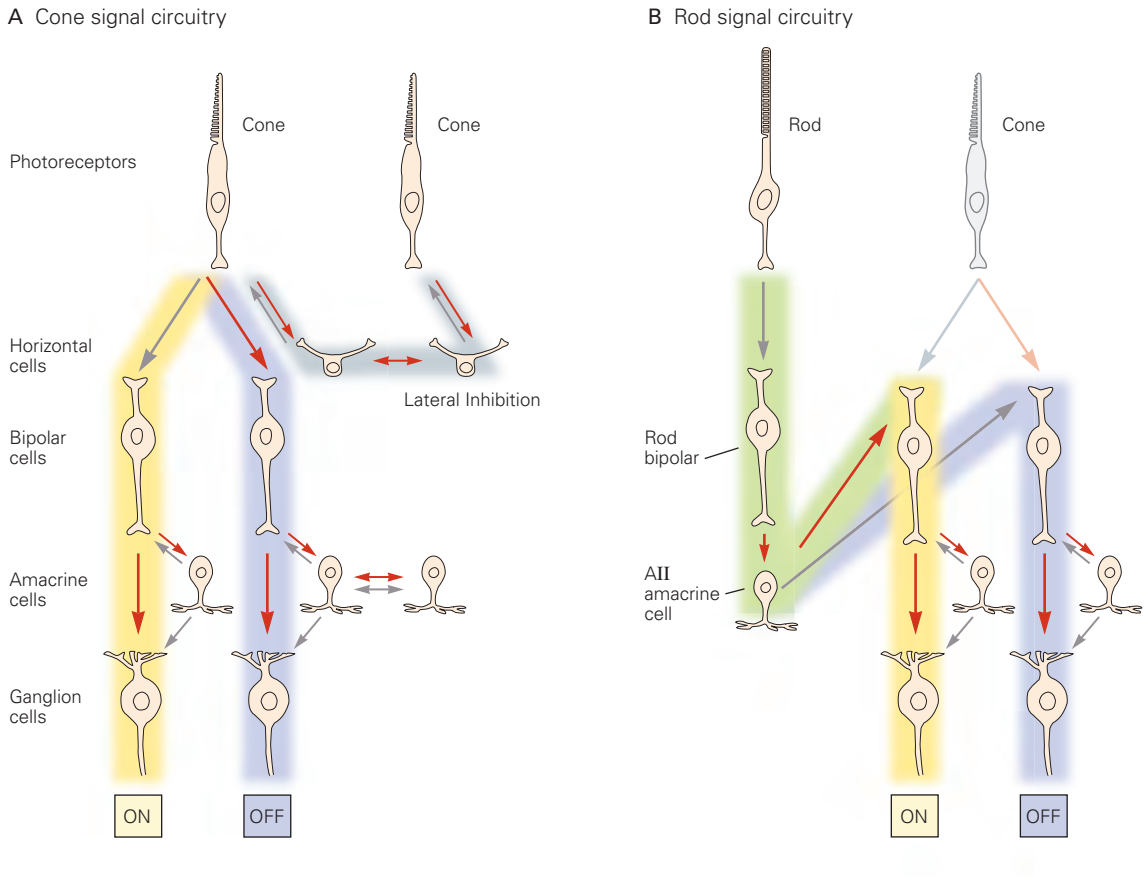


Figure 22–3 The retinal circuitry.

A. The circuitry for cone signals, showing the split into ON cell and OFF cell pathways (see Figure 22–10) as well as the pathway for lateral inhibition in the outer layer. **Red arrows** indicate sign-preserving connections through electrical or glutamatergic synapses. **Gray arrows** represent sign-inverting connections through GABAergic, glycinergic, or glutamatergic synapses.

B. Rod signals feed into the cone circuitry through AII amacrine cells, where the ON and OFF cell pathways diverge.

corresponds to a blind spot in the visual field of each eye. Because the disc lies nasal to the fovea of each eye, light coming from a single point never falls on both blind spots simultaneously, so that normally we are unaware of them. We can experience the blind spot by using only one eye (Figure 22–4). The blind spot demonstrates what blind people experience—not blackness, but simply nothing. This explains why damage to the peripheral retina often goes unnoticed. It is usually through accidents, such as bumping into an unnoticed object, or through clinical testing that a deficit of sight is revealed.

The blind spot is a necessary consequence of the inside-out design of the retina, which has puzzled and amused biologists for generations. The purpose of this organization may be to enable the tight apposition of photoreceptors with the retinal pigment epithelium, which plays an essential role in the turnover of retinal pigment and recycles photoreceptor membranes by phagocytosis.

There Are Two Types of Photoreceptors: Rods and Cones

All photoreceptor cells have a common structure with four functional regions: the outer segment, located at the distal surface of the neural retina; the inner segment, located more proximally; the cell body; and the synaptic terminal (Figure 22–5A).

Most vertebrates have two types of photoreceptors, rods and cones, distinguished by their morphology. A rod has a long, cylindrical outer segment within which the stacks of discs are separated from the plasma membrane, whereas a cone often has a shorter, tapered outer segment, and the discs are continuous with the outer membrane (Figure 22–5B).

Figure 22–4 The blind spot of the human retina. Locate the blind spot in your left eye by shutting the right eye and fixating the cross with the left eye. Hold the book about 12 inches from your eye and move it slightly nearer or farther until the circle on the left disappears. Now place a pencil vertically on the page and sweep it sideways over the circle. Note the pencil appears unbroken, even though no light can reach your retina from the region of the circle. Next, move the pencil lengthwise and observe what happens when its tip enters the circle. (Adapted, with permission, from Hurvich 1981.)

