03
阿部 エリカ	P2-042	浅井 邦彦	P1-066	代 紅梅	P1-070		SY5-01
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学会掲示板

自然科学研究機構・生理学研究所・分子神経生理部門 非常勤研究員（ポスドク）募集

研究内容：糖鎖は細胞間相互作用に重要な役割を果たしています。本公募では神経発生や神経疾患における糖蛋白質糖鎖の役割解明に意欲を持って取り組む人を募集します。

募集対象：生理学研究所非常勤研究員 1名

応募資格：平成17年10月1日現在35歳未満で、理科系大学院博士号取得者および取得見込みの方（糖関連の研究に従事されていた方が望ましい。神経系の研究でなくても可）

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（財）ノバルティス科学振興財団平成18年度研究集会助成

・助成対象研究集会（日本神経化学会からの推薦枠1件）

生物・生命科学およびそれに関連する化学の領域において、わが国で開催される研究集会に対し、運営経費の一部を助成する。助成対象は下記の選考基準に基づく。

- 1) かなりの数の国外からの参加者を含み、国際性豊かで、学術的意義の大きい研究集会であること。
- 2) 1,000名を越す大規模な研究集会は、原則として助成の対象としないが、国内の学会および機関が主催する集会において行われるシンポジウム、招待講演、セミナーなどは助成対象とする。
- 3) 2国間の研究集会は、原則として助成の対象としない。
- 4) 他のソースから多額の寄付を集められると予想される研究集会よりも、当財団からの助成を必要とする程度の高い研究集会を優先する。
- 5) 平成18年4月以降平成19年3月末までに開催される研究集会であること。
・助成金は1件50万円を限度とし、予算範囲内で助成を行う。

・資料請求／問合せ先

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応募〆切：2005 年 9 月 2 日必着（日本神経化学会締切日）

内藤記念科学振興賞（日本神経化学会からの推薦枠 1 件）

【趣旨】

人類の健康の増進に寄与す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（日本神経化学会からの推薦枠 1 件）

後期：2006 年 7 月 1 日～2006 年 12 月 31 日に外国の研究者を招聘するもの

・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

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応募〆切：2005 年 9 月 5 日必着（日本神経化学会締切日）

東レ科学振興会第 46 回科学技術賞（日本神経化学会からの推薦枠 2 件）

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。

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。したがって平成 16 年度に推薦された候補者は平成 17 年度候補者としての再度推薦の必要はありません。ただし、この 1 年間に推薦書の内容に追加すべき顕著な業績または発表や受賞があり加筆が必要な場合は、再提出いただいても結構です。

候補者の対象につきまして、東レ科学振興会の内規において「国家的褒賞（文化功労者・日本学士院賞）受賞者は対象外とする。ただし、新しい業績については対象とする。」と規定いたしておりますので、ご留意くださるようお願い致します。

褒 賞：賞状、金メダル、賞金（500 万円） 受賞者は 2 名前後

東レ科学振興会第 46 回科学技術研究助成（日本神経化学会からの推薦枠 2 件）

対 象：国内の研究機関において萌芽的基礎研究を活発に行い、かつ本人が主体性をもって研究を遂行できる若手研究者（原則として推薦時 45 歳以下）

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。

選考委員は以下の通りです。

浅島 誠 委員長

末松 安晴、長濱 嘉孝、井上 明久、村橋 俊一、永嶺 謙忠、高柳 邦夫

佐藤 知正、成宮 周

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

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選考委員は上記ホームページをご覧ください。

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。

各助成・褒賞におきましても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にてご送付ください。

< 事務局連絡先 >

〒 160-0016 新宿区信濃町 35 信濃町煉瓦館

国際医学情報センター内

日本神経化学会

TEL.03-5361-7107

FAX.03-5361-7091

東レ科学振興会 第55回科学講演会

日時：2005年9月22日（木）開場16時30分 開演17時00分～（20:00終演）

会場：有楽町朝日ホール

東京都千代田区有楽町2-5-1 有楽町マリオン11F（JR有楽町駅前）

テーマ：宇宙の謎に挑む

1. 太陽系外に惑星を探す ―宇宙に生命を求めて―

田村 元秀（自然科学研究機構国立天文台助教授）

2. 宇宙の誕生と進化 ―現代物理学の描く創世記―

佐藤 勝彦（東京大学大学院理学系研究科教授）

*入場料無料・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

問合せ先：財団法人 東レ科学振興会

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第14回日本バイオイメーシング学会学術集会

主催：日本バイオイメーシング学会

会期：平成17年10月26日（水）～28日（金）

会場：東京大学農学部弥生講堂・一条ホール（〒113-8657 東京都文京区弥生1-1-1）

大会長：田之倉 優（東京大学大学院農学生命科学研究科教授）

副大会長：山本 健二（国立国際医療センター研究所副所長）

菊地 和也（東京大学大学院薬学系研究科助教授）

【スケジュール】

10月26日（水）13:00～16:50

公開シンポジウム：「たんぱく質のかたちと病気」

10月27日（木）～28日（金）

特別講演：「水とイオンチャネルを中心とした構造生理学研究」

一般講演・ポスター

シンポジウムⅠ～Ⅳ

【シンポジウム題目】

Ⅰ「分子・オルガネラ・細胞イメージング」

Ⅱ「新規計測技術によるバイオイメーシング」

Ⅲ「微細粒子製造・化工・操作技術とその生命科学への展開」

Ⅳ「タンパク質のバイオイメーシング」

詳細は大会ホームページをご覧ください。

<http://www.nih.go.jp/yoken/bioimaging/index-j.html>

【連絡先】

第14回日本バイオイメーシング学会大会長 田之倉 優

〒113-8567 東京都文京区弥生1-1-1

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千里ライフサイエンス技術講習会 第42回

「SNP、DNAチップの最新技術と応用」

日 時：平成17年11月4日（金）午後1時～5時
会 場：千里ライフサイエンスセンタービル6階（展示場）
（地下鉄御堂筋線千里中央駅北口すぐ）

ね ら い：ゲノムデータが整備され、ゲノム解析技術も新しい局面を迎えている。短期間に全ゲノムのSNPを鳥瞰できるようになり、またDNAチップも遺伝子発現解析以外の種々の応用も可能になっている。

本講習会ではこれらの進歩をふまえ、両技術の基本から最新の応用まで習得する。

コーディネーター：戸田達史 大阪大学大学院 医学系研究科 臨床遺伝学 教授

プログラム：

講 義 1：SNP解析の基礎と応用

講 義 2：DNAチップによる解析と最新技術

実 習：実際の解析機器での講習とデータ解析

講 師：戸田達史 大阪大学大学院 医学系研究科 臨床遺伝学 教授

油谷浩幸 東京大学先端科学技術研究センター ゲノムサイエンス 教授

定 員：30名

参 加 費：5,000円

申込方法：氏名、勤務先、所属、役職名、〒、所在地、電話およびFAX番号を明記の上、郵便、FAXまたはE-mailで下記宛お申し込み下さい。事務局より受付の通知を返送いたしますので、そこに記載した振込先口座に参加費をお振込みください。入金を確認後、通常1週間以内に領収書兼参加証をお届けいたします。

申込締切：平成17年9月30日（財団必着）但し、定員を超過した場合は参加者の調整を行う場合があります。

申 込 先：（財）千里ライフサイエンス振興財団 技術講習会G42係

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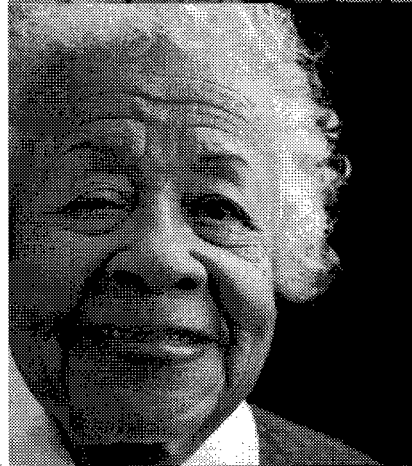
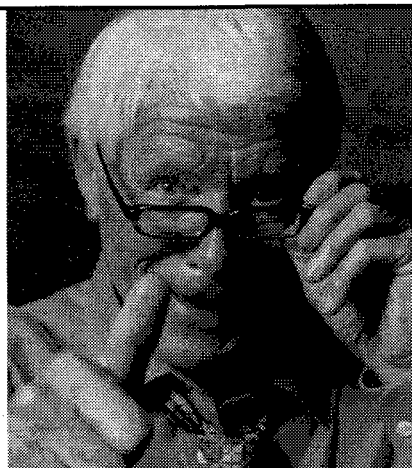
虚弱な体質で神経がたかぶって、怒りやすい、イライラする、眠れないなどの症状を訴える場合に使用します。

興奮性、焦燥感などの神経症症状(認知症患者の周辺症状など)や日常生活動作(ADL)を改善します。¹⁾

抗不安作用を示します。(マウス)²⁾

主な副作用は偽アルドステロン症、ミオパシーなどです。

【文献】 1) K.Iwasaki, et al.: J.Clin. Psychiatry, 66(2)248(2005) 2) 栗山久・他: 精神神経薬理, 18(3)179(1996)



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3. 相互作用 併用注意(併用に注意すること)

【薬剤名等: カンゾウ含有製剤 グリチルリチン酸及びその塩類を含有する製剤】

4. 副作用 本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していないため、発現頻度は不明である。 (1)重大な副作用 1)偽アルドステロン症: 低カリウム血症、血圧上昇、ナトリウム・体液の貯留、浮腫、体重増加等の偽アルドステロン症があらわれることがあるので、観察(血清カリウム値の測定等)を十分に行い、異常が認められた場合には投与を中止し、カリウム剤の投与等の適切な処置を行うこと。 2)ミオパシー: 低カリウム血症の結果としてミオパシーがあらわれることがあるので、観察を十分に行い、脱力感、四肢痙攣・麻痺等の異常が認められた場合には投与を中止し、カリウム剤の投与等の適切な処置を行うこと。(2003年9月改訂)

