This Week in The Journal

● Cellular/Molecular

Morphine Exposure Affects GIRK Channel Distribution

Rounak Nassirpour, Laia Bahima, Arnaud L. Lalive, Christian Lüscher, Rafael Luján, et al.

(see pages 13419–13430)

Basal activity of G-protein-gated inwardly rectifying potassium (GIRK) channels produces a small outward current that helps set the neuronal resting membrane potential. Activation of pertussis-sensitive G-proteins ($G_{i/o}$) by G-protein-coupled receptors—including dopamine, serotonin, opioid, and $GABA_B$ receptors—further activates GIRK channels, producing hyperpolarizing potentials and inhibiting spiking. Nassirpour et al. report that morphine exposure increased expression of GIRK channels in cultured rat hippocampal neurons, thereby increasing tonic and serotonin-induced GIRK currents. Moreover, morphine decreased the percentage of GIRK channels in dendritic shafts, increased the percentage in spines, and increased colocalization of GIRK channels with postsynaptic density protein PSD95. These effects were mimicked by constitutively active CaMKII, blocked by calcium chelators and CaMKII inhibitors, and unaffected by pertussis toxin, suggesting they were mediated by G-protein Gq, which activates the CaMKII pathway. Indeed, activation of metabolic glutamate receptors, which also activate Gq, increased colocalization of GIRK channels with PSD95.

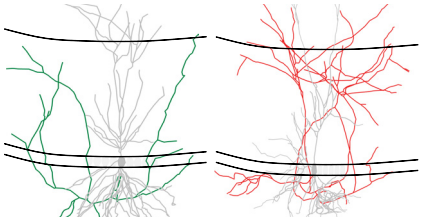
▲ Development/Plasticity/Repair

Nogo-A Regulates Hippocampal Neuron Growth

Marta Zagrebelsky, Rüdiger Schweigreiter, Christine E. Bandtlow, Martin E. Schwab, and Martin Korte

(see pages 13220–13234)

Proper functioning of adaptive neuronal networks requires a balance between synaptic plasticity, to allow formation of new connections, and stability, to retain useful



Axons of CA3 pyramidal neurons grow longer and develop more branches after Nogo-A function is blocked (right) than in controls (left). Complexity is especially increased in distal stratum radiatum (demarcated by top two black lines). See the article by Zagrebelsky et al. for details.

connections. Nogo-A is thought to help regulate this balance, in part because its upregulation helps to define the end of critical periods during development. Myelin-associated Nogo-A contributes to the inhibitory environment that limits regeneration of injured axons, but its role in the healthy adult nervous system has not been extensively explored. Nogo-A is expressed in neurons in adult hippocampus, where—as Zagrebelsky et al. show—it inhibits both axonal and dendritic growth, particularly of CA3 pyramidal neurons and their targets. In mature mouse hippocampal slice cultures, disruption of Nogo-A function increased the length and complexity of CA3 axonal recurrent collaterals, and increased dendritic branching specifically in apical regions innervated by these collaterals. Nogo-A disruption similarly increased the complexity of CA1 basal dendrites, which receive inputs from some CA3 Schaffer collaterals.

■ Behavioral/Systems/Cognitive

Motor Learning Occurs Without Cerebellar LTD

Eric Burguière, Arnaud Arabo, Frederic Jarlier, Chris I. De Zeeuw, and Laure Rondi-Reig

(see pages 13265–13271)

Lesion studies have long implicated the cerebellum in the acquisition and performance of fine motor skills, but its exact role remains elusive. The discovery that long-term depression (LTD) occurs at synapses between parallel fibers and Purkinje cells led to the hypothesis that this LTD underlies motor learning. But subsequent studies in which cerebellar LTD was eliminated by inhibiting the underlying biochemical pathways have produced conflicting results: some suggested that LTD is required for proper timing in eye blink conditioning, whereas others suggested no role for LTD in either this type of classical conditioning or other adaptive motor learning. Burguière et al. investigated the role of LTD in aversive operant conditioning, using a water-maze task in which cues signaled mice to turn right or left to avoid an aversive stimulus. Knock-out of a protein crucial for LTD did not stop the animals learning the cue–direction association, but it reduced the efficiency of the animals' response, suggesting cerebellar LTD is involved in response optimization.

♦ Neurobiology of Disease

Human Tau Worsens Effect of Presenilin Knock-out

Erica Peethumnongsin, Li Yang, Verena Kallhoff-Muñoz, Lingyun Hu, Akihiko Takashima, et al.

(see pages 13409–13418)

Phosphorylation of microtubule-associated protein tau decreases its ability to bind to and stabilize microtubules, promote neurite formation, and regulate kinesin-dependent axon transport. In Alzheimer's disease (AD), tau becomes abnormally hyperphosphorylated and aggregates to form neurofibrillary tangles. Although tau mutations have been linked to other human dementias, none have been linked to AD, suggesting mutations in other genes cause hyperphosphorylation and aggregation of tau. A likely candidate for this role is presenilin—the secretase that cleaves amyloid precursor protein—which is mutated in familial forms of AD. Tau becomes hyperphosphorylated in presenilin-null (PS cDKO) mice, and Peethumnongsin et al. report that expressing human tau in these mice magnified the pathology: abnormal tau phosphorylation occurred earlier and was accompanied by a reduction in axonal transport rate, lower levels of brain-derived neurotrophic factor (BDNF) at synapses, reduced activation of BDNF targets, and increased neurodegeneration. Expressing tau also worsened contextual memory and long-term potentiation in PS cDKO mice.