

This Week in The Journal

● Cellular/Molecular

Keeping CaMKII at the Synapse

K. Ulrich Bayer, Éric LeBel, Greg L. McDonald, Heather O'Leary, Howard Schulman, and Paul De Koninck

(see pages 1164–1174)

Ca²⁺/calmodulin (CaM)-dependent kinase (CaMKII) and the NMDA receptor subunit NR2B are established contributors to synaptic plasticity. This week, Bayer et al. show that the activity- and NMDA-receptor-dependent translocation of CaMKII to the synapse has two phases. In cultured hippocampal neurons, persistent translocation of GFP (green fluorescent protein)-labeled CaMKII to synapses depended on NMDA receptor activation but not on CaMKII autophosphorylation at the T286 site. Using site-directed mutagenesis, the authors document a two-phase binding scheme whereby transient activity elicited Ca²⁺/CaM-dependent binding of NR2B to CaMKII at its substrate-binding site (“S-site”), whereas prolonged activity led to persistent binding at the T286-binding site (“T-site”). This interaction prevented binding of the regulatory region, thus creating a second mechanism (in addition to autophosphorylation) that allows sustained CaMKII activity and compartment-

talization at synapses. Although Ca²⁺/CaM was not required for the T-site binding, it may speed the transition.

▲ Development/Plasticity/Repair

A Bloodless Role for the Erythropoietin Receptor

Peter T. Tsai, John Ohab, Nathalie Kertesz, Matthias Groszer, Cheryl Matter, Jing Gao, Xin Liu, Hong Wu, and S. Thomas Carmichael

(see pages 1269–1274)

Although named for its effect on red cell production and made infamous by “blood doping” in athletes, the growth factor erythropoietin (EPO) and its receptor (EPOR) also provide important signaling in brain. In this week's *Journal*, Tsai et al. examined the role of endogenous EPO and EPOR in neurogenesis. Deletion of either the *Epo* or *EpoR* gene resulted in similar effects: incomplete neural tube closure at embryonic day 10.5 (E10.5) and severe neurogenic defects by E13.5. Thus, the authors surmised that the EPOR was essential for EPO-mediated developmental neurogenesis. Using the loxp/Cre system, they created conditional knock-down mice that lacked brain EPOR expression after E14. The mutant mice had fewer cells in the subventricular zone at postnatal day 15 and at 6 months. After ischemic injury in a focal stroke model, EPOR did not afford neuroprotection. Rather, EPOR-deficient poststroke mice displayed reduced neurogenesis because of impaired neuroblast migration.

■ Behavioral/Systems/Cognitive

Modeling Perceptual Decisions

Kong-Fatt Wong and Xiao-Jing Wang

(see pages 1314–1328)

Making decisions can be tough and can take considerable time, at least for some of us. Several groups have examined perceptual decision making in primates using forced-choice visual motion discrimination tasks. On these tasks, firing in the lateral intraparietal cortex (LIP) correlates

with the reaction time and the correctness of the choice. This activity builds over several hundred milliseconds, suggesting that LIP could be integrating information before a decision. This week, Wang and Wong built a spiking-neuron network model that was able to mimic these activity patterns. The model was based on a previous network model including thousands of neurons, but the authors used a reduced version containing only two dynamical variables. Despite the simplifications and assumptions, the model revealed useful insights. Reverberant excitation mediated by NMDA receptors was critical for the slow time integration. The model also explained the experimentally observed longer reaction time in error trials compared with correct trials.

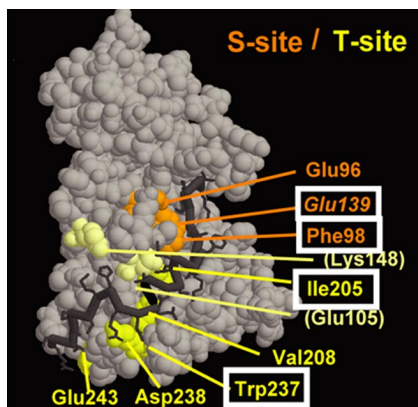
◆ Neurobiology of Disease

Painful Action Potentials

Laiche Djouhri, Stella Koutsikou, Xin Fang, Simon McMullan, and Sally N. Lawson

(see pages 1281–1292)

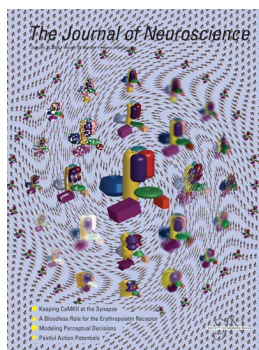
Neuropathic pain is characterized by shooting, burning, stabbing, and electrical sensations that are thought to arise from spontaneous activity of injured afferent nerves. This week, Djouhri et al. recorded spontaneous foot lifting as an indicator of spontaneous pain in nerve-injured rats. Spinal nerve axotomy (SNA) of L5 did not evoke spontaneous foot lifting, but a modified SNA (mSNA) procedure did. In addition to L5 axotomy, the mSNA involved loose ligation of the adjacent L4 spinal nerve with chromic gut, providing a key inflammatory component. Another group of animals was injected with complete Freund's adjuvant, causing peripheral inflammation. Using intracellular recordings from ipsilateral L4 dorsal root ganglion neurons, the authors found that spontaneous firing rate of intact C-type nociceptive neurons correlated with spontaneous foot lifting. The results suggest that both neuropathic pain and spontaneous firing depend on an inflammatory component, at least in this model system.



The NR2B-binding surface on CaMKII is shown with residues implicated in the interaction with the autoregulatory domain. The “S-site” and “T-site” are shown in orange and yellow, respectively. See the article by Bayer et al. for details.

