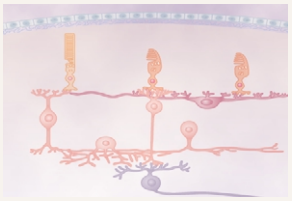
The Eye: II. Receptor and Neural Function of the Retina



The retina is the light-sensitive portion of the eye that contains (1) the *cones,* which are responsible for color vision, and (2) the *rods,* which are mainly responsible for black and white vision and vision in the dark. When either rods or cones are excited, signals are transmitted first through successive layers of neurons in the retina itself and, finally, into optic nerve fibers and the cerebral cortex. The purpose of this chapter is to explain the mechanisms by which the rods and cones detect light and color and convert the visual image into optic nerve signals.

Anatomy and Function of the Structural Elements of the Retina

Layers of the Retina. Figure 50–1 shows the functional components of the retina which are arranged in layers from the outside to the inside as follows: (1) pigmented layer, (2) layer of rods and cones projecting to the pigment, (3) outer nuclear layer containing the cell bodies of the rods and cones, (4) outer plexiform layer, (5) inner nuclear layer, (6) inner plexiform layer, (7) ganglionic layer, (8) layer of optic nerve fibers, and (9) inner limiting membrane.

After light passes through the lens system of the eye and then through the vitreous humor, it *enters the retina from the inside* (see Figure 50–1); that is, it passes first through the ganglion cells and then through the plexiform and nuclear layers before it finally reaches the layer of rods and cones located all the way on the outer edge of the retina. This distance is a thickness of several hundred micrometers; visual acuity is decreased by this passage through such nonhomogeneous tissue. However, in the central foveal region of the retina, as discussed subsequently, the inside layers are pulled aside to decrease this loss of acuity.

Foveal Region of the Retina and Its Importance in Acute Vision. The *fovea* is a minute area in the center of the retina, shown in Figure 50–2, occupying a total area a little more than 1 square millimeter; it is especially capable of acute and detailed vision. The *central fovea,* only 0.3 millimeter in diameter, is composed almost entirely of cones; these cones have a special structure that aids their detection of detail in the visual image. That is, the foveal cones have especially long and slender bodies, in contradistinction to the much fatter cones located more peripherally in the retina. Also, in the foveal region, the blood vessels, ganglion cells, inner nuclear layer of cells, and plexiform layers are all displaced to one side rather than resting directly on top of the cones. This allows light to pass unimpeded to the cones.

Rods and Cones. Figure 50–3 is a diagrammatic representation of the essential components of a photoreceptor (either a rod or a cone). As shown in Figure 50–4, the outer segment of the cone is conical in shape. In general, the rods are narrower and longer than the cones, but this is not always the case. In the peripheral portions of the retina, the rods are 2 to 5 micrometers in diameter, whereas the cones are 5 to 8 micrometers in diameter; in the central part of the retina, in the fovea, there are rods, and the cones are slender and have a diameter of only 1.5 micrometers.

To the right in Figure 50–3 are labeled the major functional segments of either a rod or a cone: (1) the *outer segment,* (2) the *inner segment,* (3) the *nucleus,* and (4) the *synaptic body.* The light-sensitive photochemical is found in the outer segment. In the case of the rods, this is *rhodopsin;* in the cones, it is one of three "color"

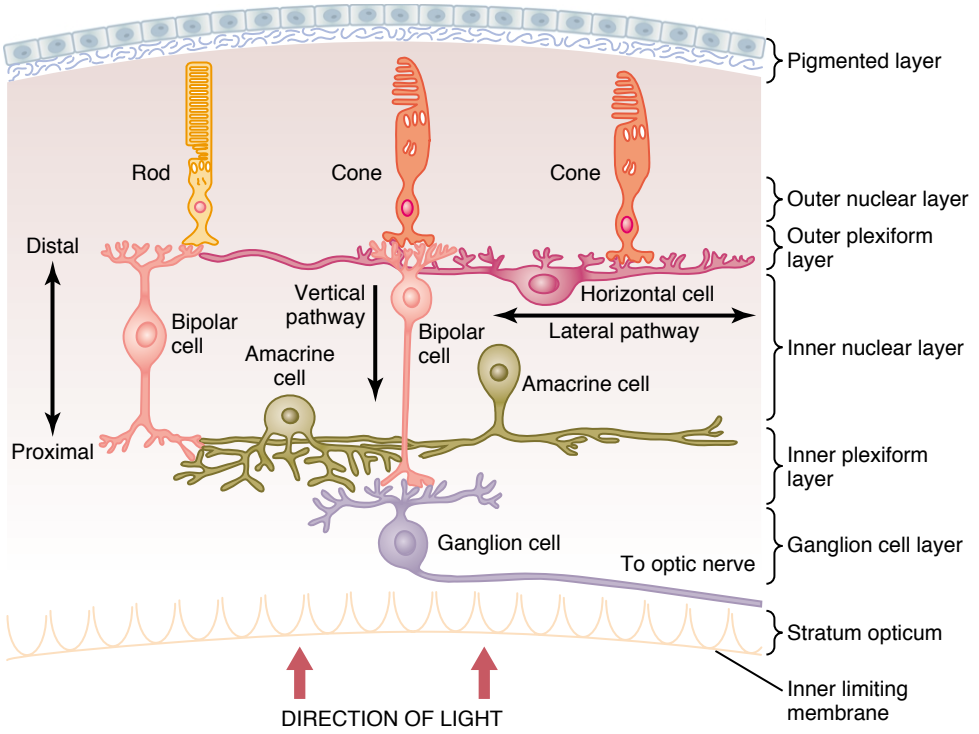


Figure 50–1

Layers of retina.

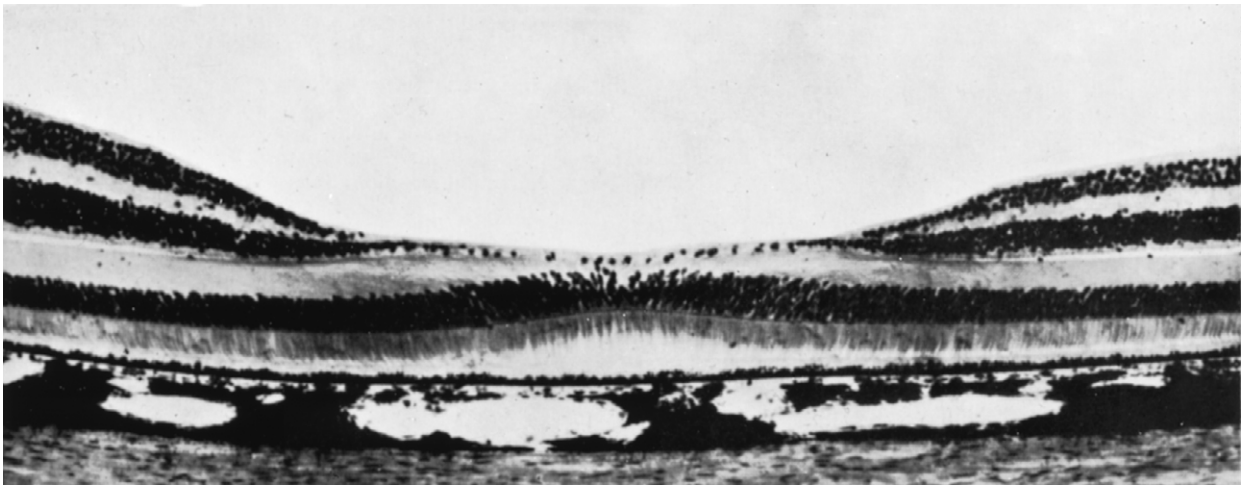


Figure 50–2

Photomicrograph of the macula and of the fovea in its center. Note that the inner layers of the retina are pulled to the side to decrease interference with light transmission. (From Fawcett DW: Bloom and Fawcett: A Textbook of Histology, 11th ed. Philadelphia: WB Saunders, 1986; courtesy H. Mizoguchi.)

photochemicals, usually called simply *color pigments*, that function almost exactly the same as rhodopsin except for differences in spectral sensitivity.

