This Week in The Journal

● Cellular/Molecular

A Choline Transporter and Autoimmune Hearing Loss

Thankam S. Nair, Kelley E. Kozma, Nickoleta L. Hoefling, Pavan K. Kommareddi, Yo Ueda, Tzy-Wen Gong, Margaret I. Lomax, Christopher D. Lansford, Steven A. Telian, Bulent Satar, H. Alexander Arts, Hussam K. El-Kashlan, Wayne E. Berryhill, Yehoash Raphael, and Thomas E. Carey
(see pages 1772-1779)

Antibodies to neural antigens cause several neurological diseases, myasthenia gravis with its acetylcholine receptor antibodies being perhaps the best known. Autoimmune damage is also suspected as a cause of rapidly progressive hearing loss. In this issue, Nair et al. track down the antigen underlying hearing loss that is caused by an antibody (KHRI-3) generated against the guinea pig organ of Corti. They isolated and sequenced the inner ear supporting cell antigen as choline transporter-like protein 2 (CTL2). Supporting cells bound KHRI-3 and anti-CTL2 with a punctate, "wine-glass" pattern. A similar pattern also can be seen in humans with autoimmune hearing loss. CTL2 is expressed in humans, although its function is not yet known. Because the antibody binds to carbohydrate moieties on the putative extracellular domain of CTL2, the authors speculate that the antibody blocks a possible transporter function.

▲ Development/Plasticity/Repair

Serotonin in the Marginal Zone

Skirmantas Janušonis, Vicko Gluncic, and Pasko Rakic
(see pages 1652-1659)

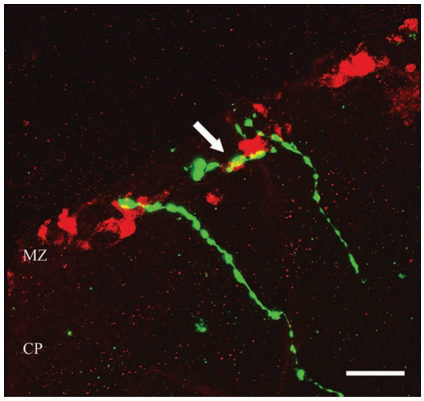
Neurotransmitters can play distinctive roles in early brain development and in disorders with cortical columnar abnormalities such as autism and schizophrenia. In this week's *Journal*, Janušonis et al. examine one of the early targets of cortical serotonergic projections, Cajal-Retzius (CR) cells in the marginal zone (MZ). CR cells secrete reelin, which is necessary for correct laminar and columnar development of the cerebral cortex. The authors report that serotonergic inputs form synaptic contacts with CR cells beginning on embryonic day 17. To disrupt serotonin input, they injected pregnant mice with 5-methoxytryptamine, a nonspecific serotonin receptor agonist. At birth, the progeny mice had reduced levels of reelin, and at postnatal day 7, they displayed poorly formed minicolumns in the presubicular cortex. The results provide an intriguing clue that may link early serotonin innervation with the role of Cajal-Retzius cells in the development of the cerebral cortex.

■ Behavioral/Systems/Cognitive

Basic Training in Visual Area V4

Tianming Yang and John Maunsell
(see pages 1617-1626)

Perceptual learning, the improvement in sensory performance after extensive training, has been related to changes in the properties of cortical neurons in the somatosensory and auditory cortex. However, neurons in the primary visual cortex (V1) show only modest changes in their properties after extensive training, despite improvements in visual abilities. This week, Yang and Maunsell investigate whether such plasticity occurs later in visual pathways. Neurons of V4, at the mid-level of visual processing, have defined receptive fields and respond to objects of specific orientation. After several months of training with a match-to-sample orientation task, monkeys improved their orientation discrimination. V4 neurons in the trained hemifield had stronger responses and narrower orientation tuning curves, consistent with a role for V4 in perceptual visual learning. The results suggest that there's some truth to the old adage, "You will only see it if you look for it," assuming you look again and again!



Confocal microphotograph of serotonergic fibers (green) contacting CR cells (red) in the MZ. See the article by Janušonis et al. for details.

♦ Neurobiology of Disease

Rheumatic Fever, Murine-Style

Kurt L. Hoffman, Mady Hornig, Kavitha Yaddanapudi, Omar Jabado, and W. Ian Lipkin
(see pages 1780-1791)

Many of us were dragged to the pediatrician at some point with a "strep throat" out of a concern for the dreaded rheumatic fever (RF), a delayed consequence of streptococcal infection. Thanks to the use of antibiotics, RF is now less common. When this presumed autoimmune disorder affects the brain, it can cause jerky involuntary (choreiform) movements, once called "St. Vitus' dance" (a name apparently derived from a major outbreak near Strasbourg in the 15th century). Infection with group A β-hemolytic streptococcus (GABHS) also can be associated with other neurological symptoms, such as obsessive–compulsive disorder and attention deficit/hyperactivity disorder. Now Hoffman et al. examine the possibility that antibodies raised against bacterial antigens may cross-react with brain proteins and contribute to the motor and behavioral symptoms. They created an animal model by immunizing mice with GABHS antibodies. A subset of the mice produced antibodies that were immunoreactive to selected brain regions, including deep cerebellar nuclei, and had IgG deposits in brain. These mice also showed disrupted rearing and ambulatory behavior. This animal model may be useful in further investigation of this neurological complication of a bacterial infection.

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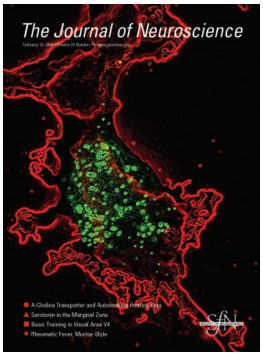

Cover Picture: Deconvoluted image of immunocytochemical labeling of a developing oligodendrocyte using the anti-04 monoclonal antibody (red) and a polyclonal anti-catalase antibody (green) showing peroxisomal localization of catalase. For details, see the article by Baud et al. in this issue (pages 1531–1540).

