

This Week in The Journal

● Cellular/Molecular

An Anti-Apoptotic Action of Glia Lipoproteins

Hideki Hayashi, Robert B. Campenot, Dennis E. Vance, and Jean E. Vance

(see pages 1933–1941)

Apolipoprotein E (apoE), an apolipoprotein contained in lipoproteins secreted by CNS glia, is perhaps best known because its $\epsilon 4$ allele is a risk factor for late-onset Alzheimer's disease. This week, Hayashi et al. outline a signaling pathway by which these apoE-containing lipoproteins can inhibit apoptosis. The authors induced apoptosis in cultured rat retinal ganglion cells by removing trophic factors from the media. Glia-conditioned media or glia-secreted lipoproteins protected neurons from apoptosis. Protection specifically required apoE and was blocked either by receptor-associate protein, which competes with ligands of low-density lipoprotein receptors (LDLrs), or by inhibition of the apoE receptor LDLr-related protein (LRP). Downstream of LRP, signaling involved protein kinase C δ , possibly by phosphorylating and inactivating the proapoptotic glycogen synthase kinase-3 β . ApoE3 was more effective in preventing apoptosis than apoE4.

▲ Development/Plasticity/Repair

Myelination and Remyelination in the Pregnant Mouse

Christopher Gregg, Viktor Shikar, Peter Larsen, Gloria Mak, Andrew Chojnacki, V. Wee Yong, and Samuel Weiss

(see pages 1812–1823)

This week, Gregg et al. report that pregnancy in rats increased myelin-forming oligodendrocytes and myelin formation, an effect the authors attribute to prolactin. In corpus callosum and spinal cord, oligodendrocyte precursor cells (OPCs) increased in early pregnancy, followed by an increase in oligodendrocytes. Postpartum, pregnancy-generated oligodendrocytes extended processes. There was also an associated increase in myelination of callosal axons. To test the effects of pregnancy

on the repair of demyelinating lesions, the authors injected lysolecithin into the spinal cord. Pregnant rats displayed smaller lesions, fewer demyelinated axons, and more remyelinated axons. The prolactin (PRL) receptor, expressed by OPCs, was required for pregnancy-induced OPC proliferation. Furthermore, exogenous PRL administered to virgin rats increased OPC generation and remyelination similar to pregnant rats. The authors suggest that such changes might affect axon function and/or remyelination in situations such as multiple sclerosis.

■ Behavioral/Systems/Cognitive

Multisensory Modulation of Auditory Processing

Christopher Kayser, Christopher I. Petkov, Mark Augath, and Nikos K. Logothetis

(see pages 1824–1835)

Putting it all together when it comes to combining information from our senses is usually attributed to “higher” centers in

association cortex, yet recent studies suggest that multisensory integration can also occur in primary sensory cortex. This week, Kayser et al. used functional magnetic resonance imaging in macaques to examine visual modulation of auditory receptive fields. The authors used sounds of various frequency and bandwidth to stimulate “core” (primary auditory) and “belt” (nonprimary auditory) fields. In anesthetized animals, most fields were activated only by auditory stimuli, but some areas responded just to visual stimuli. Combined auditory and visual stimuli produced enhanced responses particularly in caudal fields. In awake animals, too, visual and auditory stimuli activated overlapping fields including those in the core. Visual activation and audiovisual enhancement also occurred in the caudal parts of the so-called parabelt. Characteristic of sensory integration, enhancement was stronger for less effective stimuli.

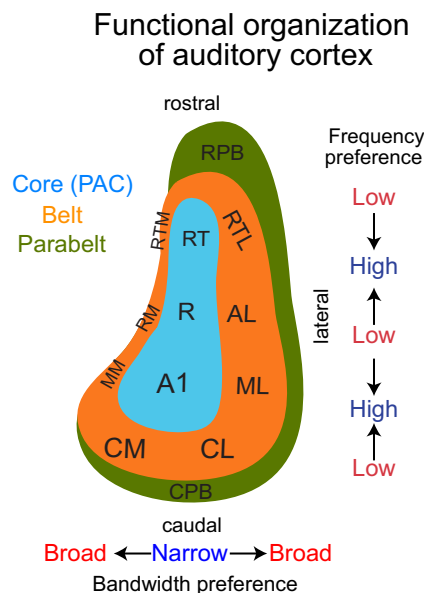
◆ Neurobiology of Disease

Reelin and the Hippocampus, after Status Epilepticus

Chao Gong, Tsu-Wei Wang, Holly S. Huang, and Jack M. Parent

(see pages 1803–1811)

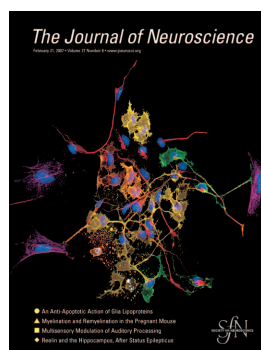
Temporal lobe epilepsy in humans is associated with abnormal lamination of the dentate gyrus and ectopic hilar location of some dentate granule cells (DGCs). Similar changes are seen in rodent models of hippocampal epilepsy. This week, Gong et al. provide evidence that this abnormal distribution of DGCs results from deficient signaling by the secreted guidance factor Reelin. Reelin immunoreactivity in the dentate gyrus was reduced after pilocarpine-induced status epilepticus in adult rats. The authors ascribed this loss to the death of Reelin-expressing inhibitory interneurons, a principal source of Reelin in the adult. In mouse dentate gyrus explants cultured in a gel matrix, progenitor cells migrated in chains. Exogenous Reelin caused cell detachment and disruption of the migratory chains, consistent with a direct effect of Reelin on the migration of DGC progenitors.



The functional organization of the auditory cortex is shown in this schematic with the core, belt, and parabelt regions (blue, orange, and green, respectively). The differential preferences for sound frequency and bandwidth were used to obtain a functional parcellation of auditory fields. See the article by Kayser et al. for details.

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Cover legend: A representative example of the multiphenotype progeny derived from *in vitro* clonal expansion of a single multipotential neural stem cell isolated from embryonic rat telencephalon. The cells were fluorescently labeled using lineage-selective markers including cholera toxin B subunit (green), anti-9-O-acetylated GD3 (orange), anti-vimentin (red), and anti-GFAP (pink), and the cell nuclei were counterstained using DAPI (blue). The progeny include vimentin⁺ neural stem cells and radial glia, GFAP⁺ astrocytes, cholera toxin⁺ neurons, and 9-O-acetylated GD3⁺ neuroglial neuronal progenitors. For more information, see the article by Maric et al. in this issue (pages 1836–1852).

