

This Week in The Journal

● Cellular/Molecular

Role of Voltage-Gated Sodium Channels in Neurite Outgrowth

William J. Brackenbury, Tigwa H. Davis, Chunling Chen, Emily A. Slat, Matthew J. Detrow, Travis L. Dickendesher, Barbara Ranscht, and Lori L. Isom

(see pages 3246–3256)

The $\beta 1$ subunit of the voltage-gated sodium channel participates in homophilic and heterophilic cell adhesion and increases neurite outgrowth *in vitro*, in addition to modulating electrical excitability. It interacts with several other cell adhesion molecules (CAMs), and these CAMs activate two signaling pathways: one that involves *fyn* kinase and one that involves the fibroblast growth factor receptor (FGFR). To determine whether the $\beta 1$ subunit relies on these same signaling pathways, Brackenbury et al. examined the growth of dissociated cerebellar neurons on $\beta 1$ -expressing and control cell lines. $\beta 1$ expression enhanced neurite outgrowth from wild-type neurons, as expected, and FGFR antagonists did not diminish this effect. But $\beta 1$ expression did not enhance outgrowth from *Fyn* null neurons, suggesting that *fyn* kinase, but not FGFR, is involved in $\beta 1$ potentiation of neurite growth. Examination of axon growth in $\beta 1$ null mice suggested that $\beta 1$ is involved in axon fasciculation *in vivo*.

▲ Development/Plasticity/Repair

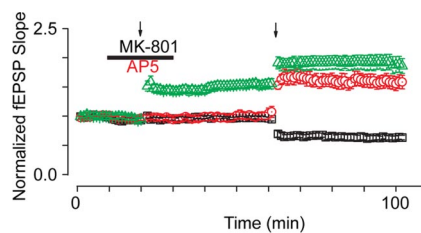
Effects of NMDA Receptor Lateral Diffusion on Synaptic Plasticity

Jiang Zhao, Yi Peng, Zhuo Xu, Rongqing Chen, Qin-hua Gu, Zheng Chen, and Wei Lu

(see pages 3060–3070)

Synaptic plasticity depends on the receptors present at the synapse; the response to a stimulus can change if the receptors change. For example, the subunit composition of NMDA receptors (NMDARs) influences whether long-term potentiation

(LTP) or long-term depression (LTD) is produced by a given stimulus. Zhao et al. show that the composition of synaptic NMDARs can change as a result of lateral diffusion of NMDARs in the membrane. When only synaptic NMDARs were blocked, EPSC amplitude recovered after washout. But when both synaptic and extrasynaptic NMDARs were blocked, EPSCs did not recover. This suggests that the recovery after synaptic block depended on diffusion of extrasynaptic NMDARs into the synapse. The decay time of spontaneous and evoked NMDAR-mediated EPSCs was longer after recovery, suggesting a change in the subunit composition of synaptic receptors. This change was paralleled by a change in synaptic plasticity: a stimulus that normally produced LTP instead induced LTD.



A stimulus (arrows) that induced LTP in control rat hippocampal slices (green) also induced LTD after recovery from reversible block of NMDA receptors (AP-5; red), but induced LTD after irreversible block (MK-801; black). See the article by Zhao et al. for details.

■ Behavioral/Systems/Cognitive

Olfactory Learning in *Drosophila*

Michael J. Krashes and Scott Waddell

(see pages 3103–3113)

Learning often requires multiple training sessions spaced over time. This is true of aversive, but not appetitive, olfactory conditioning in *Drosophila*. When an odor is paired with sucrose, flies learn to follow that odor after a single training session, whereas 5–10 sessions are required to avoid an odor paired with shock. Despite this difference, Krashes and Waddell now report that appetitive long-term memory (LTM) involves many of the same neural processes previously shown to underlie

aversive LTM. Like aversive LTM, appetitive LTM requires protein synthesis and activation of cAMP response element-binding protein (CREB) in mushroom bodies (MBs). Both require activity in DPM and MB $\alpha'\beta'$ neurons for consolidation and require MB $\alpha\beta$ neurons for retrieval. The main difference between aversive and appetitive LTM appears to be that appetitive LTM requires the *radish* gene, which is expressed in mushroom body $\alpha\beta$ neurons and produces a protein of unknown function.

◆ Neurobiology of Disease

Endocannabinoids and Epilepsy

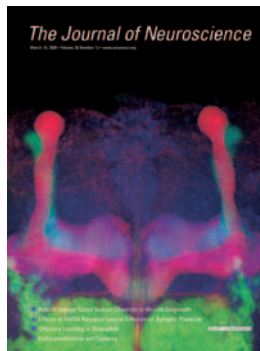
Anikó Ludányi, Loránd Erőss, Sándor Czirják, János Vajda, Péter Halász, Masahiko Watanabe, Miklós Palkovits, Zsófia Maglóczky, Tamás F. Freund, and István Katona

(see pages 2976–2990)

CB₁ endocannabinoid receptors are expressed on presynaptic terminals, where they decrease transmitter release and are thought to help control hyperexcitability. In this week's *Journal*, Ludányi et al. present evidence of decreased endocannabinoid signaling in people with intractable epilepsy. Compared to controls, hippocampi removed from epileptic brains had dramatically reduced levels of CB₁ mRNA. Levels of the CB₁-associated protein cannabinoid receptor interacting protein 1a and of diacylglycerol lipase, which synthesizes an endocannabinoid, were significantly reduced in sclerotic hippocampi (i.e., those with principal cell loss), but not in nonsclerotic epileptic hippocampi. Immunostaining indicated that CB₁ expression was reduced throughout sclerotic and nonsclerotic hippocampi. Ultrastructural analysis revealed that in epileptic dentate gyrus, a smaller fraction of glutamatergic terminals expressed CB₁ than in controls, whereas the fraction of GABAergic terminals with CB₁ was comparable across samples. These results support the hypothesis that loss of cannabinoid signaling in glutamatergic neurons contributes to epilepsy in humans.

