

This Week in The Journal

● Cellular/Molecular

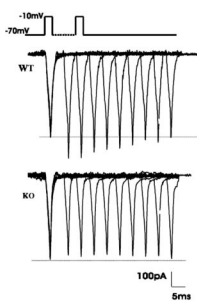
Calcium Channel Subtypes and Short-Term Synaptic Plasticity

Carlota González Inchauspe, Francisco J. Martini, Ian D. Forsythe, and Osvaldo D. Uchitel

(see pages 10379–10383)

Anita Scheuber, Richard Miles, and Jean Christophe Poncer
(see pages 10402–10409)

Facilitation of transmitter release occurs with successive calcium channel openings, but the molecules mediating the phenomenon are still unclear. This week, two papers examine the roles of presynaptic calcium channels in facilitation. González Inchauspe et al. measured calcium currents and transmitter release at the giant calyx of Held synapse in mice lacking Cav2.1, the pore-forming subunit of P/Q-type calcium channels. N-type calcium channels (Cav2.2) were able to support vesicle release, but paired-pulse facilitation of synaptic responses and presynaptic calcium currents were absent. The authors suggest that P/Q channels underlie facilitation. Scheuber et al. examine a similar question in the rat CA3/CA1 hippocampal pathway but come to a different conclusion. They pharmacologically separated calcium channel types and found that facilitation was augmented when Cav2.1 was blocked but diminished with Cav2.2 block. Voltage-dependent relief of G-protein-mediated channel inhibition of Cav2.2 channels was responsible for this form of short-term plasticity.



Presynaptic calcium current facilitation evoked by paired-pulse stimulation was present in calyx of Held nerve terminals from wild-type animals (WT), but absent in terminals from mice lacking the Cav2.1 subunit of P/Q-type calcium channels. KO, Knock-out. See the article by González Inchauspe et al. for details.

▲ Development/Plasticity/Repair

Decoying the Nogo-66 Receptor

Shuxin Li, Betty P. Liu, Stephane Budel, Mingwei Li, Benxiu Ji, Lee Walus, Weiwei Li, Adrienna Jirik, Sylvia Rabacchi, Eugene Choi, Dane Worley, Dinah W. Y. Sah, Blake Pepinsky, Daniel Lee, Jane Relton, and Stephen M. Strittmatter

(see pages 10511–10520)

Myelin-derived inhibitory factors limit recovery from spinal cord injury by preventing sprouting and regrowth of axons. These molecules [Nogo, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp)] work at the axonal Nogo receptor (NgR). Efforts to block the function of NgR *in vivo* have been moderately successful, and now Li et al. provide more promising results. They created a soluble peptide of the ligand-binding domain of NgR and coupled it to rat IgG1 Fc. They delivered it intrathecally to rats after a spinal cord injury. Axons showed increased sprouting, and rats showed recovery of movement beyond that seen with Nogo antibody treatment, presumably because the peptide disrupts all three receptor–agonist interactions. Electrophysiological measurements showed that improved synapse efficacy accompanied the behavioral improvements. Corticospinal tract neurons and serotonergic, raphespinal neurons contributed to the axonal sprouting. Although NgR–NgR interactions are possible, the authors suggest that the peptide acts like a decoy, sequestering ligand from the endogenous receptor.

■ Behavioral/Systems/Cognitive

Stimulus-Specific Adaptation in the Cat Auditory Cortex

Nachum Ulanovsky, Liora Las, Dina Farkas, and Israel Nelken
(see pages 10440–10453)

Adaptation is one mechanism that the nervous system uses to sort the rare from the common. In neurons from the primary auditory cortex (area A1 in the cat), action potential firing shows strong stimulus-specific adaptation. In this issue, Ulanovsky et al. examine this single-cell adaptation in response to different patterns of

pure tones delivered to cats through custom-fitting earphones. These feline musicologists listened to several patterns that the authors called oddball, switching-oddball, and response-curve. Not unexpectedly, adaptation was greater when deviant stimuli in the oddball pattern occurred at a high probability. Overall, the time course of stimulus-specific adaptation spanned a time course from hundreds of milliseconds to tens of seconds. The behavior of the neurons seemed to fit linear models that incorporated both the short- and long-term stimulus history. Adaptation also biased the neurons toward novel or eccentric stimuli. This property appears to be unique to A1 neurons within auditory pathways, because it was not present in auditory thalamic neurons.

◆ Neurobiology of Disease

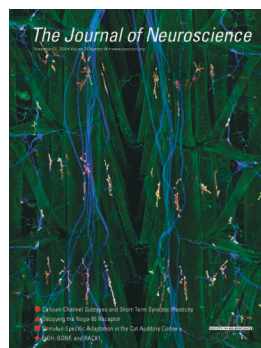
EtOH, BDNF, and RACK1

Nancy N. H. McGough, Dao-Yao He, Marian L. Logrip, Jerome Jeanblanc, Khanhky Phamluong, Ken Luong, Viktor Kharazia, Patricia H. Janak, and Dorit Ron
(see pages 10542–10552)

How is it that some of us can drink in moderation whereas others fall victim to the physical and psychosocial devastation that is chronic alcoholism? One idea is that chronic excessive alcohol intake results in a series of biochemical adaptations that result in addiction if allowed to proceed unchecked. In this week's *Journal*, McGough et al. identify brain-derived neurotrophic factor (BDNF) as one of the possible brakes on runaway adaptations of this sort. BDNF has already been implicated in control of other drug-addiction pathways. The authors report that BDNF mRNA in neurons *in vitro* increased with acute ethanol exposure and decreased with continuous exposure. Likewise *in vivo*, real-time PCR revealed increases in hippocampal and dorsal striatal BDNF. Purely correlation? Perhaps, but male heterozygous mice lacking one BDNF allele consumed more alcohol than did wild-type controls. The authors traced changes in BDNF expression to the scaffolding protein RACK1 that translocates to the nucleus and regulates BDNF gene expression.

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Cover picture: Three segments of a dissected third-instar *Drosophila* larva. Green muscles are stained with anti-Discs large, red synapses are stained with anti-DVGLUT (*Drosophila* vesicular glutamate transporter), and blue nerves are stained with anti-HRP (horseradish peroxidase). For details, see the article by Daniels et al. in this issue (pages 10466–10474).

