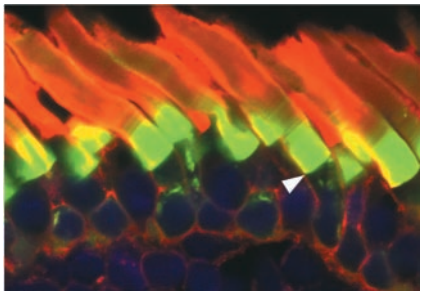
This Week in The Journal

● Cellular/Molecular

Targeting Proteins to the Outer Segment

Wenqin Luo, Nicholas Marsh-Armstrong, Amir Rattner, and Jeremy Nathans
(see pages 2623–2632)

Rods and cones are prototypic polarized cells with the protein machinery for phototransduction segregated in the outer segment (OS), whereas the basal side functions as a presynaptic nerve terminal. Maintaining this polarity in the face of rapid protein turnover in the OS requires an efficient sorting system. Rhodopsin is trafficked to the OS by a recently identified VXPX sequence at its C terminus. The importance of this sequence is underscored by human valine or proline mutations that cause one form of retinitis pigmentosa. Now Luo et al. report a similar localization signal, (V/I)XPX, in another OS protein, photoreceptor retinol dehydrogenase (prRDH). However prRDH, unlike rhodopsin, is mainly cytosolic; thus the authors looked to see how it might be retained in the OS. Using a series of green fluorescent protein (GFP) fusion proteins, they determined that fatty acylation of one or more cysteine residues in the C-terminal domain is necessary for membrane association and thus retention of the targeted protein in the OS.



The C-terminal segment from bovine photoreceptor retinol dehydrogenase, under the control of the zebrafish rhodopsin promoter, preferentially distributes to the basal region of the rod outer segment (GFP; green). The cell nuclei are stained dark blue, and the outer segments are stained red. See the article by Luo et al. for details.

▲ Development/Plasticity/Repair

Cortical Interneuron Development

Qing Xu, Inma Cobos, Estanislao De La Cruz, John L. Rubenstein, and Stewart A. Anderson
(see pages 2612–2622)

GABAergic interneurons can be subdivided based on their shape and connectivity as well as differential expression of markers such as parvalbumin, calretinin, and somatostatin. In this week's *Journal*, Xu et al. explore whether interneurons also originate from different sources. Many interneurons arise from the ventral telencephalon before migrating tangentially into the cortex. Thus the authors compared interneurons present in wild-type mice with those from mice deficient for the homeobox-containing genes *Nkx2.1*, in which the medial ganglionic eminence (MGE) does not form, or *Dlx1/2*−/−, both of which have greatly reduced numbers of interneurons. *Nkx2.1*−/− mice die at birth from lung defects. Thus the authors grew cultured neurons from the proliferative zones (PZ) of the subcortical telencephalon on cortical feeder layers and assayed interneuronal type by immunohistochemistry. Parvalbumin- and somatostatin-expressing interneurons were absent in *Nkx2.1*−/− cells, whereas calretinin was nearly absent in *Dlx1/2*−/− cells, consistent with distinct origins in the medial and caudal ganglionic eminence, respectively.

■ Behavioral/Systems/Cognitive

A Gut Feeling with CB1 and CCK

Galina Burdyga, Simon Lal, Andrea Varro, Rod Dimaline, David G. Thompson, and Graham J. Dockray
(see pages 2708–2715)

That cannabinoids cause an increase in appetite, the munchies, was appreciated long before endocannabinoids and their receptors, CB1 and CB2, were identified. This week, Burdyga et al. examine the role of the CB1 receptor as an enteric neuromodulator. They show that CB1 receptors are expressed by vagal sensory afferent neurons that carry appetitive signals between the gut and the brainstem. The same neurons expressed receptors for another appetite modulator, cholecystokinin (CCK) that acts as a gut satiety signal. CCK is released in the gut in response to fat or protein, and it now seems that it also actively regulates CB1 receptor expression. CB1 mRNA and protein were present at high levels in fasted rats when CCK levels were low. However, with refeeding or CCK delivery, CB1 was rapidly downregulated, suggesting that CCK may in part inhibit food intake in the peripheral nervous system by countering the action of endocannabinoids.

♦ Neurobiology of Disease

The Nuclear Envelope and Mutant TorsinA

Pedro Gonzalez-Alegre and Henry L. Paulson
(see pages 2593–2601)

DYT1, a disabling autosomal dominant form of dystonia, shares some common threads with other neurological disorders. Although the disease protein [TorsinA (TA)] and its mutation have been isolated, the dysfunction, and indeed the normal function, of the protein are unknown. TorsinA is a so-called AAA protein, which stands for ATPase associated with various cellular activities. Wild-type TA is distributed diffusely in the cytoplasm, consistent with endoplasmic reticulum (ER) localization, but mutant TA, due to a single glutamic acid deletion near the C terminus, is associated with intracellular membranous inclusions. Now Gonzalez-Alegre and Paulson report that the nuclear envelope rather than the ER may be the site of dysfunction in DYT1. To track the movements of mutant TA, the authors created an inducible PC12 cell model of the disorder. Mutant TA, but not wild-type TA, accumulated in the nuclear envelope, leading to formation of inclusions. These results add to several other studies implicating the nuclear envelope in neurological disorders.