Rods and cones also differ in function, most importantly in their sensitivity to light. Rods can signal the absorption of a single photon and are responsible for vision under dim illumination such as moonlight. But as the light level increases toward dawn, the electrical response of rods becomes saturated and the cells cease to respond to variations in intensity. Cones are much less sensitive to light; they make no contribution to night vision but are solely responsible for vision in daylight. Their response is considerably faster than that of rods. Primates have only one type of rod but three kinds of cone photoreceptors, distinguished by the range of wavelengths to which they respond: the L (long-wave), M (medium-wave), and S (short-wave) cones (Figure 22–6).

The human retina contains approximately 100 million rods and 5 million cones, but the two cell types are differently distributed. The central fovea contains no rods but is densely packed with small cones. A few millimeters outside the fovea, rods greatly outnumber cones. All photoreceptors become larger and more widely spaced toward the periphery of the retina.

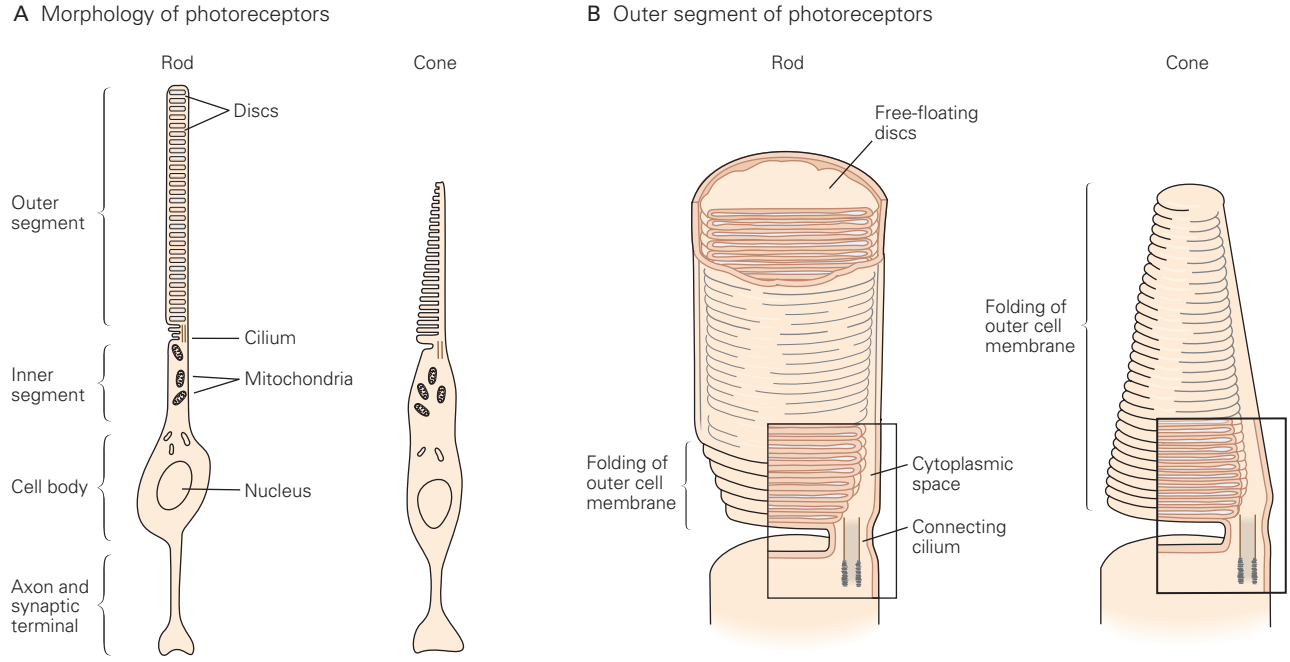


Figure 22–5 Rod and cone photoreceptors have similar structures.

A. Both rod and cone cells have specialized regions called the outer and inner segments. The outer segment is attached to the inner segment by a cilium and contains the light-transducing apparatus. The inner segment holds mitochondria and much of the machinery for protein synthesis.

B. The outer segment consists of a stack of membranous discs that contain the light-absorbing photopigments. In both types of cells, these discs are formed by infolding of the plasma membrane. In rods, however, the folds pinch off from the membrane so that the discs are free-floating within the outer segment, whereas in cones, the discs remain part of the plasma membrane. (Adapted, with permission, from O'Brien 1982. Copyright © 1982 AAAS; Young 1970.)

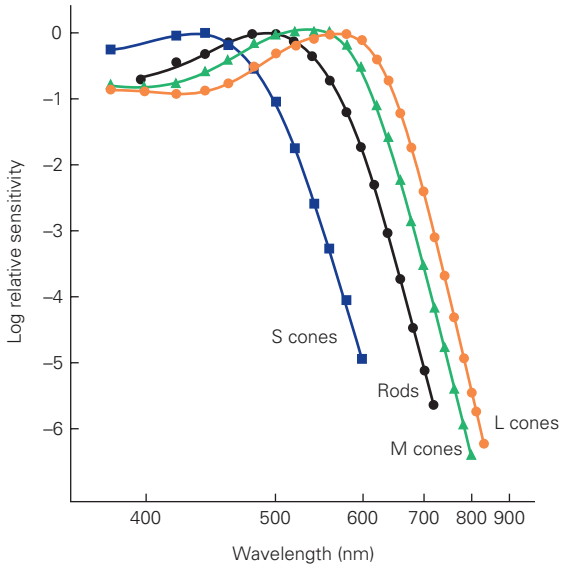


Figure 22–6 Sensitivity spectra for the three types of cones and the rod. At each wavelength, the sensitivity is inversely proportional to the intensity of light required to elicit a criterion response in the sensory neuron. Sensitivity varies over a large range and thus is shown on a logarithmic scale. The different classes of photoreceptors are sensitive to broad and overlapping ranges of wavelengths. (Reproduced, with permission, from Schnapf et al. 1988.)

