

# This Week in The Journal

## ● Cellular/Molecular

### *Taking Flip-Flops to the Membrane*

Sarah K. Coleman, Tommi Möykkynen, Chunlin Cai, Lotta von Ossowski, Esa Kuismanen, Esa R. Korpi, and Kari Keinänen

(see pages 11220–11229)

Just when you thought you knew everything about AMPA receptor trafficking, Coleman et al. shed additional light on the steps involved in the passage of receptors from endoplasmic reticulum (ER) to the membrane. AMPA receptors are assembled from four subunit types, each of which can be alternatively spliced as either a “flip” or a “flop” version. The extracellular flip/flop region influences channel activity, as flops desensitize and deactivate more rapidly than flips. Using transfected cell lines, Coleman et al. demonstrated that the flip isoform undergoes complex glycosylation in the ER and reaches the plasma membrane at 10 times higher amounts than flop isoforms, which tends to get trapped in the ER. The flip/flop trafficking differences did not seem to depend on the same amino acids that regulate channel activity and could be rescued by coexpression with the receptor-binding protein stargazin.

## ▲ Development/Plasticity/Repair

### *RET Signaling in Dopamine Neurons*

Sanjay Jain, Judith P. Golden, David Wozniak, Elizabeth Pehek, Eugene M. Johnson Jr, and Jeffrey Milbrandt

(see pages 11230–11238)

Midbrain dopaminergic neurons get a lot of attention, and with just cause. They are the neurons lost in Parkinson’s disease and also are thought to fuel reward behavior and addiction. Previous work had indicated that the glial cell-line derived neurotrophic factor (GDNF) enhances the survival of dopaminergic neurons and improves symptoms of Parkinson’s disease, possibly through a RET tyrosine kinase signaling pathway. Because GDNF or RET knock-out mice die before birth, this signaling pathway has been difficult to examine. Thus, the authors created mice lacking RET expression specifically in do-

paminergic neurons using the Cre-Lox system. The transgenic animals had the same striatal dopamine levels and behavioral measurements as normal controls. There was also no difference in the number, size, or appearance of dopaminergic neurons. Contrary to expectations, it appears that RET is not critical to the development, survival, or function of midbrain dopaminergic neurons . . . at least in normal adult mice.

## ■ Behavioral/Systems/Cognitive

### *Following the Rules*

Eveline A. Crone, Sarah E. Donohue, Ryan Honomichl, Carter Wendelken, and Silvia A. Bunge

(see pages 11239–11247)

With age, children get better at a lot of things, including their ability to switch between tasks. This week, Crone et al. used functional magnetic resonance imaging

(fMRI) to identify patterns of brain activity in volunteers, aged 8–25, cued to switch between two different tasks. Switching between tasks involves two components: rule retrieval, or the ability to learn and use prescribed rules of action to guide behavior, and task set suppression, or the ability to suppress one set of rules and access another. In adults, the ventrolateral prefrontal cortex (VLPFC) is implicated in the first component, and (pre)-supplementary motor areas (pre-SMA/SMA) in the second. The authors determined that whereas the pre-SMA/SMA function underlying suppression processes showed the same pattern of activity in adults and adolescents, the activation pattern in the VLPFC was not yet mature in adolescents. It’s food for thought for parents.

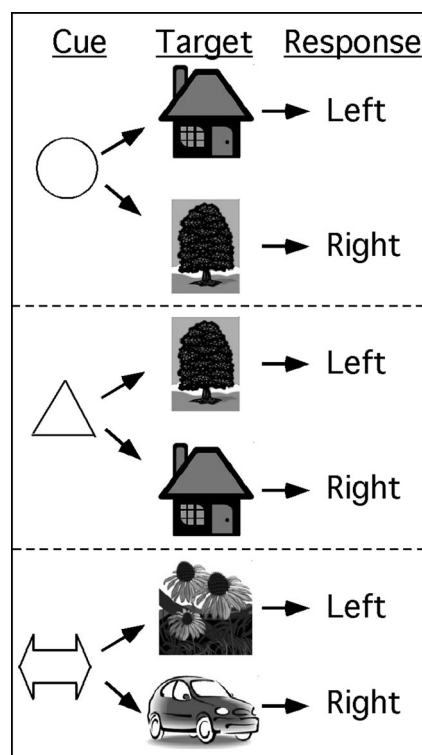
## ◆ Neurobiology of Disease

### *The SMN Protein and Motor Axon Function*

Tessa L. Carrel, Michelle L. McWhorter, Eileen Workman, Honglai Zhang, Elizabeth C. Wolstencroft, Christian Lorson, Gary Bassell, Arthur H. M. Burghes, and Christine E. Beattie

(see pages 11014–11022)

The motor neuron disease spinal muscular atrophy (SMA) results from low levels of the SMN protein. SMN is well known for its role in the biogenesis of the spliceosomal small nuclear ribonucleoprotein (snRNP), a function required in all cell types. But what function might SMN play specifically in motor neurons? Carrel et al. sought to find out. The authors previously showed that decreasing SMN levels in zebrafish using antisense morpholinos resulted in motor axon defects. In the current study, they coinjected the morpholinos with RNAs encoding different versions of the human SMN gene. Coexpression of normal SMN RNA rescued motor axons defects, whereas RNAs carrying human SMA mutations did not. However, some mutant SMN forms retained properties necessary for snRNP biogenesis, whereas other SMN forms rescued motor axons but lacked snRNP functions. SMN, therefore, has additional, snRNP-independent functions, which are essential for motor axon outgrowth.



During fMRI scanning, participants viewed a cue for 1 s; then, after a 0.5 s delay, the target stimulus was presented for 2.5 s. The left or right response was required depending on the relevant stimulus–response mapping learned before the scanning. See Crone et al. for details.

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**Cover legend:** The figure shows “cone clock” diagrams of responses recorded from parvocellular cells in the marmoset lateral geniculate nucleus. The vectors show the response phase and relative amplitude of response to L (red) and M (green) cone-isolating stimuli presented to the receptive field. Response phase is shown relative to the response to luminance modulation (vertical). Background shading distinguishes on-type from off-type luminance response. Increasing lag is shown by counterclockwise vector rotation. Thick vectors show excitatory cone inputs; thin vectors show inhibitory cone inputs. Each row shows a different cell class (from top): green-on, red-on, non-opponent on, green-off, red-off, non-opponent off. For opponent cells, the inhibitory inputs are in approximate opposite phase and arise from the opposite cone type, compared with the excitatory inputs. Numbers show receptive field eccentricity (distance from the fovea). For more details, see the article by Buzás et al. in this issue (pages 11148–11161).

