

This Week in The Journal

● Cellular/Molecular

ATP Receptor Involvement in Neuropathic Pain

Kimiko Kobayashi, Hiroki Yamanaka, Tetsuo Fukuoka, Yi Dai, Koichi Obata, and Koichi Noguchi

(see pages 2892–2902)

Nerve injury often leads to neuropathic pain, such as thermal hyperalgesia and mechanical allodynia, a painful response to normally innocuous stimuli. Microglia are thought to play a prominent role in neuropathic pain, in part by releasing inflammatory molecules. Phosphorylation of p38 mitogen-activated protein kinase (MAPK) in microglia also appears to be involved. Kobayashi et al. now suggest that release of ATP from injured nerves may be a first step in the development of neuropathic pain. They show that after nerve injury, the levels of an ADP/ATP receptor, P2Y₁₂, increased in microglia in the spinal cord. Both an antagonist of and antisense oligonucleotides against P2Y₁₂ significantly reduced mechanical allodynia and thermal hyperalgesia following nerve injury, and they also prevented the increase in p38 phosphorylation that normally follows injury. In contrast, a P2Y₁₂ agonist induced mechanical allodynia and thermal hyperalgesia, both of which were attenuated by coadministration of a p38 MAPK inhibitor.

▲ Development/Plasticity/Repair

Regulation of Synaptic Plasticity by Nogo-66 Receptor

Hakjoo Lee, Stephen J. Raiker, Karthik Venkatesh, Rebecca Geary, Laurie A. Robak, Yu Zhang, Hermes H. Yeh, Peter Shrager, and Roman J. Giger

(see pages 2753–2765)

Although growth inhibitors are problematic when nerve regeneration is desired, they are assumed to play important roles in stabilizing synapses and regulating plasticity. Lee et al. now report that the

Nogo-66 receptor, NgR1, plays such a role. NgR1 mediates the inhibitory effects of several myelin-associated proteins, and in adult mice, NgR1 is expressed on neurons throughout the neocortex. Lee et al. found that NgR1 was highly expressed at synapses, particularly postsynaptically. Although the brains of NgR1 mutant mice had normal numbers of neurons, dendrites, and spines, the spine morphology was altered: more spines were stubby, and fewer were mushroom shaped than in controls. In addition, the mutants had impaired long-term depression and enhanced long-term potentiation; but, importantly, the latter only occurred when fibroblast growth factor 2 (FGF2) was present. Surprisingly, the authors found that FGF2 binds directly to NgR1, and transfection of NgR1 into rat cortical neurons prevented FGF-induced axonal branching.

■ Behavioral/Systems/Cognitive

Enhancement of Memory by Exposure to Predators

Michael V. Orr and Ken Lukowiak

(see pages 2726–2734)

Some stress is good for memory, according to experiments on pond snails reported by Orr and Lukowiak. Snails breathe through a pneumostome when in air; by touching the pneumostome when it opens, experimenters can operantly condition the snails to avoid pneumostome opening. Orr and Lukowiak trained snails in normal pond water or water that had held crayfish, a natural snail predator. A single training session given in pond water produced memory lasting 3 h, but one given in crayfish water produced memory lasting 48 h. Similarly, memory induced by two training sessions was extended from 24 h to 8 d by giving the training in crayfish water. Furthermore, unlike training in the presence of food odors, training in crayfish water produced memories that generalized to other contexts. The neural basis of this enhanced learning might be found in RPeD1, a neuron that exhibited decreased spontaneous

firing whenever the conditioned memory was observed.

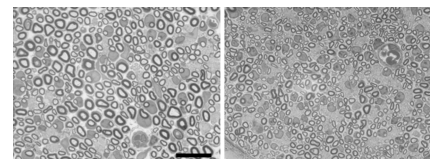
◆ Neurobiology of Disease

A Role for Mitochondrial Protein AFG3L2 in Axonal Development

Francesca Maltecca, Asadollah Aghaie, David G. Schroeder, Laura Cassina, Benjamin A. Taylor, Sandra J. Phillips, Mariachiara Malaguti, Stefano Previtali, Jean-Louis Guénet, Angelo Quattrini, Gregory A. Cox, and Giorgio Casari

(see pages 2827–2836)

Mitochondrial dysfunction has been implicated in several neurodegenerative diseases, including hereditary spastic paraplegia (HSP). HSP is characterized by degeneration of corticospinal axons, which results in spasticity of the legs. Many genetic mutations have been implicated in HSP, including defects in paraplegin, a component of *m*-AAA protease, which resides in the inner mitochondrial membrane and is involved in assembly and degradation of respiratory chain proteins. Maltecca et al. discovered that in mice, mutations in AFG3L2, the other component of *m*-AAA protease, resulted in progressive paralysis and death by postnatal day 16. This paralysis did not appear to result from axon degeneration, but rather from impaired development of the corticospinal tract. Axons had smaller diameters, likely because they had fewer neurofilaments, and more axons were unmyelinated in mutants than in controls. Basal respiratory rates were normal in the brains of mutant mice, but metabolism involving respiratory complexes I and III was impaired.



More large-caliber axons are visible in semithin sections of sciatic nerve from control (left) than from *Afg3l2* (right) mutant mice. Scale bar, 20 μ m. See the article by Maltecca et al. for details.

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Cover legend: Dragonflies have two multifaceted compound eyes and three simple lens eyes known as ocelli. In this picture, a dragonfly views a panoramic ultraviolet and green display specifically designed to stimulate the large neurons in the retina of its median (middle) ocellus. Intracellular potential recordings of these cells reveal that they are directionally selective to movements of ultraviolet bars and gratings but become wide-field sensors, insensitive to direction, when only green light is present. For more information, see the article by van Kleef et al. in this issue (pages 2845–2855).

i This Week in The Journal

Toolbox

- 2681 ***Drd1a*-tdTomato BAC Transgenic Mice for Simultaneous Visualization of Medium Spiny Neurons in the Direct and Indirect Pathways of the Basal Ganglia**
Jessica A. Shuen, Meng Chen, Bernd Gloss, and Nicole Calakos

Journal Club

- 2686 **Carpet Cells Regulate Glial Cell Motility in the Developing *Drosophila* Eye**
Patrick Cafferty
- 2688 **Knocking Down Glycosaminoglycan Synthesis**
Jennifer W. J. Wong

Brief Communications

- 2814 **μ -Opioid Receptor-Mediated Depression of the Hypothalamic Hypocretin/Orexin Arousal System**
Ying Li and Anthony N. van den Pol

Articles

CELLULAR/MOLECULAR

- 2820 **Golgi Cell Dendrites Are Restricted by Purkinje Cell Stripe Boundaries in the Adult Mouse Cerebellar Cortex**
Roy V. Sillitoe, Seung-Hyuk Chung, Jean-Marc Fritschy, Monica Hoy, and Richard Hawkes
- 2892 **P2Y₁₂ Receptor Upregulation in Activated Microglia Is a Gateway of p38 Signaling and Neuropathic Pain**
Kimiko Kobayashi, Hiroki Yamanaka, Tetsuo Fukuoka, Yi Dai, Koichi Obata, and Koichi Noguchi