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Cover picture: Alternative splicing is the major source of polypeptide diversity within the nervous system. Alternative splicing regulates the structure of the C terminus of the NR1 subunit of the NMDA receptor complex and determines the repertoire of cytoplasmic proteins with which NR1 associates. Many NR1-interacting proteins are also alternatively spliced, creating tens of thousands of combinations of possible NMDA receptor signaling complexes. An article in this week's *Journal* examines the role of the alternatively spliced C terminus of NR1 in local and long-range NMDA receptor signaling. For details, see the article by Bradley et al. in this issue (pages 1065–1076).

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JOURNAL CLUB

Carry on Eating: Neural Pathways Mediating Conditioned Potentiation of Feeding

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The Journal of Neuroscience, January 25, 2006 • 26(4):1061–1062

Target-Derived Cues Instruct Synaptic Differentiation

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The Journal of Neuroscience, January 25, 2006 • 26(4):1063–1064

BRIEF COMMUNICATIONS

Long-Term Depression of NMDA Receptor-Mediated Synaptic Transmission Is Dependent on Activation of Metabotropic Glutamate Receptors and Is Altered to Long-Term Potentiation by Low Intracellular Calcium Buffering

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Synaptic plasticity of NMDA receptor (NMDAR)-mediated transmission was investigated in the rat dentate gyrus *in vitro*. Isolated NMDAR EPSCs were recorded from granule cells of the dentate gyrus in response to stimulation of the medial perforant path. Long-term potentiation (LTP) or long-term depression (LTD) of NMDAR EPSCs was observed in response to brief high-frequency stimulation (HFS), with the direction and extent of plasticity dependent on the concentration and type (EGTA vs BAPTA) of the intracellular Ca²⁺ buffer. LTD was induced in higher concentrations of EGTA and BAPTA than LTP, and BAPTA was ~100-fold more potent than EGTA. Although LTD was induced in a high concentration of EGTA (10 mM), a high concentration of BAPTA (10 mM) blocked both LTP and LTD. LTP of AMPA receptor (AMPA)-EPSCs exhibited a lower dependency on Ca²⁺ buffering than LTP of NMDAR EPSCs, because LTP of AMPAR EPSCs was induced by HFS in high EGTA (10 mM). We also identified a role for metabotropic glutamate receptor 5 (mGluR5) in NMDAR plasticity. HFS LTD was blocked by the group I/II mGluR antagonist LY341495 ((2S)-2-amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl)propanoic acid) and by the mGluR5-selective antagonist 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP). Similarly, low-frequency stimulation-induced LTD of NMDAR EPSCs was also blocked by MPEP. These findings suggest that the direction of plasticity of NMDARs is determined by the intracellular free Ca²⁺ concentration and is dependent on activation of mGluR5.

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Goal Representation in Human Anterior Intraparietal Sulcus

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When a child reaches toward a cookie, the watching parent knows immediately what the child wants. The neural basis of this ability to interpret other people's actions in terms of their goals has been the subject of much speculation. Research with infants has shown that 6 month olds respond when they see an adult reach to a novel goal but habituate when an adult reaches to the same goal repeatedly. We used a similar approach in an event-related functional magnetic resonance imaging experiment. Adult participants observed a series of movies depicting goal-directed actions, with the sequence controlled so that some goals were novel and others repeated relative to the previous movie. Repeated presentation of the same goal caused a suppression of the blood oxygen level-dependent response in two regions of the left intraparietal sulcus. These regions were not sensitive to the trajectory taken by the actor's hand. This result demonstrates that the anterior intraparietal sulcus represents the goal of an observed action.

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Long-Lasting Memories of Obstacles Guide Leg Movements in the Walking Cat

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We examined the ways in which memories of previously seen obstacles can alter the stepping of walking cats. Cats were paused after the forelegs, but not the hindlegs, had stepped over an obstacle. Near the beginning of a variable delay period, the obstacle was lowered. On the subsequent step, the path of the hindlegs allowed us to make

inferences about whether the memory of the obstacle was influencing leg movements. We present two main findings. First, the memory of the obstacle persisted for the duration that the animal straddled the original location of the obstacle. In one instance, this interval was 10 min. Second, this memory includes information regarding the size and position of the obstacle relative to the animal. This information is used to plan foot placement and to redirect the step in mid-swing to avoid the previous position of the obstacle.

The Journal of Neuroscience, January 25, 2006 • 26(4):1175–1178

A Critical Role of Erythropoietin Receptor in Neurogenesis and Post-Stroke Recovery

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Erythropoietin (EPO) is the principal growth factor regulating the production of red blood cells. Recent studies demonstrated that exogenous EPO acts as a neuroprotectant and regulates neurogenesis. Using a genetic approach, we evaluate the roles of endogenous EPO and its classical receptor (EPOR) in mammalian neurogenesis. We demonstrate severe and identical embryonic neurogenesis defects in animals null for either the *Epo* or *EpoR* gene, suggesting that the classical EPOR is essential for EPO action during embryonic neurogenesis. Furthermore, by generating conditional *EpoR* knock-down animals, we demonstrate that brain-specific deletion of *EpoR* leads to significantly reduced cell proliferation in the subventricular zone and impaired post-stroke neurogenesis. *EpoR* conditional knockdown leads to a specific deficit in post-stroke neurogenesis through impaired migration of neuroblasts to the peri-infarct cortex. Our results suggest that both EPO and EPOR are essential for early embryonic neural development and that the classical EPOR is important for adult neurogenesis and for migration of regenerating neurons during post-injury recovery.