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Brief Communications

Decreased Phosphorylation of NMDA Receptor Type 1 at Serine 897 in Brains of Patients with Schizophrenia

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NMDA receptor hypofunction in schizophrenia has been inferred by a large number of clinical and preclinical observations; however, whether and how NMDA receptors are exactly involved in the pathogenesis of schizophrenia are still unknown and subject to interpretation. Here we show, in two independent samples of brains from patients with schizophrenia, a significant decrease in the phosphorylation level at serine 897 (S897) of the NMDA receptor type 1 (NR1) subunit. Our finding, together with a previous report that antipsychotics increase phosphorylation of NR1 at S897 *in vivo*, strongly suggests that insufficient phosphorylation at S897 may contribute to the neuronal pathology underlying schizophrenia.

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A Neural Correlate of Reward-Based Behavioral Learning in Caudate Nucleus: A Functional Magnetic Resonance Imaging Study of a Stochastic Decision Task

Masahiko Haruno,[1] **Tomoe Kuroda,**[1] **Kenji Doya,**[1,2] **Keisuke Toyama,**[3] **Minoru Kimura,**[4] **Kazuyuki Samejima,**[1,2] **Hiroshi Imamizu,**[1] **and Mitsuo Kawato**[1]

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Humans can acquire appropriate behaviors that maximize rewards on a trial-and-error basis. Recent electrophysiological and imaging studies have demonstrated that neural activity in the midbrain and ventral striatum encodes the error of reward prediction. However, it is yet to be examined whether the striatum is the main locus of reward-based behavioral learning. To address this, we conducted functional magnetic resonance imaging (fMRI)AQ: D of a stochastic decision task involving monetary rewards, in which subjects had to learn behaviors involving different task difficulties that were controlled by probability. We performed a correlation analysis of fMRI data by using the explanatory variables derived from subject behaviors. We found that activity in the caudate nucleus was correlated with short-term reward and, furthermore, paralleled the magnitude of a subject's behavioral change during learning. In addition, we confirmed that this parallelism between learning and activity in the caudate nucleus is robustly maintained even when we vary task difficulty by controlling the probability. These findings suggest that the caudate nucleus is one of the main loci for reward-based behavioral learning.

The Journal of Neuroscience, February 18, 2004 • 24(7):1660–1665

Dynamic Gain Control of Dopamine Delivery in Freely Moving Animals

P. Read Montague,[1] **Samuel M. McClure,**[1] **P. R. Baldwin,**[1] **Paul E. M. Phillips,**[2,3,4] **Evgeny A. Budygin,**[3,4] **Garret D. Stuber,**[2,3,4] **Michaux R. Kilpatrick,**[3,4] **and R. Mark Wightman**[3,4]

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Activity changes in a large subset of midbrain dopamine neurons fulfill numerous assumptions of learning theory by encoding a prediction error between actual and predicted reward. This computational interpretation of dopaminergic spike activity invites the important question of how changes in spike rate are translated into changes in dopamine delivery at target neural structures. Using electrochemical detection of rapid dopamine release in the striatum of freely moving rats, we established that a single dynamic model can capture all the measured fluctuations in dopamine delivery. This model revealed three independent short-term adaptive processes acting to control dopamine release. These short-term components generalized well across animals and stimulation patterns and were preserved under anesthesia. The model has implications for the dynamic filtering interposed between changes in spike production and forebrain dopamine release.

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Articles

CELLULAR/MOLECULAR

GABA Release from Proopiomelanocortin Neurons

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Neural networks controlling food intake and energy homeostasis clearly involve proopiomelanocortin (POMC) neurons and their peptide transmitters. α-melanocyte-stimulating hormone from arcuate POMC neurons potently reduces food intake, whereas arcuate neuropeptide Y (NPY) neurons act in opposition to stimulate food intake. In addition to orexigenic peptides, NPY neurons also release the inhibitory neurotransmitter GABA, which can act in a local circuit to inhibit POMC neuron activity. Whether or not reciprocal inhibition could occur has not yet been determined, because the presence of a rapid neurotransmitter in POMC neurons has not been demonstrated previously. Here, we used primary cultures of fluorescently labeled POMC neurons that had formed recurrent synapses (autapses) to detect the release of neurotransmitter. When an action potential was evoked in the axon of a POMC neuron with autapses, a short-latency synaptic current was recorded in the same cell. The autaptic current was abolished by $GABA_A$ receptor antagonists and substantially inhibited by opioids. Double-label *in situ* RNA hybridization for POMC and glutamic acid decarboxylase, the GABA synthetic enzyme, revealed colocalization of mRNAs in approximately one-third of POMC neurons *in vivo*. Our results suggest that these neurons can exert rapid inhibitory effects via the release of GABA, in addition to the more sustained actions provided by POMC peptides.AQ: B However, this rapid inhibition may not play a major role within local hypothalamic circuits, but rather is likely to be important in more distant projection areas as indicated by the colocalization of vesicular GABA transporter immunoreactivity predominately in extrahypothalamic POMC terminals.

The Journal of Neuroscience, February 18, 2004 • 24(7):1578–1583

Disruption of Endocannabinoid Release and Striatal Long-Term Depression by Postsynaptic Blockade of Endocannabinoid Membrane Transport

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Activation of the CB1 cannabinoid receptor inhibits neurotransmission at numerous synapses in the brain. Indeed, CB1 is essential for certain types of both short- and long-term synaptic depression. It was demonstrated recently that CB1 is critical for activity-dependent long-term depression (LTD) at glutamatergic corticostriatal synapses in acute brain slice preparations. Here, we show that CB1 activation is necessary, but not solely sufficient, for induction of LTD and that the requisite signaling by endocannabinoids (eCBs) occurs during a time window limited to the first few minutes after high-frequency stimulation delivery. In addition, we have applied intracellularly anandamide membrane transporter inhibitors to provide novel evidence that postsynaptic transport mechanisms are responsible for the release of eCBs from striatal medium spiny neurons. These findings shed new light on the mechanisms by which transient eCB formation participates in the induction of long-lasting changes in synaptic efficacy that could contribute to brain information storage.