DEVELOPMENT/PLASTICITY/REPAIR

- 2753 **Synaptic Function for the Nogo-66 Receptor NgR1: Regulation of Dendritic Spine Morphology and Activity-Dependent Synaptic Strength**
Hakjoo Lee, Stephen J. Raiker, Karthik Venkatesh, Rebecca Geary, Laurie A. Robak, Yu Zhang, Hermes H. Yeh, Peter Shrager, and Roman J. Giger
- 2903 **Rapid Loss of Dendritic Spines after Stress Involves Derangement of Spine Dynamics by Corticotropin-Releasing Hormone**
Yuncai Chen, Céline M. Dubé, Courtney J. Rice, and Tallie Z. Baram
- 2919 **Functional Maturation of the First Synapse in Olfaction: Development and Adult Neurogenesis**
Matthew S. Grubb, Antoine Nissant, Kerren Murray, and Pierre-Marie Lledo

2941 **Misplacement of Purkinje Cells during Postnatal Development in Bax Knock-Out Mice: A Novel Role for Programmed Cell Death in the Nervous System?**
A-rong Jung, Tae Woo Kim, Im Joo Rhyu, Hyun Kim, Young Don Lee, Sharon Vinsant, Ronald W. Oppenheim, and Woong Sun

2949 **Okadaic Acid-Sensitive Protein Phosphatases Constrain Phrenic Long-Term Facilitation after Sustained Hypoxia**
Julia E. R. Wilkerson, Irawan Satriotomo, Tracy L. Baker-Herman, Jyoti J. Watters, and Gordon S. Mitchell

BEHAVIORAL/SYSTEMS/COGNITIVE

2690 **Capture of Auditory Motion by Vision Is Represented by an Activation Shift from Auditory to Visual Motion Cortex**
Arjen Alink, Wolf Singer, and Lars Muckli

2710 **Age-Related Regional Network of Magnetic Resonance Imaging Gray Matter in the Rhesus Macaque**
Gene E. Alexander, Kewei Chen, Melaney Aschenbrenner, Tricia L. Merkle, Laura E. Santerre-Lemmon, Jul Lea Shamy, William E. Skaggs, Michael H. Buonocore, Peter R. Rapp, and Carol A. Barnes

2719 **Appetitive Motivation Predicts the Neural Response to Facial Signals of Aggression**
John D. Beaver, Andrew D. Lawrence, Luca Passamonti, and Andrew J. Calder

2726 **Electrophysiological and Behavioral Evidence Demonstrating That Predator Detection Alters Adaptive Behaviors in the Snail *Lymnaea***
Michael V. Orr and Ken Lukowiak

2745 **Human Insula Activation Reflects Risk Prediction Errors As Well As Risk**
Kerstin Preuschoff, Steven R. Quartz, and Peter Bossaerts

2766 **A Role for Non-Rapid-Eye-Movement Sleep Homeostasis in Perceptual Learning**
Daniel Aeschbach, Alex J. Cutler, and Joseph M. Ronda

2773 **Nicotine Self-Administration Differentially Regulates Hypothalamic Corticotropin-Releasing Factor and Arginine Vasopressin mRNAs and Facilitates Stress-Induced Neuronal Activation**
Guoliang Yu, Hao Chen, Wenyan Zhao, Shannon G. Matta, and Burt M. Sharp

2793 **Rapid Interactions between the Ventral Visual Stream and Emotion-Related Structures Rely on a Two-Pathway Architecture**
David Rudrauf, Olivier David, Jean-Philippe Lachaux, Christopher K. Kovach, Jacques Martinerie, Bernard Renault, and Antonio Damasio

2804 **Adaptive Control of Saccades via Internal Feedback**
Haiyin Chen-Harris, Wilsaan M. Joiner, Vincent Ethier, David S. Zee, and Reza Shadmehr

2837 **NMDA Receptor Plasticity in the Perirhinal and Prefrontal Cortices Is Crucial for the Acquisition of Long-Term Object-in-Place Associative Memory**
Gareth R. I. Barker and E. Clea Warburton

2845 **Directional Selectivity in the Simple Eye of an Insect**
Joshua van Kleef, Richard Berry, and Gert Stange

2864 **Learning-Related Plasticity of Temporal Coding in Simultaneously Recorded Amygdala-Cortical Ensembles**
Stephen E. Grossman, Alfredo Fontanini, Jeffrey S. Wieskopf, and Donald B. Katz

2883 **Motor Adaptation as a Process of Reoptimization**
Jun Izawa, Tushar Rane, Opher Donchin, and Reza Shadmehr

2912 **Structural Organization of the Corpus Callosum Predicts the Extent and Impact of Cortical Activity in the Nondominant Hemisphere**
Mary Colvin Putnam, Gagan S. Wig, Scott T. Grafton, William M. Kelley, and Michael S. Gazzaniga

- 2933 **Serotonin 5-HT_{2B} Receptors Are Required for 3,4-Methylenedioxymethamphetamine-Induced Hyperlocomotion and 5-HT Release *In Vivo* and *In Vitro***
Stéphane Doly, Emmanuel Valjent, Vincent Setola, Jacques Callebert, Denis Hervé, Jean-Marie Launay, and Luc Maroteaux

NEUROBIOLOGY OF DISEASE

- 2698 **A New Nerve Growth Factor-Mimetic Peptide Active on Neuropathic Pain in Rats**
Anna Maria Colangelo, Maria Rosaria Bianco, Luigi Vitagliano, Carlo Cavaliere, Giovanni Cirillo, Luca De Gioia, Donatella Diana, Daniele Colombo, Cristina Redaelli, Laura Zaccaro, Giancarlo Morelli, Michele Papa, Paolo Sarmientos, Lilia Alberghina, and Enzo Martegani
- 2735 **Progressive Ganglion Cell Degeneration Precedes Neuronal Loss in a Mouse Model of Glaucoma**
Brian P. Buckingham, Denise M. Inman, Wendi Lambert, Ericka Oglesby, David J. Calkins, Michael R. Steele, Monica L. Vetter, Nicholas Marsh-Armstrong, and Philip J. Horner
- 2783 **N-Terminal Mutant Huntingtin Associates with Mitochondria and Impairs Mitochondrial Trafficking**
Adam L. Orr, Shihua Li, Chuan-En Wang, He Li, Jianjun Wang, Juan Rong, Xingshun Xu, Pier Giorgio Mastroberardino, J. Timothy Greenamyre, and Xiao-Jiang Li
- 2827 **The Mitochondrial Protease AFG3L2 Is Essential for Axonal Development**
Francesca Maltecca, Asadollah Aghaie, David G. Schroeder, Laura Cassina, Benjamin A. Taylor, Sandra J. Phillips, Mariachiara Malaguti, Stefano Previtali, Jean-Louis Guénet, Angelo Quattrini, Gregory A. Cox, and Giorgio Casari
- 2856 **Neuropathic Pain-Like Behavior after Brachial Plexus Avulsion in Mice: The Relevance of Kinin B₁ and B₂ Receptors**
Nara L. M. Quintão, Giselle F. Passos, Rodrigo Medeiros, Ana F. Paszcuk, Fabiana L. Motta, João B. Pesquero, Maria M. Campos, and João B. Calixto
- 2874 **Flotillin-Dependent Clustering of the Amyloid Precursor Protein Regulates Its Endocytosis and Amyloidogenic Processing in Neurons**
Anja Schneider, Lawrence Rajendran, Masanori Honsho, Matthias Gralle, Gerald Donnert, Fred Wouters, Stefan W. Hell, Mikael Simons
- Correction:** In the article "Release of the Styryl Dyes from Single Synaptic Vesicles in Hippocampal Neurons" by Xi Chen, Sebastian Barg, and Wolfhard Almers, which appeared on pages 1894–1903 of the February 20, 2008 issue, there was an error in Equation 3 (page 1898, in the legend for Fig. 3). The correct equation is as follows:

$$y(S) = A_0 \exp[-0.5(S/q - c)^2/w_m^2] + \sum_i A_i \exp[-0.5(S/q - c - ir)^2/(w_m^2 + iw_r^2)].$$

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μ -Opioid Receptor-Mediated Depression of the Hypothalamic Hypocretin/Orexin Arousal System

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Arousal and maintenance of a wake state is dependent on the hypothalamic hypocretin/orexin system. We found that hypocretin neurons are depressed by opiates, drugs of abuse that reduce cognitive alertness. Met-enkephalin (mENK), an endogenous opioid, and exogenous opiates such as morphine inhibited the hypocretin system by direct actions on the cell body that include reduced spike frequency, hyperpolarization, increased G-protein-coupled inwardly rectifying K^+ channel current, and attenuated calcium current, and indirectly through reducing excitatory synaptic tone by a presynaptic mechanism. CTAP (H-D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH₂) and naloxone, antagonists of μ -opioid receptors, blocked μ agonist actions. In the absence of exogenous opioids, μ receptor antagonists enhanced activity of the hypocretin system, suggesting ongoing inhibition by endogenous receptors. Morphine pretreatment attenuated subsequent excitatory responses to hypocretin, suggesting a long-lasting depression caused by opiate exposure. Chronic exposure to morphine reduced subsequent responses to morphine and to mENK, but increased the response to opioid receptor antagonists. Together, these data are consistent with the view that the hypocretin system may be an important direct target for drugs of abuse, including opiates, that induce sedation and mental lethargy.

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Articles

CELLULAR/MOLECULAR

Golgi Cell Dendrites Are Restricted by Purkinje Cell Stripe Boundaries in the Adult Mouse Cerebellar Cortex

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Despite the general uniformity in cellular composition of the adult cerebellar cortex, there is a complex underlying pattern of parasagittal stripes of Purkinje cells with characteristic molecular phenotypes and patterns of connectivity. It is not known whether interneuron processes are restricted at stripe boundaries. To begin to address the issue, three strategies were used to explore how cerebellar Golgi cell dendrites are organized with respect to parasagittal stripes: first, double immunofluorescence staining combining anti-neurogranin to identify Golgi cell dendrites with the Purkinje cell compartmentation antigens zebrin II/aldolase C, HNK-1, and phospholipase *C* β 4; second, zebrin II immunohistochemistry combined with a rapid Golgi–Cox impregnation procedure to reveal Golgi cell dendritic arbors; third, stripe antigen expression was used on sections of a GlyT2-EGFP transgenic mouse in which reporter expression is prominent in Golgi cell dendrites. In each case, the dendritic projections of Golgi cells were studied in the vicinity of Purkinje cell stripe boundaries. The data presented here show that the dendrites of a cerebellar interneuron, the Golgi cell, respect the fundamental cerebellar stripe cytoarchitecture.

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P2Y₁₂ Receptor Upregulation in Activated Microglia Is a Gateway of p38 Signaling and Neuropathic Pain

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Microglia in the spinal cord may play an important role in the development and maintenance of neuropathic pain. A metabotropic ATP receptor, P2Y₁₂, has been shown to be expressed in spinal microglia constitutively and be involved in chemotaxis. Activation of p38 mitogen-activated protein kinase (MAPK) occurs in spinal microglia after nerve injury and may be related to the production of cytokines and other mediators, resulting in neuropathic pain. However, it remains unknown whether any type of P2Y receptor in microglia is involved in the activation of p38 MAPK and the pain behaviors after nerve injury.

Using the partial sciatic nerve ligation (PSNL) model in the rat, we found that P2Y₁₂ mRNA and protein increased in the spinal cord and peaked at 3 d after PSNL. Double labeling studies revealed that cells expressing increased P2Y₁₂ mRNA and protein after nerve injury were exclusively microglia. Both pharmacological blockades by intrathecal administration of P2Y₁₂ antagonist and antisense knockdown of P2Y₁₂ expression suppressed the development of pain behaviors and the phosphorylation of p38 MAPK in spinal microglia after PSNL. The intrathecal infusion of the P2Y₁₂ agonist 2-(methylthio) adenosine 5'-diphosphate trisodium salt into naive rats mimicked the nerve injury-induced activation of p38 in microglia and elevated pain behaviors.

These data suggest a new mechanism of neuropathic pain, in which the increased P2Y₁₂ works as a gateway of the following events in microglia after nerve injury. Activation of this receptor by released ATP or the hydrolyzed products activate p38 MAPK pathway and may play a crucial role in the generation of neuropathic pain. The Journal of Neuroscience, March 12, 2008 • 28(11):2892–2902

DEVELOPMENT/PLASTICITY/REPAIR

Synaptic Function for the Nogo-66 Receptor NgR1: Regulation of Dendritic Spine Morphology and Activity-Dependent Synaptic Strength