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Correction: In the article “Learning Modifies Subsequent Induction of Long-Term Potentiation-Like and Long-Term Depression-Like Plasticity in Human Motor Cortex,” which appeared on pages 1666–1672 of the February 18, 2004 issue, the name of an author was spelled incorrectly. The second author’s name should have read Tihomir V. Ilić.

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Functional Compensation of P/Q by N-Type Channels Blocks Short-Term Plasticity at the Calyx of Held Presynaptic Terminal

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Calcium channels of the P/Q subtype mediate transmitter release at the neuromuscular junction and at many central synapses, such as the calyx of Held. Transgenic mice in which α_{1A} channels are ablated provide a powerful tool with which to test compensatory mechanisms at the synapse and to explore mechanisms of presynaptic regulation associated with expression of P/Q channels. Using the calyx of Held preparation from the knock-out (KO) mice, we show here that N-type channels functionally compensate for the absence of P/Q subunits at the calyx and evoke giant synaptic currents [approximately two-thirds of the magnitude of wild-type (WT) responses]. However, although evoked paired-pulse facilitation is prominent in WT, this facilitation is greatly diminished in the KO. In addition, direct recording of presynaptic calcium currents revealed that the major functional difference was the absence of calcium-dependent facilitation at the calyx in the P/Q KO animals. We conclude that one physiological function of P/Q channels is to provide additional facilitatory drive, so contributing to maintenance of transmission as vesicles are depleted during high throughput synaptic transmission.

The Journal of Neuroscience, November 17, 2004 • 24(46):10379–10383

Memory Consolidation and Reconsolidation in the Rat Pup Require Protein Synthesis

Nadège Gruet, Paulette Richer, and Bernard Hars

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Little is known about the ontogenesis of memory, whether it appears with its full characteristics or whether they emerge progressively with development. In the adult, basic characteristics of memory processing are consolidation of memory after acquisition and reconsolidation after retrieval. Here, using a conditioned aversion paradigm and postlearning or postreactivation injection of a protein synthesis inhibitor, we show that memory acquired by rat pups as early as postnatal day 3 requires time-dependent protein synthesis after both learning and reactivation. These results present the first evidence suggesting that consolidation and reconsolidation are original properties of memory function.

The Journal of Neuroscience, November 17, 2004 • 24(46):10289–10301

Articles

CELLULAR/MOLECULAR

D₂ Dopamine Receptor-Mediated Modulation of Voltage-Dependent Na⁺ Channels Reduces Autonomous Activity in Striatal Cholinergic Interneurons

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Striatal cholinergic interneurons are critical elements of the striatal circuitry controlling motor planning, movement, and associative learning. Intrastriatal release of dopamine and inhibition of interneuron activity is thought to be a critical link between behaviorally relevant events, such as reward, and alterations in striatal function. However, the mechanisms mediating this modulation are unclear. Using a combination of electrophysiological, molecular, and computational approaches, the studies reported here show that D₂ dopamine receptor modulation of Na⁺ currents underlying autonomous spiking contributes to a slowing of discharge rate, such as that seen *in vivo*. Four lines of evidence support this conclusion. First, D₂ receptor stimulation in tissue slices reduced the autonomous spiking in the presence of synaptic blockers. Second, in acutely isolated neurons, D₂ receptor activation led to a reduction in Na⁺ currents underlying pacemaking. The modulation was mediated by a protein kinase C-dependent enhancement of channel entry into a slow-inactivated state at depolarized potentials. Third, the sodium channel blocker TTX mimicked the effects of D₂ receptor agonists on pacemaking. Fourth, simulation of cholinergic interneuron pacemaking revealed that a modest increase in the entry of Na⁺ channels into the slow-inactivated state was sufficient to account for the slowing of pacemaker discharge. These studies establish a cellular mechanism linking dopamine and the reduction in striatal cholinergic interneuron activity seen in the initial stages of associative learning.

The Journal of Neuroscience, November 17, 2004 • 24(46):10493–10501

Structural Abnormalities at Neuromuscular Synapses Lacking Multiple Syntrophin Isoforms

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The syntrophins are modular adapter proteins that function by recruiting signaling molecules to the cytoskeleton via their direct association with proteins of the dystrophin protein family. We investigated the physiological function of β 2-syntrophin by generating a line of mice lacking this syntrophin isoform. The β 2-syntrophin null mice show no overt phenotype, or muscular dystrophy, and form structurally normal neuromuscular junctions (NMJs). To determine whether physiological consequences caused by the lack of β 2-syntrophin were masked by compensation from the α -syntrophin isoform, we crossed these mice with our previously described α -syntrophin null mice to produce mice lacking both isoforms. The α/β 2-syntrophin null mice have NMJs that are structurally more aberrant than those lacking only α -syntrophin. The NMJs of the α/β 2-syntrophin null mice have fewer junctional folds than either parent strain, and the remaining folds are abnormally shaped with few openings to the synaptic space. The levels of acetylcholine receptors are reduced to 23% of wild type in mice lacking both syntrophin isoforms. Furthermore, the α/β 2-syntrophin null mice ran significantly shorter distances on voluntary exercise wheels despite having normal neuromuscular junction transmission as determined by microelectrode recording of endplate potentials. We conclude that both α -syntrophin and β 2-syntrophin play distinct roles in forming and maintaining NMJ structure and that each syntrophin can partially compensate for the loss of the other.

The Journal of Neuroscience, November 17, 2004 • 24(46):10302–10309

The Subcellular Organization of Cortactin in Hippocampus

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Spines may undergo rapid, activity-dependent changes in shape and size, reflecting reorganization of the actin cytoskeleton. This remodeling is implicated in development and also in the late phase of long-term potentiation. However, the cellular mechanisms that convert activity into morphological change remain poorly understood, and little is known about the anatomical distribution of the actin-regulating proteins that mediate this remodeling. Using immunocytochemistry, we demonstrate here that cortactin (a protein implicated in actin filament nucleation, branching, and stabilization) is concentrated in hippocampal spines, where it colocalizes with F-actin. Cortactin has a Shank-binding domain; recent studies report that synaptic activity may trigger actin remodeling via this interaction with Shank. However, our immunogold electron microscopic data show that cortactin concentrates within the spine core, 100–150 nm away from the postsynaptic density (PSD); only a small fraction of the cortactin in spines lies adjacent to the PSD. These data suggest that the adult dendritic spine contains two functional pools of cortactin: a large pool in the spine core that may help to mediate changes in spine shape and a small synaptic pool that may modify the PSD in response to synaptic activity.

