This Week in The Journal

Cellular/Molecular

Calcium Influx Through Retinal TRPV4 Channels Triggers Apoptosis

Daniel A. Ryskamp, Paul Witkovsky, Peter Barabas, Wei Huang, Christopher Koehler, et al.

(see pages 7089 –7101)

Glaucoma is characterized by gradual axonal degeneration and apoptosis of retinal ganglion cells (RGCs). Elevated intraocular pressure (IOP) contributes to RGC degeneration, but how it might cause apoptosis is unclear. Ryskamp et al. found that mouse RGCs express the mechanosensitive transient receptor potential channel TRPV4 and, in dissociated cultures, TRPV4 agonists caused calcium influx along with transient increases in spontaneous spiking. Although calcium elevations returned to baseline during exposure to agonists, prolonged exposure caused RGC death. Reducing osmolarity of the culture medium caused RGC swelling accompanied by calcium increases that, like TRPV4 agonist-mediated increases, subsided after prolonged exposure. After habituation to hypotonic solution, the effect of TRPV4 agonist was occluded. Moreover, TRPV4 blockers reduced calcium influx without affecting swelling in response to hypotonic solution. These results suggest that distortion of cell membrane—which occurs with cell swelling and may result if increased IOP causes retinal stretching—induces calcium influx through TRPV4 channels, which can trigger apoptosis.

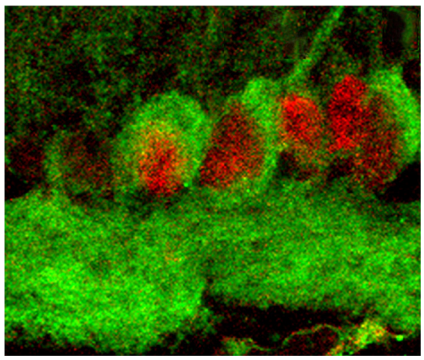
Development/Plasticity/Repair

NMDA Receptors Activate Transcription via NO-Dependent Pathways

Eduardo F. Gallo and Costantino Iadecola

(see pages 6947– 6955)

Nitric oxide (NO) is a diffusible second messenger involved in learning and memory. It is synthesized by neuronal nitric oxide synthase (nNOS), which is anchored near NMDA receptors (NMDARs) and is activated upon calcium influx. Most effects of NO are mediated by activation of soluble guanylyl cyclase, producing cGMP that in turn activates protein kinase G (PKG) and cyclic nucleotide-gated channels. How these early steps in NO signaling are linked to long-term plasticity are poorly understood. To address this question, Gallo and Iadecola used bicuculline to suppress GABAergic inhibition in mouse cortical cultures, thus inducing synchronous bursting that required activation of NMDARs. This treatment resulted in NMDAR-dependent phosphorylation of the kinase ERK1/2 followed by ERK1/2-dependent increases in the transcription factors c-Fos and Egr-1, brain-derived neurotrophic factor (BDNF), and Arc. These effects were prevented by inhibitors of nNOS, guanylyl cyclase, or PKG, suggesting they are downstream effectors of NO signaling.



TRPV4 (green) is expressed throughout RGCs. Somata are labeled with an RGC-specific marker (red). See the article by Ryskamp et al. for details.

Behavioral/Systems/Cognitive

Adenosine Mediates Cognitive Effects of Sleep Deprivation

Cédrick Florian, Christopher G. Vecsey, Michael M. Halassa, Philip G. Haydon, and Ted Abel

(see pages 6956 – 6962)

Sleep deprivation impairs many brain functions, including consolidation of hippocampal-dependent memories. When an animal is awake, extracellular adenosine levels gradually increase, which has been proposed to promote sleepiness. Most extracellular adenosine appears to be derived by metabolism of ATP released from astrocytes. Preventing astrocytic ATP release via conditional expression of dominant-negative (dn) SNARE protein reduces extracellular adenosine and the amount of sleep mice exhibit after sleep deprivation, consistent with a role for adenosine in sleep homeostasis. Florian et al. hypothesized that extracellular adenosine also mediates the effects of sleep deprivation on cognitive function. Indeed, late-phase long-term potentiation (L-LTP) was disrupted in hippocampal slices from sleep-deprived wild-type mice, but not from sleep-deprived dnSNARE mice, and adenosine A_1 receptor antagonist reduced the effect of sleep deprivation on L-LTP in wild-type mice. In addition, sleep-deprived wild-type mice appeared to have impaired spatial-object recognition, and this effect was diminished in mice treated with A_1 receptor antagonist or expressing dnSNARE.

Neurobiology of Disease

Impaired Inhibitory Function Causes Abnormal Sleep Behaviors

Patricia L. Brooks and John H. Peever

(see pages 7111–7121)

During REM sleep, motor output is normally suppressed. The mechanisms mediating this suppression are incompletely understood, but they likely include GABAergic and/or glycinergic inhibition of spinal motor neurons. Motor-suppressing circuitry is dysfunctional in people with REM sleep behavior disorder (RBD), which is characterized by enactment of dreams during REM sleep. Brooks and Peever propose that RBD results from impaired GABAergic or glycinergic functioning. Transgenic mice in which such function is impaired exhibited many features of RBD, including coordinated movements resembling running and chewing during REM sleep, increased frequency and amplitude of muscle twitches during REM and non-REM sleep, and sleep fragmentation resulting from frequent arousal. Like in humans, arousal from sleep in RBD mice occurred independently of twitches and motor activity, and two drugs that enhance inhibitory transmission differed in their ability to control these symptoms, indicating that effects of inhibitory transmission on sleep maintenance and motor suppression are dissociable.