* その他の使用上の注意、組成・性状等は製品添付文書をご覧ください。

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(2005年7月制作)

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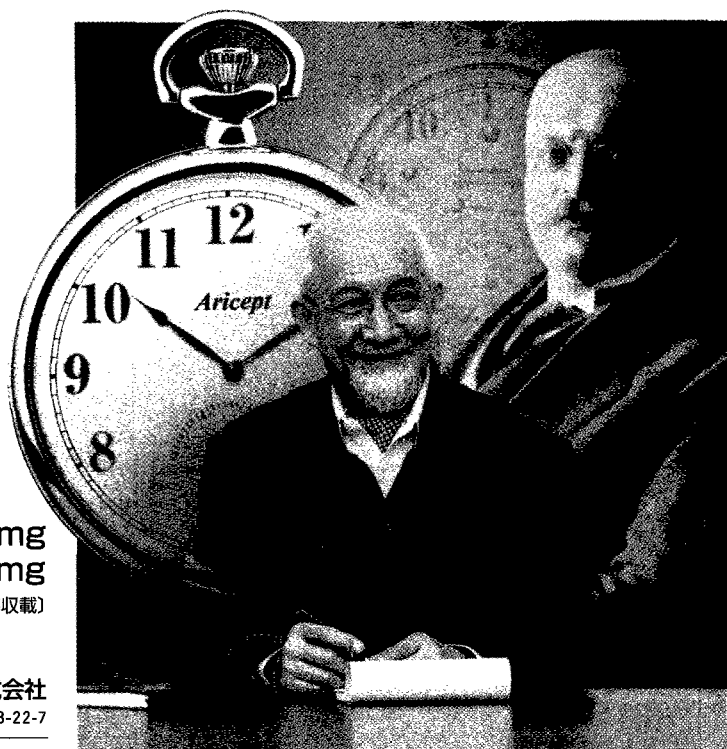


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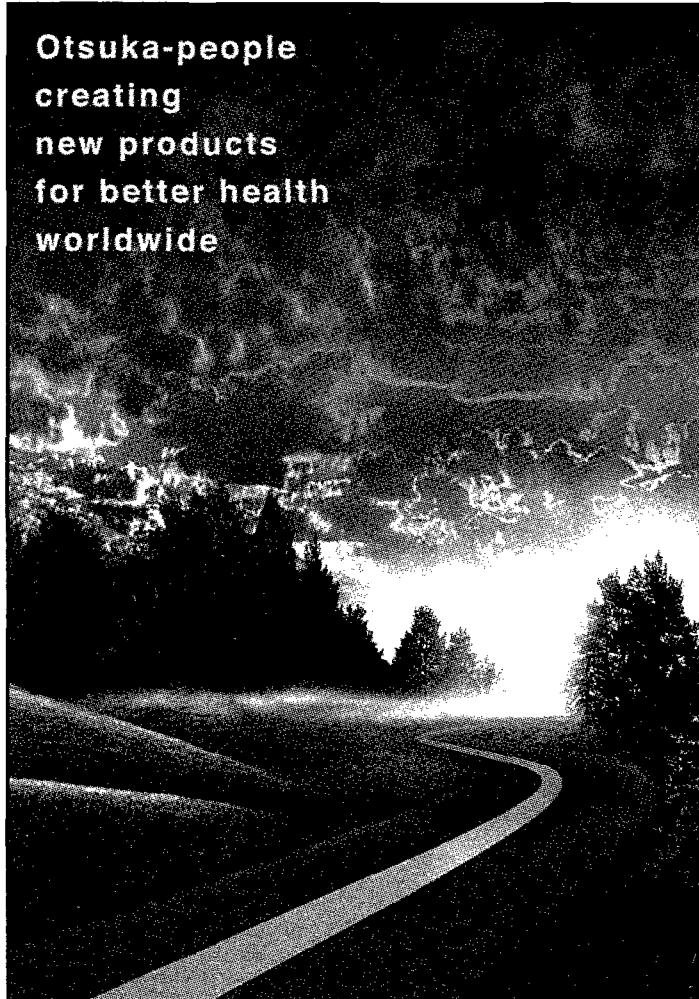


アルツハイマー病は、Alois Alzheimer博士によって発見されました。

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ダイナミックで複雑な脳の働きを新しい切り口でとらえ直す

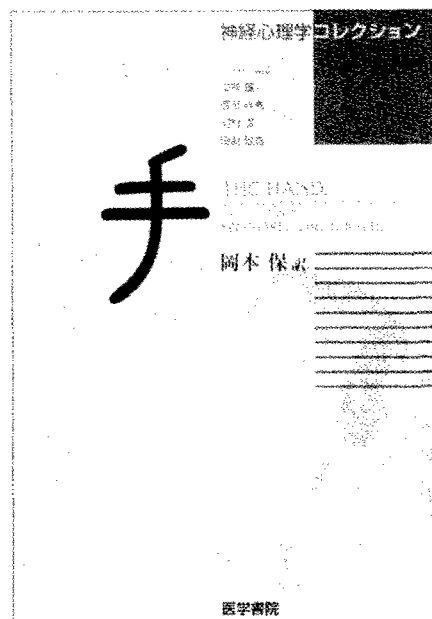
手

原著=Sir Charles Bell K.G.H.

訳=岡本 保 富坂診療所神経内科

新刊

「表情を解剖する」に次ぐチャールズ・ベルの名著発掘の第2弾。ヒトのヒトたるゆえんを「手」に象徴させ、手の比較解剖学的検討から、その生理的、解剖学的な機能とその広範な作用を自筆の多数の美しいイラストとともに供覧する。ダーウィンの「種の起源」に影響を与え、進化論の誕生を促した古典中の古典。



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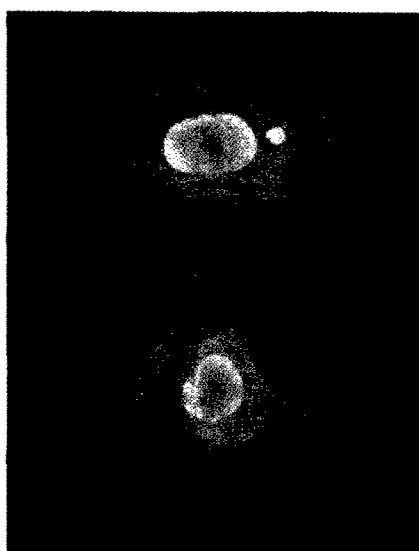
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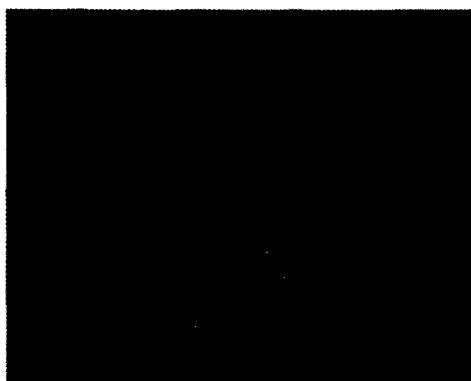
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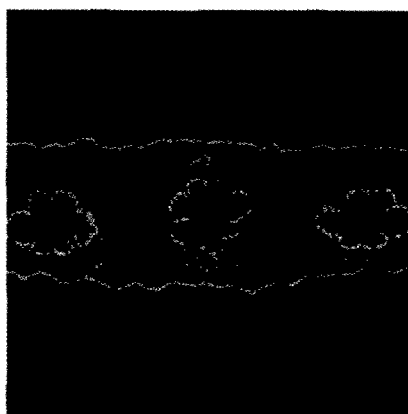
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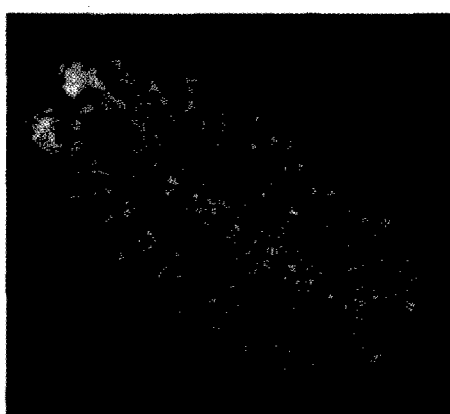
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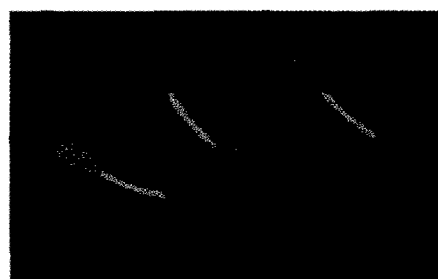