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**Correction:** In the article "Retraction of Synapses and Dendritic Spines Induced by Off-Target Effects of RNA Interference," by Veronica A. Alvarez, Dennis A. Ridenour, and Bernardo L. Sabatini, which appeared on pages 7820–7825 of the July 26, 2006 issue, there was an error in the Materials and Methods section in the sequence of shLUCI. The correct sequence for shLUCI is CGTACGCGGAATACTTCGATTgagctcAATCGAAGTATTCGCGTACGctttt.

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## Articles

### CELLULAR/MOLECULAR

## Genetic and Physiological Evidence That Oligodendrocyte Gap Junctions Contribute to Spatial Buffering of Potassium Released during Neuronal Activity

**Daniela M. Menichella,<sup>1,5\*</sup> Marta Majdan,<sup>1\*</sup> Rajeshwar Awatramani,<sup>3</sup> Daniel A. Goodenough,<sup>2</sup> Erich Sirkowski,<sup>4</sup> Steven S. Scherer,<sup>4</sup> and David L. Paul<sup>1</sup>**

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Mice lacking the K<sup>+</sup> channel Kir4.1 or both connexin32 (Cx32) and Cx47 exhibit myelin-associated vacuoles, raising the possibility that oligodendrocytes, and the connexins they express, contribute to recycling the K<sup>+</sup> evolved during neuronal activity. To study this possibility, we first examined the effect of neuronal activity on the appearance of vacuoles in mice lacking both Cx32 and Cx47. The size and number of myelin vacuoles was dramatically increased when axonal activity was increased, by either a natural stimulus (eye opening) or pharmacological treatment. Conversely, myelin vacuoles were dramatically reduced when axonal activity was suppressed. Second, we used genetic complementation to test for a relationship between the function of Kir4.1 and oligodendrocyte connexins. In a Cx32-null background, haploinsufficiency of either Cx47 or Kir4.1 did not affect myelin, but double heterozygotes developed vacuoles, consistent with the idea that oligodendrocyte connexins and Kir4.1 function in a common pathway. Together, these results implicate oligodendrocytes and their connexins as having critical roles in the buffering of K<sup>+</sup> released during neuronal activity.

The Journal of Neuroscience, October 25, 2006 • 26(43):10984–10991

## A Large-Conductance Calcium-Selective Mechanotransducer Channel in Mammalian Cochlear Hair Cells

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Sound stimuli are detected in the cochlea by opening of hair cell mechanotransducer (MT) channels, one of the few ion channels not yet conclusively identified at a molecular level. To define their performance *in situ*, we measured MT channel properties in inner hair cells (IHCs) and outer hair cells (OHCs) at two locations in the rat cochlea tuned to different characteristic frequencies (CFs). The conductance (in 0.02 mM calcium) of MT channels from IHCs was estimated as 260 pS at both low-frequency and mid-frequency positions, whereas that from OHCs increased with CFs from 145 to 210 pS. The combination of MT channel conductance and tip link number, assayed from scanning electron micrographs, accounts for variation in whole-cell current amplitude for OHCs and its invariance for IHCs. Channels from apical IHCs and OHCs having a twofold difference in unitary conductance were both highly calcium selective but were distinguishable by a small but significant difference in calcium permeability and in their response to lowering ionic strength. The results imply that the MT channel has properties possessed by few known candidates, and its diversity suggests expression of multiple isoforms.

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## Spine Ca<sup>2+</sup> Signaling in Spike-Timing-Dependent Plasticity

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Calcium is a second messenger, which can trigger the modification of synaptic efficacy. We investigated the question of whether a differential rise in postsynaptic Ca<sup>2+</sup> ([Ca<sup>2+</sup>]<sub>i</sub>) alone is sufficient to account for the induction of long-term potentiation (LTP) and long-term depression (LTD) of EPSPs in the basal dendrites of layer 2/3 pyramidal neurons of the somatosensory cortex. Volume-averaged [Ca<sup>2+</sup>]<sub>i</sub> transients were measured in spines of the basal dendritic arbor for spike-timing-dependent plasticity induction protocols. The rise in [Ca<sup>2+</sup>]<sub>i</sub> was uncorrelated to the direction of the change in synaptic efficacy, because several pairing protocols evoked similar spine [Ca<sup>2+</sup>]<sub>i</sub> transients but resulted in either LTP or LTD. The sequence dependence of near-coincident presynaptic and postsynaptic activity on the direction of changes in synaptic strength suggested that LTP and LTD were induced by two processes, which were controlled separately by postsynaptic [Ca<sup>2+</sup>]<sub>i</sub> levels. Activation of voltage-dependent Ca<sup>2+</sup> channels before metabotropic glutamate receptors (mGluRs) resulted in the phospholipase C-dependent (PLC-dependent) synthesis of endocannabinoids, which acted as a retrograde messenger to induce LTD. LTP required a large [Ca<sup>2+</sup>]<sub>i</sub> transient evoked by NMDA receptor activation. Blocking mGluRs abolished the induction of LTD and uncovered the Ca<sup>2+</sup>-dependent induction of LTP.

We conclude that the volume-averaged peak elevation of [Ca<sup>2+</sup>]<sub>i</sub> in spines of layer 2/3 pyramids determines the magnitude of long-term changes in synaptic efficacy. The direction of the change is controlled, however, via a mGluR-coupled signaling cascade. mGluRs act in conjunction with PLC as sequence-sensitive coincidence detectors

when postsynaptic precede presynaptic action potentials to induce LTD. Thus presumably two different  $\text{Ca}^{2+}$  sensors in spines control the induction of spike-timing-dependent synaptic plasticity.