The S cones make up only 10% of all cones and are absent from the central fovea.

The retinal center of gaze is clearly specialized for daytime vision. The dense packing of cone photoreceptors in the fovea sets the limits of our visual acuity. In fact, the smallest letters we can read on a doctor's eye chart have strokes whose images are just one to two cone diameters wide on the retina, a visual angle of about 1 minute of arc (Figure 22–1C). At night, the central fovea is blind owing to the absence of rods. Astronomers know that one must look just to the side of a dim star to see it at all. During nighttime walks in the forest, we nonastronomers tend to follow our daytime reflex of looking straight at the source of a suspicious sound. Mysteriously, the object disappears, only to jump back into our peripheral field of view as we avert our gaze.

Phototransduction Links the Absorption of a Photon to a Change in Membrane Conductance

As in many other neurons, the membrane potential of a photoreceptor is regulated by the balance of membrane conductances to Na^+ and K^+ ions, whose transmembrane gradients are maintained by metabolically active pumps (Chapter 9). In the dark, Na^+ ions flow into the photoreceptor through nonselective cation channels that are activated by the second messenger cyclic guanosine 3′-5′ monophosphate (cGMP).

Absorption of a photon by the pigment protein sets in motion a biochemical cascade that ultimately lowers the concentration of cGMP, thus closing the cGMP-gated channels and moving the cell closer to the K^+ equilibrium potential. In this way, light hyperpolarizes the photoreceptor (Figure 22–7). Here, we describe this sequence of events in detail. Most of this knowledge derives from studies of rods, but the mechanism in cones is very similar.

Figure 22–7 (Opposite) Phototransduction.

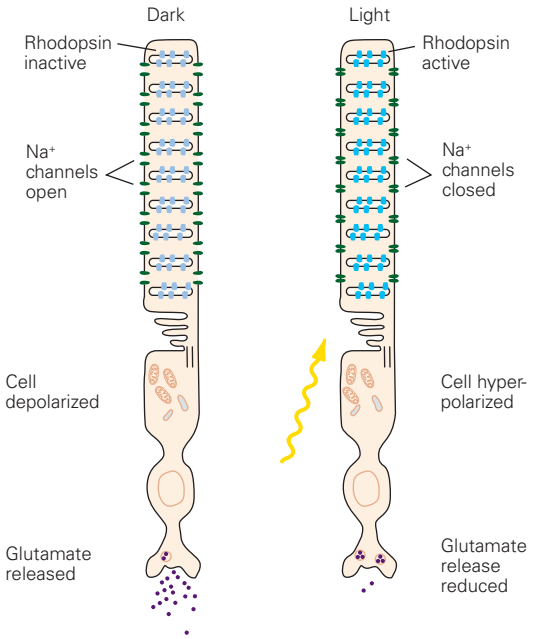
A. The rod cell responds to light. Rhodopsin molecules in the outer-segment discs absorb photons, which leads to the closure of cyclic guanosine 3′-5′ monophosphate (**cGMP**)-gated channels in the plasma membrane. This channel closure hyperpolarizes the membrane and reduces the rate of release of the neurotransmitter glutamate. (Adapted from Alberts 2008.)

B. 1. Molecular processes in phototransduction. cGMP is produced by a guanylate cyclase (**GC**) from guanosine triphosphate (**GTP**) and hydrolyzed by a phosphodiesterase (**PDE**). In the dark, the phosphodiesterase activity is low, the cGMP concentration is high, and the cGMP-gated channels are open, allowing the influx of Na^+ and Ca^{2+}. In the light, rhodopsin (**R**) is excited by absorption of a photon, then activates transducin (**T**), which in turn activates the PDE; the cGMP level drops, the membrane channels close, and less Na^+ and Ca^{2+} enter the cell. The transduction enzymes are all located in the internal membrane discs, and the soluble ligand cGMP serves as a messenger to the plasma membrane.

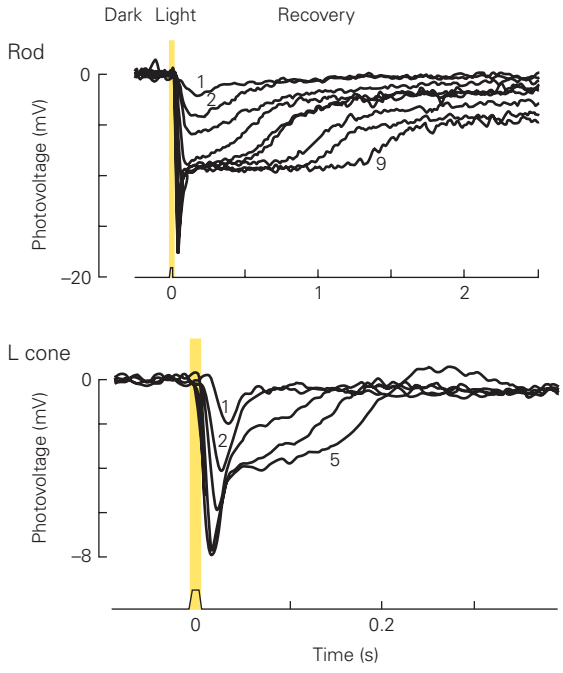
2. Calcium ions have a negative feedback role in the reaction cascade in phototransduction. Stimulation of the network by light leads to the closure of the cGMP-gated channels. This causes a drop in the intracellular concentration of Ca^{2+}. Because Ca^{2+} modulates the function of at least three components of the cascade—rhodopsin, GC, and the cGMP-gated channel—the drop in Ca^{2+} counteracts the excitation caused by light.