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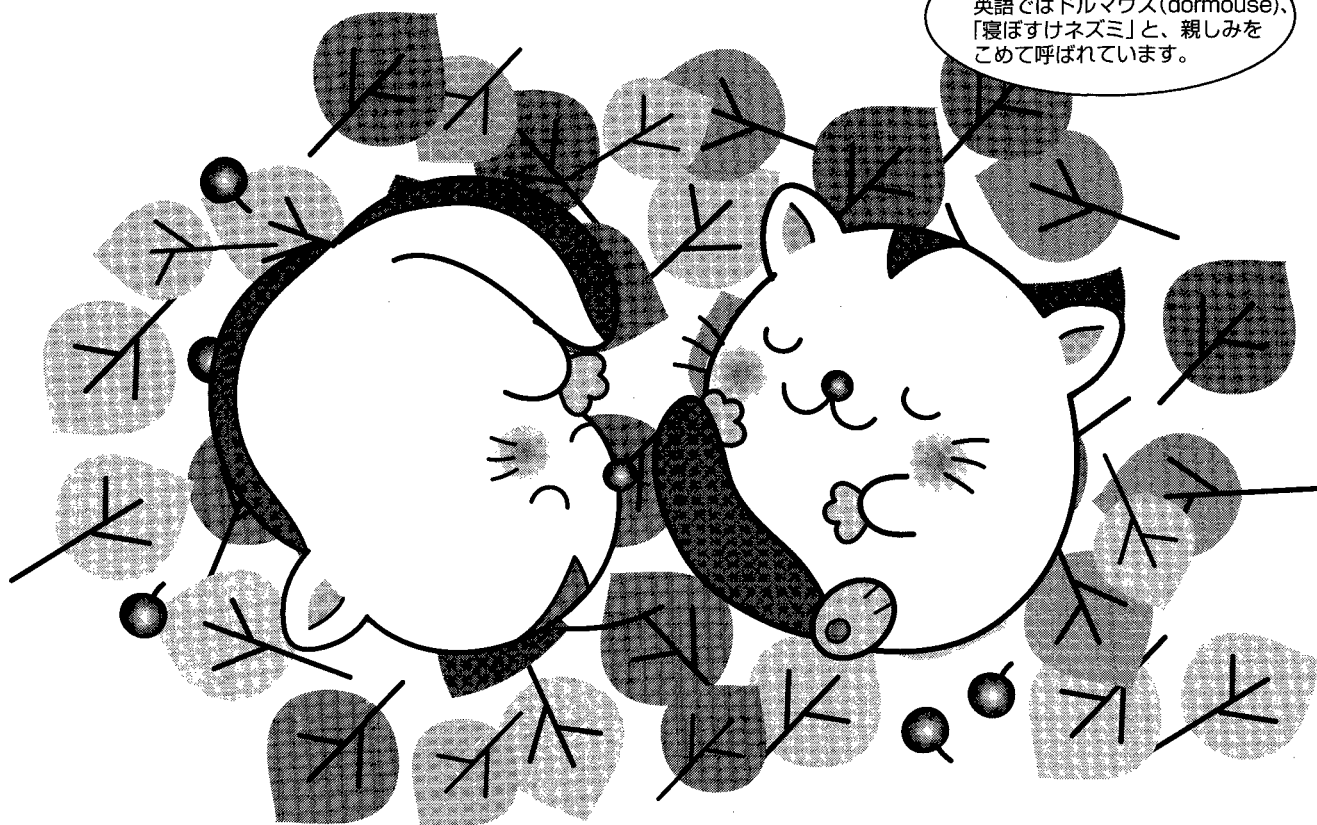
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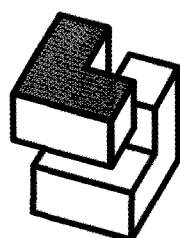
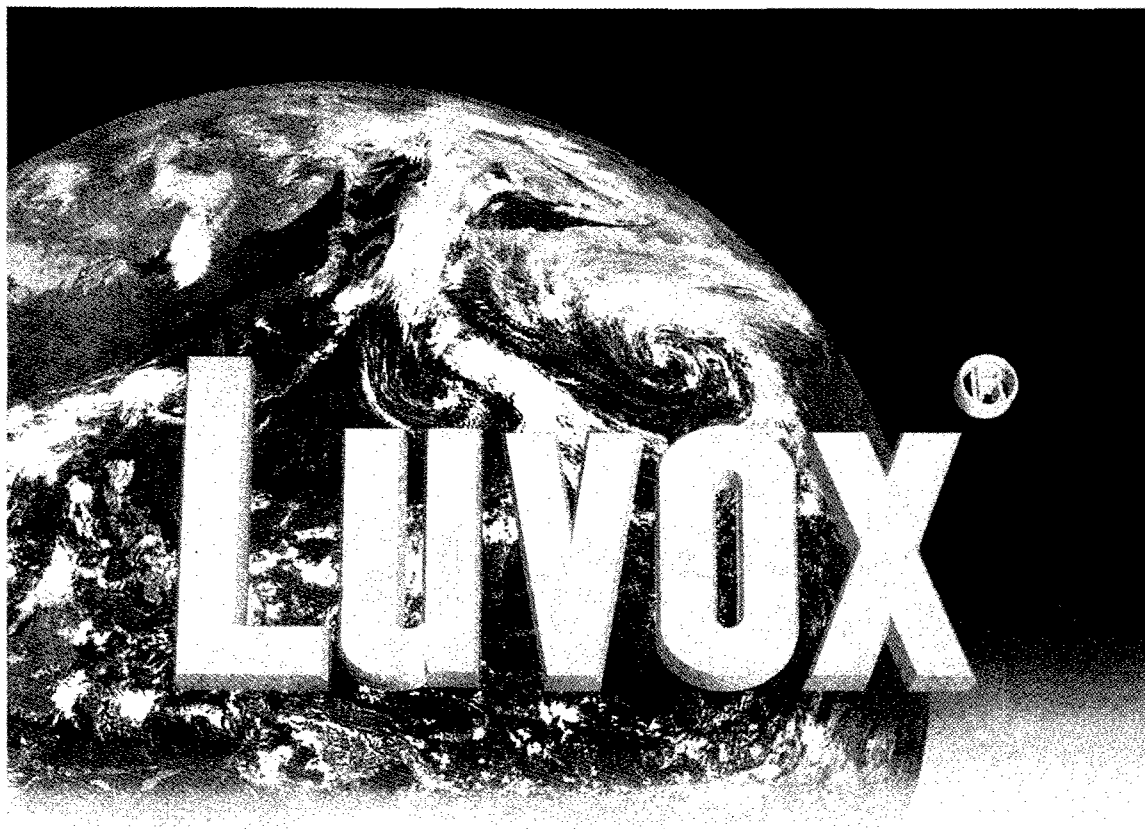


発売
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大阪市中央区平野町2-6-9



プロモーション提携
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DR-(A4) 2005年4月作成



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薬価基準収載

*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) 昏睡状態の患者[昏睡状態を悪化させるおそれがある。]
- 2) バルビツール酸誘導体等の中枢神経抑制剤の強い影響下にある患者[中枢神経抑制作用が増強されることがある。]
- 3) エピネフリンを投与中の患者[「相互作用」の項参照]
- 4) 本剤の成分に対し過敏症の患者

【組成・性状】

1. 組成

	成分・分量	添加物
リスパダール錠 1mg	1錠中 リスベリドン1.00mg	乳糖、トウモロコシデンプン、結晶セルロース、ヒドロキシプロピルメチルセルロース2910、ラウリル硫酸ナトリウム、軽質無水ケイ酸、ステアリン酸マグネシウム、酸化チタン、タルク、プロピレングリコール、マクロゴール6000、カルナウバロウ
リスパダール錠 2mg	1錠中 リスベリドン2.00mg	
リスパダール錠 3mg	1錠中 リスベリドン3.00mg	
リスパダール細粒 1%	1g中 リスベリドン10.0mg	乳糖、ヒドロキシプロピルメチルセルロース2910、軽質無水ケイ酸

2. 性状

リスパダール錠: 白色のフィルムコーティング錠

	外形	直径 (mm)	厚さ (mm)	重量 (g)	識別番号
1mg	表裏面 裏面 側面	6.6	3.1	0.10	JK101
2mg	表裏面 裏面 側面	7.1	3.8	0.13	JK102
3mg	表裏面 裏面 側面	8.1	4.3	0.20	JK103

リスパダール細粒:

	剤形	色
細粒1%	細粒	白色

リスパダール内用液1mg/mL: 1mL中リスベリドン1.0mgを含有する無色澄明の液である。添加物として酒石酸、安息香酸、水酸化ナトリウムを含有する。pHは2.0~4.0

【効能・効果】統合失調症

【用法・用量】

【錠・細粒】 通常、成人にはリスベリドンとして1回1mg1日2回より始め、徐々に増量する。維持量は通常1日2~6mgを原則として1日2回に分けて経口投与する。なお、年齢、症状により適宜増減する。但し、1日量は12mgをこえないこと。

【内用液】 通常、成人にはリスベリドンとして1回1mg (1mL) 1日2回より始め、徐々に増量する。維持量は通常1日2~6mg (2~6mL) を原則として1日2回に分けて経口投与する。なお、年齢、症状により適宜増減する。但し、1日量は12mg (12mL) をこえないこと。

参考:内用液の使用法

1. 本剤を直接服用するか、もしくは1回の服用量を水、ジュース又は汁物に混ぜて、コップ一杯(約150mL)くらいに、希釈して使用すること。なお、希釈後はなるべく速やかに使用するよう指導すること。2. 茶葉抽出飲料(紅茶、烏龍茶、日本茶等)及びコーラは、混合すると含量が低下することがあるので、希釈して使用することは避けるよう指導すること。3. 添付のビペットの目盛はそれぞれ約0.5mL、1mL、1.5mL、2mL、2.5mL及び3mLに相当する。

【使用上の注意】(一部抜粋)

1. 慎重投与(次の患者には慎重に投与すること)

1) 心・血管系疾患、低血圧、又はそれらの疑いのある患者[一過性の血圧降下が見られることがある。] 2) パーキンソン病のある患者[錐体外路症状が悪化するおそれがある。] 3) てんかん等の痙攣性疾患、又はこれらの既往歴のある患者[痙攣閾値を低下させるおそれがある。] 4) 自殺企図の既往及び自殺念慮を有する患者[症状を悪化させるおそれがある。] 5) 肝障害のある患者[肝障害を悪化させるおそれがある。] 6) 腎障害のある患者[本剤の半減期の延長及びAUCが増大することがある。] 7) 糖尿病又はその既往歴のある患者、あるいは糖尿病の家族歴、高血糖、肥満等の糖尿病の危険因子を有する患者[血糖値が上昇することがある。] 8) 高齢者[「高齢者への投与」の項参照] 9) 小児[「小児等

