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Visual Processing by the Retina

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VISUAL PERCEPTION BEGINS in the retina and occurs in two stages. Light entering the cornea is projected onto the back of the eye, where it is converted into an electrical signal by a specialized sensory organ, the retina. These signals are then sent through the optic nerve to higher centers in the brain for further processing necessary for perception. In this chapter we describe the neural processing of visual signals in the retina. The next three chapters explain, in cell-physiological terms, how processing in higher centers underlies the perception of form, motion, and color.

The retina bears careful examination for several reasons. First, it is useful for understanding sensory transduction in general because photoreceptors in the retina are perhaps the best understood of all sensory cells. Second, unlike other sensory structures, such as the cochlea or somatic receptors in the skin, the retina is not a peripheral organ but part of the central nervous system, and its synaptic organization is similar to that of other central neural structures. At the same time, the retina is relatively simple compared with other brain regions. It contains only five major classes of neurons, linked in an intricate pattern of connections but with an orderly, layered anatomical arrangement. This combination of physiological diversity and relatively simple structural organization makes the retina useful for understanding how information is processed by complex neural circuits in the brain.

For these reasons we describe neural processing in the retina in considerable detail. This chapter is divided into two parts. In the first part we describe how photo-receptors transduce light into an electrical signal. In the second we consider how these signals are shaped by other retinal neurons before being sent to the brain and

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how synaptic connections among the retinal neurons are organized to accomplish this processing. Before discussing phototransduction, however, we shall review the organization of the retina and the basic physiological properties of the photoreceptor cells.

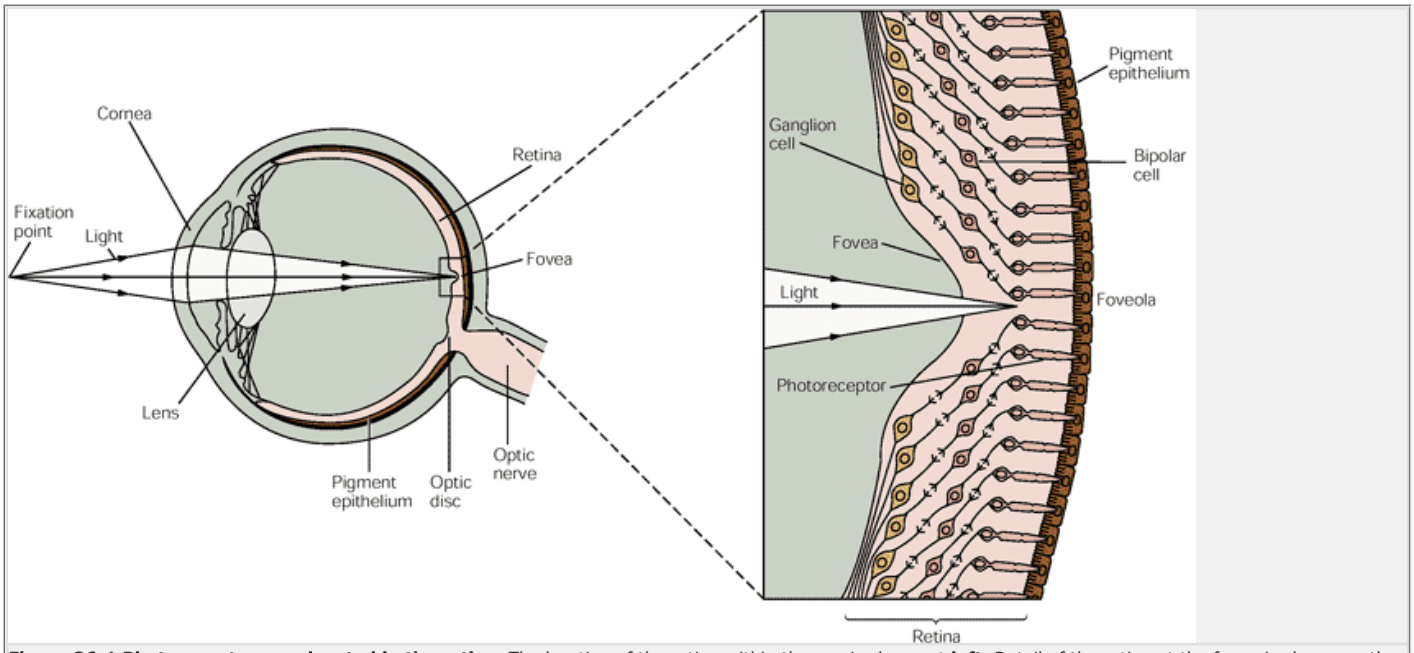

Figure 26-1 Photoreceptors are located in the retina. The location of the retina within the eye is shown at **left.** Detail of the retina at the fovea is shown on the **right** (the diagram has been simplified by eliminating lateral connections mediated by interneurons; see Figure 26-6). In most of the retina light must pass through layers of nerve cells and their processes before it reaches the photoreceptors. In the center of the fovea, or foveola, these proximal neurons are shifted to the side so that light has a direct pathway to the photoreceptors. As a result, the visual image received at the foveola is the least distorted.

The Retina Contains the Eye's Receptor Sheet

The eye is designed to focus the visual image on the retina with minimal optical distortion. Light is focused by the cornea and the lens, then traverses the vitreous humor that fills the eye cavity before reaching photoreceptors in the retina (Figure 26-1). The retina lies in front of the pigment epithelium that lines the back of the eye. Cells in the pigment epithelium are filled with the black pigment melanin, which absorbs any light not captured by the retina. This prevents light from being reflected off the back of the eye to the retina again (which would degrade the visual image).

Because the photoreceptors lie in the back of the eye, immediately in front of the pigment epithelium, all other retinal cells lie in front of the photoreceptors, closer to the lens. Therefore, light must travel through layers of other retinal neurons before striking the photoreceptors. To allow light to reach the photoreceptors without being absorbed or greatly scattered (which would distort the visual image), the axons of neurons in the proximal layers of the retina are unmyelinated so that these layers of cells are relatively transparent. Moreover, in one region of the retina, the *fovea*, the cell bodies of the proximal retinal neurons are shifted to the side, enabling the photoreceptors there to receive the visual image in its least distorted form (Figure 26-1). This shifting is most pronounced at the center of the fovea, the *foveola.* Humans therefore constantly move their eyes so that scenes of interest are projected onto the fovea. The retina also contains a region called the optic disc, where the optic nerve fibers leave the retina. This region has no photoreceptors and therefore is a blind spot in the visual field (see Figure 27-2). The projection of the visual field onto the two retinas is described in Chapter 27.

There Are Two Types of Photoreceptors: Rods and Cones

The human retina contains two types of photoreceptors, rods and cones. Cones are responsible for day vision;

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people who lose functioning in the cones are legally blind. Rods mediate night vision; total loss of rods produces only night blindness. Rods are exquisitely sensitive to light and therefore function well in the dim light that is present at dusk or at night, when most stimuli are too weak to excite the cones.

Table 26-1 Differences Between Rods and Cones and Their Neural Systems

Rods	Cones
High sensitivity to light, specialized for night vision	Lower sensitivity, specialized for day vision
More photopigment, capture more light	Less photopigment
High amplification, single photon detection	Lower amplification
Low temporal resolution: slow response, long integration time	High temporal resolution: fast response, short integration time
More sensitive to scattered light	Most sensitive to direct axial rays
Rod system	**Cone system**
Low acuity: not present in central fovea, highly convergent retinal pathways	High acuity: concentrated in fovea, dispersed retinal pathways
Achromatic: one type of rod pigment	Chromatic: three types of cones, each with a distinct pigment that is most sensitive to a different part of the visible light spectrum

Cones perform better than rods in all visual tasks except the detection of dim stimuli. Cone-mediated vision is of higher acuity than rod-mediated vision and provides better resolution of rapid changes in the visual image (ie, better temporal resolution). Cones also mediate color vision. Although the rod system is more light-sensitive than the cone system, it is achromatic. These differences in performance are due partly to properties of the rods and cones themselves and partly to the connections they make with other neurons in the retina (the rod and cone systems).

The most important factors that contribute to these differences are summarized in Table 26-1 and discussed next.