C. Voltage response of a primate rod and cone to brief flashes of light of increasing intensity. Higher numbers on the traces indicate greater intensities of illumination (not all traces are labeled). For dim flashes, the response amplitude increases linearly with intensity. At high intensities, the receptor saturates and remains hyperpolarized steadily for some time after the flash; this leads to the afterimages that we perceive after a bright flash. Note that the response peaks earlier for brighter flashes and that cones respond faster than rods. (Reproduced, with permission, from Schneeweis and Schnapf 1995. Copyright © 1995 AAAS.)

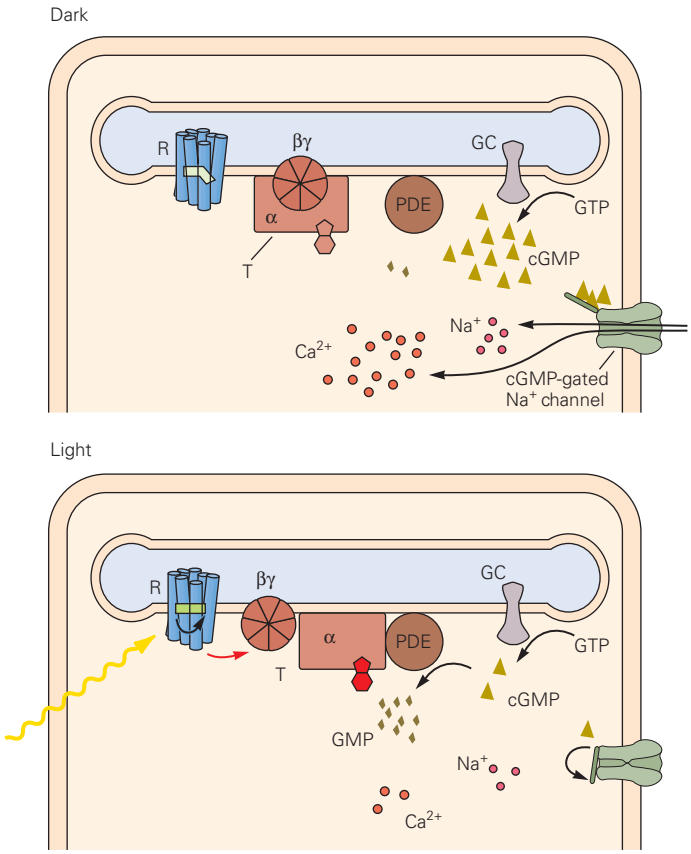
A Phototransduction and neural signaling



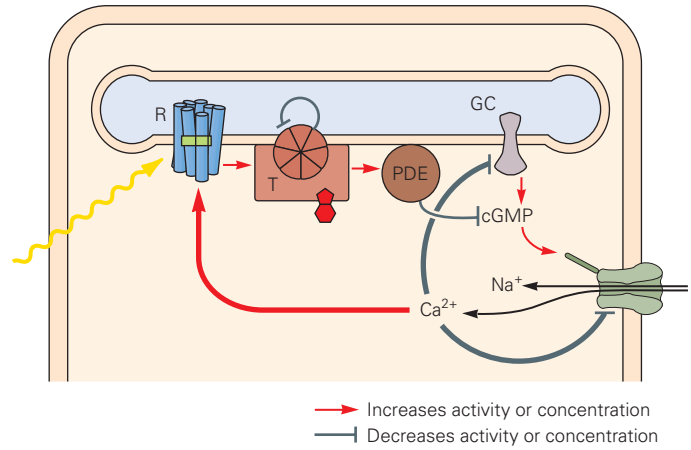
C Voltage response to light



B1 Molecular processes in phototransduction



B2 Reaction network in phototransduction



Light Activates Pigment Molecules in the Photoreceptors

Rhodopsin, the visual pigment in rod cells, has two components. The protein portion, *opsin*, is embedded in the disc membrane and does not by itself absorb visible light. The light-absorbing moiety, *retinal*, is a small molecule whose 11-*cis* isomer is covalently linked to a lysine residue of opsin (Figure 22–8A). Absorption of a photon by retinal causes it to flip from the 11-*cis* to the all-*trans* configuration. This reaction is the only light-dependent step in vision.

