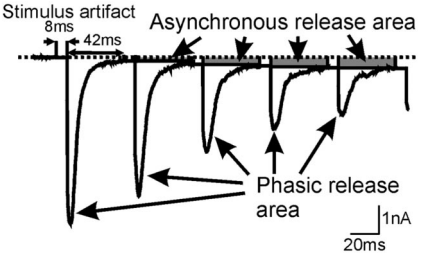
This Week in The Journal

● Cellular/Molecular

Asynchronous Transmitter Release at Excitatory Synapses

Yo Otsu, Vahid Shahrezaei, Bo Li, Lynn A. Raymond, Kerry R. Delaney, and Timothy H. Murphy
(see pages 420–433)

The spontaneous quantal release of neurotransmitter, "minis," may turn out to be more important than just a handy tool for quantitatively minded neurophysiologists. This week Otsu et al. report competition between phasic (evoked) release and asynchronous (spontaneous) release at hippocampal autapses in culture. Trains of stimuli depleted the readily releasable pool (RRP) of vesicles, resulting in depression of phasic release, yet synchronous release continued at a high rate. Asynchronous release also was unaffected by sucrose-induced depletion of the RRP. In contrast, blocking asynchronous release by reducing basal cytoplasmic calcium levels actually enhanced evoked release. Although both modes appear to share a common vesicle pool, recovery of asynchronous release after RRP depletion may be limited only by vesicle refilling while at the same time requiring a lower level of "bulk" intraterminal calcium. The authors suggest that under some circumstances, synapses may be able to maintain transmission at near maximal rates by using asynchronous release as a backup mechanism.



EPSC induced by phasic and asynchronous release during 20 Hz stimulation. See the article by Otsu et al. for details.

▲ Development/Plasticity/Repair

CaMKIV and Cortical Plasticity

Jasmin Lalonde, Pascal E. D. Lachance, and Avi Chaudhuri
(see pages 554–564)

CaMKIV expression in cell nuclei can contribute to neuroprotection and adaptive plasticity by activating CREB-dependent gene expression. This week, Lalonde et al. examined the pattern of CaMKIV expression in monkey visual cortex (V1). In infants, kinase immunoreactivity was high in nuclei of interneurons, whereas in adults the expression was primarily cytoplasmic. Prolonged monocular deprivation did not affect the CaMKIV expression pattern in infants, but nuclear kinase gradually increased in adults, apparently because of translocation from the cytoplasm. Expression overlapped with certain interneuronal markers such as parvalbumin (e.g. , chandelier cells) and calretinin (e.g. , Cajal-Retzius cells), suggesting that kinase translocation occurred primarily in interneurons with horizontal connectivity between columns. Although high expression of CaMKIV during developmental plasticity might be expected, the spatial and temporal pattern of CaMKIV expression in the adult may provide clues to the residual plasticity in the adult neocortex.

■ Behavioral/Systems/Cognitive

A Mechanism for Vocal Learning in Songbirds

Long Ding and David J. Perkel
(see pages 488–494)

Fathers get to act as tutors for young songbirds as they learn their signature song that persists into adulthood. Although the neural pathways of the so-called song system are well mapped, the cellular mechanisms underlying this neural plasticity are less clearly understood. Now Ding and Perkel describe a Hebbian long-term potentiation (LTP) that seems to fit the bill. They examined activity-dependent synaptic potentiation in spiny neurons of area X, a basal ganglia nucleus that receives glutamatergic input from the higher vocal center (HVC) and dopaminergic input from the ventral tegmental area (VTA). The potentiation required activation of both NMDA and D1 receptors and could be induced only in finches that were >47 d old, an age that correlates with the transition from the sensory learning to the practice phase of song learning. The authors also point out an intriguing correlation between the age of LTP expression and the innervation of area X by dopaminergic neurons from the VTA.

♦ Neurobiology of Disease

Implicating Astrocytes in β-Amyloid Toxicity

Andrey Y. Abramov, Laura Canevari, and Michael R. Duchen
(see pages 565–575)

Alzheimer's disease (AD) is marked by accumulation of β-amyloid (βA)-containing plaques. Although the role of βA as a diagnostic feature is clearly established, the mechanisms underlying the neurotoxicity of βA are less clear. While AD is usually thought of as a disease of neurons, Abramov et al. report that in neuron-astrocyte cultures, βA induced a collapse of the mitochondrial membrane potential in astrocytes. Astrocyte mitochondrial responses to βA showed several patterns: rapid depolarizations associated with cytoplasmic calcium increases as well as a slow collapse of the mitochondrial potential developing over several minutes. The latter was prevented by antioxidants and by glutamate acting as a metabolic substrate. The authors suggest that the collapse arises from oxidative stress on the metabolic enzymes that provide energy for mitochondrial respiration. They tracked the reactive oxygen species (ROS) to NADPH oxidase. The authors suggest that astrocyte injury may secondarily lead to βA-induced neuronal death.

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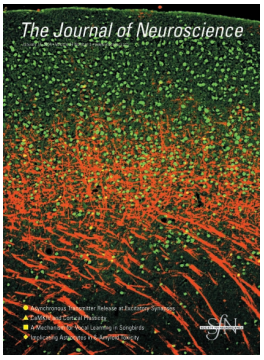

Cover picture: Wild-type cells (stained with an anti-β-galactosidase antibody; green fluorescence) in a p35 mutant background migrate to the top half of the cortex to form a "supercortex." Normal myelination of the supercortex is revealed by 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) antibody staining of thin fibers (red fluorescence), whereas abnormal thick fiber fascicles normally present in the brains of p35 mutant mice remain underneath. Additional analysis of these p35 mutant/wild-type chimeric brains demonstrates that p35 exerts both cell-autonomous and non cell-autonomous effects on cortical neuron migration and layering. For details, see the article by Hammond et al. in this issue (pages 576–587).