への投与」の項参照] 10) 薬物過敏症の患者 11) 脱水・栄養不良状態等を伴う身体的疲弊のある患者[Syndrome malin(悪性症候群)が起こりやすい。]

2. 重要な基本的注意

1) 治療初期にα交感神経遮断作用に基づく起立性低血圧があらわれることがあるので、少量から徐々に増量し、低血圧があらわれた場合は減量等、適切な処置を行うこと。2) 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、本剤投与中の患者には自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。3) 興奮、誇大性、敵意等の陽性症状を悪化させる可能性があるため観察を十分に行い、悪化がみられた場合には他の治療法に切り替えるなど適切な処置を行うこと。

3. 相互作用

本剤は主として肝代謝酵素CYP2D6で代謝される。

1) 併用禁忌(併用しないこと): エピネフリン(ボスミン)

2) 併用注意(併用に注意すること): 中枢神経抑制剤(バルビツール酸誘導体等)、ドパミン作動薬、降圧薬、アルコール、カルバマゼピン

4. 副作用

総症例4038例中、副作用(臨床検査値異常を含む)は1183例2931件(29.30%)に認められた。その主なものはアカシジア201件(4.98%)、不眠(症)173件(4.28%)、便秘111件(2.75%)、振戦108件(2.67%)、流涎103件(2.55%)、眠気100件(2.48%)、不安98件(2.43%)、筋強剛92件(2.28%)、焦躁感87件(2.15%)、倦怠(感)84件(2.08%)であった。

1) 重大な副作用

(1) Syndrome malin(悪性症候群)(0.1%未満): 無動減黙、強度の筋強剛、嚥下困難、頻脈、血圧の変動、発汗等が現れ、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、水分補給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。なお、高熱が持続し、意識障害、呼吸困難、循環虚脱、脱水症状、急性腎不全へと移行し、死亡することがある。

(2) 遅発性ジスキネジア(0.1~5%未満): 長期投与により、口周囲等の不随意運動があらわれ、投与中止後も持続することがある。

(3) 麻痺性イレウス(頻度不明): 他の抗精神病薬で、腸管麻痺(食欲不振、悪心・嘔吐、著しい便秘、腹部の膨満あるいは弛緩及び腸内容物のうっ滞等の症状)を来し、麻痺性イレウスに移行することがあるので、本剤との併用により腸管麻痺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。なお、本剤は動物実験(イヌ)で制吐作用を有することから、悪心・嘔吐を不顕性化する可能性があるため注意すること。

(4) 抗利尿ホルモン不適合分泌症候群(SIADH)(頻度不明): 低ナトリウム血症、低浸透圧血症、尿中ナトリウム排泄量の増加、高尿尿、痙攣、意識障害等を伴う抗利尿ホルモン不適合分泌症候群(SIADH)があらわれることがある。

(5) 肝機能障害、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、投与を中止し、適切な処置を行うこと。

(6) 横紋筋融解症(0.1%未満): 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、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。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) 不整脈(0.1%未満): 心房細動、心室性期外収縮等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するなど、適切な処置を行うこと。

(8) 脳血管障害(0.1%未満): 脳血管障害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。

●その他「使用上の注意」等は製品添付文書をご覧ください。

錠・細粒: ※2004年8月改訂 内用液: ※2004年8月改訂
※2003年8月改訂 ※2003年8月改訂

製造発売元【資料請求先】



ヤンセン ファーマ株式会社

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■ パキシルの特性

- 1 日本で初めて、「うつ病・うつ状態」に加え、「パニック障害」の効能・効果を取得しました。
- 2 1日1回夕食後投与の簡便なSSRI（選択的セロトニン再取り込み阻害剤）です。
- 3 世界100カ国以上で承認され、1億人以上の使用実績があります。本邦においても、発売4年間で約100万人以上に使用されました。
- 4 国内使用成績調査（回収症例数：3,000例）において、うつ病・うつ状態、パニック障害に対して承認時同様の有効性および安全性が認められました。
- 5 市販後臨床試験において、日本で初めてうつ病患者に対するQOLスコア（SF-36）の改善効果が認められました。（うつ病治療でのQOL評価は、総合的な患者満足度、健康状態の改善を意味します。）
- 6 市販後臨床試験において、うつ病・うつ状態患者の不安症状に対しても不安スコア（STAI）の有意な改善効果が認められました。

副作用発現率は、49.8%（324/650例）でした。

- 7 その主な内容は、嘔気（14.3%）、傾眠（13.1%）、口渇（9.2%）、めまい（6.0%）等でした。臨床検査値の異常変動としては、軽度～中等度のALT（GPT）上昇（7.1%）、γ-GTP上昇（4.6%）等がみられました（承認時）。重大な副作用として、「セロトニン症候群」、「悪性症候群」、「錯乱、痙攣」、「抗利尿ホルモン不適合分泌症候群（SIADH）」、「重篤な肝機能障害」が報告されました。

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. MAO阻害剤を投与中あるいは投与中止後2週間以内の患者（「相互作用」及び「重大な副作用」の項参照）
3. チオリダジンを投与中の患者（「相互作用」の項参照）
4. 18歳未満の患者（大うつ病性障害患者*）（「小児等への投与」の項参照） * DSM-IV参照

■ 効能・効果

うつ病・うつ状態、パニック障害

■ 用法・用量

うつ病・うつ状態：通常、成人には1日1回夕食後、パキシルとして20～40mgを経口投与する。投与は1回10～20mgより開始し、原則として1週ごとに10mg/日ずつ増量する。なお、症状により1日40mgを超えない範囲で適宜増減する。パニック障害：通常、成人には1日1回夕食後、パキシルとして30mgを経口投与する。投与は1回10mgより開始し、原則として1週ごとに10mg/日ずつ増量する。なお、症状により1日30mgを超えない範囲で適宜増減する。

■ 用法・用量に関連する使用上の注意

肝障害及び高度の腎障害のある患者では、血中濃度が上昇することがあるので、増量が必要の場合は、最小限にとどめること。（「薬物動態」の項参照）

■ 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) 躁病の既往歴のある患者【躁転があらわれることがある。】
- (2) てんかんの既往歴のある患者【てんかん発作があらわれることがある。】
- (3) 緑内障のある患者【眩暈があらわれることがある。】
- (4) 抗精神病薬を投与中の患者【悪性症候群があらわれるおそれがある。（「相互作用」の項参照）】
- (5) 高齢者（「高齢者への投与」の項参照）
- (6) 出血の危険性を高める薬剤を併用している患者、出血傾向又は出血性素因のある患者【皮膚及び粘膜出血（胃腸出血等）が報告されている。】

2. 重要な基本的注意

- (1) 眠気、めまい等があらわれることがあるので、自動車の運転等危険を伴う機械を操作する際には十分注意を要する。これらの症状は治療開始早期に多くみられている。（2）うつ病・うつ状態の患者は自殺企図のおそれがあるため、このような患者には、特に治療開始早期は注意深く観察しながら投与すること。また、うつ病・うつ状態以外で本剤の適応となる精神疾患においても自殺企図のおそれがあり、さらにうつ病・うつ状態を伴う場合もあるので、このような患者にも注意深く観察しながら投与すること。（3）投与中止（特に突然の中止）又は減量により、めまい、知覚障害（錯覚、電気ショック様感覚等）、睡眠障害（悪夢を含む）、不安、焦燥、興奮、嘔気、錯乱、錯乱、発汗、頭痛、下痢等があらわれることがある。症状の多くは投与中止後数日以内にあらわれ、軽症から中等症であり、2週間程度で軽快するが、患者によっては重症であったり、また、回復までに2、3ヶ月以上かかる場合もある。これまでに得られた情報からはこれらの症状は薬物依存によるものではないと考えられている。本剤の減量又は投与中止に際しては、以下の点に注意すること。1）突然の投与中止を避けること。投与を中止す

る際は、患者の状態を見ながら数週間又は数ヶ月かけて徐々に減量すること。2）減量又は投与中止後に耐えられない症状が発現した場合には、減量又は中止前の用量にて投与を再開し、より緩やかに減量することを検討すること。3）患者の判断で本剤の服用を中止することのないよう十分な服薬指導をすること。また、飲み忘れにより上記のめまい、知覚障害等の症状が発現することがあるため、患者に必ず指示されたとおり服用するよう指導すること。

3. 相互作用

本剤は、主として肝代謝酵素CYP2D6で代謝される。また、CYP2D6の阻害作用をもつ。

(1) 併用禁忌（併用しないこと）

MAO阻害剤：塩酸セレギリン（エフビー）／チオリダジン（メリル）

(2) 併用注意（併用に注意すること）

セロトニン作用薬：炭酸リチウム、選択的セロトニン再取り込み阻害剤、トリプタン系薬剤（スマトリプタン等）、セロトニン前駆物質（L-トリプタン、5-HTDロキシトリプタン等）含有製剤又は食品等、トラマドール、リネゾリド、セイヨウオトギリソウ（St. John's Wort）、セント・ジョーンズ・ワート含有食品等／フェノチアジン系抗精神病薬／バルブエナジン／リスベリドン／三環系抗うつ剤：塩酸アミトリプチン、塩酸ノルトリプチン、塩酸イミプラミン、抗不整脈剤：塩酸フロパフェノン、酢酸フレカイニド／β-遮断剤：マレイン酸チモロール／酒石酸メトプロロール／キニジン、シメチジン／フェニトイン、フェリバルブール、カルバマゼピン、リファンピシン／ワルファリン／ジゴキシン／アルコール（飲酒）

4. 副作用

うつ病・うつ状態患者及びパニック障害患者を対象とした本邦での臨床試験において、本剤が投与された総症例650例中324例（49.8%）に643件の副作用が発現した。その主な内容は、嘔気（14.3%）、傾眠（13.1%）、口渇（9.2%）、めまい（6.0%）等であった。臨床検査値の異常変動としては、軽度～中等度のALT（GPT）上昇（7.1%）、γ-GTP上昇（4.8%）等がみられた（承認時）。使用成績調査3112例中、487例（15.7%）に臨床検査値異常を含む副作用が報告された。その主なものは、嘔気（4.9%）、傾眠（3.6%）、食欲不振（1.3%）、めまい（1.3%）であった（第7回安全性定期報告時）。

