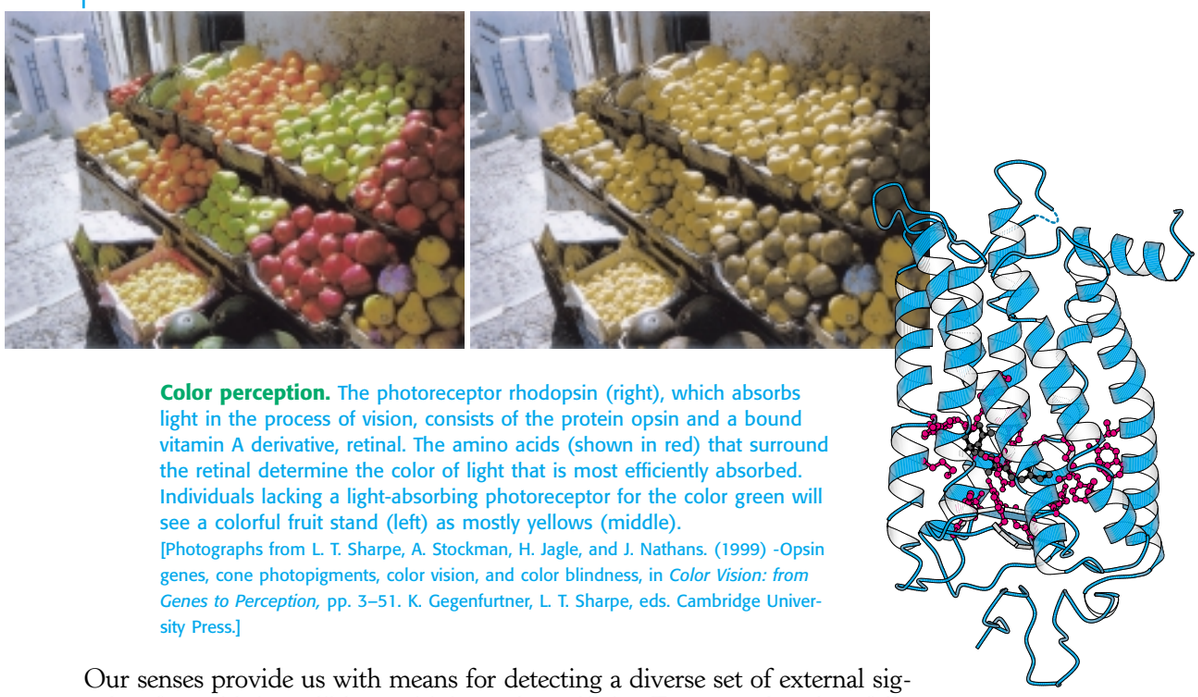
CHAPTER 32

Sensory Systems



Color perception. The photoreceptor rhodopsin (right), which absorbs light in the process of vision, consists of the protein opsin and a bound vitamin A derivative, retinal. The amino acids (shown in red) that surround the retinal determine the color of light that is most efficiently absorbed. Individuals lacking a light-absorbing photoreceptor for the color green will see a colorful fruit stand (left) as mostly yellows (middle).
[Photographs from L. T. Sharpe, A. Stockman, H. Jagle, and J. Nathans. (1999) -Opsin genes, cone photopigments, color vision, and color blindness, in *Color Vision: from Genes to Perception,* pp. 3–51. K. Gegenfurtner, L. T. Sharpe, eds. Cambridge University Press.]

Our senses provide us with means for detecting a diverse set of external signals, often with incredible sensitivity and specificity. For example, when fully adapted to a darkened room, our eyes allow us to sense very low levels of light, down *to a limit of less than ten photons*. With more light, we are able to distinguish millions of colors. Through our senses of smell and taste, we are able to detect thousands of chemicals in our environment and sort them into categories: pleasant or unpleasant? healthful or toxic? Finally, we can perceive mechanical stimuli in the air and around us through our senses of hearing and touch.

How do our sensory systems work? How are the initial stimuli detected? How are these initial biochemical events transformed into perceptions and experiences? We have previously encountered systems that sense and respond to chemical signals—namely, receptors that bind to growth factors and hormones. Our knowledge of these receptors and their associated signal-transduction pathways provides us with concepts and tools for unraveling some of the workings of sensory systems. For example, 7TM receptors (seven-transmembrane receptors, Section 15.x.x) play key roles in olfaction, taste, and vision. Ion channels that are sensitive to mechanical stress are essential for hearing and touch.

In this chapter, we shall focus on the five major sensory systems found in human beings and other mammals: olfaction (the sense of smell; i.e., the detection of small molecules in the air), taste or gustation (the detection of selected organic compounds and ions by the tongue), vision (the detection of light), hearing (the detection of sound, or

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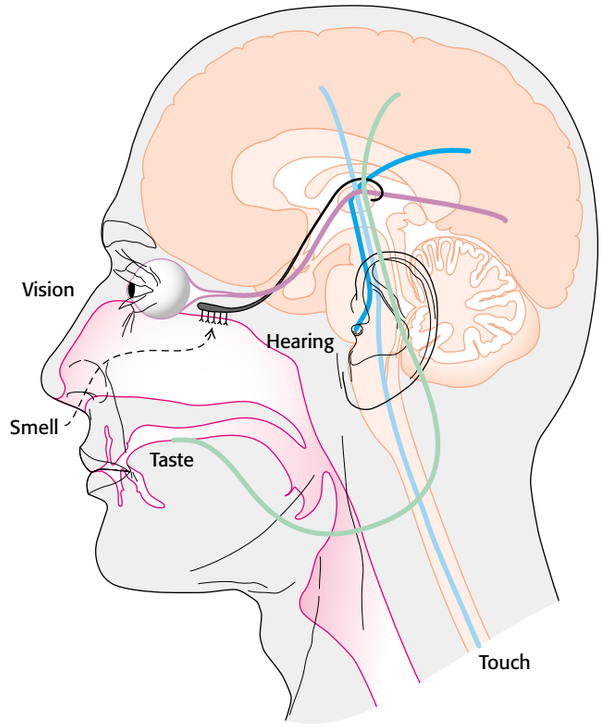
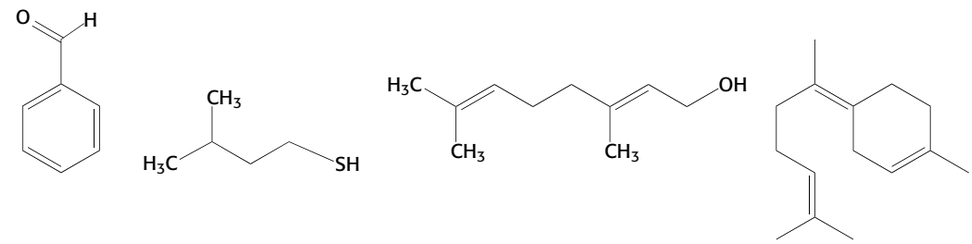


FIGURE 32.1 Sensory connections to the brain. Sensory nerves connect sensory organs to the brain and spinal cord.

pressure waves in the air), and touch (the detection of changes in pressure, temperature, and other factors by the skin). Each of these primary sensory systems contains specialized sensory neurons that transmit nerve impulses to the central nervous system (Figure 32.1). In the central nervous system, these signals are processed and combined with other information to yield a perception that may trigger a change in behavior. By these means, our senses allow us to detect changes in our environments and to adjust our behavior appropriately.

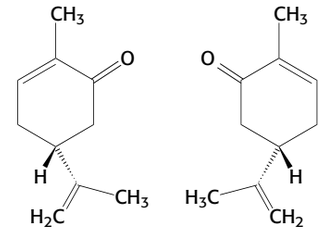
32.1 A WIDE VARIETY OF ORGANIC COMPOUNDS ARE DETECTED BY OLFACTION

Human beings can detect and distinguish thousands of different compounds by smell, often with considerable sensitivity and specificity. Most odorants are relatively small organic compounds with sufficient volatility that they can be carried as vapors into the nose. For example, a major component responsible for the smell of almonds is the simple aromatic compound benzaldehyde, whereas the sulfhydryl compound 3-methylbutane-1-thiol is a major component of the smell of skunks.



Benzaldehyde (Almond) **3-Methylbutane-1-thiol (Skunk)** **Geraniol (Rose)** **Zingiberene (Ginger)**

What properties of these molecules are responsible for their smells? First, *the shape of the molecule rather than its other physical properties is crucial*. We can most clearly see the importance of shape by comparing molecules such as those responsible for the smells of spearmint and caraway. These compounds are identical in essentially all physical properties such as hydrophobicity because they are exact mirror images of one another. Thus, the smell produced by an odorant depends not on a physical property but on the compound's interaction with a specific binding surface, most likely a protein receptor. Second, some human beings (and other animals) suffer from *specific anosmias*; that is, they are incapable of smelling specific compounds even though their olfactory systems are otherwise normal. Such anosmias are often inherited. These observations suggest that mutations in individual receptor genes lead to the loss of the ability to detect a small subset of compounds.



***R*-Carvone (Spearmint)** ***S*-Carvone (Caraway)**

32.1.1 Olfaction Is Mediated by an Enormous Family of Seven-Transmembrane-Helix Receptors

Odorants are detected in a specific region of the nose, called the *main olfactory epithelium*, that lies at the top of the nasal cavity (Figure 32.2). Approximately 1 million sensory neurons line the surface of this region. Cilia containing the odorant-binding protein receptors project from these neurons into the mucous lining of the nasal cavity.

Biochemical studies in the late 1980s examined isolated cilia from rat olfactory epithelium that had been treated with odorants. Exposure to the odorants increased the cellular level of cAMP, and this increase was observed only in the presence of GTP. On the basis of what was known about signal-transduction systems, *the participation of cAMP and GTP strongly suggested the involvement of a G protein and, hence, 7TM receptors.* Indeed, Randall Reed purified and cloned a G protein α subunit, termed $G_{(olf)}$, which is uniquely expressed in olfactory cilia. The involvement of 7TM receptors suggested a strategy for identifying the olfactory receptors themselves. cDNAs were sought that (1) were expressed primarily in the sensory neurons lining the nasal epithelium, (2) encoded members of the 7TM receptor family, and (3) were present as a large and diverse family to account for the range of odorants. Through the use of these criteria, cDNAs for odorant receptors from rats were identified in 1991 by Richard Axel and Linda Buck.

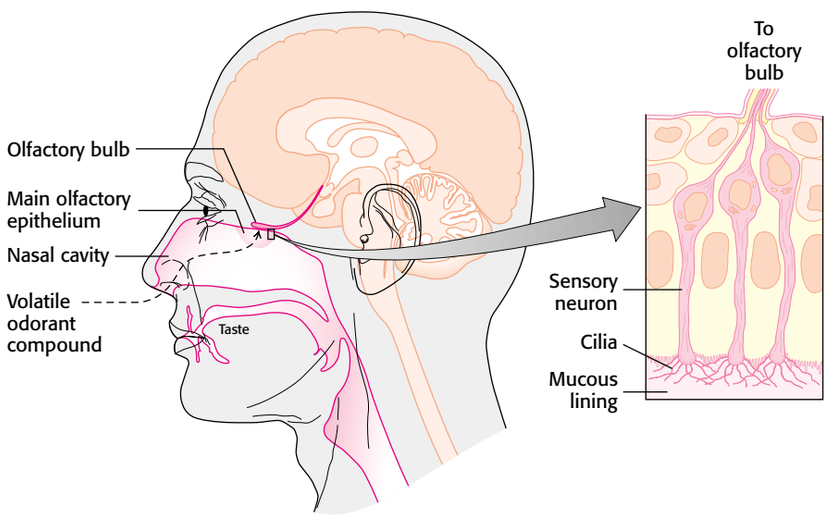


FIGURE 32.2 The main nasal epithelium. This region of the nose, which lies at the top of the nasal cavity, contains approximately 1 million sensory neurons. Nerve impulses generated by odorant molecules binding to receptors on the cilia travel from the sensory neurons to the olfactory bulb.