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Brief Communications

Differential Calcium-Dependent Modulation of NMDA Currents in CA1 and CA3 Hippocampal Pyramidal Cells

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Neuronal Ca^{2+} influx via NMDAAQ: A receptors (NMDARs) is essential for the development and plasticity of synapses but also triggers excitotoxic cell death when critical intracellular levels are exceeded. Therefore, finely equilibrated mechanisms are necessary to ensure that NMDAR function is maintained within a homeostatic range. Here we describe a pronounced difference in the modulation of NMDA currents in two closely related hippocampal cell types, the CA1 and the CA3 pyramidal cells (PCs). Manipulations that increase intracellular Ca^{2+} levels strongly depressed NMDA currents in CA3 with only minor effects in CA1 PCs. Furthermore, activation of AQ: BG_q-coupled metabotropic receptors potentiated NMDA currents in CA1 PCs but depressed them in CA3 PCs. Interestingly, the CA3 type modulation of NMDARs could be converted into CA1-like behavior, and vice versa, by increasing Ca^{2+} buffering in CA3 cells or decreasing Ca^{2+} buffering in CA1 cells, respectively. Our data suggest that a differential Ca^{2+} sensitivity of the regulatory cascades targeting NMDARs plays a key role in determining the direction and magnitude of NMDA responses in various types of neurons. These findings may have important implications for NMDA receptor-dependent synaptic plasticity and the differential sensitivity of CA1 and CA3 PCs to NMDAR-dependent ischemic cell death.
The Journal of Neuroscience, January 14, 2004 • 24(2):350 –355

Improvement and Decline in Tactile Discrimination Behavior after Cortical Plasticity Induced by Passive Tactile Coactivation

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Perceptual learning can be induced by passive tactile coactivation without attention or reinforcement. We used functional MRI (fMRI) and psychophysics to investigate in detail the specificity of this type of learning for different tactile discrimination tasks and the underlying cortical reorganization. We found that a few hours of Hebbian coactivation evoked a significant increase of primary (SI) and secondary (SII)AQ: C somatosensory cortical areas representing the stimulated body parts. The amount of plastic changes was strongly correlated with improvement in spatial discrimination performance. However, in the same subjects, frequency discrimination was impaired after coactivation, indicating that even maladaptive processes can be induced by intense passive sensory stimulation.
The Journal of Neuroscience, January 14, 2004 • 24(2):442– 446

Immunoblockage of 9-*O*-Acetyl GD3 Ganglioside Arrests the *In Vivo* Migration of Cerebellar Granule Neurons

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During development of the cerebellum, radial glial cells guide the migration of granule cell precursors from the external granular cell layer toward the internal granular cell layer. The cellular membranes of migrating neurons and glial fibers organize a specialized migration junction at the site of contact between these cells, and several molecules have been implicated in the control of this glial-guided neuronal migration program. The monoclonal antibody Jones (mAb Jones) recognizes the ganglioside 9-*O*-acetyl GD3, which is expressed in migratory profiles in the developing and adult CNS.AQ: A Recently, this ganglioside was suggested to play a role in neuronal migration in cerebellar cultures. In this report, we use antibody perturbation assays to investigate a possible role of 9-*O*-acetyl GD3 in the neuronal migration program *in vivo*. The results show that chronic intracerebroventricular administration of mAb Jones arrests neuronal migration in the developing cerebellum of live animals. Proliferating granule cell precursors were labeled with 5-bromo-2′-deoxyuridine (BrdU), and their migratory behavior was analyzed and compared with control groups. Immunoblockage of 9-*O*-acetyl GD3 arrests 43% of the BrdU-labeled granule precursors in the external granular cell layer. Together with our previous results, this report strongly suggests that the ganglioside 9-*O*-acetyl GD3 plays a crucial role in the migration of cerebellar granule cells along radial glial fibers in the developing rat cerebellum.
The Journal of Neuroscience, January 14, 2004 • 24(2):474 – 478

Androgens Increase Spine Synapse Density in the CA1 Hippocampal Subfield of Ovariectomized Female Rats

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The effects of androgen on the density of spine synapses on pyramidal neurons in the CA1 area of the hippocampus were studied in ovariectomized (OVX) adult female rats. Treatment of OVX rats with testosterone propionate (TP; 500 μg/d, s.c., 2 d) significantly increased spine synapse density (from 0.661 $\pm$ 0.016 spine synapse/μm^3 in OVX rats to 1.081 $\pm$ 0.018 spine synapse/μm^3 after TP treatment). A smaller, but still statistically significant, increase in synapse density (0.955 $\pm$ 0.029 spine synapse/μm^3) was observed in OVX animals after treatment with the nonaromatizable androgen dihydrotestosterone (DHT; 500 μg/d, s.c., 2 d). Administration of 1 mg of letrozole, a powerful nonsteroidal aromatase inhibitor, 1 hr before the steroid injections almost completely blocked the synaptic response to testosterone, resulting in a mean synapse density (0.723 $\pm$ 0.003 spine synapse/μm^3) only slightly higher than in OVX control rats. By contrast, the response to DHT was unaffected by letrozole pretreatment. These data suggest that androgen secretion during the female reproductive cycle may contribute to cyclical changes in hippocampal synaptic density. They also indicate that androgen treatment may be as effective as estrogen replacement in reversing the decline in hippocampal CA1 spine synapses that follows loss of ovarian function. Induction of hippocampal synapse formation by androgen is not mediated entirely via intracerebral estrogen biosynthesis, however, because aromatase-independent mechanisms also significantly affect CA1 spine synapse density.

The Journal of Neuroscience, January 14, 2004 • 24(2):495–499

Suppression of p75NTR Does Not Promote Regeneration of Injured Spinal Cord in Mice

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The neurotrophin receptor p75NTR is the coreceptor for NogoAQ: A receptor, mediating growth cone collapse *in vitro* by MAG, myelin oligodendrocyte glycoprotein (Omgp), and Nogo. Whether p75NTR plays any role in the failure of nerve regeneration *in vivo* is not known. Immunohistochemical data showed that p75NTR was expressed in only a very small subset of ascending sensory axons but not in any corticospinal axons in the dorsal column of either normal or injured spinal cord. Using p75NTR-deficient mice, we showed that the depletion of the functional p75NTR did not promote the regeneration of the descending corticospinal tract and ascending sensory neurons in the spinal cord 2 weeks after spinal cord injury. Local administration of p75NTR-Fc fusion molecule, the dominant-negative receptor to block the function of neurite outgrowth inhibitors, did not improve regeneration of ascending sensory neurons in the injured spinal cord. Our results suggest that p75NTR may not be a critical molecule mediating the function of myelin-associated inhibitory factors *in vivo*.