The Journal of Neuroscience, February 18, 2004 • 24(7):1673–1679

Minimum Essential Factors Required for Vesicle Mobilization at Hippocampal Synapses

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Studies on the mechanisms that underlie the function of small central presynaptic terminals have been hampered by the inaccessibility of these synapses to soluble reagents. Here, we permeabilized hippocampal synapses in culture, manipulated their interior, and monitored the resulting changes in vesicle mobilization with the styryl dye FM2-10. Using this method, we found that 1 μM Ca^{2+} after incubation with GTP or GTP-γ-S could mobilize ~90% of the total recycling pool, whereas 1 μM Ca^{2+} application after dialysis of permeabilized synapses with GDP-β-S mobilized ~30% of the recycling vesicles, presumably corresponding to the readily releasable pool. In electron micrographs of permeabilized hippocampal synapses stimulated with 1 μM Ca^{2+}, we could detect significant vesicle depletion after preincubation with GTP-γ-S, whereas preincubation with GDP-β-S left the total vesicle pool relatively intact. Taken together, in this system replenishment of the readily releasable pool by the reserve vesicles was strictly GTP dependent. In contrast, vesicle replenishment and release did not require ATP or *N*-ethylmaleimide-sensitive factor (NSF); however, this process involved formation of new soluble NSF-attachment protein receptor (SNARE) complexes as judged by its sensitivity to tetanus toxin. These results suggest that in hippocampal synapses, vesicle mobilization and replenishment of the readily releasable pool require GTP and Ca^{2+} but do not necessitate ATP-dependent priming and SNARE recycling.

The Journal of Neuroscience, February 18, 2004 • 24(7):1680–1688

Single Spine Ca^{2+} Signals Evoked by Coincident EPSPs and Backpropagating Action Potentials in Spiny Stellate Cells of Layer 4 in the Juvenile Rat Somatosensory Barrel Cortex

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The precise timing of presynaptic and postsynaptic activity results in synaptic modifications, which depend on calcium influx. [Ca^{2+}] transients in the spines of spiny neurons in layer 4 (L4) of the somatosensory barrel cortex of young rats were investigated in thalamocortical brain slices by two-photon excitation microscopy to determine the spike timing dependence of the Ca^{2+} signal during near-coincident presynaptic and postsynaptic activity. [Ca^{2+}] transients evoked by backpropagating action potentials (bAPs) were mediated by voltage-dependent Ca^{2+} channels and were of comparable size in a spine and adjacent dendritic shaft. They decreased with the distance of the spine from the soma. EPSP-evoked [Ca^{2+}] transients were restricted to spine heads and were mediated almost entirely by Ca^{2+} influx through NMDA receptors (NMDARs)AQ: D. Their amplitude was independent of the position of the spine along the dendritic arbor. bAPs interacted with EPSPs to generate sublinear or supralinear Ca^{2+} signals in a spine when EPSP and bAP occurred within a time window of ~50 msec. Synaptic stimulation, coincident with a bAP, evoked a large postsynaptic Ca^{2+} influx that was restricted to a single spine, even after EPSPs were blocked by the AMPA receptorAQ: E antagonist NBQX that rendered synapses effectively "electrically silent."

We conclude that the spines of L4 cells can act as sharply tuned detectors for patterns of APs occurring in the boutons of the afferents to L4 cells and the spines of L4 cell dendrites. The readout for near-coincident presynaptic and postsynaptic APs is a large transient Ca^{2+} influx into synaptically active spines mediated by the brief unblocking of NMDARs during the dendritic bAP.

The Journal of Neuroscience, February 18, 2004 • 24(7):1689–1699

Heat Shock Protein 70 Participates in the Neuroprotective Response to Intracellularly Expressed β-Amyloid in Neurons

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Intracellular β-amyloid 42 (Aβ42) accumulation is increasingly recognized as an early event in the pathogenesis of Alzheimer's disease (AD). We have developed a doxycycline-inducible adenoviral-based system that directs intracellular Aβ42 expression and accumulation into the endoplasmic reticulum of primary neuronal cultures in a regulated manner. Aβ42 exhibited a perinuclear distribution in cell bodies and an association with vesicular compartments. Virally expressed intracellular Aβ42 was toxic to neuronal cultures 24 hr after induction in a dose-dependent manner. Aβ42 expression prompted the rapid induction of stress-inducible Hsp70 protein in neurons, and virally mediated Hsp70 overexpression rescued neurons from the toxic effects of intracellular Aβ accumulation. Together, these results implicate the cellular stress response as a possible modulator of Aβ-induced toxicity in neuronal cultures.

The Journal of Neuroscience, February 18, 2004 • 24(7):1700–1706

The *CACNA1F* Gene Encodes an L-Type Calcium Channel with Unique Biophysical Properties and Tissue Distribution

John E. McRory,[1] Jawed Hamid,[2] Clinton J. Doering,[2,3] Esperanza Garcia,[1] Robin Parker,[4] Kevin Hamming,[1] Lina Chen,[2] Michael Hildebrand,[1] Aaron M. Beedle,[2] Laura Feldcamp,[2] Gerald W. Zamponi,[2] and Terrance P. Snutch[1]

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Glutamate release from rod photoreceptors is dependent on a sustained calcium influx through L-type calcium channels. Missense mutations in the *CACNA1F* gene in patients with incomplete X-linked congenital stationary night blindness implicate the $Ca_v1.4$ calcium channel subtype. Here, we describe the functional and pharmacological properties of transiently expressed human $Ca_v1.4$ calcium channels. $Ca_v1.4$ is shown to encode a dihydropyridine-sensitive calcium channel with unusually slow inactivation kinetics that are not affected by either calcium ions or by coexpression of ancillary calcium channel β subunits. Additionally, the channel supports a large window current and activates near −40 mV in 2 mM external calcium, making $Ca_v1.4$ ideally suited for tonic calcium influx at typical photoreceptor resting potentials. Introduction of base pair changes associated with four incomplete X-linked congenital night blindness mutations showed that only the G369D alteration affected channel activation properties. Immunohistochemical analyses show that, in contrast with previous reports, $Ca_v1.4$ is widely distributed outside the retina, including in the immune system, thus suggesting a broader role in human physiology.