Note in the *outer segments* of the rods and cones in Figures 50–3 and 50–4 the large numbers of *discs*. Each of the discs is actually an infolded shelf of cell membrane. There are as many as 1000 discs in each rod or cone.

Both rhodopsin and the color pigments are conjugated proteins. They are incorporated into the membranes of the discs in the form of transmembrane proteins. The concentrations of these photosensitive pigments in the discs are so great that the pigments themselves constitute about 40 per cent of the entire mass of the outer segment.

The *inner segment* of the rod or cone contains the usual cytoplasm with cytoplasmic organelles. Particularly important are the mitochondria; as explained later, these mitochondria play the important role of providing energy for function of the photoreceptors.

The *synaptic body* is the portion of the rod or cone that connects with subsequent neuronal cells, the

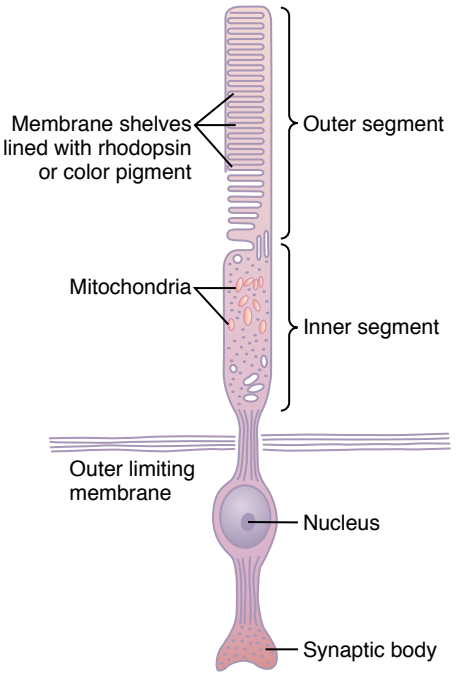


Figure 50–3

Schematic drawing of the functional parts of the rods and cones.

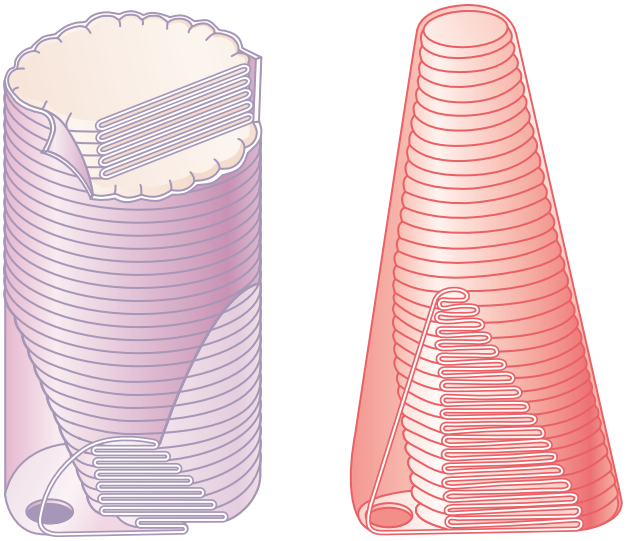


Figure 50–4

Membranous structures of the outer segments of a rod *(left)* and a cone *(right).* (Courtesy Dr. Richard Young.)

horizontal and *bipolar cells*, that represent the next stages in the vision chain.

Pigment Layer of the Retina. The black pigment *melanin* in the pigment layer prevents light reflection throughout the globe of the eyeball; this is extremely important for clear vision. This pigment performs the same function in the eye as the black coloring inside the bellows of a camera. Without it, light rays would be reflected in all directions within the eyeball and would cause diffuse lighting of the retina rather than the normal contrast between dark and light spots required for formation of precise images.

The importance of melanin in the pigment layer is well illustrated by its absence in *albinos,* people who are hereditarily lacking in melanin pigment in all parts of their bodies. When an albino enters a bright room, light that impinges on the retina is reflected in all directions inside the eyeball by the unpigmented surfaces of the retina and by the underlying sclera, so that a single discrete spot of light that would normally excite only a few rods or cones is reflected everywhere and excites many receptors. Therefore, the visual acuity of albinos, even with the best optical correction, is seldom better than 20/100 to 20/200 rather than the normal 20/20 values.

The pigment layer also stores large quantities of *vitamin A.* This vitamin A is exchanged back and forth through the cell membranes of the outer segments of the rods and cones, which themselves are embedded in the pigment. We show later that vitamin A is an important precursor of the photosensitive chemicals of the rods and cones.

Blood Supply of the Retina—The Central Retinal Artery and the Choroid. The nutrient blood supply for the internal layers of the retina is derived from the central retinal artery, which enters the eyeball through the center of the optic nerve and then divides *to supply the entire inside retinal surface.* Thus, the inner layers of the retina have their own blood supply independent of the other structures of the eye.

However, the outermost layer of the retina is adherent to the *choroid,* which is also a highly vascular tissue lying between the retina and the sclera. The outer layers of the retina, especially the outer segments of the rods and cones, depend mainly on diffusion from the choroid blood vessels for their nutrition, especially for their oxygen.

Retinal Detachment. The neural retina occasionally *detaches from the pigment epithelium*. In some instances, the cause of such detachment is injury to the eyeball that allows fluid or blood to collect between the neural retina and the pigment epithelium. Detachment is occasionally caused by contracture of fine collagenous fibrils in the vitreous humor, which pull areas of the retina toward the interior of the globe.

Partly because of diffusion across the detachment gap and partly because of the independent blood supply to the neural retina through the retinal artery, the detached retina can resist degeneration for days and can become functional again if it is surgically replaced in its normal relation with the pigment epithelium. If it is not replaced soon, however, the retina will be destroyed and will be unable to function even after surgical repair.

Photochemistry of Vision

Both rods and cones contain chemicals that decompose on exposure to light and, in the process, excite the nerve fibers leading from the eye. The light-sensitive chemical in the *rods* is called *rhodopsin;* the light-sensitive chemicals in the *cones,* called *cone pigments* or *color pigments,* have compositions only slightly different from that of rhodopsin.

In this section, we discuss principally the photochemistry of rhodopsin, but the same principles can be applied to the cone pigments.

Rhodopsin-Retinal Visual Cycle, and Excitation of the Rods

Rhodopsin and Its Decomposition by Light Energy. The outer segment of the rod that projects into the pigment layer of the retina has a concentration of about 40 per cent of the light-sensitive pigment called *rhodopsin,* or *visual purple.* This substance is a combination of the protein *scotopsin* and the carotenoid pigment *retinal* (also called "retinene"). Furthermore, the retinal is a particular type called 11-*cis* retinal. This *cis* form of retinal is important because only this form can bind with scotopsin to synthesize rhodopsin.

When light energy is absorbed by rhodopsin, the rhodopsin begins to decompose within a very small fraction of a second, as shown at the top of Figure 50–5. The cause of this is photoactivation of electrons in the retinal portion of the rhodopsin, which leads to instantaneous change of the *cis* form of retinal into an all-*trans* form that still has the same chemical structure as the *cis* form but has a different physical structure—a straight molecule rather than an angulated molecule. Because the three-dimensional orientation of the reactive sites of the all-*trans* retinal no longer fits with the orientation of the reactive sites on the protein *scotopsin,* the all-*trans* retinal begins to pull away from the scotopsin. The immediate product is *bathorhodopsin,* which is a partially split combination of the all-*trans* retinal and scotopsin. Bathorhodopsin is extremely unstable and decays in nanoseconds to *lumirhodopsin.* This then decays in microseconds to *metarhodopsin I,* then in about a millisecond to *metarhodopsin II,* and finally, much more slowly (in seconds), into the completely split products *scotopsin* and all-*trans* retinal.

It is the metarhodopsin II, also called *activated rhodopsin,* that excites electrical changes in the rods, and the rods then transmit the visual image into the central nervous system in the form of optic nerve action potential, as we discuss later.