The Journal of Neuroscience, October 25, 2006 • 26(43):11001–11013

## Hes6 Inhibits Astrocyte Differentiation and Promotes Neurogenesis through Different Mechanisms

Sumit Jhas, Sorana Ciura,\* Stephanie Belanger-Jasmin,\* Zhifeng Dong, Estelle Llamosas, Francesca M. Theriault, Kerline Joachim, Yeman Tang, Lauren Liu, Jisheng Liu, and Stefano Stifani

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The mechanisms regulating the generation of cell diversity in the mammalian cerebral cortex are beginning to be elucidated. In that regard, Hairy/Enhancer of split (Hes) 1 and 5 are basic helix-loop-helix (bHLH) factors that inhibit the differentiation of pluripotent cortical progenitors into neurons. In contrast, a related Hes family member termed Hes6 promotes neurogenesis. It is shown here that knockdown of endogenous Hes6 causes supernumerary cortical progenitors to differentiate into cells that exhibit an astrocytic morphology and express the astrocyte marker protein GFAP. Conversely, exogenous Hes6 expression in cortical progenitors inhibits astrocyte differentiation. The negative effect of Hes6 on astrocyte differentiation is independent of its ability to promote neuronal differentiation. We also show that neither its proneuronal nor its anti-gliogenic functions appear to depend on Hes6 ability to bind to DNA via the basic arm of its bHLH domain. Both of these activities require Hes6 to be localized to nuclei, but only its anti-gliogenic function depends on two short peptides, LNHL and WRPW, that are conserved in all Hes6 proteins. These findings suggest that Hes6 is an important regulator of the neurogenic phase of cortical development by promoting the neuronal fate while suppressing astrocyte differentiation. They suggest further that separate molecular mechanisms underlie the proneuronal and anti-gliogenic activities of Hes6 in cortical progenitor cells.

The Journal of Neuroscience, October 25, 2006 • 26(43):11061–11071

## The Low-Density Lipoprotein Receptor-Related Protein Is a Pro-Survival Receptor in Schwann Cells: Possible Implications in Peripheral Nerve Injury

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Schwann cells undergo phenotypic modulation in peripheral nerve injury. In the adult rodent, Schwann cells are resistant to death-promoting challenges. The responsible receptors and signaling pathways are incompletely understood. In this study, we demonstrate that low-density lipoprotein receptor-related protein-1 (LRP-1) is expressed in adult sciatic nerve. After crush injury, LRP-1 is lost from the axoplasm and substantially upregulated in Schwann cells. Increased LRP-1 mRNA expression was observed locally at the injury site in multiple forms of sciatic nerve injury, including crush injury, chronic constriction injury, and axotomy. Endogenously produced tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) was mostly responsible for the increase in LRP-1 expression; this activity was reproduced by direct injection of TNF- $\alpha$  into injured nerves in the TNF- $\alpha$  gene knock-out mouse. TNF receptor II was primarily involved. TNF- $\alpha$  also increased LRP-1 mRNA in Schwann cells in primary culture. Silencing of Schwann cell LRP-1 with siRNA decreased phosphorylated Akt and increased activated caspase-3. Equivalent changes in cell signaling were observed in LRP-1-deficient murine embryonic fibroblasts. Schwann cell death was induced *in vitro* by serum withdrawal or TNF- $\alpha$ , to a greater extent when LRP-1 was silenced. Schwann cell death was induced *in vivo* by injecting the LRP-1 antagonist, receptor-associated protein, into axotomy sites in adult rats. These results support a model in which LRP-1 functions as a pro-survival receptor in Schwann cells.

The Journal of Neuroscience, October 25, 2006 • 26(43):11197–11207

## Isoform-Specific Early Trafficking of AMPA Receptor Flip and Flop Variants

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Flip and flop splice variants of AMPA receptor subunits are expressed in distinct but partly overlapping patterns and impart different desensitization kinetics to cognate receptor channels. In the absence of specific antibodies, isoform-specific differences in trafficking or localization of native flip and flop subunits remain uncharacterized. We report that in several transfected cell lines, transport of homomeric glutamate receptor (GluR)-D<sub>flip</sub> receptors is largely blocked at the endoplasmic reticulum (ER) exit, whereas GluR-D<sub>flop</sub> undergoes complex glycosylation and reaches the plasma membrane at  $>10\times$  higher levels than GluR-D<sub>flip</sub>, as determined by immunofluorescence, patch-clamp recordings and biochemical assays. The transport difference between flip and flop is independent of activity, is primarily determined by amino acid residue 780 (Leu in flop, Val in flip), and is manifested even in the secretion of the soluble ligand-binding domain, suggesting it is independent of oligomerization. Coexpression with stargazin or with the flip isoform rescues the surface expression of GluR-D<sub>flip</sub> near to the level exhibited by GluR-D<sub>flop</sub>. Our results demonstrate that the extracellular flip/flop region, via interactions with ER luminal splice form-specific protein(s), plays a hitherto unappreciated and important role in AMPA-receptor trafficking.

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## Functional Genomic Analysis of Oligodendrocyte Differentiation

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To better understand the molecular mechanisms governing oligodendrocyte (OL) differentiation, we have used gene profiling to quantitatively analyze gene expression in synchronously differentiating OLs generated from pure oligodendrocyte precursor cells *in vitro*. By comparing gene expression in these OLs to OLs generated *in vivo*, we discovered that the program of OL differentiation can progress normally in the absence of heterologous cell–cell interactions. In addition, we found that OL differentiation was unexpectedly prolonged and occurred in at least two sequential stages, each characterized by changes in distinct complements of transcription factors and myelin proteins. By disrupting the normal dynamic expression patterns of transcription factors regulated during OL differentiation, we demonstrated that these sequential stages of gene expression can be independently controlled. We also uncovered several genes previously uncharacterized in OLs that encode transmembrane, secreted, and cytoskeletal proteins that are as highly upregulated as myelin genes during OL differentiation. Last, by comparing genomic loci associated with inherited increased risk of multiple sclerosis (MS) to genes regulated during OL differentiation, we identified several new positional candidate genes that may contribute to MS susceptibility. These findings reveal a previously unexpected complexity to OL differentiation and suggest that an intrinsic program governs successive phases of OL differentiation as these cells extend and align their processes, ensheath, and ultimately myelinate axons.

