**This Week in The Journal**

- **Cellular/Molecular**

  **Cav Shapes BK\textsubscript{Ca} Kinetics**
  Henrike Berkefeld and Bernd Fakler
  (see pages 8238 – 8245)
  Large-conductance Ca\textsuperscript{2+}- and voltage-activated potassium (BK\textsubscript{Ca}) channels contribute to membrane repolarization after action potentials, shape dendritic spikes, and influence neurotransmitter release. Increasing intracellular calcium concentration shifts the activation potential of BK\textsubscript{Ca}, which is essential for the channels to be activated at physiological voltages. A sufficient shift in activation potential occurs only when BK\textsubscript{Ca} channels form complexes with voltage-activated calcium (Cav) channels. Now, Berkefeld and Fakler report that the onset and upward slope of BK\textsubscript{Ca} activation—which varies widely across cell types—may largely be determined by which Cav channels the BK\textsubscript{Ca} channels cluster with. When clustered with P/Q-type calcium channels (Cav2.1), BK\textsubscript{Ca} activated at more hyperpolarized potentials and had a faster rise time than when clustered with L-type calcium channels (Cav1.2). The complexes also responded differently to simulated action potentials: action potentials with short duration reliably activated BK\textsubscript{Ca} in BK\textsubscript{Ca}–Cav2.1 complexes, whereas they often failed to activate BK\textsubscript{Ca} in BK\textsubscript{Ca}–Cav1.2 complexes.

- **Development/Plasticity/Repair**

  **NF-κB Phosphorylation State Determines Effect on Growth**
  Humberto Gutierrez, Gerard W. O’Keeffe, Núria Gavalda, Denis Gallagher, and Alun M. Davies
  (see pages 8246 – 8256)
  The transcription factor nuclear factor κB (NF-κB) regulates many cellular functions, including neurite outgrowth from nodose ganglion neurons. Gutierrez et al. now report that NF-κB stimulates or inhibits neurite growth depending on the phosphorylation state of one amino acid. Superior cervical ganglion sympathetic neurons and nodose sensory neurons were cultured from neonatal mice and then transfected with proteins that either increased or decreased NF-κB-mediated transcription. In sympathetic neurons, NF-κB signaling was unnecessary for neurite growth, but enhancing NF-κB transcriptional activity inhibited neurite outgrowth. In sensory neurons, surprisingly, some treatments that enhanced NF-κB function increased neurite outgrowth, and others decreased outgrowth. These effects were traced to the activity of a kinase that phosphorylates NF-κB, which was constitutively active in sympathetic neurons. Eliminating the phosphorylation site on NF-κB prevented inhibition of neurite growth, whereas mutating it to mimic constitutive phosphorylation inhibited neurite growth in both sensory and sympathetic neurons.

- **Behavioral/Systems/Cognitive**

  **Reward Activates Primary Somatosensory Cortex**
  Burkhard Pleger, Felix Blankenburg, Christian C. Ruff, Jon Driver, and Raymond J. Dolan
  (see pages 8161 – 8168)
  Receiving a reward activates sensory cortex, which might improve future performance, according to Pleger et al. Human subjects discriminated the frequency of two electrical stimuli applied to a finger. Before stimulation, a visual cue indicated the amount of reward given for a correct discrimination. After the subjects’ response, a visual signal indicated whether they received the anticipated reward (for correct discrimination) or no reward (for incorrect answers). Functional magnetic resonance imaging revealed that finger stimulation activated primary somatosensory cortex (SI) the same amount regardless of the size of the anticipated reward. Remarkably, however, SI was activated again by receipt of the reward, in proportion to the size of the reward. Moreover, after a reward was received, SI was more activated by stimulation on the next trial, and this effect was also larger for larger rewards. This reward-related activation, which was distinguishable from attention-related activation, was correlated with improved discrimination performance.

- **Neurobiology of Disease**

  **Proteasome Dysfunction Causes Neurodegeneration**
  (see pages 8189 – 8198)
  The ubiquitin-proteasome system helps maintain cellular function by limiting the lifespan of regulatory proteins and degrading defective proteins. The addition of polyubiquitin chains to such proteins targets them for degradation by the 26S proteasome complex. Accumulation of ubiquitinated proteins characterizes many neurodegenerative diseases, including Parkinson’s disease, suggesting that dysfunction of the proteasome system is involved in these diseases. But direct tests of this hypothesis have produced controversial results. This week, Bedford et al. provide definitive evidence that loss of proteasome function causes neurodegeneration. They produced mice in which an essential component of the 26S proteasome complex was conditionally knocked out in forebrain or substantia nigra neurons. This greatly reduced the number of 26S proteasome complexes in the affected neurons without affecting ubiquitin-independent degradation. Ubiquitinated proteins accumulated in the neurons, forming inclusions like those seen in neurodegenerative diseases, and this ultimately led to neurodegeneration and apoptosis.
Embryonic (day 17) retinal ganglion cells (RGCs) require contact-mediated signals from neighboring cell types to become synaptically receptive. Here embryonic neurons are plated on top of a confluent layer of mixed retinal cells, which are sufficient to induce synapse formation. Dendrites are stained with MAP2 (green), and synaptic puncta are shown as an overlap synaptotagmin (blue) and PSD-95 (red). For more information, see the article by Barker et al. in this issue (pages 8150 – 8160).
Nervous Wreck and Cdc42 Cooperate to Regulate Endocytic Actin Assembly during Synaptic Growth
Avital A. Rodal, Rebecca N. Motola-Barnes, and J. Troy Littleton

Cdk5 Phosphorylation of WAVE2 Regulates Oligodendrocyte Precursor Cell Migration through Nonreceptor Tyrosine Kinase Fyn
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Regulation of Axonal Elongation and Pathfinding from the Entorhinal Cortex to the Dentate Gyrus in the Hippocampus by the Chemokine Stromal Cell-Derived Factor 1α
Yoichi Ohshima, Takekazu Kubo, Ryuta Koyama, Masaki Ueno, Masanori Nakagawa, and Toshihide Yamashita

