This Week in The Journal

Cellular/Molecular
Calcium Channels Interact With Endocytic Proteins
Hiroyasu Watanabe, Takayuki Yamashita, Naoto Saitoh, Shigeki Kiyonaka, Akihiko Iwamatsu, Kevin Campbell, Yasuo Mori, and Tomoyuki Takahashi
(see pages 655–660)

At synaptic terminals, calcium influx through voltage-sensitive calcium channels (VSCCs) is required for synaptic vesicles to fuse with the plasma membrane. Interactions between an intracellular synaptoflat protein-interaction (synprint) domain of VSCCs and syntaxin, SNAP-25, and synaptotagmin are also thought to be essential for vesicle release, because injection of synprint peptide fragments blocks release. Watanabe et al. show, however, that the effect of synprint fragments might be mediated mainly by decreasing endocytosis. They found that AP-2, an adaptor protein involved in endocytosis, binds to the synprint domain of VSCCs, as well as to synaptotagmin. Increases in calcium concentration increased binding of synaptotagmin to the synprint domain, and this reduced AP-2–synprint binding. Injection of synprint fragments into calyx of Held synapses in rat brainstem slices reduced endocytosis but not exocytosis. Thus, previously reported effects of synprint fragments on exocytosis might have resulted from depletion of synaptic vesicles resulting from reduced endocytic vesicle recycling.

Development/Plasticity/Repair
Daidzein Helps Axons Overcome Growth Inhibition
Thong C. Ma, Aline Campana, Philipp S. Lange, Hsin-Hwa Lee, Kasturi Banerjee, J. Barney Bryson, Lata Mahishi, Shabnam Alam, Roman J. Giger, Stephen Barnes, Sidney M. Morris Jr., Dianna E. Willis, Jeffrey L. Twiss, Marie T. Filbin, and Rajiv R. Ratan
(see pages 739–748)

Inhibition of axon growth by myelin-associated proteins is a main obstacle to regeneration after nerve injury and stroke. An effective strategy for overcoming myelin-mediated growth inhibition is increasing cAMP levels. Unfortunately, drugs that do this cause disabling nausea in patients. The effects of cAMP are mediated in part by cAMP response element binding protein (CREB), which increases transcription of arginase 1, an enzyme that stimulates synthesis of polyamines, which in turn enable axons to grow on myelin. Ma et al. therefore screened clinically approved drugs and natural compounds for their ability to upregulate arginase 1. The soy isoflavone and estrogen receptor agonist daidzein increased arginase expression without increasing cAMP levels or activating CREB. Daidzein increased neurite outgrowth from PNS and CNS neurons cultured on cells expressing myelin-associated proteins, and inhibiting arginase activity blocked this effect. Moreover, subcutaneous administration of daidzein after optic nerve crush increased the growth of a subset of axons.

Behavioral/Systems/Cognitive
Color Opponency Is Present in S Cones
Orin S. Packer, Jan Verweij, Peter H. Li, Julie L. Schnapf, and Dennis M. Dacey
(see pages 568–572)

Although individual cone photoreceptors are maximally sensitive to long (L cones), middle (M), or short (S) wavelengths, the probability that a photon will be absorbed also depends on the photon density. Therefore, color discrimination requires comparison of activity across cone types, which is achieved in two parallel channels: one for red–green opponency, which is derived from signals from L vs M cones, and one for blue–yellow opponency, which is derived from S vs L+M signals. The circuits that generate this opponency remain poorly defined. But this week, Packer et al. report that blue–yellow opponency is already present in S cones. Whole-cell recordings in primate retina indicated that blue light evoked outward currents from S cones, whereas yellow light that stimulated surrounding L and M cones evoked inward currents in S cones. The opponent signal is likely generated by modulation of a voltage-activated calcium current by input from H2 horizontal cells.

Neurobiology of Disease
CRMP4a Is Linked to Death of SOD1-Mutant Neurons
Laure Duplan, Nathalie Bernard, Wilfrid Casseron, Keith Dudley, Eric Thouenot, Jérôme Honnorat, Véronique Rogemond, Béatrice De Bovis, Patrick Aebischer, Philippe Marin, Cédric Raoul, Christopher E. Henderson, and Brigitte Pettmann
(see pages 785–796)

Mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1) are one of the few known causes of amyotrophic lateral sclerosis. Why this ubiquitously expressed protein causes selective death of large-caliber motor neurons is not known, but one contributing factor might be a motor-neuron-specific cell-death pathway that is activated by death receptors and nitric oxide. SOD1-mutant motor neurons are more susceptible to activation of this pathway than wild-type neurons. To determine the molecular mechanisms by which the pathway might contribute to motor neuron death, Duplan et al. searched for proteins upregulated by NO specifically in mice expressing mutated SOD1 but not in wild-type mice. They identified a single protein: collapsin response-mediator protein 4a (CRMP4a). In SOD1-mutant mice, expression of CRMP4a increased in some motor neurons as degeneration began. Furthermore, knockdown of CRMP4 failed to prevent NO-induced motor neuron death in culture and virally mediated overexpression of CRMP4a in motor neurons increased death in vivo.