

This Week in The Journal

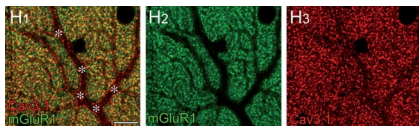
● Cellular/Molecular

A Functional Link Between T-type Channels and mGluR1

Michael E. Hildebrand, Philippe Isope, Taisuke Miyazaki, Toshitaka Nakaya, Esperanza Garcia, et al.

(see pages 9668–9682)

The activation of T-type voltage-dependent calcium channels permits calcium influx in cells, which, in the case of neurons, leads to excitation and neurotransmitter release. T-type channels are present in the dendritic spines of many types of neurons, including the Purkinje cells (PCs) of the cerebellum, which also express the metabotropic glutamate receptor-subtype 1 (mGluR1). This receptor plays a central role in inducing long-term potentiation at the synapses between parallel fibers and PC dendrites. Hildebrand et al. have therefore looked for a possible interaction between mGluR1 receptors and T-type channels. They found that the Cav3.1 T-type channel boosts calcium currents within rodent PC dendritic spines in response to trains of parallel fiber stimulations and that this activity is selectively modulated by mGluR1. The association between the two channels, the authors suggest, could confine the activation of T-type calcium channels to synaptically activated dendritic spines.



Double immunofluorescence with mGluR1 (green) showed an extensive overlap with Cav3.1 staining (red) in Purkinje cell dendritic spines but not in dendritic shafts (marked by asterisk). See article by Hildebrand et al. for details.

▲ Development/Plasticity/Repair

Serotonin Receptors Play a Role in Enteric Neurogenesis

Min-Tsai Liu, Yung-Hui Kuan, Jingwen Wang, René Hen, and Michael D. Gershon

(see pages 9683–9699)

Aging can have some unpleasant “side effects,” such as less frequent bowel movements. Neurons in the gut (enteric neurons), which are responsible for gastrointestinal motility and secretion, express many types of serotonin (5-hydroxytryptamine, 5-HT) receptor. Defects in these receptors have been linked to chronic constipation, a condition also associated with a decline in the number of enteric neurons. Enteric neuron stem cells are present in the postnatal murine bowel and could provide a source of new neurons later in life. To test this possibility, Liu et al. genetically engineered mice in which the 5-HT receptor isoform 5-HT4 was inactivated, or knocked out. Whereas in wild-type mice the number of enteric neurons increases through 4 months of age and declines thereafter, in the 5-HT4 knock-out mice the early increase does not occur and the later decline is more severe; moreover, drugs that activate 5-HT4 receptors stimulate the generation of new enteric neurons.

■ Behavioral/Systems/Cognitive

The Lateral Amygdala and the Memory of Fear

Jeong-Tae Kwon and June-Seek Choi

(see pages 9700–9703)

Simply hearing the repeating two-note musical theme from the 1970s thriller “Jaws” sends shivers up the spine. That’s because fearful experiences are not easily forgotten. To study how the memory of fear is established, researchers typically use a Pavlovian conditioning scheme. A neutral conditioned stimulus, such as a tone, is associated with an aversive unconditioned stimulus, such as a foot shock, until an animal learns to respond to the previously neutral stimulus with a defensive response, such as freezing. Evidence from many studies suggests that the lateral

amygdala (LA) is involved in the acquisition and storage of fear memory, but until now its role had not been directly demonstrated. Here, Kwon and Choi show that the conditioned stimulus can be replaced with electrical stimulation of the medial division of the medial geniculate nucleus of the thalamus, which projects directly to the LA. Pairing this stimulation in rats with foot shocks resulted in long-term potentiation in the LA and freezing responses.

◆ Neurobiology of Disease

Increased Synaptic Activity May Protect from Alzheimer’s Disease

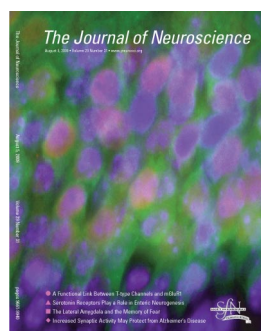
Davide Tampellini, Nawreen Rahman, Eduardo F. Gallo, Zhenyong Huang, Magali Dumont, et al.

(see pages 9704–9713)

Does increasing synaptic activity have positive or negative outcomes for people with Alzheimer’s disease (AD)? Tampellini et al. set out to address this question by looking at the effects of amyloid beta ($A\beta$)—the rogue peptide that accumulates in the neurons of AD patients—on synapses. Several studies have indicated that increased synaptic activity promotes the secretion of $A\beta$ to the extracellular space. Although both intracellular and extracellular $A\beta$ have been shown to have toxic effects, Tampellini et al. reveal that synaptic activity increases extracellular $A\beta$ and at the same time reduces intraneuronal $A\beta$, and that the overall effect is beneficial to the functioning of synapses. The increase in extracellular $A\beta$ occurs because synaptic activity promotes the anterograde transport of the amyloid precursor protein in dendrites to synapses, where it is cleaved to produce $A\beta$. On the other hand, the decrease in intraneuronal $A\beta$ is due to the action of the protease neprilysin.

