

This Week in The Journal

● Cellular/Molecular

Zinc Inhibition of Kainate Receptors

David D. Mott, Morris Benveniste, and Raymond J. Dingledine

(see pages 1659–1671)

This week, Mott et al. present evidence that zinc inhibits glutamatergic kainate receptors in a pH-dependent manner. Zinc is packaged with glutamate in mossy fiber terminals, which synapse onto CA3 pyramidal cells. Mott et al. found that zinc chelators increased kainate receptor-dependent facilitation of field EPSPs produced by 100 Hz stimulation of mossy fibers in rat hippocampal slices. Furthermore, exogenous zinc abolished kainate-mediated miniature EPSCs (mEPSCs) without affecting AMPA-mediated mEPSCs. When mossy fibers were stimulated antidromically, kainate increased firing synchrony and the size of the population spike; this potentiation was also blocked by zinc. Examination of kainate receptors expressed in oocytes revealed that those with KA1 and KA2 subunits were most sensitive to zinc. Lower pH reduced zinc inhibition of kainate receptors, with greatest effects on KA2-containing receptors. Because neurotransmission alters synaptic pH, these data suggest that activity can modulate kainate receptor function by modulating inhibition by zinc.

▲ Development/Plasticity/Repair

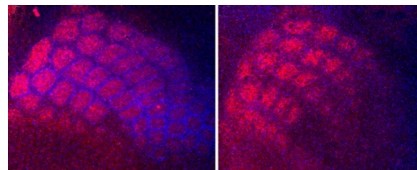
Effects of Neurofibromin on Cortical Organization

Mark E. Lush, Yun Li, Chang-Hyuk Kwon, Jian Chen, and Luis F. Parada

(see pages 1580–1587)

Neurofibromin, the tumor suppressor protein mutated in neurofibromatosis type 1 (NF1), is important for cortical development, report Lush et al. this week. Using the Cre/Lox method, the authors produced mice in which neurofibromin was knocked out only in cortical progeni-

tors and thus was absent from most cortical neurons and astrocytes. Although these mice had normal numbers of cortical neurons and no obvious defects in cortical layering or thalamic inputs, the organization of the neurons was disrupted. Aggregation of neurons was disrupted throughout the somatosensory cortex, but this was particularly obvious in the barrel cortex, where the barrel structure was completely absent. Nonetheless, expression levels of other proteins known to disrupt barrel formation, including NMDA receptors, phospholipase C- β 1, protein kinase A-RII β , and SynGAP, were unchanged in these mice. It is conceivable that similar defects in cortical organization might underlie intellectual deficits and autism spectrum disorders seen in some NF1 patients.



Nuclear staining (blue) shows that neurons do not segregate into barrels in the somatosensory cortex of neurofibromin conditional knock-out mice (right), although thalamic axon (red) innervation and segregation is similar to controls (left). For details, see the article by Lush et al.

■ Behavioral/Systems/Cognitive

Filtering Self-Generated Sensory Information

Nathaniel B. Sawtell and Alan Williams

(see pages 1598–1612)

As an animal explores its surroundings, its own movements create sensory feedback that it must distinguish from sensory signals from the environment. Sawtell and Williams have studied this problem in mormyrid electric fish. Mormyrids sense their environment by producing an electric field and sensing perturbations to this field via electrosensory receptors that cover their bodies. Sawtell and Williams show that the activity of these electroreceptors is strongly affected by tail move-

ments—more strongly, in fact, than by nearby objects. In contrast, secondary sensory neurons in the electrosensory lobe (ELL), a cerebellar-like structure, are much more sensitive to object locations than to tail movements. As a result, the output of ELL neurons carries much more information about environmental objects than the sensory afferents. This transformation partly depends on proprioceptive inputs about tail position, which provide input to neurons of the ELL via parallel fibers.

◆ Neurobiology of Disease

New and Improved Mouse Model for Alzheimer's Disease

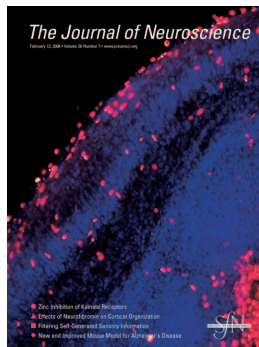
Donna M. Wilcock, Matthew R. Lewis, William E. Van Nostrand, Judianne Davis, Mary Lou Previti, Nastaran Gharkholonarehe, Michael P. Vitek, and Carol A. Colton

(see pages 1537–1545)

Most attempts to create transgenic mice that exhibit all the pathological features of Alzheimer's disease (AD)—amyloid- β ($A\beta$) plaques, neurofibrillary tangles of hyperphosphorylated tau, and neuronal loss—have been only partially successful. This week's report by Wilcock et al. is therefore a welcome advance. The authors produced mice that have a mutant form of amyloid precursor protein (APP) and that also lack inducible nitric oxide synthase (iNOS). These mice showed levels of $A\beta$ staining similar to that in mice with mutant APP alone, but they had greater defects in spatial learning. Furthermore, unlike APP single-mutant mice, the double mutants had significant neuronal degeneration and increased phosphorylation and aggregation of tau, particularly in the hippocampus and subiculum—brain regions that expressed high levels of APP. Moreover, neurons expressing neuropeptide Y were especially susceptible to death in these mice, as in human AD patients, further strengthening the usefulness of this mouse as a model for AD.