Rods Detect Dim Light

Rods contain more photosensitive visual pigment than cones, enabling them to capture more light. Even more important, rods amplify light signals more than cones do. A single photon can evoke a detectable electrical response in a rod; in contrast, tens or hundreds of photons must be absorbed by a cone to evoke a similar response. In addition, the rod system is highly convergent: Many rods have synapses on the same target interneuron, known as the bipolar cell (see below). Thus, signals from the rods are pooled in the bipolar cell and reinforce one another, strengthening the signals evoked by light in individual receptors and increasing the ability of the brain to detect dim lights. In contrast, fewer cones converge on each bipolar cell. In fact, cones in the foveola have small diameters, are closely spaced, and do not converge at all; each bipolar cell receives input from a single cone.

Cones Mediate Color Vision

There are three types of cones, each containing a visual pigment that is sensitive to a different part of the light spectrum (see below). As we shall see in Chapter 29, the brain obtains information about color by comparing the responses of the three types of cones. In contrast, rods contain only one type of pigment and therefore respond in the same way to different wavelengths.

Although rods outnumber cones by roughly 20 to 1, the cone system has better spatial resolution for two reasons. First, because many neighboring rods converge onto a single bipolar cell, differences in the responses of the rods are averaged out in the interneuron. Second, cones are concentrated in the fovea, where the visual image is least distorted.

Like some other sensory receptors, rods and cones do not fire action potentials. Instead, they respond to light with graded changes in membrane potential. Rods respond slowly, so that the effects of all the photons absorbed during a 100 ms interval are summed together. This helps rods detect small amounts of light, but prevents them from resolving light that is flickering faster

than about 12 Hz. The response of cones is much faster; they can detect flicker up to at least 55 Hz.

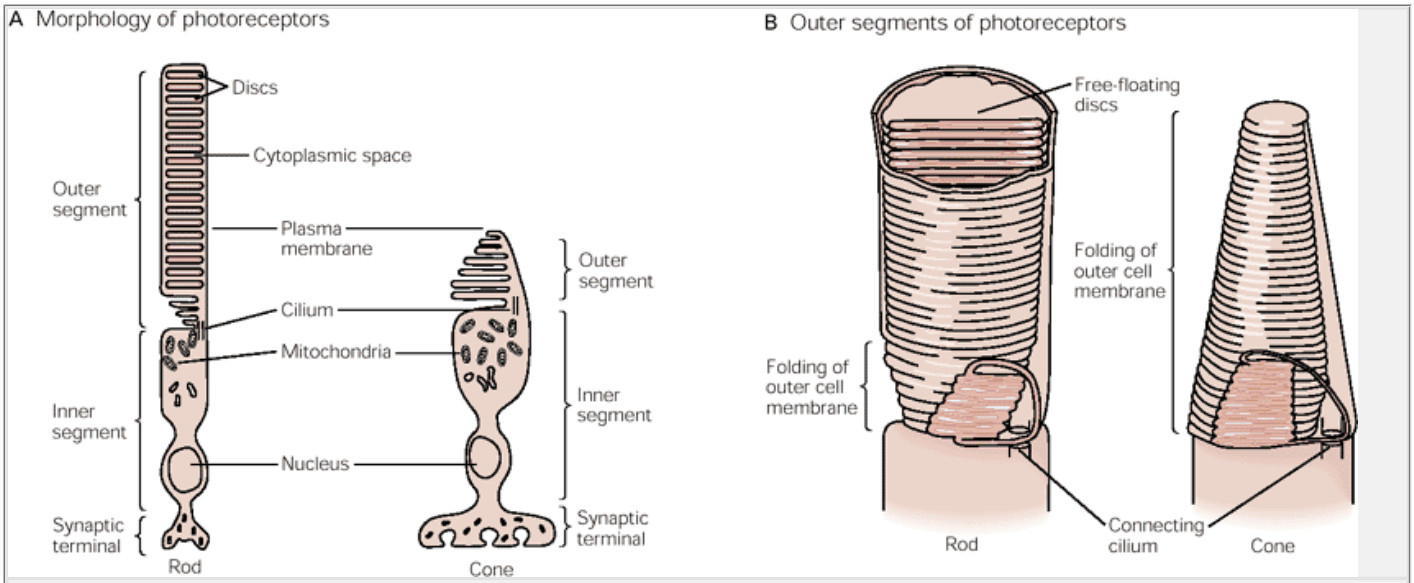

Figure 26-2 The two types of photoreceptors, rods and cones, have similar structures. (Adapted from O'Brien 1982 and Young 1970.)

A. Both rod and cone cells have inner and outer segments connected by a cilium. The inner segment contains the cell's nucleus and most of its biosynthetic machinery. The outer segment contains the light-transducing apparatus.

B. The outer segment consists of a stack of membranous discs, which 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.

Light Is Absorbed by Visual Pigments in the Photoreceptors

Both rods and cones have three major functional regions (Figure 26-2):

- The *outer segment*, located at the outer or distal surface of the retina, is specialized for phototransduction.
- The *inner segment*, located more proximally within the retina, contains the cell's nucleus and most of its biosynthetic machinery.
- A *synaptic terminal* makes contact with the photo-receptor's target cells.

The outer segments of rods and cones are filled with light-absorbing visual pigments. Each pigment molecule comprises a small light-absorbing molecule attached to a large membrane-spanning protein. Rods and cones can contain a remarkably large number of these membrane proteins (as many as 10^8 in each cell), because they have evolved an elaborate system of stacked membranous discs in their outer segments that dramatically increase the surface area of the membrane in these cells (Figure 26-2B). These discs develop as a series of invaginations of the cell's plasma membrane, ultimately arranging themselves like a roll of pennies in a bank wrapper. In cones the discs are continuous with the plasma membrane, while in rods they pinch off from the plasma membrane and become intracellular organelles.

Like other neurons, photoreceptors do not divide, but their outer segments are constantly renewed. New discs are formed at a rapid rate; in rods about three discs are synthesized every hour. Old discs are discarded at the tips of photoreceptors and removed by the phagocytotic activity of the pigment epithelial cells.

Phototransduction Results From a Three-Stage Cascade of Biochemical Events in the Photoreceptors

The absorption of light by visual pigments in rods and cones triggers a cascade of events that leads to a change in ionic fluxes across the plasma membrane of these cells, and consequently a change in membrane potential. A key molecule in the cascade is the nucleotide cyclic guanosine 3°-5° monophosphate (cGMP). In rods the (cGMP) molecule acts as a second messenger, carrying

information through the cytoplasm connecting the freely floating discs, where light is absorbed, to the cell's plasma membrane, where ionic fluxes are altered. In cones, since the discs are continuous with the plasma membrane, a cytoplasmic messenger is not necessary; nonetheless, cGMP is used in these cells in the same way as in rods. Cyclic GMP controls ionic fluxes by opening a specialized species of ion channels, the cGMP-gated ion channels, which allow an inward current carried largely by Na^+ ions to flow into the cell.