The change in shape of the retinal molecule causes a conformational change in the opsin to an activated state called *metarhodopsin II*, thus triggering the second

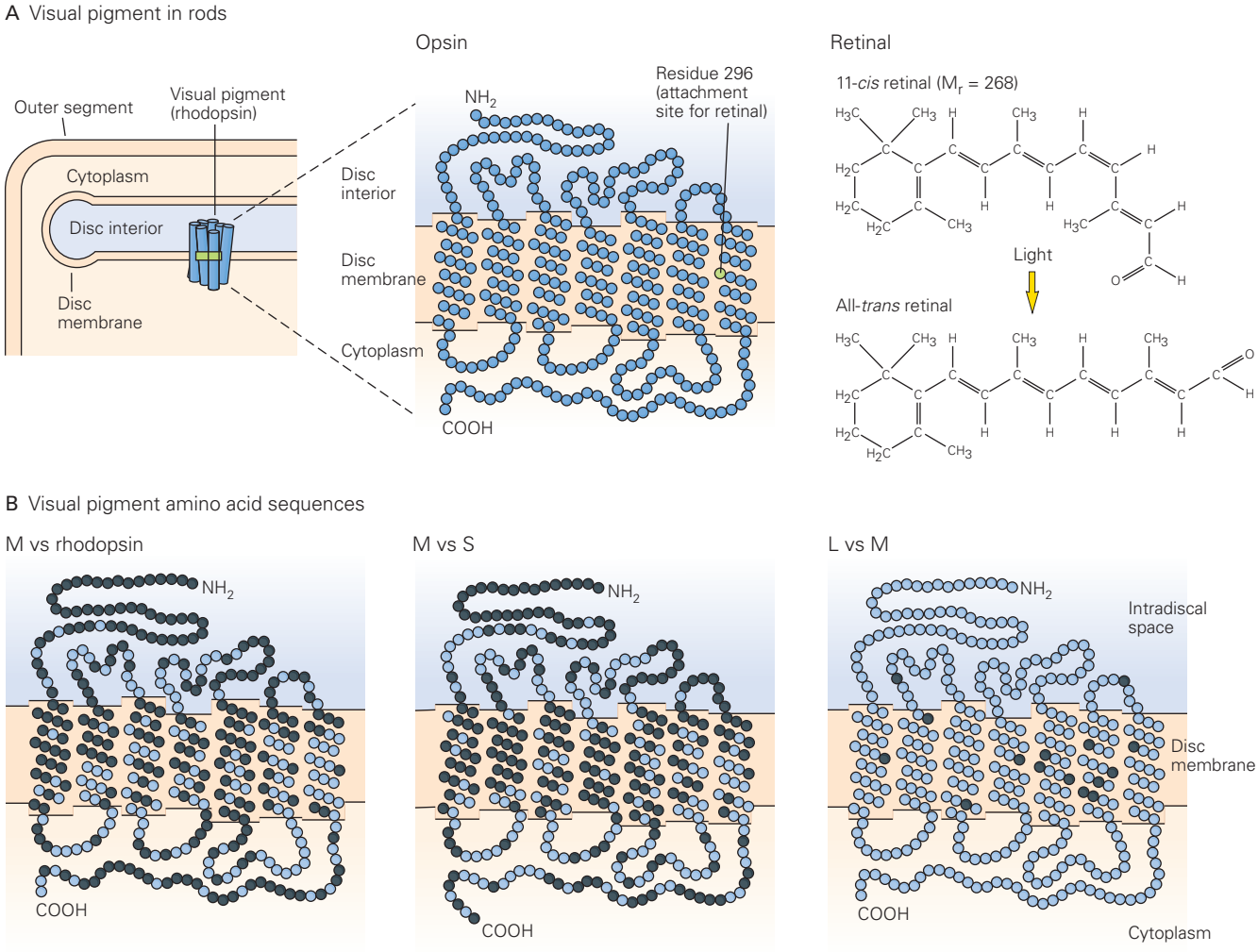


Figure 22–8 Structure of the visual pigments.

A. The visual pigment in rod cells, rhodopsin, is the covalent complex of two components. Opsin is a large protein with 348 amino acids and a molecular mass of approximately 40,000 daltons. It loops back and forth seven times across the membrane of the rod disc. Retinal is a small light-absorbing compound covalently attached to a side chain of lysine 296 in opsin's seventh membrane-spanning region. Absorption of light by 11-*cis* retinal causes a rotation around the double bond. As retinal adopts the more stable all-*trans* configuration, it causes a conformational change in opsin that triggers the subsequent events of visual transduction. (Adapted, with permission, from Nathans and Hogness 1984.)

B. The **blue circles** denote identical amino acids; **black circles** denote differences. The forms of opsin in the three types of cone cells (L, M, and S) resemble each other as well as the rhodopsin in rod cells, suggesting that all four evolved from a common precursor by duplication and divergence. The L and M opsins are most closely related, with 96% identity in their amino acid sequences. They are thought to have evolved from a gene-duplication event approximately 30 million years ago, after Old World monkeys, which have three visual pigments, separated from New World monkeys, which generally have only two.

step of phototransduction. Metarhodopsin II is unstable and splits within minutes, yielding opsin and free all-*trans* retinal. The all-*trans* retinal is then transported from rods to pigment epithelial cells, where it is reduced to all-*trans* retinol (vitamin A), the precursor of 11-*cis* retinal, which is subsequently transported back to rods.

All-*trans* retinal is thus a crucial compound in the visual system. Its precursors, such as vitamin A, cannot be synthesized by humans and so must be a regular part of the diet. Deficiencies of vitamin A can lead to night blindness and, if untreated, to deterioration of receptor outer segments and eventually to blindness.

Each type of cone in the human retina produces a variant of the opsin protein. These three cone pigments are distinguished by their *absorption spectrum*, the dependence on wavelength of the efficiency of light absorption (see Figure 22–6). The spectrum is determined by the protein sequence through the interaction between retinal and certain amino acid side chains near the binding pocket. Red light excites L cones more than the M cones, whereas green light excites the M cones more. Therefore, the relative degree of excitation in these cone types contains information about the spectrum of the light, independent of its intensity. The brain's comparison of signals from different cone types is the basis for color vision.