FIGURE 32.3 Evolution of odorant receptors. Odorant receptors appear to have lost function through conversion into pseudogenes in the course of primate evolution. The percentage of OR genes that appear to be functional for each species is shown in parentheses.

The odorant receptor (hereafter, OR) family is even larger than expected: *more than 1000 OR genes are present in the mouse and the rat, whereas the human genome encodes between an estimated 500 and 750 ORs*. The OR family is thus one of the largest gene families in human beings. However, more than half the human odorant receptor genes appear to be pseudogenes (Section 31.x.x); that is, they contain mutations that prevent the generation of a full-length, proper odorant receptor. In contrast, essentially all rodent OR genes are fully functional. Further analysis of primate OR genes reveals that the fraction of pseudogenes is greater in species more closely related to human beings (Figure 32.3). Thus, we may have a glimpse at the evolutionary loss of acuity in the sense of smell as higher mammals presumably became less dependent on this sense for survival.

The OR proteins are typically 20% identical in sequence to the β-adrenergic receptor (Section 15.x.x) and from 30 to 60% identical with each other. Several specific sequence features are present in most or all OR family members (Figure 32.4). The central region, particularly transmembrane helices 4 and 5, is highly variable, suggesting that this region is the site of odorant binding. That site must be different in odorant receptors that bind distinct odorant molecules.

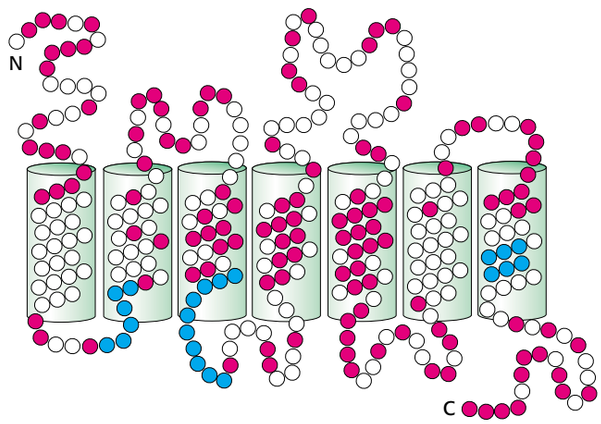


FIGURE 32.4 Conserved and variant regions in odorant receptors. Odorant receptors are members of the 7TM receptor family. The green cylinders represent the seven presumed transmembrane helices. Strongly conserved residues characteristic of this protein family are shown in blue, whereas highly variable residues are shown in red.

What is the relation between OR gene expression and the individual neuron? Interestingly, *each olfactory neuron expresses only a single OR gene*, among hundreds available. Apparently, the precise OR gene expressed is determined largely at random. The mechanism by which all other OR genes are excluded from expression remains to be elucidated. The binding of an odorant to an OR on the neuronal surface initiates a signal-transduction cascade that results in an action potential (Figure 32.5). The ligand-bound OR activates $G_{(olf)}$, the specific G protein mentioned earlier. $G_{(olf)}$ is initially in its GDP-bound form. When activated, it releases GDP, binds GTP, and releases its associated $\beta\gamma$ subunits. The α subunit then activates a specific adenylate cyclase, increasing the intracellular concentration of cAMP. The rise in the intracellular concentration of cAMP activates a nonspecific cation channel that allows calcium and other cations into the cell. The flow of cations through the channel depolarizes the neuronal membrane and initiates an action potential. This action potential, combined with those from other olfactory neurons, leads to the perception of a specific odor.

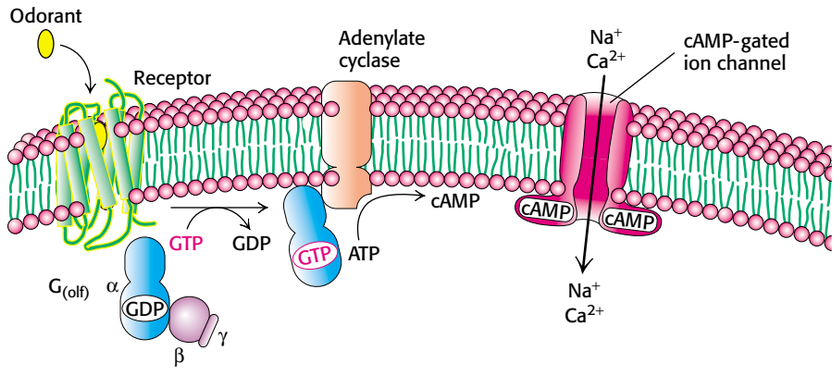


FIGURE 32.5 The olfactory signal-transduction cascade. The binding of odorant to the olfactory receptor activates a signaling pathway similar to those initiated in response to the binding of some hormones to their receptors (see Section 15.x.x.). The final result is the opening of cAMP-gated ion channels and the initiation of an action potential.

CONCEPTUAL INSIGHTS, Signaling Pathways: Response and Recovery *presents an animated version of Figure 32.5 and a comparison to visual signal transduction (Figure 32.25).*

32.1.2 Odorants Are Decoded by a Combinatorial Mechanism

An obvious challenge presented to the investigator by the large size of the OR family is to match up each OR with the one or more odorant molecules to which it binds. Exciting progress has been made in this regard. Initially, an OR was matched with odorants by overexpressing a single, specific OR gene in rats. This OR responded to straight-chain aldehydes, most favorably to *n*-octanal and less strongly to *n*-heptanal and *n*-hexanal. More dramatic progress was made by taking advantage of our knowledge of the OR signal-transduction pathway and the power of PCR (Section 6.1.5). A section of nasal epithelium from a mouse was loaded with the calcium-sensitive dye Fura-2 (Section 15.x.x). The tissue was then treated with different odorants, one at a time, at a specific concentration. If the odorant bound to and activated an OR, that neuron could be detected under a microscope by the change in fluorescence caused by the influx of calcium that occurs as part of the signal-transduction process. To determine which OR was responsible for the response, cDNA was generated from mRNA that had been isolated from single identified neurons. The cDNA was then subjected to PCR with the use of primers that are effective in amplifying most or all OR genes. The sequence of the PCR product from each neuron was then determined and analyzed.

Using this approach, investigators analyzed the responses of neurons to a series of compounds having varying chain lengths and terminal functional groups (Figure 32.6). The results of these experiments appear surprising at first glance (Figure 32.7). Importantly, there is not a simple 1:1 correspondence between odorants and

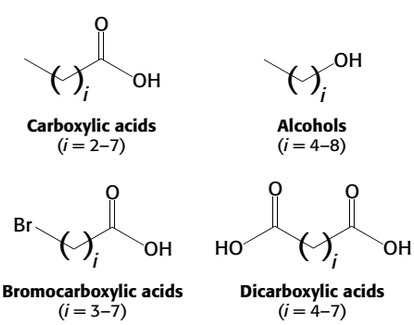


FIGURE 32.6 Four series of odorants tested for olfactory receptor activation.

FIGURE 32.7 Patterns of olfactory receptor activation. Fourteen different receptors were tested for responsiveness to the compounds shown in Figure 32.6. A colored box indicates that the receptor at the top responded to the compound at the left. Darker colors indicate that the receptor was activated at a lower concentration of odorant.

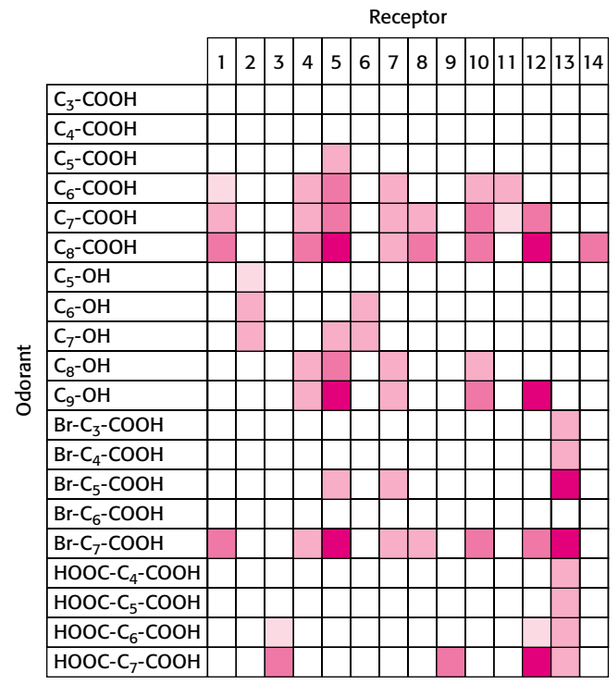


FIGURE 32.8 Converging olfactory neurons. This section of the nasal cavity is stained to reveal processes from sensory neurons expressing the same olfactory receptor. The processes converge to a single location in the olfactory bulb. [From P. Mombaerts, F. Wang, C. Dulac, S. K. Chao, A. Nemes, M. Mendelsohn, J. Edmondson, and R. Axel. *Cell* 87(1996):675–689.]

FIGURE 32.9 The Cyranose 320. The electronic nose may find uses in the food industry, animal husbandry, law enforcement, and medicine. [Courtesy of Cyrano Sciences.]

receptors. *Almost every odorant activates a number of receptors* (usually to different extents) and *almost every receptor is activated by more than one odorant*. Note, however, that each odorant activates a unique combination of receptors. In principle, this combinatorial mechanism allows even a relatively small array of receptors to distinguish a vast number of odorants.

How is the information about which receptors have been activated transmitted to the brain? Recall that each neuron expresses only one OR and that the pattern of expression appears to be largely random. A substantial clue to the connections between receptors and the brain has been provided by the creation of mice that express a gene for an easily detectable colored marker in conjunction with a specific OR gene. Olfactory neurons that express the OR–marker protein combination were traced to their destination in the brain, a structure called the olfactory bulb (Figure 32.8). The processes from neurons that express the same OR gene were found to connect to the same location in the olfactory bulb. Moreover, this pattern of neuronal connection was found to be identical in all mice examined. Thus, *neurons that express specific ORs are linked with specific sites in the brain*. This property creates a spatial map of odorant-responsive neuronal activity within the olfactory bulb.

Can such a combinatorial mechanism truly distinguish many different odorants? An "electronic nose" that functions by the same principles provides compelling evidence that it can (Figure 32.9). The receptors for the electronic nose are polymers that bind a range of small molecules. Each polymer binds every odorant, but to varying degrees. Importantly, the electrical properties of these polymers change on odorant binding. A set of 32 of these polymer sensors, wired together so that the pattern of responses can be evaluated, is capable of distinguishing individual compounds such as *n*-pentane and *n*-hexane as well as complex mixtures such as the odors of fresh and spoiled fruit.

32.1.3 Functional Magnetic Resonance Imaging Reveals Regions of the Brain Processing Sensory Information

Can we extend our understanding of how odorants are perceived to events in the brain? Biochemistry has provided the basis for powerful methods for examining responses within the brain. One method, called *functional magnetic resonance imaging* (fMRI), takes advantage of two key observations. The first is that, when a specific part of the brain is active, blood vessels relax to allow more blood flow to the active region. Thus, a more active region of the brain will be richer in oxyhemoglobin. The second observation is that the iron center in hemoglobin undergoes substantial structural changes on binding oxygen (Section 10.4.1). These changes are associated with a rearrangement of electrons such that the iron in deoxyhemoglobin acts as a strong magnet, whereas the iron in oxyhemoglobin does not. The difference between the magnetic properties of these two forms of hemoglobin can be used to image brain activity.