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Cover legend: Projected view of a confocal micrograph of the mushroom bodies and antennal lobes from a *Drosophila* brain triple-labeled with c305a;uas-CD8::GFP (green) and anti-FASII (red) anti-TRIO (blue) antibodies. Image courtesy of Benjamin Leung. For more information, see the article by Krashes and Waddell in this issue (pages 3103–3113).

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- 3257 **Erratum:** In the article "Synapse-Specific Expression of Functional Presynaptic NMDA Receptors in Rat Somatosensory Cortex" by Daniel J. Brasier and Daniel E. Feldman, which appeared on pages 2199–2211 of the February 27, 2008 issue, there was a labeling error in Figure 5D. The labels "L4-L2/3" and "L2/3-L2/3" were reversed. The corrected Figure 5 is printed in this issue.

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A Critical Role of the Adenosine A_{2A} Receptor in Extrastriatal Neurons in Modulating Psychomotor Activity as Revealed by Opposite Phenotypes of Striatum and Forebrain A_{2A} Receptor Knock-Outs

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Nelson Rebola,⁴ Liqun Yu,¹ Detlev Boison,⁵ Rodrigo A. Cunha,⁴ Joel Linden,³ Joe Z. Tsien,² and Jiang-Fan Chen¹

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The function of striatal adenosine A_{2A} receptors (A_{2A}Rs) is well recognized because of their high expression levels and the documented antagonistic interaction between A_{2A}Rs and dopamine D₂ receptors in the striatum. However, the role of extrastriatal A_{2A}Rs in modulating psychomotor activity is largely unexplored because of the low level of expression and lack of tools to distinguish A_{2A}Rs in intrinsic striatal versus nonstriatal neurons. Here, we provided direct evidence for the critical role of A_{2A}Rs in extrastriatal neurons in modulating psychomotor behavior using newly developed striatum-specific A_{2A}R knock-out (st-A_{2A}R KO) mice in comparison with forebrain-specific A_{2A}R KO (fb-A_{2A}R KO) mice. In contrast to fb-A_{2A}R KO (deleting A_{2A}Rs in the neurons of striatum as well as cerebral cortex and hippocampus), st-A_{2A}R KO mice exhibited Cre-mediated selective deletion of the A_{2A}R gene, mRNA, and proteins in the neurons (but not astrocytes and microglial cells) of the striatum only. Strikingly, cocaine- and phencyclidine-induced psychomotor activities were enhanced in st-A_{2A}R KO but attenuated in fb-A_{2A}R KO mice. Furthermore, selective inactivation of the A_{2A}Rs in extrastriatal cells by administering the A_{2A}R antagonist KW6002 into st-A_{2A}R KO mice attenuated cocaine effects, whereas KW6002 administration into wild-type mice enhanced cocaine effects. These results identify a critical role of A_{2A}Rs in extrastriatal neurons in providing a prominent excitatory effect on psychomotor activity. These results indicate that A_{2A}Rs in striatal and extrastriatal neurons exert an opposing modulation of psychostimulant effects and provide the first direct demonstration of a predominant facilitatory role of extrastriatal A_{2A}Rs.

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Orexin Signaling Mediates the Antidepressant-Like Effect of Calorie Restriction

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During periods of reduced food availability, animals must respond with behavioral adaptations that promote survival. Despite the fact that many psychiatric syndromes include disordered eating patterns as a component of the illness, little is known about the neurobiology underlying behavioral changes induced by short-term calorie restriction. Presently, we demonstrate that 10 d of calorie restriction, corresponding to a 20–25% weight loss, causes a marked antidepressant-like response in two rodent models of depression and that this response is dependent on the hypothalamic neuropeptide orexin (hypocretin). Wild-type mice, but not mice lacking orexin, show longer latency to immobility and less total immobility in the forced swim test after calorie restriction. In the social defeat model of chronic stress, calorie restriction reverses the behavioral deficits seen in wild-type mice but not in orexin knock-out mice. Additionally, chronic social defeat stress induces a prolonged reduction in the expression of prepro-orexin mRNA via epigenetic modification of the orexin gene promoter, whereas calorie restriction enhances the activation of orexin cells after social defeat. Together, these data indicate that orexin plays an essential role in mediating reduced depression-like symptoms induced by calorie restriction.

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Hypocretin-1 Potentiates NMDA Receptor-Mediated Somatodendritic Secretion from Locus Coeruleus Neurons

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Shi-Rong Wang,³ Wei Xiong,³ Wei Huang,^{1,3} Tao Liu,³ Liang-Hong Zheng,³ Claire Xi Zhang,³ Li-Huan Li,⁵
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Our previous observations showed that several stimuli, including high-K⁺ solution, glutamate, and voltage pulses, induce somatic noradrenaline (NA) secretion from locus coeruleus (LC) neurons. Hypocretin (orexin), a hypothalamic peptide critical for normal wakefulness, has been shown to evoke NA release from the axon terminals of LC neurons. Here, we used amperometry to test the effect of hypocretin-1 (HCRT) on NMDA receptor-mediated somatodendritic release in LC neurons. Either HCRT or NMDA applied alone dose-dependently induced somatodendritic secretion. Bath application of HCRT notably potentiated NMDA receptor-mediated somatodendritic NA release. This potentiation was blocked by SB 334867, a selective HCRT receptor (Hcrtr 1) antagonist, or bisindolylmaleimide, a specific protein kinase C (PKC) inhibitor, indicating the involvement of Hcrtr 1 and PKC. Consistent with this, phorbol 12-myristate 13-acetate, a PKC activator, mimicked the HCRT-induced potentiation. Furthermore, HCRT enhanced NMDA-induced intracellular Ca²⁺ elevation via activation of Hcrtr 1 and PKC, which may contribute to HCRT-potentiated somatodendritic secretion. These

results suggest that HCRT modulates LC activity not only by regulating noradrenergic input to its targets, but also by affecting noradrenergic communication in the soma and dendrites.