(1) 重大な副作用

- 1) セロトニン症候群（1%未満）：不安、焦燥、興奮、錯乱、幻覚、反射亢進、ミオクロヌス、発汗、戦慄、頻脈、振戦等があらわれるおそれがある。セロトニン作用薬との併用時に発現する可能性が高くなるため、特に注意すること（「相互作用」の項参照）。異常が認められた場合には、投与を中止し、水分補給等の全身管理とともに適切な処置を行うこと。2) 悪性症候群（1%未満）：無動、強直、強度の筋弛緩、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がある。抗精神病薬との併用時にあらわれることが多いため、特に注意すること。異常が認められた場合には、抗精神病薬及び本剤の投与を中止し、体冷却、水分補給等の全身管理とともに適切な処置を行うこと。本症発現時には、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。3) 錯乱、幻覚、せん妄、痙攣（1%未満）：錯乱、幻覚、せん妄、痙攣があらわれることがある。異常が認められた場合には、減量又は投与を中止する等適切な処置を行うこと。4) 抗利尿ホルモン不適合分泌症候群（SIADH）（頻度不明^{(1),(2)}）：主に高齢者において、低ナトリウム血症、痙攣等があらわれることが報告されている。異常が認められた場合には、投与を中止し、水分摂取の制限等適切な処置を行うこと。5) 重篤な肝機能障害（頻度不明^{(1),(2)}）：肝不全、肝壊死、肝炎、黄疸等があらわれることがある。必要に応じて肝機能検査を行い、異常が認められた場合には、投与を中止する等適切な処置を行うこと。

注1）自発報告又は海外のみで認められている副作用については頻度不明とした。

注2）海外での頻度：0.01%未満

- 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。

うつ病・うつ状態、パニック障害に、1日1回のSSRI。

選択的セロトニン再取り込み阻害剤（SSRI） 薬価基準収載

パキシル[®] 錠20mg
錠10mg

Paxil[®] 塩酸パロキセチン水和物 劇薬・指定医薬品・処方せん医薬品^(注)

注）注意－医師等の処方せんにより使用すること。

製造販売元・資料請求先

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

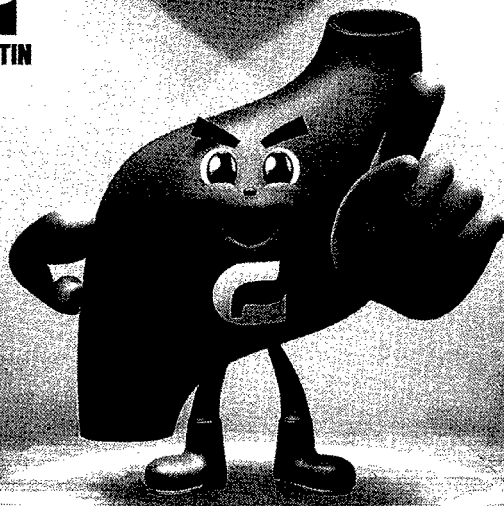
http://www.glaxosmithkline.co.jp

http://www.paxil.jp

プロモーション提携

吉富薬品株式会社

大阪市中央区淡路町2-5-6



消化管運動促進剤

指定医薬品

ガスモチン[®]

〈クエン酸モサブリド製剤〉

GASMOTIN[®]

■薬価基準収載

錠5mg
錠2.5mg
散

特徴

- 1 セロトニン5-HT₄受容体の選択的刺激作用。〔in vitro, イヌ〕
- 2 食前・食後投与が可能。
- 3 薬効は速やかに発現。
- 4 ドパミンD₂受容体遮断作用はない。(マウス, ラット, イヌ)
- 5 慢性胃炎に伴う消化器症状(胸やけ, 悪心・嘔吐)の改善に有用。
- 6 承認時の副作用発現率は4.0%(40例/998例)。

その主なもの；下痢・軟便1.8%(18件), 口渇0.5%(5件), 倦怠感0.3%(3件)等。

承認時の臨床検査値の異常変動は3.8%(30例/792例)。

その主なもの；好酸球増多1.1%(6件/528例), 中性脂肪の上昇1.0%(5件/511例), AST(GOT)上昇0.4%(3件/770例), ALT(GPT)上昇0.4%(3件/768例), ALP上昇0.4%(3件/740例), γ-GTP上昇0.4%(3件/719例), BUN上昇0.4%(3件/730例)等。

重大な副作用；劇症肝炎, 肝機能障害, 黄疸(いずれも0.1%未満)。

■効能・効果

慢性胃炎に伴う消化器症状(胸やけ, 悪心・嘔吐)

■用法・用量

通常, 成人には, クエン酸モサブリド無水物として1日15mgを3回に分けて食前または食後に経口投与する。

■使用上の注意

1. 重要な基本的注意

一定期間(通常2週間)投与しても消化器症状の改善がみられない場合, 長期にわたって漫然と投与しないこと。

2. 相互作用

併用注意(併用に注意すること)

薬剤名	臨床症状・措置方法	機序・危険因子
抗コリン作用を有する薬剤 硫酸アトロピン 臭化ブチルスコポラミン等	本剤の作用が減弱する可能性があるため, 抗コリン剤を服用する場合は, 服用間隔をあけるなど注意すること。	本剤の消化管運動の促進作用は, コリン作動性神経の賦活により発現するため, 抗コリン剤の併用により本剤の作用が抑制される。

3. 副作用

998例中40例(4.0%)に副作用がみられた。その主なものは下痢・軟便(1.8%), 口渇(0.5%), 倦怠感(0.3%)等であった。臨床検査値では792例中30例(3.8%)に異常変動がみられた。その主なものは好酸球増多(1.1%), 中性脂肪の上昇(1.0%), AST(GOT), ALT(GPT), ALPおよびγ-GTPの上昇(各0.4%)等であった。(承認時)

(1) 重大な副作用

劇症肝炎, 肝機能障害, 黄疸(いずれも0.1%未満)

劇症肝炎, 著しいAST(GOT), ALT(GPT), γ-GTPの上昇等を伴う重篤な肝機能障害, 黄疸があらわれることがあり, 死亡に至った例もあるので, 観察を十分に行い, 異常が認められた場合には, 直ちに投与を中止し, 適切な処置を行うこと。

(2) その他の副作用

分類	0.1~5%未満	頻度不明
過敏症	浮腫	発疹, 蕁麻疹
血液	好酸球増多, 白血球減少	
消化器	下痢・軟便, 口渇, 腹痛, 嘔気・嘔吐, 味覚異常	腹部膨満感, 口内しびれ感(舌, 口唇等を含む)
肝臓	AST(GOT), ALT(GPT), ALP, γ-GTP, ビリルビンの上昇	
循環器	心悸亢進	
精神神経系	めまい・ふらつき, 頭痛	
その他	倦怠感, 中性脂肪の上昇	振戦