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GABAergic Neurons Are Less Selective to Stimulus Orientation than Excitatory Neurons in Layer II/III of Visual Cortex, as Revealed by *In Vivo* Functional Ca^{2+} Imaging in Transgenic Mice

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Most neurons in the visual cortex are selectively responsive to visual stimulation of a narrow range of orientations, and GABAergic neurons are considered to play a role in the formation of such orientation selectivity. This suggests that response properties of GABAergic neurons may be different from those of excitatory neurons. This view remains unproved, however. To address this issue, we applied *in vivo* two-photon functional Ca^{2+} imaging to transgenic mice, in which GABAergic neurons express enhanced green fluorescent protein. Astroglia were stained by an astrocyte-specific dye. The three types of cells, GABAergic neurons, excitatory neurons, and astrocytes, in layer II/III of the visual cortex were differentially identified by using different wavelengths of excitation light and a dichroic mirror for emitted fluorescence, and their responses to moving visual stimuli at different orientations were measured with changes in the intensity of fluorescence of a Ca^{2+} -sensitive dye. We found that almost all GABAergic neurons have orientation-insensitive responses, whereas most of excitatory neurons have orientation-selective responses.

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Articles

CELLULAR/MOLECULAR

M-Channels (Kv7/KCNQ Channels) That Regulate Synaptic Integration, Excitability, and Spike Pattern of CA1 Pyramidal Cells Are Located in the Perisomatic Region

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To understand how electrical signal processing in cortical pyramidal neurons is executed by ion channels, it is essential to know their subcellular distribution. M-channels (encoded by Kv7.2–Kv7.5/KCNQ2–KCNQ5 genes) have multiple important functions in neurons, including control of excitability, spike afterpotentials, adaptation, and theta resonance. Nevertheless, the subcellular distribution of these channels has remained elusive. To determine the M-channel distribution within CA1 pyramidal neurons, we combined whole-cell patch-clamp recording from the soma and apical dendrite with focal drug application, in rat hippocampal slices. Both a M-channel opener (retigabine [*N*-(2-amino-4-(4-fluorobenzylamino)-phenyl) carbamic acid ethyl ester]) and a blocker (XE991 [10,10-bis(4-pyridinylmethyl)-9(10*H*)-anthracenone]) changed the somatic subthreshold voltage response but had no observable effect on local dendritic responses. Under conditions promoting dendritic Ca^{2+} spikes, local somatic but not dendritic application of M-channel blockers (linopirdine and XE991) enhanced the Ca^{2+} spikes. Simultaneous dendritic and somatic whole-cell recordings showed that the medium afterhyperpolarization after a burst of spikes underwent strong attenuation along the apical dendrite and was fully blocked by somatic XE991 application. Finally, by combining patch-clamp and extracellular recordings with computer simulations, we found that perisomatic M-channels reduce the summation of EPSPs. We conclude that functional M-channels appear to be concentrated in the perisomatic region of CA1 pyramidal neurons, with no detectable M-channel activity in the distal apical dendrites.

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Dopamine Gates Action Potential Backpropagation in Midbrain Dopaminergic Neurons

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Dopamine is released from both axonal and somatodendritic sites of midbrain dopaminergic neurons in an action potential-dependent manner. In contrast to the majority of central neurons, the axon of dopaminergic neurons typically originates from a dendritic site, suggesting a specialized computational function. Here, we examine the initiation and spread of action potentials in dopaminergic neurons of the substantia nigra pars reticulata and reveal that the displacement of the axon to a dendritic site allows highly compartmentalized electrical signaling. In response to a train of synaptic input, action potentials initiated at axon-bearing dendritic sites formed a variable trigger for invasion to the soma and contralateral dendritic tree, with action potentials often confined to the axon-bearing dendrite. The application of dopamine increased this form of electrical compartmentalization, an effect mediated by a tonic membrane potential hyperpolarization leading to an increased availability of a class of voltage-dependent potassium channel. These data suggest that the release of dopamine from axonal and somatodendritic sites are dissociable, and that dopamine levels within the midbrain are dynamically controlled by the somatodendritic spread of action potentials.

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Dominant Role of $\beta\gamma$ Subunits of G-Proteins in Oxytocin-Evoked Burst Firing

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Pulsatile neuropeptide secretion is associated with burst firing patterns; however, intracellular signaling cascades leading to bursts remain unclear. We explored mechanisms underlying burst firing in oxytocin (OT) neurons in the supraoptic nucleus in brain slices from lactating rats. Application of 10 pM OT for 30 min or progressively rising OT concentrations from 1 to 100 pM induced burst firing in OT neurons in patch-clamp recordings. Burst generation was blocked by OT antagonist and ionotropic glutamate receptor blockers or tetanus toxin. Blocking G-protein activation with suramin or intracellular GDP- β -S, but not intracellularly administered antibody against the OT-receptor (OTR) C terminus, blocked bursts. Moreover, pretreatment of slices with pertussis toxin, an inhibitor of $G_{i/o}$ -proteins, did not block OT-evoked bursts, suggesting that G_i/G_o activation is unnecessary for burst generation. Thus, we further examined $G_{\alpha_{q/11}}$ -associated signaling pathways in OT-evoked bursts. Inhibition of phospholipase C or RhoA/Rho kinase did not block bursts. Activation of $G\beta\gamma$ subunits using myristoylated $G\beta\gamma$ -binding peptide (mSIRK) caused bursts, whereas intracellularly loaded antibody against $G\beta$ subunit blocked OT-evoked bursts. Blocking Src family kinase, but not phosphatidylinositol 3-kinase, occluded OT-evoked bursts. Similar to the effects of OT on EPSCs, mSIRK inhibited tonic EPSCs and elicited EPSC clustering. Finally, suckling caused dissociation of OTRs and $G\beta\gamma$ subunits from $G_{\alpha_{q/11}}$ subunits shown by coimmunoprecipitation and immunocytochemistry, supporting crucial roles for OTRs and $G\beta\gamma$ subunits in the milk-ejection reflex. We conclude that $G\beta\gamma$ subunits play a dominant role in burst firing evoked by applied OT or by suckling.