Subfunctionalization of a Retinoid-Binding Protein Provides Evidence for Two Parallel Visual Cycles in the Cone-Dominant Zebrafish Retina
Valerie C. Fleisch, Helia B. Schonthaler, Johannes von Lintig, and Stephan C. F. Neuhauss

Nuclear Factor κB Signaling Either Stimulates or Inhibits Neurite Growth Depending on the Phosphorylation Status of p65/RelA
Humberto Gutierrez, Gerard W. O’Keeffe, Núria Gavalda, Denis Gallagher, and Alun M. Davies

Cortisol Inhibits Neuroplasticity Induction in Human Motor Cortex
Martin V. Sale, Michael C. Ridding, and Michael A. Nordstrom

Repulsive Wnt Signaling Inhibits Axon Regeneration after CNS Injury
Yaobo Liu, Xiaofei Wang, Chin-Chun Lu, Rachel Kerman, Oswald Steward, Xiao-Ming Xu, and Yimin Zou

Reward Facilitates Tactile Judgments and Modulates Hemodynamic Responses in Human Primary Somatosensory Cortex
Burkhard Pleger, Felix Blankenburg, Christian C. Ruff, Jon Driver, and Raymond J. Dolan

Failure to Mount Adaptive Responses to Stress Results in Dysregulation and Cell Death in the Midbrain Raphe
Jonathan G. McEuen, Sheryl G. Beck, and Tracy L. Bale

Constitutively Active Rap2 Transgenic Mice Display Fewer Dendritic Spines, Reduced Extracellular Signal-Regulated Kinase Signaling, Enhanced Long-Term Depression, and Impaired Spatial Learning and Fear Extinction
Jubin Ryu, Kensuke Futai, Monica Feliu, Richard Weinberg, and Morgan Sheng

Intra-Amygdala and Systemic Antagonism of NMDA Receptors Prevents the Reconsolidation of Drug-Associated Memory and Impairs Subsequently Both Novel and Previously Acquired Drug-Seeking Behaviors

Amygdala and Orbitofrontal Cortex Lesions Differentially Influence Choices during Object Reversal Learning
Peter H. Rudebeck and Elisabeth A. Murray

Representation of Eye Movements and Stimulus Motion in Topographically Organized Areas of Human Posterior Parietal Cortex
Christina S. Konen and Sabine Kastner
Depletion of 26S Proteasomes in Mouse Brain Neurons Causes Neurodegeneration and Lewy-Like Inclusions Resembling Human Pale Bodies

Loss of PINK1 Function Affects Development and Results in Neurodegeneration in Zebrafish
Oleg Anichtchik, Heike Diekmann, Angeleen Fleming, Alan Roach, Paul Goldsmith, and David C. Rubinsztein

Microglial Dysfunction and Defective β-Amyloid Clearance Pathways in Aging Alzheimer’s Disease Mice
Suzanne E. Hickman, Elizabeth K. Allison, and Joseph El Khoury

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Very Slow EEG Fluctuations Predict the Dynamics of Stimulus Detection and Oscillation Amplitudes in Humans

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Our ability to perceive weak signals is correlated among consecutive trials and fluctuates slowly over time. Although this “streaking effect” has been known for decades, the underlying neural network phenomena have remained largely unidentified. We examined the dynamics of human behavioral performance and its correlation with infraslow (0.01–0.1 Hz) fluctuations in ongoing brain activity. Full-band electroencephalography revealed prominent infraslow fluctuations during the execution of a somatosensory detection task. Similar fluctuations were predominant also in the dynamics of behavioral performance. The subjects’ ability to detect the sensory stimuli was strongly correlated with the phase, but not with the amplitude of the infraslow EEG fluctuations. These data thus reveal a direct electrophysiological correlate for the slow fluctuations in human psychophysical performance. We then examined the correlation between the phase of infraslow EEG fluctuations and the amplitude of 1–40 Hz neuronal oscillations in six frequency bands. Like the behavioral performance, the amplitudes in these frequency bands were robustly correlated with the phase of the infraslow fluctuations. These data hence suggest that the infraslow fluctuations reflect the excitability dynamics of cortical networks. We conclude that ongoing 0.01–0.1 Hz EEG fluctuations are prominent and functionally significant during execution of cognitive tasks.

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Developmental Control of Synaptic Receptivity

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Are neurons born with the ability to form and receive synapses or do they acquire these abilities during development? We have previously found that purified postnatal retinal ganglion cells (RGCs) require soluble astrocyte-derived signals to form synapses in vitro and in vivo. Here we show that newly generated embryonic day 17 (E17) RGCs are able to form but not receive synapses under these conditions. Dendrite growth is not sufficient to trigger receptivity; rather, the ability of newly generated RGCs to receive synapses is acquired at E19 in response to direct contact by neighboring cell types. Direct contact with astrocytes, which are not present at E17 but are normally generated by E19, is sufficient to induce synaptic receptivity in E17 RGCs. In contrast, amacrine contact does not induce synaptic receptivity. Interestingly, astrocyte contact alters the localization of the synaptic adhesion molecule neurexin away from dendrites. In addition, dendritic expression of neurexin is sufficient to prevent astrocyte contact-mediated increases in synapse number, suggesting a molecular mechanism by which astrocyte contact regulates neuronal synaptic receptivity. Thus, synaptic receptivity is not induced simply by dendritic elaboration but must be signaled by both contact-mediated signaling from astrocytes and a shift in the dendritic localization of neurexin.