The Journal of Neuroscience, January 14, 2004 • 24(2):542–546

Articles

CELLULAR/MOLECULAR

The Effects of Vesicular Volume on Secretion through the Fusion Pore in Exocytotic Release from PC12 Cells

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Many spikes in amperometric records of exocytosis events initially exhibit a prespike feature, or foot, which represents a steady-state flux of neurotransmitter through a stable fusion pore spanning both the vesicle and plasma membranes and connecting the vesicle lumen to the extracellular fluid. Here, we present the first evidence indicating that vesicular volume before secretion is strongly correlated with the characteristics of amperometric foot events. L-3,4-Dihydroxyphenylalanine and reserpine have been used to increase and decrease, respectively, the volume of single pheochromocytoma cell vesicles. Amperometry and transmission electron microscopy have been used to determine that as vesicle size is decreased the frequency with which foot events are observed increases, the amount and duration of neurotransmitter released in the foot portion of the event decreases, and vesicles release a greater percentage of their total contents in the foot portion of the event. This previously unidentified correlation provides new insight into how vesicle volume can modulate the activity of the exocytotic fusion pore.

The Journal of Neuroscience, January 14, 2004 • 24(2):303–309

Locking the Dimeric $GABA_B$ G-Protein-Coupled Receptor in Its Active State

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G-protein-coupled receptors (GPCRs) play a major role in cell– cell communication in the CNS. These proteins oscillate between various inactive and active conformations, the latter being stabilized by agonists. Although mutations can lead to constitutive activity, most of these destabilize inactive conformations, and none lock the receptor in an active state. Moreover, GPCRs are known to form dimers, but the role of each protomer in the activation process remains unclear. Here, we show that the heterodimeric GPCR for the main inhibitory neurotransmitter, the $GABA_B$ receptor, can be locked in its active state by introducing two cysteines expected to form a disulphide bridge to maintain the binding domain of the $GABA_{B1}$ subunit in a closed form. This constitutively active receptor cannot be inhibited by antagonists, but its normal functioning, activation by agonists, and inhibition by antagonists can be restored after reduction with dithiothreitol. These data show that the closed state of the binding domain of $GABA_{B1}$ is sufficient to turn ON this heterodimeric receptor and illustrate for the first time that a GPCR can be locked in an active conformation.

The Journal of Neuroscience, January 14, 2004 • 24(2):370 –377

PSD93 Regulates Synaptic Stability at Neuronal Cholinergic Synapses

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Neuronal cholinergic synapses play important roles in both the PNS and CNS.AQ: B However, the mechanisms that regulate the formation, maturation, and stability of neuronal cholinergic synapses are poorly understood. In this study, we use the readily accessible mouse superior cervical ganglion (SCG) and submandibular ganglion (SMG) to examine the assembly of the postsynaptic complex of neuronal cholinergic synapses. We find that novel splicing forms of PSD93 (postsynaptic density 93)AQ: C are expressed in SCG. By immunostaining, we show that PSD93 proteins precisely colocalize with neuronal nicotinic acetylcholine receptors (nAChRs) at synapses of the SCG and SMG. Subcellular fractionation demonstrates that PSD93 is enriched in the PSD fraction of SCG, and coimmunoprecipitation shows that PSD93 and neuronal nAChRs form a complex *in vivo*. Furthermore, two additional components of the well characterized glutamatergic postsynaptic complex, GKAP/SAPAP (guanylate kinase domain-associated protein/synapse-associated protein-associated protein) and Shank/ProSAP family proteins, are also present at neuronal cholinergic synapses. To assess the function of this protein complex at neuronal cholinergic synapses *in vivo*, we examined ganglia in mice that lack PSD93. We find that neuronal cholinergic synapses form properly in PSD93 null mice. After denervation, however, synaptic clusters of nAChRs disassemble much faster in mice lacking PSD93 than those in AQ: Dwild-type mice. These results demonstrate that PSD93 is a key component of the postsynaptic scaffold at neuronal cholinergic synapses and plays an important role in synaptic stability. In addition, these results suggest that the mechanism of postsynaptic scaffolding is conserved between neuronal cholinergic and glutamatergic synapses.

The Journal of Neuroscience, January 14, 2004 • 24(2):378 –388

Competition between Phasic and Asynchronous Release for Recovered Synaptic Vesicles at Developing Hippocampal Autaptic Synapses

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Developing hippocampal neurons in microisland culture undergo rapid and extensive transmitter release-dependent depression of evoked (phasic) excitatory synaptic activity in response to 1 sec trains of 20 Hz stimulation. Although evoked phasic release was attenuated by repeated stimuli, asynchronous (miniature like) release continued at a high rate equivalent to ~2.8 readily releasable pools (RRPs) of quanta/sec. Asynchronous release reflected the recovery and immediate release of quanta because it was resistant to sucrose-induced depletion of the RRP. Asynchronous and phasic release appeared to compete for a common limited supply of release-ready quanta because agents that block asynchronous release, such as EGTA-AM, led to enhanced steady-state phasic release, whereas prolongation of the asynchronous release time course by LiCl delayed recovery of phasic release from depression. Modeling suggested that the resistance of asynchronous release to depression was associated with its ability to out-compete phasic release for recovered quanta attributable to its relatively low release rate (up to 0.04/msec per vesicle) stimulated by bulk intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) that could function over prolonged intervals between successive stimuli. Although phasic release was associated with a considerably higher peak rate of release (0.4/msec per vesicle), the $[Ca^{2+}]_i$ microdomains that trigger it are brief (1 msec), and with asynchronous release present, relatively few quanta can accumulate within the RRP to be available for phasic release. We conclude that despite depression of phasic release during train stimulation, transmission can be maintained at a near-maximal rate by switching to an asynchronous mode that takes advantage of a bulk presynaptic $[Ca^{2+}]_i$.