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Apolipoprotein E-Containing Lipoproteins Protect Neurons from Apoptosis via a Signaling Pathway Involving Low-Density Lipoprotein Receptor-Related Protein-1

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Apolipoprotein E (apoE)-containing lipoproteins (LPs) are secreted by glia and play important roles in lipid homeostasis in the CNS. Glia-derived LPs also promote synaptogenesis and stimulate axon growth of CNS neurons. Here, we provide evidence that glia-derived LPs protect CNS neurons from apoptosis by a receptor-mediated signaling pathway. The protective effect was greater for apolipoprotein E3 than for apolipoprotein E4, the expression of which is a risk factor for Alzheimer's disease. The anti-apoptotic effect of LPs required the association of apolipoprotein E with lipids but did not require cholesterol. Apoptosis was not prevented by lipids alone or by apoA1- or apoJ-containing lipoproteins. The prevention of neuronal apoptosis was initiated after the binding of LPs to the low-density lipoprotein receptor-related protein (LRP), a multifunctional receptor of the low-density lipoprotein receptor family. We showed that inhibition of LRP activation, by treatment of neurons with receptor-associated protein or anti-LRP antibodies, or by LRP gene-silencing experiments, reduced the protective effect of LPs. Furthermore, another LRP ligand, α_2 -macroglobulin, also protected the neurons from apoptosis. After binding to LRP, LPs initiate a signaling pathway that involves activation of protein kinase C δ and inactivation of glycogen synthase kinase-3 β . These findings indicate the potential for using glial lipoproteins or an activator of the LRP signaling pathway for treatment for neurodegenerative disorders such as Alzheimer's disease.

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Kv4.3-Mediated A-Type K⁺ Currents Underlie Rhythmic Activity in Hippocampal Interneurons

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Hippocampal-dependent learning and memory processes are associated with theta frequency rhythmic activity. Interneuron and pyramidal cell network interactions underlie this activity, but contributions of interneuron voltage-gated membrane conductances remain unclear. We show that interneurons at the CA1 lacunosum-moleculare (LM) and radiatum (RAD) junction (LM/RAD) display voltage-dependent subthreshold membrane potential oscillations (MPOs) generated by voltage-gated tetrodotoxin-sensitive Na⁺ and 4-aminopyridine (4-AP)-sensitive K⁺ currents. They also exhibit prominent 4-AP-sensitive A-type K⁺ currents, with gating properties showing activation at subthreshold membrane potentials. We found that LM/RAD cells are part of specific interneuron subpopulations expressing the K⁺ channel subunit Kv4.3 and their transfection with Kv4.3 small interfering RNA selectively impaired A-type K⁺ currents and MPOs. Thus, our findings reveal a novel function of Kv4.3-mediated A-type K⁺ currents in the generation of intrinsic MPOs in specific subpopulations of interneurons that may participate in hippocampal theta-related rhythmic activity.

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Long-Term Upregulation of Protein Kinase A and Adenylate Cyclase Levels in Human Smokers

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Repeated injections of cocaine and morphine in laboratory rats cause a variety of molecular neuroadaptations in the cAMP signaling pathway in nucleus accumbens and ventral tegmental area. Here we report similar neuroadaptations in postmortem tissue from the brains of human smokers and former smokers. Activity levels of two major

components of cAMP signaling, cAMP-dependent protein kinase A (PKA) and adenylate cyclase, were abnormally elevated in nucleus accumbens of smokers and in ventral midbrain dopaminergic region of both smokers and former smokers. Protein levels of the catalytic subunit of PKA were correspondingly higher in the ventral midbrain dopaminergic region of both smokers and former smokers. Protein levels of other candidate neuroadaptations, including glutamate receptor subunits, tyrosine hydroxylase, and other protein kinases, were within normal range. These findings extend our understanding of addiction-related neuroadaptations of cAMP signaling to tobacco smoking in human subjects and suggest that smoking-induced brain neuroadaptations can persist for significant periods in former smokers.

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Long-Term Depression of a Dopamine IPSC

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Two determinants of dopamine release from terminals in striatal and limbic structures are the pattern and rate of dopamine neuron firing in the ventral midbrain. This activity is regulated in part by somatodendritic release of dopamine and subsequent feedback inhibition through activation of D₂ receptors on dopamine neuron cell bodies and dendrites. This study describes stimulus-dependent long-term depression (LTD) of IPSCs mediated by dopamine. This LTD was blocked by chelation of postsynaptic intracellular calcium, was dependent on the activation of D₂ receptors and was independent of glutamate-mediated transmission. Application of a high concentration of dopamine mimicked depression of the IPSC and prevented additional attempts to induce LTD, suggesting that the mechanism of the depression is agonist-dependent receptor activation. Using extracellular recording, there is an inhibition of firing that follows electrical stimulation, and after the induction of LTD the duration of that inhibition was decreased. Reduced inhibition could increase burst firing and action potential-dependent release of dopamine in terminal regions *in vivo*.

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Estrogen Mobilizes a Subset of Estrogen Receptor- α -Immunoreactive Vesicles in Inhibitory Presynaptic Boutons in Hippocampal CA1

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Although the classical mechanism of estrogen action involves activation of nuclear transcription factor receptors, estrogen also has acute effects on neuronal signaling that occur too rapidly to involve gene expression. These rapid effects are likely to be mediated by extranuclear estrogen receptors associated with the plasma membrane and/or cytoplasmic organelles. Here we used a combination of serial-section electron microscopic immunocytochemistry, immunofluorescence, and Western blotting to show that estrogen receptor- α is associated with clusters of vesicles in perisomatic inhibitory boutons in hippocampal CA1 and that estrogen treatment mobilizes these vesicle clusters toward synapses. Estrogen receptor- α is present in approximately one-third of perisomatic inhibitory boutons, and specifically in those that express cholecystokinin, not parvalbumin. We also found a high degree of extranuclear estrogen receptor- α colocalization with neuropeptide Y. Our results suggest a novel mode of estrogen action in which a subset of vesicles within a specific population of inhibitory boutons responds directly to estrogen by moving toward synapses. The mobilization of these vesicles may influence acute effects of estrogen mediated by estrogen receptor- α signaling at inhibitory synapses.

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A Developmental Switch to GABAergic Inhibition Dependent on Increases in Kv1-Type K⁺ Currents

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Mature nucleus magnocellularis (NM) neurons, the avian homolog of bushy cells of the mammalian anteroventral cochlear nucleus, maintain high [Cl[−]]_i and depolarize in response to GABA. Depolarizing GABAergic postsynaptic potentials (GPSPs) activate both the synaptic conductance and large outward currents, which, when coupled together, inhibit spikes via shunting and spike threshold accommodation. We studied the maturation of the synaptic and voltage-dependent components of inhibition in embryonic NM neurons using whole-cell and gramicidin-perforated patch-clamp techniques to measure Cl[−] reversal potential, GABAergic synaptic responses, and voltage-dependent outward currents. We found that GABA enhanced excitability in immature NM neurons, undergoing a switch to inhibitory between embryonic day 14 (E14) and E18. Low-voltage-activated Kv1-type (dendrotoxin-I sensitive) K⁺ currents increased in amplitude between E14 and E18, whereas Cl[−] reversal potential and synaptic conductances remained relatively stable during this period. GABA was rendered inhibitory because of this increase in low-voltage activated outward currents. GPSPs summed with other inputs to increase spike probability at E14. GPSPs shunted spikes at E18, but blocking Kv1 channels transformed this inhibition to excitation, similar to E14 neurons. Subthreshold depolarizing current steps, designed to activate outward currents similar to depolarizing GPSPs, enhanced excitability at E14 but inhibited spiking in E18 neurons. Blocking Kv1 channels reversed this effect, rendering current steps excitatory. We present the novel finding that the developmental transition of GABAergic processing from increasing neuronal excitability to inhibiting spiking can depend on changes in the expression of voltage-gated channels rather than on a change in Cl[−] reversal potential.