Nuclear magnetic resonance techniques (Section 4.5.1) detect signals that originate primarily from the protons in water molecules but are altered by the magnetic properties of hemoglobin. With the use of appropriate techniques, images can be generated that reveal differences in the relative amounts of deoxy- and oxyhemoglobin and thus the relative activity of various parts of the brain.

These noninvasive methods reveal areas of the brain that process sensory information. For example, subjects have been imaged while breathing air that either does or does not contain odorants. When odorants are pres-

ent, the fMRI technique detects an increase in the level of hemoglobin oxygenation (and, hence, brain activity) in several regions of the brain (Figure 32.10). Such regions include those in the primary olfactory cortex as well as other regions in which secondary processing of olfactory signals presumably takes place. Further analysis reveals the time course of activation of particular regions and other features. Functional MRI shows tremendous potential for mapping regions and pathways engaged in processing sensory information obtained from all the senses. Thus, *a seemingly incidental aspect of the biochemistry of hemoglobin has yielded the basis for observing the brain in action*.

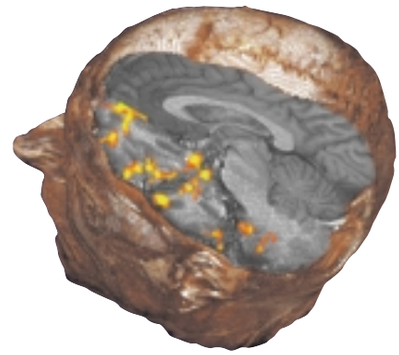


FIGURE 32.10 Brain response to odorants. A functional magnetic resonance image reveals brain response to odorants. The light spots indicate regions of the brain activated by odorants. [N. Sobel et al., *J. Neurophysiol.* 83:537–551 2000 537; courtesy of Nathan Sobel.]

32.2 TASTE IS A COMBINATION OF SENSES THAT FUNCTION BY DIFFERENT MECHANISMS

The inability to taste food is a common complaint when nasal congestion reduces the sense of smell. Thus, smell greatly augments our sense of taste (also known as *gustation*), and taste is, in many ways, the sister sense to olfaction. Nevertheless, the two senses differ from each other in several important ways. First, we are able to sense several classes of compounds by taste that we are unable to detect by smell; salt and sugar have very little odor, yet they are primary stimuli of the gustatory system. Second, whereas we are able to discriminate thousands of odorants, discrimination by taste is much more modest. Five primary tastes are perceived: *bitter, sweet, sour, salty,* and *umami* (the taste of glutamate from the Japanese word for "deliciousness"). These five tastes serve to classify compounds into potentially nutritive and beneficial (sweet, salty, umami) or potentially harmful or toxic (bitter, sour). Tastants (the molecules sensed by taste) are quite distinct for the different groups (Figure 32.11).

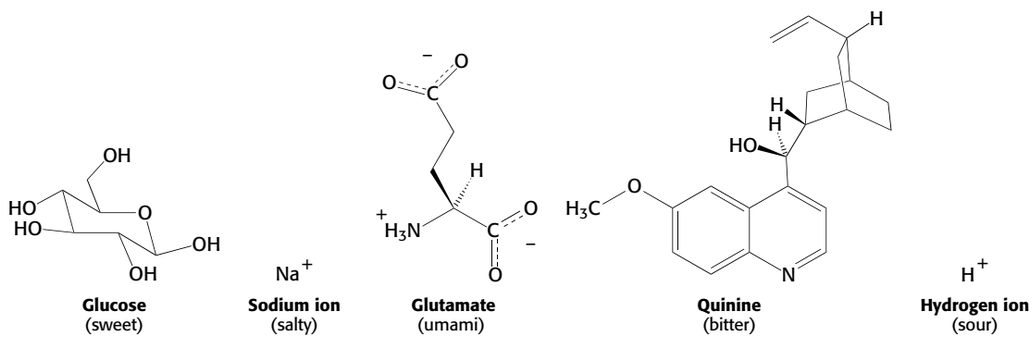


FIGURE 32.11 Examples of tastant molecules. Tastants fall into five groups: sweet, salty, umami, bitter, and sour.

The simplest tastant, the hydrogen ion, is perceived as sour. Other simple ions, particularly sodium ion, are perceived as salty. The taste called umami is evoked by the amino acid glutamate, often encountered as the flavor enhancer monosodium glutamate (MSG). In contrast, *tastants perceived as bitter or sweet are extremely diverse*. Many bitter compounds are alkaloids or other plant products of which many are toxic. However, they do not have any common structural elements or other common properties. Carbohydrates such as glucose and sucrose are perceived as sweet, as are other compounds including some simple peptide derivatives, such as aspartame, and even some proteins.

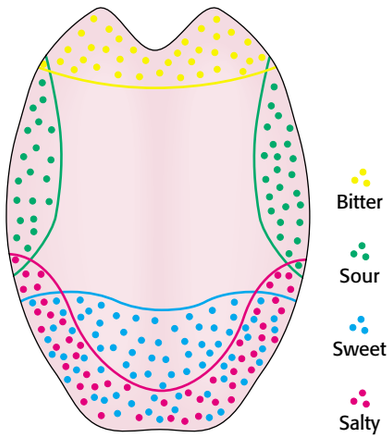
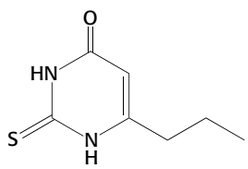
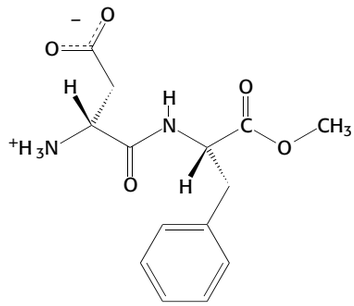


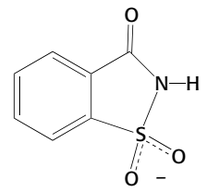
FIGURE 32.12 Taste-sensitive areas of the tongue. The tongue contains overlapping regions that are particularly sensitive to specific taste stimuli.



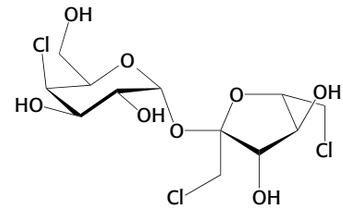
6-*n*-Propyl-2-thiouracil (PROP)



Aspartame



Saccharin



Sucrolose

These differences in specificity among the five tastes are due to differences in their underlying biochemical mechanisms. The sense of taste is, in fact, a number of independent senses all utilizing the same organ, the tongue, for their expression.

Tastants are detected by specialized structures called *taste buds*, which contain approximately 150 cells, including sensory neurons. Projections called *taste papillae* contain numerous taste buds. Papillae somewhat specialized to detect different taste types are concentrated in distinct regions across the surface of the tongue. Consequently, different regions of the tongue are particularly sensitive to specific classes of tastants (Figure 32.12).

32.2.1 Sequencing the Human Genome Led to the Discovery of a Large Family of 7TM Bitter Receptors

Just as in olfaction, a number of clues pointed to the involvement of G proteins and, hence, 7TM receptors in the detection of bitter and sweet tastes. The evidence included the isolation of a specific G protein α subunit termed *gustducin*, which is expressed primarily in taste buds (Figure 32.13). How could the 7TM receptors be identified? The ability to detect some compounds depends on specific genetic loci in both human beings and mice. For instance, the ability to taste the bitter compound 6-*n*-propyl-2-thiouracil (PROP) was mapped to a region on human chromosome 5 by comparing DNA markers of persons who vary in sensitivity to this compound.

This observation suggested that this region might encode a 7TM receptor that responded to PROP. Approximately 450 kilobases in this region had been sequenced early in the human genome project. This sequence was searched by computer for potential 7TM receptor genes, and, indeed, one was detected and named *T2R-1*. Additional database searches for sequences similar to this one detected 12 genes encoding full-length receptors as well as 7 pseudogenes within the sequence of the human genome known at

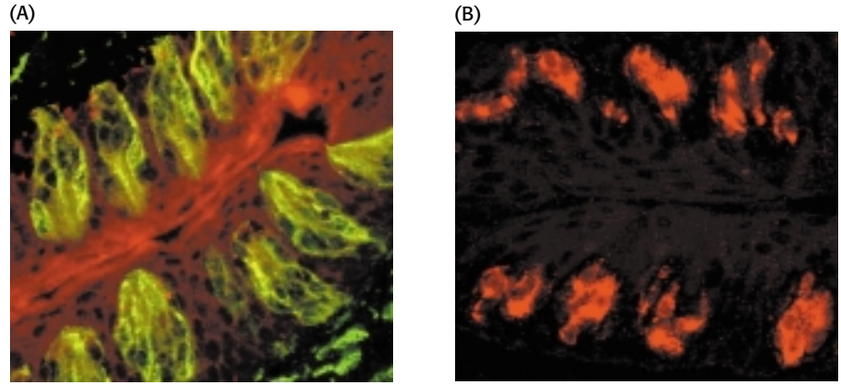


FIGURE 32.13 Expression of gustducin in the tongue. (A) A section of tongue stained with a fluorescent antibody reveals the position of the taste buds. (B) The same region stained with a antibody directed against gustducin reveals that this G protein is expressed in taste buds. [Courtesy of Charles S. Zuker.]

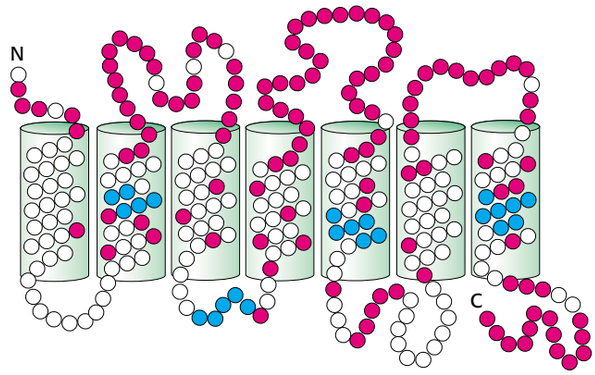


FIGURE 32.14 Conserved and variant regions in bitter receptors. The bitter receptors are members of the 7TM receptor family. Strongly conserved residues characteristic of this protein family are shown in blue, and highly variable residues are shown in red.

the time. The encoded proteins were between 30 and 70% identical with T2R-1 (Figure 32.14). *Further analysis suggests that there are from 50 to 100 members of this family of 7TM receptors in the entire human genome*. Similar sequences have been detected in the mouse and rat genomes.

Are these proteins, in fact, bitter receptors? Several lines of evidence suggest that they are. First, their genes are expressed in taste-sensitive cells—in fact, in many of the same cells that express gustducin. Second, cells that express individual members of this family respond to specific bitter compounds. For example, cells that express a specific mouse receptor (mT2R-5) responded when exposed specifically to cycloheximide. Third, mice that had been found unresponsive to cycloheximide were found to have point mutations in the gene encoding mT2R-5. Finally, cycloheximide specifically stimulates the binding of GTP analogs to gustducin in the presence of the mT2R-5 protein (Figure 32.15).

Importantly, each taste receptor cell expresses many different members of the T2R family. This pattern of expression stands in sharp contrast to the pattern of one receptor type per cell that characterizes the olfactory system (Figure 32.16). The difference in expression patterns accounts for the much greater specificity of our perceptions of smells compared with tastes. *We are able to distinguish among subtly different odors because each odorant stimulates*

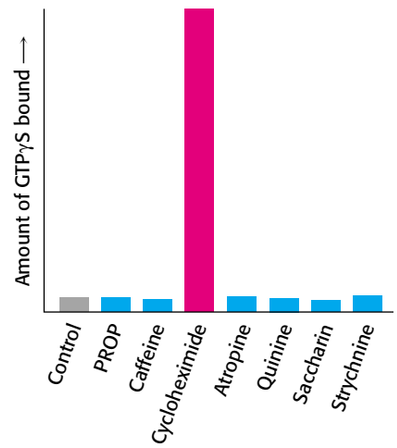


FIGURE 32.15 Evidence that T2R proteins are bitter taste receptors. Cycloheximide uniquely stimulates the binding of the GTP analog GTPγS to gustducin in the presence of the mT2R protein. [Adapted from J. Chandrashekar, K. L. Mueller, M. A. Hoon, E. Adler, L. Feng, W. Guo, C. S. Zuker, and N. J. Ryba. *Cell* 100(2000):703.]

