This Week in The Journal

● Cellular/Molecular

Transducin Can Translocate in Cones

Ekaterina S. Lobanova, Rolf Herrmann, Stella Finkelstein, Boris Reidel, Nikolai P. Skiba, et al.

(see pages 6815–6824)

Upon photon absorption, photopigment molecules activate transducin, causing the α subunit to dissociate from β and γ subunits and activate phosphodiesterase (PDE). These interactions take place in the membranes of photoreceptor outer segments, where transducin subunits are held by interactions with each other or with PDE. When rods are exposed to bright light, however, activated α subunits outnumber available PDE. The excess subunits therefore dissociate from the membrane and diffuse into the inner segment. This limits phototransduction and is thought to extend the functional range of rods and/or protect them from light-induced damage. Transducin translocation does not occur in cones, however, even under prolonged bright light. Lobanova et al. show that this is because transducin activation and inactivation in cones is tightly regulated to ensure that the level of activated α subunits never exceeds that of PDE. Translocation occurred in cones when transducin inactivation was slowed or when transducin activation was increased.

▲ Development/Plasticity/Repair

Myelin Proteins Act Synergistically to Inhibit Axon Growth

William B. J. Cafferty, Philip Duffy, Eric Huebner, and Stephen M. Strittmatter

(see pages 6825–6837)

CNS myelin produces proteins that inhibit axonal growth and thus limit regeneration after injury. Three of these proteins—Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp)—bind Nogo receptor 1 to inhibit axon growth in vitro, but their interactions and relative potency in vivo have not been investigated. To address this, Cafferty et al. compared mice lacking Nogo-A with MAG/OMgp double knock-outs and Nogo/MAG/OMgp triple knock-outs. Nogo-A-null mice showed more axonal sprouting and functional recovery after spinal cord injury than wild-type mice, whereas double knock-outs were no different than controls. Triple-knockout mice, however, showed more sprouting and recovery than Nogo-A single mutants. Similarly, axons of wild-type dorsal root ganglion neurons grew no better when cocultured with MAG/OMgp-null myelin than with wild-type myelin, but they grew longer with Nogo-A-null myelin, and longer still with Nogo/MAG/OMgp-null myelin. These data suggest that Nogo-A acts synergistically with MAG and/or OMgp to inhibit axonal regrowth in vivo.

■ Behavioral/Systems/Cognitive

Midbrain Dopaminergic Neurons Release Glutamate


(see pages 7105–7110)

In vitro experiments have suggested that ro- dent midbrain dopaminergic neurons corelease glutamate onto targets in the forebrain. Whether this occurs in vivo has been debated, however, primarily because few dopaminergic neurons express the glutamate transporter thought to be necessary for synaptic glutamate release. It was therefore argued that glutamatergic EPSPs in vitro resulted from incidental stimulation of nondopaminergic cells or from abnormal synapse formation in culture. To resolve this issue, Tecuapetla et al. expressed channelrhodopsin-2 specifically in dopaminergic neurons in the ventral tegmental area of mice. Light pulses were then used to elicit action potentials specifically in dopaminergic afferents in nucleus accumbens slices. These spikes elicited time-locked, short-latency EPSCs in spiny projection neu- rons. EPSCs were blocked by AMPA receptor antagonists and by tetrodotoxin, were partially blocked by NMDA receptor antagonist, and were apparently unaffected by dopamine receptor antagonists and dopamine depletion. The data suggest that glutamatergic signaling plays a role in processing of reward.

● Neurobiology of Disease

Presenilin 1 Mutations Disrupt Notch-1 Regulation of Differentiation

Karthikeyan Veeraraghavalu, Se Hoon Choi, Xiaojing Zhang, and Sangram S. Sisodia

(see pages 6903–6915)

Presenilin 1 (PS1) is a γ-secretase that cleaves amyloid precursor protein (APP) to form β-amyloid (Aβ). PS1 mutations that increase production of toxic Aβ cause inherited forms of Alzheimer’s disease (AD). But PS1 cleaves proteins besides APP, including Notch-1, a protein involved in cell fate determination. Veeraraghavalu et al. report that AD-associated PS1 mutations alter proliferation and differentiation of subventricular zone (SVZ) neural progenitor cells (NPCs), in part by disrupting Notch-1 signaling. Mice expressing mutant PS1 had fewer proliferating NPCS in the SVZ than did wild-type mice, and SVZ NPCs extracted from adult mutant mice—as well as wild-type NPCs transfected with mutant PS1—showed less self-renewal and proliferation than did wild-type NPCs, and more of them differentiated into neurons in culture. Notch-1-dependent gene expres- sion was lower in NPCs expressing mutant PS1 than in control NPCs, and expression of constitutively active Notch-1 in mutant NPCs restored normal levels of self-renewal and neuronal differentiation.