This Week in The Journal

● Cellular/Molecular

ATP Receptor Involvement in Neuropathic Pain

Kimiko Kobayashi, Hiroki Yamanaka, Tetsuo Fukuoka, Yi Dai, Koichi Obata, and Koichi Noguchi

(see pages 2892–2902)

Nerve injury often leads to neuropathic pain, such as thermal hyperalgesia and mechanical allodynia, a painful response to normally innocuous stimuli. Microglia are thought to play a prominent role in neuropathic pain, in part by releasing inflammatory molecules. Phosphorylation of p38 mitogen-activated protein kinase (MAPK) in microglia also appears to be involved. Kobayashi et al. now suggest that release of ATP from injured nerves may be a first step in the development of neuropathic pain. They show that after nerve injury, the levels of an ADP/ATP receptor, P2Y12, increased in microglia in the spinal cord. Both an antagonist of and antisense oligonucleotides against P2Y12 significantly reduced mechanical allodynia and thermal hyperalgesia following nerve injury, and they also prevented the increase in p38 phosphorylation that normally follows injury. In contrast, a P2Y12 agonist induced mechanical allodynia and thermal hyperalgesia, both of which were attenuated by coadministration of a p38 MAPK inhibitor.

▲ Development/Plasticity/Repair

Regulation of Synaptic Plasticity by Nogo-66 Receptor

Hakjoo Lee, Stephen J. Raiker, Karthik Venkatesh, Rebecca Geary, Laurie A. Robak, Yu Zhang, Hermes H. Yeh, Peter Shrager, and Roman J. Giger

(see pages 2753–2765)

Although growth inhibitors are problematic when nerve regeneration is desired, they are assumed to play important roles in stabilizing synapses and regulating plasticity. Lee et al. now report that the Nogo-66 receptor, NgR1, plays such a role. NgR1 mediates the inhibitory effects of several myelin-associated proteins, and in adult mice, NgR1 is expressed on neurons throughout the neocortex. Lee et al. found that NgR1 was highly expressed at synapses, particularly postsynaptically. Although the brains of *NgR1* mutant mice had normal numbers of neurons, dendrites, and spines, the spine morphology was altered: more spines were stubby, and fewer were mushroom shaped than in controls. In addition, the mutants had impaired long-term depression and enhanced long-term potentiation; but, importantly, the latter only occurred when fibroblast growth factor 2 (FGF2) was present. Surprisingly, the authors found that FGF2 binds directly to NgR1, and transfection of NgR1 into rat cortical neurons prevented FGF-induced axonal branching.

■ Behavioral/Systems/Cognitive

Enhancement of Memory by Exposure to Predators

Michael V. Orr and Ken Lukowiak

(see pages 2726–2734)

Some stress is good for memory, according to experiments on pond snails reported by Orr and Lukowiak. Snails breathe through a pneumostome when in air; by touching the pneumostome when it opens, experimenters can operantly condition the snails to avoid pneumostome opening. Orr and Lukowiak trained snails in normal pond water or water that had held crayfish, a natural snail predator. A single training session given in pond water produced memory lasting 3 h, but one given in crayfish water produced memory lasting 48 h. Similarly, memory induced by two training sessions was extended from 24 h to 8 d by giving the training in crayfish water. Furthermore, unlike training in the presence of food odors, training in crayfish water produced memories that generalized to other contexts. The neural basis of this enhanced learning might be found in RPeD1, a neuron that exhibited decreased spontaneous firing whenever the conditioned memory was observed.

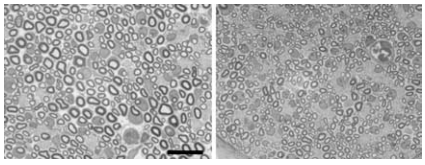
♦ Neurobiology of Disease

A Role for Mitochondrial Protein AFG3L2 in Axonal Development

Francesca Maltecca, Asadollah Aghaie, David G. Schroeder, Laura Cassina, Benjamin A. Taylor, Sandra J. Phillips, Mariachiara Malaguti, Stefano Previtali, Jean-Louis Guénet, Angelo Quattrini, Gregory A. Cox, and Giorgio Casari

(see pages 2827–2836)

Mitochondrial dysfunction has been implicated in several neurodegenerative diseases, including hereditary spastic paraplegia (HSP). HSP is characterized by degeneration of corticospinal axons, which results in spasticity of the legs. Many genetic mutations have been implicated in HSP, including defects in paraplegin, a component of *m*-AAA protease, which resides in the inner mitochondrial membrane and is involved in assembly and degradation of respiratory chain proteins. Maltecca et al. discovered that in mice, mutations in AFG3L2, the other component of *m*-AAA protease, resulted in progressive paralysis and death by postnatal day 16. This paralysis did not appear to result from axon degeneration, but rather from impaired development of the corticospinal tract. Axons had smaller diameters, likely because they had fewer neurofilaments, and more axons were unmyelinated in mutants than in controls. Basal respiratory rates were normal in the brains of mutant mice, but metabolism involving respiratory complexes I and III was impaired.



More large-caliber axons are visible in semithin sections of sciatic nerve from control (left) than from *Afg3l2* (right) mutant mice. Scale bar, 20 μm. See the article by Maltecca et al. for details.