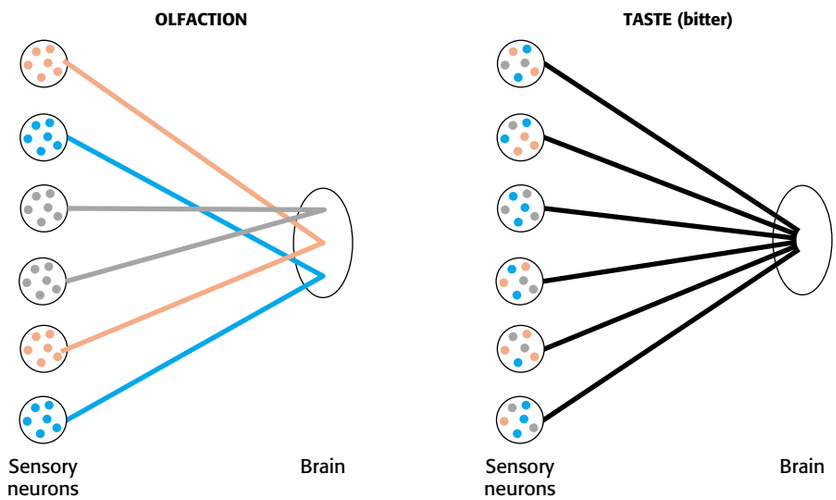


FIGURE 32.16 Differing gene expression and connection patterns in olfactory and bitter taste receptors. In olfaction, each neuron expresses a single OR gene, and the neurons expressing the same OR converge to specific sites in the brain, enabling specific perception of different odorants. In gustation, each neuron expresses many bitter receptor genes, so the identity of the tastant is lost in transmission.

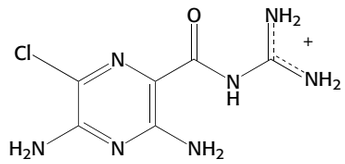
a unique pattern of neurons. In contrast, many tastants stimulate the same neurons. Thus, we perceive only "bitter" without the ability to discriminate cycloheximide from quinine.

32.2.2 A Family of 7TM Receptors Almost Certainly Respond to Sweet Compounds

Most sweet compounds are carbohydrates, energy rich and easily digestible. However, as noted in Chapter 11, carbohydrates are structurally diverse. Moreover, some noncarbohydrate compounds such as aspartame also taste sweet. The structural diversity among sweet-tasting compounds, though less than that among bitter compounds, strongly suggests that a family of receptors detects these compounds. The *sweet receptors are very likely coupled to the G protein gustducin and, hence, are members of the 7TM superfamily*. This likelihood was most sharply revealed in studies that disrupted the gene for gustducin in mice. These mice lost much of their ability to sense both bitter and sweet compounds. Genes for candidate receptors have been cloned but have not yet been proved to be functional sweet receptors.

32.2.3 Salty Tastes Are Detected Primarily by the Passage of Sodium Ions Through Channels

Salty tastants are not detected by 7TM receptors. Rather, they are detected directly by their passage through ion channels expressed on the surface of cells in the tongue. Evidence for the role of these ion channels comes from examining known properties of sodium channels characterized in other biological contexts. One class of channels, characterized first for their role in salt reabsorption, are thought to be important in salt taste detection because they are sensitive to the compound *amiloride*, which mutes the taste of salt and significantly lowers sensory neuron activation in response to sodium.



Amiloride

An *amiloride-sensitive sodium channel* comprises four subunits that may be either identical or distinct but in any case are homologous. An individual subunit ranges in length from 500 to 1000 amino acids and includes two presumed membrane-spanning helices as well as a large extracellular domain in between them (Figure 32.17). The extracellular region includes two (or, sometimes, three) distinct regions rich in cysteine residues (and, presumably, disulfide bonds). A region just ahead of the second membrane-spanning helix appears to form part of the pore in a manner analogous to the structurally characterized potassium channel (Section 13.5.6). The members of the amiloride-sensitive sodium-channel family are numerous and diverse in their biological roles. We shall encounter them again in the context of the sense of touch.

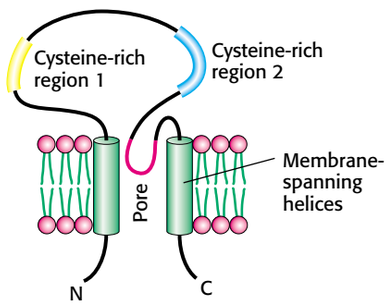


FIGURE 32.17 Schematic structure of the amiloride-sensitive sodium channel. Only one of the four subunits that constitute the functional channel is illustrated. The amiloride-sensitive sodium channel belongs to a superfamily having common structural features, including two hydrophobic membrane-spanning regions, intracellular amino and carboxyl termini; and a large, extracellular region with conserved cysteine-rich domains.

Sodium ions passing through these channels produce a significant transmembrane current. Amiloride blocks this current, accounting for its effect on taste. However, about 20% of the response to sodium remains even in the presence of amiloride, suggesting that other ion channels also contribute to salt detection.

32.2.4 Sour Tastes Arise from the Effects of Hydrogen Ions (Acids) on Channels

Like salty tastes, *sour tastes are also detected by direct interactions with ion channels*, but the incoming ions are hydrogen ions (in high concentrations) rather than sodium ions. For example, in the absence of high concentrations of sodium, hydrogen ion flow can induce substantial transmembrane currents through amiloride-sensitive sodium channels. However, hydrogen ions are also sensed by mechanisms other than their direct passage through

membranes. Binding by hydrogen ions blocks some potassium channels and activates other types of channels. Together, these mechanisms lead to changes in membrane polarization in sensory neurons that produce the sensation of sour taste.

32.2.5 Umami, the Taste of Glutamate, Is Detected by a Specialized Form of Glutamate Receptor

Glutamate is an abundant amino acid that is present in protein-rich foods as well as in the widely used flavor enhancer monosodium glutamate. This amino acid has a taste, termed *umami*, that is distinct from the other four basic tastes. Adults can detect glutamate at a concentration of approximately 1 mM. Glutamate is also a widely used neurotransmitter, and thus, not surprisingly, several classes of receptors for glutamate have been identified in the nervous system. One class, called *metabotrophic glutamate receptors*, are 7TM receptors with large amino-terminal domains of approximately 600 amino acids. Sequence analysis reveals that the first half of the amino-terminal region is most likely a ligand-binding domain, because it is homologous to such domains found in the Lac repressor (Section 31.x.x) and other bacterial ligand-binding proteins.

One glutamate receptor gene, encoding a protein called the metabotrophic glutamate receptor 4 (mGluR4), has been found to be expressed in taste buds. Further analysis of the mRNA that is expressed in taste buds reveals that this mRNA lacks the region encoding the first 309 amino acids in brain mGluR4, which includes most of the high-affinity glutamate-binding domain (Figure 32.18). The glutamate receptor found in taste buds shows a lowered affinity for glutamate that is appropriate to glutamate levels in the diet. Thus, *the receptor responsible for the perception of glutamate taste appears to have evolved simply by changes in the expression of an existing glutamate-receptor gene*. We shall consider an additional receptor related to taste, that responsible for the "hot" taste of spicy food, when we deal with mechanisms of touch perception.

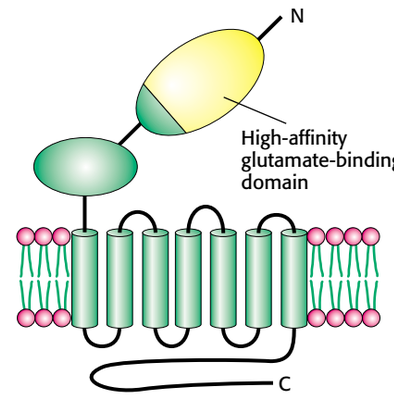


FIGURE 32.18 Schematic structure of a metabotrophic glutamate receptor. The umami receptor is a variant of a brain glutamate receptor. A substantial part of the high-affinity glutamate-binding domain (shown in yellow) is missing in the form expressed in the tongue.

32.3 PHOTORECEPTOR MOLECULES IN THE EYE DETECT VISIBLE LIGHT

Vision is based on the absorption of light by photoreceptor cells in the eye. These cells are sensitive to light in a relatively narrow region of the electromagnetic spectrum, the region with wavelengths between 300 and 850 nm (Figure 32.19). Vertebrates have two kinds of photoreceptor cells, called *rods* and *cones* because of their distinctive shapes. Cones function in bright light and are responsible for color vision, whereas rods function in dim light but do not perceive color. A human retina contains about 3 million cones and 100 million rods. Remarkably, a rod cell can respond to a single photon, and the brain requires fewer than 10 such responses to register the sensation of a flash of light.

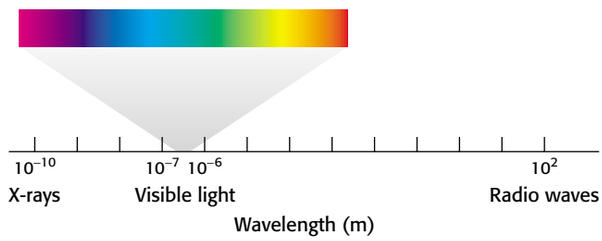
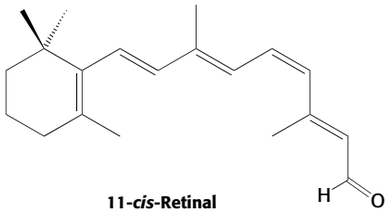


FIGURE 32.19 The electromagnetic spectrum. Visible light has wavelengths between 300 and 850 nanometers.



11-*cis*-Retinal

32.3.1 Rhodopsin, a Specialized 7TM Receptor, Absorbs Visible Light

Rods are slender elongated structures; the outer segment is specialized for photoreception (Figure 32.20). It contains a stack of about 1000 discs, which are membrane-enclosed sacs densely packed with photoreceptor molecules. The photosensitive molecule is often called a *visual pigment* because it is highly colored owing to its ability to absorb light. The photoreceptor molecule in rods is *rhodopsin* (Section 15.x.x), which consists of the protein *opsin* linked to *11*-cis-*retinal*, a prosthetic group.

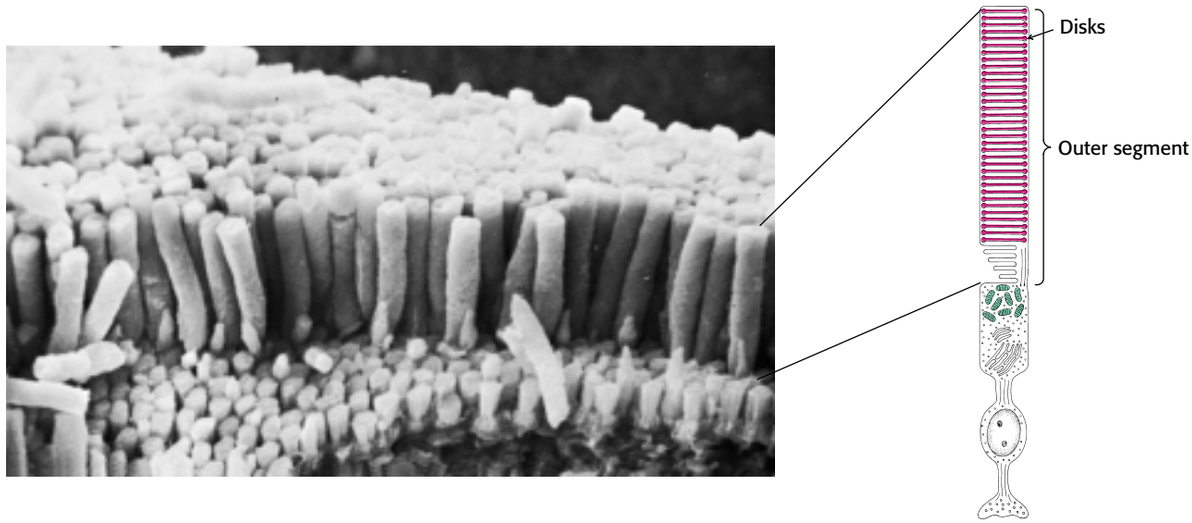


FIGURE 32.20 The rod cell. (Left) Scanning electron micrograph of retinal rod cells. (Right) Schematic representation of a rod cell. [Photograph courtesy of Dr. Deric Bownds.]