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Articles

CELLULAR/MOLECULAR

Structural Correlates of Efficient GABAergic Transmission in the Basal Ganglia–Thalamus Pathway

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Giant inhibitory terminals with multiple synapses, the counterparts of excitatory “detonator” or “driver” terminals, have not been described in the forebrain. Using three-dimensional reconstructions of electron microscopic images, we quantitatively characterize a GABAergic pathway that establishes synaptic contacts exclusively via multiple synapses. Axon terminals of the nigrothalamic pathway formed, on average, 8.5 synapses on large-diameter dendrites and somata of relay cells in the ventromedial nucleus of the rat thalamus. All synapses of a given terminal converged on a single postsynaptic element. The vast majority of the synapses established by a single terminal were not separated by astrocytic processes. Nigrothalamic terminals in the macaque monkey showed the same ultrastructural features both in qualitative and quantitative terms (the median number of synapse per target was also 8.5). The individual synapses were closely spaced in both species. The nearest-neighbor synaptic distances were 169 nm in the rat and 178 nm in the monkey. The average number of synapses within 0.75 μm from any given synapse was 3.8 in the rat and 3.5 in the monkey. The arrangement of synapses described in this study creates favorable conditions for intersynaptic spillover of GABA among the multiple synapses of a single bouton, which can result in larger charge transfer. This could explain faithful and efficient GABAergic signal transmission in the nigrothalamic pathway in the healthy condition and during Parkinson’s disease. In addition, our structural data suggest that the rodent nigrothalamic pathway can be a valid model of the primate condition, when the mechanism of GABAergic transmission is studied.

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Mobility and Turnover of Vesicles at the Synaptic Ribbon

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Ribbon synapses release neurotransmitter continuously at high rates, and the ribbons tether a large pool of synaptic vesicles. To determine whether the tethered vesicles are actually released, we tracked vesicles labeled with styryl dye in mouse retinal bipolar cell terminals whose ribbons had been labeled with a fluorescent peptide. We photobleached vesicles in regions with ribbons and without them and then followed recovery of fluorescence as bleached regions were repopulated by labeled vesicles. In the resting terminal, fluorescence recovered by ~50% in non-ribbon regions but by only ~20% at ribbons. Thus, at rest, vesicles associated with ribbons cannot exchange freely with cytoplasmic vesicles. Depolarization stimulated vesicle turnover at ribbons as bleached, immobile vesicles were released by exocytosis and were then replaced by fluorescent vesicles from the cytoplasm, producing an additional increase in fluorescence specifically at the ribbon location. We conclude that vesicles immobilized at synaptic ribbons participate in the readily releasable pool that is tapped rapidly during depolarization.

The Journal of Neuroscience, March 19, 2008 • 28(12):3150–3158

Deafferentation-Induced Activation of NFAT (Nuclear Factor of Activated T-Cells) in Cochlear Nucleus Neurons during a Developmental Critical Period: A Role for NFATc4-Dependent Apoptosis in the CNS

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During the development and maturation of sensory neurons, afferent activity is required for normal maintenance. There exists a developmental window of time when auditory neurons, including neurons of the anteroventral cochlear nucleus (AVCN), depend on afferent input for survival. This period of time is often referred to as a critical period. The cellular and molecular mechanisms that underlie AVCN neuron susceptibility to deafferentation-induced death remain unknown. Here, we show that only during this critical period deafferentation of mouse AVCN neurons by *in vivo* cochlea removal results in rapid nuclear translocation and activation of the transcription factor NFATc4 (nuclear factor of activated T-cells isoform 4). NFAT activation is abolished by *in vivo* treatment with the calcineurin inhibitor FK506 and the specific NFAT-inhibitor 11R-VIVIT. Inhibition of NFAT significantly attenuates deafferentation-induced apoptosis of AVCN neurons and abolishes NFAT-mediated expression of

FasL, an initiator of apoptotic pathways, in the cochlear nucleus. These data suggest that NFAT-mediated gene expression plays a role in deafferentation-induced apoptosis of cochlear nucleus neurons during a developmental critical period.
The Journal of Neuroscience, March 19, 2008 • 28(12):3159–3169

Phosphorylation of Sodium Channel $\text{Na}_v1.8$ by p38 Mitogen-Activated Protein Kinase Increases Current Density in Dorsal Root Ganglion Neurons

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The sensory neuron-specific sodium channel $\text{Na}_v1.8$ and p38 mitogen-activated protein kinase are potential therapeutic targets within nociceptive dorsal root ganglion (DRG) neurons in inflammatory, and possibly neuropathic, pain. $\text{Na}_v1.8$ channels within nociceptive DRG neurons contribute most of the inward current underlying the depolarizing phase of action potentials. Nerve injury and inflammation of peripheral tissues cause p38 activation in DRG neurons, a process that may contribute to nociceptive neuron hyperexcitability, which is associated with pain. However, how substrates of activated p38 contribute to DRG neuron hyperexcitability is currently not well understood. We report here, for the first time, that $\text{Na}_v1.8$ and p38 are colocalized in DRG neurons, that $\text{Na}_v1.8$ within DRG neurons is a substrate for p38, and that direct phosphorylation of the $\text{Na}_v1.8$ channel by p38 regulates its function in these neurons. We show that direct phosphorylation of $\text{Na}_v1.8$ at two p38 phospho-acceptor serine residues on the L1 loop (S551 and S556) causes an increase in $\text{Na}_v1.8$ current density that is not accompanied by changes in gating properties of the channel. Our study suggests a mechanism by which activated p38 contributes to inflammatory, and possibly neuropathic, pain through a p38-mediated increase of $\text{Na}_v1.8$ current density.
The Journal of Neuroscience, March 19, 2008 • 28(12):3190–3201

Competition between Calcium-Activated K^+ Channels Determines Cholinergic Action on Firing Properties of Basolateral Amygdala Projection Neurons