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Early Expression of Sodium Channel Transcripts and Sodium Current by Cajal-Retzius Cells in the Preplate of the Embryonic Mouse Neocortex

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In mouse, the first neurons are generated at embryonic day (E) 12 and form the preplate (PP), which contains a mix of future marginal zone cells, including Cajal-Retzius cells, and subplate cells. To detect developmental changes in channel populations in these earliest-generated neurons of the cerebral cortex, we studied the electrophysiological properties of proliferative cells of the ventricular zone and postmitotic neurons of the PP at E12 and E13, using whole-cell patch-clamp recordings. We found an inward sodium current in 55% of PP cells. To determine whether sodium currents occur in a specific cell type, we stained recorded cells with an antibody for calretinin, a calcium-binding protein found specifically in Cajal-Retzius cells. All calretinin-positive cells had sodium currents, although so did some calretinin-negative cells. To correlate the Na current expression to Na channel gene expression with the Cajal-Retzius cell phenotype, we performed single-cell reverse transcription-PCR on patch-clamp recorded cells to detect expression of the Cajal-Retzius cell marker reelin and the Na channel isoforms SCNAQ: B 1, 2, and 3. These results showed that virtually all Cajal-Retzius cells (97%), as judged by reelin expression, express the SCN transcript identified as the SCN3 isoform. Of these, 41% presented a functional Na current. There is, however, a substantial SCN-positive population in the PP (27% of SCN-positive cells) that does not express reelin. These results raise the possibility that populations of pioneer neurons of the PP, including Cajal-Retzius cells, gain neuronal physiological properties early in development via expression of the $Na_v1.3$ (SCN3) Na channel isoform.

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Tumor Necrosis Factor Death Receptor Signaling Cascade Is Required for Amyloid-β Protein-Induced Neuron Death

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Tumor necrosis factor type I receptor (TNFRI), a death receptor, mediates apoptosis and plays a crucial role in the interaction between the nervous and immune systems. A direct link between death receptor activation and signal cascade-mediated neuron death in brains with neurodegenerative disorders remains inconclusive. Here, we show that amyloid-β protein (Aβ), a major component of plaques in the Alzheimer's diseasedAQ: B brain, induces neuronal apoptosis through TNFRI by using primary neurons overexpressing TNFRI by viral infection or neurons from TNFRI knock-out mice. This was mediated via alteration of apoptotic protease-activating factor (Apaf-1) expression that in turn induced activation of nuclear factor κB (NF-κB). Aβ-induced neuronal apoptosis was reduced with lower Apaf-1 expression, and little NF-κB activation was found in the neurons with mutated Apaf-1 or a deletion of TNFRI compared with the cells from wild-type (WT) mice. Our studies suggest a novel neuronal response of Aβ, which occurs through a TNF receptor signaling cascade and a caspase-dependent death pathway.

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Identification and Characterization of Choline Transporter-Like Protein 2, an Inner Ear Glycoprotein of 68 and 72 kDa That Is the Target of Antibody-Induced Hearing Loss

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The Kresge Hearing Research Institute-3AQ: B (KHRI-3) antibody binds to a guinea pig inner ear supporting cell antigen (IESCA) and causes hearing loss. To gain insight into the mechanism of antibody-induced hearing loss, we used antibody immunoaffinity purification to isolate the IESCA, which was then sequenced by mass spectroscopy, revealing 10 guinea pig peptides identical to sequences in human choline transporter-like protein 2 (CTL2). Full-length CTL2 cDNA sequenced from guinea pig inner ear has 85.9% identity with the human cDNA. Consistent with its expression on the surface of supporting cells in the inner ear, CTL2 contains 10 predicted membrane-spanning regions with multiple N-glycosylation sites. The 68 and 72 kDa molecular forms of inner ear CTL2 are distinguished by sialic acid modification of the carbohydrate. The KHRI-3 antibody binds to an N-linked carbohydrate on CTL2 and presumably damages the organ of Corti by blocking the transporter function of this molecule. CTL2 mRNA and protein are abundantly expressed in human inner ear. Sera from patients with autoimmune hearing loss bind to guinea pig inner ear with the same pattern as CTL2 antibodies. Thus, CTL2 is a possible target of autoimmune hearing loss in humans.

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Glutathione Peroxidase–Catalase Cooperativity Is Required for Resistance to Hydrogen Peroxide by Mature Rat Oligodendrocytes

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Oxidative mechanisms of injury are important in many neurological disorders, including hypoxic–ischemic brain damage. Cerebral palsy after preterm birth is hypothesized to be caused by hypoxic–ischemic injury of developing oligodendrocytes (OLs). Here we examined the developmental sensitivity of OLs to exogenous hydrogen peroxide (H_2O_2) with stage-specific rat oligodendrocyte cultures. We found that H_2O_2 itself or that generated by glucose oxidase was more toxic to developing than to mature OLs. Mature OLs were able to degrade H_2O_2 faster than developing OLs, suggesting that higher antioxidant enzyme activity might be the basis for their resistance. Catalase expression and activity were relatively constant during oligodendrocyte maturation, whereas glutathione peroxidase (GPx) was upregulated with a twofold to threefold increase in its expression and activity. Thus, it appeared that the developmental change in resistance to H_2O_2 was caused by modulation of GPx but not by catalase expression. To test the relative roles of catalase and GPx in the setting of oxidative stress, we measured enzyme activity in cells exposed to H_2O_2 and found that H_2O_2 induced a decrease in catalase activity in developing but not in mature OLs. Inhibition of GPx by mercaptosuccinate led to an increase in the vulnerability of mature OLs to H_2O_2 as well as a reduction in catalase activity. Finally, H_2O_2-dependent inactivation of catalase in developing OLs was prevented by the GPx mimic ebselen. These data provide evidence for a key role for GPx– catalase cooperativity in the resistance of mature OLs to H_2O_2-induced cell death.
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Mechanisms of Dendritic Elaboration of Sensory Neurons in *Drosophila*: Insights from *In Vivo* Time Lapse

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In vivo time-lapse multiphoton microscopy was used to analyze the remodeling of the dendritic arborizingAQ: A (da) sensory neuron known as dorsal dendritic arborizing neuron E (ddaE) during metamorphosis. After its larval processes have been removed, the cell body of ddaE repositions itself on the body wall between 25 and 40 hr after puparium formation (APF) and begins its adult outgrowth at 40 hr APF. The scaffold of the arbor is laid down between 40 and 54 hr APF, when growth is characterized by high filopodial activity at both terminal and interstitial positions and by branch retraction along with branch establishment. Later in development, filopodial activity remains high but is confined to terminal branches, and branch retraction is no longer seen. Treatment with the insect hormone juvenile hormone (JH), a key regulator of metamorphosis, alters the shape and complexity of the adult dendritic tree in a time-dependent manner. Early treatments with juvenile hormone mimic (JHm) appear to repress extension programs and maintain retraction programs. With later JHm treatments, extension programs appear normal, but retraction programs are maintained beyond their normal time. The JH treatments show the importance of retraction programs in establishing the overall arbor shape.
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Conditional Ablation of the Neural Cell Adhesion Molecule Reduces Precision of Spatial Learning, Long-Term Potentiation, and Depression in the CA1 Subfield of Mouse Hippocampus