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Deletion of *Nf1* in Neurons Induces Increased Axon Collateral Branching after Dorsal Root Injury

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Ras-mediated signaling pathways participate in multiple aspects of neural development and function. For example, Ras signaling lies downstream of neurotrophic factors and Trk family receptor tyrosine kinases to regulate neuronal survival and morphological differentiation, including axon extension and target innervation. Neurofibromin, the protein encoded by the tumor suppressor gene *Nf1*, is a negative regulator of Ras [Ras-GAP (GTPase-activating protein)], and we previously demonstrated that *Nf1* null embryonic sensory and sympathetic neurons can survive and differentiate independent of neurotrophin support. In this report, we demonstrate that *Nf1* loss in adult sensory neurons enhances their intrinsic capacity for neurite outgrowth and collateral branching *in vitro* and *in vivo* after dorsal root injury. In contrast to the permanent sensory deficits observed in control mice after dorsal rhizotomy, neuron-specific *Nf1* mutant mice spontaneously recover proprioceptive function. This phenomenon appears to be mediated both by a cell-autonomous capacity of spared *Nf1*^{−/−} DRG neurons for increased axonal sprouting, and by non-cell-autonomous contribution from *Nf1*^{−/−} neurons in the denervated spinal cord.

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Number and Density of AMPA Receptors in Individual Synapses in the Rat Cerebellum as Revealed by SDS-Digested Freeze-Fracture Replica Labeling

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The number of AMPA receptor (AMPA) is the major determinant of synaptic strength at glutamatergic synapses, but little is known about the absolute number and density of AMPARs in individual synapses. Using SDS-digested freeze-fracture replica labeling, which has high detection efficiency comparable with electrophysiological noise analysis for functional AMPAR, we analyzed three kinds of excitatory synapses in the molecular layer of the adult rat cerebellum. In parallel fiber (PF)–Purkinje cell (PC) synapses, we found large variability in the number (38.1 ± 34.4 particles per synapse, mean $\pm$ SD; range, 2–178 particles per synapse) and density (437 ± 277 particles/ μm^2 ; range, 48–1210 particles/ μm^2) of immunogold-labeled AMPARs. Two-dimensional view and high sensitivity of this method revealed irregular-shaped small AMPAR clusters within synapses. Climbing fiber (CF)–PC synapses had higher number of AMPAR labeling (68.6 ± 34.5 particles per synapse) than PF–PC and PF–interneuron synapses (36.8 ± 14.4 particles per synapse). Furthermore, AMPAR density at CF–PC and PF–interneuron synapses was approximately five times higher and more uniform than that at PF–PC synapses. These results suggest input- and target-dependent regulation of AMPAR-mediated synaptic strength.

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DEVELOPMENT/PLASTICITY/REPAIR

White Matter Plasticity and Enhanced Remyelination in the Maternal CNS

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Myelination, the process in which oligodendrocytes coat CNS axons with a myelin sheath, represents an important but poorly understood form of neural plasticity that may be sexually dimorphic in the adult CNS. Remission of multiple sclerosis during pregnancy led us to hypothesize that remyelination is enhanced in the maternal brain. Here we report an increase in the generation of myelin-forming oligodendrocytes and in the number of myelinated axons in the maternal murine CNS. Remarkably, pregnant mice have an enhanced ability to remyelinate white matter lesions. The hormone prolactin regulates oligodendrocyte precursor proliferation and mimics the regenerative effects of pregnancy. This suggests that maternal white matter plasticity imparts a striking ability to repair demyelination and identifies prolactin as a potential therapeutic agent.

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Self-Renewing and Differentiating Properties of Cortical Neural Stem Cells Are Selectively Regulated by Basic Fibroblast Growth Factor (FGF) Signaling via Specific FGF Receptors

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Developmental processes mediating the initiation of lineage commitment from self-renewing neural stem cells (NSCs) remain mostly unclear because of the persisting ambiguity in identifying true NSCs from proliferative lineage-restricted progenitors (LRPs), which are directly or indirectly derived from NSCs. Our multilineage immunohistochemical analyses of early embryonic rat telencephalon at the onset of neurogenesis revealed clear dorsoventral gradients in the emergence of two types of neuronal progenitors (NPs) from multilineage-negative NSCs. Enumeration of NSCs using comprehensive flow cytometric analysis demonstrated that their precipitous decline *in vivo* involved both active differentiation into NPs and an increased propensity toward apoptosis. Both processes paralleled the dorsoventral changes in fibroblast growth factor receptor (FGFR) expressions. NSCs residing in the dorsal telencephalon coexpressed FGFR1 and FGFR3, whereas those residing in the ventral telencephalon also expressed FGFR2. NSCs exposed to basic fibroblast growth factor (bFGF) *in vitro* generated four stereotypical clonal expansion states: efficiently self-renewing, inefficiently self-renewing limited by apoptosis, exclusively neurogenic, and multipotential, generating up to five types of LRPs. The plasticity among these expansion states depended on ambient [bFGF], telencephalic developmental stage, and differential activation/inactivation of specific FGFRs. Coactivation of FGFR1 and FGFR3 promoted symmetrical divisions of NSCs (self-renewal), whereas inactivation of either triggered asymmetrical divisions and neurogenesis from these cells. Developmental upregulation of FGFR2 expression correlated with a shift of NSCs into a multipotential state or apoptosis. These results provide new insights regarding the roles of FGFRs in diversification of NSC properties and initiation of neural lineage-restricted differentiation.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Functional Imaging Reveals Visual Modulation of Specific Fields in Auditory Cortex