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Cover legend: High-magnification image of the granule cell layer of the developing dentate gyrus showing expression of a novel late-phase transcriptional regulator of dentate granule neuron maturation, Krüppel-like factor-9 (Klf-9) and the mature neuronal marker calbindin. Klf-9 and calbindin are not expressed in immature neurons (blue) that reside in the inner half of the developing dentate gyrus. For more information, see the article by Scobie et al. in this issue (see pages 9875–9887).

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Cornering the Fear Engram: Long-Term Synaptic Changes in the Lateral Nucleus of the Amygdala after Fear Conditioning

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Use-dependent synaptic modifications in the lateral nucleus of the amygdala (LA) have been suggested to be the cellular analog of memory trace after pavlovian fear conditioning. However, whether neurophysiological changes in the LA are produced as a direct consequence of associative learning awaits additional proof. Using microstimulation of the medial geniculate nucleus of the thalamus as the conditioned stimulus (CS), we demonstrated that contingent pairings of the brain-stimulation CS and a footshock unconditioned stimulus lead to enhanced synaptic efficacy in the thalamic input to the LA, supporting the hypothesis that localized synaptic alterations underlie fear memory formation.

The Journal of Neuroscience, August 5, 2009 • 29(31):9700–9703

Do We Really Need Vision? How Blind People “See” the Actions of Others

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Observing and learning actions and behaviors from others, a mechanism crucial for survival and social interaction, engages the mirror neuron system. To determine whether vision is a necessary prerequisite for the human mirror system to develop and function, we used functional magnetic resonance imaging to compare brain activity in congenitally blind individuals during the auditory presentation of hand-executed actions or environmental sounds, and the motor pantomime of manipulation tasks, with that in sighted volunteers, who additionally performed a visual action recognition task. Congenitally blind individuals activated a premotor–temporoparietal cortical network in response to aurally presented actions that overlapped both with mirror system areas found in sighted subjects in response to visually and aurally presented stimuli, and with the brain response elicited by motor pantomime of the same actions. Furthermore, the mirror system cortex showed a significantly greater response to motor familiar than to unfamiliar action sounds in both sighted and blind individuals. Thus, the mirror system in humans can develop in the absence of sight. The results in blind individuals demonstrate that the sound of an action engages the mirror system for action schemas that have not been learned through the visual modality and that this activity is not mediated by visual imagery. These findings indicate that the mirror system is based on supramodal sensory representations of actions and, furthermore, that these abstract representations allow individuals with no visual experience to interact effectively with others.

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Boundary Vector Cells in the Subiculum of the Hippocampal Formation

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“Boundary vector cells” were predicted to exist by computational models of the environmental inputs underlying the spatial firing patterns of hippocampal place cells (O’Keefe and Burgess, 1996; Burgess et al., 2000; Hartley et al., 2000). Here, we report the existence of cells fulfilling this description in recordings from the subiculum of freely moving rats. These cells may contribute environmental information to place cell firing, complementing path integrative information. Their relationship to other cell types, including medial entorhinal “border cells,” is discussed.

The Journal of Neuroscience, August 5, 2009 • 29(31):9771–9777

Articles

CELLULAR/MOLECULAR

Functional Coupling between mGluR1 and Ca_v3.1 T-Type Calcium Channels Contributes to Parallel Fiber-Induced Fast Calcium Signaling within Purkinje Cell Dendritic Spines

Michael E. Hildebrand,^{1*} Philippe Isope,^{2*} Taisuke Miyazaki,⁶ Toshitaka Nakaya,⁶ Esperanza Garcia,¹ Anne Feltz,² Toni Schneider,⁵ Jürgen Hescheler,⁵ Masanobu Kano,³ Kenji Sakimura,⁴ Masahiko Watanabe,⁶ Stéphane Dieudonné,² and Terrance P. Snutch¹

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T-type voltage-gated calcium channels are expressed in the dendrites of many neurons, although their functional interactions with postsynaptic receptors and contributions to synaptic signaling are not well understood. We combine electrophysiological and ultrafast two-photon calcium imaging to demonstrate that mGluR1 activation potentiates cerebellar Purkinje cell Ca_v3.1 T-type currents via a G-protein- and tyrosine-phosphatase-dependent pathway. Immunohistochemical and electron microscopic investigations on wild-type and Ca_v3.1 gene knock-out animals show that Ca_v3.1 T-type channels are preferentially expressed in Purkinje cell dendritic spines and colocalize with mGluR1s. We further demonstrate that parallel fiber stimulation induces fast subthreshold calcium signaling in dendritic spines and that the synaptic Ca_v3.1-mediated calcium transients are potentiated by mGluR1 selectively during bursts of excitatory parallel fiber inputs. Our data identify a new fast calcium signaling pathway in Purkinje cell dendritic spines triggered by short burst of parallel fiber inputs and mediated by T-type calcium channels and mGluR1s.