In night vision, only the rods are active, so all functional photoreceptors have the same absorption spectrum. A green light consequently has exactly the same effect on the visual system as a red light of a greater intensity. Because a single-photoreceptor system cannot distinguish the spectrum of a light from its intensity, "at night all cats are gray." By comparing the sensitivity of a rod to different wavelengths of light, one obtains the absorption spectrum of rhodopsin. It is a remarkable fact that one can measure this molecular property accurately just by asking human subjects about the appearance of various colored lights (Figure 22–9). The quantitative study of perception, or psychophysics, provides similar insights into other mechanisms of brain processing (Chapter 17).

Excited Rhodopsin Activates a Phosphodiesterase Through the G Protein Transducin

Activated rhodopsin in the form of metarhodopsin II diffuses within the disc membrane where it encounters transducin, a member of the G protein family (Chapter 14). As is the case for other G proteins, the inactive form of transducin binds a molecule of guanosine diphosphate (GDP). Interaction with metarhodopsin II promotes the exchange of GDP for guanosine triphosphate (GTP). This leads to dissociation of transducin's subunits into an active α-subunit carrying the GTP (Tα-GTP) and the β- and γ-subunits (Tβγ). Metarhodopsin II can activate hundreds of additional transducin molecules, thus significantly amplifying the cell's response.

The active transducin subunit Tα-GTP forms a complex with a cyclic nucleotide phosphodiesterase, another protein associated with the disc membrane. This interaction greatly increases the rate at which the enzyme hydrolyzes cGMP to 5′-GMP. Each phosphodiesterase molecule can hydrolyze more than 1,000 molecules of cGMP per second, thus increasing the degree of amplification.

The concentration of cGMP controls the activity of the cGMP-gated channels in the plasma membrane of the outer segment. In darkness, when the cGMP concentration is high, a sizeable Na^+ influx through the open channels maintains the cell at a depolarized level

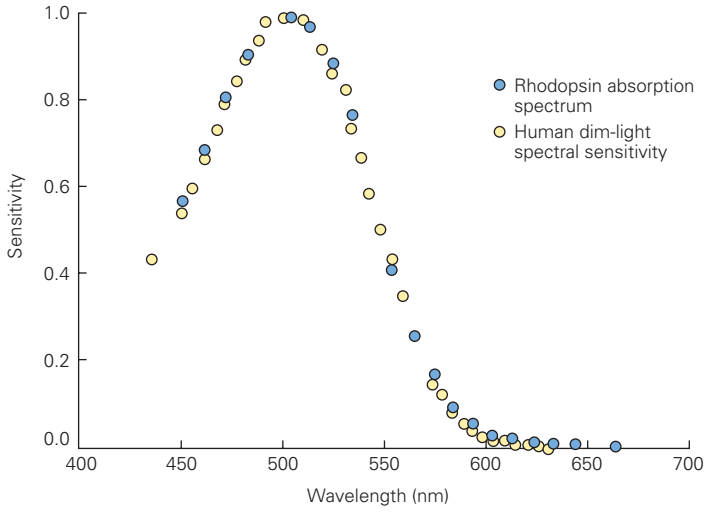


Figure 22–9 Absorption spectrum of rhodopsin. The absorption spectrum of human rhodopsin measured in a cuvette is compared with the spectral sensitivity of human observers to very dim light flashes. The psychophysical data have been corrected for absorption by the ocular media. (Reproduced, with permission, from Wald and Brown 1956. Copyright © 1956 Springer Nature.)

of approximately –40 mV. As a consequence, the cell's synaptic terminal continuously releases the transmitter glutamate. The light-evoked decrease in cGMP results in the closure of the cGMP-gated channels, thus reducing the inward flux of Na^+ ions and hyperpolarizing the cell (Figure 22–7B1). Hyperpolarization slows the release of neurotransmitter from the photoreceptor terminal, thereby initiating a neural signal.

Multiple Mechanisms Shut Off the Cascade

The photoreceptor's response to a single photon must be terminated so that the cell can respond to another photon. Metarhodopsin II is inactivated through phosphorylation by a specific rhodopsin kinase followed by binding of the soluble protein arrestin, which blocks the interaction with transducin.

Active transducin (Tα-GTP) has an intrinsic GTPase activity, which eventually converts bound GTP to GDP. Tα-GDP then releases phosphodiesterase and recombines with Tβγ, ready again for excitation by rhodopsin. Once the phosphodiesterase has been inactivated, the cGMP concentration is restored by a guanylate cyclase that produces cGMP from GTP. At this point, the membrane channels open, the Na^+ current resumes, and the photoreceptor depolarizes back to its dark potential.

In addition to these independent mechanisms that shut off individual elements of the cascade, an important feedback mechanism ensures that large responses are terminated more quickly. This is mediated by a change in the Ca^{2+} concentration in the cell. Calcium ions enter the cell through the cGMP-gated channels and are extruded by rapid cation exchangers. In the dark, the intracellular Ca^{2+} concentration is high, but during the cell's light response, when the cGMP-gated channels close, the Ca^{2+} level drops quickly to a few percent of the dark level.