※その他の使用上の注意等詳細は添付文書をご参照ください。

使用上の注意の改訂に十分ご留意ください。

製造販売元 〔資料請求先〕



大日本製薬

〒541-0045 大阪市中央区道修町2-6-8

2005年7月作成

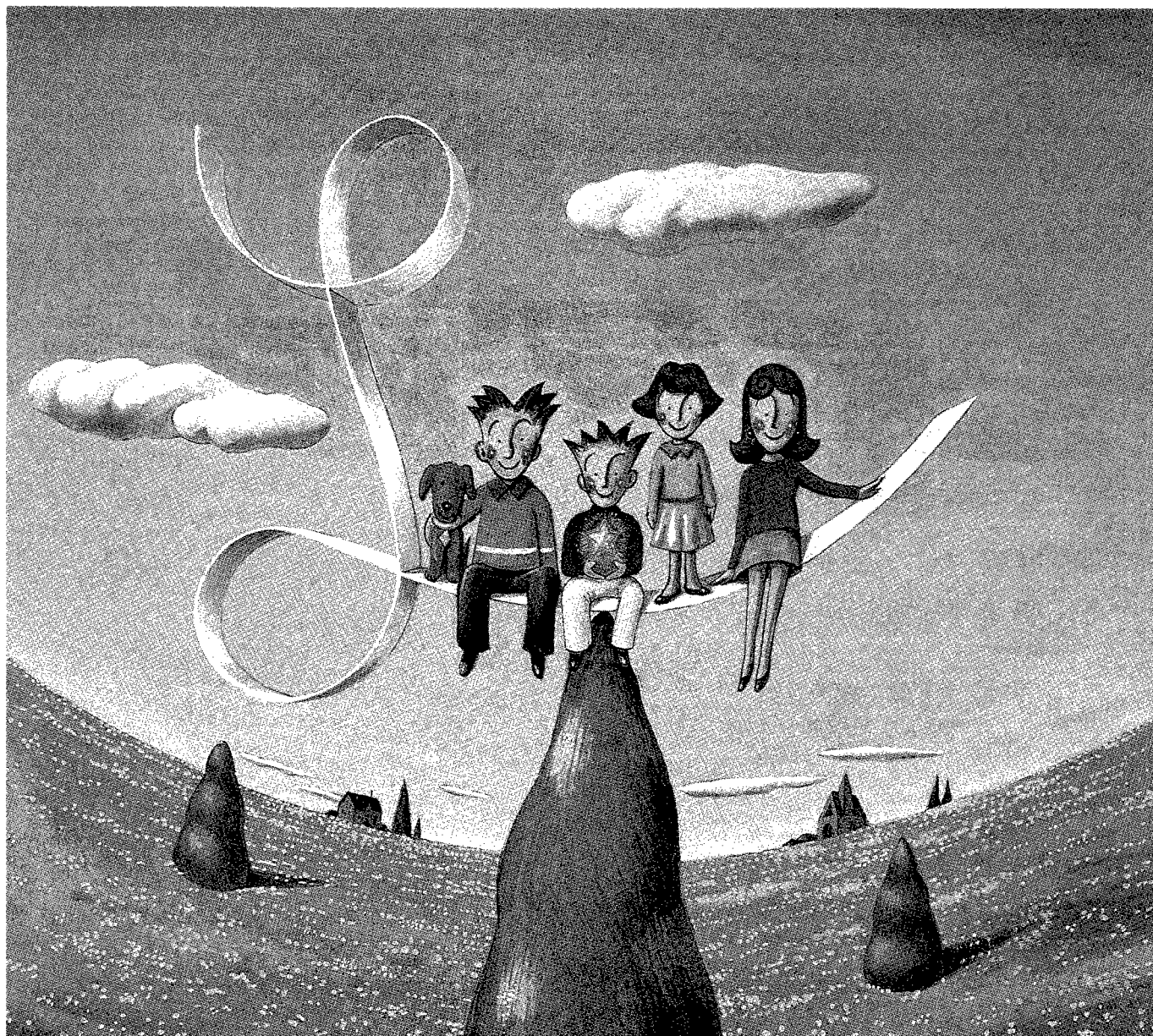


DAINIPPON
SUMITOMO
PHARMA

大日本製薬と住友製薬は2005年10月1日から「大日本住友製薬」へ



大日本製薬



抗精神病剤 ————— 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）

ルーラン錠[®] 48

Lullan[®] 塩酸ペロスピロン 水和物 —————

■ 効能・効果、用法・用量および禁忌を含む使用上の注意等につきましては、製品添付文書をご覧ください。

住友製薬 | 製造発売元 (資料請求先)
住友製薬株式会社
〒541-8510 大阪市中央区道修町2丁目2番8号

〈製品に関するお問い合わせ先〉 ぐすり情報センター ☎ 0120-03-4389
(受付時間) 月～金 9:00～17:30 (祝・祭日を除く)
<http://e-medicine.sumitomopharm.co.jp>

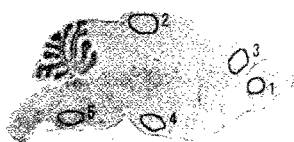
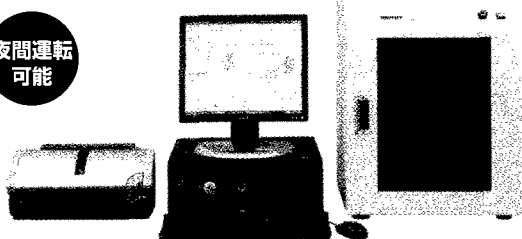
吉富薬品 | 提携
吉富薬品株式会社
〒541-0047 大阪市中央区淡路町2丁目5番6号

クラボウの プレパレート関連製品

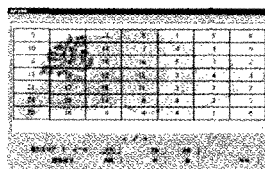
面倒なプレパレートの顕微鏡解析が省力化!!

AP-200

夜間運転
可能



*切片スコアリングイメージ図



プレパレートイメージャー
(プレパレート自動画像撮込解析装置)

特許出願中!!

組織切片全体像の色ムラ(顕微鏡データ貼り合わせ時)が解消!

- 高解像度のスキャナで自動的に組織切片全体を撮影・保存!
- 各組織切片の発現量を定量化!
- 一度に組織切片全体を解析できる為、色ムラのない切片全体像を表示!
- プレパレートは最大200枚セット(W76×D26mm)可能!

◆運転内容

プレパレートを収納ラックにセット(準備)

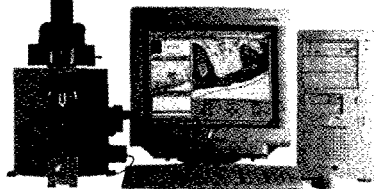
- 1 自動で収納ラックからスキャナ部へ搬送
- 2 自動でプレパレート画像撮り込み
(全体スキャン/サンプル部画像撮り込み/画像ストレージ)
- 3 自動でスキャナ部から収納ラックに返送

*1~3の
自動運転

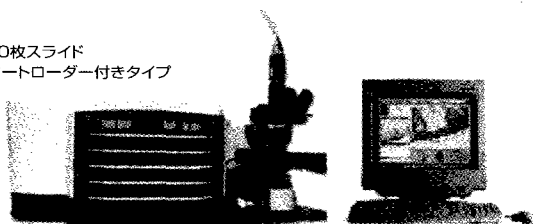
離れた場所でも瞬時にイメージの取得が可能!

MedMicro

MedMicro
基本システム



50枚スライド
オートローダー付きタイプ



リアルタイム・ テレパソロジー・システム

TRESTLE

表現型解析の強力なツール

- 顕微鏡を覗くのと変わらないスピードで、リアルタイムイメージを転送。
- ステージの移動やピントの調整・レンズの切り替えも、離れた場所からインタラクティブにアクセス可能。
- 病理サンプルを輸送すると思わぬトラブルが… 本システムがあれば、世界中どこにいても、インターネットを通じて標本を観察できます。
- マルチメディア
→複数のサイトで、同じ顕微鏡画像を見ながらのテレ・カンファレンスに。
→時差のある海外とのやりとりに。最大50枚のスライドを、どこからでも自由自在に操れます。(スライドオートローダー搭載時)
→病理サンプルのテレ・コンサルテーションに。

★プレパレート関連製品の詳細については、別途お問合せ下さい。

※本製品は医療器具ではなく、研究用に限定して販売しています。医薬品の製造、品質管理、各種診断、治療および研究など、その使用目的にかかわらず、人体には使用しないで下さい。

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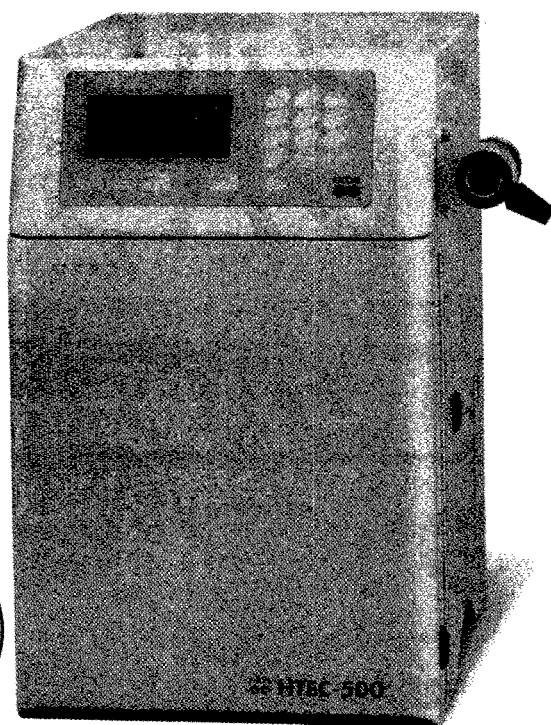
HTEC-500

生体内神経伝達物質の高感度分析に
多用されているエイコム300シリーズ。
HTEC-500はさらに安定性・
感度が上がりました。

生体内神経活動をリアルタイムで観察することは、
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エイコムでは今以上の高感度分析には一体化が
必要だと考え分析に必要なユニットを
すべてまとめてHTEC-500型を完成しました。
専用器的な高感度分析計として、限りなく
目標に近づくことを目指します。

- 感度はドーパミン・セロトニン
で30fgを実現。
- 設置面積はB4サイズ。

マイクロダイアリス
の分析計としても
最適です。



酸化窒素分析システム

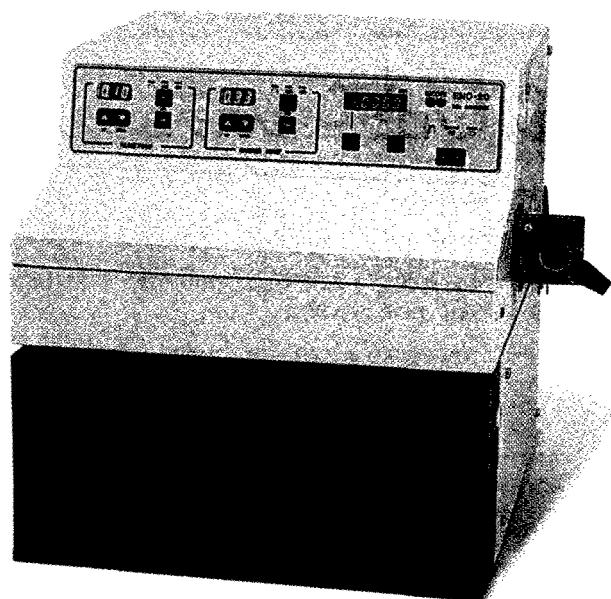
ENO-20

生体液中の窒素酸化物測定
のために開発されました。

液体クロマトグラフとグリース試薬法の
ドッキングで大きな特長を得ました。

- 0.1ピコモルの他に例を見ない高感度。
- NO_2^- 、 NO_3^- を高精度で分離測定。
- 安定性と再現性が良い高稼働率測定器。

NO_2^- 、 NO_3^- の
測定から生体内
NOの動態を知ることが
できます。



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笑顔への起き上がり、SNRI

トレドミンは、日本初のセロトニン・ノルアドレナリン再取り込み阻害剤です。



セロトニン・ノルアドレナリン再取り込み阻害剤 (SNRI) 薬価基準収載

トレドミン[®]錠 15/25

Toledomin[®] Tablets

* 劇薬、指定医薬品、処方せん医薬品 塩酸ミルナシブラン錠

※注意—医師等の処方せん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. モノアミン酸化酵素阻害剤を投与中の患者【「使用上の注意 3. 相互作用」の項参照】
3. 尿閉(前立腺疾患等)のある患者【本剤はノルアドレナリン再取り込み阻害作用を有するため、症状を悪化させるおそれがある。】