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Ca Currents Activated by Spontaneous Firing and Synaptic Disinhibition in Neurons of the Cerebellar Nuclei

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In neurons of the cerebellar nuclei, long-term potentiation of EPSCs is induced by high-frequency synaptic excitation by mossy fibers followed by synaptic inhibition by Purkinje cells. Induction requires activation of synaptic receptors as well as voltage-gated Ca channels. To examine how Purkinje-mediated inhibition of nuclear neurons affects Ca levels during plasticity-inducing stimuli, we have combined electrophysiology, Ca imaging, and pharmacology of cerebellar nuclear neurons in mouse cerebellar slices. We find that spontaneous firing generates tonic Ca signals in both somata and dendrites, which drop during 500 ms, 100 Hz trains of Purkinje IPSPs or hyperpolarizing steps. Although the presence of low-voltage-activated (T-type) Ca channels in nuclear neurons has fostered the inference that disinhibition activates these channels, synaptic inhibition with a physiological chloride equilibrium potential (E_{Cl}) (–75 mV) fails to hyperpolarize neurons sufficiently for T-type channels to recover substantially. Consequently, after IPSPs, Ca signals return to baseline, although firing is accelerated by ~20 Hz for ~300 ms. Only after hyperpolarizations beyond E_{Cl} does Ca rise gradually beyond baseline, as firing further exceeds spontaneous rates. Cd²⁺ (100 μM), which nearly eliminates L-type, N-type, P/Q-type, and R-type Ca currents while sparing approximately one-half the T-type current, prevents Ca changes during and after hyperpolarizations to E_{Cl} . Thus, high-frequency IPSPs in cerebellar nuclear neurons evoke little postinhibitory current through T-type channels. Instead, inhibition regulates Ca levels simply by preventing action potentials, which usually permit Ca influx through high-voltage-activated channels. The decreases and restoration of Ca levels associated with Purkinje-mediated inhibition are likely to contribute to synaptic plasticity.

The Journal of Neuroscience, August 5, 2009 • 29(31):9826–9838

M1 Receptors Mediate Cholinergic Modulation of Excitability in Neocortical Pyramidal Neurons

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ACh release into the rodent prefrontal cortex is predictive of successful performance of cue detection tasks, yet the cellular mechanisms underlying cholinergic modulation of cortical function are not fully understood. Prolonged (“tonic”) muscarinic ACh receptor (mAChR) activation increases the excitability of cortical pyramidal neurons, whereas transient (“phasic”) mAChR activation generates inhibitory and/or excitatory responses, depending on neuron subtype. These cholinergic effects result from activation of “M1-like” mAChRs (M1, M3, and M5 receptors), but the specific receptor subtypes involved are not known. We recorded from cortical pyramidal neurons from wild-type mice and mice lacking M1, M3, and/or M5 receptors to determine the relative contribution of M1-like mAChRs to cholinergic signaling in the mouse prefrontal cortex. Wild-type neurons in layer 5 were excited by tonic mAChR stimulation, and had biphasic inhibitory followed by excitatory, responses to phasic ACh application. Pyramidal neurons in layer 2/3 were substantially less responsive to tonic and phasic cholinergic input. Cholinergic effects were largely absent in neurons from mice lacking M1 receptors, but most were robust in neurons lacking M3, M5, or both M3 and M5 receptors. The exception was tonic cholinergic suppression of the afterhyperpolarization

in layer 5 neurons, which was absent in cells lacking either M1 or M3 receptors. Finally, we confirm a role for M1 receptors in behavior by demonstrating cue detection deficits in M1-lacking mice. Together, our results demonstrate that M1 receptors facilitate cue detection behaviors and are both necessary and sufficient for most direct effects of ACh on pyramidal neuron excitability.

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Early Development of the Thalamic Inhibitory Feedback Loop in the Primary Somatosensory System of the Newborn Mice

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Spontaneous neuronal activity plays an important role during the final development of the brain circuits and the formation of the primary sensory maps. In young rats, spindle bursts have been recorded in the primary somatosensory cortex. They are correlated with spontaneous muscle twitches and occur before active whisking. They bear similarities with the spindles recorded in adult brain that occur during early stages of sleep and rely on a thalamic feedback loop between the glutamatergic nucleus ventroposterior medialis (nVPM) and the GABAergic nucleus reticularis thalami (nRT). However, whether a functional nVPM–nRT loop exists in newborn rodents is unknown. We studied the reciprocal synaptic connections between nVPM and nRT in thalamic acute slices from mice from birth [postnatal day 0 (P0)] until P9. We first demonstrated that nVPM-to-nRT EPSCs could be distinguished from corticothalamic EPSCs by their inhibition by 5-HT attributable to the transient expression of functional presynaptic serotonin 1B receptors. The nVPM-to-nRT EPSCs and nRT-to-nVPM IPSCs were both detected the first day after birth; their amplitude near 2 nS was relatively stable until P5. At P6–P7, there was a rapid and simultaneous increase of both nVPM-to-nRT EPSCs and nRT-to-nVPM IPSCs that reached 8 and 9 nS, respectively. Our results show that the thalamic synapses implicated in spindle activity are functional shortly after birth, suggesting that they could already generate spindles during the first postnatal week. Our results also suggest an inhibitory action of 5-HT on the spindle bursts of the newborn mice.

