This Week in The Journal

● Cellular/Molecular

Calcium Decreases Synaptic Endocytosis Rate

Jeremy Leitz and Ege T. Kavalali

(see pages 16318–16326)

Calcium influx at synaptic terminals triggers fusion of vesicles with the plasma membrane. Maintenance of the vesicle pool in active neurons requires vesicle endocytosis, but how endocytosis keeps pace with vesicle release is not clear. An obvious candidate for this role is calcium, which activates the phosphatase calcineurin, which in turn regulates endocytic proteins. Studies of calcium's role in synaptic endocytosis have produced conflicting results, however. Unlike previous studies that relied on bulk measurements of endocytosis, Leitz and Kavalali optically monitored endocytosis of single, labeled vesicles in synaptic boutons of cultured hippocampal neurons. At physiological external $[Ca^{2+}]$, synaptic vesicle endocytosis following low-frequency stimulation was fast. Surprisingly, however, increasing extracellular $[Ca^{2+}]$ slowed endocytosis while increasing release probability. Inhibiting calcineurin blocked this effect. During high-frequency stimulation—which leads to progressive increase in $[Ca^{2+}]$ in the terminal—endocytosis rates progressively slowed. This mechanism might help to regulate release rate by allowing vesicle pool depletion.

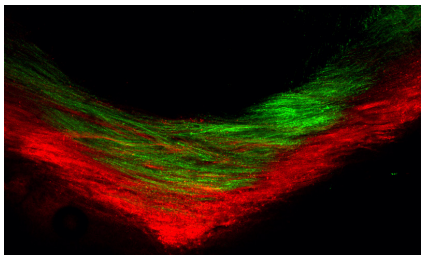
▲ Development/Plasticity/Repair

EphA3 Differentially Guides Lateral and Medial Callosal Axons

Mitsuaki Nishikimi, Koji Oishi, Hidenori Tabata, Kenichi Torii, and Kazunori Nakajima

(see pages 16251–16260)

Axons projecting through the corpus callosum (CC) rely on multiple guidance cues as they grow toward homotypic areas of the opposite hemisphere. Pioneering callosal axons from medial cortex are guided in part by midline glia and neurons



Axons from medial (green) and lateral (red) cortical areas are segregated into dorsal and ventral CC, respectively. See the article by Nishikimi et al. for details.

within the CC, and this requires EphB receptors and ephrin-B ligands. Nishikimi et al. report that callosal axons from lateral and medial cortex remain segregated in the CC: the former (e.g., from secondary somatosensory cortex) traverse the ventral CC, whereas the latter (e.g., from cingulate and motor cortex) pass through dorsal CC. This segregation required EphA3 receptors, which interact with ephrin-A5. Ephrin-A5 is expressed at higher levels in medial than lateral cortex, and in explant cultures, growth of lateral, but not medial axons was inhibited by ephrin-A5. Furthermore, blocking EphA3 caused axons from medial and lateral cortical axons to intermingle in culture, and knockdown of EphA3 *in utero* caused misrouting of lateral axons after they had entered the CC.

■ Behavioral/Systems/Cognitive

Methamphetamine Makes Sex More Rewarding

Karla S. Frohmader, Michael N. Lehman, Steven R. Laviolette, and Lique M. Coolen

(see pages 16473–16482)

Methamphetamine users report that the drug enhances sexual pleasure. To explore the neurophysiological bases for this, Frohmader et al. injected male rats with methamphetamine shortly before allowing them to mate, and later examined the animals' preferences for methamphetamine and sex. When mating was paired with nausea-inducing injections, rats that experienced methamphetamine and mating simultaneously took longer to develop conditioned aversion than naive rats and rats that experienced methamphetamine and mating separately. Moreover, given a choice between a chamber in which they experienced sex with methamphetamine and a chamber in which they experienced one or the other, rats preferred the former. Finally, after experiencing sex with methamphetamine, rats developed conditioned place preference (CPP) for a single low dose of methamphetamine, but they no longer developed CPP for sex alone, suggesting that mating alone was no longer rewarding. Such alteration in reward processing may explain increased engagement in risky sexual behaviors by methamphetamine users.

♦ Neurobiology of Disease

fMRI-Based Feedback Can Improve Parkinson's Symptoms

Leena Subramanian, John V. Hindle, Stephen Johnston, Mark V. Roberts, Masud Husain, et al.

(see pages 16309–16317)

Motor learning requires feedback about how successful actions are. When the result of an action is imperceptible through normal sensory channels, instruments can be used to monitor the effects. With biofeedback, for example, people can learn to control heart rate, blood pressure, and tension headaches. Furthermore, EEG-based neurofeedback may help control epilepsy, attention deficit, and autism spectrum disorders. The advent of real-time functional magnetic resonance imaging (fMRI) has extended the ability to monitor brain activity to shape motor learning. Subramanian et al. found that real-time fMRI neurofeedback improved motor symptoms in people with early-stage Parkinson's disease. Patients were instructed to use imagery without overt movement to increase activation of the supplemental motor area (SMA). Patients who could monitor SMA activation increased its activation to levels occurring during actual movement, and with practice, showed improved motor function. In contrast, patients who did not receive feedback neither increased SMA activation nor improved motor symptoms.