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In the mature nervous system, changes in synaptic strength correlate with changes in neuronal structure. Members of the Nogo-66 receptor family have been implicated in regulating neuronal morphology. Nogo-66 receptor 1 (NgR1) supports binding of the myelin inhibitors Nogo-A, MAG (myelin-associated glycoprotein), and OMgp (oligodendrocyte myelin glycoprotein), and is important for growth cone collapse in response to acutely presented inhibitors *in vitro*. After injury to the corticospinal tract, NgR1 limits axon collateral sprouting but is not important for blocking long-distance regenerative growth *in vivo*. Here, we report on a novel interaction between NgR1 and select members of the fibroblast growth factor (FGF) family. FGF1 and FGF2 bind directly and with high affinity to NgR1 but not to NgR2 or NgR3. In primary cortical neurons, ectopic NgR1 inhibits FGF2-elicited axonal branching. Loss of NgR1 results in altered spine morphologies along apical dendrites of hippocampal CA1 neurons *in vivo*. Analysis of synaptosomal fractions revealed that NgR1 is enriched synaptically in the hippocampus. Physiological studies at Schaffer collateral–CA1 synapses uncovered a synaptic function for NgR1. Loss of NgR1 leads to FGF2-dependent enhancement of long-term potentiation (LTP) without altering basal synaptic transmission or short-term plasticity. NgR1 and FGF receptor 1 (FGFR1) are colocalized to synapses, and mechanistic studies revealed that FGFR kinase activity is necessary for FGF2-elicited enhancement of hippocampal LTP in NgR1 mutants. In addition, loss of NgR1 attenuates long-term depression of synaptic transmission at Schaffer collateral–CA1 synapses. Together, our findings establish that physiological NgR1 signaling regulates activity-dependent synaptic strength and uncover neuronal NgR1 as a regulator of synaptic plasticity.

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Rapid Loss of Dendritic Spines after Stress Involves Derangement of Spine Dynamics by Corticotropin-Releasing Hormone

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Chronic stress causes dendritic regression and loss of dendritic spines in hippocampal neurons that is accompanied by deficits in synaptic plasticity and memory. However, the responsible mechanisms remain unresolved. Here, we found that within hours of the onset of stress, the density of dendritic spines declined in vulnerable dendritic domains. This rapid, stress-induced spine loss was abolished by blocking the receptor (CRFR₁) of corticotropin-releasing hormone (CRH), a hippocampal neuropeptide released during stress. Exposure to CRH provoked spine loss and dendritic regression in hippocampal organotypic cultures, and selective blockade of the CRFR₁ receptor had the opposite effect. Live, time-lapse imaging revealed that CRH reduced spine density by altering dendritic spine dynamics: the peptide selectively and reversibly accelerated spine retraction, and this mechanism involved destabilization of spine F-actin. In addition, mice lacking the CRFR₁ receptor had augmented spine density. These findings support a mechanistic role for CRH–CRFR₁ signaling in stress-evoked spine loss and dendritic remodeling.

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Functional Maturation of the First Synapse in Olfaction: Development and Adult Neurogenesis

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The first synapse in olfaction undergoes considerable anatomical plasticity in both early postnatal development and adult neurogenesis, yet we know very little concerning its functional maturation at these times. Here, we used whole-cell recordings in olfactory bulb slices to describe olfactory nerve inputs to developing postnatal neurons and to maturing adult-born cells labeled with a GFP-encoding lentivirus. In both postnatal development and adult neurogenesis, the maturation of olfactory nerve synapses involved an increase in the relative contribution of AMPA over NMDA receptors, and a decrease in the contribution of NMDA receptors containing the NR2B subunit. These postsynaptic transformations, however, were not mirrored by presynaptic changes: in all cell groups, paired-pulse depression remained constant as olfactory nerve synapses matured. Although maturing cells may therefore offer, transiently, a functionally distinct connection for inputs from the nose, presynaptic function at the first olfactory connection remains remarkably constant in the face of considerable anatomical plasticity.

The Journal of Neuroscience, March 12, 2008 • 28(11):2919–2932

Misplacement of Purkinje Cells during Postnatal Development in Bax Knock-Out Mice: A Novel Role for Programmed Cell Death in the Nervous System?

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During early postnatal development, the orchestrated regulation of proliferation, migration and the survival versus elimination of neurons is essential for histogenesis of the cerebellum. For instance, Purkinje cells (PCs) promote the proliferation and migration of external granule cells (EGCs), whereas EGCs in turn play a role in the migration of PCs. Considering that a substantial number of neurons undergo programmed cell death (PCD) during cerebellar development, it seems likely that neuronal loss could have a significant role in the histogenesis of the cerebellum. To address this question, we examined postnatal development of the cerebellum in Bax-knock-out (KO) mice in which the PCD of PC has been reported to be selectively reduced or eliminated, whereas EGCs are unaffected. We confirmed the absence of PC PCD as well as the normal PCD of EGCs in Bax-KO mice. We also observed a subpopulation of PCs that were misplaced in the inner granule cell layer of Bax-KO mice on postnatal day 5 (P5) to P10 and that, by the end of the major period of cerebellar histogenesis (P14), lose expression of the PC marker calbindin. These results suggest that the removal of ectopically located neurons may be a previously unrecognized function of developmental PCD.

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Okadaic Acid-Sensitive Protein Phosphatases Constrain Phrenic Long-Term Facilitation after Sustained Hypoxia

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Phrenic long-term facilitation (pLTF) is a serotonin-dependent form of pattern-sensitive respiratory plasticity induced by intermittent hypoxia (IH), but not sustained hypoxia (SH). The mechanism(s) underlying pLTF pattern sensitivity are unknown. SH and IH may differentially regulate serine/threonine protein phosphatase activity, thereby inhibiting relevant protein phosphatases uniquely during IH and conferring pattern sensitivity to pLTF. We hypothesized that spinal protein phosphatase inhibition would relieve this braking action of protein phosphatases, thereby revealing pLTF after SH. Anesthetized rats received intrathecal (C4) okadaic acid (25 nM) before SH (25 min, 11% O₂). Unlike (vehicle) control rats, SH induced a significant pLTF in okadaic acid-treated rats that was indistinguishable from rats exposed to IH (three 5 min episodes, 11% O₂). IH and SH with okadaic acid may elicit pLTF by similar, serotonin-dependent mechanisms, because intravenous methysergide blocks pLTF in rats receiving IH or okadaic acid plus SH. Okadaic acid did not alter IH-induced pLTF. In summary, pattern sensitivity in pLTF may reflect differential regulation of okadaic acid-sensitive serine/threonine phosphatases; presumably, these phosphatases are less active during/after IH versus SH. The specific okadaic acid-sensitive phosphatase(s) constraining pLTF and their spatiotemporal dynamics during and/or after IH and SH remain to be determined.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Capture of Auditory Motion by Vision Is Represented by an Activation Shift from Auditory to Visual Motion Cortex

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The brain is capable of integrating motion information arising from visual and auditory input. Such integration between sensory modalities can aid one another and helps to stabilize the motion percept. However, if motion information differs between sensory modalities, it can also result in an illusory auditory motion percept. This phenomenon is referred to as the cross-modal dynamic capture (CDC) illusion. We used functional magnetic resonance imaging to investigate whether early visual and auditory motion areas are involved in the generation of this illusion. Among the trials containing conflicting audiovisual motion, we compared the trials in which CDC occurred to those in which it did not and used a region of interest approach to see whether the auditory motion complex (AMC) and the visual motion area hMT/V5+ were affected by this illusion. Our results show that CDC reduces activation in bilateral auditory motion areas while increasing activity in the bilateral hMT/V5+. Interestingly, our data show that the CDC illusion is preceded by an enhanced activation that is most dominantly present in the ventral intraparietal sulcus. Moreover, we assessed the effect of motion coherency, which was found to enhance activation in bilateral hMT/V5+ as well as in an area adjacent to the right AMC. Together, our results show that audiovisual integration occurs in early motion areas. Furthermore, it seems that the cognitive state of subjects before stimulus onset plays an important role in the generation of multisensory illusions.