The Journal of Neuroscience, January 14, 2004 • 24(2):420 – 433

5-Aminoimidazole-4-Carboxamide-1-β-4-Ribofuranoside Inhibits Proinflammatory Response in Glial Cells: A Possible Role of AMP-Activated Protein Kinase

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AMP-activated protein kinase (AMPK) is tightly regulated by the cellular AMP:ATP ratio and plays a central role in the regulation of energy homeostasis and metabolic stress. A pharmacological activator of AMPK, 5-amino-4-imidazole carboxamide riboside (AICAR) inhibited lipopolysaccharide (LPSAQ: D)-induced expression of proinflammatory cytokines (tumor necrosis factor α, interleukin-1β, and interleukin-6) and inducible nitric oxide synthaseAQ: E in primary rat astrocytes, microglia, and peritoneal macrophages. AICAR attenuates the LPS-induced activation of nuclear factor κB via downregulation of IκB kinase α/βAQ: F activity. It also inhibits nuclear translocation of CCAAT/enhancer-binding protein (C/EBP) transcription factor by inhibiting the expression of C/EBP-δ in brain glial cellsAQ: G. The dominant negative form of AMPKα_2 (D157A) and its antisense documentsAQ: H a possible role of AMPK in the regulation of the cellular proinflammatory process. AICAR also inhibited the production of inflammatory mediators in serum and their expression in CNS of rats injected with a sublethal dose of LPS by intraperitoneal injection. These observations in cultured cells as well as in the animal model suggest that AICAR may be of therapeutic value in treating inflammatory diseases.

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Brain-Derived Neurotrophic Factor Modulates Fast Synaptic Inhibition by Regulating $GABA_A$ Receptor Phosphorylation, Activity, and Cell-Surface Stability

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The efficacy of GABAergic synaptic inhibition is a principal factor in controlling neuronal activity. We demonstrate here that brain-derived neurotrophic factorAQ: C modulates the activity of $GABA_A$ receptors, the main sites of fast synaptic inhibition in the brain, within minutes of application. Temporally, this comprised an early enhancement in the miniature IPSCAQ: D amplitude, followed by a prolonged depression. This modulation was concurrent with enhanced PKC-mediated phosphorylation, followed by protein phosphatase 2A (PP2A)-mediated dephosphorylation of the $GABA_A$ receptor. Mechanistically, these events were facilitated by differential recruitment of PKC, receptor for activated C-kinaseAQ: E, and PP2A to $GABA_A$ receptors, depending on the phosphorylation state of the receptor β_3-subunit. Thus, transient formation of $GABA_A$ receptor signaling complexes has the potential to provide a basis for acute changes in receptor function underlying GABAergic synaptic plasticity.

The Journal of Neuroscience, January 14, 2004 • 24(2):522–530

DEVELOPMENT/PLASTICITY/REPAIR

Semaphorin3D Guides Retinal Axons along the Dorsoventral Axis of the Tectum

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We examined the role of Sema3D,AQ: A a semaphorin of previously unknown function, in guiding retinal ganglion cell (RGC) axons to the optic tectum in the developing zebrafish. Sema3D is expressed more strongly in the ventral versus dorsal tectum, suggesting that it may participate in guiding RGC axons along the dorsoventral axis of the tectum. Ubiquitous misexpression of Sema3D in transgenic zebrafish inhibits ventral but not dorsal RGC axon growth. In addition, ventral RGC axons avoid or stop at individual cells misexpressing Sema3D along their pathway. Sema3D ubiquitous misexpression at later stages also causes ventral RGC axon arbors to spread more widely along the dorsoventral axis of the tectum. Knock-down of Sema3D with morpholino antisense causes ventral RGC axons to extend aberrantly into the ventral tectum. These results suggest that Sema3D in the ventral tectum normally acts to inhibit ventral RGCs from extending into ventral tectum, ensuring their correct innervation of dorsal tectum.

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Activation of cAMP Signaling Facilitates the Morphological Maturation of Newborn Neurons in Adult Hippocampus

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Previous studies have demonstrated that activation of the cAMP cascade, including the cAMP response element-binding protein (CREB), increases the proliferation and survival of newborn neurons in adult mouse hippocampus. In the present study, we determined whether the cAMP–CREBAQ: A cascade also influences the morphological maturation of newborn neurons in the subgranular zone of the hippocampus. Rolipram, a selective inhibitor of the cAMP-specific phosphodiesterase type 4AQ: B, was administered to activate the cAMP cascade, and neuronal morphology was determined by analysis of Golgi-impregnated neurons in the subgranular zone of hippocampus. Rolipram administration significantly increased the number of branch points and length of dendrites relative to vehicle treatment. Increased branch number and length were accompanied by increased levels of phosphorylated CREB, the active form of this transcription factor, in immature neurons. In contrast, the morphology of Golgi-impregnated neurons was not significantly influenced by rolipram treatment in inducible transgenic mice expressing a dominant-negativeAQ: C mutant of CREB in hippocampus. We also tested the influence of cAMP analogs in primary hippocampal cultures and found that activation of the cAMP pathway increased and inhibition of the cAMP cascade decreased the number of branches and length of processes as observed *in vivo*. These findings indicate that the cAMP–CREB cascade plays an important role in the differentiation and maturation of newborn neurons in hippocampus.

