

verted to inactive all-*trans* retinol and the retinol leaves the photoreceptor. For large bleaches, all-*trans* retinal is converted to all-*trans* retinol before most of the pigment is regenerated (Kennedy et al., 2001). The photoreceptors remain desensitized, and the equivalent background seems then to be produced mostly by opsin itself, which stimulates the cascade, though with low probability (Cornwall and Fain, 1994). This remaining opsin continues to activate the cascade and depress sensitivity until all of the photopigment has been regenerated.

## Summary

Photoreceptors respond to that part of the electromagnetic spectrum that we call light. They do this with the pigment rhodopsin, consisting of a retinal chromophore covalently attached to the protein opsin. From archaeobacteria to human, the mechanism of photon absorption is remarkably conserved. The chromophore is a derivative of vitamin A, called retinal, and the absorption of light produces an isomerization; in archaeobacteria all-*trans* retinal is converted to 13-*cis*, whereas in animals 11-*cis* is converted to all-*trans*. For most visual pigments the chromophore in the dark is protonated and forms a salt bridge with an adjacent, negatively charged amino acid. Isomerization produces a change in the shape of the chromophore within the opsin-binding pocket that breaks the salt bridge, triggering a change in conformation of the rhodopsin to an active form that initiates the sensory cascade.

In archaeobacteria, phototransduction is much like chemotaxis. Light produces an alteration of the concentration of phosphorylated CheY protein, which acts as a second messenger controlling the flagellar motor. In all animals, the visual pigment is a G protein-coupled receptor that activates a trimeric G protein and triggers a metabotropic cascade. Several different G protein families and transduction cascades have been implicated in phototransduction, sometimes even in different cells of the same organism. The most thoroughly studied cascades are those that produce the depolarizing responses of the arthropods *Limulus* and *Drosophila*, and those for the hyperpolarizations of vertebrate rods and cones.

In both *Limulus* and *Drosophila*, the photopigment is contained within numerous microvilli that are collectively referred to as a rhabdomere, which greatly increase the surface area of the plasma membrane. Rh<sup>\*</sup> activates a trimeric G protein with an  $\alpha_q$  subunit to produce  $\alpha_q$ -GTP. This then stimulates a PLC $\beta$ , generating the two second messengers IP<sub>3</sub> and DAG. Despite many years of intense effort, it is still not clear which, if either of these second messengers is directly responsible for gating the opening of the ion channels. The channels, at least in *Drosophila*, appear to be members of the TRP family of proteins, of which three different forms are expressed in the photoreceptor: TRP, TRPL, and TRP $\gamma$ . In *Limulus*, on the other hand, the channels may be gated by cyclic nucleotides.

Light produces a large increase in intracellular  $\text{Ca}^{2+}$ , in *Drosophila*, mostly the result of  $\text{Ca}^{2+}$  entering the light-dependent channels and in *Limulus*, from  $\text{IP}_3$ -gated  $\text{Ca}^{2+}$  release. In both species, the increase in  $\text{Ca}^{2+}$  plays an important role both in activation and modulation of the transduction cascade. Several different components of transduction are affected by  $\text{Ca}^{2+}$ , but it is not yet known which are responsible for controlling the gain and sensitivity.

In the rods and cones of vertebrates, transduction occurs in a part of the cell called the outer segment, which contains the photopigment, transduction enzymes, and channels necessary for producing the light response.  $\text{Rh}^*$  excites a G protein, called transducin, that is a member of the  $\alpha_i/\alpha_o$  family and is coupled to a PDE. The  $T_\alpha$ -GTP binds to the PDE inhibitory subunits, stimulating the PDE to hydrolyze cGMP. Rod and cone outer segments contain cation-permeable channels gated by cyclic nucleotides, which are open in darkness and allow a large influx of both  $\text{Na}^+$  and  $\text{Ca}^{2+}$ . The decrease in cGMP concentration caused by PDE activation leads to closing of the channels, reduction in ion influx, and hyperpolarization of the membrane potential. The transduction cascade is turned off by the quenching of  $\text{Rh}^*$ , produced by C terminal phosphorylation of serines and threonines by rhodopsin kinase, followed by the binding of arrestin. The  $T_\alpha$ -GTP is quenched when GTP is hydrolyzed to GDP, and the rate of this reaction is greatly accelerated by GAP proteins, including the RGS-9/G $\beta$ 5L complex and the inhibitory  $\gamma$  subunit of the PDE.

The  $\text{Ca}^{2+}$  coming into the rod through the cyclic nucleotide-gated channels in darkness is extruded by a transporter that exploits the energy of both the  $\text{Na}^+$  and  $\text{K}^+$  gradients. Light closes the cyclic nucleotide-gated channels, and continued extrusion by the  $\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$  transporter produces a decrease in intracellular  $\text{Ca}^{2+}$  concentration. The change in  $\text{Ca}^{2+}$  is thought to have several effects on the transduction cascade, but the most important seems to be the modulation of the rate of the guanylyl cyclase via small-molecular-weight binding proteins, called GCAPs. As the  $\text{Ca}^{2+}$  concentration decreases in the light,  $\text{Ca}^{2+}$  comes off the GCAP proteins and the cyclase is speeded up, increasing the cGMP concentration and reopening the channels. This accelerates the return of the photoreceptor current back to its dark level.  $\text{Ca}^{2+}$  also plays an important role in light adaptation, since if changes in outer segment  $\text{Ca}^{2+}$  concentration are prevented, adaptation cannot occur. The  $\text{Ca}^{2+}$  regulation of cyclase makes an important contribution to adaptation by preventing saturation of photoreceptor responses, but  $\text{Ca}^{2+}$  is also thought to regulate the cascade in other ways, including reduction of the lifetime of  $\text{Rh}^*$  by acceleration of the rate of rhodopsin kinase and regulation of the cyclic nucleotide-gated channels.

After bright light exposure, rods and cones slowly recover sensitivity. The all-*trans* retinal is released from the photopigment, converted to all-*trans* retinol, and transported to an adjacent cell layer, either the retinal pigment epithelium or glial cells. There the all-*trans* retinol is reconverted to 11-*cis* retinal, which diffuses or is transported back to the photoreceptor to recom-

bine with opsin and regenerate rhodopsin. During this process, the sensitivity of the photoreceptor is depressed, much as in the presence of background light. In molecular terms, this decrease in sensitivity is produced by a low level of stimulation of the transduction cascade by *intermediates of bleaching*, including opsin itself, which can activate the cascade, though with much less effectiveness than  $Rh^*$ .