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Cover legend: Immunohistochemistry against BrdU in microtransplantation slice assay in which E13.5 *Cxcr4*^{-/-} MGE explant obtained from acutely BrdU-injected females was transplanted to the ventricular zone of E13.5 wild-type slices. For more information, see the article by López-Bendito et al. in this issue (pages 1613–1624).

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Correction: For the article “The Neural Coding of Stimulus Intensity: Linking the Population Response of Mechanoreceptive Afferents with Psychophysical Behavior,” by Michael A. Muniak, Supratim Ray, Steven S. Hsiao, J. Frank Dammann, and Sliman J. Bensmaia, which appeared on pages 11687-11699 of the October 24, 2007 issue, the formula for r_{max} (Eq. 6) (page 11695, in Results, Population firing rate), is incorrect. The fraction within the parentheses should be flipped. The correct formula, used in all subsequent calculations and derivations, is as follows:

$$r_{max} = r_0 \left(\frac{A_0}{10^\beta} \right)^{\frac{1}{2}}.$$

Please note that this equation was incorrectly reproduced in the Corrections section of the January 30, 2008 issue.

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Axonal Transport Rates *In Vivo* Are Unaffected by Tau Deletion or Overexpression in Mice

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Elevated tau expression has been proposed as a possible basis for impaired axonal transport in Alzheimer's disease. To address this hypothesis, we analyzed the movement of pulse radiolabeled proteins *in vivo* along retinal ganglion cell (RGC) axons of mice that lack tau or overexpress human tau isoforms. Here, we show that the global axonal transport rates of slow and fast transport cargoes in axons are not significantly impaired when tau expression is eliminated or increased. In addition, markers of slow transport (neurofilament light subunit) and fast transport (snap25) do not accumulate in retinas and are distributed normally along optic axons in mice that lack or overexpress tau. Finally, ultrastructural analyses revealed no abnormal accumulations of vesicular organelles or neurofilaments in RGC perikarya or axons in mice overexpressing or lacking tau. These results suggest that tau is not essential for axonal transport and that transport rates *in vivo* are not significantly affected by substantial fluctuations in tau expression.

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Coordinate Transformation is First Completed Downstream of Primary Motor Cortex

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It was suggested previously that the transformation of action to muscle-based coding is completed in the primary motor cortex (M1). This is consistent with a predominant direct pathway leading from M1 to motoneurons. Accordingly, spinal segmental interneurons that are located downstream to M1 are expected to show muscle-like coding properties. We addressed this hypothesis using simultaneous recording of cortical and spinal activity in primates performing an isometric wrist task with multiple targets and two hand postures. Here we show that while the motor cortex follows an intermediate coordinate frame, spinal interneurons already follow a muscle-like coordinate frame. We thus suggest that the final steps in coordinate transformation of motor commands take place downstream of M1 via corticospinal interactions.

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Articles

CELLULAR/MOLECULAR

The Activation Gate and Gating Mechanism of the NMDA Receptor

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The NMDA receptor opens in response to binding of NMDA and glycine. However, it remains unclear where and how gating of the NMDA receptor pore is accomplished. We show that different point mutations between S645 and I655 (thus including the highly conserved SYTANLAAF motif) of M3c in NR2B lead to constitutively open channels. The current through these constitutively open channels are readily blocked by external Mg^{2+} and MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohept-5,10-imine maleate]. Also, the open-channel blocker MK-801 can no longer be trapped in these channels when NMDA and glycine are washed off. Moreover, M3c residues at or below A651(NR2B, A7 in SYTANLAAF) react with external methanethiosulfonate (MTS) reagents ~500 to 1000-fold faster in the presence than in the absence of agonists NMDA and glycine. In fact, the MTS modification rate shows exactly the same NMDA concentration dependence as channel activation. In contrast, those residues external to A651 are always modified with similar kinetics whether NMDA and glycine are present or not. Interestingly, MTS modification of A651C(NR2B) holds the channel constitutively open. Mutations of A651(NR2B) into arginine, tryptophan, or phenylalanine, and similar mutations of the corresponding A652 in NR1 also lead to constitutively open channels. Double-mutant cycle analysis further shows that the effects of A652(NR1) and A651(NR2B) mutations are evidently non-additive (i.e., cooperative) if mutated into residues with large side chains or with compensatory charges [e.g., A652E(NR1) + A651R(NR2B)]. The side chain of A7 thus plays a determinant role in the intersubunit distance at this level, which is directly responsible for the activation gate and activation–deactivation gating of the NMDA receptor.