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## Olfactory Ensheathing Cells Do Not Exhibit Unique Migratory or Axonal Growth-Promoting Properties after Spinal Cord Injury

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Olfactory ensheathing cells (OECs) have been reported to migrate long distances and to bridge lesion sites, guiding axonal regeneration after spinal cord injury (SCI). To understand mechanisms of OEC migration and axonal guidance, we injected lamina propria OECs 1 mm rostral and caudal to C4 SCI sites. One month later, OECs formed an apparent migrating cell tract continuously extending from the injection site through the lesion, physically bridging the lesion. Confocal immunolabeling demonstrated that, whereas this cell tract displaced host astrocytes, descending or ascending long tract axons did not preferentially extend into the cell tract and OECs failed to support bridging of corticospinal axons. Notably, the “bridging” tract of OECs formed within 1 h of cell injection, raising the possibility that cells passively spread from the pressure injection site rather than actively migrating. Control injections of bone marrow stromal cells (MSCs) or fibroblasts 1 mm from the lesion site also rapidly dispersed into the lesion cavity. Cell tracts extending into the lesion site were not seen when cells were injected either at low volumes, into spinal cord gray matter, or 3 d before or 9 d after SCI. OECs proliferated in injection sites, cell tracts, and lesion sites, indicating that OECs can also accumulate through cell proliferation. Thus, OECs do not appear to exhibit significant migratory properties when grafted to the spinal cord, exhibit no detectable difference in promoting axon growth into a SCI site compared with MSCs or fibroblasts, and do not support bridging of corticospinal axons beyond a dorsal column lesion.

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## Distinct Roles of the $\beta 1$ -Class Integrins at the Developing and the Mature Hippocampal Excitatory Synapse

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Integrins are a large family of cell adhesion receptors involved in a variety of cellular functions. To study their roles at central synapses, we used two *cre* recombinase lines to delete the *Itgb1*  $\beta 1$  integrin gene in forebrain excitatory neurons at different developmental stages. Removal of the  $\beta 1$  integrins at an embryonic stage resulted in severe cortical lamination defects without affecting the cellular organization of pyramidal neurons in the CA3 and CA1 regions of the hippocampus. Whereas the hippocampal neurons underwent normal dendritic and synaptic differentiation, the adult synapses exhibited deficits in responses to high-frequency stimulation (HFS), as well as in long-term potentiation (LTP). Deletion of  $\beta 1$  integrin at a later postnatal stage also impaired LTP but not synaptic responses to HFS. Thus, the  $\beta 1$ -class integrins appear to play distinct roles at different stages of synaptic development, critical for the proper maturation of readily releasable pool of vesicles during early development but essential for LTP throughout adult life.

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## RET Is Dispensable for Maintenance of Midbrain Dopaminergic Neurons in Adult Mice

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Glial cell-line derived neurotrophic factor (GDNF)-mediated RET tyrosine kinase signaling is implicated in the survival of several PNS and CNS neuronal populations that are important in the pathogenesis of several disorders including Parkinson's disease and drug addiction. However, it has been difficult to study these processes and the physiological importance of this pathway in adult mice because of the neonatal lethality of *Gdnf* and *Ret* null mice. We report successful creation of RET conditional reporter mice to investigate postnatal physiologic roles of RET and monitor the fate of RET-expressing cell types. To delete RET specifically in dopaminergic neurons and determine the physiologic requirement of RET in the maintenance of substantia nigra compacta (SNC) and ventral tegmental area (VTA), we bred the RET conditional mice with mice that specifically express Cre from the dopamine transporter (*Dat*) locus. A detailed morphometric and biochemical analysis including dopaminergic neuron number and size in SNC and VTA, and fiber density in the striatum and nucleus accumbens, and dopamine levels indicate that RET is not required for providing global trophic support to midbrain dopaminergic neurons in adult mice. Furthermore, RET deficiency in these neurons does not cause major sensorimotor abnormalities. Hence our results support the idea that RET signaling is not critical for the normal physiology of the SNC and VTA in adult mice.

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### BEHAVIORAL/SYSTEMS/COGNITIVE

## Probabilistic Encoding of Vocalizations in Macaque Ventral Lateral Prefrontal Cortex

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We examined strategies for classifying macaque vocalizations into their corresponding categories, as well as whether or not there was evidence that prefrontal auditory neurons were related to this process. We found that static estimates of the spectral and temporal contrasts of the calls were not effective features for discriminating among the call classes. A hidden Markov model (HMM), however, was more effective at discriminating among the call classes, reaching a performance of almost 75% correct. Finally, we found that the responses of prefrontal auditory neurons could be predicted more effectively as linear functions of the probabilistic output of the HMM than as linear functions of the spectral features of the calls. This provides evidence that, for call recognition, the macaque auditory system likely performs dynamic processing of vocalizations, and that prefrontal auditory neurons carry a signal related to the output of this processing.

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## Central Administration of a Cytochrome P450-7B Product 7 $\alpha$ -Hydroxypregnenolone Improves Spatial Memory Retention in Cognitively Impaired Aged Rats

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Pregnenolone (PREG) and dehydroepiandrosterone (DHEA) have been reported to improve memory in aged rodents. In brain, these neurosteroids are transformed predominantly into 7 $\alpha$ -hydroxylated metabolites by the cytochrome P450-7B1 (CYP7B). The biological role of steroid B-ring hydroxylation is unclear. It has been proposed to generate bioactive derivatives that enhance cognition, immune, and other physiological processes. In support, 7 $\alpha$ -hydroxylated DHEA increases the immune response in mice with greater potency than the parent steroid. Whether the memory-enhancing effects of PREG in rats is mediated via its 7 $\alpha$ -hydroxylated metabolite 7 $\alpha$ -hydroxyPREG is not known. We investigated this by treating memory-impaired aged rats (identified by their spatial memory performances in the Morris water maze task compared with young controls) with 7 $\alpha$ -hydroxyPREG or PREG administered intracerebroventricularly using osmotic minipumps and then tested the rats during week 2 of steroid treatment in the eight-arm radial-arm version of the water maze (RAWM) that allows repeated assessment of learning. CYP7B bioactivity in hippocampal tissue (percentage conversion of [<sup>14</sup>C]DHEA to [<sup>14</sup>C]7 $\alpha$ -hydroxyDHEA) was decreased selectively in memory-impaired aged rats compared with both young and memory-intact aged rats. 7 $\alpha$ -hydroxyPREG (100 ng/h) but not PREG (100 ng/h) administration to memory-impaired aged rats for 11 d enhanced spatial memory retention (after a 30 min delay between an exposure trial 1 and test trial 2) in the RAWM. These data provide evidence for a biologically active enzyme product 7 $\alpha$ -hydroxyPREG and suggests that reduced CYP7B function in the hippocampus of memory-impaired aged rats may, in part, be overcome by administration of 7 $\alpha$ -hydroxyPREG.