Rhodopsin absorbs light very efficiently in the middle of the visible spectrum, its absorption being centered on 500 nm, which nicely matches the solar output (Figure 32.21). A rhodopsin molecule will absorb a high percentage of the photons of the correct wavelength that strike it, as indicated by the extinction coefficient of 40,000 $M^{-1}cm^{-1}$ at 500 nm. The extinction coefficient for rhodopsin is more than an order of magnitude greater than that for tryptophan, the most efficient absorber in proteins that lack prosthetic groups.

Opsin, the protein component of rhodopsin, is a member of the 7TM receptor family. Indeed, rhodopsin was the first member of this family to be purified, its gene was the first to be cloned and sequenced, and its three-dimensional structure was the first to be determined. The color of rhodopsin and its responsiveness to light depend on the presence of the light-absorbing group (*chromophore*) 11-*cis*-retinal. This compound is a powerful absorber of light because it is a polyene; its six alternating single and double bonds constitute a long, unsaturated electron network. Recall that alternating single and double bonds account for the chromophoric properties of chlorophyll (Section 20.x.x). The aldehyde group of 11-*cis*-retinal forms a Schiff base (Figure 32.22) with the ϵ-amino group of lysine residue 296, which lies in the center of the seventh transmembrane helix. Free retinal absorbs maximally at 370 nm, and its unprotonated Schiff-base adduct absorbs at 380 nm, whereas the protonated Schiff base absorbs at 440 nm or longer wavelengths. Thus, *the 500-nm absorption maximum for rhodopsin strongly suggests that the Schiff base is protonated*; additional interactions

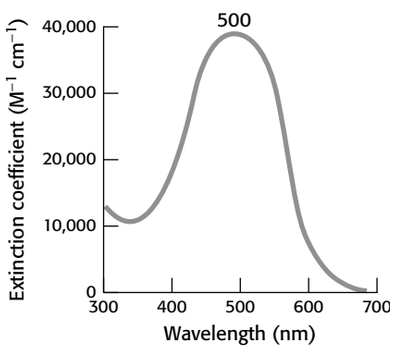


FIGURE 32.21 Rhodopsin absorption spectrum.

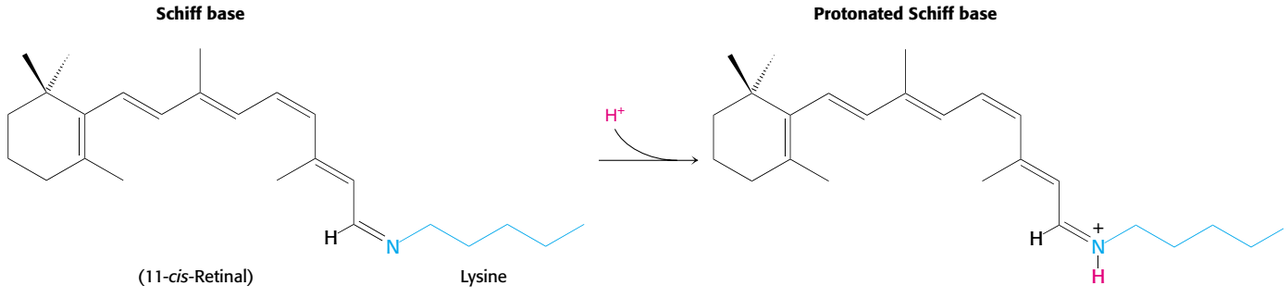


FIGURE 32.22 Retinal–lysine linkage. Retinal is linked to lysine 296 in opsin by a Schiff-base linkage. In the resting state of rhodopsin, this Schiff base is protonated.

with opsin shift the absorption maximum farther toward the red. The positive charge of the protonated Schiff base is compensated by the negative charge of glutamate 113 located in helix 2; the glutamate residue closely approaches the lysine–retinal linkage in the three-dimensional structure of rhodopsin.

STRUCTURAL INSIGHTS, Rhodopsin: A G Protein Coupled 7TM Receptor
offers a more detailed look at rhodopsin structure and function (Figure 32.5).

32.3.2 Light Absorption Induces a Specific Isomerization of Bound 11-*cis*-Retinal

How does the absorption of light by the retinal Schiff base generate a signal? George Wald and his coworkers discovered that *light absorption results in the isomerization of the 11-*cis*-retinal group of rhodopsin to its all-*trans *form* (Figure 32.23). This isomerization causes the Schiff-base nitrogen atom to move approximately 5 Å, assuming that the cyclohexane ring of the retinal group remains fixed. In essence, *the light energy of a photon is converted into atomic motion*. The change in atomic positions, like the binding of a ligand to other 7TM receptors, sets in train a series of events that lead to the closing of ion channels and the generation of a nerve impulse.

The isomerization of the retinal Schiff base takes place within a few picoseconds of a photon being absorbed. The initial product, termed *bathorhodopsin*, contains a strained all-*trans*-retinal group. Within approximately 1 millisecond, this intermediate is converted through several additional intermediates into *metarhodopsin II*. In metarhodopsin II, the Schiff base is deprotonated and the opsin protein has undergone significant reorganization.

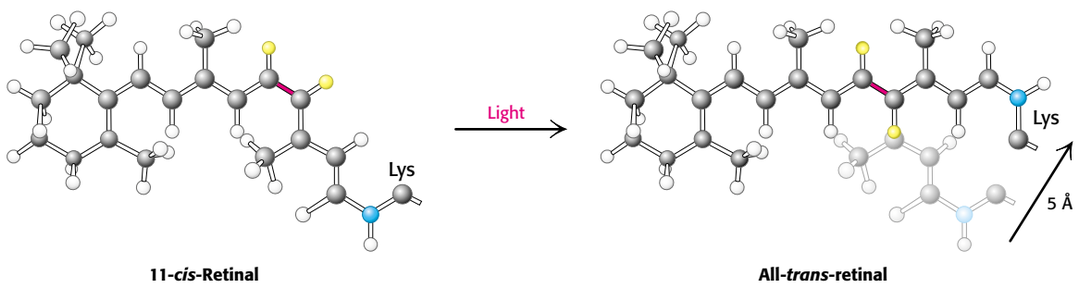


FIGURE 32.23 Atomic motion in retinal. The Schiff-base nitrogen atom moves 5 Å as a consequence of the light-induced isomerization of 11-*cis*-retinal to all-*trans*-retinal by rotation about the bond shown in red.

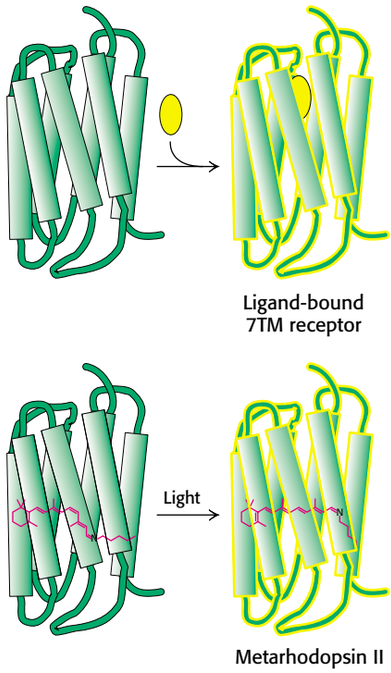


FIGURE 32.24 Analogous 7TM receptors. The conversion of rhodopsin into metarhodopsin II activates a signal-transduction pathway analogously to the activation induced by the binding of other 7TM receptors to appropriate ligands.

Metarhodopsin II (also referred to as R^*) is analogous to the ligand-bound state of 7TM receptors such as the β_2-adrenergic receptor (Section 15.x.x) and the odorant and tastant receptors heretofore discussed (Figure 32.24). Like these receptors, this form of rhodopsin activates a heterotrimeric G protein that propagates the signal. The G protein associated with rhodopsin is called *transducin*. Metarhodopsin II triggers the exchange of GDP for GTP by the α subunit of transducin (Figure 32.25). On the binding of GTP, the $\beta\gamma$ subunits of transducin are released and the α subunit switches on a *cGMP phosphodiesterase* by binding to and removing an inhibitory subunit. The activated phosphodiesterase is a potent enzyme that rapidly hydrolyzes cGMP to GMP. The reduction in cGMP concentration causes cGMP-gated ion channels to close, leading to hyperpolarization of the membrane and neuronal signaling. *At each step in this process, the initial signal—the absorption of a single photon—is amplified so that it leads to sufficient membrane hyperpolarization to result in signaling.*

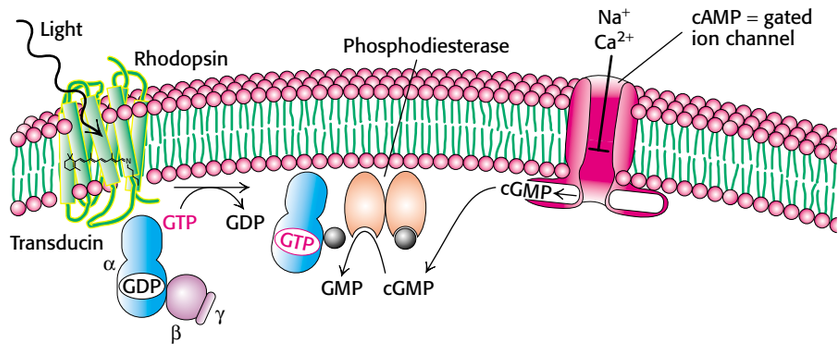


FIGURE 32.25 Visual signal transduction. The light-induced activation of rhodopsin leads to the hydrolysis of cGMP, which in turn leads to ion channel closing and the initiation of an action potential.

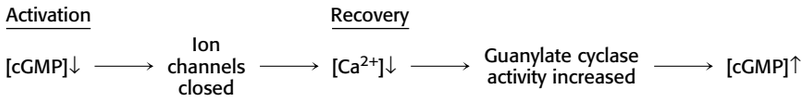
CONCEPTUAL INSIGHTS, Signaling Pathways: Response and Recovery *presents an animated version of Figure 32.25 and a comparison to olfactory signal transduction (Figure 32.5).*

32.3.3 Light-Induced Lowering of the Calcium Level Coordinates Recovery

As we have seen, the visual system responds to changes in light and color within a few milliseconds, quickly enough that we are able to perceive continuous motion at nearly 1000 frames per second. To achieve a rapid response, the signal must also be terminated rapidly and the system must be returned to its initial state. First, activated rhodopsin must be blocked from continuing to activate transducin. *Rhodopsin kinase* catalyzes the phosphorylation of the carboxyl terminus of R* at multiple serine and threonine residues. *Arrestin*, an inhibitory protein (Section 15.x.x), then binds phosphorylated R* and prevents additional interaction with transducin.