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Distinct Deep Short-Axon Cell Subtypes of the Main Olfactory Bulb Provide Novel Intrabulbar and Extrabulbar GABAergic Connections

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A universal feature of neuronal microcircuits is the presence of GABAergic interneurons that control the activity of glutamatergic principal cells and each other. In the rat main olfactory bulb (MOB), GABAergic granule and periglomerular cells innervate mitral and tufted cells, but the source of their own inhibition remains elusive. Here, we used a combined electrophysiological and morphological approach to investigate a rather mysterious cell population of the MOB. Deep short-axon cells (dSACs) of the inframitral layers are GABAergic and have extensive and characteristic axonal ramifications in various layers of the bulb, based on which unsupervised cluster analysis revealed three distinct subtypes. Each dSAC subtype exhibits different electrical properties but receives similar GABAergic and glutamatergic inputs. The local axon terminals of all dSAC subtypes selectively innervate GABAergic granule and periglomerular cells and evoke GABA_A receptor-mediated IPSCs. One subpopulation of dSACs (GL-dSACs) creates a novel intrabulbar projection from deep to superficial layers. Another subpopulation (GCL-dSACs) is labeled by retrogradely transported fluorescent microspheres injected into higher olfactory areas, constituting a novel projection-cell population of the MOB. Our results reveal multiple dSAC subtypes, each specialized to influence MOB activity by selectively innervating GABAergic interneurons, and provide direct evidence for novel intrabulbar and extrabulbar GABAergic projections.

The Journal of Neuroscience, August 13, 2008 • 28(33):8217–8229
Repolarizing Responses of BK<sub>Ca</sub>–Cav Complexes Are Distinctly Shaped by Their Cav Subunits

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Large-conductance Ca<sup>2+</sup>- and voltage-activated potassium (BK<sub>Ca</sub>) channels shape the firing pattern in many types of excitable cell through their repolarizing K<sup>+</sup> conductance. The onset and duration of the BK<sub>Ca</sub>-mediated currents typically initiated by action potentials (APs) appear to be cell-type specific and were shown to vary between 1 ms and up to a few tens of milliseconds. In recent work, we showed that reliable activation of BK<sub>Ca</sub> channels under cellular conditions is enabled by their integration into complexes with voltage-activated Ca<sup>2+</sup> (Cav) channels that provide Ca<sup>2+</sup> ions at concentrations sufficiently high (>,=10 μM) for activation of BK<sub>Ca</sub> in the physiological voltage range. Formation of BK<sub>Ca</sub>–Cav complexes is restricted to a subset of Cav channels, Cav1.2 (L-type) and Cav2.1/2.2 (P/Q- and N-type), which differ greatly in their expression pattern and gating properties. Here, we reconstituted distinct BK<sub>Ca</sub>–Cav complexes in Xenopus oocytes and culture cells and used patch-clamp recordings to compare the functional properties of BK<sub>Ca</sub>–Cav1.2 and BK<sub>Ca</sub>–Cav2.1 complexes. Under steady-state conditions, K<sup>+</sup> currents mediated by BK<sub>Ca</sub>–Cav1.2 complexes exhibit a considerably faster rise time and reach maximum at potentials markedly more negative than complexes formed by BK<sub>Ca</sub> and Cav1.2, in line with the distinct steady-state activation and gating kinetics of the two Cav subtypes. When AP waveforms were used as a voltage command, K<sup>+</sup> currents mediated by BK<sub>Ca</sub>–Cav2.1 occurred at shorter APs and lasted longer than that of BK<sub>Ca</sub>–Cav1.2. These results demonstrate that the repolarizing K<sup>+</sup> currents through BK<sub>Ca</sub>–Cav complexes are shaped by the respective Cav subunit and that the distinct Cav channels may adapt BK<sub>Ca</sub> currents to the particular requirements of distinct types of cell.

The Journal of Neuroscience, August 13, 2008 • 28(33):8238 – 8245

Phorbol Esters Modulate Spontaneous and Ca<sup>2+</sup>-Evoked Transmitter Release via Acting on Both Munc13 and Protein Kinase C

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Diacylglycerol (DAG) and phorbol esters strongly potentiate transmitter release at synapses by activating protein kinase C (PKC) and members of the Munc13 family of presynaptic vesicle priming proteins. This PKC/Munc13 pathway has emerged as a crucial regulator of release probability during various forms of activity-dependent enhancement of release. Here, we investigated the relative roles of PKC and Munc13-1 in the phorbol ester potentiation of evoked and spontaneous transmitter release at the calyx of Held synapse. The phorbol ester phorbol 12,13-dibutyrate (1 μM) potentiated the frequency of miniature EPSCs, and the amplitudes of evoked EPSCs with a similar time course. Preincubating slices with the PKC blocker Ro33-8220 reduced the potentiation, mainly by affecting a late phase of the phorbol ester potentiation. The Ro33-8220-resistant potentiation was most likely mediated by Munc13-1, because in organotypic slices of Munc13-1<sup>−/−</sup> knock-in mice, in which DAG binding to Munc13-1 is abolished, the potentiation of spontaneous release by phorbol ester was strongly suppressed. Using direct presynaptic depolarizations in paired recordings, we show that the phorbol ester potentiation does not go along with an increase in the number of readily releasable vesicles, despite an increase in the cumulative EPSC amplitude during 100 Hz stimulation trains. Our data indicate that activation of Munc13 and PKC both contribute to an enhancement of the fusion probability of readily releasable vesicles. Thus, docked and readily releasable vesicles are a substrate for modulation via intracellular second-messenger pathways that act via Munc13 and PKC.

