This Week in The Journal

● Cellular/Molecular

Clock Genes Regulate ATP Release from Cortical Astrocytes

Luciano Marpegan, Adrienne E. Swanstrom, Kevin Chung, Tatiana Simon, Philip G. Haydon, et al.

(see pages 8342–8350)

Astrocytes release ATP, which is metabolized extracellularly to ADP, AMP, and adenosine. By activating neuronal receptors, ATP derivatives regulate transmitter release, thermoregulation, and hormone secretion. Increases in extracellular adenosine are also thought to underlie the feeling of sleepiness and the drive to sleep. Like most cells, astrocytes have an endogenous circadian rhythm, and the level of ATP release from rodent cortical astrocytes varies throughout the day. Marpegan et al. found that knocking out any of the canonical clock proteins—the transcription factors BMAL1 and CLOCK and their target genes, *Period* and *Cryptochrome*—prevented circadian variations in ATP release by cultured mouse astrocytes. Although sleep drive is reduced in transgenic mice in which vesicular gliotransmission is impaired, cyclical changes in ATP release were normal in astrocyte cultures from these mice, indicating that circadian variation does not require vesicular release and that the measured cyclical variation in ATP release is insufficient to drive sleep.

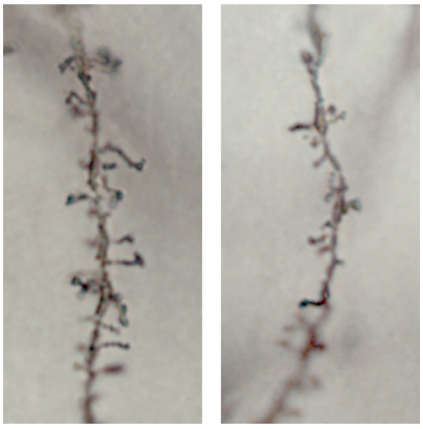
▲ Development/Plasticity/Repair

DCC Haploinsufficiency Alters Dopaminergic Input to mPFC

Colleen Manitt, Andrea Mimee, Conrad Eng, Matthew Pokinko, Thomas Stroh, et al.

(see pages 8381–8394)

Dopamine release in the medial prefrontal cortex (mPFC) and striatum, and interactions between these areas, are essential for reinforcement learning and altering behavior under changing conditions. Dopamine release in mPFC and striatum is interdependent: activation of dopamine receptors in mPFC decreases drug- or stress-induced release of dopamine in striatum. Whereas midbrain dopaminergic projections to the ventral striatum mature shortly after birth, however, projections to the mPFC grow during adolescence. The development of mPFC projections might therefore contribute to cognitive development during adolescence. Improper development of these projections has been proposed to contribute to psychiatric disorders, like schizophrenia, that emerge in adolescence. Previous studies suggested that the netrin-1 receptor DCC is involved in the development of dopaminergic projections to the mPFC. Manitt et al. support this hypothesis by showing that the volume occupied by dopaminergic boutons was increased, while dendritic development was reduced, in the mPFC of mice with heterozygous loss of DCC.



Compared with wild-type mice (left), DCC-haploinsufficient mice (right) have reduced spine density in basilar dendrites of mPFC pyramidal neurons. See the article by Manitt et al. for details.

■ Behavioral/Systems/Cognitive

Sustained OFF Amacrines Tonically Inhibit Ganglion Cells

Saskia E. J. de Vries, Stephen A. Baccus, and Markus Meister

(see pages 8595–8604)

Retinal amacrine cells are a diverse group that form synapses with bipolar, ganglion, and other amacrine cells. The mammalian retina is estimated to have approximately 30 different functional classes of amacrine cells distinguishable by the neurotransmitter expressed and response to visual stimuli. Few classes of amacrine have been fully characterized, however, particularly with regard to their specific effect on retinal ganglion cells (RGCs). de Vries et al. have undertaken this task for a group of salamander amacrine cells they call "sustained OFF amacrines" (SOAs), which respond to light pulses with sustained hyperpolarization lasting as long as the stimulus. Hyperpolarization of an SOA caused increased spiking in nearby RGCs, indicating that SOAs tonically inhibit RGCs. This inhibition appeared to be indirect, likely via inhibition of bipolar cell terminals. SOA depolarization decreased the sensitivity of nearby RGCs to light, but increased sensitivity of more distant RGCs, and thus might enhance detection of moving stimuli.

♦ Neurobiology of Disease

Oligodendrocytic IRF-1 Contributes to Autoimmune Demyelination

Zhihua Ren, Yan Wang, Duan Tao, David Liebenson, Thomas Liggett, et al.

(see pages 8329–8341)

Multiple sclerosis (MS) is an autoimmune disease in which T lymphocytes that recognize myelin antigens become activated in the periphery. Activated T cells then infiltrate the CNS, where they are further stimulated to secrete cytokines that trigger inflammation, demyelination, and axonal degeneration. One of these cytokines, interferon-γ, is associated with MS lesions, and allelic variations in a cellular effector of interferon-γ—the transcription factor interferon regulatory factor 1 (IRF-1)—are associated with increased risk of MS. Moreover, several genes that are regulated by IRF-1 are involved in oligodendrocyte death. Knock-out of IRF-1 reduces susceptibility to an MS-like pathological condition, experimental autoimmune encephalomyelitis (EAE), that is induced in mice when they are injected with myelin antigens. Previous studies suggested that this protection from EAE stems from loss of IRF-1 in oligodendrocytes. Ren et al. confirm this hypothesis by overexpressing dominant-negative IRF-1 specifically in oligodendrocytes. This significantly reduced demyelination and axonal degeneration after EAE induction.