This Week in The Journal

Cellular/Molecular

SLEEPLESS Accelerates Activation of Shaker Channels

Terry Dean, Rong Xu, William Joiner, Amita Sehgal, and Toshinori Hoshi

(see pages 11387–11395)

SLEEPLESS (SSS) is a *Drosophila* protein that is attached to the extracellular surface of cells via a lipid anchor. Loss of SSS function decreases sleep and also reduces the expression and conductance of the Shaker-type voltage-gated potassium channel, another protein whose mutation decreases sleep. When coexpressed in HEK cells, SSS associates with Shaker in lipid rafts and decreases the time to peak of Shaker current. Dean et al. found that SSS increased the activation rate of Shaker channels and reduced the rate of slow, C-type inactivation, whereas fast, N-type inactivation and deactivation were unaffected. SSS-induced acceleration of Shaker channel activation was prevented when lipid rafts were disrupted by a cholesterol chelator. Using a kinetic model, the authors estimated that slower activation in the absence of SSS accounts for ~40% of the decreased magnitude in Shaker current in SSS-mutant flies. The remainder, they hypothesize, results from reduced expression of the channels.

Development/Plasticity/Repair

NOS and AMPARs Are Required for Adult Somatosensory Plasticity

James Dachtler, Neil R. Hardingham, Stanislaw Glazewski, Nicholas F. Wright, Emma J. Blain, et al.

(see pages 11220–11230)

Formation and strengthening of excitatory synapses during development and experience-dependent plasticity are thought to be mediated in part by insertion of AMPA-type glutamate receptors (AMPARs) following activation of NMDA receptors. NMDA receptor activation also activates neuronal nitric oxide synthase (nNOS), leading to production of NO, which also contributes to synaptic plasticity. Most studies examining the roles of AMPARs and NO in synaptic plasticity have used neuronal cultures or immature animals, however, and some studies using adults have concluded that different mechanisms are involved. Dachtler et al. propose that both NO and AMPARs contribute to experience-dependent plasticity in mouse barrel cortex. Knocking out either GluR1 or nNOS reduced, but did not eliminate, plasticity induced by removing all but one whisker. Knocking out both proteins, or knocking out GluR1 and inhibiting nNOS, eliminated such changes, however. Interestingly, barrels still developed normally, indicating that other mechanisms of plasticity can compensate for the loss of these proteins during development.

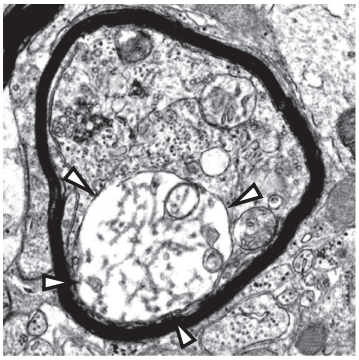
Behavioral/Systems/Cognitive

NMDARs in PFC and Striatum Contribute to Conditioning

Jones G. Parker, Lisa R. Beutler, and Richard D. Palmiter

(see pages 11362–11369)

Dopamine neurons in the ventral tegmental area (VTA) fire when a reward is received. After appetitive Pavlovian conditioning, in which a conditioned stimulus (CS) is repeatedly paired with food reward, the CS acquires predictive value and VTA dopamine neurons begin to fire when the CS appears. At the same time, the animal develops conditioned approach behavior, i.e., it approaches the site of reward delivery when the CS is presented. As in other forms of learning, NMDA receptors (NMDARs) contribute to this form of conditioning. Parker et al. sought to pinpoint where in the pathway NMDARs are required. They previously reported that inactivating NMDARs in VTA dopamine neurons did not reduce conditioned approach behaviors. They now extend this work, showing that NMDARs are required both in prefrontal neurons that project to the VTA and in striatal medium spiny neurons that express D1 dopamine receptors, a target of VTA dopamine neurons.



A myelinated anterior horn axon from an iPLPA2β-null mouse showing characteristic tubulovesicular structures and abnormal mitochondria with tubular and branching cristae (white arrowheads). See the article by Beck et al. for details.

Neurobiology of Disease

Loss of iPLPA$_2\beta$ Causes Mitochondrial Degradation

Goichi Beck, Yuki Sugiura, Koei Shinzawa, Shinsuke Kato, Mitsutoshi Setou, et al.

(see pages 11411–11420)

Infantile neuroaxonal dystrophy (INAD) is a recessive disease that affects young children. It is characterized by sensory, motor, and cognitive impairments, and it leads to death within 10 years. The main pathological hallmark of INAD is swellings, called spheroids, that form in axons throughout the CNS and PNS and are filled with accumulated membranes. The disease is caused by various mutations in *PLA2G6*, which encodes calcium-independent group VIA phospholipase A_2 (iPLPA$_2\beta$), a protein that hydrolyzes phospholipids and is involved in membrane remodeling and cell signaling. Using *PLA2G6*-null mice as a model for INAD, Beck et al. provide evidence that spheroids contain aggregations of degraded mitochondria. Membranous granules resembling mitochondria with disintegrated inner membranes were first detected at 15 weeks in mutant mice. These were immunolabeled with antibodies against outer mitochondrial membrane proteins and, less commonly, with markers of inner membrane proteins. At later stages, such granules filled spheroids, which became widespread.