The Journal of Neuroscience, March 12, 2008 • 28(11):2690–2697

Age-Related Regional Network of Magnetic Resonance Imaging Gray Matter in the Rhesus Macaque

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Human structural neuroimaging studies have supported the preferential effects of healthy aging on frontal cortex, but reductions in other brain regions have also been observed. We investigated the regional network pattern of gray matter using magnetic resonance imaging (MRI) in young adult and old rhesus macaques (RMs) to evaluate age effects throughout the brain in a nonhuman primate model of healthy aging in which the full complement of Alzheimer's disease (AD) pathology does not occur. Volumetric T1 MRI scans were spatially normalized and segmented for gray matter using statistical parametric mapping (SPM2) voxel-based morphometry. Multivariate network analysis using the scaled subprofile model identified a linear combination of two gray matter patterns that distinguished the young from old RMs. The combined pattern included reductions in bilateral dorsolateral and ventrolateral prefrontal and orbitofrontal and superior temporal sulcal regions with areas of relative preservation in vicinities of the cerebellum, globus pallidus, visual cortex, and parietal cortex in old compared with young RMs. Higher expression of this age-related gray matter pattern was associated with poorer performance in working memory. In the RM model of healthy aging, the major regionally distributed effects of advanced age on the brain involve reductions in prefrontal regions and in the vicinity of the superior temporal sulcus. The age-related differences in gray matter reflect the effects of healthy aging that cannot be attributed to AD pathology, providing support for the targeted effects of aging on the integrity of frontal lobe regions and selective temporal lobe areas and their associated cognitive functions.

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Appetitive Motivation Predicts the Neural Response to Facial Signals of Aggression

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The “behavioral approach system” (BAS) (Gray, 1990) has been primarily associated with reward processing and positive affect. However, additional research has demonstrated that the BAS plays a role in aggressive behavior, heightened experience of anger, and increased attention to facial signals of aggression. Using functional magnetic resonance imaging, we show that variation in the BAS trait in healthy participants predicts activation in neural regions implicated in aggression when participants view facial signals of aggression in others. Increased BAS drive (appetitive motivation) was associated with increased amygdala activation and decreased ventral anterior cingulate and ventral striatal activation to facial signals of aggression, relative to sad and neutral expressions. In contrast, increased behavioral inhibition was associated with increased activation in the dorsal anterior cingulate, a region involved in the perception of fear and threat. Our results provide the first demonstration that appetitive motivation constitutes a significant factor governing the function of neural regions implicated in aggression, and have implications for understanding clinical disorders of aggression.

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Electrophysiological and Behavioral Evidence Demonstrating That Predator Detection Alters Adaptive Behaviors in the Snail *Lymnaea*

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Stress has been shown to both impair and enhance learning, long-term memory (LTM) formation, and/or its recall. The pond snail, *Lymnaea stagnalis*, both detects and responds to the scent of a crayfish predator with multiple stress-related behavioral responses. Using both behavioral and electrophysiological evidence, this investigation is a first attempt to characterize how an environmentally relevant stressor (scent of a predator) enhances LTM formation in *Lymnaea*. Using a training procedure that, in “standard” pond water (PW), results in an intermediate-term memory that persists for only 3 h, we found that training snails in “crayfish effluent” (CE) induces a memory that persists for 48 h (i.e., its now an LTM). In addition, if we use a training procedure that in PW produces an LTM that persists for 1 d, we find that snails trained in CE have an LTM that persists for at least 8 d. Furthermore, we describe how a single neuron (RPeD1), which has been shown to be a necessary site for LTM formation, reflects the behavioral changes in its firing properties that persist for the duration of the LTM. Finally, *Lymnaea* exhibit context-specific memory, that is, when a memory is formed in a specific context (food odorant), it is only recalled in that context. Here, we found that snails trained in CE demonstrate context generalization, that is, memory is recalled in multiple contexts. All data are consistent with the hypothesis that learning in a stressful, yet biologically relevant, environment enhances LTM and prolongs its retention.

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Human Insula Activation Reflects Risk Prediction Errors As Well As Risk

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Understanding how organisms deal with probabilistic stimulus-reward associations has been advanced by a convergence between reinforcement learning models and primate physiology, which demonstrated that the brain encodes a reward prediction error signal. However, organisms must also predict the level of risk associated with reward forecasts, monitor the errors in those risk predictions, and update these in light of new information. Risk prediction serves a dual purpose: (1) to guide choice in risk-sensitive organisms and (2) to modulate learning of uncertain rewards. To date, it is not known whether or how the brain accomplishes risk prediction. Using functional imaging during a simple gambling task in which we constantly changed risk, we show that an early-onset activation in the human insula correlates significantly with risk prediction error and that its time course is consistent with a role in rapid updating. Additionally, we show that activation previously associated with general uncertainty emerges with a delay consistent with a role in risk prediction. The activations correlating with risk prediction and risk prediction errors are the analogy for risk of activations correlating with reward prediction and reward prediction errors for reward expectation. As such, our findings indicate that our understanding of the neural basis of reward anticipation under uncertainty needs to be expanded to include risk prediction.

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A Role for Non-Rapid-Eye-Movement Sleep Homeostasis in Perceptual Learning

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Slow-wave activity (SWA; EEG power density in the 0.75–4.5 Hz range) in non-rapid-eye-movement (NREM) sleep is the primary marker of sleep homeostasis and thought to reflect sleep need. But it is unknown whether the generation of SWA itself serves a fundamental function. Previously, SWA has been implicated in brain plasticity and learning, yet the evidence for a causal role remains correlative. Here, we used acoustic slow-wave suppression to test whether overnight improvement in visual texture discrimination, a form of perceptual learning, directly depends on SWA during sleep. Two groups of subjects were trained on a texture discrimination task (TDT) after baseline sleep, and were tested 24 h later, after a 4 h experimental (EX) sleep episode (with or without SWA suppression), and again after a night of recovery sleep. In the suppression group, SWA during EX sleep was reduced by 30% compared with the control group, whereas total sleep time and REM sleep were not affected. Texture discrimination improved after EX sleep in the control group but not in the suppression group. Moreover, overnight improvement in TDT performance correlated with EEG power density during NREM sleep in the frequency range of SWA (maximum $r = 0.75$ at 0.75–1.0 Hz) over brain areas involved in TDT learning. We conclude that SWA is an important determinant of sleep-dependent gains in perceptual performance, a finding that directly implicates processes of sleep homeostasis in learning.