The Journal of Neuroscience, January 25, 2006 • 26(4):1269–1274

Brief Communications

A Critical Role for Dorsal Progenitors in Cortical Myelination

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Much controversy regarding the anatomical sources of oligodendrocytes in the spinal cord and hindbrain has been resolved. However, the relative contribution of dorsal and ventral progenitors to myelination of the cortex is still a subject of debate. To assess the contribution of dorsal progenitors to cortical myelination, we ablated the basic helix-loop-helix transcription factor *Olig2* in the developing dorsal telencephalon. In *Olig2*-ablated cortices, myelination is arrested at the progenitor stage. Under these conditions, ventrally derived oligodendrocytes migrate dorsally into the *Olig2*-ablated territory but cannot fully compensate for myelination deficits observed at postnatal stages. Thus, spatially restricted ablation of *Olig2* function unmasks a contribution of dorsal progenitors to cortical myelination that is much greater than hitherto appreciated.

The Journal of Neuroscience, January 25, 2006 • 26(4):1275–1280

Articles

CELLULAR/MOLECULAR

Splice Variants of the NR1 Subunit Differentially Induce NMDA Receptor-Dependent Gene Expression

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Subunits of the NMDA receptor (NMDAR) associate with many postsynaptic proteins that substantially broaden its signaling capacity. Although much work has been focused on the signaling of NR2 subunits, little is known about the role of the NR1 subunit. We set out to elucidate the role of the C terminus of the NR1 subunit in NMDAR signaling. By introducing a C-terminal deletion mutant of the NR1 subunit into cultured neurons from *NR1*^{-/-} mice, we found that the C terminus was essential for NMDAR inactivation, downstream signaling, and gene expression, but not for global increases in intracellular Ca²⁺. Therefore, whereas NMDARs can increase Ca²⁺ throughout the neuron, NMDAR-dependent signaling, both local and long range, requires coupling through the NR1 C terminus. Two major NR1 splice variants differ by the presence or absence of a C-terminal domain, C1, which is determined by alternative splicing of exon 21. Analysis of these two variants showed that removal of this domain significantly

reduced the efficacy of NMDAR-induced gene expression without affecting receptor inactivation. Thus, the NR1 C terminus couples to multiple downstream signaling pathways that can be modulated selectively by RNA splicing.

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Novel Blockade of Protein Kinase A-Mediated Phosphorylation of AMPA Receptors

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The phosphorylation state of the glutamate receptor subtype 1 (GluR1) subunit of the AMPA receptor (AMPA) plays a critical role in synaptic expression of the receptor, channel properties, and synaptic plasticity. Several G_s-coupled receptors that couple to protein kinase A (PKA) readily recruit phosphorylation of GluR1 at S845. Conversely, activation of the ionotropic glutamate NMDA receptor (NMDAR) readily recruits dephosphorylation of the same GluR1 site through Ca²⁺-mediated recruitment of phosphatase activity. In a physiological setting, receptor activation often overlaps and crosstalk between coactivation of multiple signaling cascades can result in differential regulation of a given substrate. After investigating the effect of coactivation of the NMDAR and the G_s-coupled β-adrenergic receptor on GluR1 phosphorylation state, we have observed a novel signal that prevents PKA-mediated phosphorylation of GluR1 at serine site 845. This blockade of GluR1 phosphorylation is dependent on cellular depolarization recruited by either NMDAR or AMPAR activation, independent of Ca²⁺ and independent of calcineurin, protein phosphatase 1, and/or protein phosphatase 2A activity. Thus, in addition to the typical kinase–phosphatase rivalry mediating protein phosphorylation state, we have identified a novel form of phospho-protein regulation that occurs at GluR1 and may also occur at several other PKA substrates.

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Arrestin Translocation Is Induced at a Critical Threshold of Visual Signaling and Is Superstoichiometric to Bleached Rhodopsin

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Light induces massive translocation of major signaling proteins between the subcellular compartments of photoreceptors. Among them is visual arrestin responsible for quenching photoactivated rhodopsin, which moves into photoreceptor outer segments during illumination. Here, for the first time, we determined the light dependency of arrestin translocation, which revealed two key features of this phenomenon. First, arrestin translocation is triggered when the light intensity approaches a critical threshold corresponding to the upper limits of the normal range of rod responsiveness. Second, the amount of arrestin entering rod outer segments under these conditions is superstoichiometric to the amount of photoactivated rhodopsin, exceeding it by at least 30-fold. We further showed that it is not the absolute amount of excited rhodopsin but rather the extent of downstream cascade activity that triggers translocation. Finally, we demonstrated that the total amount of arrestin in the rod cell is nearly 10-fold higher than previously thought and therefore sufficient to inactivate the entire pool of rhodopsin at any level of illumination. Thus, arrestin movement to the outer segment leads to an increase in the free arrestin concentration and thereby may serve as a powerful mechanism of light adaptation.

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Dendrites Contain a Spacing Pattern

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The distinctive branching patterns of dendritic arbors are essential for neuronal information processing. The final shape of an arbor is the result of intrinsic and extrinsic factors. However, the cellular mechanisms that underlie branch patterning are unknown. In many biological systems, locally acting factors are intrinsically organized into spacing patterns that guide patterned morphogenesis. Here, we show that neurons contain two types of periodic and regular elements (PADREN1s and PADREN2s) that are arranged into a spacing pattern. The wavelength of the pattern is ~20 μm. Dendritic branches occur preferentially within PADREN1s, and specific PADREN lengths correspond to specific arbor types. The lengths of the PADRENs also change over time and can be modified by activity. However, PADRENs are intrinsically organized, possibly by a reaction-diffusion process. PADRENs reveal a previously unrecognized level of neuronal organization that may provide insight into how the distinct branching patterns of the dendrites are intrinsically organized.