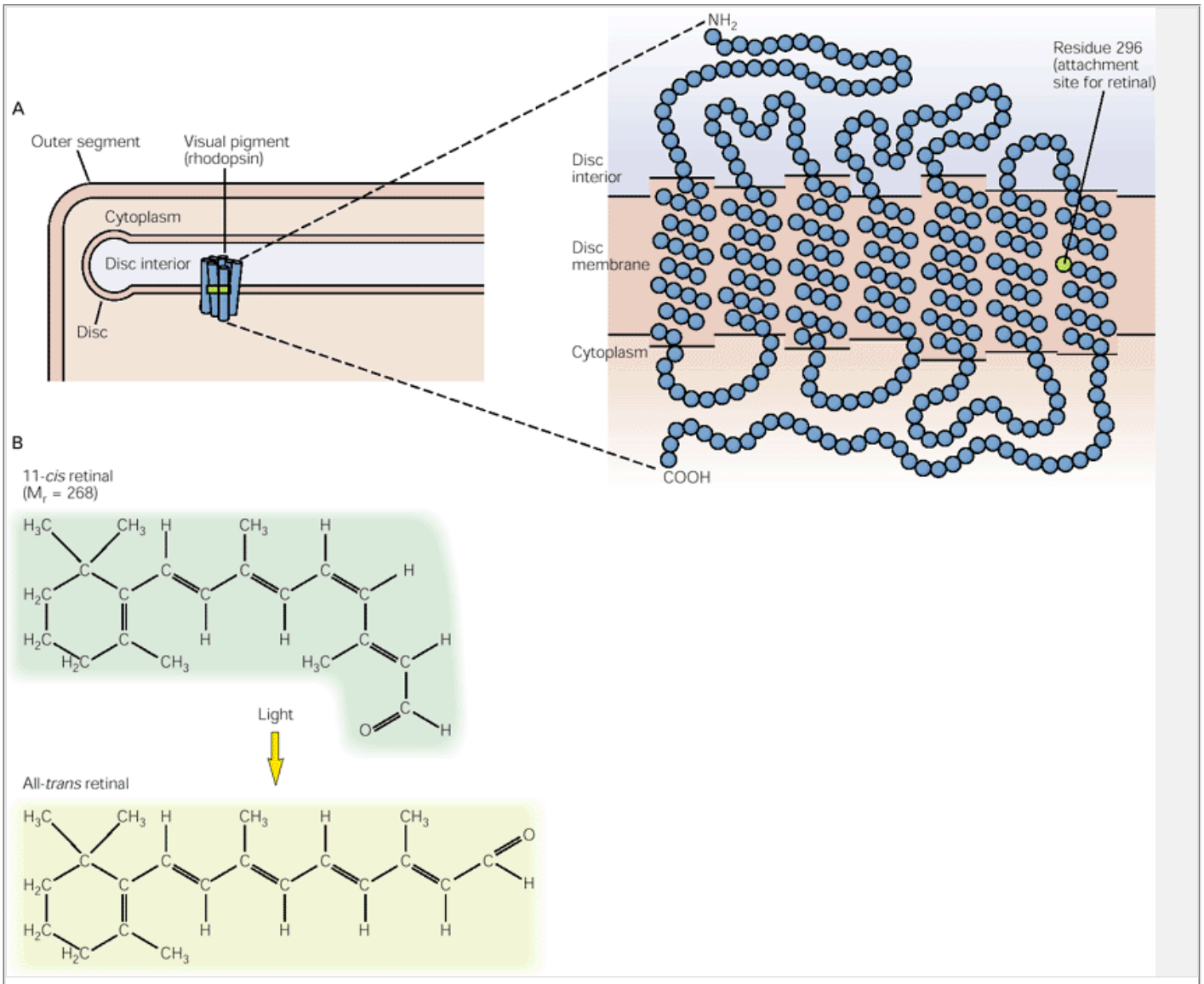

Figure 26-3 Rhodopsin, the visual pigment in rod cells, is the covalent complex of a large protein, opsin, and a small light-absorbing compound, retinal. The absorption of light by retinal causes a change in the three-dimensional structure of rhodopsin.

A. Opsin has 348 amino acids and a molecular weight of about 40,000. It loops back and forth seven times across the membrane of the rod disc. Retinal (**green rectangle**) is covalently attached to a side chain of lysine 296 in the protein's seventh membrane-spanning region. (Adapted from Nathans and Hogness 1984.)

B. In its nonactivated form rhodopsin contains the 11-*cis* isomer of retinal. Absorption of light by 11-*cis* retinal causes a rotation around the 11-*cis* double bond. As retinal returns to its more stable all-*trans* configuration, it brings about a conformational change in the opsin portion of rhodopsin, which triggers the other events of visual transduction.

In the dark the concentration of cGMP is relatively high, thus maintaining the cGMP-gated channels in an open state and allowing the inward current they carry to maintain the cell in a relatively depolarized state. Phototransduction then occurs in three stages: (1) Light activates visual pigments; (2) these activated molecules stimulate cGMP phosphodiesterase, an enzyme that reduces the concentration of cGMP in the cytoplasm; and (3) the reduction in cGMP concentration closes the cGMP-gated channels, thus hyperpolarizing the photo- receptor. We shall now examine these events step by step.

Stage 1: Light Activates Pigment Molecules in the Photoreceptors

In rod cells the visual pigment, rhodopsin, has two parts. The protein portion, *opsin*, is embedded in the

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disc membrane and does not by itself absorb light. The light-absorbing portion, *retinal*, is a derivative of vitamin A. Retinal can assume several different isomeric conformations, two of which are important in different phases of the visual cycle. In its nonactivated form rhodopsin contains the 11-*cis* isomer of retinal, which fits snugly into a binding site in the opsin molecule (Figure 26-3A).

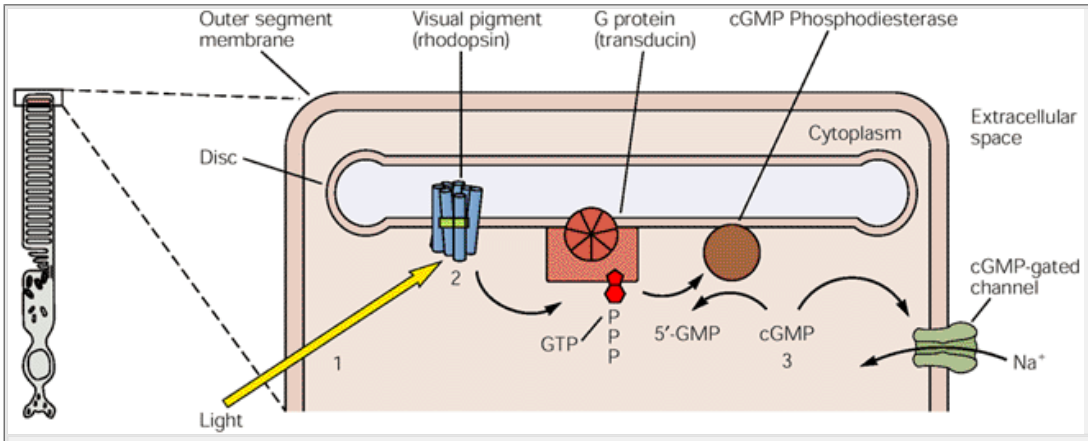

Figure 26-4 Phototransduction involves the closing of cation channels in the outer segment of the photoreceptor membrane. In the absence of light these cation channels are kept open by intracellular cGMP and conduct an inward current, carried largely by Na^+.

When light strikes the photoreceptor (illustrated here by a rod cell) the cGMP-gated channels are closed by a three-step process. (**1**) Light is absorbed by and activates pigment molecules (rhodopsin in rods) in the disc membrane (the **green rectangle** in the rhodopsin molecule represents the light-absorbing portion, retinal). (**2**) The activated pigment stimulates a G protein (transducin in rods), which in turn activates cGMP phosphodiesterase. This enzyme catalyzes the breakdown of cGMP to 5c-GMP. (**3**) As the cGMP concentration is lowered, the cGMP-gated channels close, thereby reducing the inward current and causing the photoreceptor to hyperpolarize.

Activation of rhodopsin starts with the absorption of light, which causes retinal to change from the 11-*cis* to the all-*trans* configuration (Figure 26-3B). This reaction is the only light-dependent step in vision. As a result of this conformational change, retinal no longer fits into the binding site in opsin. The opsin, therefore, undergoes a conformational change to a semistable conformation called metarhodopsin II, which triggers the second step of phototransduction discussed below.

Metarhodopsin II is unstable and splits within minutes, yielding opsin and all-*trans* retinal. The all-*trans* retinal is then transported from the rods to pigment epithelial cells, where it is reduced to all-*trans* retinol (vitamin A), the precursor in the synthesis of 11-*cis* retinal, which is transported back to the rods. All-*trans* retinol is thus a crucial compound in the visual system and, because it cannot be synthesized by humans, must be supplied in the diet. Deficiencies of vitamin A can lead to night blindness and, if untreated, to a deterioration of receptor outer segments and eventually total blindness.

In the retina of primates each of the three types of cone cells contains a different pigment optimized for absorption of light in a different part of the visible light spectrum. As in rods, the visual pigments in cones are composed of two parts: a protein called cone opsin and a light-absorbing portion, 11-*cis* retinal. Each type of cone pigment contains a different isoform of cone opsin that interacts with 11-*cis* retinal in a distinct way, causing it to be most sensitive to a particular part of the visible spectrum. The existence of three types of cones with different absorption characteristics underlies trivariant color vision in humans (see Chapter 29).