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Nicotine Self-Administration Differentially Regulates Hypothalamic Corticotropin-Releasing Factor and Arginine Vasopressin mRNAs and Facilitates Stress-Induced Neuronal Activation

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Acute nicotine is a potent stimulus for activation of the stress-responsive hypothalamic–pituitary–adrenal (HPA) axis, while chronic nicotine self-administration (SA) desensitizes the ACTH response to self-administered nicotine but cross-sensitizes to mild footshock stress (mFSS). To identify underlying mechanisms, we investigated (1) the effects of chronic nicotine SA on the coexpression of corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) mRNAs, the primary hypothalamic neuropeptides regulating ACTH release, in the parvocellular division of paraventricular nucleus (pcPVN), and (2) mFSS-induced activation of these neurons during nicotine SA. Adult male Sprague Dawley rats were given 23 h/d unlimited access to self-administer nicotine (0.03 mg/kg per injection, i.v.) for 19 d. Brains were double labeled with fluorescence *in situ* hybridization of CRF and AVP mRNAs and triple labeled after mFSS exposure for CRF and AVP mRNAs and c-Fos protein. Chronic nicotine SA significantly increased AVP mRNA signal and the number of pcPVN AVP-positive (AVP⁺) neurons (twofold to threefold), reduced the number of CRF-positive (CRF⁺) neurons by ~60%, but increased pcPVN CRF⁺/AVP⁺ neuronal number fivefold. Significantly, although chronic nicotine SA did not affect total c-Fos expression induced by mFSS in pcPVN CRF⁺ neurons, the majority of the new CRF⁺/AVP⁺ population was activated by this heterotypic stressor. These phenotypic neuronal alterations may provide the pivotal mechanism underlying the capacity of chronically self-administered nicotine to cross-sensitize the HPA response to specific stressors, suggesting that nicotine may augment HPA responsiveness to specific stressors in human smokers.

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Rapid Interactions between the Ventral Visual Stream and Emotion-Related Structures Rely on a Two-Pathway Architecture

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Visual attention can be driven by the affective significance of visual stimuli before full-fledged processing of the stimuli. Two kinds of models have been proposed to explain this phenomenon: models involving sequential processing along the ventral visual stream, with secondary feedback from emotion-related structures (“two-stage models”); and models including additional short-cut pathways directly reaching the emotion-related structures (“two-pathway models”). We tested which type of model would best predict real magnetoencephalographic responses in subjects presented with arousing visual stimuli, using realistic models of large-scale cerebral architecture and neural biophysics. The results strongly support a “two-pathway” hypothesis. Both standard models including the retinotectal pathway and nonstandard models including cortical–cortical long-range fasciculi appear plausible.

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Adaptive Control of Saccades via Internal Feedback

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Ballistic movements like saccades require the brain to generate motor commands without the benefit of sensory feedback. Despite this, saccades are remarkably accurate. Theory suggests that this accuracy arises because the brain relies on an internal forward model that monitors the motor commands, predicts their sensory consequences, and corrects eye trajectory midflight. If control of saccades relies on a forward model, then the forward model should adapt whenever its predictions fail to match sensory feedback at the end of the movement. Using optimal feedback control theory, we predicted how this adaptation should alter saccade trajectories. We trained subjects on a paradigm in which the horizontal target jumped vertically during the saccade. With training, the final position of the saccade moved toward the second target. However, saccades became increasingly curved, i.e., suboptimal, as oculomotor commands were corrected on-line to steer the eye toward the second target. The adaptive response had two components: (1) the motor commands that initiated the saccades changed slowly, aiming the saccade closer to the jumped target. The adaptation of these earliest motor commands displayed little forgetting during the rest periods. (2) Late in saccade trajectory, another adaptive response steered it still closer to the jumped target, producing curvature. Adaptation of these late motor commands showed near-complete forgetting during the rest periods. The two components adapted at different timescales, with the late-acting component displaying much faster rates. It appears that in controlling saccades, the brain relies on an internal feedback that has the characteristics of a fast-adapting forward model.

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NMDA Receptor Plasticity in the Perirhinal and Prefrontal Cortices Is Crucial for the Acquisition of Long-Term Object-in-Place Associative Memory

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A key process for recognition memory is the formation of associations between an object and the place in which it was encountered, a process that has been shown to require the perirhinal (PRH) and medial prefrontal (mPFC) cortices. Here we demonstrate, for the first time, the importance of glutamatergic neurotransmission, within the PRH and mPFC, for object-in-place associative recognition memory. Unilateral blockade of AMPA receptors (by CNQX) in the PRH and mPFC in opposite hemispheres impaired an object-in-place task in rats, confirming that these cortical regions operate within a neural network for object-in-place recognition memory. Intra-mPFC infusions of AP5 (NMDA receptor antagonist) impaired short-term memory and the acquisition of long-term memory, but had no effect on retrieval. AP5 infusions into the PRH disrupted acquisition of long-term memory, but not short-term memory or retrieval. Significantly, crossed AP5 infusions into both the PRH and mPFC disrupted acquisition of long-term memory but were without effect on short-term memory. Finally a unilateral infusion of the selective kainate (GLU_{K5}) receptor antagonist UBP302 [(S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl)pyrimidine-2,4-dione] into the PRH combined with a unilateral infusion of AP5 into the contralateral mPFC significantly impaired short-term object-in-place associative memory. These data show that the PRH and mPFC make distinct contributions to object-in-place associative memory and that the encoding of long-term but not short-term memory requires concurrent NMDA receptor activation in both cortical regions. In contrast, short-term object-in-place memory appears to be dependent on kainate receptor activation in the PRH and NMDA receptor activation in the mPFC.

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Directional Selectivity in the Simple Eye of an Insect

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Among other sensory modalities, flight stabilization in insects is performed with the aid of visual feedback from three simple eyes (ocelli). It is thought that each ocellus acts as a single wide-field sensor that detects changes in light intensity. We challenge this notion by providing evidence that, when light-adapted, the large retinal L-neurons in the median ocellus of the dragonfly respond in a directional way to upward moving bars and gratings. This ability is pronounced under UV illumination but weak or nonexistent in green light and is optimal at angular velocities of $\sim 750^\circ \text{ s}^{-1}$. Using a reverse-correlation technique, we analyze the functional organization of the receptive fields of the L-neurons. Our results reveal that L-neurons alter the structure of their linear spatiotemporal receptive fields with changes in the illuminating wavelength, becoming more inseparable and directional in UV light than in green. For moving bars and gratings, the strength of directionality predicted from the receptive fields is consistent with the measured values. Our results strongly suggest that, during the day, the retinal circuitry of the dragonfly median ocellus performs an early linear stage of motion processing. The likely advantage of this computation is to enhance pitch control.