The Journal of Neuroscience, January 25, 2006 • 26(4):1154–1163

Transition from Reversible to Persistent Binding of CaMKII to Postsynaptic Sites and NR2B

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Changes in protein–protein interactions and activity states have been proposed to underlie persistent synaptic remodeling that is induced by transient stimuli. Here, we show an unusual stimulus-dependent transition from a short-lived to long-lasting binding between a synaptic receptor and its transducer. Both molecules, the NMDA receptor subunit NR2B and Ca²⁺/calmodulin (CaM)-dependent protein kinase II (CaMKII), are strongly implicated in mediating synaptic plasticity. We show that CaMKII reversibly translocates to synaptic sites in response to brief stimuli, but its resident time at the synapse increases after longer stimulation. Thus, CaMKII localization reflects temporal patterns of synaptic stimulation. We have identified two surface regions of CaMKII involved in short-lived and long-term interactions with NR2B. Our results support an initial reversible and Ca²⁺/CaM-dependent binding at the substrate-binding site (“S-site”). On longer stimulation, a persistent interaction is formed at the T286-binding site (“T-site”), thereby keeping the autoregulatory domain displaced and enabling Ca²⁺/CaM-independent kinase activity. Such dual modes of interaction were observed *in vitro* and in HEK cells. In hippocampal neurons, short-term stimulation initiates a reversible translocation, but an active history of stimulation beyond some threshold produces a persistent synaptic localization of CaMKII. This activity-dependent incorporation of CaMKII into postsynaptic sites may play a role in maturation and plasticity of synapses.

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Peripheral Myelin Protein 22 Is in Complex with $\alpha 6\beta 4$ Integrin, and Its Absence Alters the Schwann Cell Basal Lamina

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Peripheral myelin protein 22 (PMP22) is a tetraspan membrane glycoprotein, the misexpression of which is associated with hereditary demyelinating neuropathies. Myelinating Schwann cells (SCs) produce the highest levels of PMP22, yet the function of the protein in peripheral nerve biology is unresolved. To investigate the potential roles of PMP22, we engineered a novel knock-out (–/–) mouse line by replacing the first two coding exons of *pmp22* with the *lacZ* reporter. PMP22-deficient mice show strong β -galactosidase reactivity in peripheral nerves, cartilage, intestines, and lungs, whereas phenotypically they display the characteristics of tomaculous neuropathy. In the absence of PMP22, myelination of peripheral nerves is delayed, and numerous axon–SC profiles show loose basal lamina, suggesting altered interactions of the glial cells with the extracellular matrix. The levels of $\beta 4$ integrin, a molecule involved in the linkage between SCs and the basal lamina, are severely reduced in nerves of PMP22-deficient mice. During early stages of myelination, PMP22 and $\beta 4$ integrin are coexpressed at the cell surface and can be coimmunoprecipitated together with laminin and $\alpha 6$ integrin. In agreement, in clone A colonic carcinoma cells, epitope-tagged PMP22 forms a complex with $\beta 4$ integrin. Together, these data indicate that PMP22 is a binding partner in the integrin/laminin complex and is involved in mediating the interaction of SCs with the extracellular environment.

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Rab3 Superprimes Synaptic Vesicles for Release: Implications for Short-Term Synaptic Plasticity

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Presynaptic vesicle trafficking and priming are important steps in regulating synaptic transmission and plasticity. The four closely related small GTP-binding proteins Rab3A, Rab3B, Rab3C, and Rab3D are believed to be important for these steps. In mice, the complete absence of all Rab3s leads to perinatal lethality accompanied by a 30% reduction of probability of Ca²⁺-triggered synaptic release. This study examines the role of Rab3 during Ca²⁺-triggered release in more detail and identifies its impact on short-term plasticity. Using patch-clamp electrophysiology of autaptic neuronal cultures from Rab3-deficient mouse hippocampus, we show that excitatory Rab3-deficient neurons display unique time- and frequency-dependent short-term plasticity characteristics in response to spike trains. Analysis of vesicle release and repriming kinetics as well as Ca²⁺ sensitivity of release indicate that Rab3 acts on a subset of primed, fusion competent vesicles. They lower the amount of Ca²⁺ required for action potential-triggered release, which leads to a boosting of release probability, but their action also introduces a significant delay in the supply of these modified vesicles. As a result, Rab3-induced modifications to primed vesicles causes a transient increase in the transduction efficacy of synaptic action potential trains and optimizes the encoding of synaptic information at an intermediate spike frequency range.

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Compartmentalized and Signal-Selective Gap Junctional Coupling in the Hearing Cochlea

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Gap junctional intercellular communication (GJIC) plays a major role in cochlear function. Recent evidence suggests that connexin 26 (Cx26) and Cx30 are the major constituent proteins of cochlear gap junction channels, possibly in a unique heteromeric configuration. We investigated the functional and structural properties of native cochlear gap junctions in rats, from birth to the onset of hearing [postnatal day 12 (P12)]. Confocal immunofluorescence revealed increasing Cx26 and Cx30 expression from P0 to P12. Functional GJIC was assessed by coinjection of Lucifer yellow (LY) and Neurobiotin (NBN) during whole-cell recordings in cochlear slices. At P0, there was restricted dye transfer between supporting cells around outer hair cells. Transfer was more extensive between supporting cells around inner hair cells. At P8, there was extensive transfer of both dyes between all supporting cell types. By P12, LY no longer transferred between the supporting cells immediately adjacent to hair cells but still transferred between more peripheral cells. NBN transferred freely, but it did not transfer between inner and outer pillar cells. Freeze fracture further demonstrated decreasing GJIC between inner and outer pillar cells around the onset of hearing. These data are supportive of the appearance of signal-selective gap junctions around the onset of hearing, with specific properties required to support auditory function. Furthermore, they suggest that separate medial and lateral buffering compartments exist in the hearing cochlea, which are individually dedicated to the homeostasis of inner hair cells and outer hair cells.