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Odorant Receptor Expression Patterns Are Restored in Lesion-Recovered Rat Olfactory Epithelium

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Lesions of the olfactory periphery provide a means for examining the reconstitution of a diverse and highly regulated population of sensory neurons and the growth, *en masse*, of nascent axons to the bulb. The olfactory epithelium and its projection onto the bulb are reconstituted after ablation by methyl bromide gas, and some measure of olfactory function is restored. The extent to which the system regenerates the full repertoire of odorant receptor-expressing neurons, particularly their spatially restricted distribution across the epithelial sheet, is unknown, however, and altered odorant receptor expression might contribute to the persistent distortion of odorant quality that is observed in the lesioned-recovered animals. To address the question of receptor expression in the recovered epithelium, we performed *in situ* hybridization with digoxigenin-labeled riboprobes for eight odorant receptors on the olfactory epithelium from unilaterally methyl bromide-lesioned and control rats. The data demonstrate that the distribution of sensory neuron types, as identified and defined by odorant receptor expression, is restored to normal or nearly so by 3 months after lesion. Likewise, the numbers of probe-labeled neurons in the lesioned-recovered epithelium are nearly equivalent to the unlesioned side at this time. Finally, our evidence suggests that odorant receptors are distributed in multiple overlapping bands in the normal, unlesioned, and lesioned-recovered epithelium rather than in the conventionally accepted three or fourAQ: A zones. Thus, the primary sensory elements required for functional recovery of the olfactory system after damage are restored, and altered function implies the persistence of a more central failure in regeneration.

The Journal of Neuroscience, January 14, 2004 • 24(2):356–369

Keratan Sulfate Proteoglycan Phosphacan Regulates Mossy Fiber Outgrowth and Regeneration

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We have examined the role of chondroitin sulfate proteoglycans (CSPGs) and keratan sulfate proteoglycans (KSPGs) in directing mossy fiber (MF) outgrowth and regeneration in rat hippocampal slice cultures. MFs normally exhibit a very specific innervation pattern that is restricted to the stratum lucidum (SL). In addition, MFs in hippocampal slice cultures will regenerate this specific innervation pattern after transection. CSPGs are one of the best characterized inhibitory axon guidance molecules in the CNS and are widely expressed in all areas of the hippocampus except SL. KSPGs are also widely expressed in the hippocampus, but their role in axon outgrowth has not been extensively studied in the CNS where phosphacan is the only protein that appears to contain KS-GAGs. Cultured hippocampal slices were treated with either chondroitin ABC lyase or keratanases to reduce the inhibitory axon guidance properties of CS and KS proteoglycans, respectively. The ability of transected MFs to regenerate their normal innervation pattern after digestion of CS and KS-GAGS sugars with these enzymes was examined. Only keratanase treatment resulted in misrouting of MFs. Identifying the mechanism by which keratanase produced MF misrouting is complicated by the presence of splice variants of the phosphacan gene that include the extracellular form of phosphacan and the transmembrane receptor protein tyrosine phosphatase β/ζ (RPTPβ/ζ). Both forms of phosphacan are made by astrocytes, suggesting that keratanase alters MF outgrowth by modifying astrocyte function.

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Limited Role of Developmental Programmed Cell Death Pathways in *Drosophila norpA* Retinal Degeneration

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We examined the role of programmed cell death (PCD) pathways in retinal degeneration caused by a mutation in the AQ: A*norpA* gene. *norpA* degeneration shows morphological hallmarks of programmed cell death, specifically cytoplasmic condensation and engulfment of the dying photoreceptor cells by neighboring retinal pigment cells. However, genetic mosaic analysis of adult photoreceptors lacking *rpr*, *hid*, and *grim* show that these PCD inducers are not required for *norpA* degeneration. We showed previously that ectopic expression of either *rpr* or *hid* triggers rapid PCD in adult photoreceptors, and this is completely suppressed by the coexpression of the baculoviral P35 caspase inhibitor. In contrast, expression of P35 does not suppress *norpA* retinal degeneration, although a small delay in the rate of degeneration is observed in low light–low temperature conditions. P35 does not alter the morphological characteristics of *norpA* cell death. Overexpression of the *Drosophila* inhibitor of apoptosis Diap1 or a dominant-negative form of the Dronc caspase, even when coexpressed with P35, does not dramatically alter the time course of *norpA* degeneration. These results establish that the pathways responsible for PCD in development do not play a major role in adult retinal degeneration caused by *norpA*.

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The Central Fragment of Reelin, Generated by Proteolytic Processing *In Vivo*, Is Critical to Its Function during Cortical Plate Development

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AQ: BReelin is a large extracellular protein that controls cortical development. It binds to lipoprotein receptors very-low-density lipoprotein receptor and apolipoprotein-E receptor type 2,AQ: C thereby inducing phosphorylation of the adapter Dab1. *In vivo*, Reelin is cleaved into three fragments, but their respective function is unknown. Here we show the following: (1) the central fragment is necessary and sufficient for receptor binding *in vitro* and for Dab1 phosphorylation in neuronal cultures; (2) Reelin does not bind the protocadherin cadherin-related neuronal receptor (CNR1) as reported previously; (3) Reelin and its central fragment are equally able to rescue the *reeler* phenotype in a slice culture assay; and (4) anti-receptor antibodies can induce Dab1 phosphorylation but do not correct the *reeler* phenotype in slices. These observations show that the function of Reelin is critically dependent on the central fragment generated by processing but primarilyAQ: D independent of interactions with CNR1 and on the N-terminal region. They also indicate that events acting in parallel to Dab1 phosphorylation might be required for full activity.

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Monocular Enucleation Induces Nuclear Localization of Calcium/Calmodulin-Dependent Protein Kinase IV in Cortical Interneurons of Adult Monkey Area V1

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Elevation of intracellular Ca^{2+} levels activates calcium/calmodulin-dependent protein kinase (CaMK) IV, which in turn plays an important role in neuroprotection and neuroplasticity. The possibility that CaMKIV is similarly involved in neocortical tissue has not been examined previously, especially with regard to the plastic nature of ocular dominance features in the primary visual cortex (area V1). We addressed this question by way of monocular enucleation (ME) to disrupt sensory input and examine CaMKIV expression changes in monkey area V1. Immunohistochemical staining of area V1 in normal infants showed a nuclear presence of CaMKIV, which did not changed after ME. However, a striking set of layer- and time-dependent changes in nuclear CaMKIV expression was observed in adult area V1 after ME. A strong increase in nuclear CaMKIV levels was evident in cortical layers II/III and VI after 1 d of ME and in layer IVC after 5 d of ME. These specific laminar changes persisted after 30 d of ME and, most notably, showed a columnar profile in which CaMKIV expression was linked to open-eye columns. Real-time quantitative reverse transcription-PCR and Western blot analysis showed that total amounts of CaMKIV mRNA and protein remained unchanged after ME, suggesting that a nuclear translocation may occur from the cytoplasm. Finally, double-label immunohistochemical staining with a pyramidal cell marker (SMI-32) showed that CaMKIV was absent in this subtype, whereas coincidental expression with GABA, parvalbumin, and calretinin, but not calbindin, showed its clear presence in a subset of interneurons. We propose that CaMKIV activity within diverse groups of cortical interneurons may play an important role in adaptive plastic reorganization of adult neocortical tissue.