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Efficient Recruitment of Layer 2/3 Interneurons by Layer 4 Input in Single Columns of Rat Somatosensory Cortex

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Interneurons in layers 2/3 are excited by pyramidal cells within the same layer (Reyes et al., 1998; Gupta et al., 2000), but little is known about translaminar innervation of these interneurons by spiny neurons in the main cortical input layer 4 (L4). Here, we investigated (1) how efficiently L4 spiny neurons excite L2/3 interneurons via monosynaptic connections, (2) whether glutamate release from axon terminals of L4 spiny neurons depends on the identity of the postsynaptic interneuron, and (3) how L4-to-L2/3 interneuron connections compare with L4-to-L2/3 pyramidal neuron connections. We recorded from pairs of L4 spiny neurons and L2/3 interneurons in acute slices of rat barrel cortex of postnatal day 20 (P20) to P29 rats. The L4-to-L2/3 interneuron connections had an average unitary EPSP of 1.2 ± 0.2 mV. We found an average of 2.3 ± 0.8 contacts per connection, and the L4-to-L2/3 interneuron innervation domains were mostly column restricted. Unitary EPSP amplitudes and paired-pulse ratios in the L4-to-L2/3 interneuron connections depended on the “group” of the postsynaptic interneuron. Averaged over all L4-to-L2/3 interneuron connections, unitary EPSP amplitudes were 1.8-fold higher than in the translaminar L4-to-L2/3 pyramidal cell connections. Our results suggest that L4 spiny neurons may more efficiently recruit L2/3 interneurons than L2/3 pyramidal neurons, and that glutamate release from transsynaptic boutons of L4 spiny neuron axons is target cell specific.

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A Novel Purification Method for CNS Projection Neurons Leads to the Identification of Brain Vascular Cells as a Source of Trophic Support for Corticospinal Motor Neurons

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One of the difficulties in studying cellular interactions in the CNS is the lack of effective methods to purify specific neuronal populations of interest. We report the development of a novel purification scheme, cholera toxin β (CTB) immunopanning, in which a particular CNS neuron population is selectively labeled via retrograde axonal transport of the cell-surface epitope CTB, and then purified via immobilization with anti-CTB antibody. We have demonstrated the usefulness and versatility of this method by purifying both retinal ganglion cells and corticospinal motor neurons (CSMNs). Genomic expression analyses of purified CSMNs revealed that they express significant levels of many receptors for growth factors produced by brain endothelial cells; three of these factors, CXCL12, pleiotrophin, and IGF2 significantly enhanced purified CSMN survival, similar to previously characterized CSMN trophic factors BDNF and IGF1. In addition, endothelial cell conditioned medium significantly promoted CSMN neurite outgrowth. These findings demonstrate a useful method for the purification of several different types of CNS projection neurons, which in principle should work in many mammalian species, and provide evidence that endothelial-derived factors may represent an overlooked source of trophic support for neurons in the brain.

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Mitochondrial Membrane Potential in Axons Increases with Local Nerve Growth Factor or Semaphorin Signaling

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Neurons concentrate mitochondria at sites in the cell that have a high demand for ATP and/or calcium buffering. To accomplish this, mitochondrial transport and docking are thought to respond to intracellular signaling pathways. However, the cell might also concentrate mitochondrial function by locally modulating mitochondrial activity. We tested this hypothesis by measuring the membrane potential of individual mitochondria throughout the axons of chick sensory neurons using the dye tetramethylrhodamine methyl ester (TMRM). We found no difference in the TMRM mitochondrial-to-cytoplasmic fluorescence ratio \( \frac{F_m}{F_c} \) among three functionally distinct regions: axonal branch points, distal axons, and the remaining axon shaft. In addition, we found no difference in \( \frac{F_m}{F_c} \) among stationary, retrogradely moving, or anterogradely moving mitochondria. However, \( \frac{F_m}{F_c} \) was significantly higher in the lamellipodia of growth cones, and among a small fraction of mitochondria throughout the axon. To identify possible signals controlling membrane potential, we used beads covalently coupled to survival and guidance cues to provide a local stimulus along the axon shaft. NGF- or semaphorin 3A-coupled beads caused a significant increase in \( \frac{F_m}{F_c} \) in the immediately adjacent region of axon, and this was diminished in the presence of the PI3 kinase inhibitor LY294002 [2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one] or the MAP (mitogen-activated protein) kinase inhibitor U0126 (1,4-diamino-2,3-dicyano-1,4-bis[2-amino-phenylthio]butadiene), demonstrating that signaling pathways downstream of both ligands affect the \( \Delta \Psi_m \) of mitochondria. In addition, general inhibition of receptor tyrosine kinase activity produced a profound global decrease in \( \frac{F_m}{F_c} \). Thus, two guidance molecules that exert different effects on growth cone motility both elicit local, receptor-mediated increases in membrane potential.

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Nervous Wreck and Cdc42 Cooperate to Regulate Endocytic Actin Assembly during Synaptic Growth

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Regulation of synaptic morphology depends on endocytosis of activated growth signal receptors, but the mechanisms regulating this membrane-trafficking event are unclear. Actin polymerization mediated by Wiskott-Aldrich syndrome protein (WASP) and the actin-related protein 2/3 complex generates forces at multiple stages of endocytosis. FCH-BIN amphiphysin RVS (F-BAR)/SH3 domain proteins play key roles in this process by coordinating membrane deformation with WASP-dependent actin polymerization. However, it is not known how other WASP ligands, such as the small GTPase Cdc42, coordinate with F-BAR/SH3 proteins to regulate actin polymerization at membranes. Nervous Wreck (Nwk) is a conserved neuronal F-BAR/SH3 protein that localizes to periactive zones at the Drosophila larval neuromuscular junction (NMJ) and is required for regulation of synaptic growth via bone morphogenic protein signaling. Here, we show that Nwk interacts with the endocytic proteins dynamin and Dap160 and functions together with Cdc42 to promote WASP-mediated actin polymerization in vitro and to regulate synaptic growth in vivo. Cdc42 function is associated with Rab11-dependent recycling endosomes, and we show that Rab11 colocalizes with Nwk at the NMJ. Together, our results suggest that synaptic growth activated by growth factor signaling is controlled at an endosomal compartment via coordinated Nwk and Cdc42-dependent actin assembly.