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Synaptic Vesicle Protein 2 Enhances Release Probability at Quiescent Synapses

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We report a thorough analysis of neurotransmission in cultured hippocampal neurons lacking synaptic vesicle protein 2 (SV2), a membrane glycoprotein present in all vesicles that undergo regulated secretion. We found that SV2 selectively enhances low-frequency neurotransmission by priming morphologically docked vesicles. Loss of SV2 reduced initial release probability during a train of action potentials but had no effect on steady-state responses. The amount and decay rate of asynchronous release, two measures sensitive to presynaptic calcium concentrations, are not altered in SV2 knock-outs, suggesting that SV2 does not act by modulating presynaptic calcium. Normal neurotransmission could be temporarily recovered by delivering an exhaustive stimulus train. Our results indicate that SV2 primes vesicles in quiescent neurons and that SV2 function can be bypassed by an activity-dependent priming mechanism. We propose that SV2 action modulates synaptic networks by ensuring that low-frequency neurotransmission is faithfully conveyed.

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DEVELOPMENT/PLASTICITY/REPAIR

Simultaneous NMDA-Dependent Long-Term Potentiation of EPSCs and Long-Term Depression of IPSCs in Cultured Rat Hippocampal Neurons

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A fundamental issue in understanding activity-dependent long-term plasticity of neuronal networks is the interplay between excitatory and inhibitory synaptic drives in the network. Using dual whole-cell recordings in cultured hippocampal neurons, we examined synaptic changes occurring as a result of a transient activation of NMDA receptors in the network. This enhanced transient activation led to a long-lasting increase in synchrony of spontaneous activity of neurons in the network. Simultaneous long-term potentiation of excitatory synaptic strength and a pronounced long-term depression of inhibitory synaptic currents (LTDi) were produced, which were independent of changes in postsynaptic potential and Ca^{2+} concentrations. Surprisingly, miniature inhibitory synaptic currents were not changed by the conditioning, whereas both frequency and amplitudes of miniature EPSCs were enhanced. LTDi was mediated by activation of a presynaptic GABA_B receptor, because it was blocked by saclofen and CGP55845 [(2S)-3-[[[(1S)-1-(3,4-dichlorophenyl)ethyl]amino-2-hydroxypropyl](phenylmethyl)phosphinic acid]]. The cAMP antagonist Rp-adenosine 3',5'-cyclic monophosphothioate abolished all measured effects of NMDA-dependent conditioning, whereas a nitric oxide synthase inhibitor was ineffective. Finally, network-induced plasticity was not occluded by a previous spike-timing-induced plasticity, indicating that the two types of plasticity may not share the same mechanism. These results demonstrate that network plasticity involves opposite effects on inhibitory and excitatory neurotransmission.

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Involvement of the CA3–CA1 Synapse in the Acquisition of Associative Learning in Behaving Mice

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One of the brain sites more directly related with learning and memory processes is the hippocampus. We recorded, in conscious mice, the activity-dependent changes taking place at the hippocampal CA3–CA1 synapse during the acquisition, extinction, recall, and reconditioning of an associative task. Mice were classically conditioned to evoke eyelid responses using a trace [conditioned stimuli (CS), tone; unconditioned stimuli (US), shock] paradigm. A single electrical pulse presented to the Schaffer collateral–commissural pathway during the CS–US interval evoked a monosynaptic field EPSP (fEPSP) at ipsilateral CA1 pyramidal cells. The slope of evoked fEPSPs increased across conditioning sessions and decreased during extinction, being linearly related to learning evolution. In contrast, fEPSPs were not modified when evoked in control mice in the absence of a conditioning protocol. Long-term potentiation (LTP) evoked by high-frequency stimulation of Schaffer collaterals prevented acquisition, extinction, recall, or reconditioning, depending on the moment when it was triggered. Learning and memory impairments evoked by LTP induction resulted probably from the functional saturation of the CA3–CA1 synapse, although an additional disturbance of the subsequent information transfer toward postsynaptic circuits cannot be discarded. CGP 39551 [(E)-(±)-2-amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester] (an NMDA antagonist) prevented LTP induction in behaving mice, as well as the acquisition of an eyelid learned response, and the synaptic changes taking place at the CA3–CA1 synapse across conditioning. In conclusion, the responsiveness of the CA3–CA1 synapse seems to be modulated during associative learning, and both processes are prevented by experimental LTP or NMDA-receptor inactivation. Our results provide evidence of a relationship between activity-dependent synaptic plasticity and associative learning in behaving mice.

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Allocentric Spatial Referencing of Neuronal Activity in Macaque Posterior Cingulate Cortex

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Neuronal activity in posterior cingulate cortex (CGp) is modulated by visual stimulation, saccades, and eye position, suggesting a role for this area in visuospatial transformations. The goal of this study was to determine whether neuronal responses in CGp are anchored to the eyes, head, or outside the body (allocentrically). To discriminate retinocentric from nonretinocentric spatial referencing, the activity of single CGp neurons was recorded while monkeys (*Macaca mulatta*) performed delayed-saccade trials initiated randomly from three different starting positions to a linear array of targets passing through the neuronal response field. For most neurons, tuning curves, segregated by fixation point, aligned more closely when plotted with respect to the display than when plotted with respect to the eye, suggesting a nonretinocentric frame of reference. A second experiment differentiated between spatial referencing in coordinates anchored to the head or body and allocentric spatial referencing. Monkeys shifted gaze from a central fixation point to the array of previously used targets both before and after whole-body rotation with respect to the display. For most neurons, tuning curves, segregated by fixation position, aligned more closely when plotted as a function of target position in the room than when plotted as a function of target position with respect to the monkey. These data indicate that a population of CGp neurons encodes visuospatial events in allocentric coordinates.