【効能・効果】 うつ病・うつ状態

【効能・効果に関連する使用上の注意】 18歳未満の患者に投与する際は、リスクとベネフィットを考慮すること。【「小児等への投与」の項参照】

【用法・用量】 通常、成人には、塩酸ミルナシブランとして1日50mgを初期用量とし、1日100mgまで漸増し、食後、分割経口投与する。なお、年齢、症状により適宜増減する。ただし、高齢者には、1日30mgを初期用量とし、1日60mgまで漸増し、食後、分割経口投与する。

【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) 排尿困難のある患者【本剤はノルアドレナリン再取り込み阻害作用を有するため、症状を悪化させるおそれがある。】
- (2) 緑内障又は眼内圧亢進のある患者【症状を悪化させるおそれがある。】
- (3) 心疾患のある患者【血圧上昇、頻脈等があらわれ、症状を悪化させるおそれがある。】
- (4) 肝障害のある患者【高い血中濃度が持続するおそれがある。】
- (5) 腎障害のある患者【外国における腎機能障害患者での体内薬物動態試験で、高い血中濃度が持続する傾向が認められているので、投与量を減じて使用すること。】
- (6) てんかん等の痙攣性疾患又はこれらの既往歴のある患者【痙攣を起こすことがある。】
- (7) 躁うつ病患者【躁転、自殺企図があらわれることがある。】
- (8) 脳の器質障害又は統合失調症の素因のある患者【精神症状を増悪させることがある。】
- (9) 小児【「7. 小児等への投与」の項参照】
- (10) 高齢者【「5. 高齢者への投与」の項参照】

2. 重要な基本的注意

- (1) 眠気、めまい等が起こることがあるので、本剤投与中の患者には、自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。
- (2) うつ症状を呈する患者は自殺企図のおそれがあるので、このような患者には、注意深く観察しながら投与すること。

3. 相互作用

- (1) 併用禁忌(併用しないこと)

モノアミン酸化酵素阻害剤(塩酸セレギリン(エフビー))

- (2) 併用注意(併用に注意すること)

アルコール、中枢神経抑制剤(バルビツール酸誘導体等)、降圧剤(クロニジン等)、炭酸リチウム、5-HT_{1A}/1D受容体作動薬(コハク酸スマトリプタン等)、ジゴキシン、エビネブリン、ノルエビネブリン

4. 副作用

総症例467例中、150例(32.1%)に副作用が報告された。発現件数は236件で、主な副作用は、口渇35件(7.5%)、悪心・嘔吐28件(6.0%)、便秘27件(5.8%)、眠気19件(4.1%)

等であった。臨床検査値の異常変動は、AST(GOT)、ALT(GPT)、γ-GTP、トリグリセライドの上昇等が認められた。(承認時)

(1) 重大な副作用

- 1) 悪性症候群(Syndrome malin)(頻度不明): 無動緘黙、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悪性症候群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、体冷却、水分補給等の全身管理とともに適切な処置を行うこと。
- 2) セロトニン症候群(頻度不明): セロトニン症候群があらわれることがあるので、激越、錯乱、発汗、幻覚、反射亢進、ミオクロス、戦慄、頻脈、振戦、発熱、協調異常等が認められた場合には、投与を中止し、水分補給等の全身管理とともに適切な処置を行うこと。
- 3) 痙攣(頻度不明): 痙攣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、投与を中止し、適切な処置を行うこと。
- 4) 白血球減少(頻度不明): 白血球減少があらわれることがあるので、血液検査等の観察を十分に行い、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。
- 5) 重篤な皮膚障害(頻度不明): 皮膚粘膜眼症候群(Stevens-Johnson症候群)等の重篤な皮膚障害があらわれることがあるので、観察を十分に行い、発熱、紅斑、そう痒感、脱皮、口内炎等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。
- 6) 抗利尿ホルモン不適合分泌症候群(SIADH)(頻度不明): 低ナトリウム血症、低浸透圧血症、尿中ナトリウム増加、高張尿、意識障害等を伴う抗利尿ホルモン不適合分泌症候群があらわれることがあるので、食欲不振、頭痛、嘔気、嘔吐、全身倦怠感等があらわれた場合には電解質の測定を行い、異常が認められた場合には、投与を中止し、水分摂取制限等の適切な処置を行うこと。
- 7) 肝機能障害、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し、適切な処置を行うこと。

5. 高齢者への投与

高齢者での体内薬物動態試験で、血中濃度が上昇し、薬物の消失が遅延する傾向が認められているので、少量(1日30mg)から投与を開始するとともに患者の状態を観察しながら慎重に投与すること。また、低ナトリウム血症、抗利尿ホルモン不適合分泌症候群は主に高齢者において報告されているので、注意すること。

7. 小児等への投与

1. 小児等に対する安全性は確立していない(使用経験がない)。
2. 本剤の小児に対する有効性及び安全性を検証するための試験は行われていない。塩酸パロキセチンにおいて海外で実施された7~18歳における大うつ病性障害(DSM-IV*)における分類)患者を対象としたプラセボ対照の臨床試験において有効性が確認できず、また、自殺念慮、自殺企図等の発現頻度がプラセボ群に比較して高かったとの報告がある。

また、18歳未満の大うつ病性障害患者に投与する場合は、投与開始早期から注意深く患者を観察し、新たな自傷、気分変動等の情動不安定の発現もしくは、これらの症状の増悪が観察された場合には徐々に減量するなど慎重に投与を中止すること。

* DSM-IV: American Psychiatric Association(米国精神医学会)のDiagnostic and Statistical Manual of Mental Disorders, 4th edition(DSM-IV精神疾患の診断・統計マニュアル)

■その他の「使用上の注意」については、製品添付文書をご参照下さい。禁忌を含む使用上の注意等の改訂に十分ご留意下さい。

*2005年4月改訂(第11版)

製造販売元(資料請求先)

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H17.05

患者さんひとりひとりの 治療ゴールへ

ジプレキサ®の特徴

- 統合失調症における幻覚・妄想などの陽性症状を改善します。
(海外データ)
- 統合失調症における感情的引きこもり・自閉などの
陰性症状を改善します。(海外データ)
- 主な錐体外路症状の発現率は、アカシジア11.9%(69/580例)、
振戦11.4%(66/580例)などでした。(承認時)
- 1日1回10mg投与で治療効果を示します。

副作用発現率(377例/580例)

国内臨床試験において安全性解析の対象となった計580例中、副作用が377例(65.0%)に認められた。主な副作用は不眠123例(21.2%)、眠気97例(16.7%)、体重増加95例(16.4%)、アカシジア69例(11.9%)、振戦66例(11.4%)、倦怠感62例(10.7%)、不安・焦燥62例(10.7%)、及び興奮・易刺激性58例(10.0%)であった。また、主な臨床検査値異常はALT(GPT)上昇(15.8%)、プロラクチン上昇(14.5%)、AST(GOT)上昇(11.5%)、トリグリセリド上昇(10.3%)であった。(承認時)

重大な副作用

- 1) 高血糖、糖尿病性ケトアシドーシス、糖尿病性昏睡
- 2) Syndrome malin(悪性症候群)
- 3) 肝機能障害、黄疸
- 4) 痙攣
- 5) 遅発性ジスキネジア
- 6) 横紋筋融解症

【警告】

1. 著しい血糖値の上昇から、糖尿病性ケトアシドーシス、糖尿病性昏睡等の重大な副作用が発現し、死亡に至る場合があるので、本剤投与中は、血糖値の測定等の観察を十分に行うこと。
2. 投与にあたっては、あらかじめ上記副作用が発現する可能性があることを、患者及びその家族に十分に説明し、口渇、多飲、多尿、頻尿等の異常に注意し、このような症状があらわれた場合には、直ちに投与を中断し、医師の診察を受けるよう、指導すること。[「重要な基本的注意」の項参照]

【禁忌(次の患者には投与しないこと)】

1. 昏睡状態の患者[昏睡状態を悪化させるおそれがある。]
2. パルビツール酸誘導体等の中枢神経抑制剤の強い影響下にある患者[中枢神経抑制作用が増強される。]
3. 本剤の成分に対し過敏症の既往歴のある患者
4. エピネフリンを投与中の患者[「相互作用」の項参照]
5. 糖尿病の患者、糖尿病の既往歴のある患者

【効能・効果】

統合失調症

【用法・用量】

通常、成人にはオランザピンとして5~10mgを1日1回経口投与により開始する。維持量として1日1回10mg経口投与する。なお、年齢、症状により適宜増減する。ただし、1日量は20mgを超えないこと。

〈ザイデス錠〉

〈用法・用量に関連する使用上の注意〉

本剤は口腔内で速やかに崩壊することから唾液のみ(水なし)でも服用可能であるが、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。

【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) 尿閉、麻痺性イレウス、狭角緑内障のある患者[抗コリン作用により症状を悪化させることがある。]
- (2) てんかん等の痙攣性疾患又はこれらの既往歴のある患者[痙攣閾値を低下させることがある。]
- (3) 肝障害のある患者又は肝毒性のある薬剤による治療を受けている患者[肝障害を悪化させることがある。]
- (4) 高齢者[「高齢者への投与」の項参照]
- (5) 本剤のクリアランスを低下させる要因(非喫煙者、女性、高齢者)を併せ持つ患者[本剤の血漿中濃度が増加することがある。]
- (6) 糖尿病の家族歴、高血糖あるいは肥満等の糖尿病の危険因子を有する患者[「重要な基本的注意」の項参照]