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Merging the information from different senses is essential for successful interaction with real-life situations. Indeed, sensory integration can reduce perceptual ambiguity, speed reactions, or change the qualitative sensory experience. It is widely held that integration occurs at later processing stages and mostly in higher association cortices; however, recent studies suggest that sensory convergence can occur in primary sensory cortex. A good model for early convergence proved to be the auditory cortex, which can be modulated by visual and tactile stimulation; however, given the large number and small size of auditory fields, neither human imaging nor microelectrode recordings have systematically identified which fields are susceptible to multisensory influences. To reconcile findings from human imaging with anatomical knowledge from nonhuman primates, we exploited high-resolution imaging (functional magnetic resonance imaging) of the macaque monkey to study the modulation of auditory processing by visual stimulation. Using a functional parcellation of auditory cortex, we localized modulations to individual fields. Our results demonstrate that both primary (core) and nonprimary (belt) auditory fields can be activated by the mere presentation of visual scenes. Audiovisual convergence was restricted to caudal fields [prominently the core field (primary auditory cortex) and belt fields (caudomedial field, caudolateral field, and mediomedial field)] and continued in the auditory parabelt and the superior temporal sulcus. The same fields exhibited enhancement of auditory activation by visual stimulation and showed stronger enhancement for less effective stimuli, two characteristics of sensory integration. Together, these findings reveal multisensory modulation of auditory processing prominently in caudal fields but also at the lowest stages of auditory cortical processing.

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Estradiol Induces Diurnal Shifts in GABA Transmission to Gonadotropin-Releasing Hormone Neurons to Provide a Neural Signal for Ovulation

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Ovulation is initiated by a surge of gonadotropin-releasing hormone (GnRH) secretion by the brain. GnRH is normally under negative feedback control by ovarian steroids. During sustained exposure to estradiol in the late follicular phase of the reproductive cycle, however, the feedback action of this steroid switches to positive, inducing the surge. Here, we used an established ovariectomized, estradiol-treated (OVX + E) mouse model exhibiting daily surges to investigate the neurobiological mechanisms underlying this switch. Specifically, we examined changes in GABA transmission to GnRH neurons, which can be excited by GABA_A receptor activation. Spontaneous GABAergic postsynaptic currents (PSCs) were recorded in GnRH neurons from OVX + E and OVX mice in coronal and sagittal slices. There were no diurnal changes in PSC frequency in cells from OVX mice in either slice orientation. In OVX + E cells in both orientations, PSC frequency was low during negative feedback but increased at surge onset. During the surge peak, this increase subsided in coronal slices but persisted in sagittal slices. Comparison of PSCs before and during tetrodotoxin (TTX) treatment showed TTX decreased PSC frequency in OVX + E cells in sagittal slices, but not coronal slices. This indicates estradiol acts on multiple GABAergic afferent populations to increase transmission through both activity-dependent and -independent mechanisms. Estradiol also increased PSC amplitude during the surge. Estradiol and the diurnal

cycle thus interact to induce shifts in both GABA transmission and postsynaptic response that would produce appropriate changes in GnRH neuron firing activity and hormone release.

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Multisensory Integration in the Ventral Intraparietal Area of the Macaque Monkey

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The goal of this study was to characterize multisensory interaction patterns in cortical ventral intraparietal area (VIP). We recorded single-unit activity in two alert monkeys during the presentation of visual (drifting gratings) and tactile (low-pressure air puffs) stimuli. One stimulus was always positioned inside the receptive field of the neuron. The other stimulus was defined so as to manipulate the spatial and temporal disparity between the two stimuli. More than 70% of VIP cells showed a significant modulation of their response by bimodal stimulations. These cells included both bimodal cells, i.e., cells responsive to both tested modalities, and seemingly unimodal cells, i.e., cells responding to only one of the two tested modalities. This latter observation suggests that postsynaptic latent mechanisms are involved in multisensory integration. In both cell categories, neuronal responses are either enhanced or depressed and reflect nonlinear sub-, super-, or additive mechanisms. The occurrence of these observations is maximum when stimuli are in temporal synchrony and spatially congruent. Interestingly, introducing spatial or temporal disparities between stimuli does not affect the sign or the magnitude of interactions but rather their occurrence. Multisensory stimulation also affects the neuronal response latencies of bimodal stimuli. For a given neuron, these are on average intermediate between the two unimodal response latencies, again suggesting latent postsynaptic mechanisms. In summary, we show that the majority of VIP neurons perform multisensory integration, following general rules (e.g., spatial congruency and temporal synchrony) that are closely similar to those described in other cortical and subcortical regions.

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Contribution of NMDA and AMPA Receptors to Temporal Patterning of Auditory Responses in the Inferior Colliculus

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Although NMDA receptors (NMDARs) are associated with synaptic plasticity, they form an essential part of responses to sensory stimuli. We compared contributions of glutamatergic NMDARs and AMPA receptors (AMPA receptors) to auditory responses in the inferior colliculus (IC) of awake, adult mustached bats. We examined the magnitude and temporal pattern of responses to tonal signals in single units before, during, and after local micro-iontophoretic application of selective antagonists to AMPARs [NBQX (1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide)] and NMDARs [CPP ((±)3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid)]. Combined blockade of AMPARs and NMDARs eliminated excitatory responses in nearly all neurons, whereas separate blockade of each receptor was quantitatively similar, causing substantial (>50%) spike reductions in ~75% of units. The major result was that effects of receptor blockade were most closely related to the first-spike latency of a unit. Thus, AMPAR blockade substantially reduced spikes in all short-latency units (<12 ms) but never in long-latency units (≥12 ms). NMDAR blockade had variable effects on short-latency units but reduced spikes substantially for all long-latency units. There were no distinct contributions of AMPARs and NMDARs to early and late elements of responses. Thus, AMPAR blockade reduced early (onset) spikes somewhat more effectively than NMDAR blockade in short-latency units, but NMDAR blockade reduced onset spikes more effectively in long-latency units. AMPAR and NMDAR blockade were equally effective in reducing later elements of sustained responses in short-latency units, whereas NMDAR blockade was much more effective in long-latency units. These results indicate that NMDARs play multiple roles for signal processing in adult IC neurons.

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Integration of Lobula Plate Output Signals by DNOVS1, an Identified Premotor Descending Neuron

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Many motion-sensitive tangential cells of the lobula plate in blowflies are well described with respect to their visual response properties and the connectivity among them. They have large and complex receptive fields with different preferred directions in different parts of their receptive fields matching the optic flow that occurs during various flight maneuvers. However, much less is known about how tangential cells connect to postsynaptic neurons descending to the motor circuits in the thoracic ganglion and how optic flow is represented in these downstream neurons. Here we describe the physiology and the connectivity of a prominent descending neuron called DNOVS1 (for descending neurons of the ocellar and vertical system). We find that DNOVS1 is electrically coupled to a subset of vertical system cells. The specific wiring leads to a preference of DNOVS1 for rotational flow fields around a particular body axis. In addition, DNOVS1 receives input from interneurons connected to the ocelli.