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Medullary Raphe Neurons Facilitate Brown Adipose Tissue Activation

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Recent evidence suggests that neurons in the medullary raphe are critical to the activation of brown adipose tissue (BAT), the major source of nonshivering heat production in the rat. Yet it is unclear which medullary raphe cells participate in cold defense and how participating cells contribute to BAT activation. Therefore, we recorded extracellularly from raphe cells during three thermoregulatory challenges that evoked an increase in BAT temperature in anesthetized rats: central cold, ambient cold, or intracerebroventricular prostaglandin E₂ (PGE₂) injection. Physiologically identified serotonergic (p5HT) cell discharge increased in response to cold or PGE₂ administration and was positively correlated with BAT temperature. However, none of the 147 physiologically identified non-serotonergic (non-p5HT) cells recorded responded to thermoregulatory challenges that evoked an increase in BAT temperature. To test for modulation of BAT activation by non-p5HT cells that are either excited (ON cells) or inhibited (OFF cells) by noxious cutaneous stimulation, noxious stimuli were applied during evoked BAT temperature increases. Noxious stimulation suppressed BAT activation, suggesting that cells inhibited by noxious stimulation facilitate spinal circuits controlling BAT. To test whether medullary OFF cells modulate BAT activity, the μ -opiate receptor agonist (D-Ala², N-Me-Phe⁴, Gly-ol⁵)-enkephalin (DAMGO) was microinjected into the raphe magnus, a manipulation that selectively activates OFF cells. DAMGO microinjection blocked noxious stimulation-evoked suppression of PGE₂-induced BAT temperature increases. Thus, both p5HT and non-p5HT OFF cells in the medullary raphe facilitate BAT activation in response to cold challenge or pyrogen.

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Prefrontal Set Activity Predicts Rule-Specific Neural Processing during Subsequent Cognitive Performance

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Prefrontal neurons have been shown to represent task rules. Here we show the mechanisms by which the rule-selective activity in the prefrontal cortex influences subsequent cognitive performance based on that rule. Using functional magnetic resonance imaging, we found that the frontopolar cortex interacted with posterior areas differently depending on whether subjects were going to perform a phonological or semantic task. Moreover, we found that the sustained “set” activity in this region predicted the activity that could be recorded in the posterior areas during the performance, as well as the speed of that performance. We argue that the prefrontal set activity does not reflect simple maintenance of the task rules but the process of implementing the rule for subsequent cognitive performance and that this is done through rule-selective interactions with areas involved in execution of the tasks.

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Barrel Cortex Microcircuits: Thalamocortical Feedforward Inhibition in Spiny Stellate Cells Is Mediated by a Small Number of Fast-Spiking Interneurons

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Inhibitory and excitatory neurons located in rodent barrel cortex are known to form functional circuits mediating vibrissal sensation. Excitatory neurons located in a single barrel greatly outnumber interneurons, and form extensive reciprocal excitatory synaptic contacts. Inhibitory and excitatory networks must interact to shape information ascending to cortex. The details of these interactions, however, have not been completely explored. Using paired intracellular recordings, we studied the properties of synaptic connections between spiny neurons (i.e., spiny stellate and pyramidal cells) and interneurons, as well as integration of thalamocortical (TC) input, in layer IV barrels of rat thalamocortical slices. Results show the following: (1) the strength of unitary excitatory connections of spiny neurons is similar among different targets; (2) although inhibition from regular-spiking nonpyramidal interneurons to spiny neurons is comparable in strength to excitatory connections, inhibition mediated by fast-spiking (FS) interneurons is 10 times more powerful; (3) TC EPSPs elicit reliable and precisely timed action potentials in FS neurons; and (4) a small number of FS neurons mediate thalamocortical feedforward inhibition in each spiny neuron and can powerfully shunt TC-mediated excitation. The ready activation of FS cells by TC inputs, coupled with powerful feedforward inhibition from these neurons, would profoundly influence sensory processing and constrain runaway excitation *in vivo*.

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Involvement of the AMPA Receptor GluR-C Subunit in Alcohol-Seeking Behavior and Relapse

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Craving and relapse are core symptoms of drug addiction and alcoholism. It is suggested that, after chronic drug consumption, long-lasting neuroplastic changes within the glutamatergic system are important determinants of addictive behavior. Here, we show that the AMPA type glutamate receptor plays a crucial role in alcohol craving and relapse. We observed, in two animal models of alcohol craving and relapse, that the AMPA antagonist GYKI 52466 [1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine] dose-dependently reduced cue-induced reinstatement of alcohol-seeking behavior and the alcohol deprivation effect. The involvement of the AMPA receptor in these phenomena was further studied using mice deficient for the GluR-C AMPA subunit [*GluR-C* knock-out (KO)]. *GluR-C* KOs displayed a blunted, cue-induced reinstatement response and alcohol deprivation effect, when compared with wild-type controls; however, no differences between genotypes could be observed regarding ethanol self-administration under operant or home cage drinking conditions. These results imply a role for GluR-C in alcohol relapse, although this phenotype could also be attributable to a reduction in the total number of AMPA receptors in specific brain areas. In conclusion, AMPA receptors seem to be involved in the neuroplastic changes underlying alcohol seeking behavior and relapse. Thus, AMPA receptors represent a novel therapeutic target in preventing relapse.