John M. Power and Pankaj Sah

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Acetylcholine (ACh) is an important modulator of learning, memory, and synaptic plasticity in the basolateral amygdala (BLA) and other brain regions. Activation of muscarinic acetylcholine receptors (mAChRs) suppresses a variety of potassium currents, including sI_{AHP} , the calcium-activated potassium conductance primarily responsible for the slow afterhyperpolarization (AHP) that follows a train of action potentials. Muscarinic stimulation also produces inositol 1,4,5-trisphosphate (IP_3), releasing calcium from intracellular stores. Here, we show using whole-cell patch-clamp recordings and high-speed fluorescence imaging that focal application of mAChR agonists evokes large rises in cytosolic calcium in the soma and proximal dendrites in rat BLA projection neurons that are often associated with activation of an outward current that hyperpolarizes the cell. This hyperpolarization results from activation of small conductance calcium-activated potassium (SK) channels, secondary to the release of calcium from intracellular stores. Unlike bath application of cholinergic agonists, which always suppressed the AHP, focal application of ACh often evoked a paradoxical enhancement of the AHP and spike-frequency adaptation. This enhancement was correlated with amplification of the action potential-evoked calcium response and resulted from the activation of SK channels. When SK channels were blocked, cholinergic stimulation always reduced the AHP and spike-frequency adaptation. Conversely, suppression of the sI_{AHP} by the β -adrenoreceptor agonist, isoprenaline, potentiated the cholinergic enhancement of the AHP. These results suggest that competition between cholinergic suppression of the sI_{AHP} and cholinergic activation of the SK channels shapes the AHP and spike-frequency adaptation.
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Voltage-Gated Na^+ Channel $\beta 1$ Subunit-Mediated Neurite Outgrowth Requires Fyn Kinase and Contributes to Postnatal CNS Development *In Vivo*

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Voltage-gated Na^+ channel $\beta 1$ subunits are multifunctional, participating in channel modulation and cell adhesion *in vitro*. We previously demonstrated that $\beta 1$ promotes neurite outgrowth of cultured cerebellar granule neurons (CGNs) via homophilic adhesion. Both lipid raft-associated kinases and nonraft fibroblast growth factor (FGF) receptors are implicated in cell adhesion molecule-mediated neurite extension. In the present study, we reveal that $\beta 1$ -mediated neurite outgrowth is abrogated in *Fyn* and contactin (*Cntn*) null CGNs. $\beta 1$ protein levels are unchanged in *Fyn* null brains, whereas levels are significantly reduced in *Cntn* null brain lysates. FGF or EGF (epidermal growth factor) receptor kinase inhibitors have no effect on $\beta 1$ -mediated neurite extension. These results suggest that $\beta 1$ -mediated neurite outgrowth occurs through a lipid raft signaling mechanism that requires the presence of both *fyn* kinase and contactin. *In vivo*, *Scn1b* null mice show defective CGN axon extension and fasciculation indicating that $\beta 1$ plays a role in cerebellar microorganization. In addition, we find that axonal pathfinding and fasciculation are abnormal in corticospinal tracts of *Scn1b* null mice consistent with the suggestion that $\beta 1$ may have widespread effects on postnatal neuronal development. These data are the first to demonstrate a cell-adhesive role for $\beta 1$ *in vivo*. We conclude that voltage-gated Na^+ channel $\beta 1$ subunits signal via multiple pathways on multiple timescales and play important roles in the postnatal development of the CNS.

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Synaptic Metaplasticity through NMDA Receptor Lateral Diffusion

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Lateral diffusion of glutamate receptors was proposed as a mechanism for regulating receptor numbers at synapses and affecting synaptic functions, especially the efficiency of synaptic transmission. However, a direct link between receptor lateral diffusion and change in synaptic function has not yet been established. In the present study, we demonstrated NMDA receptor (NMDAR) lateral diffusion in CA1 neurons in hippocampal slices by detecting considerable recovery of spontaneous or evoked EPSCs from the block of (+)-MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate], an irreversible NMDAR open-channel blocker. We observed changes on both the number and the composition of synaptic NMDAR on recovery. More importantly, after the recovery, long-term potentiation (LTP)-producing protocol induced only LTD (long-term depression) instead of LTP. In contrast, a complete recovery from competitive NMDAR blocker D,L-AP-5 was observed without subsequent changes on synaptic plasticity. Our data suggest a revised model of NMDAR trafficking wherein extrasynaptic NMDARs, mostly NR1/NR2B receptors, move laterally into synaptic sites, resulting in altered rule of synaptic modification. Thus, CA1 synapses exhibit a novel form of metaplasticity in which the direction of synaptic modification can be reverted through subtype-specific lateral diffusion of NMDA receptors.

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Evidence for Muscle-Dependent Neuromuscular Synaptic Site Determination in Mammals

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Recent evidence challenges the prevalent view that neural factors induce the formation of a *de novo* postsynaptic apparatus during development of the vertebrate neuromuscular junction. The latest experiments suggest an alternative model in which the muscle fiber induces a nascent postsynaptic apparatus and sets the location of the future synapse. On axonal contact, these sites, laid out in a prepattern in the central area of developing muscle fibers, mature into synapses by the combined action of neural factors such as agrin and ACh. We sought to test in mammals these two models of neuromuscular synaptogenesis. Previously, we showed that continuous prenatal muscle expression of constitutively active ErbB2 (CAErbB2) led to synaptic loss, exuberant axonal sprouting, and lethality at birth. Here, we transiently induced CAErbB2 during midgestation and examined synapse restoration after inducer withdrawal. Centrally enriched ACh receptor (*AChR*) transcription and clustering were abolished after transient CAErbB2 induction. After inducer withdrawal, synapses were restored but were distributed widely over the entire diaphragm muscle. Under the nerve-dependent model, this distribution is explained by the wide pattern of axonal sprouting triggered by CAErbB2. Yet, in the absence of the nerve, introduced in our animals by mating to *Hb9*^{+/-} mice, a very similar, wide distribution of aneural AChR clusters resulted. Thus, transient expression of CAErbB2 in skeletal muscles leads to reprogramming of the endogenous muscle AChR prepattern. This, and not the nerve, seems primarily responsible for the widely distributed pattern of synapses in our experimental animals.