Stage 2: Activation of Pigment Molecules Reduces the Cytoplasmic Concentration of Cyclic GMP

The activation of pigment molecules by light leads to a reduction in the cytoplasmic concentration of the second messenger cGMP. The concentration of cGMP is controlled by two enzymes. It is synthesized from GTP by guanylyl cyclase, and it is broken down to 5°-GMP by cGMP phosphodiesterase, a protein peripherally associated with the disc membrane (see Figure 26-4). The concentration of cGMP is affected by light because cGMP phosphodiesterase is itself controlled by the visual pigments. In darkness cGMP phosphodiesterase is only weakly active, and the concentration of cGMP is therefore relatively high. Activation of pigment molecules by light leads to the activation of the phosphodiesterase,

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which breaks down cGMP and lowers its concentration.

Box 26-1 The Dark Current

In darkness two currents predominate in a photoreceptor. An inward current flows through cGMP-gated channels, which are confined to the photoreceptor's outer segment, while an outward K^+ current flows through nongated K^+-selective channels, which are like those of other neurons and are confined to the inner segment. The outward current carried by the K^+ channels tends to hyperpolarize the photoreceptor toward the equilibrium potential for K^+ (around -70 mV). The

inward current tends to depolarize the photoreceptor. The photoreceptor is able to maintain steady intracellular concentrations of Na^+ and K^+ in the face of these large fluxes because its inner segment has a high density of Na^+-K^+ pumps, which pump out Na^+ and pump in K^+ (Figure 26-5A).

In darkness the cytoplasmic concentration of cGMP is high, thus maintaining the cGMP-gated channels in an open state and allowing a steady inward current, called the dark current (Figure 26-5B). As a result, in darkness the photoreceptor's membrane potential is around -40 mV, significantly more depolarized than that of most neurons. When light reduces the level of cGMP, thus closing cGMP-gated channels, the inward current that flows through these channels is reduced and the cell becomes hyperpolarized (Figure 26-5C).

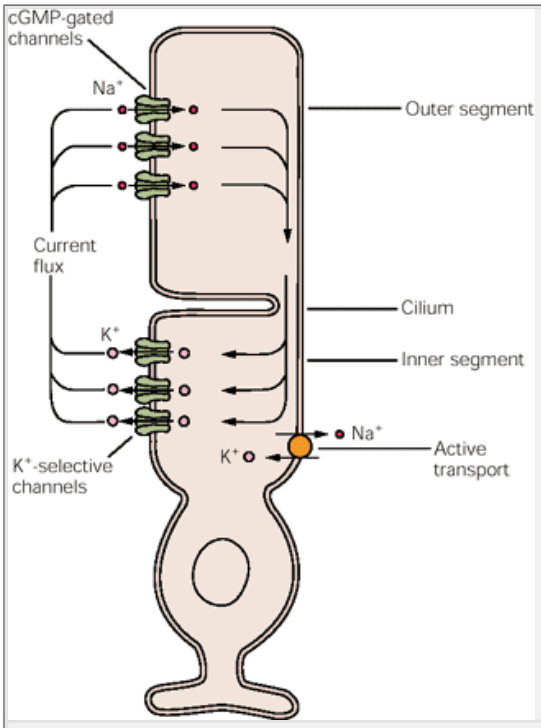

Figure 26-5A An inward current flows into a photoreceptor through cGMP-gated channels and out of the cell, through nongated K^+ channels. Active transport (Na^+-K^+) pumps maintain the cell's Na^+ and K^+ concentrations at steady levels.

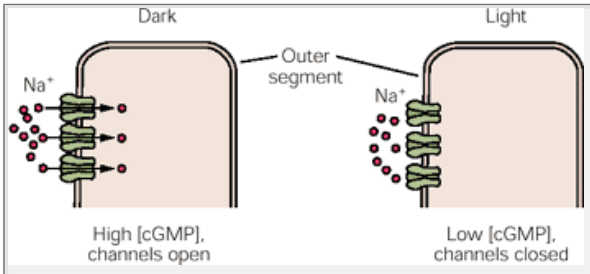

Figure 26-5B A reduction in the cytoplasmic concentration of cGMP closes the cGMP-gated channels.

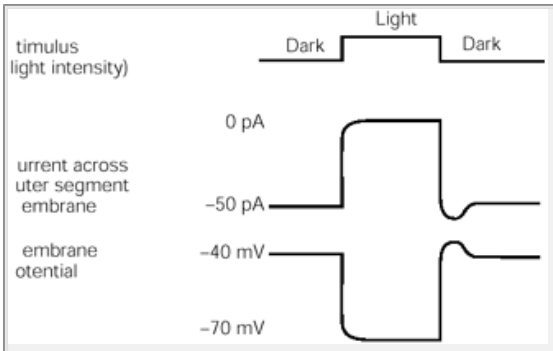

Figure 26-5C An inward current of -50 pA is suppressed by a bright light, hyperpolarizing the cell to -70 mV, the equilibrium potential for K^+. A light of intermediate intensity would hyperpolarize the cell to potentials between -40 and -70 mV.

Box 26-2 Calcium and Light Adaptation

Calcium modulates the function of several proteins of the phototransduction pathway. The recovery of the cone membrane potential and the desensitization of the cone that underlie light adaptation are mediated by a slow decrease in Ca^{2+} concentration in the cone outer segment during prolonged illumination (the opposite changes occur during dark adaptation).

In darkness Ca^{2+} constantly flows into the outer segment of the cone through the cGMP-gated channels. (Calcium accounts for about one-seventh of the current that flows through these channels). The Ca^{2+} that enters is extruded by a specialized Ca^{2+} carrier in the outer segment membrane, and this process maintains a constant Ca^{2+} concentration in the outer segment. During prolonged illumination the cGMP-gated channels close, thus reducing the influx of Ca^{2+}. This reduction in influx leads to a slow decrease in the intracellular Ca^{2+} concentration because the extrusion of Ca^{2+} continues.

The slow decrease in Ca^{2+} concentration allows the cone membrane potential to recover from its initial hyperpolarizing response to bright illumination because Ca^{2+} inhibits guanylyl cyclase, the enzyme that synthesizes cGMP from GTP. Thus, in darkness, when the Ca^{2+} level is relatively high, guanylyl cyclase is maintained in a partially inhibited state. The slow decrease in Ca^{2+} concentration during illumination relieves the inhibitory effect of Ca^{2+} on guanylyl cyclase. As a result, more cGMP is synthesized, and the concentration of cGMP slowly increases. This results in the reopening of cGMP-gated channels and, consequently, slow depolarization of the cone.

The slow decrease in Ca^{2+} concentration also causes the desensitization of the cone during light adaptation, at least partly through effects on the visual pigments and the cGMP-gated channels. Lowering the Ca^{2+} concentration is believed to speed up the inactivation of the visual pigments, so that the effectiveness of a given light flash in activating cGMP phosphodiesterase is reduced. A lower concentration of Ca^{2+} also decreases the sensitivity of the cGMP-gated channels to changes in cGMP. Because of these effects of Ca^{2+}, a more intense light stimulus is required to close the same number of cGMP-gated channels. Whether these effects entirely account for the desensitization is unknown.

Photoactivation of a single rhodopsin molecule can lead to the hydrolysis of more than 10^5 molecules of cGMP per second. An activated rhodopsin molecule diffuses within the disc membrane and activates hundreds of molecules of the regulatory protein transducin, each of which stimulates a phosphodiesterase molecule. Each phosphodiesterase molecule in turn is capable of hydrolyzing over 10^3 molecules of cGMP per second.

The biochemical cascade initiated by the photoactivation of rhodopsin resembles the cascades triggered by the binding of many hormones and neurotransmitters to their receptors. Indeed, the rod and cone opsins show a high degree of structural similarity with the family of hormone and transmitter receptors that couple to G proteins (see Chapter 13). Moreover, transducin is a member of the trimeric G protein family. As with other G proteins, the activation of transducin involves a characteristic interaction with guanine nucleotides (see Figure 13-3). Inactive transducin binds a molecule of GDP tightly; upon interaction with activated rhodopsin in the disc membrane, however, transducin exchanges GDP for GTP and itself becomes active. Transducin becomes in- activated because it also has GTPase activity, which breaks down the bound GTP molecule into GDP (see Figure 13-4).