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Target Selection Signals for Arm Reaching in the Posterior Parietal Cortex

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The selection of visual stimuli as a target for a motor action may depend on external as well as internal variables. The parietal reach region (PRR) in the posterior parietal cortex plays an important role in the transformation of visual information into reach movement plans. We asked how neurons in PRR of macaque monkeys reflect the decision process of selecting one of two visual stimuli as a target for a reach movement. Spiking activity was recorded while the animal performed a free-choice task with one target presented in the preferred direction and the other in the off direction of the cell. Stimulus-onset asynchrony (SOA) was adjusted to ensure that both targets were selected equally often and the amount of reward was fixed. Neural activity in PRR was action specific for arm reaching and reflected the timing of the SOA as well as the selection of reach targets. In individual trials, activity was strongly linked to the choice of the animal, and, for the majority of cells, target selections could be predicted from activity in the stimulation or planning period, i.e., before the movement started. Many neurons were gain modulated by the fixation position, but gain modulation did not influence the target selection process directly. Finally, it was found that target selection for saccade movements was only weakly represented in PRR. These findings suggest that PRR is involved in decision making for reach movements and that separate cortical networks exist for target selection of different types of action.

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Bed Nucleus of the Stria Terminalis Subregions Differentially Regulate Hypothalamic–Pituitary–Adrenal Axis Activity: Implications for the Integration of Limbic Inputs

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Limbic and cortical neurocircuits profoundly influence hypothalamic–pituitary–adrenal (HPA) axis responses to stress yet have little or no direct projections to the hypothalamic paraventricular nucleus (PVN). Numerous lines of evidence suggest that the bed nucleus of the stria terminalis (BST) is well positioned to relay limbic information to the PVN. The BST comprises multiple anatomically distinct nuclei, of which some are known to receive direct limbic and/or cortical input and to heavily innervate the PVN. Our studies test the hypothesis that subregions of the BST differentially regulate HPA axis responses to acute stress. Male Sprague Dawley rats received bilateral ibotenate lesions, targeting either the principal nucleus in the posterior BST or the dorsomedial/fusiform nuclei in the anteroventral BST. Posterior BST lesions elevated plasma ACTH and corticosterone in response to acute restraint stress, increased stress-induced PVN *c-fos* mRNA, and elevated PVN corticotropin-releasing hormone (CRH) and parvocellular arginine vasopressin (AVP) mRNA expression relative to sham-lesion animals. In contrast, anterior BST lesions attenuated the plasma corticosterone response and decreased *c-fos* mRNA induction in the PVN but did not affect CRH and parvocellular AVP mRNA expression in the PVN. These data suggest that posterior BST nuclei are involved in inhibition of the HPA axis, whereas the anteroventral BST nuclei are involved in HPA axis excitation. The results indicate that the BST contains functional subdomains that play different roles in integrating and processing limbic information in response to stress and further suggest that excitatory as well as inhibitory limbic information is funneled through these important cell groups.

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Upregulation of Substance P in Low-Threshold Myelinated Afferents Is Not Required for Tactile Allodynia in the Chronic Constriction Injury and Spinal Nerve Ligation Models

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It has been proposed that substance P and calcitonin gene-related peptide (CGRP) are upregulated in low-threshold myelinated primary afferents after certain types of nerve injury, and that release of substance P from these afferents contributes to the resulting tactile allodynia. To test this hypothesis, we looked for neuropeptides in A β primary afferent terminals in the ipsilateral gracile nucleus and spinal dorsal horn in three nerve injury models: sciatic nerve transection (SNT), spinal nerve ligation (SNL), and chronic constriction injury (CCI). We also looked for evidence of neurokinin 1 (NK1) receptor internalization in the dorsal horn after electrical stimulation of A β afferents. We found no evidence of either substance P or CGRP expression in injured A β terminals in the spinal cord in any of the models. Although substance P was not detected in terminals of injured afferents in the gracile nucleus, CGRP was expressed in between 32 and 68% of these terminals, with a significantly higher proportion in the SNL and CCI models, compared with SNT. In addition, we did not detect any A β -evoked NK1 receptor internalization in neurons from laminae I, III, or IV of the dorsal horn in the CCI or SNL models. These results do not support the proposal that substance P is present at significant levels in the terminals of injured A β primary afferents in neuropathic models. They also suggest that any release of substance P from injured A β afferents is unlikely to activate NK1 receptors in the dorsal horn or contribute to neuropathic pain.

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Dopaminergic Regulation of Inhibitory and Excitatory Transmission in the Basolateral Amygdala–Prefrontal Cortical Pathway

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Projections from the basolateral amygdala (BLA) and dopamine (DA) input from the ventral tegmental area (VTA) converge in the medial prefrontal cortex (mPFC), forming a neural circuit implicated in certain cognitive and emotional processes. However, the role that DA plays in modulating activity in the BLA–mPFC pathway is unknown. The present study investigated the mechanisms by which DA modulates BLA-evoked changes in mPFC neural activity, using extracellular single-unit recordings in urethane-anesthetized rats. BLA stimulation evoked two distinct types of responses in separate populations of mPFC neurons: monosynaptic, excitatory responses and, more commonly, inhibition of spontaneous firing. Stimulation of the VTA or local iontophoretic application of DA attenuated BLA-evoked inhibition of PFC neuron firing. Administration of selective DA receptor agonists revealed that these effects were mediated by D_2 and D_4 (but not D_1) receptors. In addition, VTA stimulation or DA application attenuated BLA-evoked firing of a separate population of mPFC neurons in a frequency-dependent manner; firing evoked by higher-frequency stimulation of the BLA was less inhibited than that evoked by single-pulse stimulation. Attenuation of BLA-evoked firing was also induced by D_1 (but not D_2 or D_4) receptor agonists. These data indicate that dissociable DA receptor mechanisms regulate the balance of excitatory and inhibitory transmission in BLA–mPFC circuits, biasing toward an increase in the excitatory influence that the BLA exerts over populations of mPFC neurons. These findings may have important implications for understanding the pathophysiology underlying emotional and cognitive disturbances present in disorders such as depression and drug addiction.

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Synchronization of Electrically Coupled Pairs of Inhibitory Interneurons in Neocortex

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We performed a systematic analysis of phase locking in pairs of electrically coupled neocortical fast-spiking (FS) and low-threshold-spiking (LTS) interneurons and in a conductance-based model of a pair of FS cells. Phase–response curves (PRCs) were obtained for real interneurons and the model cells. We used PRCs and the theory of weakly coupled oscillators to make predictions about phase-locking characteristics of cell pairs. Phase locking and the robustness of phase-locked states to differences in intrinsic frequencies of cells were directly examined by driving interneuron pairs through a wide range of firing frequencies.