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AQ: BNCAM, a neural cell adhesion molecule of the immunoglobulin superfamily, is involved in neuronal migration and differentiation, axon outgrowth and fasciculation, and synaptic plasticity. To dissociate the functional roles of NCAM in the adult brain from developmental abnormalities, we generated a mutant in which the NCAM gene is inactivated by cre-recombinase under the control of the AQ: Ccalcium– calmodulin-dependent kinase II promoter, resulting in reduction of NCAM expression predominantly in the hippocampus. This mutant (NCAMff+) did not show the overt morphological and behavioral abnormalities previously observed in constitutive NCAM-deficient (NCAM−/−) mice. However, similar to the NCAM−/− mouse, a reduction in long-term potentiation (LTP) in the CA1 region of the hippocampus was revealed. Long-term depression was also abolished in NCAMff+ mice. The deficit in LTP could be rescued by elevation of extracellular Ca^{2+} concentrations from 1.5 or 2.0 to 2.5 mM, suggesting an involvement of NCAM in regulation of Ca^{2+}-dependent signaling during LTP. Contrary to the NCAM−/− mouse, LTP in the CA3 region was normal, consistent with normal mossy fiber lamination in NCAMff+ as opposed to abnormal lamination in NCAM−/− mice. NCAMff+ mutants did not show general deficits in short- and long-term memory in global landmark navigation in the water maze but were delayed in the acquisition of precise spatial orientation, a deficit that could be overcome by training. Thus, mice conditionally deficient in hippocampal NCAM expression in the adult share certain abnormalities characteristic of NCAM−/− mice, highlighting the role of NCAM in the regulation of synaptic plasticity in the CA1 region.
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Counteracting the Nogo Receptor Enhances Optic Nerve Regeneration If Retinal Ganglion Cells Are in an Active Growth State

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Mature retinal ganglion cells (RGCs), like other CNS neurons, cannot regrow injured axons into a myelin-rich environment. If stimulated by macrophage-derived factors, however, RGCs can regenerate their axons for considerable distances through the distal optic nerve. Using this "sensitized background," we investigated the effects of either increasing the expression or suppressing the activity of the NogoAQ: C receptor (NgR). NgR mediates the growth-inhibiting effects of three myelin proteins, Nogo, OMgp (oligodendrocyte–myelin glycoprotein), and MAG (myelin-associated glycoprotein).AQ: D Transfecting growth-sensitized RGCs with adeno-associated viruses expressing a dominant-negative form of NgR (NgR^{DN}) increased axon regeneration several-fold; however, when the growth program of RGCs was not activated, NgR^{DN} expression had no beneficial effects. Overexpression of wild-type NgR blocked almost all regeneration from growth-sensitized RGCs and caused axons proximal to the lesion site to retract. We conclude that gene therapy is an effective approach to enhancing axon regeneration in the CNS and that inactivation of NgR functioning greatly enhances axon regeneration provided the intrinsic growth program of neuronsAQ: E is activated.

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Early Serotonergic Projections to Cajal-Retzius Cells: Relevance for Cortical Development

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Although the serotonergic system plays an important role in various neurological disorders, the role of early serotonergic projections to the developing cerebral cortex is not well understood. Because serotonergic fibers enter the marginal zone (MZ) before birth, it has been suggested that they may influence cortical development through synaptic contacts with Cajal-Retzius (CR) cells. We used immunohistochemistry combined with confocal and electron microscopy to show that the earliest serotonergic projections to the MZ form synaptic contacts with the somata and proximal dendrites of CR cells as early as embryonic day 17. To elucidate the functional significance of these early serotonergic contacts with CR cells, we perturbed their normal development by injecting pregnant mice with 5-methoxytryptamine. Lower reelin levels were detected in the brains of newborn pups from the exposed animals. Because reelin plays an important role in the cortical laminar and columnar organization during development, we killedAQ: A some pups from the same litters on postnatal day 7 and analyzed their presubicular cortex. We found that the supragranular layers of the presubicular cortex (which normally display a visible columnar deployment of neurons) were altered in the treated animals. Our results suggest a mechanism of how serotonergic abnormalities during cortical development may disturb the normal cortical organization; and, therefore, may be relevant for understanding neurological disorders in which abnormalities of the serotonergic system are accompanied by cortical pathology (such as autism).

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Learning Modifies Subsequent Induction of Long-Term Potentiation-Like and Long-Term Depression-Like Plasticity in Human Motor Cortex

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Learning may alter rapidly the output organization of adult motor cortex. It is a long-held hypothesis that modification of synaptic strength along cortical horizontal connections through long-term potentiation (LTP) and long-term depression (LTD) forms one important mechanism for learning-induced cortical plasticity. Strong evidence in favor of this hypothesis was provided for rat primary motor cortex (M1) by showing that motor learning reduced subsequent LTP but increased LTD. Whether a similar relationship exists in humans is unknown. Here, we induced LTP-like and LTD-like plasticity in the intact human M1 by an established paired associative stimulation (PAS) protocol. PAS consisted of 200 pairs of electrical stimulation of the right median nerve, followed by focal transcranial magnetic stimulation of the hand area of the left M1 at an interval equaling the individual N20 latency of the median nerve somatosensory-evoked cortical potential (PAS_{N20}) or N20–5 msec (PAS_{N20-5}). PAS_{N20} induced reproducibly a LTP-like long-lasting (>30 min) increase in motor-evoked potentials from the left M1 to a thumb abductor muscle of the right hand, whereas PAS_{N20-5} induced a LTD-like decrease. Repeated fastest possible thumb abduction movements resulted in learning, defined by an increase in maximum peak acceleration of the practiced movements, and prevented subsequent PAS_{N20}-induced LTP-like plasticity but enhanced subsequent PAS_{N20-5}-induced LTD-like plasticity. The same number of repeated slow thumb abduction movements did not result in learning and had no effects on PAS-induced plasticity. Findings support the view that learning in human M1 occurs through LTP-like mechanisms.

