This Week in The Journal

● Cellular/Molecular

mGluRs Induce Anti-Hebbian LTP in Hippocampal Interneurons

Caroline Le Duigou and Dimitri M. Kullmann

(see pages 5777–5781)

The hippocampus has numerous interneuron types that differ in morphology, molecular profile, electrophysiological properties, function in feedback versus feedforward inhibition, and synaptic plasticity. Some interneurons undergo Hebbian long-term potentiation (LTP) when high-frequency afferent stimulation is paired with postsynaptic depolarization. This LTP requires metabotropic glutamate receptors (mGluRs), but not NMDA receptors (NMDARs). In contrast, some interneurons undergo an anti-Hebbian form of LTP when afferent stimulation is paired with postsynaptic hyperpolarization. This LTP is also NMDAR independent, and it requires calcium-permeable AMPA receptors. In previous studies, activation of mGluRs did not induce LTP in hyperpolarized interneurons, indicating that Hebbian and anti-Hebbian LTP use distinct mechanisms. But Le Duigou and Kullmann argue that previously used recording techniques precluded detection of anti-Hebbian LTP. They found that mGluR agonists induced LTP in hyperpolarized interneurons and mGluR antagonists reduced induction of anti-Hebbian LTP by high-frequency afferent stimulation of hyperpolarized interneurons. Thus mGluRs appear to contribute to both anti-Hebbian and Hebbian LTP.

▲ Development/Plasticity/Repair

Neuronal DNA Endoreplication Increases with Slug Body Size

Miki Yamagishi, Etsuro Ito, and Ryota Matsuo

(see pages 5596–5604)

Many gastropods have giant neurons that contain more than diploid amounts of DNA. Extra DNA is thought to be produced by endoreplication (DNA replication in the absence of cell division) as the animal grows.

A terrestrial slug. As slugs grow, endoreplication in neurons increases. See the article by Yamagishi et al. for details.

This might be required for giant neurons to synthesize sufficient protein to supply larger axonal arbors that grow to innervate enlarged target areas. Yamagishi et al. provide evidence for this hypothesis. Well fed terrestrial slugs (*Limax valentianus*) grew much larger than unfed slugs, and brain size grew linearly with the log of body weight. Brain growth was not uniform, however—the subesophageal ganglion grew more than others. Individual neuronal somata were enlarged, but the number of neurons did not change significantly. DNA synthesis and the total amount of neuronal DNA was higher in well fed than unfed slugs, as was the number of some transcripts. Whether all DNA or only that encoding specific genes was replicated remains to be determined.

■ Behavioral/Systems/Cognitive

Some Learning Requires a Protein Restricted to Primary Cilia

Zhenshan Wang, Trongha Phan, and Daniel R. Storm

(see pages 5557–5561)

Most mammalian cells, including neurons, possess a primary cilium, a short protrusion containing nine microtubule pairs anchored to a basal body. Once thought to be vestigial structures, cilia are now recognized as specialized signaling compartments in which specific proteins are localized. Mutations that disrupt formation of, or protein trafficking into, cilia cause diseases characterized by retinal dystrophy, malformation of brain structures, and/or cognitive and behavioral impairment. Signaling cascades within cilia are important during development, but their role in adult neurons remains poorly defined. Knock-out of proteins expressed primarily in cilia can help identify cilia-dependent processes. Wang et al. report that mice lacking one such protein, adenylyl cyclase 3 (AC3), displayed poor object recognition and were slower than wild-type mice to associate a chamber with a delayed shock. Furthermore, although mutant mice showed normal contextual fear conditioning, their fear responses increased, rather than being extinguished, when they were reexposed to the training context without receiving shocks.

♦ Neurobiology of Disease

Reducing Mitochondrial Superoxide Reduces Effects of Aβ

Tao Ma, Charles A. Hoeffer, Helen Wong, Cynthia A. Massaad, Ping Zhou, et al.

(see pages 5589–5595)

During respiration, electrons are transferred from respiratory chain proteins to O_2, producing superoxide. Mitochondrial superoxide dismutase-2 (SOD-2) converts superoxide to H_2O_2, which is degraded. If not cleared quickly, superoxide induces formation of other reactive oxygen species (ROS) that damage DNA, proteins, and lipids; neuronal accumulation of ROS likely contributes to numerous neurodegenerative diseases, including Alzheimer's (AD). Previous studies found that overexpression of SOD-2 in mouse models of AD reduced β-amyloid (Aβ) deposition and memory impairments. Ma et al. now show that reducing ROS pharmacologically or by genetic manipulation reduced Aβ-induced deficits in long-term potentiation (LTP). Exogenous Aβ strongly impaired LTP and significantly increased superoxide production by mitochondria. Mitochondrial antioxidants prevented both effects. Superoxide is also produced by a membrane-associated oxidase when NMDA receptors are activated, and this is required for activation of kinases involved in LTP. Inhibiting that oxidase did not affect Aβ-induced impairment of LTP, however, suggesting that mitochondrial superoxide production is the main culprit.