Second, the α subunit of transducin must be returned to its inactive state to prevent further signaling. Like other G proteins, the α subunit possesses built-in GTPase activity that hydrolyzes bound GTP to GDP. Hydrolysis takes place in less than a second when transducin is bound to the phosphodiesterase. The GDP form of transducin then leaves the phosphodiesterase and reassociates with the $\beta\gamma$ subunits, and the phosphodiesterase returns to its inactive state. Third, the level of cGMP must be raised to reopen the cGMP-gated ion channels. *The action of guanylate cyclase accomplishes this third step by synthesizing cGMP from GTP.*

Calcium ion plays an essential role in controlling guanylate cyclase because it markedly inhibits the activity of the enzyme. In the dark, Ca^{2+} as well as Na^+ enter the rod outer segment through the cGMP-gated channels. Calcium ion influx is balanced by its efflux through an exchanger, a transport system that uses the thermodynamically favorable flow of four Na^+ ions into the cell and one K^+ ion out of the cell to extrude one Ca^{2+} ion. After illumination, the entry of Ca^{2+} through the cGMP-gated channels stops, but its export through the exchanger continues. Thus, the cytosolic Ca^{2+} level drops from 500 nM to 50 nM after illumination. This drop markedly stimulates guanylate cyclase, rapidly restoring the concentration of cGMP to reopen the cGMP-gated channels.



By controlling the rate of cGMP synthesis, *Ca^{2+} levels govern the speed with which the system is restored to its initial state*.

32.3.4 Color Vision Is Mediated by Three Cone Receptors That Are Homologs of Rhodopsin

Cone cells, like rod cells, contain visual pigments. Like rhodopsin, these photoreceptor proteins are members of the 7TM receptor family and utilize 11-*cis*-retinal as their chromophore. In human cone cells, there are three distinct photoreceptor proteins with absorption maxima at 426, 530, and ~560 nm (Figure 32.26). *These absorbances correspond to (in fact, define) the blue, green, and red regions of the spectrum*. Recall that the absorption maximum for rhodopsin is 500 nm.

The amino acid sequences of the cone photoreceptors have been compared with each other and with rhodopsin. The result is striking. Each of the cone photoreceptors is approximately 40% identical in sequence with rhodopsin. Similarly, the blue photoreceptor is 40% identical with each of the green and red photoreceptors. The green and red photoreceptors, however, are > 95% identical with each other, differing in only 15 of 364 positions (Figure 32.27).

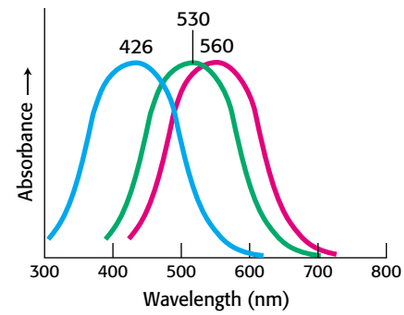


FIGURE 32.26 Cone-pigment absorption spectra. The absorption spectra of the cone visual pigment responsible for color vision.

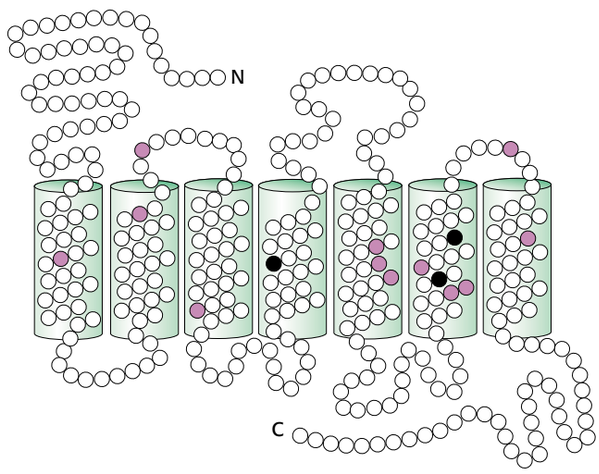


FIGURE 32.27 Comparison of the amino acid sequences of the green and red photoreceptors. Open circles correspond to identical residues, whereas colored circles mark residues that are different. The differences in the three black positions are responsible for most of the difference in their absorption spectra.

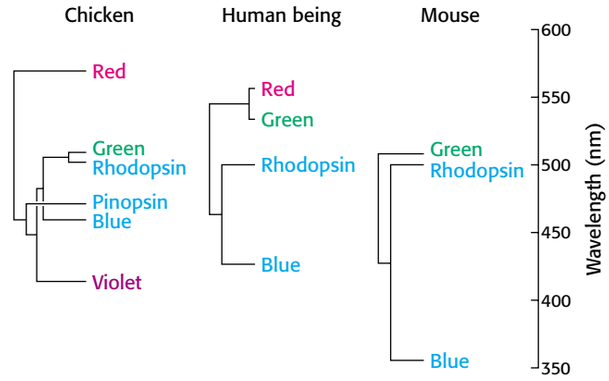


FIGURE 32.28 Evolutionary relationships among visual pigments. Visual pigments have evolved by gene duplication along different branches of the animal evolutionary tree. The branch lengths of the "trees" correspond to the percentage of amino acid divergence. [Adapted from Nathans, J. *Neuron* 24(1999):299; by permission of Cell Press.]

These observations are sources of insight into photoreceptor evolution. First, the green and red photoreceptors are clearly products of a recent evolutionary event (Figure 32.28). The green and red pigments appear to have diverged in the primate lineage approximately 35 million years ago. Mammals, such as dogs and mice, that diverged from primates earlier have only two cone photoreceptors, blue and green. They are not sensitive to light as far toward the infrared region as we are, and they do not discriminate colors as well. In contrast, birds such as chickens have a total of six pigments: rhodopsin, four cone pigments, and a pineal visual pigment called *pinopsin*. Birds have highly acute color perception.

Second, the high level of similarity between the green and red pigments has made it possible to identify the specific amino acid residues that are responsible for spectral tuning. Three residues (at positions 180, 277, and 285) are responsible for most of the difference between the green and red pigments. In the green pigment, these residues are alanine, phenylalanine, and alanine, respectively; in the red pigment, they are serine, tyrosine, and threonine. A hydroxyl group has been added to each amino acid in the red pigment. The hydroxyl groups can interact with the photoexcited state of retinal and lower its energy, leading to a shift toward the lower-energy (red) region of the spectrum.

STRUCTURAL INSIGHTS, Rhodopsin: A G Protein Coupled 7TM Receptor
explores the structural basis of color vision and night blindness in more detail.

32.3.5 Rearrangements in the Genes for the Green and Red Pigments Lead to "Color Blindness"

The genes for the green and red pigments lie adjacent to each other on the human X chromosome. These genes are more than 98% identical in nucleotide sequence, including introns and untranslated regions as well as the protein-coding region. Regions with such high similarity are very susceptible to unequal homologous recombination.

Homologous recombination— The exchange of DNA segments at equivalent positions between chromosomes with substantial sequence similarity.

Recombination can take place either between or within transcribed regions of the gene (Figure 32.29). If recombination takes place between transcribed regions, the product chromosomes will differ in the number of pigment genes that they carry. One chromosome will lose a gene and thus may lack the gene for, say, the green pigment; the other chromosome will gain a gene. Consistent with this scenario, approximately 2% of human X chromosomes carry only a single color pigment gene, approximately 20% carry two, 50% carry three, 20% carry four, and 5% carry five or more. A person lacking the gene for the green pigment will have trouble distinguishing red and green color, characteristic of the most common form of color blindness.

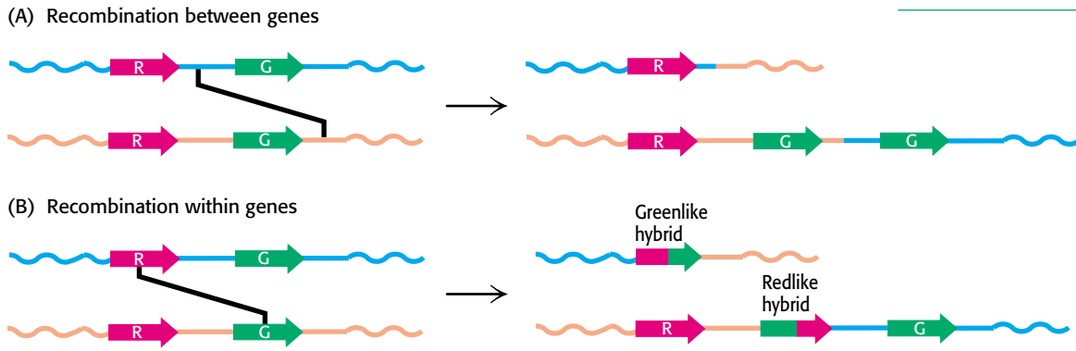


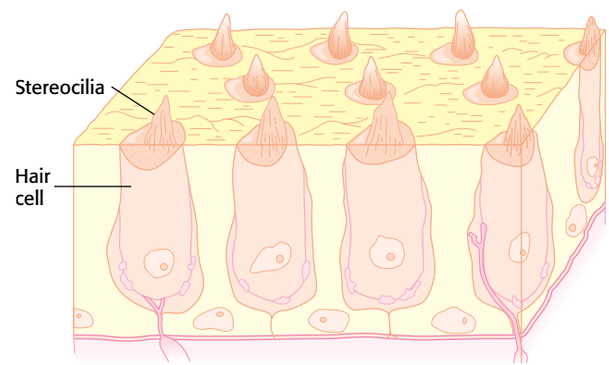
FIGURE 32.29 Recombination pathways leading to color blindness. Rearrangements in the course of DNA replication may lead to (A) the loss of visual pigment genes or (B) the formation of hybrid pigment genes that encode photoreceptors with anomolous absorption spectra. Because the amino acids most important for determining absorption spectra are in the carboxyl-terminal half of each photoreceptor protein, the part of the gene that encodes this region most strongly affects the absorption characteristics of hybrid receptors. [Adapted from J. Nathans. *Neuron* 24(1999):299–312; by permission of Cell Press.]

Approximately 5% of males have this form of color blindness. Recombination can also take place within the transcription units, resulting in genes that encode hybrids of the green and red photoreceptors. The absorption maximum of such a hybrid lies between that of the red and green pigments. A person with such hybrid genes who also lacks either a functional red or a functional green pigment gene does not discriminate color well.

32.4 HEARING DEPENDS ON THE SPEEDY DETECTION OF MECHANICAL STIMULI

Hearing and touch are based on the detection of mechanical stimuli. Although the proteins of these senses have not been as well characterized as those of the senses already discussed, anatomical, physiological, and biophysical studies have elucidated the fundamental processes. *A major clue to the mechanism of hearing is its speed.* We hear frequencies ranging from 200 to 20,000 Hz (cycles per second), corresponding to times of 5 to 0.05 ms. Furthermore, our ability to locate sound sources, one of the most important functions of hearing, depends on the ability to detect the time delay between the arrival of a sound at one ear and its arrival at the other. Given the separation of our ears and the speed of sound, we must be able to accurately sense time differences of 0.7 ms. In fact, human beings can locate sound sources associated with temporal delays as short as 0.02 ms. This high time resolution implies that hearing must employ direct transduction mechanisms that do not depend on second messengers. Recall that, in vision, for which speed also is important, the signal-transduction processes take place in milliseconds.

FIGURE 32.30 Hair cells, the sensory neurons crucial for hearing. [Adapted from Hudspeth, A. J. *Nature* 341(1989):397.]