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Learning-Related Plasticity of Temporal Coding in Simultaneously Recorded Amygdala–Cortical Ensembles

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Emotional learning requires the coordinated action of neural populations in limbic and cortical networks. Here, we performed simultaneous extracellular recordings from gustatory cortical (GC) and basolateral amygdalar (BLA) neural ensembles as awake, behaving rats learned to dislike the taste of saccharin [via conditioned taste aversion (CTA)]. Learning-related changes in single-neuron sensory responses were observed in both regions, but the nature of the changes was region specific. In GC, most changes were restricted to relatively late aspects of the response (starting ~ 1.0 s after stimulus administration), supporting our hypothesis that in this paradigm palatability-related information resides exclusively in later cortical responses. In contrast, and consistent with data suggesting the amygdala's primary role in judging stimulus palatability, CTA altered all components of BLA taste responses, including the earliest. Finally, learning caused dramatic increases in the functional connectivity (measured in terms of cross-correlation peak heights) between pairs of simultaneously recorded BLA and GC neurons, increases that were evident only during taste processing. Our simultaneous assays of the activity of single neurons in multiple relevant brain regions across learning suggest that the transmission of taste information through amygdala–cortical circuits plays a vital role in CTA memory formation.

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Motor Adaptation as a Process of Reoptimization

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Adaptation is sometimes viewed as a process in which the nervous system learns to predict and cancel effects of a novel environment, returning movements to near baseline (unperturbed) conditions. An alternate view is that cancellation is not the goal of adaptation. Rather, the goal is to maximize performance in that environment. If performance criteria are well defined, theory allows one to predict the reoptimized trajectory. For example, if velocity-dependent forces perturb the hand perpendicular to the direction of a reaching movement, the best reach plan is not a straight line but a curved path that appears to overcompensate for the forces. If this environment is stochastic (changing from trial to trial), the reoptimized plan should take into account this uncertainty, removing the overcompensation. If the stochastic environment is zero-mean, peak velocities should increase to allow for more time to approach the target. Finally, if one is reaching through a via-point, the optimum plan in a zero-mean deterministic environment is a smooth movement but in a zero-mean stochastic environment is a segmented movement. We observed all of these tendencies in how people adapt to novel environments. Therefore, motor control in a novel environment is not a process of perturbation cancellation. Rather, the process resembles reoptimization: through practice in the novel environment, we learn internal models that predict sensory consequences of motor commands. Through reward-based optimization, we use the internal model to search for a better movement plan to minimize implicit motor costs and maximize rewards.

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Structural Organization of the Corpus Callosum Predicts the Extent and Impact of Cortical Activity in the Nondominant Hemisphere

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Diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) were combined to examine the relationship between callosal organization and cortical activity across hemispheres. Healthy young adults performed an incidental verbal encoding task (semantic judgments on words) while undergoing fMRI. Consistent with previous studies, the verbal encoding task was associated with left-lateralized activity in the inferior prefrontal cortex (LIPFC). When subjects were divided into two groups

based on fractional anisotropy (FA) values in the anterior corpus callosum (DTI), individuals with low anterior callosal FA were found to exhibit greater activity in a homologous region within the right inferior prefrontal cortex (RIPFC) relative to those with high anterior callosal FA. Interestingly, whereas the magnitude of RIPFC activity did not negatively impact subsequent verbal memory performance for individuals with low anterior callosal FA, greater RIPFC activity during verbal encoding was associated with poorer subsequent memory performance for individuals with high anterior callosal FA. Together, these findings provide novel evidence that individual differences in callosal organization are related to the extent of nondominant cortical activity during performance during a lateralized task, and further, that this relationship has consequences on behavior.

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Serotonin 5-HT_{2B} Receptors Are Required for 3,4-Methylenedioxymethamphetamine-Induced Hyperlocomotion and 5-HT Release *In Vivo* and *In Vitro*

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The “club drug” 3,4-methylenedioxymethamphetamine (MDMA; also known as ecstasy) binds preferentially to and reverses the activity of the serotonin transporter, causing release of serotonin [5-hydroxytryptamine (5-HT)] stores from nerve terminals. Subsequent activation of postsynaptic 5-HT receptors by released 5-HT has been shown to be critical for the unique psychostimulatory effects of MDMA. In contrast, the effects of direct activation of presynaptic and/or postsynaptic receptors by MDMA have received far less attention, despite the agonist actions of the drug itself at 5-HT₂ receptors, in particular the 5-HT_{2B} receptor. Here we show that acute pharmacological inhibition or genetic ablation of the 5-HT_{2B} receptor in mice completely abolishes MDMA-induced hyperlocomotion and 5-HT release in nucleus accumbens and ventral tegmental area. Furthermore, the 5-HT_{2B} receptor dependence of MDMA-stimulated release of endogenous 5-HT from superfused midbrain synaptosomes suggests that 5-HT_{2B} receptors act, unlike any other 5-HT receptor, presynaptically to affect MDMA-stimulated 5-HT release. Thus, our findings reveal a novel regulatory component in the actions of MDMA and represent the first demonstration that 5-HT_{2B} receptors play an important role in the brain, i.e., modulation of 5-HT release. As such, 5-HT_{2B} receptor antagonists may serve as promising therapeutic drugs for MDMA abuse.

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NEUROBIOLOGY OF DISEASE

A New Nerve Growth Factor-Mimetic Peptide Active on Neuropathic Pain in Rats

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Analysis of the structure of nerve growth factor (NGF)-tyrosine kinase receptor A (TrkA) complex, site-directed mutagenesis studies and results from chemical modification of amino acid residues have identified loop 1, loop 4, and the N-terminal region of the NGF molecule as the most relevant for its biological activity. We synthesized several peptides mimicking the two loops (1 and 4) linked together with an appropriate spacer, with or without the N-terminal region. Two peptides named NL1L4 and L1L4 demonstrated good NGF agonist activity at a concentration as low as 3 μM. They induced differentiation of chick dorsal root ganglia and stimulated tyrosine phosphorylation of TrkA, but not TrkB, receptor. In addition L1L4 was able to induce differentiation of PC12 cells. More interestingly, the peptide with the highest “*in vitro*” activity (L1L4) was shown to reduce neuropathic behavior and restore neuronal function in a rat model of peripheral neuropathic pain, thereby suggesting a potential therapeutic role for this NGF-mimetic peptide.

