This Week in The Journal

Cellular/Molecular

Retinoic Acid Drives Homeostatic Decreases in IPSC Amplitude

Federica Sarti, Zhenjie Zhang, Jessica Schroeder, and Lu Chen

(see pages 11440–11450)

Prolonged suppression of neuronal activity leads to homeostatic increases in EPSC amplitude and decreases in IPSC amplitude. The former is mediated in part by synthesis of retinoic acid (RA), which binds to mRNA-bound RA receptors (RARα), derepresses protein translation, and ultimately results in increased synthesis and insertion of AMPA receptors (AMPARs). The fragile X mental retardation protein (FMRP) is required at some point downstream of RA production and upstream of AMPAR insertion. Sarti et al. have discovered that reduction of IPSC amplitude also requires retinoic acid, RARα, and protein translation, but the end result in this case is reduced surface expression of $GABA_A$ receptors via increased endocytosis. Like increases in EPSC amplitudes, decreases in IPSC amplitude were absent in FMRP-deficient mice. Nonetheless, decreases in IPSC amplitude occurred independently of increases in EPSC amplitude: the former was prevented by blocking AMPAR insertion, while the latter was not. How protein synthesis drives an in increase in $GABA_A$ receptor endocytosis is yet to be determined.

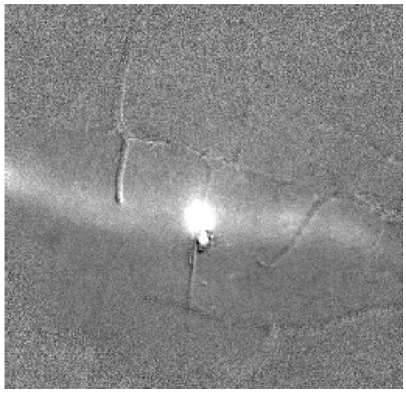
Systems/Circuits

Parallel Fibers Excite Beams of Purkinje Cells

Samuel W. Cramer, Wangcai Gao, Gang Chen, and Timothy J. Ebner

(see pages 11412–11424)

Cerebellar granule cell axons form synapses with Purkinje cell bodies before ascending into the molecular layer, where they bifurcate to form parallel fibers that extend several millimeters, contacting hundreds of Purkinje cells. Based on this anatomy, parallel fibers were originally proposed to excite "beams" of Purkinje cells. But because stimulating inputs to granule cells was found to activate patches, rather than beams of Purkinje cells, an alternative "radial" hypothesis



NMDA-mediated activation of granule cells in cerebellar Crus II leads to activation of a beam of Purkinje cells, as revealed by calcium imaging. See the article by Cramer et al. for more information.

proposed that Purkinje cells are activated primarily by synapses formed by the ascending limb of granule cell axons. Cramer et al. investigated these hypotheses using calcium imaging to visualize mouse Purkinje cell activation *in vivo*. Both electrical and pharmacological stimulation of granule cells produced beam-like activation along the length of the folium. More importantly, forelimb stimulation produced a beam-like activation pattern in Purkinje cells in Crus I, and the extent of this activation was reduced by parallel-fiber lesions. Interestingly, however, whisker stimulation produced patch-like, rather than beam-like activation in Crus II.

Behavioral/Cognitive

Novel Tastes Induce Unequal Arc Expression in Two Hemispheres

Sharon Inberg, Alina Elkobi, Efrat Edri, and Kobi Rosenblum

(see pages 11734–11743)

Taste learning and memory in rodents is associated with several molecular changes in the gustatory cortex (GC), including phosphorylation of NMDA receptor subunits, activation of the mTOR pathway, and activation of ERKI/II kinases. Although activation of the cAMP response element binding protein (CREB) is required for synaptic plasticity in many neuronal types, changes in CREB activity have not been detected in the gustatory cortex during taste learning. Inberg et al. were surprised to find that the activity-regulated cytoskeleton-associated protein Arc, a downstream target of ERKI/II that, like CREB, is associated with synaptic plasticity in other neuron types, was unchanged in GC after exposure to a novel taste. With further examination, however, they discovered that the relative expression of Arc in the two GC hemispheres differed only after rats were exposed to novel tastes. The lateralization of Arc expression decreased with repeated exposure to the novel taste, and ultimately was not significantly different than that induced by water.

Neurobiology of Disease

Inflammatory Mediators Exert Sex-Specific Neuroprotection

Pedro M. Pimentel-Coelho, Jean-Philippe Michaud, and Serge Rivest

(see pages 11556–11572)

Reduction of brain oxygen levels and blood flow during fetal and early neonatal development leads to ATP depletion, Na^+ influx, depolarization, excitotoxicity, and oxidative damage. After blood flow and oxygen are restored, damage continues, resulting in neonatal hypoxic-ischemic (HI) encephalopathy, a major cause of neurodevelopmental disabilities. HI induces inflammation, but which inflammatory agents are upregulated and whether they are harmful or beneficial are poorly understood. Pimentel-Coelho et al. investigated the roles of several inflammation-related signaling pathways in a mouse model of perinatal HI encephalopathy. Hippocampal expression of toll-like receptors (TLRs) was increased after HI, whereas expression of the chemokine fractalkine, which inhibits microglia activation, was reduced. Interestingly, knocking out the TLR-activated protein TRIF worsened HI-induced hippocampal atrophy only in male mice, but it led to HI-induced impairment of water maze performance only in females. In contrast, knocking out the fractalkine receptor CX3CR1 worsened HI-induced hippocampal atrophy and impaired maze performance in female mice. Thus, TRIF and CX3CR1 have sex-specific protective effects in perinatal HI in mice.