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# Amphetamine-Induced Place Preference and Conditioned Motor Sensitization Requires Activation of Tyrosine Kinase Receptors in the Hippocampus

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The environmental context in which abused drugs are taken contribute to the drug experience and is a powerful and persistent stimulus to elicit memories of that experience even in the abstinent addict. Using amphetamine (AMPH) as the unconditioned stimulus, the present study compared two popular context-dependent paradigms in rats, conditioned motor sensitization (CMS) and conditioned place preference (CPP), to ascertain whether particular brain regions were differentially involved. The neuronal substrates underlying these context-dependent behaviors are poorly understood, but regulators of the neuronal plasticity that accompany learning, such as neurotrophic factors and their cognate tyrosine kinase receptors (e.g., TrkB), are credible candidates. We found a significant elevation of TrkB-like immunoreactivity specifically in CA3/dentate gyrus (DG) subregions of the hippocampus after AMPH (0.3 mg/kg)-induced CPP, but not in the delayed-paired (control) AMPH condition. A higher AMPH dose (1.0 mg/kg) induced both CPP and CMS and elevated TrkB in the CA3/DG as well as in the nucleus accumbens shell. The development of both conditioned behaviors was blocked by intra-CA3/DG infusion of the Trk inhibitor K-252a. These findings reveal that CPP and CMS are induced by different doses of AMPH and are associated with TrkB changes in particular brain regions. Moreover, Trk receptors in the hippocampus are critical mediators of the neuronal changes necessary for inducing both forms of conditioning. Thus, although these two conditioning models are distinct, because they are commonly regulated by the hippocampal Trk system, these receptors may be a therapeutic target for attenuating the significance of contextual cues that otherwise strengthen the addictive properties of abused drugs.

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# Gut Vagal Afferents Are Not Necessary for the Eating-Stimulatory Effect of Intraperitoneally Injected Ghrelin in the Rat

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Ghrelin is unique among gut peptides in that its plasma level increases during fasts and its administration stimulates eating. Although ghrelin physiology has been intensively studied, whether its eating-stimulatory effect arises from endocrine-neural signal transduction at peripheral or central sites remains unresolved. To address this issue, we tested the effects of subdiaphragmatic vagal deafferentation (SDA), the most complete and selective vagal deafferentation method available, on ghrelin-induced eating. SDA was verified with a cholecystokinin satiation test, retrograde labeling of vagal motor neurons in the dorsal motor nucleus of the vagus with fluorogold, and anterograde labeling of vagal afferents in the nucleus tractus solitarius with wheat germ agglutinin-horseradish peroxidase. Intraperitoneal injections of 10–40  $\mu$ g/kg ghrelin stimulated eating as robustly in rats with verified complete SDA as in sham-operated controls. Ghrelin also stimulated eating in rats with total subdiaphragmatic vagotomies. We also recorded the electrophysiological responses of gastric load-sensitive vagal afferent neurons to intravenous ghrelin. Ghrelin (10 nmol) phasically (0–30 s) increased activity in two of seven gastric load-sensitive fibers in the absence of gastric loads and tonically (5–30 min) increased activity in only one fiber. Ghrelin did not affect any of the eight fibers tested in the presence of 1–3 ml gastric loads. We conclude that although phasic increases in plasma ghrelin may affect the activity of a fraction of gastric load-sensitive vagal afferents, the acute eating-stimulatory effect of intraperitoneal ghrelin does not require vagal afferent signaling.

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# Estrogen Upregulates T-Type Calcium Channels in the Hypothalamus and Pituitary

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Low voltage-activated (T-type)  $\text{Ca}^{2+}$  channels are responsible for generating low-threshold spikes (LTS) that facilitate burst firing and transmitter release in neurons. The T-type  $\text{Ca}^{2+}$  channels contain a regulatory  $\alpha 1$  subunit, and several isoforms of the  $\alpha 1$  subunit (Cav3.1, 3.2, 3.3) have been cloned. The Cav 3.1  $\alpha 1$  subunit is abundantly expressed in the hypothalamus. Previously, we found that 17  $\beta$ -estradiol (E2) increased the number of arcuate neurons expressing LTS. Therefore, we used an ovariectomized female guinea pig model to measure the distribution and regulation of Cav3.1 mRNA expression by E2. Guinea pig Cav3.1  $\alpha 1$  subunit sequences, which were cloned by PCR, were used in ribonuclease protection (RPA) and *in situ* hybridization assays to evaluate mRNA expression. Based on a RPA, E2 significantly increased the mRNA expression of Cav3.1  $\alpha 1$  subunit in the mediobasal hypothalamus and the pituitary. *In situ* hybridization analysis revealed that E2 significantly increased Cav 3.1 mRNA expression in medial preoptic nuclei, bed nuclei stria terminalis, and the arcuate nucleus. Whole-cell patch recordings in arcuate neurons revealed that E2 treatment significantly increased the peak T-type  $\text{Ca}^{2+}$  current density by twofold without affecting the activation/inactivation characteristics and augmented the rebound excitation by threefold to fourfold. These results suggest that estrogen regulates the mRNA expression of T-type calcium channels, which leads to increased functional expression of the channel. Increased expression of T-type channels could be one mechanism by which estrogen augments burst firing and transmitter release in hypothalamic neurons.

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## Auditory Brainstem Timing Predicts Cerebral Asymmetry for Speech

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The left hemisphere of the human cerebral cortex is dominant for processing rapid acoustic stimuli, including speech, and this specialized activity is preceded by processing in the auditory brainstem. It is not known to what extent the integrity of brainstem encoding of speech impacts patterns of asymmetry at cortex. Here, we demonstrate that the precision of temporal encoding of speech in auditory brainstem predicts cerebral asymmetry for speech sounds measured in a group of children spanning a range of language skills. Results provide strong evidence that timing deficits measured at the auditory brainstem negatively impact rapid acoustic processing by specialized structures of cortex, and demonstrate a delicate relationship between cortical activation patterns and the temporal integrity of cortical input.

