This Week in The Journal

Cellular/Molecular

Burst Firing Causes Cannabinoid-Dependent Inhibitory LTD

Thomas J. Younts, Vivien Chevaleyre, and Pablo E. Castillo

(see pages 13743–13757)

Endocannabinoid production in dendrites is triggered by activation of G-protein-coupled neurotransmitter receptors (GPCRs) and by Ca^{2+} influx through voltage-sensitive channels. By diffusing retrogradely and binding to CB1 receptors on presynaptic terminals, endocannabinoids induce short- or long-term depression (LTD) of neurotransmitter release, depending on how long the cannabinoids are present. Younts et al. discovered that stimulating pyramidal neurons in hippocampal slices to produce multiple high-frequency action potential bursts caused transient Ca^{2+}- and CB1-dependent suppression of IPSCs in the stimulated cell. Repeating this stimulation over 5 min produced LTD of inhibitory inputs to both the soma and dendrites. Surprisingly, this protocol did not cause LTD of glutamatergic inputs from Schaffer collaterals, even though CB1 receptors are present on these presynaptic terminals. Induction of LTD selectively at inhibitory inputs changed the balance of excitation and inhibition such that a given extracellular stimulus produced more action potentials after LTD was induced than before. Thus LTD of inhibition might facilitate information transmission through selected hippocampal circuits.

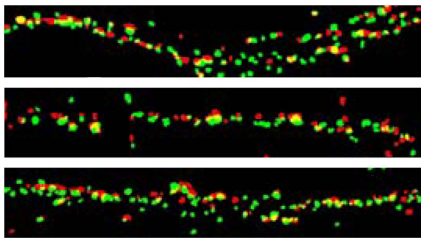
Development/Plasticity/Repair

Effects of Maternal Infection May Result from MHCI Signaling

Bradford M. Elmer, Myka L. Estes, Stephanie L. Barrow, and A. Kimberley McAllister

(see pages 13791–13804)

Activating the maternal immune system (MIA) affects fetal brain development and might increase susceptibility to schizophrenia and autism. How MIA alters brain development is unclear, but cytokine levels in offspring are increased during MIA, and cytokines increase expression of major histocompatibility complex class I (MHCI) molecules. Besides presenting intracellular proteins on the cell surface to identify infected cells for attack by T cells, MHCI has roles in synapse formation and remodeling. MHCI was previously shown to reduce synaptic density; Elmer et al. now report that myocyte enhancer factor 2 (MEF2), a transcription factor involved in activity-dependent synapse elimination, is a downstream effector of MHCI. Increasing MHCI levels in newborn rat cortical neurons—either by overexpression or more physiologically, by activating the maternal immune system at midgestation—increased MEF2 activity and reduced the density of excitatory synapses in cultures. Knocking down MEF2 blocked the effects of MHCI overexpression, and knocking down either MHCI or MEF2 rescued synaptic density in offspring exposed to MIA.



Compared with control dendrites (top), dendrites overexpressing MHCI (middle) have lower synaptic density as indicated by colocalization of presynaptic (red) and postsynaptic (green) markers. Knocking down MEF2 (bottom) rescues synaptic density. See the article by Elmer et al. for details.

Systems/Circuits

Optical Inhibition Reveals Circuit Underlying Drug Seeking

Michael T. Stefanik, Yonatan M. Kupchik, Robyn M. Brown, and Peter W. Kalivas

(see pages 13654–13662)

Abused drugs act on dopaminergic neurons in the ventral tegmental area (VTA), which project to the striatum. The ventral striatum (nucleus accumbens; NAc) is a primary locus for the rewarding properties of drugs, and NAc plasticity is essential in the development of addiction. The NAc core (NAcc) receives inputs from limbic areas as well as from the VTA, and NAcc neurons project to either the substantia nigra (SN) or the ventral pallidum (VP). To elucidate which pathways underlie one component of addiction—drug- and cue-induced reinstatement of drug seeking after extinction—Stefanik et al. expressed a light-activated inhibitory protein in various nuclei, then optically inhibited terminals in target areas. Inhibiting projections from NAcc to VP significantly reduced reinstatement of cocaine seeking, whereas inhibiting projections from NAcc to SN had no effect. Additionally, inhibiting projections from VTA to NAcc prevented reinstatement, but inhibiting projections from VP to NAcc did not. Thus, reinstatement of cocaine seeking involves a circuit comprising projections from VTA to NAcc to VP.

Behavioral/Cognitive

Nocebos Increase Pain Responses in Spinal Cord

Stephan Geuter and Christian Büchel

(see pages 13784–13790)

The experience of pain depends not only on the magnitude of nociceptor activation, but also on the context and the cognitive and emotional state of the perceiver. The power of expectations on pain perception is manifest in placebo and nocebo effects: an innocuous substance that is expected to reduce or enhance pain not only modulates reported pain intensity, but also decreases or increases, respectively, activity in brain areas involved in pain processing. Geuter and Büchel detected nocebo effects even at the level of the spinal cord. When volunteers believed that an applied cream would exacerbate pain, subsequently applied heat produced higher pain ratings and elevated activity in the spinal cord (as measured with functional magnetic resonance imaging) than when the same stimulus was applied without nocebo. The increased spinal activity likely resulted from descending modulatory input from the rostral ventromedial medulla, which integrates inputs from higher brain areas and projects to the spinal cord to control transmission at nociceptive afferent terminals.