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Control of Cortical Neuron Migration and Layering: Cell and Non Cell-Autonomous Effects of p35

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The migration, arrest, and ultimately positioning of cortical neurons require signaling activity from Reelin as well as from cyclin-dependent kinase 5 (Cdk5). Although both molecules control neuronal positioning, they achieve their effects by quite separate molecular pathways. Cdk5 is a serine–threonine kinase, the activity of which is dependent onAQ: B its activating subunits p35 and p39. Mice deficient in Cdk5, p35, or both p35 and p39 display the hallmarks of disturbed cortical development, including cortical layer inversion, neuronal disorientation, and abnormal fiber infiltration. To distinguish between the cell- and non cell-autonomous functions of p35, we constructed $p35^{+/+} \leftrightarrow p35^{-/-}$ chimeras using the *lacZ* geneAQ: C as an independent marker for $p35^{+/+}$ cells. In this shared developmental space, wild-type and mutant neurons behaved cell-autonomously with respect to layering. Wild-type cells formed a properly layered supercortex that is mirrored by an inverted mutant cortex lying underneath. However, this genotype-specific behavior was confined to the pyramidal population, and interneurons belonging to either genotype were indiscriminately distributed. However, there was also non cell-autonomous rescue of mutant neurons, and this rescue was specific only to early-born pyramidal neurons belonging to layer V. Rescued neurons reached the correct layer address and possessed appropriate neuronal morphology, orientation, and projections. Later-born neurons belonging to layers II and III were not rescued. These results demonstrate that p35 signaling can have both cell- and non cell-autonomous consequences, and their effects are not uniformly shared by cortical neurons born at different times or born at different places (projection neurons vs interneurons).

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BEHAVIORAL/SYSTEMS/COGNITIVE

Sodium Channels and Dendritic Spike Initiation at Excitatory Synapses in Globus Pallidus Neurons

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Glutamatergic inputs from the subthalamic nucleusAQ: C are suspected to provide a prominent source of excitation to globus pallidus (GP) neurons, despite their scarce number and mainly distal dendritic location. In this study we address the issue of whether dendritic sodium channels may facilitate the effect of excitatory inputs in GP. First, we examined the subcellular distribution of sodium channels using electron microscopic observations of immunoperoxidase and immunogold labeling. Voltage-gated sodium channels were found throughout GP dendrites and furthermore exhibited a specific clustering at sites of excitatory synaptic inputs. To examine the possibility that these channels could mediate dendritic spike generation, synaptic stimulation at visualized dendritic sites was performed during whole-cell recordings *in vitro*. These recordings revealed dendritic spike initiation in response to small excitatory inputs even for very distal stimulation sites. In contrast, subthreshold responses were mostly or fully attenuated at the soma for stimulation sites on distal dendrites. Computer simulations support the hypothesis that postsynaptic clustering of sodium channels allows dendritic triggering of spikes in response to inputs that would be too small to trigger a spike given uniformly distributed dendritic sodium channels. These findings indicate that postsynaptic sodium channel clustering is an effective mechanism to mediate a novel form of synaptic amplification and dendritic spike initiation. The ability of small amounts of excitation to trigger spikes in GP dendrites supports the prominent role of subthalamic input in the control of GP activity.

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Small Clusters of Electrically Coupled Neurons Generate Synchronous Rhythms in the Thalamic Reticular Nucleus

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The inhibitory neurons of the thalamic reticular nucleus (TRN) contribute to the generation of widespread oscillations in the thalamocortical system. Some TRN neurons are interconnected by electrical synapses, and here we tested the possibility that electrical synapses mediate rhythmic synchrony in juvenile rats. Both the incidence and strength of electrical coupling between pairs of TRN neurons were a steep function of intersomatic distance, and coupling was absent at distances >40 μm. Presynaptic spike bursts evoked much larger electrical postsynaptic potentials than did single presynaptic spikes. Activation of metabotropic glutamate receptors (mGluRs) with a bath-applied agonist or an endogenous ligand released during tetanic stimulation induced robust rhythms of the subthreshold membrane potential, with a mean frequency of $\sim$10 Hz. In the absence of fast chemical synaptic transmission, subthreshold rhythms and the action potentials that they evoked were well synchronized between closely spaced, electrically coupled pairs; rhythms in noncoupled cells were not synchronized. The results suggest that electrical synapses can coordinate spindle-frequency rhythms among small clusters of mGluR-activated TRN cells.

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Learning Modulation of Odor-Induced Oscillatory Responses in the Rat Olfactory Bulb: A Correlate of Odor Recognition?

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In the first relay of information processing, the olfactory bulb (OB), odors are known to generate specific spatial patterns of activity. Recently, in freely behaving rats, we demonstrated that learning modulated oscillatory activity in local field potential (LFP), in response to odors, in both β (15–40 Hz) and γ (60–90 Hz) bandsAQ: A. The present study further characterized this odor-induced oscillatory activity with emphasis on its spatiotemporal distribution over the olfactory bulb and on its relationship with improvement of behavioral performances along training. For that purpose, LFPs were simultaneously recorded from four locations in the OB in freely moving rats performing an olfactory discrimination task. Electrodes were chronically implanted near relay neurons in the mitral cell body layer. Time–frequency methods were used to extract signal characteristics (amplitude, frequency, and time course) in the two frequency bands. Before training, odor presentation produced, on each site, a power decrease in γ oscillations and a weak but significant increase in power of β oscillations ($\sim$25 Hz). When the training was achieved, these two phenomena were amplified. Interestingly, the β oscillatory response showed several significant differences between the anterodorsal and posteroventral regions of the OB. In addition, clear-cut β responses occurred in the signal as soon as animals began to master the task. As a whole, our results point to the possible functional importance of β oscillatory activity in the mammalian OB, particularly in the context of olfactory learning.