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Neural Stem Cell Detection, Characterization, and Age-Related Changes in the Subventricular Zone of Mice

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The mammalian brain contains neural stem cells (NSCs) that allow continued neurogenesis throughout the life of the animal. However, neurogenesis is known to decline during aging and, to the extent that neurogenesis is required for normal CNSAQ: A function, this may contribute to neurodegenerative disease. Decreased neurogenesis could result from loss of NSCs or dysfunction at some later step, and distinguishing these possibilities is important for understanding the cause of the decline. However, because of the inability to distinguish NSCs from their rapidly dividing progeny *in situ*, it has not been possible to quantitatively assess the NSC populations in young and old animals. In this report we show that the G1 phase-specific expression of the replication factor Mcm2 is a useful marker for detecting slowly cycling putative NSCs *in situ* and confirm the identity of these cells using both cytosine β-D-arabinofuranoside (Ara-C) treatment and a double nucleoside analog-labeling technique. The ability to distinguish NSCs from proliferative progenitors has allowed characterization of the expression of several markers including Nestin, Musashi, and GFAP in these different cell types. Furthermore, comparison of the NSC populations in the subventricular zones of young (2–4 months) and old (24–26 months) mice demonstrates an approximately twofold reduction in the older mice. A similar twofold reduction is also observed in the number of neurospheres recovered in culture from old relative to young animals. The reduction in the neural stem cell population documented here is sufficient to account for the reduced level of neurogenesis in old animals.

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P/Q-Type Ca^{2+} Channel α1A Regulates Synaptic Competition on Developing Cerebellar Purkinje Cells

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Synapse formation depends critically on the competition among inputs of multiple sources to individual neurons. Cerebellar Purkinje cells have highly organized synaptic wiring from two distinct sources of excitatory afferents. Single climbing fibers innervate proximal dendrites of Purkinje cells, whereas numerous parallel fibers converge on their distal dendrites. Here, we demonstrate that the P/Q-type Ca^{2+} channel α1A, a major Ca^{2+} channel subtype in Purkinje cells, is crucial for this organized synapse formation. In the α1A knock-out AQ: Amouse, many ectopic spines were protruded from proximal dendrites and somata of Purkinje cells. Innervation territory of parallel fibers was expanded proximally to innervate the ectopic spines, whereas that of climbing fibers was regressed to the basal portion of proximal dendrites and somata. Furthermore, multiple climbing fibers consisting of a strong climbing fiber and one or a few weaker climbing fibers, persisted in the majority of Purkinje cells and were cowired to the same somata, proximal dendrites, or both. Therefore, the lack of α1A results in the persistence of parallel fibers and surplus climbing fibers, which should normally be expelled from the compartment innervated by the main climbing fiber. These results suggest that a P/Q-type Ca^{2+} channel α1A fuels heterosynaptic competition between climbing fibers and parallel fibers and also fuels homosynaptic competition among multiple climbing fibers. This molecular function facilitates the distal extension of climbing fiber innervation along the dendritic tree of the Purkinje cellAQ: B and also establishes climbing fiber monoinnervation of individual Purkinje cells.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Limbic and Motor Circuitry Underlying Footshock-Induced Reinstatement of Cocaine-Seeking Behavior

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The role of limbic, cortical, and striatal circuitry in a footshock reinstatement model of relapse to cocaine seeking was evaluated. Transient inhibition of the central extended amygdala [CEA; including the central nucleus of the amygdala (CN), ventral bed nucleus of the stria terminalis (BNSTv), and nucleus accumbens shell (NAshell)], ventral tegmental area (VTA), and motor circuitry [including the dorsal prefrontal cortex (PFCd), nucleus accumbens core (NAcore), and ventral pallidum (VP)] blocked the ability of footshock stress to reinstate lever pressing previously associated with cocaine delivery. However, inhibition of the basolateral amygdala, mediodorsal nucleus of the thalamus, or the ventral prefrontal cortex had no effect on drug-seeking behavior. These data suggest that footshock stress activates limbic circuitry of the CEA that, via the VTA, activates motor output circuitry responsible for producing lever press responding. Consistent with this notion, the D_1/D_2 dopamine receptor antagonist fluphenazine blocked footshock-induced reinstatement when infused into the PFCd. Further, inhibition of the NAshell blocked a footshock-induced increase in dopamine within the PFC and concomitantly blocked reinstatement responding. Also supporting the idea of a CEA–VTA–motor circuit in stress-induced reinstatement of cocaine seeking, inactivation of the PFCd was shown to block stress-induced glutamate release within the NAcore while concurrently inhibiting reinstatement responding. Taken together, these data suggest that footshock activates limbic circuitry in the CEA, which in turn activates a VTA dopamine projection to the PFCd. The rise in dopamine within the PFCd initiates reinstatement via a glutamatergic projection to the NAcore.

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Acute and Chronic Ethanol Alter Glutamatergic Transmission in Rat Central Amygdala: an *In Vitro* and *In Vivo* Analysis

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The modulation of glutamatergic transmission by ethanol may contribute to ethanol intoxication, reinforcement, tolerance, and dependence. Therefore, we used *in vitro* electrophysiological and *in vivo* microdialysis techniques to investigate the effects of acute and chronic ethanol on glutamatergic transmission in the central nucleus of amygdala (CeA). Superfusion of 5–66 mM ethanol decreased compound glutamatergic EPSPs and EPSCs in CeA neurons, with half-maximal inhibition elicited by 14 mM ethanol. Ethanol (44 mM) decreased both non-NMDAR- and NMDAR-mediated EPSPs and EPSCs by 21%. Both the ethanol- and ifenprodil-induced depression of NMDAR-mediated EPSPs and EPSCs was enhanced in rats that received chronic ethanol treatment (CET). Ifenprodil also occluded the ethanol effect, suggesting that NR2B subunit-containing receptors may be involved. With local applications of NMDA, acute ethanol elicited a greater inhibition of NMDA currents in slices taken from CET (47%) compared with naive (30%) animals, suggesting that CET sensitizes NMDA receptors to ethanol. Acute ethanol also reduced paired pulse facilitation of EPSPs and EPSCs only in CET animals, suggesting acute ethanol-induced increase of glutamate release. This finding was supported by *in vivo* experiments showing that infusion of ethanol (0.1–1 M) via reverse microdialysis significantly increased glutamate release into the CeA dialysate but only after CET. Moreover, baseline CeA glutamate content was significantly higher in CET compared with naive animals. These combined findings suggest that CET and withdrawal lead to neuroadaptations of glutamatergic transmission at both presynaptic and postsynaptic sites in CeA, and glutamatergic synapses in CeA may play an important role in ethanol dependence.
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A Single Infusion of Brain-Derived Neurotrophic Factor into the Ventral Tegmental Area Induces Long-Lasting Potentiation of Cocaine Seeking after Withdrawal