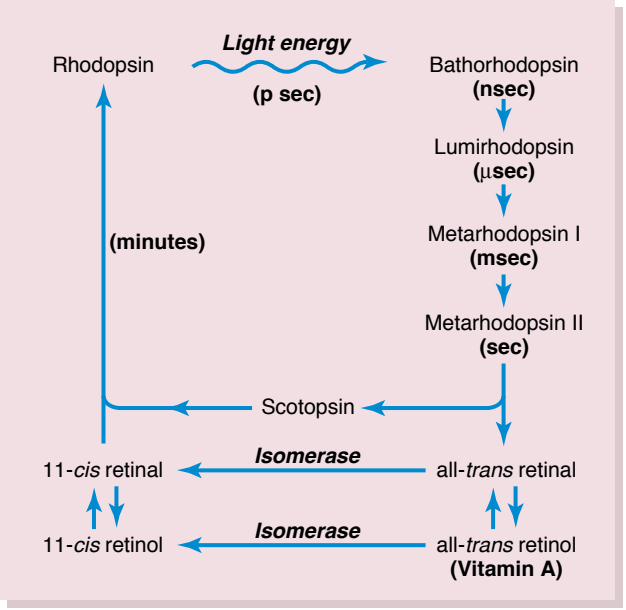


Figure 50–5

Rhodopsin-retinal visual cycle in the rod, showing decomposition of rhodopsin during exposure to light and subsequent slow reformation of rhodopsin by the chemical processes.

Re-formation of Rhodopsin. The first stage in re-formation of rhodopsin, as shown in Figure 50–5, is to reconvert the all-*trans* retinal into 11-*cis* retinal. This process requires metabolic energy and is catalyzed by the enzyme *retinal isomerase.* Once the 11-*cis* retinal is formed, it automatically recombines with the scotopsin to re-form rhodopsin, which then remains stable until its decomposition is again triggered by absorption of light energy.

Role of Vitamin A for Formation of Rhodopsin. Note in Figure 50–5 that there is a second chemical route by which all-*trans* retinal can be converted into 11-*cis* retinal. This is by conversion of the all-*trans* retinal first into all-*trans* retinol, which is one form of vitamin A. Then the all-*trans* retinol is converted into 11-*cis* retinol under the influence of the enzyme isomerase. Finally, the 11-*cis* retinol is converted into 11-*cis* retinal, which combines with scotopsin to form new rhodopsin.

Vitamin A is present both in the cytoplasm of the rods and in the pigment layer of the retina. Therefore, vitamin A is normally always available to form new retinal when needed. Conversely, when there is excess retinal in the retina, it is converted back into vitamin A, thus reducing the amount of light-sensitive pigment in the retina. We shall see later that this interconversion between retinal and vitamin A is especially important in long-term adaptation of the retina to different light intensities.

Night Blindness. Night blindness occurs in any person with severe vitamin A deficiency. The simple reason for this is that without vitamin A, the amounts of retinal and rhodopsin that can be formed are severely depressed. This condition is called *night blindness* because the amount of light available at night is too little to permit adequate vision in vitamin A–deficient persons.

For night blindness to occur, a person usually must remain on a vitamin A–deficient diet for months, because large quantities of vitamin A are normally stored in the liver and can be made available to the eyes. Once night blindness develops, it can sometimes be reversed in less than 1 hour by intravenous injection of vitamin A.

Excitation of the Rod When Rhodopsin Is Activated by Light

The Rod Receptor Potential Is Hyperpolarizing, Not Depolarizing. When the rod is exposed to light, the resulting

receptor potential is different from the receptor potentials in almost all other sensory receptors. That is, excitation of the rod causes *increased negativity* of the intrarod membrane potential, which is a state of *hyperpolarization,* meaning that there is more negativity than normal *inside* the rod membrane. This is exactly opposite to the decreased negativity (the process of "depolarization") that occurs in almost all other sensory receptors.

But how does activation of rhodopsin cause hyperpolarization? The answer is that *when rhodopsin decomposes, it decreases the rod membrane conductance for sodium ions in the outer segment of the rod.* This causes hyperpolarization of the entire rod membrane in the following way.

Figure 50–6 shows movement of sodium ions in a complete electrical circuit through the inner and outer segments of the rod. The inner segment continually pumps sodium from inside the rod to the outside, thereby creating a negative potential on the inside of the entire cell. However, the outer segment of the rod, where the photoreceptor discs are located, is entirely different; here, the rod membrane, in the *dark* state, is very leaky to sodium ions. Therefore, positively charged sodium ions continually leak back to the inside of the rod and thereby neutralize much of the negativity on the inside of the entire cell. Thus, *under normal dark conditions, when the rod is not excited, there is reduced electronegativity* inside the membrane of the rod, measuring about –40 millivolts rather than the usual –70 to –80 millivolts found in most sensory receptors.

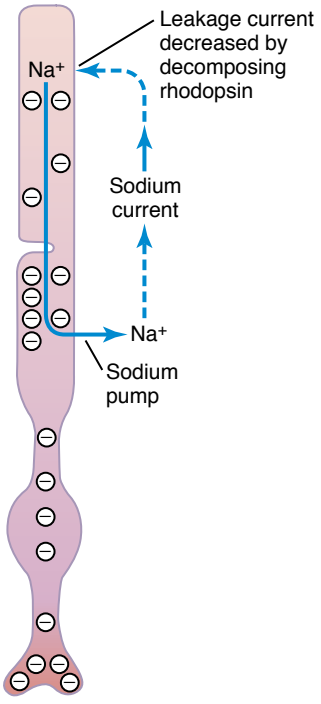


Figure 50–6

Theoretical basis for generation of a "hyperpolarization receptor potential" caused by rhodopsin decomposition, which *decreases the flow of positively charged sodium ions* into the outer segment of the rod.

Then, when the rhodopsin in the outer segment of the rod is exposed to light, the rhodopsin begins to decompose, and this *decreases* the outer segment membrane conductance of sodium to the interior of the rod, even though sodium ions continue to be pumped outward through the membrane of the inner segment. Thus, more sodium ions now leave the rod than leak back in. Because they are positive ions, their loss from inside the rod creates increased negativity inside the membrane, and the greater the amount of light energy striking the rod, the greater the electronegativity becomes—that is, the greater is the degree of *hyperpolarization.* At maximum light intensity, the membrane potential approaches –70 to –80 millivolts, which is near the equilibrium potential for potassium ions across the membrane.

Duration of the Receptor Potential, and Logarithmic Relation of the Receptor Potential to Light Intensity. When a sudden pulse of light strikes the retina, the transient hyperpolarization that occurs in the rods—that is, the *receptor potential* that occurs—reaches a peak in about 0.3 second and lasts for more than a second. In cones, the change occurs four times as fast as in the rods. A visual image impinged on the rods of the retina for only one millionth of a second can sometimes cause the sensation of seeing the image for longer than a second.

Another characteristic of the receptor potential is that it is approximately proportional to the logarithm of the light intensity. This is exceedingly important, because it allows the eye to discriminate light intensities through a range many thousand times as great as would be possible otherwise.