The Journal of Neuroscience, August 5, 2009 • 29(31):9930–9940

DEVELOPMENT/PLASTICITY/REPAIR

5-HT₄ Receptor-Mediated Neuroprotection and Neurogenesis in the Enteric Nervous System of Adult Mice

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Although the mature enteric nervous system (ENS) has been shown to retain stem cells, enteric neurogenesis has not previously been demonstrated in adults. The relative number of enteric neurons in wild-type (WT) mice and those lacking 5-HT₄ receptors [knock-out (KO)] was found to be similar at birth; however, the abundance of ENS neurons increased during the first 4 months after birth in WT but not KO littermates. Enteric neurons subsequently decreased in both WT and KO but at 12 months were significantly more numerous in WT. We tested the hypothesis that stimulation of the 5-HT₄ receptor promotes enteric neuron survival and/or neurogenesis. *In vitro*, 5-HT₄ agonists increased enteric neuronal development/survival, decreased apoptosis, and activated CREB (cAMP response element-binding protein). *In vivo*, in WT but not KO mice, 5-HT₄ agonists induced bromodeoxyuridine incorporation into cells that expressed markers of neurons (HuC/D, doublecortin), neural precursors (Sox10, nestin, Phox2b), or stem cells (Musashi-1). This is the first demonstration of adult enteric neurogenesis; our results suggest that 5-HT₄ receptors are required postnatally for ENS growth and maintenance.

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Estrogen Induces Caspase-Dependent Cell Death during Hypothalamic Development

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The sexually dimorphic population of dopamine neurons in the anteroventral periventricular nucleus of the preoptic region of the hypothalamus (AVPV) develops postnatally under the influence of testosterone, which is aromatized to estrogen. There are fewer dopaminergic neurons labeled with tyrosine hydroxylase (TH) in the male AVPV than the female, and sex steroids determine this sex difference, yet the role of cell death in specifying numbers of dopaminergic neurons in the AVPV is unknown. Estradiol treatment of the AVPV, *in vivo* and *in vitro*, was used to manipulate TH-ir cell number. *In vitro*, concurrent treatment with the estrogen receptor antagonist ICI 162,780 rescued TH-ir cells. Cyclosporin A, an inhibitor of cell death dependent on the opening of a mitochondrial permeability transition pore also blocked TH-ir cell loss. *In vivo*, estradiol increased the number of apoptotic profiles, both TUNEL and Hoechst labeled nuclei, in the AVPV. This increased apoptosis was also dependent on the presence of the α form of the estrogen receptor. To test for caspase dependent TH-ir cell loss, the pancaspase inhibitor ZVAD (*N*-benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone) was used to rescue TH-ir cells from estradiol-mediated reduction in number. Together, these data suggest that an intrinsic cell death pathway is

activated by estrogen to regulate TH-ir cell number. Thus, in contrast to the more widespread neuroprotective actions of sex steroids in the mammalian nervous system, in the AVPV estrogen regulates dopaminergic neuron number through a caspase-dependent mechanism of apoptotic cell death.
The Journal of Neuroscience, August 5, 2009 • 29(31):9714–9718

Stability of Electrical Coupling despite Massive Developmental Changes of Intrinsic Neuronal Physiology

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Gap junctions mediate metabolic and electrical interactions between some cells of the CNS. For many types of neurons, gap junction-mediated electrical coupling is most prevalent during early development, then decreases sharply with maturation. However, neurons in the thalamic reticular nucleus (TRN), which exert powerful inhibitory control over thalamic relay cells, are electrically coupled in relatively mature animals. It is not known whether TRN cells or any neurons that are electrically coupled when mature are also coupled during early development. We used dual whole-cell recordings in mouse brain slices to study the postnatal development of electrical and chemical synapses that interconnect TRN neurons. Inhibitory chemical synapses were seen as early as postnatal day 4 but were infrequent at all ages, whereas TRN cells were extensively connected by electrical synapses from birth onward. Surprisingly, the functional strength of electrical coupling, assayed under steady-state conditions or during spiking, remained relatively constant as the brain matured despite dramatic concurrent changes of intrinsic membrane properties. Most notably, neuronal input resistances declined almost eightfold during the first two postnatal weeks, but there were offsetting increases in gap junctional conductances. This suggests that the size or number of gap junctions increase homeostatically to compensate for leakier nonjunctional membranes. Additionally, we found that the ability of electrical synapses to synchronize high frequency subthreshold signals improved as TRN cells matured. Our results demonstrate that certain central neurons may maintain or even increase their gap junctional communication as they mature.