The Journal of Neuroscience, November 17, 2004 • 24(46):10310–10317

Molecular Mechanism of Pregnenolone Sulfate Action at NR1/NR2B Receptors

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NMDA receptors are highly expressed in the CNS and are involved in excitatory synaptic transmission and synaptic plasticity as well as excitotoxicity. They have several binding sites for allosteric modulators, including neurosteroids, endogenous compounds synthesized by the nervous tissue and expected to act locally. Whole-cell patch-clamp recording from human embryonic kidney 293 cells expressing NR1-1a/NR2B receptors revealed that neurosteroid pregnenolone sulfate (PS) (300 μ M), when applied to resting NMDA receptors, potentiates the amplitude of subsequent responses to 1 mM glutamate fivefold and slows their deactivation twofold. The same concentration of PS, when applied during NMDA receptor activation by 1 mM glutamate, has only a small effect. The association and dissociation rate constants of PS binding and unbinding from resting NMDA receptors are estimated to be $3.3 \pm 2.0 \text{ mM}^{-1} \text{ sec}^{-1}$ and $0.12 \pm 0.02 \text{ sec}^{-1}$, respectively, corresponding to an apparent affinity K_d of 37 μ M. The results of experiments indicate that the molecular mechanism of PS potentiation of NMDA receptor responses is attributable to an increase in the peak channel open probability (P_o). Responses to glutamate recorded in the continuous presence of PS exhibit marked time-dependent decline. Our results indicate that the decline is induced by a change of the NMDA receptor affinity for PS after receptor activation.

These results suggest that the PS is a modulator of NMDA receptor P_o , the effectiveness of which is lowered by glutamate binding. This modulation may have important consequences for the neuronal excitability.

The Journal of Neuroscience, November 17, 2004 • 24(46):10318–10325

Anosmin-1 Modulates Fibroblast Growth Factor Receptor 1 Signaling in Human Gonadotropin-Releasing Hormone Olfactory Neuroblasts through a Heparan Sulfate-Dependent Mechanism

David González-Martínez,¹ Soo-Hyun Kim,¹ Youli Hu,¹ Scott Guimond,² Jonathan Schofield,¹ Paul Winyard,³ Gabriella Barbara Vannelli,⁴ Jeremy Turnbull,² and Pierre-Marc Bouloux¹

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Defects of either anosmin-1 or fibroblast growth factor receptor 1 (FGFR1) are known to underlie hereditary Kallmann's syndrome (KS), a human disorder of olfactory and gonadotropin-releasing hormone (GnRH) neuronal ontogeny. Here, we report a functional interaction between anosmin-1 and the FGFR1–FGF2–heparan sulfate complex, leading to amplified responses in the FGFR1 signaling pathway. In human embryonic GnRH olfactory neuroblasts, wild-type anosmin-1, but not proteins with loss-of-function KS mutations, induces neurite outgrowth and cytoskeletal rearrangements through FGFR1-dependent mechanisms involving p42/44 and p38 mitogen-activated protein kinases and Cdc42/Rac1 activation. Furthermore, anosmin-1 enhances FGF2 signaling specifically through FGFR1 IIIc in heterologous BaF3 lymphoid cells in a heparan sulfate-dependent manner. Our study provides compelling evidence for anosmin-1 as an isoform-specific co-ligand modulator of FGFR signaling that amplifies and specifies FGFR1 signaling responses during human nervous system development and defines a mechanism underlying the link between autosomal and X-linked KS. The Journal of Neuroscience, November 17, 2004 • 24(46):10384–10392

Presynaptic Cav2.1 and Cav2.2 Differentially Influence Release Dynamics at Hippocampal Excitatory Synapses

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Presynaptic calcium influx at most excitatory central synapses is carried by both Cav2.1 and Cav2.2 channels. The kinetics and modulation of Cav2.1 and Cav2.2 channels differ and may affect presynaptic calcium influx. We compared release dynamics at CA3/CA1 synapses in rat hippocampus after selective blockade of either channel subtype and subsequent quantal content restoration. Selective blockade of Cav2.1 channels enhanced paired-pulse facilitation, whereas blockade of Cav2.2 channels decreased it. This effect was observed at short (50 msec) but not longer (500 msec) intervals and was maintained during prolonged bursts of presynaptic activity. It did not reflect differences in the distance of the channels from the calcium sensor. The suppression of this effect by preincubation with the G_{o/i}-protein inhibitor pertussis toxin suggests instead that high-frequency stimulation relieves inhibition of Cav2.2 by G_{o/i}, thereby increasing the number of available channels.

The Journal of Neuroscience, November 17, 2004 • 24(46):10402–10409

Nitric Oxide Synthase (NOS)-Interacting Protein Interacts with Neuronal NOS and Regulates Its Distribution and Activity

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Mechanisms governing the activity of neuronal nitric oxide synthase (nNOS), the major source of nitric oxide (NO) in the nervous system, are not completely understood. We report here a protein–protein interaction between nNOS and NOSIP (nitric oxide synthase-interacting protein) in rat brain *in vivo*. NOSIP and nNOS are concentrated in neuronal synapses and demonstrate significant colocalization in various regions of the central and peripheral nervous systems. NOSIP produces a significant reduction in nNOS activity in a neuroepithelioma cell line stably expressing nNOS. Furthermore, overexpression of NOSIP in cultured primary neurons reduces the availability of nNOS in terminal dendrites. These results thus suggest that the interaction between NOSIP and nNOS is functionally involved in endogenous mechanisms regulating NO synthesis. Furthermore, we found that the subcellular distribution and expression levels of NOSIP are dynamically regulated by neuronal activity *in vitro* as well as *in vivo*, suggesting that NOSIP may contribute to a mechanism via which neuronal activity regulates the synaptic availability and activity of nNOS.