32.4.1 Hair Cells Use a Connected Bundle of Stereocilia to Detect Tiny Motions

Sound waves are detected inside the cochlea of the inner ear. The *cochlea* is a fluid-filled, membranous sac that is coiled like a snail shell. The primary detection is accomplished by specialized neurons inside the cochlea called *hair cells* (Figure 32.30). Each cochlea contains

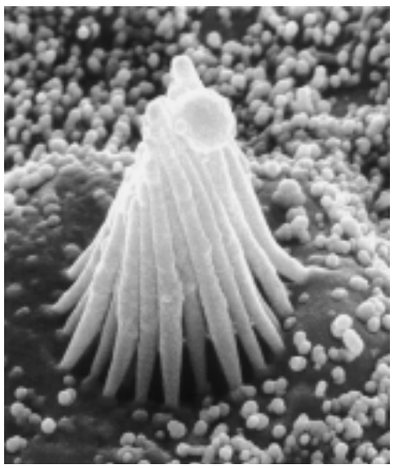


FIGURE 32.31 An electron micrograph of a hair bundle. [Courtesy of A. Jacobs and A. J. Hudspeth.]

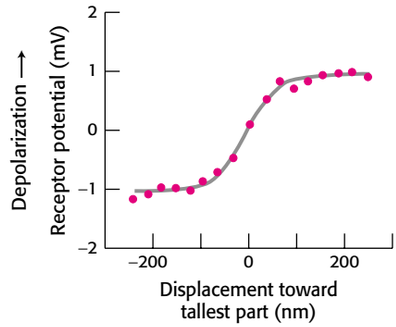


FIGURE 32.32 Micromanipulation of a hair cell. Movement toward the tallest part of the bundle depolarizes the cell as measured by the microelectrode. Movement toward the shortest part hyperpolarizes the cell. Lateral movement has no effect. [Adapted from Hudspeth, A. J. *Nature* 341(1989):397.]

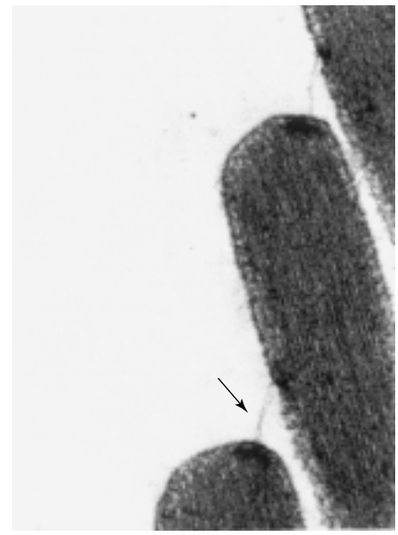


FIGURE 32.33 Electron micrograph of tip links. The tip link between two hair fibers is marked by an arrow. [Courtesy of A. Jacobs and A. J. Hudspeth.]

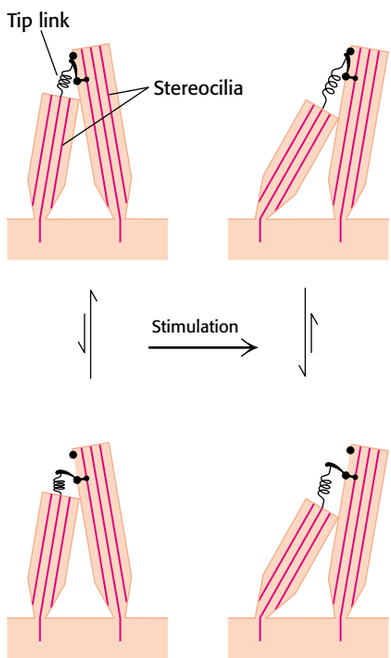


FIGURE 32.34 Model for hair-cell transduction. When the hair bundle is tipped toward the tallest part, the tip link pulls on and opens an ion channel. Movement in the opposite direction relaxes the tension in the tip link, increasing the probability that any open channels will close. [Adapted from A. J. Hudspeth. *Nature* 341 (1989):397.]

approximately 16,000 hair cells, and each hair cell contains a hexagonally shaped bundle of 20 to 300 hairlike projections called *stereocilia* (Figure 32.31). These stereocilia are graded in length across the bundle. Mechanical deflection of the hair bundle, as occurs when a sound wave arrives at the ear, creates a change in the membrane potential of the hair cell.

Micromanipulation experiments have directly probed the connection between mechanical stimulation and membrane potential. Displacement toward the direction of the tallest part of the hair bundle results in depolarization of the hair cell, whereas displacement in the opposite direction results in hyperpolarization (Figure 32.32). Motion perpendicular to the hair-length gradient does not produce any change in resting potential. Remarkably, *displacement of the hair bundle by as little as 3 Å (0.3 nm) results in a measurable (and functionally important) change in membrane potential*. This motion of 0.003 degree corresponds to a 1-inch movement of the top of the Empire State Building.

How does the motion of the hair bundle create a change in membrane potential? The rapid response, within microseconds, suggests that the movement of the hair bundle acts on ion channels directly. An important observation is that adjacent stereocilia are linked by individual filaments called *tip links* (Figure 32.33).

The presence of these tip links suggests a simple mechanical model for transduction by hair cells (Figure 32.34). The tip links are coupled to ion channels in the membranes of the stereocilia that are gated by mechanical stress. In the absence of a stimulus, approximately 15% of these channels are open. When the hair bundle is displaced toward its tallest part, the stereocilia slide across one another and the tension on the tip links increases, causing additional channels to open. The flow of ions through the newly opened channels depolarizes the membrane. Conversely, if the displacement is in the opposite direction, the tension on the tip links decreases, the open channels close, and the membrane hyperpolarizes. *Thus, the mechanical motion of the hair bundle is directly converted into current flow across the hair-cell membrane*.

32.4.2 A Candidate Mechanosensory Channel Has Been Identified in *Drosophila*

A likely ortholog of the transduction channel in hearing has been identified in fruit flies. *Drosophila* have sensory bristles used for detecting small air currents. These bristles respond to mechanical displacement in ways similar to those of hair cells; displacement of a bristle in one direction leads to substantial transmembrane current. To isolate the gene encoding the transduction channel, investigators isolated 27 different strains of mutant fruit flies that showed uncoordinated motion and clumsiness and then examined their electrophysiological responses to displacement of the sensory bristles. In one set of strains, transmembrane currents were dramatically reduced. The mutated gene in these strains was found to encode a protein of 1619 amino acids, called NompC for *no m*echanoreceptor *p*otential.

The carboxyl-terminal 469 amino acids of NompC resemble a class of ion channel proteins called TRP (transient receptor potential) channels. This region includes six putative transmembrane helices with a porelike region between the fifth and sixth helices. The amino-terminal 1150 amino acids consist almost exclusively of 29 *ankyrin repeats* (Figure 32.35). Ankyrin repeats are structural motifs formed by 33 amino acids folded into a hairpin loop followed by a helix-turn-helix. Importantly, in other proteins, regions with tandem arrays of these motifs mediate protein–protein interactions. Although the role of the ankyrin repeats in NompC has not yet been established, they likely mediate interactions with other components to couple mechanical motion to conformational changes in the channel. The *C. elegans* genome encodes an orthologous protein that also is expressed in mechanosensory neurons. Given the mechanistic parallels, homologous sequences from the human genome are strong candidates for genes encoding the transduction channel in hearing.

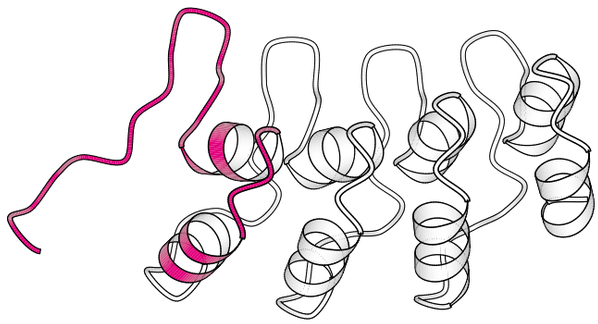


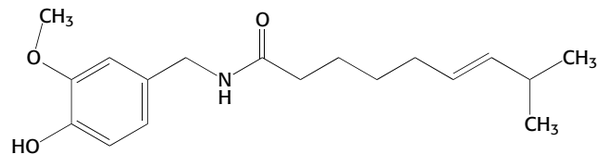
FIGURE 32.35 Ankyrin repeat structure. Four ankyrin repeats are shown with one shown in red. These domains interact with other proteins, primarily through their loops.

32.5 TOUCH INCLUDES THE SENSING OF PRESSURE, TEMPERATURE, AND OTHER FACTORS

Like taste, touch is a combination of sensory systems that are expressed in a common organ—in this case, the skin. The detection of pressure and the detection of temperature are two key components. Amiloride-sensitive sodium channels, homologous to those of taste, appear to play a role. Other systems are responsible for detecting painful stimuli such as high temperature, acid, or certain specific chemicals. Although our understanding of this sensory system is not as advanced as that of the other sensory systems, recent work has revealed a fascinating relation between pain and taste sensation, a relation well known to anyone who has eaten "spicy" food.

32.5.1 Studies of Capsaicin, the Active Ingredient in "Hot" Peppers, Reveal a Receptor for Sensing High Temperatures and Other Painful Stimuli

Our sense of touch is intimately connected with the sensation of pain. Specialized neurons, termed *nociceptors*, transmit signals to pain-processing centers in the spinal cord and brain in response to the onset of tissue damage. What is the molecular basis for the sensation of pain? An intriguing clue came from the realization that *capsaicin*, the chemical responsible for the "hot" taste of spicy food, activates nociceptors.



Capsaicin

Early research suggested that capsaicin would act by opening ion channels that are expressed in nociceptors. Thus, a cell that expresses the capsaicin receptor should take up calcium on treatment with the molecule. This insight led to the isolation of the capsaicin receptor with the use of cDNA from cells expressing this receptor. Such cells had been detected by their fluorescence when loaded with the calcium-sensitive compound Fura-2 and then treated with capsaicin or related molecules. Cells expressing the capsaicin receptor, which is called VR1 (for *v*anilloid *r*eceptor 1), respond to capsaicin below a concentration of 1 μM. The deduced 838-residue sequence of VR1 revealed it to be a member of the TRP channel family (Figure 32.36). The amino-terminal region of VR1 includes three ankyrin repeats.

Currents through VR1 are also induced by temperatures above 40°C and by exposure to dilute acid, with a midpoint for activation at pH 5.4 (Figure 32.37). Temperatures and acidity in these ranges are associated with infection and cell injury. The responses to capsaicin, temperature, and acidity are not independent. The response to heat is greater at lower pH, for example. Thus, *VR1 acts to integrate several noxious stimuli*. We feel these responses as pain and act to avoid the potentially destructive conditions that caused the unpleasant sensation. Mice that do not express VR1 suggest that this is the case; such mice do not mind food containing high concentrations of capsaicin and are, indeed, less responsive than control mice to normally noxious heat. Plants such as chili peppers presumably gained the ability to synthesize capsaicin and other "hot" compounds to protect themselves from being consumed by mammals. Birds, which play the beneficial role of spreading pepper seeds into new territory, do not appear to respond to capsaicin.

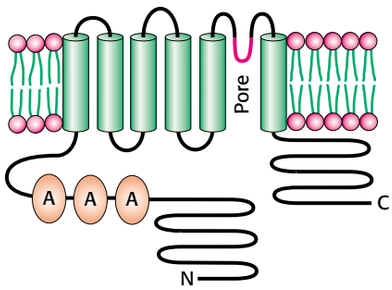


FIGURE 32.36 The membrane topology deduced for VR1, the capsaicin receptor. The proposed site of the membrane pore is indicated in red, and the three ankyrin (A) repeats are shown in orange. The active receptor comprises four of these subunits. [Adapted from Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., and Julius, D. *Nature* 389 (1997):816.]