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Temporal Dynamics and Latency Patterns of Receptor Neuron Input to the Olfactory Bulb

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Odorants are first represented in the brain by distributed patterns of activity in the olfactory bulb (OB). Although neurons downstream of sensory inputs respond to odorants with temporally structured activity, sensory inputs to glomeruli are typically described as static maps. Here, we imaged the temporal dynamics of receptor neuron input to the OB with a calcium-sensitive dye in the olfactory receptor nerve terminals in anesthetized mice. We found that diverse, glomerulus- and odorant-dependent temporal dynamics are present even at this initial input stage. Instantaneous spatial patterns of receptor input to glomeruli changed both within and between respiration cycles. Glomerular odorant responses differed in amplitude, latency, rise time, and degree of modulation by sniffing in an odorant-specific manner. Pattern dynamics within the first respiration cycle recurred in a similar manner during consecutive cycles. When sniff rate was increased artificially, pattern dynamics were preserved in the first sniff but were attenuated during subsequent sniffs. Temporal response properties were consistent across individuals on a coarse regional scale and on a fine scale of individual glomeruli. Latency and magnitude of glomerular inputs were only weakly correlated and might therefore convey independent odorant information. These data demonstrate that glomerular maps of primary sensory input to the OB are temporally dynamic. These dynamics may contribute to the representation of odorant information and affect information processing in the central olfactory system of rodents.

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Rapid Brain Discrimination of Sounds of Objects

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Electrical neuroimaging in humans identified the speed and spatiotemporal brain mechanism whereby sounds of living and man-made objects are discriminated. Subjects performed an “oddball” target detection task, selectively responding to sounds of either living or man-made objects on alternating blocks, which were controlled for in their spectrogram and harmonics-to-noise ratios between categories. Analyses were conducted on 64-channel auditory evoked potentials (AEPs) from nontarget trials. Comparing responses to sounds of living versus man-made objects, these analyses tested for modulations in local AEP waveforms, global response strength, and the topography of the electric field at the scalp. In addition, the local autoregressive average distributed linear inverse solution was applied to periods of observed modulations. Just 70 ms after stimulus onset, a common network of brain regions within the auditory “what” processing stream responded more strongly to sounds of man-made versus living objects, with differential activity within the right temporal and left inferior frontal cortices. Over the 155–257 ms period, the duration of activity of a brain network, including bilateral temporal and premotor cortices, differed between categories of sounds. Responses to sounds of living objects peaked ~12 ms later and the activity of the brain network active over this period was prolonged relative to that in response to sounds of man-made objects. The earliest task-related effects were observed at ~100 ms poststimulus onset, placing an upper limit on the speed of cortical auditory object discrimination. These results provide critical temporal constraints on human auditory object recognition and semantic discrimination processes.

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A Recurrent Network Mechanism of Time Integration in Perceptual Decisions

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Recent physiological studies using behaving monkeys revealed that, in a two-alternative forced-choice visual motion discrimination task, reaction time was correlated with ramping of spike activity of lateral intraparietal cortical neurons. The ramping activity appears to reflect temporal accumulation, on a timescale of hundreds of milliseconds, of sensory evidence before a decision is reached. To elucidate the cellular and circuit basis of such integration times, we developed and investigated a simplified two-variable version of a biophysically realistic cortical network model of decision making. In this model, slow time integration can be achieved robustly if excitatory reverberation is primarily mediated by NMDA receptors; our model with only fast AMPA receptors at recurrent synapses produces decision times that are not comparable with experimental observations. Moreover, we found two distinct modes of network behavior, in which decision computation by winner-take-all competition is instantiated with or without attractor states for working memory. Decision process is closely linked to the local dynamics, in the “decision space” of the system, in the vicinity of an unstable saddle steady state that separates the basins of attraction for the two alternative choices. This picture provides a rigorous and quantitative explanation for the dependence of performance and response time on the degree of task difficulty, and the reason for which reaction times are longer in error trials than in correct trials as observed in the monkey experiment. Our reduced two-variable neural model offers a simple yet biophysically plausible framework for studying perceptual decision making in general.

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Histaminergic Neurons Protect the Developing Hippocampus from Kainic Acid-Induced Neuronal Damage in an Organotypic Coculture System

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The central histaminergic neuron system inhibits epileptic seizures, which is suggested to occur mainly through histamine 1 (H₁) and histamine 3 (H₃) receptors. However, the importance of histaminergic neurons in seizure-induced cell damage is poorly known. In this study, we used an organotypic coculture system and confocal microscopy to examine whether histaminergic neurons, which were verified by immunohistochemistry, have any protective effect on kainic acid (KA)-induced neuronal damage in the developing hippocampus. Fluoro-Jade B, a specific marker for degenerating neurons, indicated that, after the 12 h KA (5 μM) treatment, neuronal damage was significantly attenuated in the hippocampus cultured together with the posterior hypothalamic slice containing histaminergic neurons [HI plus HY (POST)] when compared with the hippocampus cultured alone (HI) or with the anterior hypothalamus devoid of histaminergic neurons. Moreover, α-fluoromethylhistidine, an inhibitor of histamine synthesis, eliminated the neuroprotective effect in KA-treated HI plus HY (POST), and extracellularly applied histamine (1 nM to 100 μM) significantly attenuated neuronal damage only at 1 nM concentration in HI. After the 6 h KA treatment, spontaneous electrical activity registered in the CA1 subregion contained significantly less burst activity in HI plus HY (POST) than in HI. Finally, in KA-treated slices, the H₃ receptor antagonist thioperamide enhanced the neuroprotective effect of histaminergic neurons, whereas the H₁ receptor antagonists triprolidine and mepyramine dose-dependently decreased the neuroprotection in HI plus HY (POST). Our results suggest that histaminergic neurons protect the developing hippocampus from KA-induced neuronal damage, with regulation of neuronal survival being at least partly mediated through H₁ and H₃ receptors.