This reduction in Ca^{2+} concentration modulates the biochemical reactions in three ways (Figure 22–7B2). Rhodopsin phosphorylation is accelerated through the action of the calcium-binding protein recoverin on rhodopsin kinase, thus reducing activation of transducin. The activity of guanylyl cyclase is accelerated by calcium-dependent guanylyl cyclase–activating proteins. Finally, the affinity of the cGMP-gated channel for cGMP is increased through the action of Ca^{2+}-calmodulin. All these effects promote the return of the photoreceptor to the dark state.

Defects in Phototransduction Cause Disease

Not surprisingly, defects in the phototransduction machinery have serious consequences. One prominent defect is color blindness, which results from loss or abnormality in the genes for cone pigments, as discussed later.

Stationary night blindness results when rod function has been lost but cone function remains intact. This disease is heritable, and mutations have been identified in many components of the phototransduction cascade: rhodopsin, rod transducin, rod phosphodiesterase, rhodopsin kinase, and arrestin. In some cases, it appears that the rods are permanently activated, as if exposed to a constant blinding light.

Unfortunately, many defects in phototransduction lead to *retinitis pigmentosa*, a progressive degeneration of the retina that ultimately results in blindness. The disease has multiple forms, many of which have been associated with mutations that affect signal transduction in rods. Why these changes in function lead to death of the rods and subsequent degeneration of the cones is not understood.

Ganglion Cells Transmit Neural Images to the Brain

The photoreceptor layer produces a relatively simple neural representation of the visual scene: Neurons in bright regions are hyperpolarized, whereas those in dark regions are depolarized. Because the optic nerve has only about 1% as many axons as there are receptor cells, the retinal circuit must edit the information in the photoreceptors before it is conveyed to the brain.

This step constitutes *low-level visual processing*, the first stage in deriving visual percepts from the pattern of light falling on the retina. To understand this process, we must first understand the organization of the retina's output and how retinal ganglion cells respond to various patterns of light.

The Two Major Types of Ganglion Cells Are ON Cells and OFF Cells

Many retinal ganglion cells fire action potentials spontaneously even in darkness or constant illumination. If the light intensity is suddenly increased, so-called ON cells fire more rapidly. Other ganglion cells, the OFF cells, fire more slowly or cease firing altogether. When the intensity diminishes again, the ON cells fire less and OFF cells fire more. The retinal output thus includes two complementary representations that differ in the polarity of their response to light.

This arrangement serves to communicate rapidly both brightening and dimming in the visual scene. If the retina had only ON cells, a dark object would be

encoded by a decrease in firing rate. If the ganglion cell fired at a maintained rate of 10 spikes per second and then decreased its rate, it would take about 100 ms for the postsynaptic neuron to notice the change in frequency of action potentials. In contrast, an increase in firing rate to 200 spikes per second is noticeable within only 5 ms.

Many Ganglion Cells Respond Strongly to Edges in the Image

To probe the responses of a ganglion cell in more detail, one can test how the cell's firing varies with the location and time course of a small spot of light focused on different portions of the retina.

A typical ganglion cell is sensitive to light in a compact region of the retina near the cell body called the cell's *receptive field.* Within that area, one can often distinguish a *center* region and *surround* region where light produces opposite responses in the cell. An ON cell, for example, fires faster when a bright spot is focused in the cell's receptive field center but decreases its firing when the spot is focused on the surround. If light covers both the center and the surround, the response is much weaker than for center-only illumination. A bright spot on the center combined with a dark annulus covering the surround elicits very strong firing. For an OFF cell, these relationships are reversed; the cell is strongly excited by a dark spot and a bright annulus (Figure 22–10).

The output produced by a population of retinal ganglion cells thus enhances regions of spatial contrast in the input, such as an edge between two areas of different intensity, and gives less emphasis to regions of homogeneous illumination.

The Output of Ganglion Cells Emphasizes Temporal Changes in Stimuli

When an effective light stimulus appears, a ganglion cell's firing typically increases sharply from the resting level to a peak and then relaxes to an intermediate rate. When the stimulus turns off, the firing rate drops sharply then gradually recovers to the resting level.

The rapidity of decline from the peak to the resting level varies among ganglion cell types. *Transient neurons* produce a burst of spikes only at the onset of the stimulus, whereas *sustained neurons* maintain an almost steady firing rate for several seconds during stimulation (Figure 22–10).

In general, however, the output of ganglion cells favors temporal changes in visual input over periods of constant light intensity. In fact, when an image is stabilized on the retina with an eye-tracking device, it fades from view within seconds. Fortunately, this never happens in normal vision; even when we attempt to fix our gaze, small automatic eye movements (saccades) continually scan the image across the retina and prevent the world from disappearing (Chapter 25).

Retinal Output Emphasizes Moving Objects

Based on these observations, we can understand more generally the response of ganglion cells to visual inputs. For example, the edges of a moving object elicit strong firing in the ganglion cell population because these are the only regions of spatial contrast and the only regions where the light intensity changes over time (Figure 22–11).

We can easily appreciate why the retina selectively responds to these features. The outline of an object is particularly useful for inferring its shape and identity. Similarly, objects that move or change suddenly are more worthy of immediate attention than those that do not. Retinal processing thus extracts low-level features of the scene that are useful for guiding behavior and selectively transmits those to the brain. In fact, the rejection of features that are constant either in space or in time accounts for the spatiotemporal sensitivity of human perception (Box 22–1).