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Activity-Induced Synaptic Capture and Exocytosis of the Neuronal Serine Protease Neurotrypsin

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Extracellular proteolysis plays an essential role in synaptic remodeling that is indispensable for cognitive function. The extracellular serine protease neurotrypsin was implicated in cognitive function, because humans lacking a functional form of neurotrypsin suffer from severe mental retardation. By immunoelectron microscopy, neurotrypsin has been localized to presynaptic terminals, suggesting a local proteolytic function after its synaptic release. Here, we studied axonal trafficking and synaptic exocytosis of neurotrypsin by live imaging of hippocampal neurons expressing neurotrypsin fused with enhanced green fluorescent protein or its pH-sensitive variant, super-ecliptic pHluorin. In differentiated neurons, we identified neurotrypsin in mobile transport vesicles along axons and in both an intracellular and an extracellular pool at synapses. Short depolarization triggered rapid synaptic exocytosis of neurotrypsin. Once externalized, neurotrypsin lingered at its synaptic release site for several minutes before it disappeared. Cell depolarization also enhanced synaptic capture of intracellular neurotrypsin transport vesicles, and elevated synaptic activity increased both number and motility of mobile axonal neurotrypsin vesicles. We further observed trading of neurotrypsin vesicles between adjacent synapses. These activities may support the replenishment of neurotrypsin after activity-induced synaptic exocytosis. Together, the activity-dependent recruitment of neurotrypsin to synapses and its exocytosis and transient persistence at its synaptic release site argue for a spatially and temporally restricted proteolytic action at the synapse. Thereby, neurotrypsin may play a role in activity-dependent remodeling of the synaptic circuitry that is key to adaptive synaptic changes in the context of cognitive functions, such as learning and memory.

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Multiple Conductances Cooperatively Regulate Spontaneous Bursting in Mouse Olfactory Bulb External Tufted Cells

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External tufted (ET) cells are juxtglomerular neurons that spontaneously generate bursts of action potentials, which persist when fast synaptic transmission is blocked. The intrinsic mechanism of this autonomous bursting is unknown. We identified a set of voltage-dependent conductances that cooperatively regulate spontaneous bursting: hyperpolarization-activated inward current (I_h), persistent Na^+ current (I_{NaP}), low-voltage-activated calcium current (I_{LT}) mediated by T- and/or L-type Ca^{2+} channels, and large-conductance Ca^{2+} -dependent K^+ current (I_{BK}). I_h is important in setting membrane potential and depolarizes the cell toward the threshold of I_{NaP} and I_{TL} , which are essential to generate the depolarizing envelope that is crowned by a burst of action potentials. Action potentials depolarize the membrane and induce Ca^{2+} influx via high-voltage-activated Ca^{2+} channels (I_{HVA}). The combined depolarization and increased intracellular Ca^{2+} activates I_{BK} , which terminates the burst by hyperpolarizing the membrane. Hyperpolarization activates I_h and the cycle is regenerated. A novel finding is the role of L-type Ca^{2+} channels in autonomous ET cells bursting. A second novel feature is the role of BK channels, which regulate burst duration. I_L and I_{BK} may go hand-in-hand, the slow inactivation of I_L requiring I_{BK} -dependent hyperpolarization to deactivate inward conductances and terminate the burst. ET cells receive monosynaptic olfactory nerve input and drive the major inhibitory interneurons of the glomerular circuit. Modulation of the conductances identified here can regulate burst frequency, duration, and spikes per burst in ET cells and thus significantly shape the impact of glomerular circuits on mitral and tufted cells, the output channels of the olfactory bulb.

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pH-Dependent Inhibition of Kainate Receptors by Zinc

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Kainate receptors contribute to synaptic plasticity and rhythmic oscillatory firing of neurons in corticolimbic circuits including hippocampal area CA3. We use zinc chelators and mice deficient in zinc transporters to show that synaptically released zinc inhibits postsynaptic kainate receptors at mossy fiber synapses and limits frequency facilitation of kainate, but not AMPA EPSCs during theta-pattern stimulation. Exogenous zinc also inhibits the facilitatory modulation of mossy fiber axon excitability by kainate but does not suppress the depressive effect of kainate on CA3 axons. Recombinant kainate receptors are inhibited in a subunit-dependent manner by physiologically relevant concentrations of zinc, with receptors containing the KA1 subunit being sensitive to submicromolar concentrations of zinc. Zinc inhibition does not alter receptor desensitization nor apparent agonist affinity and is only weakly voltage dependent, which points to an allosteric mechanism. Zinc inhibition is reduced at acidic pH. Thus, in the presence of zinc, a fall in pH potentiates kainate receptors by relieving zinc inhibition. Acidification of the extracellular space, as occurs during repetitive activity, may therefore serve to unmask kainate receptor neurotransmission. We conclude that zinc modulation of kainate receptors serves an important role in shaping kainate neurotransmission in the CA3 region.