Calculations using PRCs accurately predicted that electrical coupling robustly synchronized the firing of interneurons over all frequencies studied (FS, ~25–80 Hz; LTS, ~10–30 Hz). The synchronizing ability of electrical coupling and the robustness of the phase-locked states were directly dependent on the strength of coupling but not on firing frequency. The FS cell model also predicted the existence of stable antiphase firing at frequencies below ~30 Hz, but no evidence for stable antiphase firing was found using the experimentally determined PRCs or in direct measures of phase locking in pairs of interneurons.

Despite significant differences in biophysical properties of FS and LTS cells, their phase-locking behavior was remarkably similar. The wide spikes and shallow action potential afterhyperpolarizations of interneurons, compared with the model, prohibited antiphase behavior. Electrical coupling between cortical interneurons of the same type maintained robust synchronous firing of cell pairs for up to ~10% heterogeneity in their intrinsic frequencies.

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Sparse and Selective Odor Coding by Mitral/Tufted Neurons in the Main Olfactory Bulb

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The mammalian olfactory system recognizes an enormous variety of odorants carrying a wide range of important behavioral cues. In the main olfactory bulb (MOB), odorants are ultimately represented through the action potential activity of mitral/tufted cells (M/Ts), whose selectivity and tuning to odorant molecules are therefore fundamental determinants of MOB sensory coding. However, the sheer number and diversity of discrete olfactory stimuli has been a major barrier to comprehensively evaluating M/T selectivity. To address this issue, we assessed M/T odorant responses in anesthetized mice to a 348-odorant panel widely and systematically distributed throughout chemical space, presented both individually and in mixtures at behaviorally relevant concentrations. We found that M/T activation by odorants was markedly selective, with neurons responding robustly, sensitively, and reliably to only a highly restricted subset of stimuli. Multiple odorants activating a single neuron commonly shared clear structural similarity, but M/T tuning also frequently extended beyond obviously defined chemical categories. Cells typically responded to effective compounds presented both individually and in mixtures, although firing rates evoked by mixtures typically showed partial suppression. Response selectivity was further confirmed in awake animals by chronic recordings of M/Ts. These data indicate that individual M/Ts encode specific odorant attributes shared by only a small fraction of compounds and imply that the MOB relays the collective molecular features of an odorant stimulus through a restricted set of M/Ts, each narrowly tuned to a particular stimulus characteristic.

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Reelin Regulates Neuronal Progenitor Migration in Intact and Epileptic Hippocampus

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Dentate granule cell (DGC) neurogenesis persists throughout life in the mammalian hippocampal dentate gyrus and increases after epileptogenic insults. The DGC layer in human and experimental mesial temporal lobe epilepsy (mTLE) often shows abnormal dispersion and the appearance of hilar-ectopic DGCs. In the pilocarpine mTLE model, hilar-ectopic DGCs arise as a result of an aberrant chain migration of neural progenitors. Reelin is a secreted migration guidance cue that persists in the adult rodent and human hippocampus. We tested the hypothesis that loss of Reelin in the epileptic dentate gyrus leads to aberrant chain migration of DGC precursors. We found that interneuron subsets typically lost in human and experimental mTLE express Reelin, and DGC progenitors express the downstream Reelin signaling molecule Disabled 1 (Dab1). Prolonged seizures decreased Reelin immunoreactivity in the adult rat dentate gyrus and increased Dab1 expression in hilar-ectopic neuroblasts. Exogenous Reelin increased detachment of chain-migrating neuroblasts in dentate gyrus explants, and blockade of Reelin signaling increased chain migration. These findings suggest that Reelin modulates DGC progenitor migration to maintain normal DGC integration in the neonatal and adult mammalian dentate gyrus. Loss of Reelin expression in the epileptic adult hippocampus, moreover, likely contributes to ectopic chain migration and aberrant integration of newborn DGCs.

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Parkin Mediates Neuroprotection through Activation of I κ B Kinase/Nuclear Factor- κ B Signaling

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Mutations in the parkin gene are a major cause of autosomal recessive Parkinson's disease. Here we show that the E3 ubiquitin ligase parkin activates signaling through the I κ B kinase (IKK)/nuclear factor κ B (NF- κ B) pathway. Our analysis revealed that activation of this signaling cascade is causally linked to the neuroprotective potential of parkin. Inhibition of NF- κ B activation by an I κ B super-repressor or a kinase-inactive IKK β interferes with the neuroprotective activity of parkin. Furthermore, pathogenic parkin mutants with an impaired neuroprotective capacity show a reduced ability to stimulate NF- κ B-dependent transcription. Finally, we present evidence that parkin interacts with and promotes degradation-independent ubiquitylation of IKK γ /NEMO (NF- κ B essential modifier) and TRAF2 [TNF (tumor necrosis factor) receptor-associated factor 2], two critical components of the NF- κ B pathway. Thus, our results support a direct link between the neuroprotective activity of parkin and ubiquitin signaling in the IKK/NF- κ B pathway.

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Endosomal Accumulation of Toll-Like Receptor 4 Causes Constitutive Secretion of Cytokines and Activation of Signal Transducers and Activators of Transcription in Niemann–Pick Disease Type C (NPC) Fibroblasts: A Potential Basis for Glial Cell Activation in the NPC Brain

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Niemann–Pick disease type C (NPC) is an inherited lipid storage disorder caused by mutations in *NPC1* or *NPC2* genes. Loss of function of either protein results in the endosomal accumulation of cholesterol and other lipids, progressive neurodegeneration, and robust glial cell activation. Here, we report that cultured human NPC fibroblasts secrete interferon- β , interleukin-6 (IL-6), and IL-8, and contain increased levels of signal transducers and activators of transcription (STATs). These cells also contained increased levels of Toll-like receptor 4 (TLR4) that accumulated in cholesterol-enriched endosomes/lysosomes, and small interfering RNA knockdown of this receptor reduced cytokine secretion. In the *NPC1*^{−/−} mouse brain, glial cells expressed TLR4 and IL-6, whereas both glial and neuronal cells expressed STATs. Genetic deletion of TLR4 in *NPC1*^{−/−} mice reduced IL-6 secretion by cultured fibroblasts but failed to alter STAT levels or glial cell activation in the brain. In contrast, genetic deletion of IL-6 normalized STAT levels and suppressed glial cell activation. These findings indicate that constitutive cytokine secretion leads to activation of STATs in NPC fibroblasts and that this secretion is partly caused by an endosomal accumulation of TLR4. These results also suggest that similar signaling events may underlie glial cell activation in the *NPC1*^{−/−} mouse brain.