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## Integration of Auditory and Visual Communication Information in the Primate Ventrolateral Prefrontal Cortex

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The integration of auditory and visual stimuli is crucial for recognizing objects, communicating effectively, and navigating through our complex world. Although the frontal lobes are involved in memory, communication, and language, there has been no evidence that the integration of communication information occurs at the single-cell level in the frontal lobes. Here, we show that neurons in the macaque ventrolateral prefrontal cortex (VLPFC) integrate audiovisual communication stimuli. The multisensory interactions included both enhancement and suppression of a predominantly auditory or a predominantly visual response, although multisensory suppression was the more common mode of response. The multisensory neurons were distributed across the VLPFC and within previously identified unimodal auditory and visual regions (O'Scalaidhe et al., 1997; Romanski and Goldman-Rakic, 2002). Thus, our study demonstrates, for the first time, that single prefrontal neurons integrate communication information from the auditory and visual domains, suggesting that these neurons are an important node in the cortical network responsible for communication.

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## Specificity of M and L Cone Inputs to Receptive Fields in the Parvocellular Pathway: Random Wiring with Functional Bias

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Many of the parvocellular pathway (PC) cells in primates show red–green spectral selectivity (cone opponency), but PC ganglion cells in the retina show no anatomical signs of cone selectivity. Here we asked whether responses of PC cells are compatible with “random wiring” of cone inputs. We measured long-wavelength-sensitive (L) and medium-wavelength-sensitive (M) cone inputs to PC receptive fields in the dorsal lateral geniculate of marmosets, using discrete stimuli (apertures and annuli) to achieve functional segregation of center and surround. Receptive fields between the fovea and 30° eccentricity were measured.

We show that, in opponent PC cells, the center is dominated by one (L or M) cone type, with normally <20% contribution from the other cone type (high “cone purity”), whereas non-opponent cells have mixed L and M cone inputs to the receptive field center. Furthermore, opponent response strength depends on the overall segregation of L and M cone inputs to center and surround rather than exclusive input from one cone type to either region. These data are consistent with random wiring. The majority of PC cells in both foveal (<8°) and peripheral retina nevertheless show opponent responses. This arises because cone purity in the receptive field surround is at least as high as in the center, and the surround in nearly all opponent PC cells is dominated by the opposite cone type to that which dominates the center. These functional biases increase the proportion of opponent PC cells, but their anatomical basis is unclear.

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## Neural Mechanisms of Expert Skills in Visual Working Memory

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Expertise can increase working memory (WM) performance, but the cognitive and neural mechanisms of these improvements remain unclear. Here, we used functional magnetic resonance imaging to assess the degree to which expertise acquisition is supported by tuning of occipitotemporal object representations and tuning of prefrontal and parietal networks that may support domain-specific WM skills. We trained subjects to become experts in a novel category of complex visual objects and examined brain activity while they performed a WM task with objects from the expert category and from an untrained category. Visual expertise training resulted in improved recognition of expert, compared with untrained objects, and this effect was eliminated in a behavioral experiment by stimulus inversion. These behavioral changes were accompanied

by increased recruitment of bilateral dorsolateral prefrontal, posterior parietal, and occipitotemporal cortices during WM encoding and maintenance. Across subjects, behavioral measures of expertise reliably predicted increased activation during maintenance of expert objects in all three regions. These neural expertise effects could not be attributed to differences in low-level stimulus characteristics between the two categories, familiarity with features of expert-domain objects, or familiarity with the WM task. These results are consistent with the idea that visual expertise improves WM performance through tuning of occipitotemporal object representations and through development of lateral prefrontal and posterior parietal networks that mediate the application of domain-specific mnemonic skills.

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## Brain Regions Mediating Flexible Rule Use during Development

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During development, children improve at retrieving and using rules to guide their behavior and at flexibly switching between these rules. In this study, we used functional magnetic resonance imaging to examine the changes in brain function associated with developmental changes in flexible rule use. Three age groups (8–12, 13–17, and 18–25 years) performed a task in which they were cued to respond to target stimuli on the basis of simple task rules. Bivalent target stimuli were associated with different responses, depending on the rule, whereas univalent target stimuli were associated with fixed responses. The comparison of bivalent and univalent trials enabled the identification of regions modulated by demands on rule representation. The comparison of rule-switch and rule-repetition trials enabled the identification of regions involved in rule switching. We have used this task previously in adults and have shown that ventrolateral prefrontal cortex (VLPFC) and the (pre)-supplementary motor area (pre-SMA/SMA) have dissociable roles in task-switching, such that VLPFC is associated most closely with rule representation, and pre-SMA/SMA is associated with suppression of the previous task set (Crone et al., 2006a). Based on behavioral data in children (Crone et al., 2004), we had predicted that regions associated with task-set suppression would show mature patterns of activation earlier in development than regions associated with rule representation. Indeed, we found an adult-like pattern of activation in pre-SMA/SMA by adolescence, whereas the pattern of VLPFC activation differed among children, adolescents, and adults. These findings suggest that two components of task-switching—rule retrieval and task-set suppression—follow distinct neurodevelopmental trajectories.