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Muscle-Specific Receptor Tyrosine Kinase Endocytosis in Acetylcholine Receptor Clustering in Response to Agrin

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Agrin, a factor used by motoneurons to direct acetylcholine receptor (AChR) clustering at the neuromuscular junction, initiates signal transduction by activating the muscle-specific receptor tyrosine kinase (MuSK). However, the underlying mechanisms remain poorly defined. Here, we demonstrated that MuSK became rapidly internalized in response to agrin, which appeared to be required for induced AChR clustering. Moreover, we provided evidence for a role of *N*-ethylmaleimide sensitive factor (NSF) in regulating MuSK endocytosis and subsequent signaling in response to agrin stimulation. NSF interacts directly with MuSK with nanomolar affinity, and treatment of muscle cells with the NSF inhibitor *N*-ethylmaleimide, mutation of NSF, or suppression of NSF expression all inhibited agrin-induced AChR clustering. Furthermore, suppression of NSF expression and NSF mutation attenuate MuSK downstream signaling. Our study reveals a potentially novel mechanism that regulates agrin/MuSK signaling cascade.

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Mitochondrial Reactive Oxygen Species Inactivate Neuronal Nicotinic Acetylcholine Receptors and Induce Long-Term Depression of Fast Nicotinic Synaptic Transmission

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Neuronal nicotinic acetylcholine receptors (nAChRs), ligand-gated ion channels implicated in a variety of cognitive, motor, and sensory behaviours, are targeted to compartments rich in mitochondria, particularly postsynaptic domains and presynaptic terminals, exposing these receptors to reactive oxygen species (ROS) generated by oxidative phosphorylation. In addition, these receptors can become exposed to ROS during the progression of certain neurodegenerative diseases. Because ROS are known to modify several membrane proteins, including some types of ion channels, it raises the question of whether elevations in cytosolic ROS alter the function of nAChRs. To address this, we elevated ROS in cultured sympathetic neurons, directly by perfusing neurons intracellularly with ROS, indirectly by blocking the mitochondrial electron transport chain, or noninvasively by transient NGF removal; we then simultaneously measured changes in cytosolic ROS levels and whole-cell ACh-evoked currents. In addition, we elevated cytosolic ROS in postganglionic neurons in intact ganglia and measured changes in nerve-evoked EPSPs. Our experiments indicate that mild elevations in cytosolic ROS, including that produced by transient interruption of NGF signaling, induce a use-dependent, long-lasting rundown of ACh-evoked currents on cultured sympathetic neurons and a long-lasting depression of fast nerve-evoked EPSPs. We show that these effects of cytosolic ROS are specific to nAChRs on neurons and do not cause rundown of ACh-evoked currents on muscle. Our results demonstrate that elevations in cytosolic ROS inactivate neuronal nAChRs in a use-dependent manner and suggest that mild oxidative stress impairs mechanisms mediated by cholinergic nicotinic signaling at neuronal–neuronal synapses.

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Two-Photon Imaging of Stroke Onset *In Vivo* Reveals That NMDA-Receptor Independent Ischemic Depolarization Is the Major Cause of Rapid Reversible Damage to Dendrites and Spines

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We adapt a mouse global ischemia model to permit rapid induction of ischemia and reperfusion in conjunction with two-photon imaging to monitor the initial ionic, structural, and functional implications of brief interruptions of blood flow (6–8 min) *in vivo*. After only 2–3 min of global ischemia, a wide spread loss of mouse somatosensory cortex apical dendritic structure is initiated during the passage of a propagating wave (3.3 mm/min) of ischemic depolarization. Increases in intracellular calcium levels occurred during the wave of ischemic depolarization and were coincident with the loss of dendritic structure, but were not triggered by reperfusion. To assess the role of NMDA receptors, we locally applied the antagonist MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate] at concentrations sufficient to fully block local NMDA agonist-evoked changes in intracellular calcium levels *in vivo*. Changes in dendritic structure and intracellular calcium levels were independent of NMDA receptor activation. Local application of the non-NMDA glutamate receptor antagonist CNQX also failed to block ischemic depolarization or rapid changes in dendrite structure. Within 3–5 min of reperfusion, damage ceased and restoration of synaptic structure occurred over 10–60 min. In contrast to a reperfusion promoting damage, over this time scale, the majority of spines and dendrites regained their original structure during reperfusion. Intrinsic optical signal imaging of sensory evoked maps indicated that reversible alteration in dendritic structure during reperfusion was accompanied by restored functional maps. Our results identify glutamate receptor-independent ischemic depolarization as the major ionic event associated with disruption of synaptic structure during the first few minutes of ischemia *in vivo*.