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CCL2/Monocyte Chemoattractant Protein-1 Mediates Enhanced Transmigration of Human Immunodeficiency Virus (HIV)-Infected Leukocytes across the Blood–Brain Barrier: A Potential Mechanism of HIV–CNS Invasion and NeuroAIDS

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Encephalitis and dementia associated with acquired immunodeficiency syndrome (AIDS) are characterized by leukocyte infiltration into the CNS, microglia activation, aberrant chemokine expression, blood–brain barrier (BBB) disruption, and eventual loss of neurons. Little is known about whether human immunodeficiency virus 1 (HIV-1) infection of leukocytes affects their ability to transmigrate in response to chemokines and to alter BBB integrity. We now demonstrate that HIV infection of human leukocytes results in their increased transmigration across our tissue culture model of the human BBB in response to the chemokine CCL2, as well as in disruption of the BBB, as evidenced by enhanced permeability, reduction of tight junction proteins, and expression of matrix metalloproteinases (MMP)-2 and MMP-9. HIV-infected cells added to our model did not transmigrate in the absence of CCL2, nor did this condition alter BBB integrity. The chemokines CXCL10/interferon-gamma-inducible protein of 10 kDa, CCL3/macrophage inflammatory protein-1α, or CCL5/RANTES (regulated on activation normal T-cell expressed and secreted) did not enhance HIV-infected leukocyte transmigration or BBB permeability. The increased capacity of HIV-infected leukocytes to transmigrate in response to CCL2 correlated with their increased expression of CCR2, the chemokine receptor for CCL2. These data suggest that CCL2, but not other chemokines, plays a key role in infiltration of HIV-infected leukocytes into the CNS and the subsequent pathology characteristic of NeuroAIDS.

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Loss of *p53* Induces Changes in the Behavior of Subventricular Zone Cells: Implication for the Genesis of Glial Tumors

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The role of multipotential progenitors and neural stem cells in the adult subventricular zone (SVZ) as cell-of-origin of glioblastoma has been suggested by studies on human tumors and transgenic mice. However, it is still unknown whether glial tumors are generated by all of the heterogeneous SVZ cell types or only by specific subpopulations of cells. It has been proposed that transformation could result from lack of apoptosis and increased self-renewal, but the definition of the properties leading to neoplastic transformation of SVZ cells are still elusive. This study addresses these questions in mice carrying the deletion of *p53*, a tumor-suppressor gene expressed in the SVZ. We show here that, although loss of *p53* by itself is not sufficient for tumor formation, it provides a proliferative advantage to the slow- and fast-proliferating subventricular zone (SVZ) populations associated with their rapid

differentiation. This results in areas of increased cell density that are distributed along the walls of the lateral ventricles and often associated with increased *p53*-independent apoptosis. Transformation occurs when loss of *p53* is associated with a mutagenic stimulus and is characterized by dramatic changes in the properties of the quiescent adult SVZ cells, including enhanced self-renewal, recruitment to the fast-proliferating compartment, and impaired differentiation.

Together, these findings provide a cellular mechanism for how the slow-proliferating SVZ cells can give rise to glial tumors in the adult brain.
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Spontaneous Pain, Both Neuropathic and Inflammatory, Is Related to Frequency of Spontaneous Firing in Intact C-Fiber Nociceptors

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Spontaneous pain, a poorly understood aspect of human neuropathic pain, is indicated in animals by spontaneous foot lifting (SFL). To determine whether SFL is caused by spontaneous firing in nociceptive neurons, we studied the following groups of rats: (1) untreated; (2) spinal nerve axotomy (SNA), L5 SNA 1 week earlier; (3) mSNA (modified SNA), SNA plus loose ligation of the adjacent L4 spinal nerve with inflammation-inducing chronic gut; and (4) CFA (complete Freund's adjuvant), intradermal complete Freund's adjuvant-induced hindlimb inflammation 1 and 4 d earlier. In all groups, recordings of SFL and of spontaneous activity (SA) in ipsilateral dorsal root ganglion (DRG) neurons (intracellularly) were made. Evoked pain behaviors were measured in nerve injury (SNA/mSNA) groups. Percentages of nociceptive-type C-fiber neurons (C-nociceptors) with SA increased in intact L4 but not axotomized L5 DRGs in SNA and mSNA (to 35%), and in L4/L5 DRGs 1–4 d after CFA (to 38–25%). SFL occurred in mSNA but not SNA rats. It was not correlated with mechanical allodynia, extent of L4 fiber damage [ATF3 (activation transcription factor 3) immunostaining], or percentage of L4 C-nociceptors with SA. However, L4 C-nociceptors with SA fired faster after mSNA (1.8 Hz) than SNA (0.02 Hz); estimated L4 total firing rates were ~5.0 and ~0.6 kHz, respectively. Similarly, after CFA, faster L4 C-nociceptor SA after 1 d was associated with SFL, whereas slower SA after 4 d was not. Thus, inflammation causes L4 C-nociceptor SA and SFL. Overall, SFL was related to SA rate in intact C-nociceptors. Both L5 degeneration and chronic gut cause inflammation. Therefore, both SA and SFL/spontaneous pain after nerve injury (mSNA) may result from cumulative neuroinflammation.

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