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Serotonin Enhances the Resistance Reflex of the Locomotor Network of the Crayfish through Multiple Modulatory Effects that Act Cooperatively

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Serotonin (5HT) is an endogenous amine that modifies posture in crustacea. Here, we examined the mechanisms of action of 5HT on the resistance reflex in crayfish legs. This reflex, which counteracts movements imposed on a limb, is based on a negative feedback system formed by proprioceptors that sense joint angle movements and activate opposing motoneurons. We performed intracellular recordings from depressor motoneurons while repetitively stretching and releasing a leg joint proprioceptor in a resting *in vitro* preparation (i.e., a preparation that lacks spontaneous rhythmic activity). 5HT increased the amplitude of the depolarization during the release phase of the proprioceptor (corresponding to an upward movement of the leg) and the discharge frequency of the motoneurons. The 5HT-induced increase in the resistance reflex is caused, to a large extent,AQ: B by polysynaptic pathways because it was very attenuated in the presence of high divalent cation solution. In addition to this activation of the polysynaptic pathways, 5HT also has postsynaptic effects that enhance the resistance reflex. 5HT causes a tonic depolarization, as well as an increase in the time constant and input resistance of motoneurons. We developed a simple mathematical model to describe the integrative properties of the motoneurons. The conclusion of this study is that the input frequency and the decay time constant of the EPSPs interact in such a way that small simultaneous changes in these parameters can cause a large effect on summation. Therefore, the conjunction of presynaptic and postsynaptic changes produces a strong cooperative effect on the resistance reflex response.

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Inactivation of Calcium-Binding Protein Genes Induces 160 Hz Oscillations in the Cerebellar Cortex of Alert Mice

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Oscillations in neuronal populations may either be imposed by intrinsically oscillating pacemakers neurons or emerge from specific attributes of a distributed network of connected neurons. Calretinin and calbindin are two calcium-binding proteins involved in the shaping of intraneuronal Ca^{2+} fluxes. However, although their physiological function has been studied extensively at the level of a single neuron, little is known about their role at the network level. Here we found that null mutations of genes encoding calretinin or calbindin induce 160 Hz local field potential oscillations in the cerebellar cortex of alert mice. These oscillations reached maximum amplitude just beneath the Purkinje cell bodies and are reinforced in the cerebellum of mice deficient in both calretinin and calbindin. Purkinje cells fired simple spikes phase locked to the oscillations and synchronized along the parallel fiber axis. The oscillations reversibly disappeared when gap junctions or either $GABA_A$ or NMDA receptors were blocked. Cutaneous stimulation of the whisker region transiently suppressed the oscillations. However, the intrinsic somatic excitability of Purkinje cells recorded in slice preparation was not significantly altered in mutant mice. Functionally, these results suggest that 160 Hz oscillation emerges from a network mechanism combining synchronization of Purkinje cell assemblies through parallel fiber excitation and the network of coupled interneurons of the molecular layer. These findings demonstrate that subtle genetically induced modifications of Ca^{2+} homeostasis in specific neuron types can alter the observed dynamics of the global network.

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Dynamic Analysis of Learning in Behavioral Experiments

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AQ: AUnderstanding how an animal's ability to learn relates to neural activity or is altered by lesions, different attentional states, pharmacological interventions, or genetic manipulations are central questions in neuroscience. Although learning is a dynamic process, current analyses do not use dynamic estimation methods, require many trials across many animals to establish the occurrence of learning, and provide no consensus as how best to identify when learning has occurred. We develop a state–space model paradigm to characterize learning as the probability of a correct response as a function of trial number (learning curve). We compute the learning curve and its confidence intervals using a state–space smoothing algorithm and define the learning trial as the first trial on which there is reasonable certainty (>0.95) that a subject performs better than chance for the balance of the experiment. For a range of simulated learning experiments, the smoothing algorithm estimated learning curves with smaller mean integrated squared error and identified the learning trials with greater reliability than commonly used methods. The smoothing algorithm tracked easily the rapid learning of a monkey during a single session of an association learning experiment and identified learning 2 to 4 d earlier than accepted criteria for a rat in a 47 d procedural learning experiment. Our state–space paradigm estimates learning curves for single animals, gives a precise definition of learning, and suggests a coherent statistical framework for the design and analysis of learning experiments that could reduce the number of animals and trials per animal that these studies require.
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Long-Term Potentiation in an Avian Basal Ganglia Nucleus Essential for Vocal Learning

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Vocal learning in songbirds provides an excellent model for sensorimotor learning in vertebrates, with an accessible, well-defined behavior and discrete neural substrate. The rich behavioral plasticity exhibited by songbirds, however, contrasts starkly with the scarcity of candidate cellular mechanisms. Here, we report for the first time on an activity-dependent form of synaptic plasticity in area X, a component of the song system required for song learning and song maintenance. In slice preparations of zebra finch area X, pairing of high-frequency presynaptic stimulation with postsynaptic depolarization induces Hebbian long-term potentiation (LTP) of the glutamatergic inputs to spiny neurons. This form of LTP requires activation of NMDA receptors and D1-like dopamine receptors. In addition, LTP is observed in birds as young as 47 d after hatching and also in adult birds but not in younger birds, providing evidence of developmental regulation of the onset of synaptic plasticity. These properties make this form of LTP the best known candidate mechanism for reinforcement-based vocal learning in juveniles and song maintenance in adult birds.
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Discrimination of Voiced Stop Consonants Based on Auditory Nerve Discharges