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Neurofibromin Is Required for Barrel Formation in the Mouse Somatosensory Cortex

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The rodent barrel cortex is a useful system to study the role of genes and neuronal activity in the patterning of the nervous system. Several genes encoding either intracellular signaling molecules or neurotransmitter receptors are required for barrel formation. Neurofibromin is a tumor suppressor protein that has Ras GTPase activity, thus attenuating the MAPK (mitogen-activated protein kinase) and PI-3 kinase (phosphatidylinositol 3-kinase) pathways, and is mutated in humans with the condition neurofibromatosis type 1 (NF1). Neurofibromin is widely expressed in the developing and adult nervous system, and a common feature of NF1 is deficits in intellectual development. In addition, NF1 is an uncommonly high disorder among individuals with autism. Thus, NF1 may have important roles in normal CNS development and function. To explore roles for neurofibromin in the development of the CNS, we took advantage of a mouse conditional allele. We show that mice that lack neurofibromin in the majority of cortical neurons and astrocytes fail to form cortical barrels in the somatosensory cortex, whereas segregation of thalamic axons within the somatosensory cortex appears unaffected.

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Neurogenic Role of the Depolarizing Chloride Gradient Revealed by Global Overexpression of KCC2 from the Onset of Development

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GABA- and glycine-induced depolarization is thought to provide important developmental signals, but the role of the underlying chloride gradient has not been examined from the onset of development. We therefore overexpressed globally the potassium–chloride cotransporter 2 (KCC2) in newly fertilized zebrafish embryos to reverse the chloride gradient. This rendered glycine hyperpolarizing in all neurons, tested at the time that motor behaviors (but not native KCC2) first appear. KCC2 overexpression resulted in fewer mature spontaneously active spinal neurons, more immature silent neurons, and disrupted motor activity. We observed fewer motoneurons and interneurons, a reduction in the elaboration of axonal tracts, and smaller brains and spinal cords. However, we observed no increased apoptosis and a normal complement of sensory neurons, glia, and progenitors. These results suggest that chloride-mediated excitation plays a crucial role in promoting neurogenesis from the earliest stages of embryonic development.

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Chemokine Signaling Controls Intracortical Migration and Final Distribution of GABAergic Interneurons

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Functioning of the cerebral cortex requires the coordinated assembly of circuits involving glutamatergic projection neurons and GABAergic interneurons. Although much is known about the migration of interneurons from the subpallium to the cortex, our understanding of the mechanisms controlling their precise integration within the cortex is still limited. Here, we have investigated in detail the behavior of GABAergic interneurons as they first enter the developing cortex by using time-lapse videomicroscopy, slice culture, and *in utero* experimental manipulations and analysis of mouse mutants. We found that interneurons actively avoid the cortical plate for a period of ~48 h after reaching the pallium; during this time, interneurons disperse tangentially through the marginal and subventricular zones. Perturbation of CXCL12/CXCR4 signaling causes premature cortical plate invasion by cortical interneurons and, in the long term, disrupts their laminar and regional distribution. These results suggest that regulation of cortical plate invasion by GABAergic interneurons is a key event in cortical development, because it directly influences the coordinated formation of appropriate glutamatergic and GABAergic neuronal assemblies.

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Smaller Dendritic Spines, Weaker Synaptic Transmission, but Enhanced Spatial Learning in Mice Lacking Shank1

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Experience-dependent changes in the structure of dendritic spines may contribute to learning and memory. Encoded by three genes, the Shank family of postsynaptic scaffold proteins are abundant and enriched in the postsynaptic density (PSD) of central excitatory synapses. When expressed in cultured hippocampal neurons, Shank promotes the maturation and enlargement of dendritic spines. Recently, Shank3 has been genetically implicated in human autism, suggesting an important role for Shank proteins in normal cognitive development. Here, we report the phenotype of Shank1 knock-out mice. Shank1 mutants showed altered PSD protein composition; reduced size of dendritic spines; smaller, thinner PSDs; and weaker basal synaptic transmission. Standard measures of synaptic plasticity were normal. Behaviorally, they had increased anxiety-related behavior and impaired contextual fear memory. Remarkably, Shank1-deficient mice displayed enhanced performance in a spatial learning task; however, their long-term memory retention in this task was impaired. These results affirm the importance of Shank1 for synapse structure and function *in vivo*, and they highlight a differential role for Shank1 in specific cognitive processes, a feature that may be relevant to human autism spectrum disorders.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Transformations of Electrosensory Encoding Associated with an Adaptive Filter