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Cdk5 Phosphorylation of WAVE2 Regulates Oligodendrocyte Precursor Cell Migration through Nonreceptor Tyrosine Kinase Fyn

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Myelin formation of the CNS is a complex and dynamic process. Before the onset of myelination, oligodendrocytes (OLs), the myelin-forming glia of the CNS, proliferate and migrate along axons. Little is known about the molecular mechanisms underlying the early myelination processes. Here, we show that platelet-derivived growth factor (PDGF), the crucial physiological ligand in early OL development, controls the migration of oligodendrocyte precursor cells (OPCs) through cyclin-dependent kinase 5 (Cdk5). PDGF stimulates Cdk5 activity in a time-dependent manner, whereas suppression of Cdk5 by the specific inhibitor roscovitine or by the retrovirus encoding short-hairpin RNA for Cdk5 impairs PDGF-dependent OPC migration. The activation of Cdk5 by PDGF is mediated by the phosphorylation of the nonreceptor tyrosine kinase, Fyn, whose inhibition reduces PDGF-dependent OPC migration. Furthermore, Cdk5 regulates PDGF-dependent OPC migration through the direct phosphorylation of WASP (Wiskott-Aldrich syndrome protein)-family verprolin-homologous protein 2 (WAVE2). Cdk5 phosphorylates WAVE2 at Ser-137 in vitro. Infection of the WAVE2 construct harboring the Ser-137-to-Ala reduces PDGF-dependent migration. Together, PDGF regulates OPC migration through an as-yet-unidentified signaling cascade coupling Fyn kinase to Cdk5 phosphorylation of WAVE2. These results provide new insights into both the role of Cdk5 in glial cells and the molecular mechanisms controlling the early developmental stage of OLs.

The Journal of Neuroscience, August 13, 2008 - 28(33):8326 – 8337

Regulation of Axonal Elongation and Pathfinding from the Entorhinal Cortex to the Dentate Gyrus in the Hippocampus by the Chemokine Stromal Cell-Derived Factor 1α

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During the early developmental stage, a neural circuit is established between the entorhinal cortex (EC) and the hippocampal dentate gyrus (DG) via the perforant pathway. However, the manner in which the perforant fibers are navigated has mostly remained a mystery. Here, we analyzed the functional role of a chemokine, namely, stromal cell-derived factor 1α (SDF-1α), in the navigation of the perforant fibers. SDF-1α was observed to promote neurite growth, which is dependent on mDia1, in cultured entorhinal cortical neurons obtained from rats at postnatal day 0. We then used entorhino-hippocampal cocultures comprising green fluorescence-labeled EC and DG slices to assess the projection of the perforant fibers from the EC. Although the specific laminar termination of the entorhinal axons was observed with this system, the number of appropriately terminating entorhinal axons decreased significantly when the SDF-1α signaling pathway was blocked by a neutralizing antibody against SDF-1α or by the specific SDF-1α receptor antagonist AMD3100 (1,1′-[1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride). Furthermore, inhibition of the SDF-1α signaling pathway resulted in a decrease in the immunoreactivity for PSD-95 (postsynaptic density protein-95) in the DG, possibly because of a reduction in the number of projecting perforant fibers. These results demonstrate that SDF-1α plays a critical role in promoting the growth of perforant fibers from the EC to the DG.

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Subfunctionalization of a Retinoid-Binding Protein Provides Evidence for Two Parallel Visual Cycles in the Cone-Dominant Zebrafish Retina

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In vertebrates, the absorption of a photon results in an 11-cis to all-trans isomerization of the retinylidene chromophore of cone and rod visual pigments. To sustain vision, metabolic pathways (visual cycles) have evolved that recycle all-trans-retinal back to 11-cis-retinal. The canonical visual cycle takes place in photoreceptor cells and the adjacent retinal pigment epithelium (RPE). Biochemical analyses provided evidence for the existence of an additional cone-specific visual cycle involving Müller glia cells, but none of its molecular components has yet been identified. Here we took advantage of the zebrafish retina to investigate the role of the cellular retinaldehyde-binding protein CRALBP in this process. We found that the zebrafish genome encodes two cralbp paralogs: cralbp a and cralbp b. These paralogs are differentially expressed in the retina. Cralbp a is exclusively expressed in the RPE, and Cralbp b is localized to Müller cells. We used an antisense morpholino approach to knock down each cralbp paralog. Analysis of 11-cis-retinal levels revealed that visual chromophore regeneration is diminished under both conditions. Visual performance, as assessed by electroretinography, revealed reduced light sensitivity in both Cralbp a- and Cralbp b-deficient larvae, but it was more pronounced in Cralbp b-deficient larvae. Cralbp b-deficient larvae also exhibited significant deficits in their visual behavior. Together, these data demonstrate that Cralbp expression in Müller cells is essential for cone vision, thereby providing evidence that both the canonical and the alternative visual cycle depend on the same type of retinoid-binding protein.

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Nuclear factor κB (NF-κB) signaling is known to promote neurite growth from developing sensory neurons and to enhance the size and complexity of pyramidal neuron dendritic arbors in the developing cerebral cortex. In marked contrast, here we show that NF-κB signaling can also exert a potent inhibitory influence on neurite growth in certain neurons, and can either promote or inhibit neurite growth in the same neurons depending on the mechanism of NF-κB activation. In neonatal superior cervical ganglion sympathetic neurons, enhancing NF-κB transcriptional activity by overexpressing either the p65 NF-κB subunit or the IκB kinase-β (IKKβ) subunit of the IκB kinase complex, or by tumor necrosis factor α (TNFα) treatment, strongly inhibits neurite growth. Paradoxically in neonatal nodose ganglion sensory neurons, enhancing NF-κB transcriptional activity by p65/p10 overexpression increases neurite growth, whereas enhancing NF-κB transcriptional activity by IKKβ overexpression inhibits neurite growth. In addition to activating NF-κB, IKKβ overexpression leads to phosphorylation of p65 on serine 536. Blockade of serine 536 phosphorylation by a S536A-p65 mutant protein prevents the growth-inhibitory effects of IKKβ overexpression in both sensory and sympathetic neurons and the growth-inhibitory effects of TNFα on sympathetic neurons. Furthermore, expression of a p65 S536D phosphomimetic mutant inhibits neurite growth from sensory neurons. These results demonstrate that NF-κB can either stimulate or inhibit neurite growth in developing neurons depending on the phosphorylation status of p65.
The Journal of Neuroscience, August 13, 2008 • 28(33):8246 – 8256