The Journal of Neuroscience, November 17, 2004 • 24(46):10454–10465

Increased Expression of the *Drosophila* Vesicular Glutamate Transporter Leads to Excess Glutamate Release and a Compensatory Decrease in Quantal Content

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Quantal size is a fundamental parameter controlling the strength of synaptic transmission. The transmitter content of synaptic vesicles is one mechanism that can affect the physiological response to the release of a single vesicle. At glutamatergic synapses, vesicular glutamate transporters (VGLUTs) are responsible for filling synaptic vesicles with glutamate. To investigate how VGLUT expression can regulate synaptic strength *in vivo*, we have identified the *Drosophila* vesicular glutamate transporter, which we name DVGLUT. DVGLUT mRNA is expressed in glutamatergic motoneurons and a large number of interneurons in the *Drosophila* CNS. DVGLUT protein resides on synaptic vesicles and localizes to the presynaptic terminals of all known glutamatergic neuromuscular junctions as well as to synapses throughout the CNS neuropil. Increasing the expression of DVGLUT in motoneurons leads to an increase in quantal size that is accompanied by an increase in synaptic vesicle volume. At synapses confronted with increased glutamate release from each vesicle, there is a compensatory decrease in the number of synaptic vesicles released that maintains normal levels of synaptic excitation. These results demonstrate that (1) expression of DVGLUT determines the size and glutamate content of synaptic vesicles and (2) homeostatic mechanisms exist to attenuate the excitatory effects of excess glutamate release.

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Time-Resolved Measurement of State-Specific P2X₂ Ion Channel Cytosolic Gating Motions

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ATP-gated P2X₂ channels undergo permeability changes through a process that is incompletely understood. In the present study, we used fluorescence resonance energy transfer (FRET) and electrophysiology to measure cytosolic gating motions in P2X₂ channels as they enter a state with increased permeability. P2X₂ channels underwent permeability changes with a time course that was similar to decreases in FRET between cyan fluorescent protein and yellow fluorescent protein attached to the cytosolic domain of P2X₂ channels. Wild-type and mutant channels that did not undergo permeability changes also did not show evidence of cytosolic gating motions. Moreover, immobilizing the cytosolic domain by tethering it to the plasma membrane prevented the switch in permeability and impaired the cytosolic gating motions. Both of these phenotypes were restored when the immobilizing tether was cleaved. The data provide a time-resolved measure of state-specific gating motions and suggest how a cytosolic domain may control ion channel permeability.

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The Role of Palmitoylation in Functional Expression of Nicotinic $\alpha 7$ Receptors

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Neuronal α -bungarotoxin receptors (BgtRs) are nicotinic receptors that require as yet unidentified post-translational modifications to achieve functional expression. In this study, we examined the role of protein palmitoylation in BgtR expression. BgtR $\alpha 7$ subunits are highly palmitoylated in neurons from brain and other cells capable of BgtR expression, such as pheochromocytoma 12 (PC12) cells. In PC12 cells, $\alpha 7$ subunits are palmitoylated with a stoichiometry of approximately one palmitate per subunit, and inhibition of palmitoylation blocks BgtR expression. In cells incapable of BgtR expression, such as human embryonic kidney cells, $\alpha 7$ subunits are not significantly palmitoylated. However, in these same cells, chimeric subunits with the N-terminal half of $\alpha 7$ fused to the C-terminal half of serotonin-3A receptor ($\alpha 7/5$ -HT_{3A}) subunits form functional BgtRs that are palmitoylated to an extent similar to that of BgtR $\alpha 7$ subunits in PC12 cells. Palmitoylation of PC12 and $\alpha 7/5$ -HT_{3A} BgtRs occurred during assembly in the endoplasmic reticulum (ER). In conclusion, our data indicate a function for protein palmitoylation in which palmitoylation of assembling $\alpha 7$ subunits in the ER has a role in the formation of functional BgtRs.

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Neurotrophin Signaling through the p75 Receptor Is Deficient in *traf6*^{−/−} Mice

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Activation of the neurotrophin receptor p75 has been shown to elicit opposing cellular signals. Depending on the context of the cell, p75 will either promote survival or induce apoptosis after neurotrophin stimulation. p75-induced apoptosis occurs through activation of c-Jun N-terminal kinase (JNK), whereas the survival signal is mediated by nuclear factor κ B (NF κ B). The receptor proximal signals that produce these responses are unknown, although several molecules have been identified that associate with the intracellular domain of p75. One such interactor, TRAF6, a member of the tumor necrosis factor receptor-associated factor family, has been implicated in p75 signaling. To assess the role of TRAF6 in p75 signaling, we analyzed mice with this gene deleted. In Schwann cells isolated from *traf6*^{+/+} animals, NGF elicited an 80% increase in transcription of an NF κ B reporter; however, in *traf6*^{−/−} cells, the NGF response was abrogated. Similarly, NGF activation of JNK was not apparent in

Schwann cells from mice lacking *traf6*. Deficiencies in p75 signaling in *traf6*^{−/−} animals resulted in a loss of p75-mediated apoptosis. In sympathetic neurons cultured from *traf6*^{+/+} superior cervical ganglia (SCGs), there was an increase in JNK activation and apoptosis after BDNF binding to p75; however, *traf6*^{−/−} neurons did not respond. *In vivo* during naturally occurring cell death, there was a 55.6% reduction in TUNEL (terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling)-positive cells in the SCG of postnatal day 4 *traf6*^{−/−} animals relative to *traf6*^{+/+} littermates. These results indicate that TRAF6 plays an essential role in mediating p75 signal transduction and induction of apoptosis.

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Dendrodendritic Electrical Synapses between Mammalian Retinal Ganglion Cells

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Electrical synapses between α -type ganglion cells were detected using combined techniques of dual patch-clamp recordings, intracellular labeling, electron microscopy, and channel subunit connexin immunocytochemistry in the albino rat retina. After intracellular injection of Neurobiotin into α -cells of inner (ON-center) and outer (OFF-center) ramifying types, measurement of tracer coupling resulted in a preferentially homologous occurrence among cells of the same morphological type ($n = 19$ of 24). In high-voltage as well as conventional electron microscopic analysis, direct dendrodendritic gap junctions (average size, 0.86 μm long) were present in contact sites between tracer-coupled α -cells. In simultaneous dual whole-cell recordings from pairs of neighboring α -cells, these cells generated TTX-sensitive sustained spiking against extrinsic current injection, and bidirectional electrical synapses (maximum coupling coefficient, 0.32) with symmetrical junction conductance (average, 1.35 nS) were observed in pairs with cells of the same morphological type. Precise temporal synchronization of spike activity (average time delay, 2.7 msec) was detected when depolarizing currents were simultaneously injected into the pairs. To address whether physiologically identified electrical synapses constitute gap junctional connectivity between cell pairs, identified neuronal connexin36 immunoreactivity was undertaken in Lucifer yellow-labeled cell pairs after patch-clamp recordings. All α -cells expressed connexin36, and confocal laser-scanning imaging demonstrated that connexin36 is primarily located at dendritic crossings between electrically coupled cells (seven sites in a pair, on average). These results give conclusive evidence for electrical synapses via dendrodendritic gap junctions involving connexin36 in α retinal ganglion cells of the same physiological type.