Mechanism by Which Rhodopsin Decomposition *Decreases* Membrane Sodium Conductance—The Excitation "Cascade." Under optimal conditions, a single photon of light, the smallest possible quantal unit of light energy, can cause a measurable receptor potential in a rod of about 1 millivolt. Only 30 photons of light will cause half saturation of the rod. How can such a small amount of light cause such great excitation? The answer is that the photoreceptors have an extremely sensitive chemical cascade that amplifies the stimulatory effects about a millionfold, as follows:

1. The *photon activates an electron* in the 11-*cis* retinal portion of the rhodopsin; this leads to the formation of *metarhodopsin II,* which is the active form of rhodopsin, as already discussed and shown in Figure 50–5.
2. The *activated rhodopsin* functions as an enzyme to activate many molecules of *transducin,* a protein present in an inactive form in the membranes of the discs and cell membrane of the rod.
3. The *activated transducin* activates many more molecules of *phosphodiesterase.*

4. *Activated phosphodiesterase* is another enzyme; it immediately hydrolyzes many molecules of *cyclic guanosine monophosphate (cGMP),* thus destroying it. Before being destroyed, the cGMP had been bound with the sodium channel protein of the rod's outer membrane in a way that "splints" it in the open state. But in light, when phosphodiesterase hydrolyzes the cGMP, this removes the splinting and allows the sodium channels to close. Several hundred channels close for each originally activated molecule of rhodopsin. Because the sodium flux through each of these channels has been extremely rapid, flow of more than a million sodium ions is blocked by the channel closure before the channel opens again. This diminution of sodium ion flow is what excites the rod, as already discussed.
5. Within about a second, another enzyme, *rhodopsin kinase,* which is always present in the rod, inactivates the activated rhodopsin (the metarhodopsin II), and the entire cascade reverses back to the normal state with open sodium channels.

Thus, the rods have developed an important chemical cascade that amplifies the effect of a single photon of light to cause movement of millions of sodium ions. This explains the extreme sensitivity of the rods under dark conditions.

The cones are about 30 to 300 times less sensitive than the rods, but even this allows color vision at any intensity of light greater than extremely dim twilight.

Photochemistry of Color Vision by the Cones

It was pointed out at the outset of this discussion that the photochemicals in the cones have almost exactly the same chemical composition as that of rhodopsin in the rods. The only difference is that the protein portions, or the opsins—called *photopsins* in the cones—are slightly different from the scotopsin of the rods. The *retinal* portion of all the visual pigments is exactly the same in the cones as in the rods. The color-sensitive pigments of the cones, therefore, are combinations of retinal and photopsins.

In the discussion of color vision later in the chapter, it will become evident that only one of three types of color pigments is present in each of the different cones, thus making the cones selectively sensitive to different colors: blue, green, or red. These color pigments are called, respectively, *blue-sensitive pigment, green-sensitive pigment,* and *red-sensitive pigment.* The absorption characteristics of the pigments in the three types of cones show peak absorbencies at light wavelengths of 445, 535, and 570 nanometers, respectively. These are also the wavelengths for peak light sensitivity for each type of cone, which begins to explain how the retina differentiates the colors. The approximate absorption curves for these three pigments are shown in Figure 50–7. Also shown is the absorption curve for the rhodopsin of the rods, with a peak at 505 nanometers.

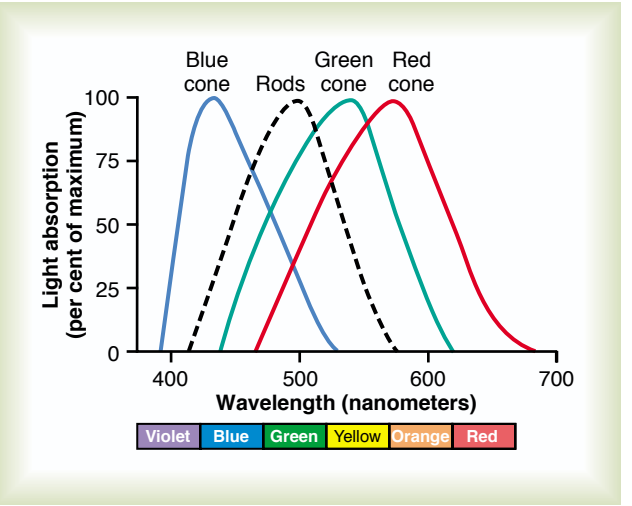


Figure 50–7

Light absorption by the pigment of the rods and by the pigments of the three color-receptive cones of the human retina. (Drawn from curves recorded by Marks WB, Dobelle WH, MacNichol EF Jr: Visual pigments of single primate cones. Science 143:1181, 1964, and by Brown PK, Wald G: Visual pigments in single rods and cones of the human retina: direct measurements reveal mechanisms of human night and color vision. Science 144:45, 1964. ® 1964 by the American Association for the Advancement of Science.)

Automatic Regulation of Retinal Sensitivity—Light and Dark Adaptation

Light and Dark Adaptation. If a person has been in bright light for hours, large portions of the photochemicals in both the rods and the cones will have been reduced to retinal and opsins. Furthermore, much of the retinal of both the rods and the cones will have been converted into vitamin A. Because of these two effects, the concentrations of the photosensitive chemicals remaining in the rods and cones are considerably reduced, and the sensitivity of the eye to light is correspondingly reduced. This is called *light adaptation.*

Conversely, if a person remains in darkness for a long time, the retinal and opsins in the rods and cones are converted back into the light-sensitive pigments. Furthermore, vitamin A is converted back into retinal to give still more light-sensitive pigments, the final limit being determined by the amount of opsins in the rods and cones to combine with the retinal. This is called *dark adaptation.*

Figure 50–8 shows the course of dark adaptation when a person is exposed to total darkness after having been exposed to bright light for several hours. Note that the sensitivity of the retina is very low on first entering the darkness, but within 1 minute, the sensitivity has already increased 10-fold—that is, the retina can respond to light of one tenth the previously required intensity. At the end of 20 minutes, the sensitivity has increased about 6000-fold, and at the end of 40 minutes, about 25,000-fold.

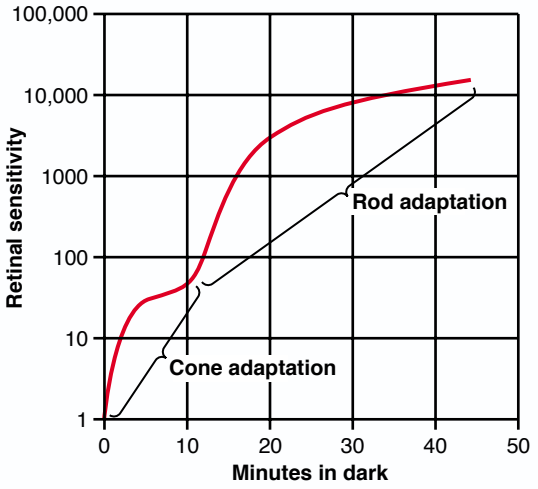


Figure 50–8

Dark adaptation, demonstrating the relation of cone adaptation to rod adaptation.

The resulting curve of Figure 50–8 is called the *dark adaptation curve.* Note, however, the inflection in the curve. The early portion of the curve is caused by adaptation of the cones, because all the chemical events of vision, including adaptation, occur about four times as rapidly in cones as in rods. However, the cones do not achieve anywhere near the same degree of sensitivity change in darkness as the rods do. Therefore, despite rapid adaptation, the cones cease adapting after only a few minutes, while the slowly adapting rods continue to adapt for many minutes and even hours, their sensitivity increasing tremendously. In addition, still more sensitivity of the rods is caused by neuronal signal convergence of 100 or more rods onto a single ganglion cell in the retina; these rods summate to increase their sensitivity, as discussed later in the chapter.

Other Mechanisms of Light and Dark Adaptation. In addition to adaptation caused by changes in concentrations of rhodopsin or color photochemicals, the eye has two other mechanisms for light and dark adaptation. The first of these is a *change in pupillary size,* as discussed in Chapter 49. This can cause adaptation of approximately 30-fold within a fraction of a second, because of changes in the amount of light allowed through the pupillary opening.

The other mechanism is *neural adaptation,* involving the neurons in the successive stages of the visual chain in the retina itself and in the brain. That is, when light intensity first increases, the signals transmitted by the bipolar cells, horizontal cells, amacrine cells, and ganglion cells are all intense. However, most of these signals decrease rapidly at different stages of transmission in the neural circuit. Although the degree of adaptation is only a fewfold rather than the many thousandfold that occurs during adaptation of the photochemical system, neural adaptation occurs in a fraction of a second, in contrast to the many minutes to hours required for full adaptation by the photochemicals.