Cortisol Inhibits Neuroplasticity Induction in Human Motor Cortex

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We investigated whether plasticity of human motor cortex (M1) is influenced by time of day, and whether changes in circulating levels of cortisol contribute to this effect. Neuroplasticity was induced using paired associative stimulation (PAS), involving electrical stimulation of left median nerve, paired with transcranial magnetic stimulation over the right M1 25 ms later (90 pairs at 0.05 Hz). Surface EMG was recorded from the left abductor pollicis brevis (APB) and first dorsal interosseous muscle. Cortisol levels were assessed from saliva. Time-of-day modulation of PAS effectiveness was assessed in 25 subjects who were tested twice, at 8:00 A.M. and 8:00 P.M. on separate days. In a second double-blind study, 17 subjects were tested with PAS at 8:00 P.M. on two occasions after administration of oral hydrocortisone (24 mg) or placebo. The motor-evoked potential (MEP) in resting APB increased significantly after PAS in the evening (when endogenous cortisol levels were low), but not in the morning. Oral hydrocortisone prevented facilitation of the APB MEP after PAS, and in the drug study, mean salivary cortisol levels were negatively associated with PAS effectiveness. The GABA_A-mediated cortical silent period for APB was longer in the morning than in the evening, and was lengthened by PAS and oral hydrocortisone. We conclude that neuroplasticity in human M1 and GABA_A-dependent intracortical inhibitory systems are influenced by time of day and modified by circulating levels of cortisol.
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Repulsive Wnt Signaling Inhibits Axon Regeneration after CNS Injury

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Failure of axon regeneration in the mammalian CNS is attributable in part to the presence of various inhibitory molecules, including myelin-associated proteins and proteoglycans enriched in glial scars. Here, we evaluate whether axon guidance molecules also regulate regenerative growth after injury in adulthood. Wnts are a large family of axon guidance molecules that can attract ascending axons and repel descending axons along the length of the developing spinal cord. Their expression (all 19 WntS) is not detectable in normal adult spinal cord by in situ hybridization. However, three of them are clearly induced after spinal cord injury. Wnt1 and Wnt5a, encoding potent repellents of the descending corticospinal tract (CST) axons, were robustly and acutely induced broadly in the spinal cord gray matter after unilateral hemisection. Ryk, the conserved repulsive Wnt receptor, was also induced in the lesion area, and Ryk immunoreactivity was found on the lesioned CST axons. Wnt4, which attracts ascending sensory axons in development, was acutely induced in areas closer to the lesion than Wnt1 and Wnt5a. Injection of function-blocking Ryk antibodies into the dorsal bilateral hemisectioned spinal cord either prevented the retraction of CST axons or promoted their regrowth but clearly enhanced the sprouting of CST collateral branches around and beyond the injury site. Therefore, repulsive Wnt signaling may be a cause of cortical spinal tract axon retraction and inhibits axon sprouting after injury.
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Reward Facilitates Tactile Judgments and Modulates Hemodynamic Responses in Human Primary Somatosensory Cortex

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Reinforcing effects of reward on action are well established, but possible effects on sensory function are less well explored. Here, using functional magnetic resonance imaging, we assessed whether reward can influence somatosensory judgments and modulate activity in human somatosensory cortex. Participants discriminated electrical somatosensory stimuli on an index finger with correct performance rewarded financially at trial end, at one of four different anticipated levels. Higher rewards improved tactile performance and led to increased hemodynamic signals from ventral striatum on rewarded trials. Remarkably, primary somatosensory cortex contralateral to the judged hand was reactivated at the point of reward delivery, despite the absence of concurrent somatosensory input at that time point. This side-specific reactivation of primary somatosensory cortex increased monotonically with level of reward. Moreover, the level of reward received on a particular trial influenced somatosensory performance and neural activity on the subsequent trial, with better discrimination and enhanced hemodynamic response in contralateral primary somatosensory cortex for trials that followed higher rewards. These results indicate that rewards can influence not only classical reward-related regions, but also early somatosensory cortex when a decision is required for that modality.

Failure to Mount Adaptive Responses to Stress Results in Dysregulation and Cell Death in the Midbrain Raphe

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Stress is a common trigger in affective disorder onset, yet the mechanism and predisposing factors of vulnerability remain unknown. Effective disease prevention requires a critical balance of responses within the serotonergic raphe nucleus, including a coordination of corticotropin-releasing factor (CRF) actions at both of its receptors, CRF receptor-1 and CRF receptor-2. Mice deficient in CRF receptor-2 (R2KO) were used as a model of maladaptive stress responsiveness to examine the physiological and molecular markers of stress dysregulation within the raphe in the absence of this receptor. After chronic stress, R2KO mice failed to display the robust stress-mediated adaptations characteristic of control mice, including elevations in tryptophan hydroxylase-2 and CRF receptor-1 expression and concordant increases in behavioral arousal. As a further indication of failed homeostatic mechanisms, R2KO mice displayed indices of cell death in the raphe after stress exposure, with elevations in proapoptotic factors but a failure to mount adaptive increases in antiapoptotic factors found in control mice. In vitro electrophysiological characterization of the specific influence of CRF on the raphe revealed both basal differences and a failure to respond to CRF administration in R2KO mice. These results support a requirement for homeostatic maintenance in response to stress in the raphe, where dysregulation may be a critical predictor of affective disorder onset.