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Saccade Target Selection in the Superior Colliculus: A Signal Detection Theory Approach

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How the brain selects one action from among multiple options is unknown. A main tenet of signal detection theory (SDT) is that sensory stimuli are represented as noisy information channels. Therefore, the accuracy of selection might be predicted by how well neuronal activity representing alternatives can be distinguished. Here, we apply an SDT framework to a motor system by recording from superior colliculus (SC) neurons during performance of a color, oddball selection task. We recorded from sets of four neurons simultaneously, each of the four representing one of the four possible targets. Because the electrode placement constrained the position of the stimuli in the visual field, the stimulus arrangement varied across experiments. This variability in stimulus arrangement led to variability in choices allowing us to explore the relationship between SC neuronal activity and performance accuracy. SC target neurons had higher levels of discharge than SC distractor neurons in subsets of trials when selection performance was very accurate. In subsets of trials when performance was poor, the discharge level decreased in target neurons and increased in distractor neurons. Accurate performance was associated with larger separations between neuronal activity from targets and distractors as quantified by the receiver operating characteristic (ROC) area and d' (an index of discriminability). Poorer performance was associated with less separation of target and distractor neuronal activity. ROC area and d' scaled approximately linearly with performance accuracy. Furthermore, ROC area and d' increased as saccade onset approached. Together, the results indicate that SC buildup neuronal activity signals the saccadic eye movement decision.

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Patterns of Bidirectional Communication between Cortex and Basal Ganglia during Movement in Patients with Parkinson Disease

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Cortico-basal ganglia networks are considered to comprise several parallel and mostly segregated loops, where segregation is achieved in space through topographic connectivity. Recently, it has been suggested that functional segregation may also be achieved in the frequency domain, by selective coupling of related activities at different frequencies. So far, however, any coupling across frequency in the human has only been modeled in terms of unidirectional influences, a misplaced assumption given the looped architecture of the basal ganglia, and has been considered in static terms. Here, we investigate the pattern of bidirectional coupling between mesial and lateral cortical areas and the subthalamic nucleus (STN) at rest and during movement, with and without pharmacological dopaminergic input, in patients with Parkinson's disease. We simultaneously recorded scalp electroencephalographic activity and local field potentials from depth electrodes and deduced patterns of directed coherence between cortical and STN levels across three frequency bands [sub- β (3–13 Hz), β (14–35 Hz), γ (65–90 Hz)] in the different states. Our results show (1) asymmetric bidirectional coupling between STN and both mesial and lateral cortical areas with greater drives from cortex to STN at frequencies <35 Hz, (2) a drop of β band coupling driven from mesial cortex to STN during movement, and (3) an increase in symmetrical bidirectional drives between STN and mesial cortex and in lateral cortical drive to STN in the γ band after dopaminergic therapy. The results confirm a bidirectional pattern of cortico-basal ganglia communication that is differentially patterned across frequency bands and changes with movement and dopaminergic input.

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Bounded Integration in Parietal Cortex Underlies Decisions Even When Viewing Duration Is Dictated by the Environment

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Decisions about sensory stimuli are often based on an accumulation of evidence in time. When subjects control stimulus duration, the decision terminates when the accumulated evidence reaches a criterion level. Under many natural circumstances and in many laboratory settings, the environment, rather than the subject, controls the stimulus duration. In these settings, it is generally assumed that subjects commit to a choice at the end of the stimulus stream. Indeed, failure to benefit from the full stream of information is interpreted as a sign of imperfect accumulation or memory leak. Contrary to these assumptions, we show that monkeys performing a direction discrimination task commit to a choice when the accumulated evidence reaches a threshold level (or bound), sometimes long before the end of stimulus. This bounded accumulation of evidence is reflected in the activity of neurons in the lateral intraparietal cortex. Thus, the readout of visual cortex embraces a termination rule to limit processing even when potentially useful information is available.

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Neural Underpinnings of Gesture Discrimination in Patients with Limb Apraxia

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Limb apraxia (LA), is a neuropsychological syndrome characterized by difficulty in performing gestures and may therefore be an ideal model for investigating whether action execution deficits are causatively linked to deficits in action understanding. We tested 33 left brain-damaged patients and 8 right brain-damaged patients for the presence of the LA. Importantly, we also tested all the patients in an ad hoc developed gesture recognition task wherein an actor performs, either correctly or incorrectly, transitive (using objects) or intransitive (without objects) meaningful conventional limb gestures. Patients were instructed to judge whether the observed gesture was correct or incorrect. Lesion analysis enabled us to evaluate the relationship between specific brain regions and behavioral performance in gesture execution and gesture comprehension. We found that LA was present in 21 left brain-damaged patients and it was linked to frontal and parietal lesions. Moreover, we found that recognition of correct execution of familiar gestures performed by others was more impaired in patients with LA than in nonapraxic patients. Crucially, the gesture comprehension deficit correlated with damage to the opercular and triangularis portions of the inferior frontal gyrus, two regions that are involved in complex aspects of action-related processing. In contrast, no such relationship was observed with lesions centered on the inferior parietal cortex. The present findings suggest that lesions to left frontal regions that are involved in planning and performing actions are causatively associated with deficits in the recognition of the correct execution of meaningful gestures.

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Differential Columnar Processing in Local Circuits of Barrel and Insular Cortices

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The columnar organization is most apparent in the whisker barrel cortex but seems less apparent in the gustatory insular cortex. We addressed here whether there are any differences between the two cortices in columnar information processing by comparing the spatiotemporal patterns of excitation spread in the two cortices using voltage-sensitive dye imaging. In contrast to the well known excitation spread in the horizontal direction in layer II/III induced in the barrel cortex by layer IV stimulation, the excitation caused in the insular cortex by stimulation of layer IV spread bidirectionally in the vertical direction into layers II/III and V/VI, displaying a columnar image pattern. Bicuculline or picrotoxin markedly extended the horizontal excitation spread in layer II/III in the barrel cortex, leading to a generation of excitation in the underlying layer V/VI, whereas those markedly increased the amplitude of optical responses throughout the whole column in the insular cortex, subsequently widening the columnar image pattern. Such synchronous activities as revealed by the horizontal and vertical excitation spreads were consistently induced in the barrel and insular cortices, respectively, even by stimulation of different layers with varying intensities. Thus, a unique functional column existed in the insular cortex, in which intracolumnar communication between the superficial and deep layers was prominent, and GABA_A action is involved in the inhibition of the intracolumnar communication in contrast to its involvement in intercolumnar lateral inhibition in the barrel cortex. These results suggest that the columnar information processing may not be universal across the different cortical areas.