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Sensory information is often acquired through active exploration. However, an animal's own movements may result in changes in patterns of sensory input that could interfere with the detection and processing of behaviorally relevant sensory signals. Neural mechanisms for predicting the sensory consequences of movements are thus likely to be of general importance for sensory systems. Such mechanisms have been identified in cerebellum-like structures associated with electrosensory processing in fish. These structures are hypothesized to act as adaptive filters, removing correlations between incoming sensory input and central predictive signals through associative plasticity at parallel fiber synapses. The present study tests the adaptive filter hypothesis in the electrosensory lobe (ELL) of weakly electric mormyrid fish. We compared the ability of electroreceptors and ELL efferent neurons to encode the position of moving objects in the presence and absence of self-generated electrosensory signals caused by tail movements. Tail movements had strong effects on the responses of electroreceptors, substantially reducing the amount of information they conveyed about object position. In contrast, responses of efferent neurons were relatively unaffected by tail movements, and the information they conveyed about object position was preserved. We provide evidence that the electrosensory consequences of tail bending are opposed by proprioceptive inputs conveyed by parallel fibers and that the effects of proprioceptive inputs to efferent cells are plastic. These results support the idea that cerebellum-like structures learn and remove the predictable sensory consequences of behavior and link mechanisms of adaptive filtering to selective encoding of behaviorally relevant sensory information.

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Presynaptic Opioid and Nicotinic Receptor Modulation of Dopamine Overflow in the Nucleus Accumbens

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Behaviorally relevant stimuli prompt midbrain dopamine (DA) neurons to switch from tonic to burst firing patterns. Similar shifts to burst activity are thought to contribute to the addictive effects of opiates and nicotine. The nucleus accumbens DA overflow produced by these drugs is a key element in their pathological effects. Using electrochemical techniques in brain slices, we explored the effects of opioids on single-spike and burst stimuli-evoked DA overflow in the dorsal and ventral striatum. In specific subregions of the nucleus accumbens, μ -opioids inhibit DA overflow elicited with single-spike stimuli while leaving that produced by burst stimuli unaffected. This is similar to published effects of nicotinic receptor blockade or desensitization, and is mediated by opioid receptor-induced inhibition of cholinergic interneurons. Whereas δ -opioids have similar effects, κ -opioids inhibit evoked DA overflow throughout the striatum in a manner that is not overcome with high-frequency stimuli. These observations reveal remarkable mechanistic overlap between the effects of nicotine and opiates within the dopamine reward pathway.

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Persistent Na⁺ and K⁺-Dominated Leak Currents Contribute to Respiratory Rhythm Generation in the Pre-Bötzing Complex *In Vitro*

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A central problem in analyzing neural circuit function is establishing how intrinsic neuronal conductances contribute to the generation of network activity. We used real-time calcium activity imaging combined with whole-cell patch-clamp recording to analyze contributions of subthreshold conductances in the excitatory rhythm-generating network in the respiratory pre-Bötzing complex (pre-BötC) of neonatal rat *in vitro* brainstem slice preparations. Voltage-clamp ramp recordings from imaged pre-BötC neurons revealed that persistent sodium (NaP) and K⁺-dominated leak currents primarily contribute to subthreshold *I*-*V* relations. We quantified NaP and leak conductance densities (g/C_m) in intrinsic oscillatory bursters and intrinsically nonbursters, the two main electrophysiological phenotypes of inspiratory neurons within the pre-BötC. Densities of g_{NaP} were significantly higher for intrinsic bursters, whereas leak conductance densities were not significantly different between intrinsic bursters and nonbursters. By pharmacologically manipulating g_{NaP} and/or g_{Leak} directly within the pre-BötC, we could modulate network oscillation frequency over a wide dynamic range and cause transitions between oscillatory and quiescent states. These results were consistent with models of the pre-BötC excitatory network consisting of heterogeneous mixtures of intrinsic bursters and nonintrinsic bursters incorporating g_{NaP} and g_{Leak} with parameter values found experimentally. We propose a paradigm whereby NaP and Leak represent a functional set of subthreshold conductances that endow the pre-BötC with rhythmogenic properties and represent targets for modulatory control of inspiratory rhythm generation.