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Progressive Ganglion Cell Degeneration Precedes Neuronal Loss in a Mouse Model of Glaucoma

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Glaucoma is characterized by retinal ganglion cell (RGC) pathology and a progressive loss of vision. Previous studies suggest RGC death is responsible for vision loss in glaucoma, yet evidence from other neurodegenerative diseases suggests axonal degeneration, in the absence of neuronal loss, can significantly affect neuronal function. To

characterize RGC degeneration in the DBA/2 mouse model of glaucoma, we quantified RGCs in mice of various ages using neuronal-specific nuclear protein (NeuN) immunolabeling, retrograde labeling, and optic nerve axon counts. Surprisingly, the number of NeuN-labeled RGCs did not decline significantly until 18 months of age, at which time a significant decrease in RGC somal size was also observed. Axon dysfunction and degeneration occurred before loss of NeuN-positive RGCs, because significant declines in RGC number assayed by retrograde tracers and axon counts were observed at 13 months. To examine whether axonal dysfunction/degeneration affected gene expression in RGC axons or somas, NeuN and neurofilament-heavy (NF-H) immunolabeling was performed along with quantitative reverse transcription-PCR for RGC-specific genes in retinas of aged DBA/2 mice. Although these mice had similar numbers of NeuN-positive RGCs, the expression of neurofilament light, Brn-3b, and Snca mRNA varied; this variation in RGC-specific gene expression was correlated with the appearance of NF-H immunoreactive RGC axons. Together, these data support a progression of RGC degeneration in this model of glaucoma, beginning with loss of retrograde label, where axon dysfunction and degeneration precede neuronal loss. This progression of degeneration suggests a need to examine the RGC axon as a locus of pathology in glaucoma.

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N-Terminal Mutant Huntingtin Associates with Mitochondria and Impairs Mitochondrial Trafficking

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Huntington's disease (HD) is caused by polyglutamine (polyQ) expansion in huntingtin (htt), a large (350 kDa) protein that localizes predominantly to the cytoplasm. Proteolytic cleavage of mutant htt yields polyQ-containing N-terminal fragments that are prone to misfolding and aggregation. Disease progression in HD transgenic models correlates with age-related accumulation of soluble and aggregated forms of N-terminal mutant htt fragments, suggesting that multiple forms of mutant htt are involved in the selective neurodegeneration in HD. Although mitochondrial dysfunction is implicated in the pathogenesis of HD, it remains unclear which forms of cytoplasmic mutant htt associate with mitochondria to affect their function. Here we demonstrate that specific N-terminal mutant htt fragments associate with mitochondria in *Hdh*(CAG)150 knock-in mouse brain and that this association increases with age. The interaction between soluble N-terminal mutant htt and mitochondria interferes with the *in vitro* association of microtubule-based transport proteins with mitochondria. Mutant htt reduces the distribution and transport rate of mitochondria in the processes of cultured neuronal cells. Reduced ATP level was also found in the synaptosomal fraction isolated from *Hdh*(CAG)150 knock-in mouse brain. These findings suggest that specific N-terminal mutant htt fragments, before the formation of aggregates, can impair mitochondrial function directly and that this interaction may be a novel target for therapeutic strategies in HD.

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The Mitochondrial Protease AFG3L2 Is Essential for Axonal Development

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The mitochondrial metalloprotease AFG3L2 assembles with the homologous protein paraplegin to form a supracomplex in charge of the essential protein quality control within mitochondria. Mutations of paraplegin cause a specific axonal degeneration of the upper motoneuron and, therefore, hereditary spastic paraplegia. Here we present two *Afg3l2* murine models: a newly developed null and a spontaneous mutant that we found carrier of a missense mutation. Contrasting with the mild and late onset axonal degeneration of paraplegin-deficient mouse, *Afg3l2* models display a marked impairment of axonal development with delayed myelination and poor axonal radial growth leading to lethality at P16. The increased severity of the *Afg3l2* mutants is explained by two main molecular features that differentiate AFG3L2 from paraplegin: its higher neuronal expression and its versatile ability to support both hetero-oligomerization and homo-oligomerization. Our data assign to AFG3L2 a crucial role by linking mitochondrial metabolism and axonal development. Moreover, we propose AFG3L2 as an excellent candidate for motoneuron and cerebellar diseases with early onset unknown etiology.

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Neuropathic Pain-Like Behavior after Brachial Plexus Avulsion in Mice: The Relevance of Kinin B₁ and B₂ Receptors

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The relevance of kinin B₁ (B₁R) and B₂ (B₂R) receptors in the brachial plexus avulsion (BPA) model was evaluated in mice, by means of genetic and pharmacological tools. BPA-induced hypernociception was absent in B₁R, but not in B₂R, knock-out mice. Local or intraperitoneal administration of the B₂R antagonist Hoe 140 failed to affect BPA-induced mechanical hypernociception. Interestingly, local or intraperitoneal treatment with B₁R antagonists, R-715 or SSR240612, dosed at the time of surgery, significantly reduced BPA-evoked mechanical hypernociception. Intrathecal or intracerebroventricular administration of these antagonists, at the surgery moment, did not prevent the hypernociception. Both antagonists, dosed by intraperitoneal or intrathecal routes (but not intracerebroventricularly) 4 d after the surgery, significantly inhibited the mechanical hypernociception. At 30 d after the BPA, only the intracerebroventricular treatment effectively reduced the hypernociception. A marked increase in B₁R mRNA was observed in the hypothalamus, hippocampus, thalamus, and cortex at 4 d after BPA and only in the hypothalamus and cortex at 30 d. In the spinal cord, a slight increase in B₁R mRNA expression was observed as early as at 2 d. Finally, an enhancement of B₁R protein expression was found in all the analyzed brain structures at 4 and 30 d after the BPA, whereas in the spinal cord, this parameter was augmented only at 4 d. The data provide new evidence on the role of peripheral and central kinin B₁R in the BPA model of neuropathic pain. Selective B₁R antagonists might well represent valuable tools for the management of neuropathic pain.

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Flotillin-Dependent Clustering of the Amyloid Precursor Protein Regulates Its Endocytosis and Amyloidogenic Processing in Neurons

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The flotillins/reggie proteins are associated with noncaveolar membrane microdomains and have been implicated in the regulation of a clathrin- and caveolin-independent endocytosis pathway. Endocytosis is required for the amyloidogenic processing of the amyloid precursor protein (APP) and thus to initiate the release of the neurotoxic β -amyloid peptide (A β), the major component of extracellular plaques found in the brains of Alzheimer's disease patients. Here, we report that small interference RNA-mediated downregulation of flotillin-2 impairs the endocytosis of APP, in both neuroblastoma cells and primary cultures of hippocampal neurons, and reduces the production of A β . Similar to tetanus neurotoxin endocytosis, but unlike the internalization of transferrin, clathrin-dependent endocytosis of APP requires cholesterol and adaptor protein-2 but is independent of epsin1 function. Moreover, on a nanoscale resolution using stimulated emission depletion microscopy and by Förster resonance energy transfer with fluorescence lifetime imaging microscopy, we provide evidence that flotillin-2 promotes the clustering of APP at the cell surface. We show that the interaction of flotillin-2 with APP is dependent on cholesterol and that clustering of APP enhances its endocytosis rate. Together, our data suggest that cholesterol/flotillin-dependent clustering of APP may stimulate the internalization into a specialized clathrin-dependent endocytosis pathway to promote amyloidogenic processing.

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