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Requirement for Protein Synthesis at Developing Synapses

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Activity and protein synthesis act cooperatively to generate persistent changes in synaptic responses. This forms the basis for enduring memory in adults. Activity also shapes neural circuits developmentally, but whether protein synthesis plays a congruent function in this process is poorly understood. Here, we show that brief periods of global or local protein synthesis inhibition decrease the synaptic vesicles available for fusion and increase synapse elimination. Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) is a critical target; its levels are controlled by rapid turnover, and blocking its activity or knocking it down recapitulates the effects of protein synthesis inhibition. Mature presynaptic terminals show decreased sensitivity to protein synthesis inhibition, and resistance coincides with a developmental switch in regulation from CaMKII to PKA (protein kinase A). These findings demonstrate a novel mechanism regulating presynaptic activity and synapse elimination during development, and suggest that protein translation acts coordinately with activity to selectively stabilize appropriate synaptic interactions.

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Transient Receptor Potential Canonical 5 Channels Activate Ca^{2+} /Calmodulin Kinase I γ to Promote Axon Formation in Hippocampal Neurons

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Functionality of neurons is dependent on their compartmentalized polarization of dendrites and an axon. The rapid and selective outgrowth of one neurite, relative to the others, to form the axon is critical in initiating neuronal polarity. Axonogenesis is regulated in part by an optimal intracellular calcium concentration. Our investigation of Ca^{2+} -signaling pathways involved in axon formation using cultured hippocampal neurons demonstrates a role for Ca^{2+} /calmodulin kinase kinase (CaMKK) and its downstream target Ca^{2+} /calmodulin kinase I (CaMKI). Expression of constitutively active CaMKI induced formation of multiple axons, whereas blocking CaMKK or CaMKI activity with pharmacological, dominant-negative, or short hairpin RNA (shRNA) methods significantly inhibited axon formation. CaMKK signals via the γ -isoform of CaMKI as shRNA to CaMKI γ , but not the other CaMKI isoforms, inhibited axon formation. Furthermore, overexpression of wild-type CaMKI γ , but not a mutant incapable of membrane association, accelerated the rate of axon formation. Pharmacological or small interfering RNA inhibition of transient receptor potential canonical 5 (TRPC5) channels, which are present in developing axonal growth cones, suppressed CaMKK-mediated activation of CaMKI γ as well as axon formation. We demonstrate using biochemical fractionation and immunocytochemistry that CaMKI γ and TRPC5 colocalize to lipid rafts. These results are consistent with a model in which highly localized calcium influx through the TRPC5 channels activates CaMKK and CaMKI γ , which subsequently promote axon formation.

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Krüppel-Like Factor 9 Is Necessary for Late-Phase Neuronal Maturation in the Developing Dentate Gyrus and during Adult Hippocampal Neurogenesis

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The dentate gyrus (DG) is modified throughout life by integration of new adult-born neurons. Similarities in neuronal maturation during DG development and adult hippocampal neurogenesis suggest that genetically encoded intrinsic regulatory mechanisms underlying these temporally distinct processes are conserved and reused. Here, we identify a novel transcriptional regulator of dentate granule neuron maturation, Krüppel-like factor 9 (*Klf-9*). We show that *Klf-9* expression is induced by neuronal activity and as dentate granule neurons functionally integrate in the developing and adult DG. During development, dentate granule neurons lacking *Klf-9* show delayed maturation as reflected by altered expression of early-phase markers, dendritic spine formation, and electrophysiological properties. Adult *Klf-9*-null mice exhibit normal stem cell proliferation and cell fate specification in the DG but show impaired differentiation of adult-born neurons and decreased neurogenesis-dependent synaptic plasticity. Behavioral analysis of *Klf-9*-null mice revealed a subtle increase in anxiety-like behavior and an impairment in contextual fear discrimination learning. Thus, *Klf-9* is necessary for late-phase maturation of dentate granule neurons both in DG development and during adult hippocampal neurogenesis. *Klf-9*-dependent neuronal maturation may therefore represent a candidate regulatory mechanism underlying these temporally distinct processes.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Spectrotemporal Response Properties of Inferior Colliculus Neurons in Alert Monkey

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Because of its central position in the ascending auditory pathway, its large number of converging auditory brainstem inputs, and its fundamental role as a relay to auditory cortex and midbrain superior colliculus, the mammalian inferior colliculus (IC) is regarded pivotal for the integration of acoustic spectral–temporal cues to mediate sound-evoked behavior. However, detailed quantitative analyses of spectrotemporal neural responses are scarce. Moreover, most studies have been performed in anesthetized preparations, and it is unclear how to extrapolate findings to awake and behaving animals. Here, we characterize spectrotemporal receptive fields (STRFs) of single units in alert monkey IC by using a variety of broadband sounds with rippled amplitude spectra. We measured the response sensitivity to the ripple parameters density, Ω (cycles/octave), velocity, w (hertz), and direction selectivity, D . We observed a variety of dynamic STRFs, with a strong preference for low ripple densities, and a generally weak direction selectivity. Most cells preferred dynamic rippled stimuli above pure amplitude modulated noise (i.e., $\Omega = 0$). Half of the cells could be characterized by good spectral–temporal separability, in which the ripple transfer function can be written as $T(w, \Omega) = F(w) \times G(\Omega)$. Inseparability could be attributed to a difference in responses to up and downward direction with respect to both amplitude and temporal phase. We tested linearity of IC neurons by using the STRF to predict neural responses to natural stimuli and broadband noise and discuss our results in the light of findings obtained from auditory cortex.