Two mechanisms terminate the light response. As described, transducin inactivates itself by hydrolyzing bound GTP. Also, once activated, rhodopsin becomes a target for phosphorylation by a specific protein kinase, opsin kinase; the phosphorylated rhodopsin then interacts with a specific regulatory protein called arrestin, leading to its rapid inactivation.

Stage 3: The Reduction in Cyclic GMP Concentration Closes cGMP-Gated Ion Channels, Thus Hyperpolarizing the Photoreceptor

The light-evoked decrease in cGMP results in the closure of cGMP-gated ion channels in the photoreceptor (Figure 26-4). Cyclic GMP gates these channels by binding directly to the cytoplasmic face of the channel; the channel is activated by the cooperative binding of at least three molecules of cGMP. The cGMP-gated channel in photoreceptors was the first known example of an ion channel regulated by a cyclic nucleotide acting directly on the channel rather than through a protein kinase. Similar channels are also present in some retinal bipolar cells (see below) and in olfactory neurons (see Chapter 32).

In the absence of a light stimulus the cGMP-gated channels conduct an inward current that tends to depolarize the photoreceptor. The light-evoked closing of

these channels reduces this current and therefore hyperpolarizes the cell (Box 26-1).

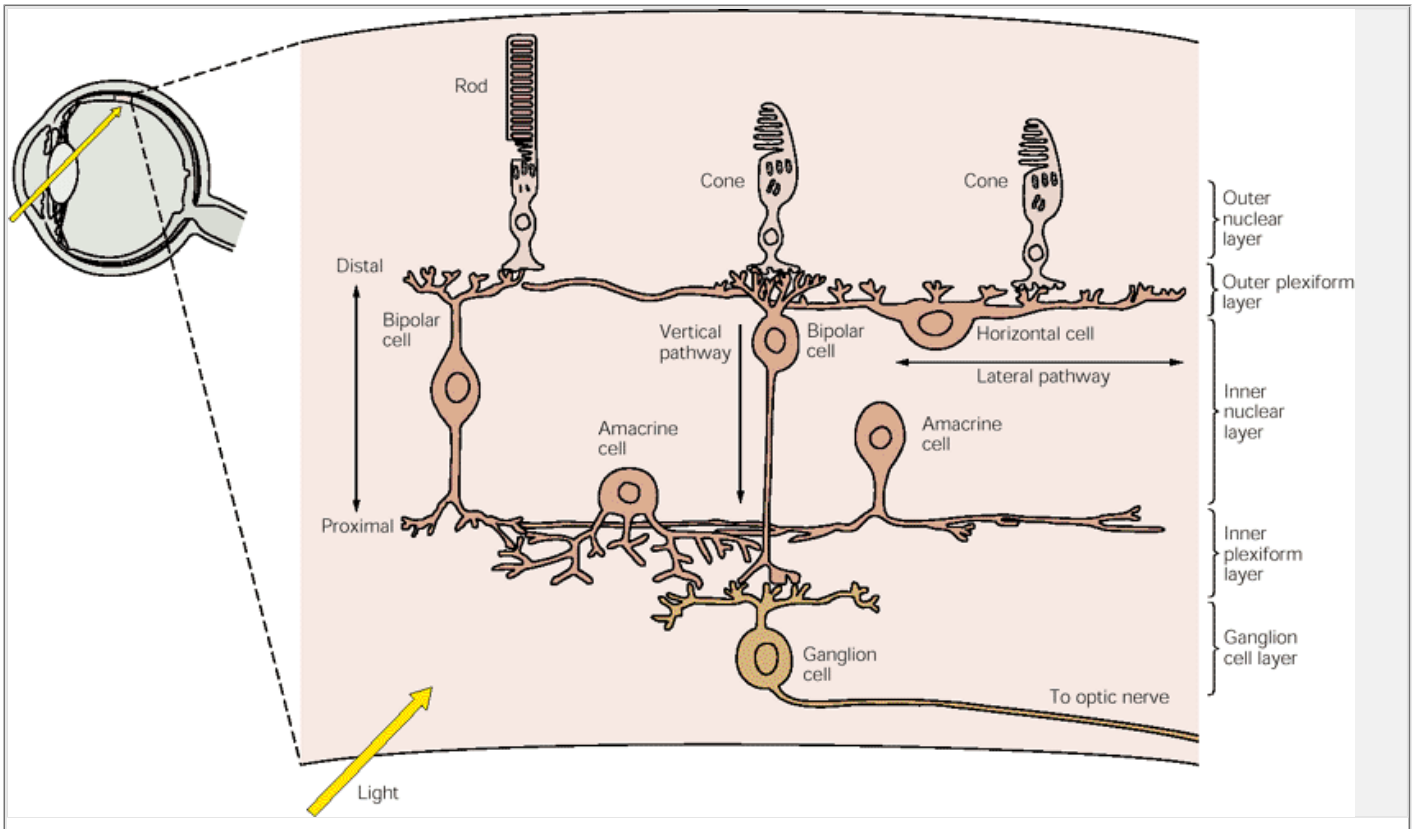

Figure 26-6 The retina has three major functional classes of neurons. Photoreceptors (rods and cones) lie in the outer nuclear layer, interneurons (bipolar, horizontal, and amacrine cells) in the inner nuclear layer, and ganglion cells in the ganglion cell layer. Photoreceptors, bipolar cells, and horizontal cells make synaptic connections with each other in the outer plexiform layer. The bipolar, amacrine, and ganglion cells make contact in the inner plexiform layer. Information flows vertically from photoreceptors to bipolar cells to ganglion cells, as well as laterally via horizontal cells in the outer plexiform layer and amacrine cells in the inner plexiform layer. (Adapted from Dowling 1979.)

Photoreceptors Slowly Adapt to Changes in Light Intensity

Whenever we step from a dark environment into bright daylight the light is blinding at first, but over a period of several seconds the eyes adapt. Likewise when we step into a dark movie theater our eyes must adapt before we are able to see our way around. Light or dark adaptation involves many changes in the retina and eye (such as a contraction or expansion of the pupil to reduce or increase the amount of light reaching the retina), but the two most important changes occur in cone photoreceptors. (We describe the events occurring during light adaptation; the opposite events occur during dark adaptation.)

The first change in cones during light adaptation is the slow recovery of the membrane potential. A very bright light closes all cGMP-gated channels, hyperpolarizing the cones to -70 mV, the equilibrium potential for K^+. In this state the cones cannot respond to further increases in light intensity. If this illumination is maintained, the cones slowly depolarize to a membrane potential between -70 and -40 mV (the resting potential), and are once again capable of hyperpolarizing in response to further increases in light intensity—the bright light is no longer blinding. The second change in cones during light adaption is the desensitization of the receptor. During prolonged illumination by a background light, the smallest increment in light intensity capable of evoking a detectable change in membrane potential increases in proportion to the background intensity, in accordance with Weber's law (Chapter 21). Both changes in the responses of cones—slow recovery of the membrane potential and desensitization—are due to a slow

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decrease in Ca^{2+} concentration, a decrease that affects the function of several proteins in the phototransduction pathway (Box 26-2).