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Cocaine addiction in humans is associated with long-term propensity to relapse. Using a rat relapse model, we found that cocaine seekingAQ: A induced by exposure to cocaine-associated cues progressively increases after withdrawal. This progressive increase is associated with increases in brain-derived nerve growth factor (BDNF) levels within the mesolimbic dopamine system. Based on these findings, we studied whether BDNF infusions into the ventral tegmental area (VTA), the cell body region of mesolimbic dopamine neurons, would potentiate cocaine seeking after withdrawal. Rats were trained to self-administer cocaine for 10 d, and cocaine seeking was measured in extinction tests 3, 10, or 30 d after withdrawal. During testing, rats were exposed to contextual cues that had predicted cocaine availability during training, and lever presses resulted in contingent presentations of a discrete tone–light cue that was previously temporally paired with cocaine infusions. BDNF (0–0.75 μg/site) or nerve growth factor (NGF; 0–0.75 μg/site) was infused into the VTA 1–2 hr after the last self-administration session. To examine the role of the mitogen-activated protein kinase (MAPK) pathway in BDNF effects, U0126 (1 μg/site), an MEK inhibitor, was used. A single intra-VTA infusion of BDNF, but not NGF, induced long-lasting enhancement of cocaine seeking for up to 30 d, an effect reversed by U0126. In contrast, neither BDNF infusions into the substantia nigra, nor acute intra-VTA BDNF infusions 2 hr before testing on day 3 of withdrawal, were effective. These data suggest that BDNF-mediated neuroadaptations in mesolimbic areas are involved in the persistent cocaine seeking induced by exposure to drug cues after withdrawal.
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Material-Specific Recognition Memory Deficits Elicited by Unilateral Hippocampal Electrical Stimulation

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Although the medial temporal lobe is thought to be critical for recognition memory (RM), the specific role of the hippocampus in RM remains uncertain. We investigated the effects of transient unilateral hippocampal electrical stimulation (ES), subthreshold for afterdischarge, on delayed item RM in epilepsy patients implanted with bilateral hippocampal depth electrodes. RM was assessed using a novel computer-controlled test paradigm in which ES to left or right hippocampus was either absent (baseline) or synchronized with item presentation. Subsequent yes–no RM performance revealed a double dissociation between material-specific RM and the lateralization of ES. Left hippocampal ES produced word RM deficits, whereas right hippocampal ES produced face RM deficits. Our findings provide the first demonstration in humans that selective unilateral stimulation-induced hippocampal disruption is sufficient to produce impairments on delayed RM tasks and provide support for the material-specific laterality of hippocampal function with respect to RM.
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The Effect of Perceptual Learning on Neuronal Responses in Monkey Visual Area V4

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Previous studies have shown that perceptual learning can substantially alter the response properties of neurons in the primary somatosensory and auditory cortices. Although psychophysical studies suggest that perceptual learning induces similar changes in primary visual cortex (V1), studies that have measured the response properties of individual neurons have failed to find effects of the size described for the other sensory systems. We have examined the effect of learning on neuronal response properties in a visual area that lies at a later stage of cortical processing, area V4. Adult macaque monkeys were trained extensively on orientation discrimination at a specific retinal location using a narrow range of orientations. During the course of training, the subjects achieved substantial improvement in orientation discrimination that was primarily restricted to the trained location. After training, neurons in V4 with receptive fields overlapping the trained location had stronger responses and narrower orientation tuning curves than neurons with receptive fields in the opposite, untrained hemifield. The changes were most prominent for neurons that preferred orientations close to the trained range of orientations. These results provide the first demonstration of perceptual learning modifying basic neuronal response properties at an intermediate level of visual cortex and give insights into the distribution of plasticity across adult visual cortex.

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Effects of Training on Neuronal Activity and Interactions in Primary and Higher Visual Cortices in the Alert Cat

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The effects of behavioral training on early visual representations have been elusive when assessed with firing rates. Learning-induced changes in performance, however, suggest that representations should encompass early cortical stages. Here, we address the question of whether training-induced effects are pertinent to neuronal activity outside the task proper, which is a requirement if subsequent perceptional processes should profit from training. To search for a neuronal signature of training effects beyond firing rates, we measured local field potentials, multiunit and isolated spike activity during passive viewing of previously learned stimulus response associations (S+ and S−) in areas 17/18 and 21a of two alert cats. Evoked potential responses as well as gamma oscillations even during the first 200 msec were found to be stronger for S+ in both areas. Most importantly, the later parts of the response (>200 msec) not only exhibit a highly significant difference in coherent gamma oscillations for S+ and S− both within and across areas, but are also characterized by a pronounced preference in firing rate for S+ in area 21a, whereas primary cortex shows a nonsignificant trend for weaker spike responses. From these results, we conclude that training-induced plasticity occurs in adult visual cortex for behaviorally relevant stimuli by changing primarily the temporal structure of neuronal activity at early stages of cortical processing, whereas later stages of cortical processing express the increased coherence of their input in elevated firing rates.