Value of Light and Dark Adaptation in Vision. Between the limits of maximal dark adaptation and maximal light adaptation, the eye can change its sensitivity to light as much as 500,000 to 1 million times, the sensitivity automatically adjusting to changes in illumination.

Because registration of images by the retina requires detection of both dark and light spots in the image, it is essential that the sensitivity of the retina always be adjusted so that the receptors respond to the lighter areas but not to the darker areas. An example of maladjustment of retinal adaptation occurs when a person leaves a movie theater and enters the bright sunlight. Then, even the dark spots in the images seem exceedingly bright, and as a consequence, the entire visual image is bleached, having little contrast among its different parts. This is poor vision, and it remains poor until the retina has adapted sufficiently so that the darker areas of the image no longer stimulate the receptors excessively.

Conversely, when a person first enters darkness, the sensitivity of the retina is usually so slight that even the light spots in the image cannot excite the retina. After dark adaptation, the light spots begin to register. As an example of the extremes of light and dark adaptation, the intensity of sunlight is about 10 billion times that of starlight, yet the eye can function both in bright sunlight after light adaptation and in starlight after dark adaptation.

Color Vision

From the preceding sections, we have learned that different cones are sensitive to different colors of light. This section is a discussion of the mechanisms by which the retina detects the different gradations of color in the visual spectrum.

Tricolor Mechanism of Color Detection

All theories of color vision are based on the well-known observation that the human eye can detect almost all gradations of colors when only red, green, and blue monochromatic lights are appropriately mixed in different combinations.

Spectral Sensitivities of the Three Types of Cones. On the basis of color vision tests, the spectral sensitivities of the three types of cones in humans have proved to be essentially the same as the light absorption curves for the three types of pigment found in the cones. These curves are shown in Figure 50–7 and slightly differently in Figure 50–9. They can explain most of the phenomena of color vision.

Interpretation of Color in the Nervous System. Referring to Figure 50–9, one can see that an orange

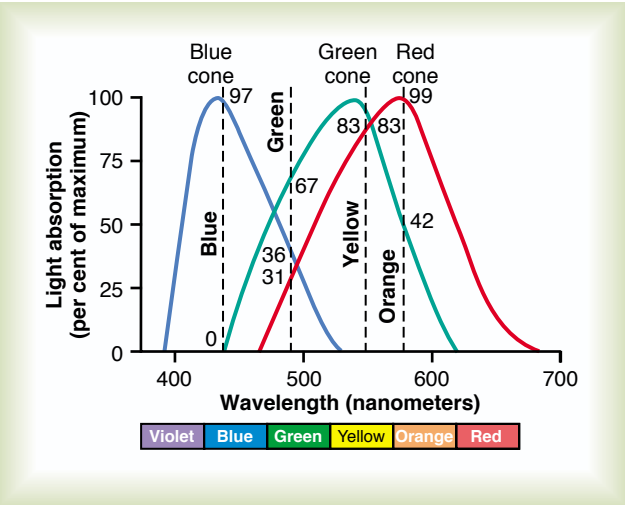


Figure 50–9

Demonstration of the degree of stimulation of the different color-sensitive cones by monochromatic lights of four colors: blue, green, yellow, and orange.

monochromatic light with a wavelength of 580 nanometers stimulates the red cones to a stimulus value of about 99 (99 per cent of the peak stimulation at optimum wavelength); it stimulates the green cones to a stimulus value of about 42, but the blue cones not at all. Thus, the ratios of stimulation of the three types of cones in this instance are 99:42:0. The nervous system interprets this set of ratios as the sensation of orange. Conversely, a monochromatic blue light with a wavelength of 450 nanometers stimulates the red cones to a stimulus value of 0, the green cones to a value of 0, and the blue cones to a value of 97. This set of ratios—0:0:97—is interpreted by the nervous system as blue. Likewise, ratios of 83:83:0 are interpreted as yellow, and 31:67:36 as green.

Perception of White Light. About equal stimulation of all the red, green, and blue cones gives one the sensation of seeing white. Yet there is no single wavelength of light corresponding to white; instead, white is a combination of all the wavelengths of the spectrum. Furthermore, the perception of white can be achieved by stimulating the retina with a proper combination of only three chosen colors that stimulate the respective types of cones about equally.

Color Blindness

Red-Green Color Blindness. When a single group of color-receptive cones is missing from the eye, the person is unable to distinguish some colors from others. For instance, one can see in Figure 50–9 that green, yellow, orange, and red colors, which are the colors between the wavelengths of 525 and 675 nanometers, are normally distinguished from one another by the red and green cones. If either of these two cones is missing, the person cannot use this mechanism for distinguishing these four colors; the person is especially unable to distinguish red from green and is therefore said to have *red-green color blindness.*

A person with loss of red cones is called a *protanope;* the overall visual spectrum is noticeably shortened at the long wavelength end because of a lack of the red cones. A color-blind person who lacks green cones is called a *deuteranope;* this person has a perfectly normal visual spectral width because red cones are available to detect the long wavelength red color.

Red-green color blindness is a genetic disorder that occurs almost exclusively in males. That is, genes in the female X chromosome code for the respective cones. Yet color blindness almost never occurs in females because at least one of the two X chromosomes almost always has a normal gene for each type of cone. Because the male has only one X chromosome, a missing gene can lead to color blindness.

Because the X chromosome in the male is always inherited from the mother, never from the father, color blindness is passed from mother to son, and the mother is said to be a *color blindness carrier;* this is true in about 8 per cent of all women.

Blue Weakness. Only rarely are blue cones missing, although sometimes they are underrepresented, which is a genetically inherited state giving rise to the phenomenon called blue weakness.

Color Test Charts. A rapid method for determining color blindness is based on the use of spot charts such as those shown in Figure 50–10. These charts are arranged with a confusion of spots of several different colors. In the top chart, the person with normal color vision reads "74," whereas the red-green color-blind person reads "21." In the bottom chart, the person with normal color vision reads "42," whereas the red-blind person reads "2," and the green-blind person reads "4."

If one studies these charts while at the same time observing the spectral sensitivity curves of the different cones depicted in Figure 50–9, it can be readily understood how excessive emphasis can be placed on spots of certain colors by color-blind people.

Neural Function of the Retina

Neural Circuitry of the Retina

Figure 50–1 shows the tremendous complexity of neural organization in the retina. To simplify this, Figure 50–11 presents the essentials of the retina's neural connections, showing at the left the circuit in the peripheral retina and at the right the circuit in the foveal retina. The different neuronal cell types are as follows:

1. The photoreceptors themselves—the *rods* and *cones*—which transmit signals to the outer plexiform layer, where they synapse with bipolar cells and horizontal cells
2. The *horizontal cells,* which transmit signals horizontally in the outer plexiform layer from the rods and cones to bipolar cells
3. The *bipolar cells,* which transmit signals vertically from the rods, cones, and horizontal cells to the inner plexiform layer, where they synapse with ganglion cells and amacrine cells