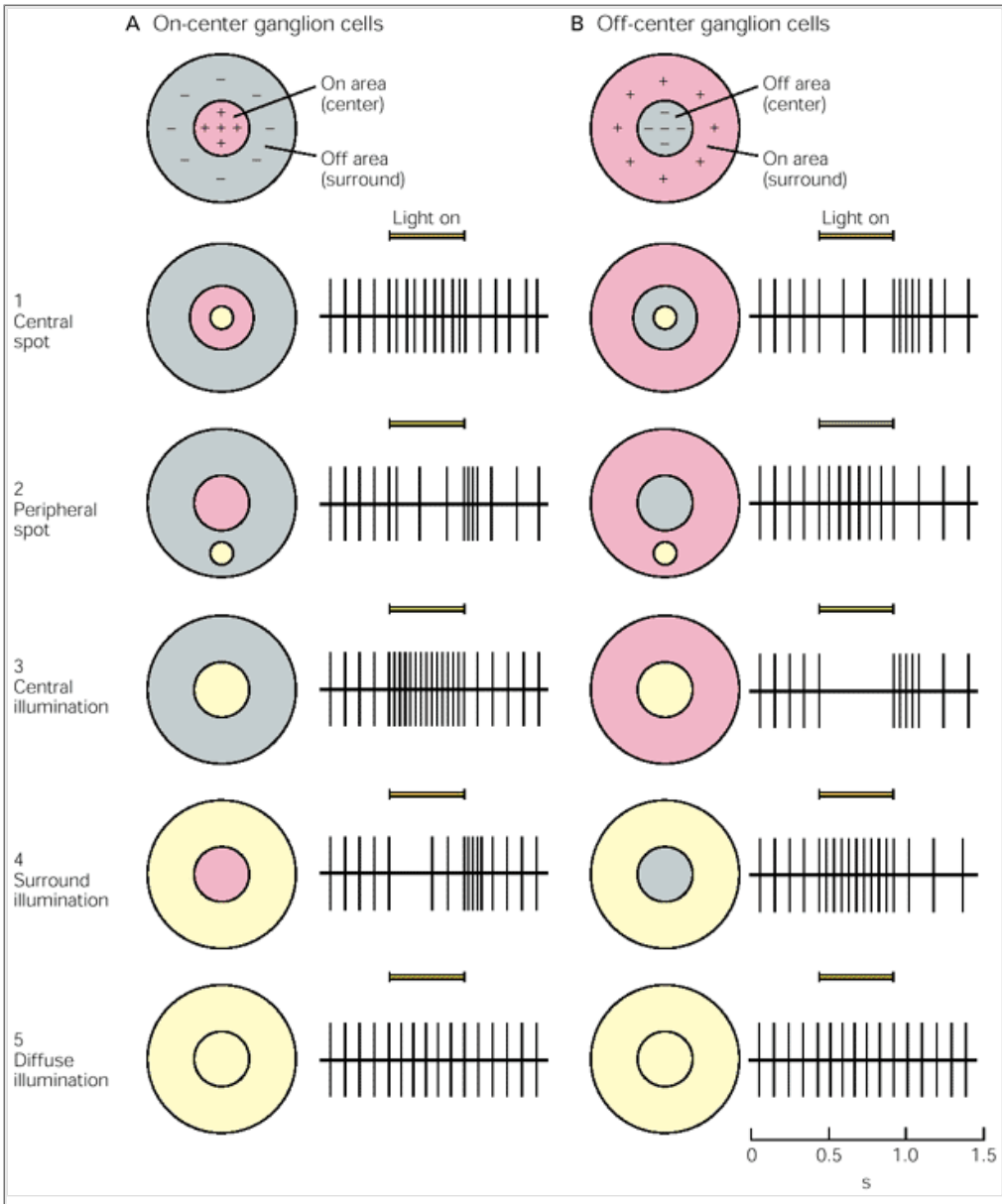

Figure 26-7 Retinal ganglion cells respond optimally to contrast in their receptive fields. Ganglion cells have circular receptive fields, with specialized center (**pink**) and surround (**gray**) regions. On-center cells are excited when stimulated by light in the center and inhibited when stimulated in the surround; off-center cells have the opposite responses. The figure shows the responses of both types of cells to five different light stimuli (the stimulated portion of the receptive field is shown in **yellow**). The pattern of action potentials fired by the ganglion cell in response to each stimulus is also shown in extracellular recordings. Duration of illumination is indicated by a bar above each record. (Adapted from Kuffler 1953.)

A. On-center cells respond best when the entire central part of the receptive field is stimulated (**3**). These cells also respond well, but less vigorously, when only a portion of the central field is stimulated by a spot of light (**1**). Illumination of the surround with a spot of light (**2**) or ring of light (**4**) reduces or suppresses the cell firing, which resumes more vigorously for a short period after the light is turned off. Diffuse illumination of the entire receptive field (**5**) elicits a relatively weak discharge because the center and surround oppose each other's effects.

B. The spontaneous firing of off-center cells is suppressed when the central area of the receptive field is illuminated (**1, 3**) but accelerates for a short period after the stimulus is turned off. Light shone onto the surround of the receptive field excites the cell (**2, 4**).

The Output of the Retina Is Conveyed by the Ganglion Cells

We now turn to the second topic of this chapter: How does the retina modify and process the signals evoked by light in photoreceptors before sending them to higher centers? The output of the retina is conveyed by the ganglion cells. Unlike photoreceptors, which respond to light with graded changes in membrane potential, ganglion cells transmit information as trains of action potentials. The axons of these cells form the optic nerve, which projects to the lateral geniculate nucleus of the thalamus and the superior colliculus as well as to the pretectum and other targets (see Chapter 27).

Between the photoreceptors and the ganglion cells are three classes of interneurons: bipolar, horizontal, and amacrine cells (Figure 26-6). These cells do not simply transmit signals from the photoreceptors to the ganglion cells; they also combine signals from several photoreceptors in such a way that the electrical responses evoked in ganglion cells depend critically on the precise spatial and temporal patterns of the light that stimulates the retina. In this section we examine the responses of ganglion cells to different patterns of light. In the final section of this chapter we discuss how the synaptic connections among the photoreceptors, interneurons, and ganglion cells are organized for carrying out the processing of the visual image.

The Receptive Field of the Ganglion Cell Has a Center and an Antagonistic Surround

Individual ganglion cells are never silent, even in the dark, but this spontaneous activity is modulated by the input from retinal interneurons. The inputs to a ganglion cell originate from neighboring photoreceptors in a circumscribed area of the retina, the *receptive field* for that cell. In effect, the ganglion cell's receptive field is the area of retina that the ganglion cell monitors. The receptive fields of ganglion cells have two important features.

First, when small spots of light on the retina are used to probe the properties of ganglion cell receptive fields, the receptive fields prove to be roughly circular.

Second, in most ganglion cells the receptive field is divided into two parts: a circular zone at the center, called the *receptive field center*, and the remaining area of the field, called the *surround.* Ganglion cells respond optimally to differential illumination of the receptive field center and surround.

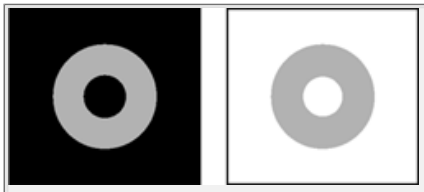

Figure 26-8 The appearance of an object depends principally on the contrast between the object and its background, not on the intensity of the light source. The two gray rings in the figures are identical in hue, but they appear to have different brightness because the different backgrounds produce different contrasts.

Two classes of ganglion cells can be distinguished by their responses to a small spot of light applied to the center of their receptive field (Figure 26-7). *On-center ganglion cells* are excited when light is directed to the center of their receptive field. Light applied to the surround inhibits the cell; the most effective inhibitory stimulus is a ring of light on the entire surround. *Off-center ganglion cells* are inhibited by light applied to the center of their receptive field. However, their firing rate increases for a short period of time after the light is removed; that is, they are excited when the spot of light on the center is turned *off.* Light excites an off-center ganglion cell when it is directed to the surround of the receptive field. In both types of cells the response evoked by a ring of light on the entire surround cancels the response evoked by light directed to the center almost completely. For this reason, diffuse illumination of the entire receptive field evokes only a small response in either type of cell (Figure 26-7). Not all ganglion cells have a center-surround receptive field organization. For example, a few ganglion cells respond to changes in the overall luminance of the visual field and are important in controlling pupillary reflexes (see Chapter 27).

On-center and off-center ganglion cells are present in roughly equal numbers, and every photoreceptor sends output to both types. Thus, ganglion cells provide two parallel pathways for the processing of visual information. In addition, their receptive fields vary in size across the retina. In the foveal region of the primate retina, where visual acuity is greatest, the receptive fields are small, with centers that are only a few minutes of arc (60 min = 1 degree). At the periphery of the retina, where acuity is low, the fields are larger, with centers of 3°-5° (1° on the retina is equal to about 0.25 mm).

Box 26-3 The Center-Surround Receptive Field of Bipolar Cells

Cone cells in the center of the receptive field of a bipolar cell synapse directly on the bipolar cell. Each cone cell synapses on both on-center and off-center bipolar cells. Cone cells release a single neurotransmitter, glutamate, which inhibits (hyperpolarizes) on-center bipolar cells and excites (depolarizes) off-center cells.