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## NEUROBIOLOGY OF DISEASE

## Matrix Metalloproteinases Expressed by Astrocytes Mediate Extracellular Amyloid- $\beta$ Peptide Catabolism

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It has been postulated that the development of amyloid plaques in Alzheimer's disease (AD) may result from an imbalance between the generation and clearance of the amyloid- $\beta$  peptide ( $A\beta$ ). Although familial AD appears to be caused by  $A\beta$  overproduction, sporadic AD (the most prevalent form) may result from impairment in clearance. Recent evidence suggests that several proteases may contribute to the degradation of  $A\beta$ . Furthermore, astrocytes have recently been implicated as a potential cellular mediator of  $A\beta$  degradation. In this study, we examined the possibility that matrix metalloproteinases (MMPs), proteases known to be expressed and secreted by astrocytes, could play a role in extracellular  $A\beta$  degradation. We found that astrocytes surrounding amyloid plaques showed enhanced expression of MMP-2 and MMP-9 in aged amyloid precursor protein (APP)/presenilin 1 mice. Moreover, astrocyte-conditioned medium (ACM) degraded  $A\beta$ , lowering levels and producing several fragments after incubation with synthetic human  $A\beta_{1-40}$  and  $A\beta_{1-42}$ . This activity was attenuated with specific inhibitors of MMP-2 and -9, as well as in ACM derived from *mmp-2* or *-9* knock-out (KO) mice. *In vivo*, significant increases in the steady-state levels of  $A\beta$  were found in the brains of *mmp-2* and *-9* KO mice compared with wild-type controls. Furthermore, pharmacological inhibition of the MMPs with *N*-[(2*R*)-2-(hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan methylamide (GM 6001) increased brain interstitial fluid  $A\beta$  levels and elimination of half-life in APPsw mice. These results suggest that MMP-2 and -9 may contribute to extracellular brain  $A\beta$  clearance by promoting  $A\beta$  catabolism.

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# DNA Polymerase- $\beta$ Is Expressed Early in Neurons of Alzheimer's Disease Brain and Is Loaded into DNA Replication Forks in Neurons Challenged with $\beta$ -Amyloid

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Cultured neurons exposed to synthetic  $\beta$ -amyloid (A $\beta$ ) fragments reenter the cell cycle and initiate a pathway of DNA replication that involves the repair enzyme DNA polymerase- $\beta$  (DNA pol- $\beta$ ) before undergoing apoptotic death. In this study, by performing coimmunoprecipitation experiments on cross-linked nucleoprotein fragments from A $\beta$ -treated neurons, we demonstrate that DNA pol- $\beta$  coimmunoprecipitates with cell division cycle 45 (Cdc45) and with DNA primase in short nucleoprotein fragments. This indicates that DNA pol- $\beta$  is loaded into neuronal DNA replication forks after A $\beta$  treatment. In response to A $\beta$  the canonical DNA-synthesizing enzyme DNA pol- $\delta$  also was loaded into neuronal replication forks, but at later times than DNA pol- $\beta$ . Methoxyamine, an inhibitor of the apurinic/apyrimidinic endonuclease that allows for the recruitment of DNA pol- $\beta$  during the process of base excision repair (BER), failed to affect coimmunoprecipitation between DNA pol- $\beta$  and Cdc45, indicating that DNA pol- $\beta$  loading to the replication forks is independent of DNA breaks. However, methoxyamine reduced DNA replication and ensuing apoptosis in neurons exposed to A $\beta$ , suggesting that an efficient BER process allows DNA replication to proceed up to the threshold for death.

These data demonstrate that DNA pol- $\beta$  is an essential component of the DNA replication machinery in A $\beta$ -treated neurons and additionally support the hypothesis of a close association of cell cycle events with neuronal death in Alzheimer's disease (AD). Accordingly, by investigating the neuronal expression of DNA pol- $\beta$ , along with phosphorylated retinoblastoma protein and neurofibrillary changes in AD brain, we show an early involvement of DNA pol- $\beta$  in the pathogenesis of AD.

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# Impaired Inactivation Gate Stabilization Predicts Increased Persistent Current for an Epilepsy-Associated *SCN1A* Mutation

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Mutations in *SCN1A* (encoding the neuronal voltage-gated sodium channel  $\alpha_1$  subunit, Na<sub>v</sub>1.1, or SCN1A) are associated with genetic epilepsy syndromes including generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy. Here, we present the formulation and use of a computational model for *SCN1A* to elucidate molecular mechanisms underlying the increased persistent sodium current exhibited by the GEFS+ mutant R1648H. Our model accurately reproduces all experimentally measured *SCN1A* whole-cell biophysical properties including biphasic whole-cell current decay, channel activation, and entry into and recovery from fast and slow inactivation. The model predicts that *SCN1A* open-state inactivation results from a two-step process that can be conceptualized as initial gate closure, followed by recruitment of a mechanism ("latch") to stabilize the inactivated state. Selective impairment of the second latching step results in an increase in whole-cell persistent current similar to that observed for the GEFS+ mutant R1648H. These results provide a deeper level of understanding of mutant *SCN1A* dysfunction in an inherited epilepsy syndrome, which will enable more precise computational studies of abnormal neuronal activity in epilepsy and may help guide new targeted therapeutic strategies.

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# Survival Motor Neuron Function in Motor Axons Is Independent of Functions Required for Small Nuclear Ribonucleoprotein Biogenesis

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Spinal muscular atrophy (SMA) is a motor neuron degenerative disease caused by low levels of the survival motor neuron (SMN) protein and is linked to mutations or loss of *SMN1* and retention of *SMN2*. How low levels of SMN cause SMA is unclear. SMN functions in small nuclear ribonucleoprotein (snRNP) biogenesis, but recent studies indicate that SMN may also function in axons. We showed previously that decreasing *Smn* levels in zebrafish using morpholinos (MO) results in motor axon defects. To determine how *Smn* functions in motor axon outgrowth, we coinjected *smn* MO with various human *SMN* RNAs and assayed the effect on motor axons. Wild-type SMN rescues motor axon defects caused by *Smn* reduction in zebrafish. Consistent with these defects playing a role in SMA, SMN lacking exon 7, the predominant form from the *SMN2* gene, and human SMA mutations do not rescue defective motor axons. Moreover, the severity of the motor axon defects correlates with decreased longevity. We also show that a conserved region in SMN exon 7, QNKE, is critical for motor axon outgrowth. To address the function of SMN important for motor axon outgrowth, we determined the ability of different SMN forms to oligomerize and bind Sm protein, functions required for snRNP biogenesis. We identified mutations that failed to rescue motor axon defects but retained snRNP function. Thus, we have dissociated the snRNP function of SMN from its function in motor axons. These data indicate that SMN has a novel function in motor axons that is relevant to SMA and is independent of snRNP biosynthesis.