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Antibody-Mediated Clearance of Amyloid- β Peptide from Cerebral Amyloid Angiopathy Revealed by Quantitative *In Vivo* Imaging

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Cerebral amyloid angiopathy (CAA) is the accumulation of amyloid- β peptide (A β) in the vessel wall of arteries in the brain. Because CAA is commonly associated with Alzheimer's disease (AD), characterized by parenchymal deposition of the same peptide in the form of senile plaques, there is considerable interest in the relationship of the two deposits in generating human disease. The study of CAA is of particular importance for immunotherapeutic approaches to AD, because reports of anti-A β immunotherapy in mice and humans have suggested that, whereas CAA appeared resistant to clearance, its response to this treatment promoted potential adverse effects, including meningoencephalitis. We used multiphoton microscopy and longitudinal imaging to monitor CAA in a mouse model of amyloid deposition to evaluate the effects of anti-A β passive immunotherapy. We found detectable clearance of CAA deposits within 1 week after a single administration of antibody directly to the brain, an effect that was short-lived. Chronic administration of antibody over 2 weeks led to more robust clearance without evidence of hemorrhage or other destructive changes. We found that the progressive clearance of A β from vessels follows distinct kinetics from what has been previously reported for clearance of plaques (parenchymal deposits of A β). This quantitative *in vivo* imaging approach directly demonstrates that CAA in a transgenic mouse model can be cleared with an optimized immunotherapy.

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Neuroprotective Effects of Regulators of the Glycogen Synthase Kinase-3 β Signaling Pathway in a Transgenic Model of Alzheimer's Disease Are Associated with Reduced Amyloid Precursor Protein Phosphorylation

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The glycogen synthase kinase-3 β (GSK3 β) pathway plays an important role in mediating neuronal fate and synaptic plasticity. In Alzheimer's disease (AD), abnormal activation of this pathway might play an important role in neurodegeneration, and compounds such as lithium that modulate GSK3 β activity have been shown to reduce amyloid production and tau phosphorylation in amyloid precursor protein (APP) transgenic (tg) mice. However, it is unclear whether regulation of GSK3 β is neuroprotective in APP tg mice. In this context, the main objective of the present study was to determine whether pharmacological or genetic manipulations that block the GSK3 β pathway might ameliorate the neurodegenerative alterations in APP tg mice and to better understand the mechanisms involved. For this purpose, two sets of experiments were performed. First, tg mice expressing mutant human APP under the Thy1 promoter (hAPP tg) were treated with either lithium chloride or saline alone. Second, hAPP tg mice were crossed with GSK3 β tg mice, in which overexpression of this signaling molecule results in a dominant-negative (DN) effect with inhibition of activity. hAPP tg mice that were treated with lithium or that were crossed with DN-GSK3 β tg mice displayed improved performance in the water maze, preservation of the dendritic structure in the frontal cortex and hippocampus, and decreased tau phosphorylation. Moreover, reduced activation of GSK3 β was associated with decreased levels of APP phosphorylation that resulted in decreased amyloid- β production. In conclusion, the present study showed that modulation of the GSK3 β signaling pathway might also have neuroprotective effects in tg mice by regulating APP maturation and processing and further supports the notion that GSK3 β might be a suitable target for the treatment of AD.

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Interferon- γ -Oligodendrocyte Interactions in the Regulation of Experimental Autoimmune Encephalomyelitis

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Experimental autoimmune encephalomyelitis (EAE) is an animal model of the human demyelinating disorder multiple sclerosis (MS). The immune cytokine interferon-gamma (IFN- γ) is believed to participate in disease pathogenesis in both EAE and MS. In the present study, we examined the significance of IFN- γ -oligodendrocyte interactions in the course of EAE. For the purpose of our study, we used the previously described [proteolipid protein/suppressor of cytokine signaling 1 (PLP/SOCS1)] transgenic mouse line that displays suppressed oligodendrocyte responsiveness to IFN- γ . PLP/SOCS1 mice developed EAE with an accelerated onset associated with enhanced early inflammation and markedly increased oligodendrocyte apoptosis. Moreover, we found that IFN- γ pretreatment of mature oligodendrocytes *in vitro* had a protective effect against oxidative stress and the inhibition of proteasome activity and resulted in upregulation in expression of a number of chemokines, including CXCL10 (IP10), CCL2 (MCP-1), CCL3 (MCP-1 α), and CCL5 (RANTES). These results suggest that IFN- γ -oligodendrocyte interactions are of significance to the clinical and

pathological aspects of EAE. In addition, the present study suggests that oligodendrocytes are not simply targets of inflammatory injury but active participants of the neuroimmune network operating during the course of EAE.

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Cathepsin D Deficiency Induces Persistent Neurodegeneration in the Absence of Bax-Dependent Apoptosis

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Neuronal ceroid lipofuscinoses/Batten disease (NCL) is a devastating group of neurodegenerative diseases caused by genetic disruptions in lysosomal function. Cathepsin D (CD) is a major lysosomal protease, and mutations in CD that render it enzymatically defective have been reported recently in subsets of NCL patients. The targeted deletion of CD in mice results in extensive neuropathology, including biochemical and morphological evidence of apoptosis and autophagic stress (aberrant autophagosome accumulation), effects that are similar to those observed in NCL. To determine the contribution of Bax-dependent apoptosis in this mouse model of NCL, combined Bax- and CD-deficient mice were generated. Morphological analysis of CD-deficient mouse brains indicated large numbers of pyknotic neurons and neurons with marked cytoplasmic swellings containing undigested lipofuscin. Cell death and apoptosis were evidenced by increases in terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL) reactivity and activation of caspase-3, respectively. DeOlmos silver-positive neurons were abundant in CD-deficient brain and correlated with neuron loss, as indicated by significant decreases in NeuN (neuronal nuclear antigen)-positive neurons. Lysosome dysfunction and autophagic stress were apparent in CD-deficient brain as indicated by the accumulation of autofluorescent storage material and by increased levels of LC3-II (light chain 3-II, a selective autophagosome marker), respectively. Bax deletion significantly inhibited caspase-3 activation and hippocampal TUNEL reactivity but did not prevent the majority of CD deficiency-induced neuropathology, including the persistence of pyknotic neurons, elevated cortical TUNEL reactivity, lysosome dysfunction and autophagic stress, neurodegeneration, and neuron loss. Together, these results suggest that CD deficiency-induced neuropathology does not require Bax-dependent apoptosis and highlights the importance of caspase-independent neuron death and neurodegeneration resulting from the genetic disruption of lysosome function.

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