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Rapid Consolidation to a *radish* and Protein Synthesis-Dependent Long-Term Memory after Single-Session Appetitive Olfactory Conditioning in *Drosophila*

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In *Drosophila*, formation of aversive olfactory long-term memory (LTM) requires multiple training sessions pairing odor and electric shock punishment with rest intervals. In contrast, here we show that a single 2 min training session pairing odor with a more ethologically relevant sugar reinforcement forms long-term appetitive memory that lasts for days. Appetitive LTM has some mechanistic similarity to aversive LTM in that it can be disrupted by cycloheximide, the dCreb2-b transcriptional repressor, and the *crammer* and *tequila* LTM-specific mutations. However, appetitive LTM is completely disrupted by the *radish* mutation that apparently represents a distinct mechanistic phase of consolidated aversive memory. Furthermore, appetitive LTM requires activity in the dorsal paired medial neuron and mushroom body $\alpha' \beta'$ neuron circuit during the first hour after training and mushroom body $\alpha\beta$ neuron output during retrieval, suggesting that appetitive middle-term memory and LTM are mechanistically linked. Last, experiments feeding and/or starving flies after training reveals a critical motivational drive that enables appetitive LTM retrieval.

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Nonlinear Integration of Binocular Optic Flow by DNOVS2, A Descending Neuron of the Fly

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For visual orientation and course stabilization, flies rely heavily on the optic flow perceived by the animal during flight. The processing of optic flow is performed in motion-sensitive tangential cells of the lobula plate, which are well described with respect to their visual response properties and the connectivity among them. However, little is known about the postsynaptic descending neurons, which convey motion information to the motor circuits in the thoracic ganglion. Here we investigate the physiology and connectivity of an identified premotor descending neuron, called DNOVS2 (for descending neuron of the ocellar and vertical system). We find that DNOVS2 is tuned in a supralinear way to rotation around the longitudinal body axis. Experiments involving stimulation of the ipsilateral and the contralateral eye indicate that ipsilateral computation of motion information is modified nonlinearly by motion information from the contralateral eye. Performing double recordings of DNOVS2 and lobula plate tangential cells, we find that DNOVS2 is connected ipsilaterally to a subset of vertical-sensitive cells. From the contralateral eye, DNOVS2 receives input most likely from V2, a heterolateral spiking neuron. This specific neural circuit is sufficient for the tuning of DNOVS2, making it probably an important element in optomotor roll movements of the head and body around the fly's longitudinal axis.

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Glutamate Release in the Nucleus Accumbens Core Is Necessary for Heroin Seeking

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Long-term changes in glutamate transmission in the nucleus accumbens core (NAcore) contribute to the reinstatement of drug seeking after extinction of cocaine self-administration. Whether similar adaptations in glutamate transmission occur during heroin and cue-induced reinstatement of heroin seeking is unknown. After 2 weeks of heroin self-administration and 2 weeks of subsequent extinction training, heroin seeking was induced by a noncontingent injection of heroin or by presentation of light/tones previously paired with heroin infusions. Microdialysis was conducted in the NAcore during reinstatement of heroin seeking in animals extinguished from heroin self-administration or in subjects receiving parallel (yoked) noncontingent saline or heroin. Reinstatement by either heroin or cue increased extracellular glutamate in the NAcore in the self-administration group, but no increase was elicited during heroin-induced reinstatement in the yoked control groups. The increase in glutamate

during heroin-induced drug seeking was abolished by inhibiting synaptic transmission in the NAc core with tetrodotoxin or by inhibiting glutamatergic afferents to the NAc core from the prefrontal cortex. Supporting critical involvement of glutamate release, heroin seeking induced by cue or heroin was blocked by inhibiting AMPA/kainate glutamate receptors in the NAc core. Interestingly, although a heroin-priming injection increased dopamine equally in animals trained to self-administer heroin and in yoked-saline subjects, inhibition of dopamine receptors in the NAc core also blocked heroin- and cue-induced drug seeking. Together, these findings show that recruitment of the glutamatergic projection from the prefrontal cortex to NAc core is necessary to initiate the reinstatement of heroin seeking.

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Design of a Neuronal Array

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Retinal ganglion cells of a given type overlap their dendritic fields such that every point in space is covered by three to four cells. We investigated what function is served by such extensive overlap. Recording from pairs of ON or OFF brisk-transient ganglion cells at photopic intensities, we confirmed that this overlap causes the Gaussian receptive field centers to be spaced at ~ 2 SDs (σ). This, together with response nonlinearities and variability, was just sufficient to provide an ideal observer with uniform contrast sensitivity across the retina for both threshold and suprathreshold stimuli. We hypothesized that overlap might maximize the information represented from natural images, thereby optimizing retinal performance for many tasks. Indeed, tested with natural images (which contain statistical correlations), a model ganglion cell array maximized information represented in its population responses with $\sim 2\sigma$ spacing, i.e., the overlap observed in the retina. Yet, tested with white noise (which lacks statistical correlations), an array maximized its information by minimizing overlap. In both cases, optimal overlap balanced greater signal-to-noise ratio (from larger receptive fields) against greater redundancy (because of larger receptive field overlap). Thus, dendritic overlap improves vision by taking optimal advantage of the statistical correlations of natural scenes.