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# Potential New Antiepileptogenic Targets Indicated by Microarray Analysis in a Rat Model for Temporal Lobe Epilepsy

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To get insight into the mechanisms that may lead to progression of temporal lobe epilepsy, we investigated gene expression during epileptogenesis in the rat. RNA was obtained from three different brain regions [CA3, entorhinal cortex (EC), and cerebellum (CB)] at three different time points after electrically induced status epilepticus (SE): acute phase [group D (1 d)], latent period [group W (1 week)], and chronic epileptic period [group M (3–4 months)]. A group that was stimulated but that had not experienced SE and later epilepsy was also included (group nS). Gene expression analysis was performed using the Affymetrix Gene Chip System (RAE230A). We used GENMAPP and Gene Ontology to identify global biological trends in gene expression data. The immune response was the most prominent process changed during all three phases of epileptogenesis. Synaptic transmission was a downregulated process during the acute and latent phases. GABA receptor subunits involved in tonic inhibition were persistently downregulated. These changes were observed mostly in both CA3 and EC but not in CB. Rats that were stimulated but that did not develop spontaneous seizures later on had also some changes in gene expression, but this was not reflected in a significant change of a biological process. These data suggest that the targeting of specific genes that are involved in these biological processes may be a promising strategy to slow down or prevent the progression of epilepsy. Especially genes related to the immune response, such as complement factors, interleukins, and genes related to prostaglandin synthesis and coagulation pathway may be interesting targets.

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# Phospholipases A<sub>2</sub> Mediate Amyloid- $\beta$ Peptide-Induced Mitochondrial Dysfunction

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Mitochondrial dysfunction has been implicated in the pathophysiology of Alzheimer's disease (AD) brains. To unravel the mechanism(s) underlying this dysfunction, we demonstrate that phospholipases A<sub>2</sub> (PLA<sub>2</sub>s), namely the cytosolic and the calcium-independent PLA<sub>2</sub>s (cPLA<sub>2</sub> and iPLA<sub>2</sub>), are key enzymes mediating oligomeric amyloid- $\beta$  peptide (A $\beta$ <sub>1–42</sub>)-induced loss of mitochondrial membrane potential and increase in production of reactive oxygen species from mitochondria in astrocytes. Whereas the action of iPLA<sub>2</sub> is immediate, the action of cPLA<sub>2</sub> requires a lag time of ~12–15 min, probably the time needed for initiating signaling pathways for the phosphorylation and translocation of cPLA<sub>2</sub> to mitochondria. Western blot analysis indicated the ability of oligomeric A $\beta$ <sub>1–42</sub> to increase phosphorylation of cPLA<sub>2</sub> in astrocytes through the NADPH oxidase and mitogen-activated protein kinase pathways. The involvement of PLA<sub>2</sub> in A $\beta$ <sub>1–42</sub>-mediated perturbations of mitochondrial function provides new insights to the decline in mitochondrial function, leading to impairment in ATP production and increase in oxidative stress in AD brains.

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# Alexander Disease-Associated Glial Fibrillary Acidic Protein Mutations in Mice Induce Rosenthal Fiber Formation and a White Matter Stress Response

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Mutations in the gene for the astrocyte specific intermediate filament, glial fibrillary acidic protein (GFAP), cause the rare leukodystrophy Alexander disease (AxD). To study the pathology of this primary astrocyte defect, we have generated knock-in mice with missense mutations homologous to those found in humans. In this report, we show that mice with GFAP-R76H and -R236H mutations develop Rosenthal fibers, the hallmark protein aggregates observed in astrocytes in AxD, in the hippocampus, corpus callosum, olfactory bulbs, subpial, and periventricular regions. Astrocytes in these areas appear reactive and total GFAP expression is elevated. Although general white matter architecture and myelination appear normal, when crossed with an antioxidant response element reporter line, the mutant mice show a distinct pattern of reporter-gene induction that is especially prominent in the corpus callosum, and histochemical staining reveals accumulation of iron in the same region. The mutant mice have a normal lifespan and show no overt behavioral defects, but are more susceptible to kainate-induced seizures. Although these mice demonstrate increased GFAP expression by themselves, further elevation of GFAP via crosses to GFAP transgenic animals leads to a shift in GFAP solubility, an increased stress response, and ultimately death. The mice do not display the full spectrum of pathology observed in human infantile AxD, but may more closely resemble the adult form of the disease. These studies provide formal proof linking GFAP mutations with Rosenthal fibers and oxidative stress, and correlate gliosis and GFAP protein levels to the severity of the disease.

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# Mitochondrial-Dependent Ca<sup>2+</sup> Handling in Huntington's Disease Striatal Cells: Effect of Histone Deacetylase Inhibitors

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Evidence suggests that neuronal dysfunction in Huntington's disease (HD) striatum involves deficits in mitochondrial function and in Ca<sup>2+</sup> handling. However, the relationship between mitochondria and Ca<sup>2+</sup> handling has been incompletely studied in intact HD striatal cells. Treatment with histone deacetylase (HDAC) inhibitors reduces cell death in HD models, but the effects of this promising therapy on cellular function are mostly unknown. Here, we use real-time functional imaging of intracellular Ca<sup>2+</sup> and mitochondrial membrane potential to explore the role of *in situ* HD mitochondria in Ca<sup>2+</sup> handling. Immortalized striatal (*STHdh*) cells and striatal neurons from transgenic mice, expressing full-length mutant huntingtin (Htt), were used to model HD. We show that (1) active glycolysis in *STHdh* cells occludes the mitochondrial role in Ca<sup>2+</sup> handling as well as the effects of mitochondrial inhibitors, (2) *STHdh* cells and striatal neurons in the absence of glycolysis are critically dependent on oxidative phosphorylation for energy-dependent Ca<sup>2+</sup> handling, (3) expression of full-length mutant Htt is associated with deficits in mitochondrial-dependent Ca<sup>2+</sup> handling that can be ameliorated by treatment with HDAC inhibitors (treatment with trichostatin A or sodium butyrate decreases the proportion of *STHdh* cells losing Ca<sup>2+</sup> homeostasis after Ca<sup>2+</sup>-ionophore challenging, and accelerates the restoration of intracellular Ca<sup>2+</sup> in striatal neurons challenged with NMDA), and (4) neurons with different response patterns to NMDA receptor activation exhibit different average somatic areas and are differentially affected by treatment with HDAC inhibitors, suggesting subpopulation or functional state specificity. These findings indicate that neuroprotection induced by HDAC inhibitors involves more efficient Ca<sup>2+</sup> handling, thus improving the neuronal ability to cope with excitotoxic stimuli.

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