In the dark the cones are depolarized (around -40 mV), so that voltage-gated Ca^{2+} channels in their synaptic terminals are open, allowing Ca^{2+} to enter the terminals and trigger the release of glutamate. This constant release of glutamate in the dark maintains the on-center bipolar cells in a hyperpolarized state. When illuminated, however, the cones become hyperpolarized, and the voltage-gated Ca^{2+} channels close, reducing the Ca^{2+} influx and therefore the amount of glutamate the cells release; as a result, the on-center bipolar cells depolarize.

Conversely, cone cells maintain off-center bipolar cells in a depolarized state in the dark. When glutamate release is reduced by light the off-center bipolar cells hyperpolarize (Figure 26-9).

Glutamate produces different responses in the two classes of bipolar cells by gating different cation channels. In off- center bipolar cells glutamate opens a type of cation channel that carries an inward (depolarizing) Na^+ current into the cells. In on-center bipolar cells the mechanism by which glutamate hyperpolarizes the cell is unusual and may be different for rods and cones. At some synapses the transmitter appears to act by opening K^+-selective ion channels. At others it closes a cGMP-gated channel that carries an inward Na^+ current. In the absence of transmitter this type of channel is kept open by a high intracellular concentration of cGMP. Glutamate appears to cause the closure of these channels in precisely the same way that light causes the closure of cGMP-gated channels in photoreceptors—by activating a specific glutamate receptor that activates a G protein, which in turn activates cGMP phosphodiesterase and lowers the cytoplasmic concentration of cGMP.

Cones in the surround of a bipolar cell's receptive field synapse on horizontal cells. Horizontal cells do not make direct synaptic contact with the bipolar cells, however. Instead, they have synapses on cones in the center of the bipolar cell's receptive field. When the surround is illuminated, the horizontal cells depolarize the cones in the center, the opposite effect of light absorption by these cones (Figure 26-10). Whether this mechanism alone accounts for the antagonism between center and surround in bipolar cells is not yet known.

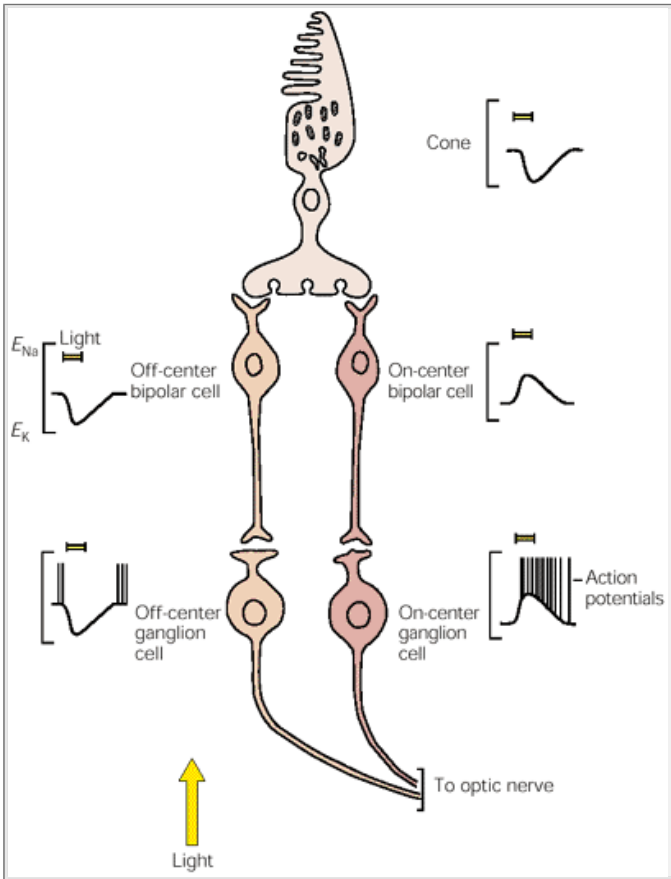

Figure 26-9 On-center and off-center bipolar cells establish parallel pathways for the signal of a single cone. Each bipolar cell makes an excitatory connection with a ganglion cell of the same type. When the cone is hyperpolarized by light, the on-center bipolar cell is excited and the off-center bipolar cell is inhibited. These opposite and simultaneous actions are initiated by the transmitter glutamate. In the dark the cone releases large amounts of transmitter because it is depolarized. Light, by hyperpolarizing the cone, causes a reduction in transmitter release. The same transmitter has different actions because the two types of bipolar cells have different postsynaptic receptors that gate different types of ion channels. The responses of the ganglion cells are largely determined by the inputs from the bipolar cells. The on-center bipolar cell, which becomes depolarized by illumination of its receptive field center, will depolarize the on-center ganglion cells; the off-center cell shows the opposite response.

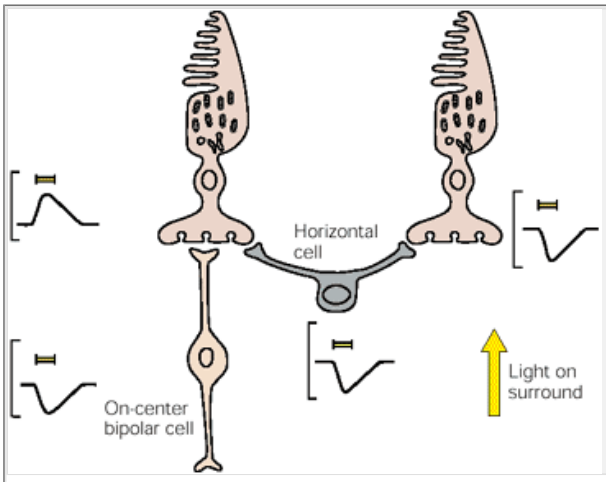

Figure 26-10 Signals from cones in the surround of a bipolar cell's receptive field are mediated by horizontal cells. Center-surround antagonism is illustrated here for an on-center bipolar cell. The horizontal cell receives input from a cone in the surround of the on-center bipolar cell and also has a connection with a postsynaptic cone in the center of the bipolar cell's receptive field. In the dark, horizontal cells release an inhibitory transmitter that maintains postsynaptic cones in the receptive field center in a slightly hyperpolarized state. Illumination of cones in the bipolar cell's surround hyperpolarizes those cones, which in turn hyperpolarize the postsynaptic horizontal cell. (In the dark the cones in the surround are maintained in a depolarized state and thus excite those horizontal cells.) This hyperpolarization of the horizontal cell reduces the amount of inhibitory transmitter released by the horizontal cell onto postsynaptic cones in the receptive field center, and as a result these cones become depolarized (the opposite effect of light absorption by these cones). This in turn allows the on-center bipolar cell to become hyperpolarized, the opposite effect of illumination in the receptive field center.

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Ganglion Cells Are Specialized for the Detection of Contrasts and Rapid Changes in the Visual Image

Why do ganglion cells have a center-surround receptive field organization, and why are there parallel on-center and off-center pathways?

As we have just seen, ganglion cells respond only weakly to uniform illumination because of the center-surround structure of their receptive fields. They respond best when the light intensities in the center and surround are quite different. They therefore report principally the contrasts in light, rather than its absolute intensity.

Most of the useful information in a visual scene is, however, contained in the pattern of contrasts. The absolute amount of light reflected by objects is relatively uninformative because it is largely determined by the intensity of the light source. Doubling the ambient light intensity will double the amount of light reflected by objects but does not alter contrasts between the objects. The center-surround organization of the receptive field of ganglion cells is therefore an adaptation for detecting useful information in the visual scene.

As we shall see in Chapters 28 and 29, perception of the brightness and color of objects relies mainly on information about contrast rather than the absolute amount of light and can therefore be influenced by the contrast between an object and its surroundings. For example, the same gray ring looks much lighter against a black background than against a white one (Figure 26-8).

Why does the detection of contrast start in the retina? In principle the information from photoreceptors could be sent directly to higher centers for this processing. However, signals transmitted through several relay steps to the cortex inevitably become slightly distorted. One way of minimizing the effect of transmission errors is for the retina itself to measure the difference and to transmit that information. This, in effect, is what the ganglion cell does. The firing rate of a ganglion cell provides a measure of the difference in the intensities of light illuminating the center and surround. In this way information about small differences in intensities is directly transmitted to higher centers.