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A Genetic Switch for Epilepsy in Adult Mice

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Premature death from seizures afflicts gene-targeted mice expressing the Q/R site-unedited glutamate receptor subunit GluR-B(Q) of AMPA receptors in central neurons. Early seizure-related death has now been circumvented by a genetic switch that restricts GluR-B(Q) expression to forebrain principal neurons from postnatal stages onward, prominently in hippocampus and striatum and less so in cortex and amygdala. When switched on, functional receptor incorporation of GluR-B(Q) could be demonstrated by imaging evoked AMPA channel-mediated spinous Ca^{2+} transients in CA1 pyramidal cells. Sustained GluR-B(Q) expression in adult mice led to smaller excitatory postsynaptic responses in the CA1 region with unchanged presynaptic fiber excitability. Notably, despite the smaller excitatory response, the CA1 cells exhibited a reduced population spike threshold, which might underlie the spontaneous manifestations of epilepsy, including myocloni and generalized seizures with limbic components, observed by synchronous video monitoring and electroencephalographic recordings. No neuropathological symptoms developed when GluR-B(Q) expression was restricted to only hippocampal neurons. Our results show that seizure susceptibility is triggered by GluR-B(Q) expression also in the adult brain and that circuit hyperexcitability is not an immediate consequence of GluR-B(Q) but requires yet unknown downstream events, likely to be induced by non-Hebbian plasticity from Ca^{2+} -permeable AMPA channels in principal neurons.

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PHCCC, a Specific Enhancer of Type 4 Metabotropic Glutamate Receptors, Reduces Proliferation and Promotes Differentiation of Cerebellar Granule Cell Neuroprecursors

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Exposure of immature rat cerebellar granule cell cultures to the type 4 metabotropic glutamate (mGlu4) receptor enhancer *N*-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC) reduced [³H]thymidine incorporation. Its action was sensitive to the growth conditions and was attenuated by two mGlu4 receptor antagonists. An antiproliferative action of PHCCC was also seen in cultures from wild-type, but not mGlu4, knock-out mice. At least in rat cultures, PHCCC was not neurotoxic and enhanced neuritogenesis. Although PHCCC reduced the increase in cAMP formation and phospho-AKT levels induced by forskolin, none of these transduction pathways significantly contributed to the reduction of [³H]thymidine incorporation. Interestingly, PHCCC reduced the expression of Gli-1, a transcription factor that mediates the mitogenic action of Sonic hedgehog. Finally, we treated newborn rats with PHCCC either intracerebrally (infusion of 5 nmol/2 μ l in the cerebellar region once every other day) or systemically (5 mg/kg, i.p., once daily) from postnatal days 3–9. Local infusion of PHCCC induced substantial changes in the morphology of the developing cerebellum. In contrast, systemic injection of PHCCC induced only morphological abnormalities of the cerebellar lobule V, which became visible 11 d after the end of the treatment. These data suggest that mGlu4 receptors are involved in the regulation of cerebellar development.

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Vascular Endothelial Cells Promote Acute Plasticity in Ependymoglia Cells of the Neuroendocrine Brain

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Glial and endothelial cells interact throughout the brain to define specific functional domains. Whether endothelial cells convey signals to glia in the mature brain is unknown but is amenable to examination in circumventricular organs. Here we report that purified endothelial cells of one of these organs, the median eminence of the hypothalamus, induce acute actin cytoskeleton remodeling in isolated ependymoglia cells and show that this plasticity is mediated by nitric oxide (NO), a diffusible factor. We found that both soluble guanylyl cyclase and cyclooxygenase products are involved in this endothelial-mediated control of ependymoglia cytoarchitecture. We also demonstrate by electron microscopy that activation of endogenous NO release in the median eminence induces rapid structural changes, allowing a direct access of neurosecretory axons containing gonadotropin-releasing hormone (GnRH) (the neuropeptide controlling reproductive function) to the portal vasculature. Local *in vivo* inhibition of NO synthesis disrupts reproductive cyclicity, a process that requires a pulsatile, coordinated delivery of GnRH into the hypothalamic–adenohypophyseal portal system. Our results identify a previously unknown function for endothelial cells in inducing neuroglial plasticity and raise the intriguing possibility that endothelial cells throughout the brain may use a similar signaling mechanism to regulate glial–neuronal interactions.

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Blockade of Nogo-66, Myelin-Associated Glycoprotein, and Oligodendrocyte Myelin Glycoprotein by Soluble Nogo-66 Receptor Promotes Axonal Sprouting and Recovery after Spinal Injury

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The growth of injured axons in the adult mammalian CNS is limited after injury. Three myelin proteins, Nogo, MAG (myelin-associated glycoprotein), and OMgp (oligodendrocyte myelin glycoprotein), bind to the Nogo-66 receptor (NgR) and inhibit axonal growth *in vitro*. Transgenic or viral blockade of NgR function allows axonal sprouting *in vivo*. Here, we administered the soluble function-blocking NgR ectodomain [aa 27–310; NgR(310)ecto] to spinal-injured rats. Purified NgR(310)ecto-Fc protein was delivered intrathecally after mid-thoracic dorsal over-hemisection. Axonal sprouting of corticospinal and raphespinal fibers in NgR(310)ecto-Fc-treated animals correlates with improved spinal cord electrical conduction and improved locomotion. The ability of soluble NgR(310)ecto to promote axon growth and locomotor recovery demonstrates a therapeutic potential for NgR antagonism in traumatic spinal cord injury.