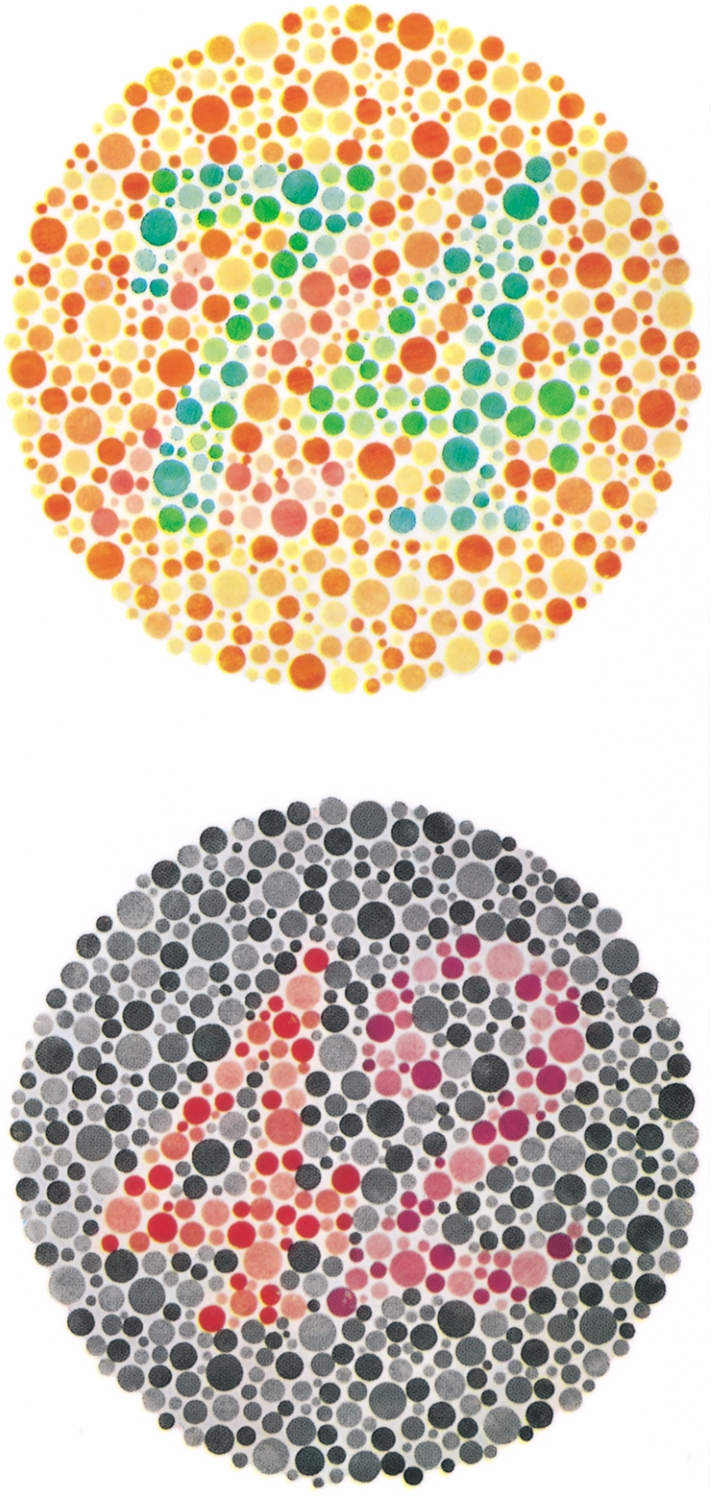


Figure 50–10

Two Ishihara charts. *Upper:* In this chart, the normal person reads "74," but the red-green color-blind person reads "21." *Lower:* In this chart, the red-blind person (protanope) reads "2," but the green-blind person (deuteranope) reads "4." The normal person reads "42." (Reproduced from Ishihara's Tests for Colour Blindness. Tokyo: Kanehara & Co., but tests for color blindness cannot be conducted with this material. For accurate testing, the original plates should be used.)

4. The *amacrine cells,* which transmit signals in two directions, either directly from bipolar cells to ganglion cells or horizontally within the inner plexiform layer from axons of the bipolar cells to dendrites of the ganglion cells or to other amacrine cells
5. The *ganglion cells,* which transmit output signals from the retina through the optic nerve into the brain

A sixth type of neuronal cell in the retina, not very prominent and not shown in the figure, is the *interplexiform* cell. This cell transmits signals in the retrograde direction from the inner plexiform layer to the outer plexiform layer. These signals are inhibitory and are believed to control lateral spread of visual signals by the horizontal cells in the outer plexiform layer. Their role may be to help control the degree of contrast in the visual image.

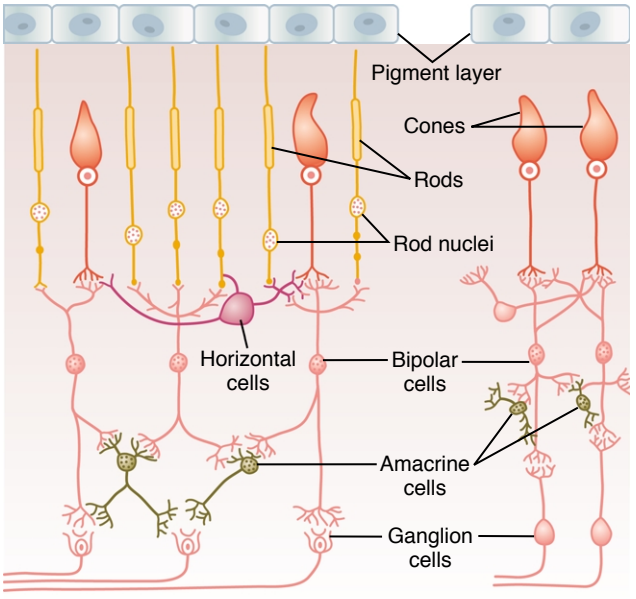


Figure 50–11

Neural organization of the retina: peripheral area to the left, foveal area to the right.

The Visual Pathway from the Cones to the Ganglion Cells Functions Differently from the Rod Pathway. As is true for many of our other sensory systems, the retina has both an old type of vision based on rod vision and a new type of vision based on cone vision. The neurons and nerve fibers that conduct the visual signals for cone vision are considerably larger than those that conduct the visual signals for rod vision, and the signals are conducted to the brain two to five times as rapidly. Also, the circuitry for the two systems is slightly different, as follows.

To the right in Figure 50–11 is the visual pathway from the *foveal portion of the retina,* representing the new, fast cone system. This shows three neurons in the direct pathway: (1) cones, (2) bipolar cells, and (3) ganglion cells. In addition, horizontal cells transmit inhibitory signals laterally in the outer plexiform layer, and amacrine cells transmit signals laterally in the inner plexiform layer.

To the left in Figure 50–11 are the neural connections for the peripheral retina, where both rods and cones are present. Three bipolar cells are shown; the middle of these connects only to rods, representing the type of visual system present in many lower animals. The output from the bipolar cell passes only to amacrine cells, which relay the signals to the ganglion cells. Thus, for pure rod vision, there are four neurons in the direct visual pathway: (1) rods, (2) bipolar cells, (3) amacrine cells, and (4) ganglion cells. Also, horizontal and amacrine cells provide lateral connectivity.

The other two bipolar cells shown in the peripheral retinal circuitry of Figure 50–11 connect with both rods and cones; the outputs of these bipolar cells pass both directly to ganglion cells and by way of amacrine cells.

Neurotransmitters Released by Retinal Neurons. Not all the neurotransmitter chemical substances used for synaptic transmission in the retina have been entirely delineated. However, both the rods and the cones release *glutamate* at their synapses with the bipolar cells. Histological and pharmacological studies have shown there to be many types of amacrine cells secreting at least eight types of transmitter substances, including *gamma-aminobutyric acid, glycine, dopamine, acetylcholine,* and *indolamine,* all of which normally function as inhibitory transmitters. The transmitters of the bipolar, horizontal, and interplexiform cells are unclear, but at least some of the horizontal cells release inhibitory transmitters.

Transmission of Most Signals Occurs in the Retinal Neurons by Electrotonic Conduction, Not by Action Potentials. The only retinal neurons that always transmit visual signals by means of action potentials are the ganglion cells, and they send their signals all the way to the brain through the optic nerve. Occasionally, action potentials have also been recorded in amacrine cells, although the importance of these action potentials is questionable. Otherwise, all the retinal neurons conduct their visual signals by *electrotonic conduction,* which can be explained as follows.

Electrotonic conduction means direct flow of electric current, not action potentials, in the neuronal cytoplasm and nerve axons from the point of excitation all the way to the output synapses. Even in the rods and cones, conduction from their outer segments, where the visual signals are generated, to the synaptic bodies is by electrotonic conduction. That is, when hyperpolarization occurs in response to light in the outer segment of a rod or a cone, almost the same degree of hyperpolarization is conducted by direct electric current flow in the cytoplasm all the way to the synaptic body, and no action potential is required. Then, when the transmitter from a rod or cone stimulates a bipolar cell or horizontal cell, once again the signal is transmitted from the input to the output by direct electric current flow, not by action potentials.