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Callosal Contributions to Simultaneous Bimanual Finger Movements

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Corpus callosum (CC) is involved in the performance of bimanual motor tasks. We asked whether its functional role could be investigated by combining a motor behavioral study on bimanual movements in multiple sclerosis (MS) patients with a quantitative magnetic resonance diffusion tensor imaging (DTI) analysis of CC, which is shown to be damaged in this disease. MS patients and normal subjects were asked to perform sequences of bimanual finger opposition movements at different metronome rates; then we explored the structural integrity of CC by means of DTI. Significant differences in motor performance, mainly referred to timing accuracy, were observed between MS patients and control subjects. Bimanual motor coordination was impaired in MS patients as shown by the larger values of the interhand interval observed at all the tested metronome rates with respect to controls. Furthermore, DTI revealed a significant reduction of fractional anisotropy (FA), indicative of microstructural tissue damage, in the CC of MS patients. By correlating the mean FA values with the different motor behavior parameters, we found that the degree of damage in the anterior callosal portions mainly influences the bimanual coordination and, in particular, the movement phase preceding the finger touch. Finally, the described approach, which correlates quantitative measures of tissue damage obtained by advanced magnetic resonance imaging tools with appropriate behavioral measurements, may help the exploration of different aspects of motor performance impairment attributable to the disease.

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NEUROBIOLOGY OF DISEASE

Downregulation of the CB₁ Cannabinoid Receptor and Related Molecular Elements of the Endocannabinoid System in Epileptic Human Hippocampus

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Endocannabinoid signaling is a key regulator of synaptic neurotransmission throughout the brain. Compelling evidence shows that its perturbation leads to development of epileptic seizures, thus indicating that endocannabinoids play an intrinsic protective role in suppressing pathologic neuronal excitability. To elucidate whether long-term reorganization of endocannabinoid signaling occurs in epileptic patients, we performed comparative expression profiling along with quantitative electron microscopic analysis in control (postmortem samples from subjects with no signs of neurological disorders) and epileptic (surgically removed from patients with intractable temporal lobe epilepsy) hippocampal tissue. Quantitative PCR measurements revealed that CB₁ cannabinoid receptor mRNA was downregulated to one-third of its control

value in epileptic hippocampus. Likewise, the cannabinoid receptor-interacting protein-1a mRNA was decreased, whereas 1b isoform levels were unaltered. Expression of diacylglycerol lipase- α , an enzyme responsible for 2-arachidonoylglycerol synthesis, was also reduced by \sim 60%, whereas its related β isoform levels were unchanged. Expression level of *N*-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D and fatty acid amide hydrolase, metabolic enzymes of anandamide, and 2-arachidonoylglycerol's degrading enzyme monoacylglycerol lipase did not change. The density of CB₁ immunolabeling was also decreased in epileptic hippocampus, predominantly in the dentate gyrus, where quantitative electron microscopic analysis did not reveal changes in the ratio of CB₁-positive GABAergic boutons, but uncovered robust reduction in the fraction of CB₁-positive glutamatergic axon terminals. These findings show that a neuroprotective machinery involving endocannabinoids is impaired in epileptic human hippocampus and imply that downregulation of CB₁ receptors and related molecular components of the endocannabinoid system may facilitate the deleterious effects of increased network excitability.

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Postmortem Brain Tissue of Depressed Suicides Reveals Increased G α Localization in Lipid Raft Domains Where It Is Less Likely to Activate Adenylyl Cyclase

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Recent *in vivo* and *in vitro* studies have demonstrated that G α migrates from a Triton X-100 (TX-100)-insoluble membrane domain (lipid raft) to a TX-100-soluble nonraft membrane domain in response to chronic, but not acute, treatment with tricyclic or selective serotonin reuptake inhibitor antidepressants. This migration resulted in a more facile association with adenylyl cyclase. Our hypothesis is that G α may be ensconced, to a greater extent, in lipid rafts during depression, and that one action of chronic antidepressant treatment is to reverse this. In this postmortem study, we examined G α membrane localization in the cerebellum and prefrontal cortex of brains from nonpsychiatric control subjects and suicide cases with confirmed unipolar depression. Sequential TX-100 and TX-114 detergent extractions were performed on the brain tissue. In the cerebellum, the ratio of TX-100/TX-114-soluble G α is \sim 2:1 for control versus depressed suicides. Results with prefrontal cortex samples from each group demonstrate a similar trend. These data suggest that depression localizes G α to a membrane domain (lipid rafts) where it is less likely to couple to adenylyl cyclase and that antidepressants may upregulate G α signaling via disruption of membrane microenvironments. Raft localization of G α in human peripheral tissue may thus serve as a biomarker for depression and as a harbinger of antidepressant responsiveness.

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Lack of Pathology in a Triple Transgenic Mouse Model of Alzheimer's Disease after Overexpression of the Anti-Apoptotic Protein Bcl-2

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Alzheimer's disease (AD) is characterized by the accumulation of plaques containing β -amyloid (A β) and neurofibrillary tangles (NFTs) consisting of modified tau. Although A β deposition is thought to precede the formation of NFTs in AD, the molecular steps connecting these two pathologies is not known. Previous studies have suggested that caspase activation plays an important role in promoting the pathology associated with AD. To further understand the contribution of caspases in disease progression, a triple transgenic Alzheimer's mouse model overexpressing the anti-apoptotic protein Bcl-2 was generated. Here we show that overexpression of Bcl-2 limited caspase-9 activation and reduced the caspase cleavage of tau. Moreover, overexpression of Bcl-2 attenuated the processing of APP (amyloid precursor protein) and tau and reduced the number of NFTs and extracellular deposits of A β associated with these animals. In addition, overexpression of Bcl-2 in 3xTg-AD mice improved place recognition memory. These findings suggest that the activation of apoptotic pathways may be an early event in AD and contributes to the pathological processes that promote the disease mechanisms underlying AD.