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Specific Inhibition of IκB Kinase Reduces Hyperalgesia in Inflammatory and Neuropathic Pain Models in Rats

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Phosphorylation of IκB through IκB kinase (IKK) is the first step in nuclear factor κB (NF-κB) activation and upregulation of NF-κB-responsive genes. Hence, inhibition of IKK activity may be expected to prevent injury-, infection-, or stress-induced upregulation of various proinflammatory genes and may thereby reduce hyperalgesia and inflammation. In the present study, we tested this hypothesis using a specific and potent IKK inhibitor (S1627). In an IKK assay, S1627 inhibited IKK activity with an IC_{50} value of 10.0 ± 1.2 nM. In cell culture experiments, S1627 inhibited interleukin (IL)-1β-stimulated nuclear translocation and DNA-binding of NF-κB. Plasma concentration time courses after intraperitoneal injection revealed a short half-life of 2.8 hr in rats. Repeated intraperitoneal injections were, therefore, chosen as the dosing regimen. S1627 reversed thermal and mechanical hyperalgesia at 3× 30 mg/kg in the zymosan-induced paw inflammation model and reduced the inflammatory paw edema at 3× 40 mg/kg. S1627 also significantly reduced tactile and cold allodynia in the chronic constriction injury model of neuropathic pain at 30 mg/kg once daily. The drug had no effect on acute inflammatory nociception in the formalin test and did not affect responses to heat and tactile stimuli in naive animals. As hypothesized, S1627 prevented the zymosan-induced nuclear translocation of NF-κB in the spinal cord and the upregulation of NF-κB-responsive genes including cyclooxygenase-2, tumor necrosis factor-α, and IL-1β. Our data indicate that IKK may prove an interesting novel drug target in the treatment of pathological pain and inflammation.

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Differential Effects of CB1 and Opioid Agonists on Two Populations of Adult Rat Dorsal Root Ganglion Neurons

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Inhibition of primary afferent neurons contributes to the antihyperalgesic effects of opioid and CB1 receptor agonists. Two bioassays were used to compare the effects of the CB1 receptor agonist CP 55,940 and morphine on dissociated adult rat DRG neurons. Both agonists inhibited the increase in free intracellular Ca^{2+} concentration evoked by depolarization; however, effects of CP 55,940 occurred primarily in large neurons (cell area, $>800\ \mu m^2$), whereas morphine inhibited the response in smaller neurons. Cotreatment with selective blockers of L-, N-, and P/Q-type voltage-dependent Ca^{2+} channels indicated that CB1 receptors on DRG neurons couple solely with N-type channels but opioid receptors couple with multiple subtypes. Experiments with selective agonists and antagonists of opioid receptors indicated that μ and δ, but not κ, receptors contributed to the inhibitory effect of morphine on voltage-dependent Ca^{2+} influx. Because Ca^{2+} channels underlie release of transmitters from neurons, the effects of opioid agonists and CP 55,940 on depolarization-evoked release of calcitonin gene-related peptide (CGRP) were compared. Morphine inhibited release through δ receptors but CP 55,940 had no effect. Colocalization of CGRP with δ-opioid but not μ-opioid or CB1 receptor immunoreactivity in superficial laminae of the dorsal horn of the spinal cord was consistent with the data for agonist inhibition of peptide release. Therefore, CB1 and opioid agonists couple with different voltage-dependent Ca^{2+} channels in different populations of DRG neurons. Furthermore, differences occur in the distribution of receptors between the cell body and terminals of DRG neurons. The complementary action of CB1 and opioid receptor agonists on populations of DRG neurons provides a rationale for their combined use in modulation of somatosensory input to the spinal cord.
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NEUROBIOLOGY OF DISEASE

Neuroprotective Role of a Proline-Rich Akt Substrate in Apoptotic Neuronal Cell Death after Stroke: Relationships with Nerve Growth Factor

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The Akt signaling pathway contributes to regulation of apoptosis after a variety of cell death stimuli. A novel proline-rich Akt substrate (PRAS) was recently detected and found to be involved in apoptosis. In our study, Akt activation was modulated by growth factors, and treatment with nerve growth factor (NGF) reduced apoptotic cell death after ischemic injury. However, the role of the PRAS pathway in apoptotic neuronal cell death after ischemia remains unknown. Phosphorylated PRAS (pPRAS) and the binding of pPRAS/phosphorylated Akt (pPRAS/pAkt) to 14-3-3 (pPRAS/14-3-3) were detected, and their expression transiently decreased in mouse brains after transient focal cerebral ischemia (tFCI). Liposome-mediated pPRAS cDNA transfection induced overexpression of pPRAS, promoted pPRAS/14-3-3, and inhibited apoptotic neuronal cell death after tFCI. The expression of pPRAS, pPRAS/pAkt, and pPRAS/14-3-3 increased in NGF-treated mice but decreased with inhibition of phosphatidylinositol-3 kinase and the NGF receptor after tFCI. These results suggest that PRAS phosphorylation and its interaction with pAkt and 14-3-3 might play an important role in neuroprotection mediated by NGF in apoptotic neuronal cell death after tFCI.
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A Murine Model for Neuropsychiatric Disorders Associated with Group A β-Hemolytic Streptococcal Infection

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A syndrome of motoric and neuropsychiatric symptoms comprising various elements, including chorea, hyperactivity, tics, emotional lability, and obsessive-compulsive symptoms, can occur in association with group A β-hemolytic streptococcal (GABHS) infection. We tested the hypothesis that an immune response to GABHS can result in behavioral abnormalities. Female AQ: CSJL/J mice were immunized and boosted with a GABHS homogenate in Freund's adjuvant, whereas controls received Freund's adjuvant alone. When sera from GABHS-immunized mice were tested for immunoreactivity to mouse brain, a subset was found to be immunoreactive to several brain regions, including deep cerebellar nuclei (DCN), globus pallidus, and thalamus. GABHS-immunized mice having serum immunoreactivity to DCN also had increased IgG deposits in DCN and exhibited increased rearing behavior in open-field and hole-board tests compared with controls and with GABHS-immunized mice lacking serum anti-DCN antibodies. Rearing and ambulatory behavior were correlated with IgG deposits in the DCN and with serum immunoreactivity to GABHS proteins in Western blot. In addition, serum from a GABHS mouse reacted with normal mouse cerebellum in nondenaturing Western blots and immunoprecipitated C4 complement protein and α-2-macroglobulin. These results are consistent with the hypothesis that immune response to GABHS can result in motoric and behavioral disturbances and suggest that anti-GABHS antibodies cross-reactive with brain components may play a role in their pathophysiology.
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