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Postnatal Neurogenesis and Gliogenesis in the Olfactory Bulb from NG2-Expressing Progenitors of the Subventricular Zone

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We used a 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP)-enhanced green fluorescent protein (EGFP) transgenic mouse to study postnatal subventricular zone (SVZ) progenitor fate, with a focus on the olfactory bulb (OB). The postnatal OB of the CNP-EGFP mouse contained EGFP⁺ interneurons and oligodendrocytes. In the anterior SVZ, the majority of EGFP⁺ progenitors were NG2⁺. These NG2⁺/EGFP⁺ progenitors expressed the OB interneuron marker Er81, the neuroblast markers doublecortin (DC) and Distalless-related homeobox (DLX), or the oligodendrocyte progenitor marker Nkx2.2. In the rostral migratory stream (RMS), EGFP⁺ cells displayed a migrating phenotype. A fraction of these cells were either NG2⁻/Er81⁺/DC⁺/DLX⁺ or NG2⁺/Nkx2.2⁺. Dil (1,1'-diiododecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate) injection into the lateral ventricle (LV) of early postnatal mice demonstrated that NG2⁺/EGFP⁺ progenitors migrate from the SVZ through the RMS into the OB. Moreover, fluorescence-activated cell-sorting-purified NG2⁺/CNP-EGFP⁺ or NG2⁺/β-actin-enhanced yellow fluorescent protein-positive (EYFP⁺) progenitors transplanted into the early postnatal LV displayed extensive rostral and caudal migration. EYFP⁺ or EGFP⁺ graft-derived cells within the RMS were DLX⁺/Er81⁺ or Nkx2.2⁺, migrated to the OB, and differentiated to interneurons and oligodendrocytes. In the subcortical white matter (SCWM), grafted cells differentiated to either oligodendrocytes or astrocytes. Transplantation of NG2⁺/EYFP⁺ progenitors selectively purified from the SVZ showed that these cells were migratory and generated glia and neurons in the OB, hippocampus, and striatum. In contrast, cortical, OB, or cerebellar NG2⁺ cells had a very limited migratory potential and gave rise to glia in the SCWM and striatum. Our findings indicate region-specific differences between NG2⁺ progenitor cells and show that NG2⁺ cells can migrate throughout the RMS and contribute to both gliogenesis and neurogenesis in the postnatal OB.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Fear-Potentiated Startle in Rats Is Mediated by Neurons in the Deep Layers of the Superior Colliculus/Deep Mesencephalic Nucleus of the Rostral Midbrain through the Glutamate Non-NMDA Receptors

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The amygdala sends heavy and broad projections to the rostral midbrain including the periaqueductal gray (PAG), the deep layers of the superior colliculus/deep mesencephalic nucleus (deep SC/DpMe), and the lateral mesencephalic reticular formation (MRF) that in turn project to the nucleus reticularis pontis caudalis (PnC), an obligatory relay in the primary acoustic startle circuit. Chemical lesions or inactivation of these areas blocked fear-potentiated startle, suggesting that these areas serve as a relay between the amygdala and the PnC. In the present study, we tried to determine more precisely which of these sites were critical for fear-potentiated startle and the role of glutamate receptors in this site in mediating fear-potentiated startle. Local infusion of the non-NMDA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*F*)-quinoxaline (NBQX) dose-dependently blocked fear-potentiated startle when infused into the deep SC/DpMe before testing but had no effect on baseline startle amplitude. NBQX did not block fear-potentiated startle when infused before training. The same dose of NBQX infused into the dorsal/lateral PAG, the lateral MRF, or the superficial layers of the SC did not affect fear-potentiated startle. However, NBQX tended to reduce contextual freezing when infused into the dorsal/lateral PAG. These findings suggest that the deep SC/DpMe is the site that serves as a critical output relay between the amygdala and the PnC in mediating fear-potentiated startle and that glutamatergic transmission is required for this action.

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State Anxiety Modulation of the Amygdala Response to Unattended Threat-Related Stimuli

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Findings from fear-conditioning studies in rats and functional neuroimaging with human volunteers have led to the suggestion that the amygdala is involved in the preattentive detection of threat-related stimuli. However, some neuroimaging findings point to attentional modulation of the amygdala response. The clinical-cognitive literature suggests that the extent to which the processing of threat-related stimuli is modulated by attention is crucially dependent on participants' anxiety levels. Here, we conducted a functional magnetic resonance imaging study with 27 healthy volunteers to examine whether amygdala responsivity to unattended threat-related stimuli varies with individual differences in state anxiety. Pairs of houses and faces (both fearful or neutral in expression) were presented, and participants attended to either the faces or the houses and matched these stimuli on identity. "Low-anxious" participants showed a reduced amygdala response to unattended versus attended fearful faces, but "high-anxious" participants showed no such reduction, having an increased amygdala response to fearful versus neutral faces regardless of attentional focus. These findings suggest that anxiety may interact with attentional focus to determine the magnitude of the amygdala response to threat-related stimuli.

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Short- and Long-Term Effects of Cholinergic Modulation on Gamma Oscillations and Response Synchronization in the Visual Cortex

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Neurons can engage in synchronized oscillatory activity in the gamma-frequency range when responding to sensory stimuli. Both the oscillatory patterning and the synchronization of responses are enhanced with arousal and attention or when the electroencephalogram is activated by electrical stimulation of the mesencephalic reticular formation. Here we show with intracortical application of cholinergic antagonists that the enhancement of gamma oscillations and response synchronization is mediated by acetylcholine and muscarinic receptors. We demonstrate further that coapplication of cholinergic agonists with synchrony-inducing light stimuli causes a lasting increase in the probability that the stimulated cells engage in gamma oscillations and response synchronization. These changes develop slowly over tens of minutes and then persist for many hours. Thus, cholinergic modulation plays a crucial role both in the fast, state-dependent facilitation of gamma oscillations and response synchronization and in use-dependent long-term modifications of cortical dynamics that favor synchronization of responses in the gamma-frequency range.