2. 重要な基本的注意

- (1) 本剤の投与により、著しい血糖値の上昇から、糖尿病性ケトアシドーシス、糖尿病性昏睡等の致命的な経過をたどることがあるので、本剤投与中は、血糖値の測定や口渇、多飲、多尿、頻尿等の観察を十分に行うこと。特に、高血糖、肥満等の糖尿病の危険因子を有する患者では、血糖値が上昇し、代謝状態を急激に悪化させるおそれがある。
- (2) 本剤の投与に際し、あらかじめ上記副作用が発現する可能性があることを、患者及びその家族に十分に説明し、口渇、多飲、多尿、頻尿等の異常に注意し、このような症状があらわれた場合には、直ちに投与を中断し、医師の診察を受けるよう、指導すること。
- (3) 本剤の投与により体重増加を来することがあるので、肥満に注意し、肥満の徴候があらわれた場合は、食事療法、運動療法等の適切な処置を行うこと。
- (4) 治療初期に、めまい、頻脈、起立性低血圧等があらわれることがある。心・血管疾患(心筋梗塞あるいは心筋虚血の既往、心不全、伝導異常等)、脳血管疾患及び低血圧が起りやすい状態(脱水、血容量減少、血圧降下剤投与による治療等)が認められる場合には注意すること。
- (5) 本剤は制吐作用を有するため、他の薬剤に基づく中毒、腸閉塞、脳腫瘍等による嘔吐症状を不顕在化することがあるので注意すること。
- (6) 傾眠、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、本剤投与中の患者には高所での作業あるいは自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。

3. 相互作用

本剤の代謝には肝薬物代謝酵素CYP1A2が関与している。また、CYP2D6も関与していると考えられている。[「薬物動態」の項参照]

(1) 併用禁忌(併用しないこと)

薬剤名等	臨床症状・措置方法	機序・危険因子
エピネフリン ボスミン	エピネフリンの作用を逆転させ、重篤な血圧降下を起こすことがある。	エピネフリンはアドレナリン様作用性 α 、 β -受容体の刺激剤であり、本剤の α -受容体遮断作用により β -受容体刺激作用が優位となり、血圧降下作用が増強される。

(2) 併用注意(併用に注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
中枢神経抑制剤 バルビツール酸誘導体等	中枢神経抑制作用があるので、減量するなど注意すること。	本剤及びこれらの薬剤は中枢神経抑制作用を有する。
アルコール	相互に作用を増強することがある。	アルコールは中枢神経抑制作用を有する。
抗コリン作用を有する薬剤 抗コリン性抗パーキンソン薬 フェノチアジン系化合物 三環系抗うつ剤等	腸管麻痺等の重篤な抗コリン性の毒性が強くあらわれることがある。	本剤及びこれらの薬剤は抗コリン作用を有する。
ドパミン作動薬 レボドパ製剤	これらの薬剤のドパミン作動性の作用が減弱することがある。	ドパミン作動性神経において、本剤がこれらの薬剤の作用に拮抗することによる。
フルボキサミン	本剤の血漿中濃度を増加させるので、本剤を減量するなど注意すること。	これらの薬剤は肝薬物代謝酵素(CYP1A2)阻害作用を有するため本剤のクリアランスを低下させる。
塩酸シプロフロキサシン	本剤の血漿中濃度を増加させる可能性がある。	
カルバマゼピン	本剤の血漿中濃度を低下させる。	これらの薬剤は肝薬物代謝酵素(CYP1A2)を誘導するため本剤のクリアランスを増加させる。
オメプラゾール リファンピシン	本剤の血漿中濃度を低下させる可能性がある。	
喫煙	本剤の血漿中濃度を低下させる。	喫煙は肝薬物代謝酵素(CYP1A2)を誘導するため本剤のクリアランスを増加させる。

4. 副作用

国内臨床試験において安全性解析の対象となった計580例中、副作用が377例(65.0%)に認められた。主な副作用は不眠123例(21.2%)、眠気97例(16.7%)、体重増加95例(16.4%)、アカシジア69例(11.9%)、振戦66例(11.4%)、倦怠感62例(10.7%)、不安・焦燥62例(10.7%)、及び興奮・易刺激性58例(10.0%)であった。また、主な臨床検査値異常はALT(GPT)上昇(15.8%)、プロラクチン上昇(14.5%)、AST(GOT)上昇(11.5%)、トリグリセリド上昇(10.3%)であった。(オランザピン錠(普通錠)承認時)

(1) 重大な副作用

- 1) 高血糖、糖尿病性ケトアシドーシス、糖尿病性昏睡:高血糖があらわれ、糖尿病性ケトアシドーシス、糖尿病性昏睡から死亡に至るなどの致命的な経過をたどることがあるので、血糖値の測定や、口渇、多飲、多尿、頻尿等の観察を十分に行い、異常が認められた場合には、投与を中止し、インスリン製剤の投与を行うなど、適切な処置を行うこと。
- 2) Syndrome malin(悪性症候群):無動痙攣、強度の筋強剛、脈拍及び血圧の変動、発汗等が発現し、それに引き続き発熱から死亡に至る場合は、投与を中止し、水分補給、体冷却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、血清CK(CPK)の上昇や白血球の増加がみられることが多い。また、ミオグロビン尿を伴う腎機能の低下に注意すること。なお、高熱が持続し、意識障害、呼吸困難、循環虚脱、脱水症状、急性腎不全へと移行し、死亡した例が報告されている。
- 3) 肝機能障害、黄疸:AST(GOT)、ALT(GPT)、 γ -GTP、ALP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。
- 4) 痙攣:痙攣(強直間代性、部分発作、ミオクロナス発作等)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。
- 5) 遅発性ジスキネジア:長期投与により、不随意運動(特に口周部)があらわれ、投与中止後も持続することがある。
- 6) 横紋筋融解症:横紋筋融解症があらわれることがあるので、筋肉痛、脱力感、CK(CPK)上昇、血中及び尿中ミオグロビン上昇等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。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。

その他の使用上の注意については添付文書をご参照下さい。

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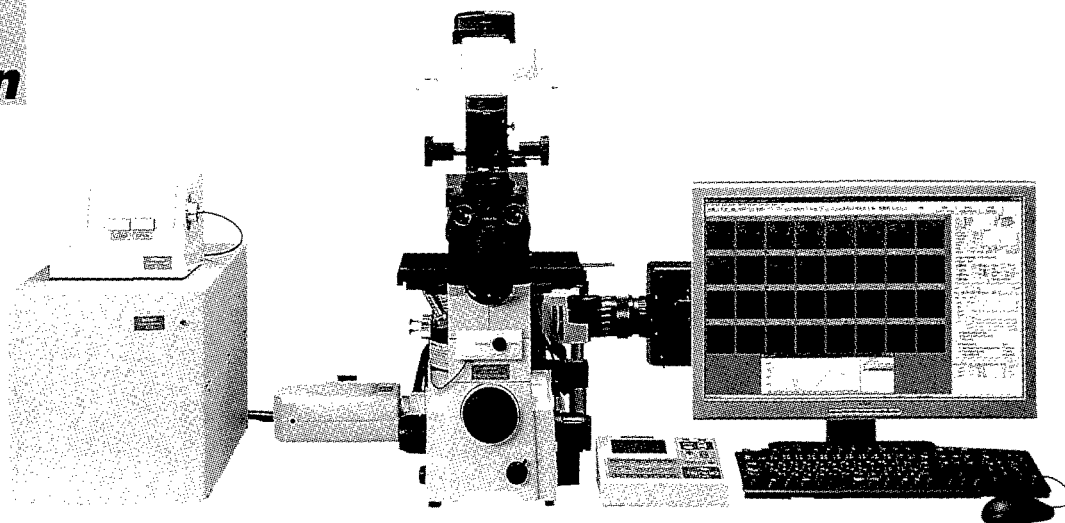
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※1 通話料は無料です。携帯電話、PHSからもご利用いただけます。

※2 祝祭日及び当社休日を除きます。

ZYP-A018(R5)

2005年6月作成



C1 Spectral Imaging System

スペクトルイメージングの世界を広げる
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生きた細胞の動態観察に威力を発揮する、同時32チャンネル
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一度のレーザ照射で広い波長範囲のスペクトルが取得できる、
生細胞にやさしいスペクトルイメージング。
波長分解能は2.5/5/10nmの三段階切替え可能。

リアルスペクトルイメージング

正確な蛍光スペクトルの取得、真の蛍光「色」の取得を実現。

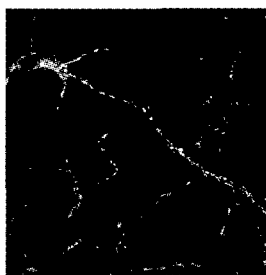
明るさを追求したスペクトルイメージング

蛍光光子を逃さない、妥協のない光学設計と信号処理。

アンミキシングでクロストークのないイメージング

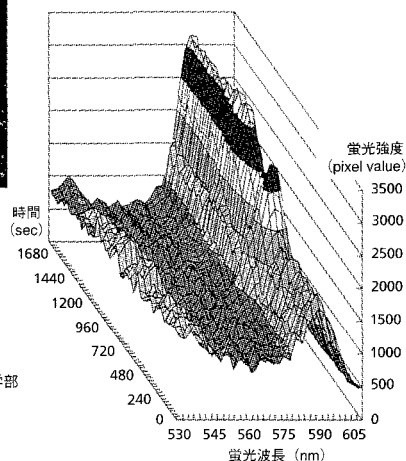
多重染色試料観察、タンパク分子の局在観察、FRET観察
などで威力を発揮。自家蛍光の分離も可能。

■膜電位蛍光標識JC-1スペクトルの時間変化



上図は時刻0秒のときのもので、
530nm～607.5nmまでを2.5nm
の波長分解能で取得した32枚を
重ね合わせたイメージ。

神経細胞にJC-1をロードし、ミトコンドリアの
膜電位の変化に伴うスペクトルの変化を30秒間隔
で観察。励起488nm/514nm。



イメージご提供：東京大学大学院医学部
細胞生物 岡田康志先生

販売元

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