Parallel on-center and off-center pathways also enhance the performance of the visual system because each type of ganglion cell responds best to either rapid increases or decreases in illumination. On-center ganglion cells have a low rate of firing under dim illumination; rapid increases in firing thus signal rapid *increases* in light intensity in their receptive

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field center. In contrast, off-center ganglion cells discharge at a low rate in the light; rapid increases in firing in these cells therefore signal rapid *decreases* in light intensity in their receptive field center. This specialization has been demonstrated by experiments in which the function of on-center ganglion cells in awake monkeys was blocked using a pharmacological agent, aminophosphorobutyrate (APB), which selectively antagonizes transmission from photoreceptors to on-center bipolar cells. Detection of rapid increases, but not decreases, in illumination was severely impaired in these animals.

Specialized Ganglion Cells Process Different Aspects of the Visual Image

In addition to contrast and rapid changes in illumination, the visual system also analyzes several other aspects of the visual image, such as color, form, and movement. As we discussed briefly in the preceding chapter and will discuss again in more detail in subsequent chapters, these features are processed in the visual cortex in parallel pathways. This parallel processing begins in the retina with parallel networks of ganglion cells.

Each region of the retina has several functionally distinct subsets of ganglion cells that convey, in parallel pathways, signals from the same photoreceptors. Most ganglion cells in the primate retina fall into two functional classes, M (for *magni*, or large) and P (for *parvi*, or small). Each class includes both on-center and off-center cells.

M cells have large receptive fields (reflected in their large dendritic arbors) and respond relatively transiently to sustained illumination. They respond optimally to large objects and are able to follow rapid changes in the stimulus. As we shall see in Chapter 27, they appear therefore to be concerned with the analysis of the gross features of a stimulus and its movement. The smaller P cells, which are more numerous, have small receptive fields, respond selectively to specific wavelengths, and are therefore involved in the perception of form and color. P cells are thought to be responsible for the analysis of fine detail in the visual image, although some M cells may also be involved in this function.

The primate retina also contains ganglion cells that do not fall into the P or M classes. The functions of these cells are largely unknown, although one type is known to report on the overall ambient light intensity.

Signals From Photoreceptors Are Relayed to Ganglion Cells Through a Network of Interneurons

How do the relatively simple signals provided by photo- receptors give rise to the complex responses of the ganglion cells? Although the circuitry connecting these cells appears complicated, on close examination it is relatively simple. Each type of retinal interneuron (horizontal, bipolar, and amacrine) plays a specific role in shaping photoreceptor signals transmitted through the retina. The role of retinal interneurons is best illustrated by focusing on the bipolar cells, as they represent the most direct pathway between receptors and ganglion cells. As a further simplification, we restrict our attention to the circuitry for cones, the circuitry that mediates vision in normal daylight.

Bipolar Cells Convey Cone Signals to Ganglion Cells Through Direct or Indirect Pathways

Visual information is transferred from cones to ganglion cells along two types of pathways in the retina. Cones in the *center* of a ganglion cell's receptive field make direct synaptic contact with bipolar cells that in turn directly contact the ganglion cells; these connections are known as direct or vertical pathways. Signals from cones in the *surround* of the ganglion cell's receptive field are also conveyed to the ganglion cell through bipolar cells but only indirectly by means of horizontal and some amacrine cells; these indirect connections are called lateral pathways. Horizontal cells, which have large dendritic trees, transfer information from distant cones to bipolar cells. (Horizontal cells are also electrically coupled to each other by gap junctions and thus are able to respond to inputs from even more distant cones that contact neighboring horizontal cells.) Curiously, the horizontal cells do not appear to convey information to the bipolar cells directly, but rather by feeding back onto cones in the center of the bipolar cell's receptive field (see Figure 26-10). Some types of amacrine cells transfer information from distant bipolar cells to ganglion cells (see Figure 26-6).

Most synaptic contacts in the retina are grouped in two plexiform (network-like) layers. The outer plexiform layer contains the processes of receptor, bipolar, and horizontal cells, while the inner plexiform layer contains the processes of bipolar, amacrine, and ganglion cells (see Figure 26-6). Thus the bipolar cells bridge the two

plexiform layers by having processes in both.

We have seen that photoreceptors respond to light with graded changes in membrane potential rather than by firing action potentials. The same is true of horizontal and bipolar cells. These cells lack voltage-gated Na^+ channels capable of generating action potentials; instead they transmit signals passively (see Chapter 8). Because these cells are small and have short processes, the signals spread to their synaptic terminals without

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significant reduction. (Passive signal spread in cells with short processes occurs in many different parts of the brain.) In contrast, the axons of ganglion cells project considerable distances to their targets in the brain and transfer information in the form of trains of action potentials. Many types of amacrine cells also fire action potentials.

The Receptive Fields of Bipolar Cells Have a Center-Surround Organization

Like ganglion cells, the bipolar cells have receptive fields with an antagonistic center-surround organization, and the cells are either on-center or off-center. When cones in the center of the receptive field are active, on-center bipolar cells depolarize, while off- center bipolar cells hyperpolarize. When cones in the surround are active, the response of the bipolar cell is opposite that evoked by illumination of the center (Box 26-3).

Different Classes of Bipolar Cells Have Excitatory Connections With Corresponding Classes of Ganglion Cells

The receptive field properties of a ganglion cell largely reflect those of the bipolar cells connected to it, because each type of bipolar cell (on-center or off-center) makes excitatory synaptic connections with the corresponding type of ganglion cell. When on-center bipolar cells are depolarized by light, they depolarize on-center ganglion cells (see Figure 26-9 in Box 26-3).

Although the responses of ganglion cells are largely determined by these direct inputs from bipolar cells, they are also shaped by amacrine cells, a group of interneurons with processes in the inner plexiform layer (see Figure 26-6). There are over 20 morphologically distinct types of amacrine cells that use at least 8 different neurotransmitters. Some amacrine cells function like horizontal cells: They mediate antagonistic inputs from bipolar cells in the ganglion cell's surround. Others have been implicated in shaping the complex receptive field properties of specific classes of ganglion cells, such as the M-type ganglion cells that process orientation information (see Chapter 28).

An Overall View

The absorption of light and its transduction into electrical signals is carried out by the photoreceptors. Visual information is then transferred from the receptors to the ganglion cells via the bipolar cells. The ganglion cells in turn project to the brain; their axons form the optic nerve. Two types of interneurons (horizontal cells and amacrine cells) provide lateral inputs to bipolar cells and ganglion cells.

The cyclic nucleotide cGMP plays a central role in phototransduction. Absorption of light by the photosensitive visual pigments in the photoreceptor triggers a second-messenger cascade. The activated pigment molecules stimulate a G protein, transducin, which in turn activates a phosphodiesterase that catalyzes the hydrolysis of cGMP. Light absorption therefore causes a reduction in the cytoplasmic concentration of cGMP. In darkness cGMP opens specialized ion channels that carry a depolarizing current into the cell, so that the reduction in the level of cGMP makes the photoreceptor hyperpolarize.

Signals from photoreceptors to ganglion cells are conveyed in parallel on-center and off-center pathways. An on-center ganglion cell is excited when light stimulates the center of its receptive field and inhibited when light stimulates its surround. An off-center ganglion cell exhibits the opposite responses; it is inhibited when light stimulates its center and excited by light on its surround. These transformations of the visual signal assist higher centers in detecting weak contrasts and rapid changes in light intensity. In addition, ganglion cells are specialized for processing different aspects of the visual image such as movement, fine spatial detail, or color.

The pattern of synaptic connections in the retina explains how the various responses of ganglion cells arise. Interposed between the photoreceptors and ganglion cells are interneurons, the bipolar cells. Bipolar cells, like ganglion cells, fall into two classes, on-center and off-center. The transmitter released by cones excites bipolar cells of one class and inhibits the others. Each cone makes contact with both types of bipolar cells. Cones in the receptive-field center of a ganglion cell synapse onto bipolar cells that make direct contact with the ganglion cell. Inputs from cones in the receptive-field surround are relayed along lateral pathways by horizontal and amacrine cells.

As we shall see in subsequent chapters, the segregation of information into parallel processing pathways and the shaping of response properties by inhibitory lateral connections are pervasive organizational principles in the visual system.

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