The importance of electrotonic conduction is that it allows *graded conduction* of signal strength. Thus, for the rods and cones, the strength of the hyperpolarizing output signal is directly related to the intensity of illumination; the signal is not all or none, as would be the case for each action potential.

Lateral Inhibition to Enhance Visual Contrast—Function of the Horizontal Cells

The horizontal cells, shown in Figure 50–11, connect laterally between the synaptic bodies of the rods and cones, as well as connecting with the dendrites of the bipolar cells. The outputs of the horizontal cells *are always inhibitory.* Therefore, this lateral connection provides the same phenomenon of lateral inhibition that is important in all other sensory systems—that is, helping to ensure transmission of visual patterns with proper visual contrast. This phenomenon is demonstrated in Figure 50–12, which shows a minute spot of light focused on the retina. The visual pathway from

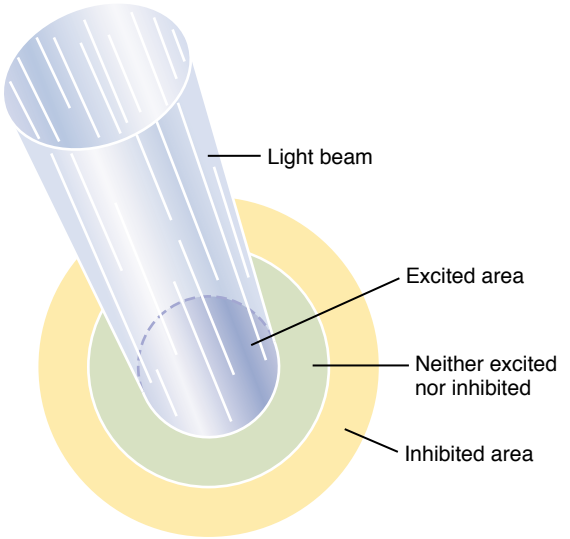


Figure 50–12

Excitation and inhibition of a retinal area caused by a small beam of light, demonstrating the principle of lateral inhibition.

the centralmost area where the light strikes is excited, whereas an area to the side is inhibited. In other words, instead of the excitatory signal spreading widely in the retina because of spreading dendritic and axonal trees in the plexiform layers, transmission through the horizontal cells puts a stop to this by providing lateral inhibition in the surrounding areas. This is essential to allow high visual accuracy in transmitting contrast borders in the visual image.

Some of the amacrine cells probably provide additional lateral inhibition and further enhancement of visual contrast in the inner plexiform layer of the retina as well.

Excitation of Some Bipolar Cells and Inhibition of Others—The Depolarizing and Hyperpolarizing Bipolar Cells

Two types of bipolar cells provide opposing excitatory and inhibitory signals in the visual pathway: (1) the *depolarizing bipolar cell* and (2) the *hyperpolarizing bipolar cell.* That is, some bipolar cells depolarize when the rods and cones are excited, and others hyperpolarize.

There are two possible explanations for this difference. One explanation is that the two bipolar cells are of entirely different types—one responding by depolarizing in response to the glutamate neurotransmitter released by the rods and cones, and the other responding by hyperpolarizing. The other possibility is that one of the bipolar cells receives direct excitation from the rods and cones, whereas the other receives its signal indirectly through a horizontal cell. Because the horizontal cell is an inhibitory cell, this would reverse the polarity of the electrical response.

Regardless of the mechanism for the two types of bipolar responses, the importance of this phenomenon is that it allows half the bipolar cells to transmit positive signals and the other half to transmit negative signals. We shall see later that both positive and negative signals are used in transmitting visual information to the brain.

Another important aspect of this reciprocal relation between depolarizing and hyperpolarizing bipolar cells is that it provides a second mechanism for lateral inhibition, in addition to the horizontal cell mechanism. Because depolarizing and hyperpolarizing bipolar cells lie immediately against each other, this provides a mechanism for separating contrast borders in the visual image, even when the border lies exactly between two adjacent photoreceptors. In contrast, the horizontal cell mechanism for lateral inhibition operates over a much greater distance.

Amacrine Cells and Their Functions

About 30 types of amacrine cells have been identified by morphological or histochemical means. The functions of about half a dozen types of amacrine cells have been characterized, and all of them are different. One type of amacrine cell is part of the direct pathway for rod vision—that is, from rod to bipolar cells to amacrine cells to ganglion cells.

Another type of amacrine cell responds strongly at the onset of a continuing visual signal, but the response dies rapidly.

Other amacrine cells respond strongly at the offset of visual signals, but again, the response dies quickly.

Still other amacrine cells respond when a light is turned either on or off, signaling simply a change in illumination, irrespective of direction.

Still another type of amacrine cell responds to movement of a spot across the retina in a specific direction; therefore, these amacrine cells are said to be *directional sensitive.*

In a sense, then, many or most amacrine cells are interneurons that help analyze visual signals before they ever leave the retina.

Ganglion Cells and Optic Nerve Fibers

Each retina contains about 100 million rods and 3 million cones; yet the number of ganglion cells is only about 1.6 million. Thus, an average of 60 rods and 2 cones converge on each ganglion cell and the optic nerve fiber leading from the ganglion cell to the brain.

However, major differences exist between the peripheral retina and the central retina. As one approaches the fovea, fewer rods and cones converge on each optic fiber, and the rods and cones also become more slender. These effects progressively increase the acuity of vision in the central retina. In the center, in the *central fovea,* there are only slender cones—about 35,000 of them—and no rods. Also, the number of optic nerve fibers leading from this part of the retina is almost exactly equal to the number of cones, as shown to the right in Figure 50–11. This explains the high degree of visual acuity in the central retina in comparison with the much poorer acuity peripherally.

Another difference between the peripheral and central portions of the retina is the much greater sensitivity of the peripheral retina to weak light. This results partly from the fact that rods are 30 to 300 times more sensitive to light than cones are, but it is further magnified by the fact that as many as 200 rods converge on a single optic nerve fiber in the more peripheral portions of the retina, so that signals from the rods summate to give even more intense stimulation of the peripheral ganglion cells and their optic nerve fibers.

Three Types of Retinal Ganglion Cells and Their Respective Fields

There are three distinct types of ganglion cells, designated W, X, and Y cells. Each of these serves a different function.

Transmission of Rod Vision by the W Cells. The W cells, constituting about 40 per cent of all the ganglion cells, are small, having a diameter less than 10 micrometers, and they transmit signals in their optic nerve fibers at the slow velocity of only 8 m/sec. These ganglion cells receive most of their excitation from rods, transmitted by way of small bipolar cells and amacrine cells. They have broad fields in the peripheral retina because the dendrites of the ganglion cells spread widely in the inner plexiform layer, receiving signals from broad areas.

On the basis of histology as well as physiologic experiments, the W cells seem to be especially sensitive for detecting directional movement in the field of vision, and they are probably important for much of our crude rod vision under dark conditions.

Transmission of the Visual Image and Color by the X Cells. The most numerous of the ganglion cells are the X cells, representing 55 per cent of the total. They are of medium diameter, between 10 and 15 micrometers, and transmit signals in their optic nerve fibers at about 14 m/sec.

The X cells have small fields because their dendrites do not spread widely in the retina. Because of this, their signals represent discrete retinal locations. Therefore, it is mainly through the X cells that the fine details of the visual image are transmitted. Also, because every X cell receives input from at least one cone, X cell transmission is probably responsible for all color vision.

Function of the Y Cells to Transmit Instantaneous Changes in the Visual Image. The Y cells are the largest of all, up to 35 micrometers in diameter, and they transmit their signals to the brain at 50 m/sec or faster. They are the least numerous of all the ganglion cells, representing only 5 per cent of the total. Also, they have broad dendritic fields, so that signals are picked up by these cells from widespread retinal areas.

