This Week in The Journal

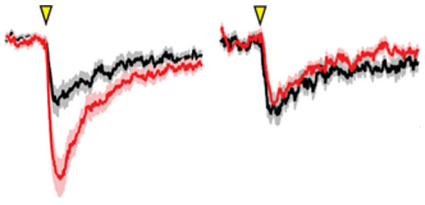
Cellular/Molecular

Phosphorylation of GluN2B by PKA Increases Ca^{2+} Influx

Jessica A. Murphy, Ivar S. Stein, C. Geoffrey Lau, Rui T. Peixoto, Teresa K. Aman, et al.

(see pages 869 – 879)

Calcium influx through NMDA receptors (NMDARs) is essential for synaptic plasticity and is regulated by protein kinase A, which is anchored near NMDARs at synapses. Murphy et al. have identified Ser1166 in the carboxy tail of NMDAR subunit GluN2B as an important site of PKA-mediated phosphorylation. Mutation that prevented phosphorylation of this site greatly reduced PKA-dependent enhancement of NMDAR Ca^{2+} permeability, and the open probability of NMDARs containing this mutation was significantly lower than that of those containing a phosphomimetic mutation at residue 1166. Activation of ß-adrenergic receptors increased phosphorylation of GluN2B at ser1166 and increased Ca^{2+} transients induced by glutamate uncaging at individual spines; but ß-adrenergic agonist did not affect Ca^{2+} transients in neurons expressing nonphosphorylatable GluN2Bs. Exposure to forced swim, which induces norepinephrine release, likewise increased phosphorylation of GluN2B at ser1166, and this effect was blocked by inhibiting PKA. Thus, some natural stressors may potentiate NMDAR currents (and NMDAR-dependent learning) by inducing PKA-dependent phosphorylation of GluN2B at ser1166.



ß-adrenergic agonist (red traces) increased the amplitude of unitary EPSCs evoked by glutamate uncaging (at time indicated by arrowheads) in neurons expressing wild-type GluN2B (left), but not in neurons expressing GluN2B in which serine 1166 was replaced with alanine (right). See the article by Murphy et al. for details.

Development/Plasticity/Repair

PCB 95 Increases Spine Density by Upregulating miR132

Adam Lesiak, Mingyan Zhu, Hao Chen, Suzanne M. Appleyard, Soren Impey, et al.

(see pages 717–725)

Polychlorinated biphenyls (PCBs) are long-lived environmental contaminants that, although banned in the 1970s, remain present in soil and food. Whether environmental exposure to PCBs is harmful to humans is controversial, but studies have suggested that prenatal and early postnatal exposure delays development of motor and mental function. PCB 95, a nondioxin-like (NDL) PCB, has been shown to stabilize ryanodine receptors in the open state, thus increasing Ca^{2+} release from internal stores and potentiating Ca^{2+} oscillations in neurons. Downstream activation of the transcription factor CREB leads to increased dendritic growth. Lesiak et al. extend these findings, showing in hippocampal neurons that PCB 95-induced activation of CREB leads to upregulation of microRNA miR132, which in turn suppresses translation of the GTPase-activating protein p250GAP and increases the number of dendritic spines and synapses. Because miR132 interacts with several proteins involved in cognitive impairment and autism spectrum disorders, the authors speculate that PCB 95 exposure may lead to similar neurodevelopmental disorders.

Behavioral/Cognitive

Transcranial Stimulation Facilitates Motor Learning

Sheena Waters-Metenier, Masud Husain, Tobias Wiestler, and Jörn Diedrichsen

(see pages 1037–1050)

Simple movements, such as pressing a key, require activation of groups of muscles, called synergies. Frequently used muscle synergies are thought to be controlled by modules in primary motor cortex (M1) that are activated in specific sequences to drive complex tasks, such as typing. Learning of motor sequences can be facilitated by increasing M1 excitability via transcranial direct current stimulation (tDCS). Waters-Metenier et al. report that tDCS of M1 also enhances learning of synergies. Practice improved people's performance of synergies involving multiple fingers whether or not tDCS was given during training, but participants who received tDCS improved more than controls, and their performance remained superior 4 weeks later. Performance not only improved for practiced synergies, but also generalized to untrained synergies and the untrained hand. Control of individual fingers also improved for trained and untrained hands in the tDCS group. Such generalization indicates that synergy training combined with tDCS may be useful for rehabilitation in people whose fine motor control is impaired by stroke.

Neurobiology of Disease

Loss of Retinal Dopamine May Underlie Diabetic Retinopathy

Moe H. Aung, Han na Park, Moon K. Han, Tracy S. Obertone, Jane Abey, et al.

(see pages 726 –736)

Diabetes has many neurological complications, including diabetic retinopathy (DR), a leading cause of blindness. DR is generally attributed to vascular damage from hyperglycemia, but abnormal electrophysiological responses and deficits in contrast sensitivity can emerge before vascular damage is detected in the retina. Because dopamine deficiency causes similar visual abnormalities and retinal dopamine levels are reduced in rodent models of diabetes, Aung et al. hypothesized that reduced dopamine levels cause the early visual disturbances in DR. Indeed, retinal dopamine levels were reduced by 15% to 25% within 4 to 5 weeks of diabetes induction in rodents, shortly after reduced contrast sensitivity and spatial-frequency thresholds were first detected. Treatment with L-DOPA slowed the onset and progression of perceptual impairments and also improved electrophysiological responses, which were diminished in the inner retina of diabetic mice. Dopamine receptor agonists also improved visual function: D1 agonist selectively improved spatial frequency threshold, whereas D4 agonist improved contrast sensitivity. Thus, targeting dopamine signaling may help preserve vision in diabetics.