This Week in The Journal

● Cellular/Molecular

NO Alters Activity of Synaptically Uncoupled Neurons

Liana Artinian, Karine Tornieri, Lei Zhong, Deborah Baro, and Vincent Rehder

(see pages 1699–1711)

Nitric oxide, produced presynaptically or postsynaptically in neurons that express NO synthase, binds to guanylyl cyclase and increases production of cGMP. cGMP directly activates cyclic-nucleotide-gated ion channels, modulates hyperpolarization-activated cyclic nucleotide-modulated channels, and indirectly modulates other channels and receptors via cGMP-dependent protein kinase. Thus, NO–cGMP signaling can have diverse effects, including depolarization, hyperpolarization, potentiation, or depression, depending on the neuron. In snail neurons, NO slows neurite outgrowth by increasing calcium influx though voltage-sensitive channels and release of calcium from intracellular stores. Artinian et al. report that NO also produces a transient increase in the rate of spiking, followed by long-lasting silencing of isolated snail neurons. These effects appeared to be mediated by inhibition of both voltage-sensitive and voltage-insensitive calcium-activated potassium channels. The effects could be elicited by stimulation of single nearby isolated neurons, demonstrating that physiological NO release can affect firing of neighboring neurons that are not synaptically coupled.

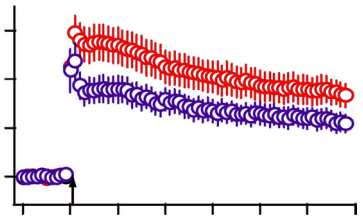
▲ Development/Plasticity/Repair

12-Lipoxygenase Knockout Impairs Some Forms of LTP

Anthony J. DeCostanzo, Iryna Voloshyna, Zev B. Rosen, Steven J. Feinmark, and Steven A. Siegelbaum

(see pages 1822–1831)

Different patterns of stimulation induce long-term potentiation (LTP) via different molecular pathways that depend on calcium influx through different types of channels. Because of this heterogeneity, determining which signaling molecules are involved in generating LTP can lead to controversy. Results presented by DeCostanzo et al. help to clarify the role of one such molecule, the arachidonic acid-metabolizing enzyme 12-lipoxygenase. Reducing 12-lipoxygenase activity by knockout or inhibition impaired LTP at CA3–CA1 hippocampal synapses of mice, but only when LTP was induced by theta-burst stimulation, which requires Ca^{2+} influx through both NMDA receptors and L-type voltage-gated calcium channels (LTCCs). Loss of 12-lipoxygenase activity had no effect when LTP was induced by 100 Hz tetanic stimulation, which requires Ca^{2+} influx solely through NMDA receptors. Further experiments showed that the component of LTP resulting from calcium influx through LTCCs was abolished by loss of 12-lipoxygenase activity, and that the 12-lipoxygenase metabolite 12(S)-HPETE likely modulates LTCCs.



LTP induced by theta-burst stimulation is reduced in mice lacking 12-lipoxygenase (blue) compared to that in wild-type mice (red). See the article by DeCostanzo et al. for details.

■ Behavioral/Systems/Cognitive

Limiting Rate of Auditory Neurons Varies With Characteristic Frequency

John C. Middlebrooks and Russell L. Snyder

(see pages 1937–1946)

Cochlear implants can be remarkably effective at restoring speech comprehension, but they do not adequately restore sensitivity to the fine temporal structure of sound, which limits users' ability to discriminate pitches, understand speech in noisy environments, and enjoy music. Because stimulation of the auditory nerve with penetrating electrodes produces shorter temporal integration time constants than stimulation with cochlear implants, Middlebrooks and Snyder hypothesized that penetrating electrodes would transmit fine temporal structure more efficiently. Indeed, the "limiting rate" of inferior colliculus neurons (i.e., the maximum stimulus rate to which neurons showed significant phase locking) was on average higher when stimuli were delivered by interneural electrodes. Surprisingly, however, this improvement was largely attributable to the fact that interneural electrodes stimulated more low-frequency neurons than traditional cochlear implants. Neurons with a given characteristic frequency had similar limiting rates regardless of the mode of stimulation, and low-frequency neurons had higher limiting rates and shorter latencies than high-frequency neurons.

♦ Neurobiology of Disease

Knockout of Zinc Transporter Impairs Learning

Paul A. Adlard, Jacqui M. Parncutt, David I. Finkelstein, and Ashley I. Bush

(see pages 1631–1636)

Zinc is co-released with glutamate at many synapses, and it modulates neurotransmission by interacting with various channels, receptors, and scaffolding proteins. Zinc is also linked to β-amyloid aggregation in Alzheimer's disease (AD) and is a key component of amyloid plaques. But evidence from Adlard et al. indicates that AD-related cognitive decline might result from sequestration of zinc rather than from amyloid deposition, per se. In mice, knock-out of zinc transporter 3 (ZnT3)—which loads zinc into synaptic vesicles—resulted in progressive loss of zinc in the hippocampus, as well as decreased expression of several presynaptic and postsynaptic proteins, including scaffolding proteins, AMPA and NMDA receptors, pro-brain-derived neurotrophic factor (pro-BDNF), and the BDNF receptor TrkB. In addition, knockout mice exhibited age-dependent impairment on the Morris water maze. Intriguingly, ZnT3 levels declined with age in normal mice and humans, indicating that similar molecular mechanisms might also contribute to normal age-related cognitive decline.