This Week in The Journal

● Cellular/Molecular

All Axonal Neurofilaments Move

Yinyun Li, Peter Jung, and Anthony Brown

(see pages 746–758)

Neurofilaments are cytoskeletal components that help maintain neuronal shape and axonal caliber. Axonal neurofilaments accumulate in several neurodegenerative diseases, and this accumulation is thought to cause degeneration by disrupting axonal transport. But, surprisingly, how neurofilaments are transported in axons remains controversial. Early studies indicated that neurofilaments form two pools, one rapidly transported and the other stationary. Later studies, however, suggested that all neurofilaments move rapidly and bidirectionally via dynein and kinesin motors, but they spend much time paused, resulting in a slow average rate. A more recent study then suggested that despite the rapid movement of some neurofilaments, >90% of filaments are deposited in stable structures that remain stationary for months. Li et al. have revisited previous results, and using computational models, show that only a stop-and-go model explains all the data. They conclude that all neurofilaments move intermittently at a broad range of rates, but none remain stationary for long periods.

▲ Development/Plasticity/Repair

TIMP-1 Contributes to Neuronal Death after Seizures

Audrey P. Le and Wilma J. Friedman

(see pages 703–712)

Nerve growth factor (NGF) is generated from proNGF, which is either cleaved in the Golgi network or secreted and cleaved extracellularly by matrix metalloproteinases (MMPs). Whereas NGF promotes neuronal survival, extracellular proNGF can induce apoptosis by binding to receptor complexes comprised of sortilin and the p75 neurotrophin receptor ($p75^{NTR}$), leading to activation of the apoptotic enzyme caspase-3. This form of apoptosis is important during development, but it contributes to neuronal loss in neurodegenerative diseases and after seizures. Le and Friedman present evidence that seizures initiate this process by inducing expression of the tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), which binds to proMMP-7, thus preventing formation of mature MMP-7. As a result, MMP-7 levels decline, proNGF levels rise, and 75^{NTR} expression and caspase activation increase. Infusing mature MMP-7 into rat hippocampus after inducing seizures reduced proNGF levels in CSF and greatly reduced neuronal death. Similar treatments might limit seizure-induced damage in humans.

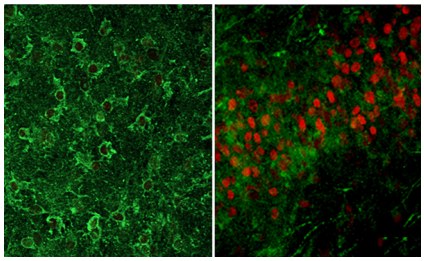
■ Behavioral/Systems/Cognitive

Prefrontal Cortex Exerts Dual Effects on Nucleus Accumbens

Ali Ghazizadeh, Frederic Ambroggi, Naomi Odean, and Howard L. Fields

(see pages 726–737)

To pursue goals efficiently, we must stop engaging in unproductive actions: both fear responses to innocuous stimuli and approach responses to unrewarding stimuli. Furthermore, we must engage in productive actions only at appropriate times. The ability to suppress unproductive responses depends on the ventromedial prefrontal cortex (vmPFC) and its projections to the nucleus accumbens (NAc), which has been proposed to tonically inhibit actions until appropriate cues are present. To explore how vmPFC projections regulate NAc neurons, Ghazizadeh et al. first trained rats to press a rewarded lever in response to a particular sound and to suppress responses to another sound. They then recorded from NAc shell neurons while pharmacologically inactivating the vmPFC. This inactivation increased unrewarded actions. The temporal activity pattern of NAc neurons led the authors to hypothesize that the vmPFC excites NAc neurons that tonically inhibit unrewarded actions and indirectly inhibits NAc neurons whose phasic activation releases rewarded actions from inhibition following specific cues.



Expression of MMP-7 (green) decreases and cell death (red) increases in rat hippocampal slices after kainic acid treatment (right). See the article by Le and Friedman for details.

♦ Neurobiology of Disease

Metabotropic Glutamate Receptors Regulate Electrical Coupling

Yongfu Wang, Ji-Hoon Song, Janna V. Denisova, Won-Mee Park, Joseph D. Fontes, et al.

(see pages 713–725)

Gap junction coupling mediated by connexin 36 (Cx36) transiently increases in mouse cortical neurons during early postnatal development. This coupling is thought to play a role in synaptogenesis and circuit formation, but it also makes neurons more susceptible to excitotoxicity. Although coupling decreases after the second postnatal week, it increases after ischemia, seizures, and traumatic brain injury (TBI), and the resulting increase in susceptibility to excitotoxicity allows degeneration to spread. The developmental upregulation of Cx36 is induced by activation of group II metabotropic glutamate receptors (mGluRIIs). Wang et al. show that synaptically released glutamate acting on mGluRIIs is also required for injury-induced upregulation of Cx36 in mature cortical neurons. mGluRII agonists increased cortical expression of Cx36 *in vivo*, whereas antagonists prevented Cx36 upregulation after ischemia. Importantly, mGluRII antagonists also reduced neuronal death after ischemia, as well as in *in vitro* models of TBI and seizure, suggesting that such antagonists can limit damage following various insults.