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Zinc and 4-Hydroxy-2-Nonenal Mediate Lysosomal Membrane Permeabilization Induced by H₂O₂ in Cultured Hippocampal Neurons

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Lysosomal membrane permeabilization (LMP) is implicated in cancer cell death. However, its role and mechanism of action in neuronal death remain to be established. In the present study, we investigate the function of cellular zinc in oxidative stress-induced LMP using hippocampal neurons. Live-cell confocal microscopy with FluoZin-3 fluorescence showed that H₂O₂ exposure induced vesicles containing labile zinc in hippocampal neurons. Double staining with LysoTracker or MitoTracker disclosed that the majority of the zinc-containing vesicles were lysosomes and not mitochondria. H₂O₂ additionally augmented the 4-hydroxy-2-nonenal (HNE) adduct level in lysosomes. Intracellular zinc chelation with TPEN [tetrakis(2-pyridylmethyl)ethylenediamine] completely blocked both HNE accumulation and neuronal death. Interestingly, within 1 h after the onset of H₂O₂ exposure, some of zinc-loaded vesicles lost their zinc signals. Consistent with the characteristics of LMP, a lysosomal enzyme, cathepsin D, was

released into the cytosol, and cathepsin inhibitors partially rescued neuronal death. We further examined the possibility that HNE or zinc mediates H₂O₂-triggered LMP. Similar to H₂O₂, exposure to HNE or zinc triggered lysosomal zinc accumulation and LMP. Moreover, isolated lysosomes underwent LMP when exposed to HNE or zinc, but not H₂O₂, supporting the direct mediation of LMP by HNE and/or zinc. The appearance of zinc-containing vesicles and the increases in levels of cathepsin D and HNE, were also observed in hippocampal neurons of rats after kainate seizures. Thus, under oxidative stress, neuronal lysosomes accumulate zinc and HNE, and eventually undergo LMP, which may constitute a key mechanism of oxidative neuronal death.

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Methylprednisolone Protects Oligodendrocytes But Not Neurons after Spinal Cord Injury

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Methylprednisolone (MP) is used to treat a variety of neurological disorders involving white matter injury, including multiple sclerosis, acute disseminated encephalomyelitis, and spinal cord injury (SCI). Although its mechanism of action has been attributed to anti-inflammatory or antioxidant properties, we examined the possibility that MP may have direct neuroprotective activities. Neurons and oligodendrocytes treated with AMPA or staurosporine died within 24 h after treatment. MP attenuated oligodendrocyte death in a dose-dependent manner; however, neurons were not rescued by the same doses of MP. This protective effect was reversed by the glucocorticoid receptor (GR) antagonist (11, 17)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (RU486) and small interfering RNA directed against GR, suggesting a receptor-dependent mechanism. MP reversed AMPA-induced decreases in the expression of anti-apoptotic Bcl-x_L, caspase-3 activation, and DNA laddering, suggesting anti-apoptotic activity in oligodendrocytes. To examine whether MP demonstrated this selective protection *in vivo*, neuronal and oligodendrocyte survival was assessed in rats subjected to spinal cord injury (SCI); groups of rats were treated with or without MP in the presence or absence of RU486. Eight days after SCI, MP significantly increased oligodendrocytes (CC-1-immunoreactive cells) after SCI, but neuronal (neuronal-specific nuclear protein-immunoreactive cells) number remained unchanged; RU486 reversed this protective effect. MP also inhibited SCI-induced decreases in Bcl-x_L and caspase-3 activation. Consistent with these findings, the volume of demyelination, assessed by Luxol fast blue staining, was attenuated by MP and reversed by RU486. These results suggest that MP selectively inhibits oligodendrocyte but not neuronal cell death via a receptor-mediated action and may be a mechanism for its limited protective effect after SCI.

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Mutational Analysis Establishes a Critical Role for the N Terminus of Fragile X Mental Retardation Protein FMRP

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Fragile X syndrome is the most common form of heritable mental retardation caused by the loss of function of the fragile X mental retardation protein FMRP. FMRP is a multidomain, RNA-binding protein involved in RNA transport and/or translational regulation. However, the binding specificity between FMRP and its various partners including interacting proteins and mRNA targets is essentially unknown. Previous work demonstrated that dFMRP, the *Drosophila* homolog of human FMRP, is structurally and functionally conserved with its mammalian counterparts. Here, we perform a forward genetic screen and isolate 26 missense mutations at 13 amino acid residues in the dFMRP coding *dfmr1*. Interestingly, all missense mutations identified affect highly conserved residues in the N terminal of dFMRP. Loss- and gain-of-function analyses reveal altered axonal and synaptic elaborations in mutants. Yeast two-hybrid assays and *in vivo* analyses of interaction with CYFIP (cytoplasmic FMR1 interacting protein) in the nervous system demonstrate that some of the mutations disrupt specific protein–protein interactions. Thus, our mutational analyses establish that the N terminus of FMRP is critical for its neuronal function.

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Enhanced Tau Phosphorylation in the Hippocampus of Mice Treated with 3,4-Methylenedioxymethamphetamine (“Ecstasy”)

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3,4-Methylenedioxymethamphetamine (MDMA) (“Ecstasy”) produces neurotoxic effects, which result into an impairment of learning and memory and other neurological dysfunctions. We examined whether MDMA induces increases in tau protein phosphorylation, which are typically associated with Alzheimer’s disease and other chronic neurodegenerative disorders. We injected mice with MDMA at cumulative doses of 10–50 mg/kg intraperitoneally, which are approximately equivalent to doses generally consumed by humans. MDMA enhanced the formation of reactive oxygen species and induced reactive gliosis in the hippocampus, without histological evidence of neuronal loss. An acute or 6 d treatment with MDMA increased tau protein phosphorylation in the hippocampus, revealed by both anti-phospho(Ser⁴⁰⁴)-tau and paired helical filament-1 antibodies. This increase was restricted to the CA2/CA3 subfields and lasted 1 and 7 d after acute and repeated MDMA treatment, respectively. Tau protein was phosphorylated as a result of two nonredundant mechanisms: (1) inhibition of the canonical Wnt (wingless-type MMTV integration site family) pathway, with ensuing activation of glycogen synthase kinase-3 β ; and (2) activation of type-5 cyclin-dependent kinase (Cdk5). MDMA induced the expression of the Wnt antagonist, Dickkopf-1, and the expression of the Cdk5-activating protein, p25. In addition, the increase in tau phosphorylation was attenuated by strategies that rescued the Wnt pathway or inhibited Cdk5. Finally, an impairment in hippocampus-dependent spatial learning was induced by doses of MDMA that increased tau phosphorylation, although the impairment outlasted this biochemical event. We conclude that tau hyperphosphorylation in the hippocampus may contribute to the impairment of learning and memory associated with MDMA abuse.

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