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GABAergic Transmission to Gonadotropin-Releasing Hormone (GnRH) Neurons Is Regulated by GnRH in a Concentration-Dependent Manner Engaging Multiple Signaling Pathways

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Gonadotropin-releasing hormone (GnRH) neurons are the central regulators of fertility. GnRH stimulates or inhibits GnRH neuronal activity depending on dose. The mechanisms for these actions remain unknown. We hypothesized GnRH acts in part by altering fast synaptic transmission to GnRH neurons. GABAergic and glutamatergic postsynaptic currents (PSCs), both of which can excite these neurons, were recorded from GnRH neurons in brain slices from adult intact and orchidectomized (ORX) males. ORX enhanced the frequency of GABA transmission to GnRH neurons, but had no effect on glutamatergic transmission. Effects of ORX on GABAergic transmission were reversed by estradiol replacement, suggesting GABA is a mediator of steroid feedback in males. GABAergic neurons express type-1 GnRH receptor (GnRHR-1). Low GnRH (20 nM) reduced GABAergic PSC frequency in GnRH neurons from both ORX and intact mice. High GnRH (2 μ M) had no effect on either GABAergic or glutamatergic transmission to GnRH neurons. To investigate mechanisms mediating low-dose GnRH suppression of GABAergic transmission, GABAergic PSCs were recorded after arresting $G_{\alpha i}$ activity with pertussis toxin (PTX). PTX abolished the suppressive effect of low GnRH. Moreover, PTX uncovered a stimulatory effect of high GnRH on GABAergic transmission. These data suggest low-dose GnRH suppresses GnRH firing rate in part by decreasing GABAergic transmission to the GnRH neurons, independent of gonadal hormone milieu. Low-dose GnRH appears to exert the suppressive effect by activating GnRHR-I coupled to $G_{\alpha i}$. The concentration-dependent effects of GnRH may be mediated in part by changes in affinity of GnRH to GnRHR-I coupled to different G_{α} proteins.

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Motor Representations of Articulators Contribute to Categorical Perception of Speech Sounds

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Listening to speech modulates activity in human motor cortex. It is unclear, however, whether the motor cortex has an essential role in speech perception. Here, we aimed to determine whether the motor representations of articulators contribute to categorical perception of speech sounds. Categorization of continuously variable acoustic signals into discrete phonemes is a fundamental feature of speech communication. We used repetitive transcranial magnetic stimulation (rTMS) to temporarily disrupt the lip representation in the left primary motor cortex. This disruption impaired categorical perception of artificial acoustic continua ranging between two speech sounds that differed in place of articulation, in that the vocal tract is opened and closed rapidly either with the lips or the tip of the tongue (/ba/-/da/ and /pa/-/ta/). In contrast, it did not impair categorical perception of continua ranging between speech sounds that do not involve the lips in their articulation (/ka/-/ga/ and /da/-/ga/). Furthermore, an rTMS-induced disruption of the hand representation had no effect on categorical perception of either of the tested continua (/ba/-/da/ and /ka/-/ga/). These findings indicate that motor circuits controlling production of speech sounds also contribute to their perception. Mapping acoustically highly variable speech sounds onto less variable motor representations may facilitate their phonemic categorization and be important for robust speech perception.

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Cortical Inhibition during Burst Suppression Induced with Isoflurane Anesthesia

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Isoflurane is a widely used anesthetic which safely and reversibly induces deep coma and associated burst suppression (BS) electroencephalographic patterns. Here we investigate possible underlying causes for the state of cortical hyperexcitability which was recently shown to be one of the characteristics of BS. Our hypothesis was that cortical inhibition is diminished during isoflurane-induced BS. Experiments were performed *in vivo* using intracellular recordings of cortical neurons to assess their responsiveness to stimulations of connected thalamic nuclei. We demonstrate that during BS EPSPs were diminished by 44%, whereas inhibitory potentials were completely suppressed. This finding was supported by additional results indicating that a decrease in neuronal input resistance normally found during inhibitory responses under low isoflurane conditions was abolished in the BS condition. Moreover, removal of inhibition occasionally revealed excitatory components which were absent during recordings before the induction of BS. We also show that the absence of inhibition during BS is not caused by a blockage of GABA receptors, since iontophoretically applied GABA shows receptor availability. Moreover, the concentration of extracellular chloride was increased during BS, as would be expected after reduced flow of chloride through GABA_A receptors. Also inhibitory responses were reinstated by selective blockage of glial glutamate transporters with dihydrokainate. These results suggest that the lack of inhibition during BS is caused by reduced excitation, probably resulting from increased glial uptake of glutamate stimulated by isoflurane, which creates a diminished activation of cortical interneurons. Thus cortical hyperexcitability during BS is favored by suppressed inhibition.