The Y ganglion cells respond, like many of the amacrine cells, to rapid changes in the visual image—either rapid movement or rapid change in light intensity—sending bursts of signals for only small fractions of a second. These ganglion cells presumably apprise the central nervous system almost instantaneously when a new visual event occurs anywhere in the visual field, but without specifying with great accuracy the location of the event, other than to give appropriate clues that make the eyes move toward the exciting vision.

Excitation of the Ganglion Cells

Spontaneous, Continuous Action Potentials in the Ganglion Cells. It is from the ganglion cells that the long fibers of the optic nerve lead into the brain. Because of the distance involved, the electrotonic method of conduction employed in the rods, cones, and bipolar cells within the retina is no longer appropriate; therefore, ganglion cells transmit their signals by means of repetitive action potentials instead. Furthermore, even when unstimulated, they still transmit continuous impulses at rates varying between 5 and 40 per second. The visual signals, in turn, are superimposed onto this background ganglion cell firing.

Transmission of Changes in Light Intensity—The On-Off Response. As noted previously, many ganglion cells are specifically excited by *changes* in light intensity. This is demonstrated by the records of nerve impulses in Figure 50–13. The upper panel shows rapid impulses for a fraction of a second when a light is first turned on, but decreasing rapidity in the next fraction of a second. The lower tracing is from a ganglion cell located lateral to the spot of light; this cell is markedly inhibited when the light is turned on because of lateral inhibition. Then, when the light is turned off, opposite effects occur. Thus, these records are called "on-off" and "off-on" responses. The opposite directions of these responses to light are caused, respectively, by the depolarizing and hyperpolarizing bipolar cells, and the transient nature of the responses is probably at least partly generated by the amacrine cells, many of which have similar transient responses themselves.

This capability of the eyes to detect *change* in light intensity is strongly developed in both the peripheral

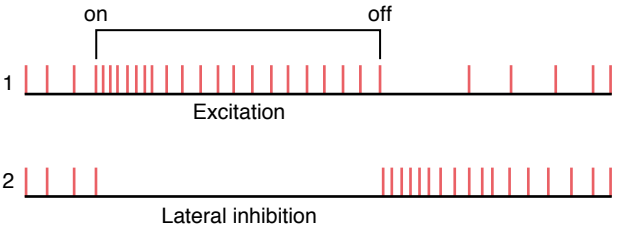


Figure 50–13

Responses of a ganglion cell to light in (1) an area excited by a spot of light and (2) an area adjacent to the excited spot; the ganglion cell in this area is inhibited by the mechanism of *lateral inhibition.* (Modified from Granit R: Receptors and Sensory Perception: A Discussion of Aims, Means, and Results of Electrophysiological Research into the Process of Reception. New Haven, Conn: Yale University Press, 1955.)

retina and the central retina. For instance, a minute gnat flying across the field of vision is instantaneously detected. Conversely, the same gnat sitting quietly remains below the threshold of visual detection.

Transmission of Signals Depicting Contrasts in the Visual Scene—The Role of Lateral Inhibition

Many ganglion cells respond mainly to contrast borders in the scene. Because this seems to be the major means by which the pattern of a scene is transmitted to the brain, let us explain how this process occurs.

When flat light is applied to the entire retina—that is, when all the photoreceptors are stimulated equally by the incident light—the contrast type of ganglion cell is neither stimulated nor inhibited. The reason for this is that signals transmitted *directly* from the photoreceptors through depolarizing bipolar cells are excitatory, while the signals transmitted *laterally* through hyperpolarizing bipolar cells as well as through horizontal cells are mainly inhibitory. Thus, the direct excitatory signal through one pathway is likely to be neutralized by inhibitory signals through lateral pathways. One circuit for this is demonstrated in Figure 50–14, which shows at the top three photoreceptors. The central receptor excites a depolarizing bipolar cell. The two receptors on each side are connected to the same bipolar cell through inhibitory horizontal cells that neutralize the direct excitatory signal if all three receptors are stimulated simultaneously by light.

Now, let us examine what happens when a contrast border occurs in the visual scene. Referring again to Figure 50–14, assume that the central photoreceptor is stimulated by a bright spot of light while one of the two lateral receptors is in the dark. The bright spot of light excites the direct pathway through the bipolar cell. The fact that one of the lateral photoreceptors is in the dark causes one of the horizontal cells to remain unstimulated. Therefore, this cell does not inhibit the bipolar cell, and this allows extra excitation of the bipolar cell. Thus, where visual contrasts occur, the signals through the direct and lateral pathways accentuate one another.

In summary, the mechanism of lateral inhibition functions in the eye in the same way that it functions in most other sensory systems—to provide contrast detection and enhancement.

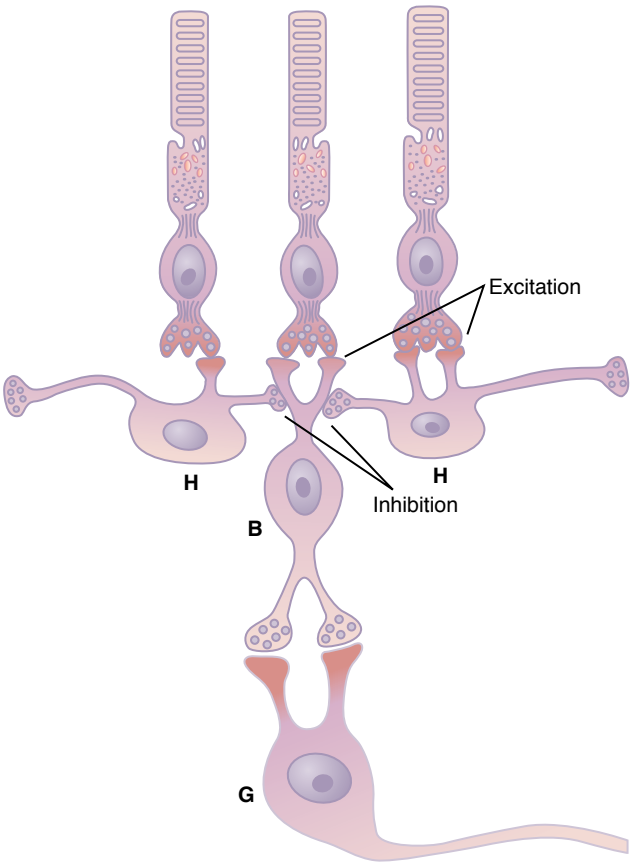


Figure 50–14

Typical arrangement of rods, horizontal cells (H), a bipolar cell (B), and a ganglion cell (G) in the retina, showing excitation at the synapses between the rods and the bipolar cell and horizontal cells, but inhibition from the horizontal cells to the bipolar cell.

Transmission of Color Signals by the Ganglion Cells

A single ganglion cell may be stimulated by several cones or by only a few. When all three types of cones—the red, blue, and green types—stimulate the same ganglion cell, the signal transmitted through the ganglion cell is the same for any color of the spectrum. Therefore, the signal from the ganglion cell plays no role in the detection of different colors. Instead, it is a "white" signal.

Conversely, some of the ganglion cells are excited by only one color type of cone but inhibited by a second type. For instance, this frequently occurs for the red and green cones, with red causing excitation and green causing inhibition, or vice versa.

The same type of reciprocal effect occurs between blue cones on the one hand and a combination of red and green cones (both of which are excited by yellow) on the other hand, giving a reciprocal excitation-inhibition relation between the blue and yellow colors.

The mechanism of this opposing effect of colors is the following: One color type of cone excites the ganglion cell by the direct excitatory route through a depolarizing bipolar cell, whereas the other color type inhibits the ganglion cell by the indirect inhibitory route through a hyperpolarizing bipolar cell.

The importance of these color-contrast mechanisms is that they represent a means by which the retina itself begins to differentiate colors. Thus, each color-contrast type of ganglion cell is excited by one color but inhibited by the "opponent" color. Therefore, color analysis begins in the retina and is not entirely a function of the brain.

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