Constitutively Active Rap2 Transgenic Mice Display Fewer Dendritic Spines, Reduced Extracellular Signal-Regulated Kinase Signaling, Enhanced Long-Term Depression, and Impaired Spatial Learning and Fear Extinction

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Within the Ras superfamily of GTPases, Rap1 and Rap2 are the closest homologs to Ras. In non-neural cells, Rap signaling can antagonize Ras signaling. In neurons, Rap also seems to oppose Ras in terms of synaptic function. Whereas Ras is critical for long-term potentiation (LTP), Rap1 has been shown to be required for long-term depression (LTD), and Rap2 has been implicated in depotentiation. Moreover, active Rap1 and Rap2 cause loss of surface AMPA receptors and reduced miniature EPSC amplitude and frequency in cultured neurons. The role of Rap signaling in vivo, however, remains poorly understood. To study the function of Rap2 in the brain and in behavior, we created transgenic mice expressing either constitutively active (Rap2V12) or dominant-negative (Rap2N17) mutants of Rap2 in postnatal forebrain. Multiple lines of Rap2N17 mice showed only weak expression of the transgenic protein, and no phenotype was observed. Rap2V12 mice displayed fewer and shorter dendritic spines in CA1 hippocampal neurons, and enhanced LTD at CA3–CA1 synapses. Behaviorally, Rap2V12 mice showed impaired spatial learning and defective extinction of contextual fear, which correlated with reduced basal phosphorylation of extracellular signal-regulated kinase (ERK) and blunted activation of ERK during fear extinction training. Our data support the idea that Rap2 opposes Ras–ERK signaling in the brain, thereby inhibiting dendritic spine development/maintenance, promoting synaptic depression rather than LTD, and impairing learning. The findings also implicate Rap2 signaling in fear extinction mechanisms, which are thought to be aberrant in anxiety disorders and posttraumatic stress disorder.
Intra-Amygdala and Systemic Antagonism of NMDA Receptors Prevents the Reconsolidation of Drug-Associated Memory and Impairs Subsequently Both Novel and Previously Acquired Drug-Seeking Behaviors

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The amygdala has long been considered a primary locus in mediating the effects of previously drug-associated stimuli on subsequent drug-seeking behavior, and the NMDA subtype of glutamate receptor within the amygdala is important for the consolidation of associations between environmental conditioned stimuli and the effects of addictive drugs. Here we demonstrate that amygdala NMDA receptors are also necessary for the reconsolidation of drug-associated memories. Using a behavioral task that specifically measures the conditioned reinforcing properties of a previously drug-paired stimulus, we show that infusion of the NMDA receptor antagonist D(-)-2-amino-5-phosphonopentanoic acid (D-APV) into the basolateral amygdala before a memory reactivation session disrupted the drug-associated memory and abolished subsequent instrumental responding for conditioned reinforcement. This effect was memory reactivation dependent, and the memory deficit persisted for at least 4 weeks. In contrast, infusion of D-APV immediately after the memory reactivation session had no effect on subsequent responding for conditioned reinforcement, indicating that NMDA receptors have a temporally limited role in the reconsolidation process. Furthermore, in molecular studies, we show that the reconsolidation-imparing effect of D-APV is correlated with downstream reductions in expression of the plasticity-related immediate early gene, zif268. We also demonstrate that systemic antagonism of NMDA receptors with MK-801 [(+)-5-methyl-10,11-dihydro-SH-dibenzo[a,d]cyclohepten-5,10-imine maleate] before memory reactivation subsequently reduced previously acquired instrumental drug-seeking behavior that depends on drug-associated cues acting as conditioned reinforcers. These data suggest that drugs modulating glutamatergic transmission at the NMDA receptor may be useful in the future treatment of relapse prevention in drug addiction through memory reconsolidation blockade.

Amygdala and Orbitofrontal Cortex Lesions Differentially Influence Choices during Object Reversal Learning

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In nonhuman primates, interaction between the orbitofrontal cortex (OFC) and the amygdala (AMG) has been seen as critical for learning and subsequently changing associations between stimuli and reinforcement. However, it is still unclear what the precise role of the OFC is in altering these stimulus–reward associations, and recent research has questioned whether the AMG makes an essential contribution at all. To gain a better understanding of the role of these two structures in flexibly associating stimuli with reinforcement, we reanalyzed a set of previously published data from groups of monkeys with either OFC or AMG lesions that had been tested on an object reversal learning task. Based on trial-by-trial analyses of rewarded and unrewarded choices, we report two new findings. First, monkeys with OFC lesions were, compared with both control and AMG groups, unable to use correctly performed trials to optimally guide subsequent choices. Second, monkeys with AMG lesions showed the opposite pattern of behavior. This group benefited more than controls from correctly performed trials that followed an error. Finally, as has been reported by others, after a change in reward contingencies, monkeys with OFC lesions also showed a slightly greater tendency to choose the previously rewarded object. These findings demonstrate that the OFC and AMG make different contributions to object reversal learning not highlighted previously.