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Validation of Decision-Making Models and Analysis of Decision Variables in the Rat Basal Ganglia

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Reinforcement learning theory plays a key role in understanding the behavioral and neural mechanisms of choice behavior in animals and humans. Especially, intermediate variables of learning models estimated from behavioral data, such as the expectation of reward for each candidate choice (action value), have been used in searches for the neural correlates of computational elements in learning and decision making. The aims of the present study are as follows: (1) to test which computational model best captures the choice learning process in animals and (2) to elucidate how action values are represented in different parts of the corticobasal ganglia circuit. We compared different behavioral learning algorithms to predict the choice sequences generated by rats during a free-choice task and analyzed associated neural activity in the nucleus accumbens (NAc) and ventral pallidum (VP). The major findings of this study were as follows: (1) modified versions of an action-value learning model captured a variety of choice strategies of rats, including win-stay-lose-switch and persevering behavior, and predicted rats' choice sequences better than the best multistep Markov model; and (2) information about action values and future actions was coded in both the NAc and VP, but was less dominant than information about trial types, selected actions, and reward outcome. The results of our model-based analysis suggest that the primary role of the NAc and VP is to monitor information important for updating choice behaviors. Information represented in the NAc and VP might contribute to a choice mechanism that is situated elsewhere.

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Robust Conjunctive Item–Place Coding by Hippocampal Neurons Parallels Learning What Happens Where

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Previous research indicates a critical role of the hippocampus in memory for events in the context in which they occur. However, studies to date have not provided compelling evidence that hippocampal neurons encode event–context conjunctions directly associated with this kind of learning. Here we report that, as animals learn different meanings for items in distinct contexts, individual hippocampal neurons develop responses to specific stimuli in the places where they have differential significance. Furthermore, this conjunctive coding evolves in the form of enhanced item-specific responses within a subset of the preexisting spatial representation. These findings support the view that conjunctive representations in the hippocampus underlie the acquisition of context-specific memories.

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NEUROBIOLOGY OF DISEASE

Synaptic Activity Reduces Intraneuronal A β , Promotes APP Transport to Synapses, and Protects against A β -Related Synaptic Alterations

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A central question in Alzheimer’s disease research is what role synaptic activity plays in the disease process. Synaptic activity has been shown to induce β -amyloid peptide release into the extracellular space, and extracellular β -amyloid has been shown to be toxic to synapses. We now provide evidence that the well established synaptotoxicity of extracellular β -amyloid requires γ -secretase processing of amyloid precursor protein. Recent evidence supports an important role for intraneuronal β -amyloid in the pathogenesis of Alzheimer’s disease. We show that synaptic activity reduces intraneuronal β -amyloid and protects against β -amyloid-related synaptic alterations. We demonstrate that synaptic activity promotes the transport of the amyloid precursor protein to synapses using live cell imaging, and that the protease neprilysin is involved in reduction of intraneuronal β -amyloid with synaptic activity.

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Cerebellothalamocortical Connectivity Regulates Penetrance in Dystonia

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Dystonia is a brain disorder characterized by sustained involuntary muscle contractions. It is typically inherited as an autosomal dominant trait with incomplete penetrance. While lacking clear degenerative neuropathology, primary dystonia is thought to involve microstructural and functional changes in neuronal circuitry. In the current study, we used magnetic resonance diffusion tensor imaging and probabilistic tractography to identify the specific circuit abnormalities that underlie clinical penetrance in carriers of genetic mutations for this disorder. This approach revealed reduced integrity of cerebellothalamocortical fiber tracts, likely developmental in origin, in both manifesting and clinically nonmanifesting dystonia mutation carriers. In these subjects, reductions in cerebellothalamic connectivity correlated with increased motor activation responses, consistent with loss of inhibition at the cortical level. Nonmanifesting mutation carriers were distinguished by an additional area of fiber tract disruption situated distally along the thalamocortical segment of the pathway, in tandem with the proximal cerebellar outflow abnormality. In individual gene carriers, clinical penetrance was determined by the difference in connectivity measured at these two sites. Overall, these findings point to a novel mechanism to explain differences in clinical expression in carriers of genes for brain disease.