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Previous studies of the neural representation of speech assumed some form of neural code, usually discharge rate or phase locking, for the representation. In the present study, responses to five synthesized CVC_CV (e.g., /dad_da/) utterances have been examined using information–theoretic distance measures [or Kullback–Leibler (KL) distance] that are independent of a priori assumptions about the neural code. The consonants in the stimuli fall along a continuum from /b/ to /d/ and include both formant–frequency (F1, F2, and F3) transitions and onset (release) bursts. Differences in responses to pairs of stimuli, based on single-fiber auditory nerve responses at 70 and 50 dB sound pressure level, have been quantified, based on KL and KL-like distances, to show how each portion of the response contributes to information coding and the fidelity of the encoding. Distances were large at best frequencies, in which the formants differ but were largest for fibers encoding the high-frequency release bursts. Distances computed at differing time resolutions show significant information in the temporal pattern of spiking, beyond that encoded by rate, at time resolutions from 1– 40 msec. Single-fiber just noticeable differences (JNDsAQ: A) for F2 and F3 were computed from the data. These results show that F2 is coded with greater fidelity than F3, even among fibers tuned to F3, and that JNDs are larger in the syllable final consonant than in the releases.
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Magnitude of Dopamine Release in Medial Prefrontal Cortex Predicts Accuracy of Memory on a Delayed Response Task

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Modulation of neural function in the prefrontal cortex (PFC) by dopamine (DA) is essential for higher cognitive processes related to attention, working memory, and planning of future behavior. The present study demonstrates that DA efflux in the PFC is increased in a phasic manner when a rat engages in search behavior for food reward on an eight arm radial maze guided by memory, independent of whether or not reward is obtained for making the correct choice. Furthermore, disruption of accurate recall of the correct pattern of arms induced by increasing the delay period from 30 min to 1 or 6 hr, is associated with attenuated DA efflux during the retrieval phase of the task. The observed increase in DA efflux in the absence of reward at a 30 min delay and the minimal increase during consumption of the same quantity of food during poor performance after an unexpected 6 hr delay, argue against a simple relationship between DA function in the PFC and reward processes. Instead, these data demonstrate a close functional relationship between the release of DA from terminals within the PFC and the retrieval of specific trial unique memories; furthermore, the magnitude of mesocortical DA efflux is predictive of the accuracy of this form of memory.

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NEUROBIOLOGY OF DISEASE

Attenuated Response to Stress and Novelty and Hypersensitivity to Seizures in 5-HT_4 Receptor Knock-Out Mice

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To study the functions of 5-HT_4 receptors, a null mutation was engineered in the corresponding gene. 5-HT_4 receptor knock-outAQ: B mice displayed normal feeding and motor behaviors in baseline conditions but abnormal feeding and locomotor behavior in response to stress and novelty. Specifically, stress-induced hypophagia and novelty-induced exploratory activity were attenuated in the knock-out mice. In addition, pentylenetetrazol-induced convulsive responses were enhanced in the knock-out mice, suggesting an increase in neuronal network excitability. These results provide the first example of a genetic deficit that disrupts the ability of stress to reduce feeding and body weight and suggest that 5-HT_4 receptors may be involved in stress-induced anorexia and seizure susceptibility.

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Dysregulated IP_3 Signaling in Cortical Neurons of Knock-In Mice Expressing an Alzheimer's-Linked Mutation in *Presenilin1* Results in Exaggerated Ca^{2+} Signals and Altered Membrane Excitability

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Disruptions in intracellular Ca^{2+} signaling are proposed to underlie the pathophysiology of Alzheimer's disease (AD), and it has recently been shown that AD-linked mutations in the *presenilin 1* gene (*PS1*) enhance inositol triphosphateAQ: B (IP_3)-mediated Ca^{2+} liberation in nonexcitable cells. However, little is known of these actions in neurons, which are the principal locus of AD pathology. We therefore sought to determine how *PS1* mutations affect Ca^{2+} signals and their subsequent downstream effector functions in cortical neurons. Using whole-cell patch-clamp recording, flash photolysis, and two-photon imaging in brain slices from 4- 5-week-old mice, we show that IP_3-evoked Ca^{2+} responses are more than threefold greater in $PS1_{M146V}$ knock-in mice relative to age-matched nontransgenic controls. Electrical excitability is thereby reduced via enhanced Ca^{2+} activation of K^+ conductances. Action potential-evoked Ca^{2+} signals were unchanged, indicating that $PS1_{M146V}$ mutations specifically disrupt intracellular Ca^{2+} liberation rather than reduce cytosolic Ca^{2+} buffering or clearance. Moreover, IP_3 receptor levels are not different in cortical homogenates, further suggesting that the exaggerated cytosolic Ca^{2+} signals may result from increased store filling and not from increased flux through additional IP_3-gated channels. Even in young animals, *PS1* mutations have profound effects on neuronal Ca^{2+} and electrical signaling: cumulatively, these disruptions may contribute to the long-term pathophysiology of AD.

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β-Amyloid Peptides Induce Mitochondrial Dysfunction and Oxidative Stress in Astrocytes and Death of Neurons through Activation of NADPH Oxidase

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β-Amyloid (βA)AQ: C peptide is strongly implicated in the neurodegeneration underlying Alzheimer's disease, but the mechanisms of neurotoxicity remain controversial. This study establishes a central role for oxidative stress by the activation of NADPH oxidase in astrocytes as the cause of βA-induced neuronal death. βA causes a loss of mitochondrial potential in astrocytes but not in neurons. The mitochondrial response consists of Ca^{2+}-dependent transient depolarizations superimposed on a slow collapse of potential. The slow response is both prevented by antioxidants and, remarkably, reversed by provision of glutamate and other mitochondrial substrates to complexes I and II. These findings suggest that the depolarization reflects oxidative damage to metabolic pathways upstream of mitochondrial respiration. Inhibition of NADPH oxidase by diphenylene iodonium or 4-hydroxy-3-methoxy-acetophenone blocks βA-induced reactive oxygen species generation, prevents the mitochondrial depolarization, prevents βA-induced glutathione depletion in both neurons and astrocytes, and protects neurons from cell death, placing the astrocyte NADPH oxidase as a primary target of βA-induced neurodegeneration.

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