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Memory-Like Alterations in *Aplysia* Axons after Nerve Injury or Localized Depolarization

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Adaptive, long-term alterations of excitability have been reported in dendrites and presynaptic terminals but not along axons. Persistent enhancement of axonal excitability has been described in proximal nerve stumps at sites of nerve section in mammals, but this hyperexcitability is considered a pathological derangement important only as a cause of neuropathic pain. Identified neurons in *Aplysia* were used to test the hypothesis that either axonal injury or the focal depolarization that accompanies axonal injury can trigger a local decrease in action potential threshold [long-term hyperexcitability (LTH)] having memory-like properties. Nociceptive tail sensory neurons and a giant secretomotor neuron, R2, exhibited localized axonal LTH lasting 24 hr after a crush of the nerve or connective that severed the tested axons. Axons of tail sensory neurons and tail motor neurons, but not R2, displayed similar localized LTH after peripheral depolarization produced by 2 min exposure to elevated extracellular $[K^+]$. Neither the induction nor expression of either form of LTH was blocked by saline containing 1% normal $[Ca^{2+}]$ during treatment or testing. However, both were prevented by local application of the protein synthesis inhibitors anisomycin or rapamycin. The features of (1) long-lasting alteration by localized depolarization, (2) restriction of alterations to intensely depolarized regions, and (3) dependence of the alterations on local, rapamycin-sensitive protein synthesis are shared with synaptic mechanisms considered important for memory formation. This commonality suggests that relatively simple, accessible axons may offer an opportunity to define fundamental plasticity mechanisms that were important in the evolution of memory.

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Chronic Back Pain Is Associated with Decreased Prefrontal and Thalamic Gray Matter Density

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The role of the brain in chronic pain conditions remains speculative. We compared brain morphology of 26 chronic back pain (CBP) patients to matched control subjects, using magnetic resonance imaging brain scan data and automated analysis techniques. CBP patients were divided into neuropathic, exhibiting pain because of sciatic nerve damage, and non-neuropathic groups. Pain-related characteristics were correlated to morphometric measures. Neocortical gray matter volume was compared after skull normalization. Patients with CBP showed 5–11% less neocortical gray matter volume than control subjects. The magnitude of this decrease is equivalent to the gray matter volume lost in 10–20 years of normal aging. The decreased volume was related to pain duration, indicating a 1.3 cm^3 loss of gray matter for every year of chronic pain. Regional gray matter density in 17 CBP patients was compared with matched controls using voxel-based morphometry and nonparametric statistics. Gray matter density was reduced in bilateral dorsolateral prefrontal cortex and right thalamus and was strongly related to pain characteristics in a pattern distinct for neuropathic and non-neuropathic CBP. Our results imply that CBP is accompanied by brain atrophy and suggest that the pathophysiology of chronic pain includes thalamocortical processes.

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“What” Becoming “Where”: Functional Magnetic Resonance Imaging Evidence for Pragmatic Relevance Driving Premotor Cortex

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Previous studies using the serial prediction task (SPT) have shown that attending to the locations of objects activates the dorsal part of premotor cortex more than attending to the sizes of objects. The opposite holds for the ventral part of the premotor cortex. The present study used functional magnetic resonance imaging to investigate whether the learning of arbitrary stimulus-response mappings influences this functional dissociation. One experimental group learned to assign stimuli to response buttons based on stimulus size; another group did so based on stimulus location. More specifically, one-half of the participants in both experimental groups learned to assign stimuli to finger movements of their right hand, whereas the other half assigned stimuli to finger movements of their left hand. During scanning, all participants performed both size SPT and location SPT. Thus, we investigated the effects of the attended stimulus property (size or location), the motor effector assigned to it (fingers of left or right hand), and the spatial arrangement of the targets (the same in all groups). As expected, without motor training, the dorsal premotor cortex was less activated during size SPT compared with location SPT. The opposite held for ventral premotor cortex. With motor training, however, this differential activity pattern vanished. Activity in dorsal premotor cortex reflected neither the attended stimulus property nor the motor effector assigned to it. Instead, its activity may be related to the spatial properties of the response targets once some object property, such as size, takes on the “pragmatic relevance” of a spatially directed response.

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Multiple Time Scales of Adaptation in Auditory Cortex Neurons

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Neurons in primary auditory cortex (A1) of cats show strong stimulus-specific adaptation (SSA). In probabilistic settings, in which one stimulus is common and another is rare, responses to common sounds adapt more strongly than responses to rare sounds. This SSA could be a correlate of auditory sensory memory at the level of single A1 neurons. Here we studied adaptation in A1 neurons, using three different probabilistic designs. We showed that SSA has several time scales concurrently, spanning many orders of magnitude, from hundreds of milliseconds to tens of seconds. Similar time scales are known for the auditory memory span of humans, as measured both psychophysically and using evoked potentials. A simple model, with linear dependence on both short-term and long-term stimulus history, provided a good fit to A1 responses. Auditory thalamus neurons did not show SSA, and their responses were poorly fitted by the same model. In addition, SSA increased the proportion of failures in the responses of A1 neurons to the adapting stimulus. Finally, SSA caused a bias in the neuronal responses to unbiased stimuli, enhancing the responses to eccentric stimuli. Therefore, we propose that a major function of SSA in A1 neurons is to encode auditory sensory memory on multiple time scales. This SSA might play a role in stream segregation and in binding of auditory objects over many time scales, a property that is crucial for processing of natural auditory scenes in cats and of speech and music in humans.

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Orexin Neurons Function in an Efferent Pathway of a Food-Entrainable Circadian Oscillator in Eliciting Food-Anticipatory Activity and Wakefulness

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Temporal restriction of feeding can entrain circadian behavioral and physiological rhythms in mammals. Considering the critical functions of the hypothalamic orexin (hypocretin) neuropeptides in promoting wakefulness and locomotor activity, we examined the role of orexin neurons in the adaptation to restricted feeding. In orexin neuron-ablated transgenic mice, the food-entrained rhythmicity of *mPer2* expression in the brain and liver, the reversal of the sleep–wake cycle, and the recovery of daily food intake were unaltered compared with wild-type littermates. In contrast, orexin neuron-ablated mice had a severe deficit in displaying the normal food-anticipatory increases in wakefulness and locomotor activity under restricted feeding. Moreover, activity of orexin neurons markedly increased during the food-anticipatory period under restricted feeding in wild-type mice. Orexin neurons thus convey an efferent signal from putative food-entrainable oscillator or oscillators to increase wakefulness and locomotor activity.