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Essential and Synergistic Roles of RP1 and RP1L1 in Rod Photoreceptor Axoneme and Retinitis Pigmentosa

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Retinitis pigmentosa 1 (RP1) is a common inherited retinopathy with variable onset and severity. The *RP1* gene encodes a photoreceptor-specific, microtubule-associated ciliary protein containing the doublecortin (DCX) domain. Here we show that another photoreceptor-specific Rp1-like protein (Rp1L1) in mice is also localized to the axoneme of outer segments (OSs) and connecting cilia in rod photoreceptors, overlapping with Rp1. *Rp1L1*^{-/-} mice display scattered OS disorganization, reduced electroretinogram amplitudes, and progressive photoreceptor degeneration, less severe and slower than in *Rp1*^{-/-} mice. In single rods of *Rp1L1*^{-/-}, photosensitivity is reduced, similar to that of *Rp1*^{-/-}. While individual heterozygotes are normal, double heterozygotes of *Rp1* and *Rp1L1* exhibit abnormal OS morphology and reduced single rod photosensitivity and dark currents. The electroretinogram amplitudes of double heterozygotes are more reduced than those of individual heterozygotes combined. In support, Rp1L1 interacts with Rp1 in transfected cells and in retina pull-down experiments. Interestingly, phototransduction kinetics are normal in single rods and whole retinas of individual or double *Rp1* and *Rp1L1* mutant mice. Together, Rp1 and Rp1L1 play essential and synergistic roles in affecting photosensitivity and OS morphogenesis of rod photoreceptors. Our findings suggest that mutations in *RP1L1* could underlie retinopathy or modify RP1 disease expression in humans.

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Systemic Lipopolysaccharide Protects the Brain from Ischemic Injury by Reprogramming the Response of the Brain to Stroke: A Critical Role for IRF3

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Lipopolysaccharide (LPS) preconditioning provides neuroprotection against subsequent cerebral ischemic injury through activation of its receptor, Toll-like receptor 4 (TLR4). Paradoxically, TLR activation by endogenous ligands after ischemia worsens stroke damage. Here, we define a novel, protective role for TLRs after ischemia in the context of LPS preconditioning. Microarray analysis of brains collected 24 h after stroke revealed a unique set of upregulated genes in LPS-pretreated animals. Promoter analysis of the unique gene set identified an overrepresentation of type I interferon (IFN)-associated transcriptional regulatory elements. This finding suggested the presence of type I IFNs or interferon regulatory factors (IRFs), which upregulate interferon-stimulated genes. Upregulation of IFN β was confirmed by real-time reverse transcription-PCR. Direct administration of IFN β intracerebroventricularly at the time of stroke was sufficient for neuroprotection. TLR4 can induce both IFN β and interferon-stimulated genes through its adapter molecule Toll/interleukin receptor domain-containing adaptor-inducing IFN β (TRIF) and the IRF3 transcription factor. We show in oxygen glucose deprivation of cortical neurons, an *in vitro* model of stroke, that activation of TRIF after stroke reduces neuronal death. Furthermore, mice lacking IRF3 were not protected by LPS preconditioning in our *in vivo* model. Our studies constitute the first demonstration of the neuroprotective capacity of TRIF/IRF3 signaling and suggest that interferon-stimulated genes, whether induced by IFN β or by enhanced TLR signaling to IRF3, are a potent means of protecting the brain against ischemic damage.

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A Switch in Retrograde Signaling from Survival to Stress in Rapid-Onset Neurodegeneration

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Retrograde axonal transport of cellular signals driven by dynein is vital for neuronal survival. Mouse models with defects in the retrograde transport machinery, including the *Loa* mouse (point mutation in dynein) and the *Tg*^{dynamitin} mouse (overexpression of dynamitin), exhibit mild neurodegenerative disease. Transport defects have also been observed in more rapidly progressive neurodegeneration, such as that observed in the *SOD1*^{G93A} transgenic mouse model for familial amyotrophic lateral sclerosis (ALS). Here, we test the hypothesis that alterations in retrograde signaling lead to neurodegeneration. *In vivo*, *in vitro*, and live-cell imaging motility assays show misregulation of transport and inhibition of retrograde signaling in the *SOD1*^{G93A} model. However, similar inhibition is also seen in the *Loa* and *Tg*^{dynamitin} mouse models. Thus, slowing of retrograde signaling leads only to mild degeneration and cannot explain ALS etiology. To further pursue this question, we used a proteomics approach to investigate dynein-associated retrograde signaling. These data indicate a significant decrease in retrograde survival factors, including P-Trk (phospho-Trk) and P-Erk1/2, and an increase in retrograde stress factor signaling, including P-JNK (phosphorylated c-Jun N-terminal kinase), caspase-8, and p75^{NTR} cleavage fragment in the *SOD1*^{G93A} model; similar changes are not seen in the *Loa* mouse. Cocultures of motor neurons and glia expressing mutant *SOD1* (mSOD1) in compartmentalized chambers indicate that inhibition of retrograde stress signaling is sufficient to block activation of cellular stress pathways and to rescue motor neurons from mSOD1-induced toxicity. Hence, a shift from survival-promoting to death-promoting retrograde signaling may be key to the rapid onset of neurodegeneration seen in ALS.

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