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NEUROBIOLOGY OF DISEASE

Progression of Amyloid Pathology to Alzheimer's Disease Pathology in an Amyloid Precursor Protein Transgenic Mouse Model by Removal of Nitric Oxide Synthase 2

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Alzheimer's disease (AD) is characterized by three primary pathologies in the brain: amyloid plaques, neurofibrillary tangles, and neuron loss. Mouse models have been useful for studying components of AD but are limited in their ability to fully recapitulate all pathologies. We crossed the APPSwdI transgenic mouse, which develops amyloid β (A β)-protein deposits only, with a nitric oxide synthase 2 (NOS2) knock-out mouse, which develops no AD-like pathology. APPSwdI/NOS2^{-/-} mice displayed impaired spatial memory compared with the APPSwdI mice, yet they have unaltered levels of A β . APPSwdI mice do not show tau pathology, whereas APPSwdI/NOS2^{-/-} mice displayed extensive tau pathology associated with regions of dense microvascular amyloid deposition. Also, APPSwdI mice do not have any neuron loss, whereas the APPSwdI/NOS2^{-/-} mice have significant neuron loss in the hippocampus and subiculum. Neuropeptide Y neurons have been shown to be particularly vulnerable in AD. These neurons appear to be particularly vulnerable in the APPSwdI/NOS2^{-/-} mice as we observe a dramatic reduction in the number of NPY neurons in the hippocampus and subiculum. These data show that removal of NOS2 from an APP transgenic mouse results in development of a much greater spectrum of AD-like pathology and behavioral impairments.

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Dissociated Gender-Specific Effects of Recurrent Seizures on GABA Signaling in CA1 Pyramidal Neurons: Role of GABA_A Receptors

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Early in development, the depolarizing GABA_Aergic signaling is needed for normal neuronal differentiation. It is shown here that hyperpolarizing reversal potentials of GABA_Aergic postsynaptic currents (E_{GABA}) appear earlier in female than in male rat CA1 pyramidal neurons because of increased potassium chloride cotransporter 2 (KCC2) expression and decreased bumetanide-sensitive chloride transport in females. Three episodes of neonatal kainic acid-induced status epilepticus (3KA-SE), each elicited at postnatal days 4 (P4)–P6, reverse the direction of GABA_Aergic responses in both sexes. In males, 3KA-SE trigger a premature appearance of hyperpolarizing GABA_Aergic signaling at P9, instead of P14. This is driven by an increase in KCC2 expression and decrease in bumetanide-sensitive chloride cotransport. In 3KA-SE females, E_{GABA} transiently becomes depolarizing at P8–P13 because of increase in the activity of a bumetanide-sensitive NKCC1 (sodium potassium chloride cotransporter 1)-like chloride cotransporter. However, females regain their hyperpolarizing GABA_Aergic signaling at P14 and do not manifest spontaneous seizures in adulthood. In maternally separated stressed controls, a hyperpolarizing shift in E_{GABA} was observed in both sexes, associated with decreased bumetanide-sensitive chloride cotransport, whereas KCC2 immunoreactivity was increased in males only. GABA_A receptor blockade at the time of 3KA-SE or maternal separation reversed their effects on E_{GABA} . These data suggest that the direction of GABA_A-receptor signaling may be a determining factor for the age and sex-specific effects of prolonged seizures in the hippocampus, because they relate to normal brain development and possibly epileptogenesis. These effects differ from the consequences of severe stress.

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Functional Characterization of Rab7 Mutant Proteins Associated with Charcot-Marie-Tooth Type 2B Disease

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Charcot-Marie-Tooth (CMT) type 2 neuropathies are a group of autosomal-dominant axonal disorders genetically and clinically heterogeneous. In particular, CMT type 2B (CMT2B) neuropathies are characterized by severe sensory loss, often complicated by infections, arthropathy, and amputations. Recently, four missense mutations in the small GTPase Rab7 associated with the Charcot-Marie Tooth type 2B phenotype have been identified. These mutations target highly conserved amino acid residues. However, nothing is known about whether and how these mutations affect Rab7 function. We investigated the biochemical and functional properties of three of the mutant proteins. Interestingly, all three proteins exhibited higher nucleotide exchange rates and hydrolyzed GTP slower than the wild-type protein. In addition, whereas 23% of overexpressed wild-type Rab7 was GTP bound in HeLa cells, the large majority of the mutant proteins (82–89%) were in the GTP-bound form, consistent with the data on GTP hydrolysis and exchange rates. The CMT2B-associated Rab7 proteins were also able to bind the Rab7 effector RILP (Rab-interacting lysosomal protein) and to rescue Rab7 function after silencing. Altogether, these data demonstrate that all tested CMT2B-associated Rab7 mutations are mechanistically similar, suggesting that activated forms of the Rab7 are responsible for CMT2B disease.

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Nuclear Factor- κ B Activation and Postischemic Inflammation Are Suppressed in CD36-Null Mice after Middle Cerebral Artery Occlusion

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CD36, a class-B scavenger receptor involved in multiple functions, including inflammatory signaling, may also contribute to ischemic brain injury through yet unidentified mechanisms. We investigated whether CD36 participates in the molecular events underlying the inflammatory reaction that accompanies cerebral ischemia and may contribute to the tissue damage. We found that activation of nuclear factor- κ B, a transcription factor that coordinates postischemic gene expression, is attenuated in CD36-null mice subjected to middle cerebral artery occlusion. The infiltration of neutrophils and the glial reaction induced by cerebral ischemia were suppressed. Treatment with an inhibitor of inducible nitric oxide synthase, an enzyme that contributes to the tissue damage, reduced ischemic brain injury in wild-type mice, but not in CD36 nulls. In contrast to cerebral ischemia, the molecular and cellular inflammatory changes induced by intracerebroventricular injection of interleukin-1 β were not attenuated in CD36-null mice. The findings unveil a novel role of CD36 in early molecular events leading to nuclear factor- κ B activation and postischemic inflammation. Inhibition of CD36 signaling may be a valuable therapeutic approach to counteract the deleterious effects of postischemic inflammation.