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Chemotherapy for the Brain: The Antitumor Antibiotic Mithramycin Prolongs Survival in a Mouse Model of Huntington's Disease

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Huntington's disease (HD) is a fully penetrant autosomal-dominant inherited neurological disorder caused by expanded CAG repeats in the Huntingtin gene. Transcriptional dysfunction, excitotoxicity, and oxidative stress have all been proposed to play important roles in the pathogenesis of HD. This study was designed to explore the therapeutic potential of mithramycin, a clinically approved guanosine–cytosine-rich DNA binding antitumor antibiotic. Pharmacological treatment of a transgenic mouse model of HD (R6/2) with mithramycin extended survival by 29.1%, greater than any single agent reported to date. Increased survival was accompanied by improved motor performance and markedly delayed neuropathological sequelae. To identify the functional mechanism for the salutary effects of mithramycin, we examined transcriptional dysfunction in R6/2 mice. Consistent with transcriptional repression playing a role in the pathogenesis of HD, we found increased methylation of lysine 9 in histone H3, a well established mechanism of gene silencing. Mithramycin treatment prevented the increase in H3 methylation observed in R6/2 mice, suggesting that the enhanced survival and neuroprotection might be attributable to the alleviation of repressed gene expression vital to neuronal function and survival. Because it is Food and Drug Administration-approved, mithramycin is a promising drug for the treatment of HD.

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Stimulus and Potassium-Induced Epileptiform Activity in the Human Dentate Gyrus from Patients with and without Hippocampal Sclerosis

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Hippocampal specimens resected to cure medically intractable temporal lobe epilepsy (TLE) provide a unique possibility to study functional consequences of morphological alterations. One intriguing alteration predominantly observed in cases of hippocampal sclerosis is an uncommon network of granule cells monosynaptically interconnected via aberrant supragranular mossy fibers. We investigated whether granule cell populations in slices from sclerotic and nonsclerotic hippocampi would develop ictal activity when challenged by low-frequency hilar stimulation in the presence of elevated extracellular potassium concentration (10 and 12 mM) and whether the experimental activity differs according to the presence of aberrant mossy fibers.

We found that ictal activity could be evoked in slices from sclerotic and nonsclerotic hippocampi (27 of 40 slices, 14 of 20 patients; and 11 of 22 slices, 6 of 12 patients, respectively). However, the two patient groups differed with respect to the pattern of ictal discharges and the potassium concentration mandatory for its induction. Seizure-like events were already induced with 10 mM K⁺. They exclusively occurred in slices from sclerotic hippocampi, of which 80% displayed stimulus-induced oscillatory population responses (250–300 Hz). In slices from nonsclerotic hippocampi, atypical negative field potential shifts were predominantly evoked with 12 mM K⁺. In both groups, the ictal activity was sensitive to ionotropic glutamate receptor antagonists and lowering of [Ca²⁺]_o.

Our results show that, in granule cell populations of hippocampal slices from TLE patients, high K⁺-induced seizure-like activity and ictal spiking coincide with basic electrophysiological abnormalities, hippocampal sclerosis, and mossy fiber sprouting, suggesting that network reorganization could play a crucial role in determining type and threshold of such activity.

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RACK1 and Brain-Derived Neurotrophic Factor: A Homeostatic Pathway That Regulates Alcohol Addiction

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Alcoholism is a devastating disease that manifests as uncontrolled drinking. Consumption of alcohol is regulated by neurochemical systems within specific neural circuits, but endogenous systems that may counteract and thus suppress the behavioral effects of ethanol intake are unknown. Here we demonstrate that BDNF plays a role in reducing the behavioral effects of ethanol, including consumption, in rodents. We found that decreasing the levels of BDNF leads to increased behavioral responses to ethanol, whereas increases in the levels of BDNF, mediated by the scaffolding protein RACK1, attenuate these behaviors. Interestingly, we found that acute exposure of neurons to ethanol leads to increased levels of BDNF mRNA via RACK1. Importantly, acute systemic administration of ethanol and voluntary ethanol consumption lead to increased levels of BDNF expression in the dorsal striatum. Taken together, these findings suggest that RACK1 and BDNF are part of a regulatory pathway that opposes adaptations that lead to the development of alcohol addiction.

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**SCIENTIFIC DIRECTOR
HEART AND STROKE FOUNDATION OF ONTARIO
CENTRE FOR STROKE RECOVERY**

The Heart and Stroke Foundation of Ontario Centre for Stroke Recovery (the Centre) is looking to recruit a Scientific Director (SD). This individual is an internationally recognized scientist and/or clinician with major involvement in a field of research relevant to brain repair after stroke. The Centre, established in 2002, is a research enterprise funded jointly by the Heart and Stroke Foundation of Ontario and three academic institutions: the Ottawa Health Research Institute in Ottawa; and in Toronto Canada Sunnybrook and Women's College Health Sciences Centre and the Baycrest Centre for Geriatric Care. The Centre is dedicated to new discoveries that would transform our approach to patient recovery after stroke. The most likely home base for the Scientific Director is Ottawa, Canada.

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Dr. A. M. Hakim
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Ottawa Health Research Institute
University of Ottawa
2413-451 Smyth Road
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Email: ahakim@ohri.ca

TRAUMATIC BRAIN INJURY

The National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services is seeking an imaginative and resourceful physician or neuroscientist to serve as Program Director for the traumatic brain injury (TBI) portfolio within the Repair and Plasticity cluster. The TBI portfolio spans basic, translational, and clinical neuroscience research with scientific topics including mechanisms of global ischemia, the molecular basis for brain injury, and approaches for neuroprotection. The role of the Program Director for TBI is to plan, evaluate, and administer research within this important and vital portfolio. Relevant experience may include basic or clinical neuroscience research, or clinical practice in academic or for profit institutions. The successful candidate will join a highly interactive group of scientists and clinicians directing research programs in all areas of modern neuroscience and neurological disorders. He/she will build and maintain active communication with the professional and lay communities as well as program staff from other institutes and agencies.

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Dr. Story Landis
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c/o Nena Wells
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Bethesda, MD 20892-2540

Applications may be faxed to (301) 402-4370 or sent via e-mail: nw15d@nih.gov. For information concerning the nature of the job, contact either the Director of Extramural Research: Dr. Robert Finkelstein (rf45c@nih.gov) or the Deputy Director of Extramural Research: Dr. Emmeline Edwards (ee48r@nih.gov). The NINDS has a strong commitment to the diversity of its workforce and a biomedical research environment that reflects the diversity of the American population (<http://oeo.od.nih.gov/>). NINDS is one of the institutes of the National Institutes of Health, a component of the Department of Health and Human Services.

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Dr. Susan G. Amara, Chair, Dept. of Neurobiology
University of Pittsburgh School of Medicine
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