Several Ganglion Cell Types Project to the Brain Through Parallel Pathways

Several different types of ganglion cells have been identified on the basis of their morphology and responses to light. The ON and OFF cells occur in every vertebrate retina, and in the primate retina, two major classes of cells, the P-cells and M-cells, each include ON and OFF types (see Figure 22–2B). At any given distance from the fovea, the receptive fields of M-cells (Latin *magno,* large) are much larger than those of P-cells (Latin *parvo,* small). The M-cells also have faster and more transient responses than P-cells. Some ganglion cells are intrinsically light-sensitive owing to expression of the visual pigment melanopsin.

In total, more than 20 types of ganglion cells have been described. The population of each type covers the retina in a tiled fashion, such that any point on the retina lies within the receptive field center of at least one ganglion cell. One can envision that the signals from each population together send a distinct neural representation of the visual field to the brain. In this view, the optic nerve conveys 20 or more neural representations that differ in polarity (ON or OFF), spatial resolution (fine or coarse), temporal responsiveness

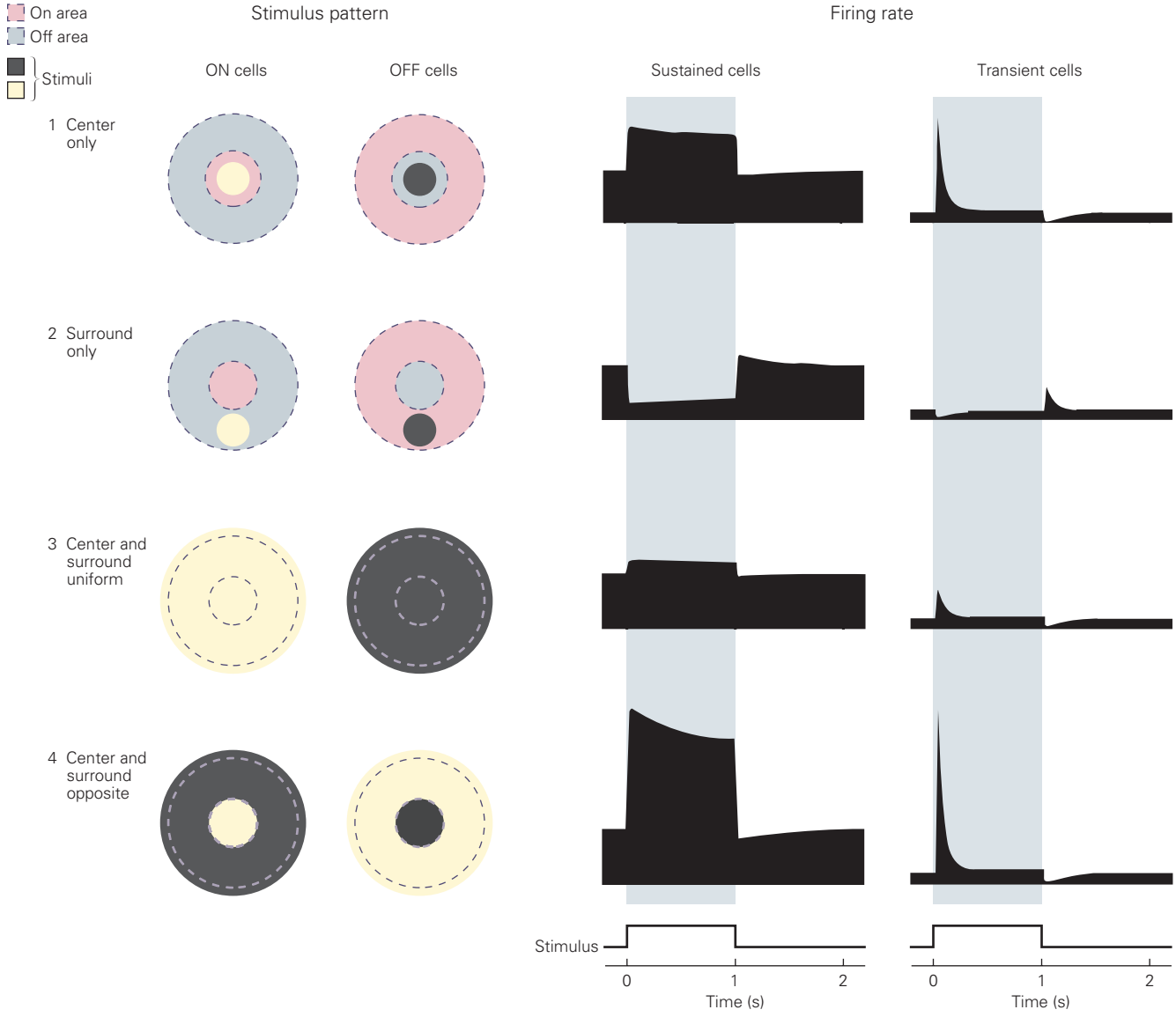


Figure 22–10 **Responses of retinal ganglion cells with center-surround receptive fields.** In these idealized experiments, the stimulus changes from a uniform gray field to the pattern of bright (**yellow**) and dark (**black**) regions indicated on the *left*. This leads to the firing rate responses shown on the *right*. **1.** ON cells are excited by a bright spot in the receptive field center, OFF cells by a dark spot. In *sustained cells*, the excitation persists throughout stimulation, whereas in *transient cells*, a brief burst of spikes occurs just after the onset of stimulation. **2.** If the same stimulus that excites the center is applied to the surround, firing is suppressed. **3.** Uniform stimulation of both center and surround elicits a response like that of the center, but much smaller in amplitude. **4.** Stimulation of the center combined with the opposite stimulus in the surround produces the strongest response.