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Pathological Effect of Homeostatic Synaptic Scaling on Network Dynamics in Diseases of the Cortex

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Slow periodic EEG discharges are common in CNS disorders. The pathophysiology of this aberrant rhythmic activity is poorly understood. We used a computational model of a neocortical network with a dynamic homeostatic scaling rule to show that loss of input (partial deafferentation) can trigger network reorganization that results in pathological periodic discharges. The decrease in average firing rate in the network by deafferentation was compensated by homeostatic synaptic scaling of recurrent excitation among pyramidal cells. Synaptic scaling succeeded in recovering the network target firing rate for all degrees of deafferentation (fraction of deafferented cells), but there was a critical degree of deafferentation for pathological network reorganization. For deafferentation degrees below this value, homeostatic upregulation of recurrent excitation had minimal effect on the macroscopic network dynamics. For deafferentation above this threshold, however, a slow periodic oscillation appeared, patterns of activity were less sparse, and bursting occurred in individual neurons. Also, comparison of spike-triggered afferent and recurrent excitatory conductances revealed that information transmission was strongly impaired. These results suggest that homeostatic plasticity can lead to secondary functional impairment in case of cortical disorders associated with cell loss.

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Free Radical Production in CA1 Neurons Induces MIP-1 α Expression, Microglia Recruitment, and Delayed Neuronal Death after Transient Forebrain Ischemia

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Several studies report microglial accumulation and activation in the CA1 area in response to transient forebrain ischemia (TFI). Here we examine the possibility that free radicals and chemokines mediate the transient activation of microglia. Free radicals are produced primarily in CA1 pyramidal neurons within 2 h of TFI. Administration of trolox, a vitamin E analog, led to the inhibition of free radical production and recruitment of microglia in the CA1 area. In addition, intrahippocampal injection of Fe²⁺ triggered free radical production in CA1 neurons, followed by the recruitment and activation of microglial cells into this area. TFI-induced expression of macrophage inflammatory protein-1 α (MIP-1 α) was increased in CA1 neurons before microglial recruitment, and blocked by trolox. Moreover, the MIP-1 α level was upregulated in cultured hippocampal neurons exposed to Fe²⁺, suggesting an essential role of free radicals in TFI-induced expression of MIP-1 α . Intracerebroventricular injection of vMIP-2 (viral macrophage inflammatory protein-2), a broad-spectrum peptide antagonist of chemokine receptors, attenuated microglial recruitment and delayed CA1 neuronal degeneration after TFI. Our data suggest that free radicals produced in CA1 neurons contribute to the recruitment and activation of microglia and neurodegeneration through MIP-1 α expression.

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Necdin Plays a Role in the Serotonergic Modulation of the Mouse Respiratory Network: Implication for Prader-Willi Syndrome

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Prader-Willi syndrome is a neurogenetic disease resulting from the absence of paternal expression of several imprinted genes, including *NECDIN*. Prader-Willi children and adults have severe breathing defects with irregular rhythm, frequent sleep apneas, and blunted respiratory regulations. For the first time, we show that Prader-Willi infants have sleep apneas already present at birth. In parallel, in wild-type and *Necdin*-deficient mice, we studied the respiratory system with *in vivo* plethysmography, *in vitro* electrophysiology, and pharmacology. Because serotonin is known to contribute to CNS development and to affect maturation and function of the brainstem respiratory network, we also investigated the serotonergic system with HPLC, immunohistochemistry, Rabies virus tracing approaches, and primary culture experiments. We report first that *Necdin*-deficiency in mice induces central respiratory deficits reminiscent of Prader-Willi syndrome (irregular rhythm, frequent apneas, and blunted respiratory regulations), second that *Necdin* is expressed by medullary serotonergic neurons, and third that *Necdin* deficiency alters the serotonergic metabolism, the morphology of serotonin vesicles in medullary serotonergic neurons but not the number of these cells. We also show that *Necdin* deficiency in neonatal mice alters the serotonergic modulation of the respiratory rhythm generator. Thus, we propose that the lack of *Necdin* expression induces perinatal serotonergic alterations that affect the maturation and function of the respiratory network, inducing breathing deficits in mice and probably in Prader-Willi patients.

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