Representation of Eye Movements and Stimulus Motion in Topographically Organized Areas of Human Posterior Parietal Cortex

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Recent imaging studies have shown that the human posterior parietal cortex (PPC) contains four topographically organized areas along the intraparietal sulcus (IPS1–IPS4). Using a memory-guided saccade paradigm, we confirmed the locations and retinotopic organization of IPS1–IPS4 and identified two additional areas, IPS5 and superior parietal lobule 1 (SPL1). IPS5 is located at the intersection of the intraparietal and postcentral sulcus; SPL1 branches off the IPS and extends into the superior parietal lobule. Both areas, as well as IPS1–IPS4, each contain a representation of the contralateral visual hemifield. We then proben core functions of the dorsal pathway in these areas, that is, the representation of eye movements and visual motion, to compare the functional characteristics of human PPC to physiologically and anatomically defined areas in monkey PPC. First, as in monkey PPC, a gradient representation of eye movements was found along the IPS with decreasing responses for saccades and increasing responses for smooth pursuit eye movements from posterior/medial to anterior/lateral. The greatest preference for saccades was found in SPL1 and for smooth pursuit in IPS2. Second, and again similar to monkey PPC, all topographically organized PPC areas responded to different types of motion including planar, circular, and radial optic flow, as assessed using adaptation paradigms. Areas in posterior IPS preferred radial optic flow over planar motion, whereas areas in anterior PPC did not show preference for a particular motion type. Together, our results indicate strikingly similar characteristics in the general functional organization of human and monkey PPC, but also reveal some notable differences.

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Depletion of 26S Proteasomes in Mouse Brain Neurons Causes Neurodegeneration and Lewy-Like Inclusions Resembling Human Pale Bodies

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Ubiquitin-positive intraneuronal inclusions are a consistent feature of the major human neurodegenerative diseases, suggesting that dysfunction of the ubiquitin proteasome system is central to disease etiology. Research using inhibitors of the 20S proteasome to model Parkinson’s disease is controversial. We report for the first time that specifically 26S proteasomal dysfunction is sufficient to trigger neurodegenerative disease. Here, we describe novel conditional genetic mouse models using the Cre/loxP system to spatially restrict inactivation of Psmc1 (Rpt2/S4) to neurons of either the substantia nigra or forebrain (e.g., cortex, hippocampus, and striatum). PSMC1 is an essential subunit of the 26S proteasome and Psmc1 conditional knock-out mice display 26S proteasome depletion in targeted neurons, in which the 20S proteasome is not affected. Impairment of specifically ubiquitin-mediated protein degradation caused intraneuronal Lewy-like inclusions and extensive neurodegeneration in the nigrostriatal pathway and forebrain regions. Ubiquitin and α-synuclein neuropathology was evident, similar to human Lewy bodies, but interestingly, inclusion bodies contained mitochondria. We support this observation by demonstrating mitochondria in an early form of Lewy body (pale body) from Parkinson’s disease patients. The results directly confirm that 26S dysfunction in neurons is involved in the pathobiology of neurodegenerative disease. The model demonstrates that 26S proteasomes are necessary for normal neuronal homeostasis and that 20S proteasome activity is insufficient for neuronal survival. Finally, we are providing the first reproducible genetic platform for identifying new therapeutic targets to slow or prevent neurodegeneration.

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Loss of PINK1 Function Affects Development and Results in Neurodegeneration in Zebrafish

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Parkinson’s disease (PD) is the second most prevalent neurodegenerative disorder in the Western world. PTEN (phosphatase/tensin homolog on chromosome 10)-induced putative kinase 1 (PINK1), a putative kinase that is mutated in autosomal recessive forms of PD, is also implicated in sporadic cases of the disease. Although the mutations appear to result in a loss of function, the roles of this protein and the pathways involved in PINK1 PD are poorly understood. Here, we generated a vertebrate model of PINK1 insufficiency using morpholino oligonucleotide knockdown in zebrafish (Danio rerio). PINK1 knockdown results in a severe developmental phenotype that is rescued by wild-type human PINK1 mRNA. Morphants display a moderate decrease in the numbers of central dopaminergic neurons and alterations of mitochondrial function, including increases in caspase-3 activity and reactive oxygen species (ROS) levels. When the morphants were exposed to several drugs with antioxidant properties, ROS levels were normalized and the associated phenotype improved. In addition, GSK3β-related mechanisms can account for some of the effects of PINK1 knockdown, as morphant fish show elevated GSK3β activity and their phenotype is partially abrogated by GSK3β inhibitors, such as LiCl and SB216763 [3-(2,4-dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)1H-pyrrole-2,5-dione]. This provides new insights into the biology of PINK1 and a possible therapeutic avenue for further investigation.

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Microglial Dysfunction and Defective β-Amyloid Clearance Pathways in Aging Alzheimer’s Disease Mice

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Early microglial accumulation in Alzheimer’s disease (AD) delays disease progression by promoting clearance of β-amyloid (Aβ) before formation of senile plaques. However, persistent Aβ accumulation despite increasing microglial numbers suggests that the ability of microglia to clear Aβ may decrease with age and progression of AD pathology. To determine the effects of aging and Aβ deposition on microglial ability to clear Aβ, we used quantitative PCR to analyze gene expression in freshly isolated adult microglia from 1.5-, 3-, 8-, and 14-month-old transgenic PS1-APP mice, an established mouse model of AD, and from their nontransgenic littermates. We found that microglia from old PS1-APP mice, but not from younger mice, have a twofold to fivefold decrease in expression of the Aβ-binding scavenger receptors scavenger receptor A (SRA), CD36, and RAGE (receptor for advanced-glycosylation endproducts), and the Aβ-degrading enzymes insulysin, neprilysin, and MMP9, compared with their littermate controls. In contrast, PS1-APP microglia had a 2.5-fold increase in the proinflammatory cytokines IL-1β (interleukin-1β) and tumor necrosis factor α (TNFα), suggesting that there is an inverse correlation between cytokine production and Aβ clearance. In support of this possibility, we found that incubation of cultured N9 mouse
microglia with TNFα decreased the expression of SRA and CD36 and reduced Aβ uptake. Our data indicate that, although early microglial recruitment promotes Aβ clearance and is neuroprotective in AD, as disease progresses, proinflammatory cytokines produced in response to Aβ deposition downregulate genes involved in Aβ clearance and promote Aβ accumulation, therefore contributing to neurodegeneration. Antiinflammatory therapy for AD should take this dichotomous microglial role into consideration.

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