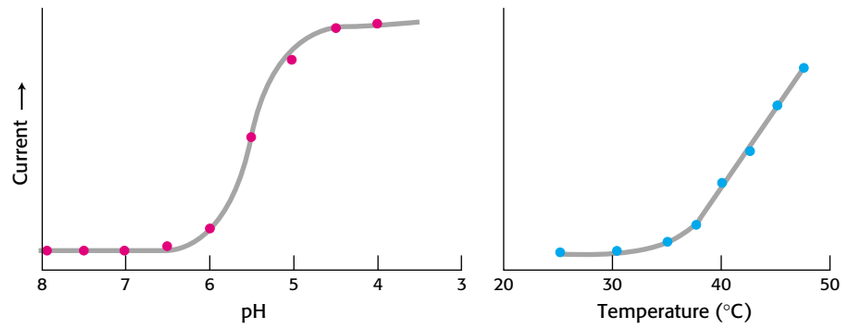


FIGURE 32.37 Response of the capsaicin receptor to pH and temperature. [Adapted from Tominaga, M., Caterina, M. J., Malmberg, A. B., Rosen, T. A., Gilbert, H., Skinner, K., Raumann, B. E., Basbaum, A. I., and Julius, D. *Neuron* 21(1998):531.]

Because of its ability to simulate VR1, capsaicin is used in pain management for arthritis, neuralgia, and other neuropathies. How can a compound that induces pain assist in its alleviation? Chronic exposure to capsaicin overstimulates pain-transmitting neurons, leading to their desensitization.

32.5.2 Subtle Sensory Systems Detect Other Environmental Factors Such as Earth's Magnetic Field

In addition to the five primary senses, human beings may have counterparts to less-familiar sensory systems characterized in other organisms. These sensory systems respond to environmental factors other than light, molecular shape, or air motion. For example, some species of bacteria are magnetotactic; that is, they move in directions dictated by Earth's magnetic field (Figure 32.38). In the Northern Hemisphere, Earth's magnetic field points northward but also has a component directed downward, toward Earth's center. Magnetotactic bacteria not only swim northward but also swim downward, away from the surface and the presence of high levels of oxygen, toxic to these bacteria. Remarkably, these bacteria synthesize intracellular chains of small particles containing a magnetic ore called magnetite (Fe_3O_4) that run through the center of each bacterium. Such chains are called *magnetosomes*. The magnetic force exerted by these particles is sufficiently strong in relation to the size of the bacterium that it causes the bacterium to become passively aligned with Earth's magnetic field. Intriguingly, similar magnetite particles have been detected in the brains of birds, fish, and even human beings, although their role in sensing magnetic fields has not yet been established.

There may exist other subtle senses that are able to detect environmental signals that then influence our behavior. The biochemical basis of these senses is now under investigation. One such sense is our ability to respond, often without our awareness, to chemical signals called pheromones, released by other persons. Another is our sense of time, manifested in our daily (circadian) rhythms of activity and restfulness. Daily changes in light exposure strongly influence these rhythms. The foundations for these senses have been uncovered in other organisms; future studies should reveal to what extent these mechanisms apply to human beings as well.

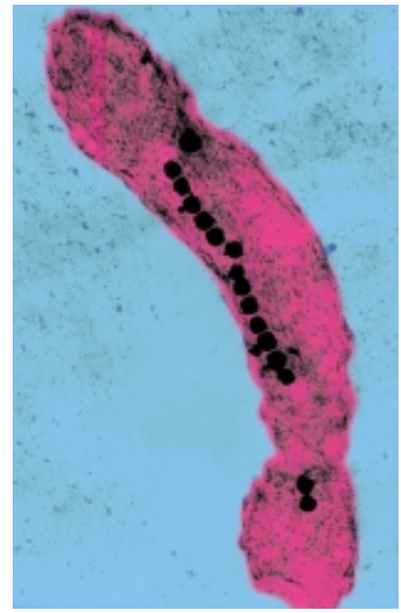


FIGURE 32.38 Magnetotactic bacterium. The magnetosome, visible as a chain of opaque membrane-bound magnetite crystals, acts as a compass to orient the bacteria with the earth's magnetic field. The bacterium is artificially colored. [Courtesy of Richard B. Frankel, California Polytechnic State University, San Luis Obispo, California.]

SUMMARY

- **Smell, taste, vision, hearing, and touch are based on signal-transduction pathways activated by signals from the environment.**
  These sensory systems function similarly to the signal-transduction pathways for many hormones. These intercellular signaling pathways appear to have been appropriated and modified to process environmental information.
- **A Wide Variety of Organic Compounds Are Detected by Olfaction**
  The sense of smell, or olfaction, is remarkable in its specificity—it can, for example, discern stereoisomers of small organic compounds as distinct aromas. The 7TM receptors that detect these odorants operate in conjunction with $G_{(olf)}$, a G protein that activates a cAMP cascade resulting in the opening of an ion channel and the generation of a nerve impulse. An outstanding feature of the olfactory system is its ability to detect a vast array of odorants. Each olfactory neuron expresses only one type of receptor and connects to a particular region of the olfactory

bulb. Odors are decoded by a combinatorial mechanism—each odorant activates a number of receptors, each to a different extent, and most receptors are activated by more than one odorant.

- **Taste Is a Combination of Senses That Function by Different Mechanisms**
We can detect only five tastes: bitter, sweet, salt, sour, and umami. The transduction pathways that detect taste are, however, diverse. Bitter and sweet tastants are experienced through 7TM receptors acting through a special G protein called gustducin. Salty and sour tastants act directly through membrane channels. Salt tastants are detected by passage though sodium channels, whereas sour taste results from the effects of hydrogen ions on a number of types of channels. The end point is the same in all cases—membrane polarization that results in the transmission of a nerve impulse. Umami, the taste of glutamate, is detected by a receptor that is a modified form of a brain receptor that responds to glutamate as a neurotransmitter rather than as a tastant.

- **Photoreceptor Molecules in the Eye Detect Visible Light**
Vision is perhaps the best understood of the senses. Two classes of photoreceptor cells exist: cones, which respond to bright lights and colors, and rods, which respond only to dim light. The photoreceptor in rods is rhodopsin, a 7TM receptor that is a complex of the protein opsin and the chromophore 11-*cis*-retinal. Absorption of light by 11-*cis*-retinal changes its structure into that of all-*trans*-retinal, setting in motion a signal-transduction pathway that leads to the breakdown of cGMP, to membrane hyperpolarization, and to a subsequent nerve impulse. Color vision is mediated by three distinct 7TM photoreceptors that employ 11-*cis*-retinal as a chromophore and absorb light in the blue, green, and red parts of the spectrum.

- **Hearing Depends on the Speedy Detection of Mechanical Stimuli**
The immediate receptors for hearing are found in the hair cells of the cochleae, which contain bundles of stereocilia. When the stereocilia move in response to sound waves, cation channels will open or close, depending on the direction of movement. The mechanical motion of the cilia is converted into current flow and then into a nerve impulse.

- **Touch Includes the Sensing of Pressure, Temperature, and Other Factors**
Touch, detected by the skin, senses pressure, temperature, and pain. Specialized nerve cells called nociceptors transmit signals that are interpreted in the brain as pain. A receptor responsible for the perception of pain has been isolated on the basis of its ability to bind capsaicin, the molecule responsible for the hot taste of spicy food. The capsaicin receptor, also called VR1, functions as a cation channel that initiates a nerve impulse.

KEY TERMS

main olfactory epithelium (p. 32-3)
$G_{(olf)}$ (p. 32-3)
functional magnetic resonance imaging (fMRI) (p. 32-6)
gustducin (p. 32-8)
amiloride-sensitive sodium channel (p. 32-10)
metabotrophic glutamate receptor (p. 31-11)
rod (p. 32-11)
cone (p. 32-11)
rhodopsin (p. 32-12)
opsin (p. 32-12)
retinal (p. 32-12)
chromophore (p. 32-12)
transducin (p. 32-14)
cGMP phosphodiesterase (p. 32-14)
rhodopsin kinase (p. 32-14)
arrestin (p. 32-14)
guanylate cyclase (p. 32-14)
cGMP-gated calcium channel (p. 32-15)
hair cell (p. 32-17)
stereocilium (p. 32-18)
tip link (p. 32-18)
nociceptor (p. 32-20)
capsaicin receptor (p. 32-20)

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PROBLEMS

1. *Of mice and rats*. As noted in Section 32.1.2, one of the first odorant receptors to be matched with its ligand was a rat receptor that responded best to *n*-octanal. The sequence of the corresponding mouse receptor differed from the rat receptor at 15 positions. Surprisingly, the mouse receptor was found to respond best to *n*-heptanal rather than *n*-octanal. The substitution of isoleucine at position 206 in the mouse for valine at this position in the rat receptor was found to be important in determining the specificity for *n*-heptanal. Propose an explanation.

2. *Olfaction in worms*. Unlike the olfactory neurons in the mammalian systems discussed herein, olfactory neurons in the nematode *C. elegans* express multiple olfactory receptors. In particular, one neuron (called AWA) expresses receptors for compounds to which the nematode is attracted, whereas a different neuron (called AWB) expresses receptors for compounds that the nematode avoids. Suppose that a transgenic nematode is generated such that one of the receptors for an attractant is expressed in AWB rather than AWA. What behavior would you expect in the presence of the corresponding attractant?

3. *Odorant matching*. A mixture of two of the compounds illustrated in Figure 32.6 is applied to a section of olfactory epithelium. Only receptors 3, 5, 9, 12, and 13 are activated,

according to Figure 32.7. Identify the likely compounds in the mixture.

4. *Timing*. Compare the aspects of taste (bitter, sweet, salty, sour) in regard to their potential for rapid time resolution.

5. *Two ears*. Our ability to determine the direction from which a sound is coming is partly based on the difference in time at which our two ears detect the sound. Given the speed of sound (350 meter/second) and the separation between our ears (0.15 meter), what difference is expected in the times at which a sound arrives at our two ears? How does this difference compare with the time resolution of the human hearing system? Would a sensory system that utilized 7TM receptors and G proteins be capable of adequate time resolution?

6. *Constitutive mutants*. What effect within the olfactory system would you expect for a mutant in which adenylate cyclase is always fully active? What effect within the visual system would you expect for a mutant in which guanylate cyclase is always fully active?

7. *Bottle choice*. A widely used method for quantitatively monitoring rodent behavior with regard to taste is the bottle-choice assay. An animal is placed in a cage with two water bottles, one of which contains a potential tastant. After a fixed period of time (24–48 hours), the amount of water remaining in each bottle is measured. Suppose that much less water remains in the bottle with the tastant after 48 hours. Do you suspect the tastant to be sweet or bitter?

8. *It's better to be bitter*. Some nontoxic plants taste very bitter to us. Suggest one or more explanations.

9. *Unexpected consequences*. Sildenafil (Viagra) is a drug widely used to treat male impotence. Sildenafil exerts its effect by inhibiting a cGMP phosphodiesterase isozyme (PDE5) that is especially prevalent in smooth muscle. Interestingly, certain airlines restrict pilots from flying for 24 hours after using sildenafil. Suggest a reason for this restriction.

Chapter Integration Problem

10. *Energy and information*. The transmission of sensory information requires the input of free energy. For each sensory system (olfaction, gustation, vision, hearing, and touch), identify mechanisms for the input of free energy that allow the transmission of sensory information.

Mechanism Problem

11. *Schiff-base formation*. Propose a mechanism for the reaction between opsin and 11-*cis*-retinal.

Media Problems

12. *Homologous proteins, analogous binding?* Odorants bind to 7TM receptors, but where they bind (and whether all bind in the same way) is unclear. Odorants might, for example, bind on the extracellular surface, or, like retinal, they might bind in the interior of the transmembrane region. Problem 1 of this chapter presents evidence for the direct involvement of residue 206 in odorant binding in receptors from mouse and rat. While these receptors' structures are not known in detail, their sequences are similar enough to rhodopsin's that the rhodopsin structure can be used to infer the approximate location of residue 206. To see the likely location, look in the **Structural Insights** module on rhodopsin. Where do you think the mouse and rat receptors bind their odorants?

13. *Deodorant?* A cAMP phosphodiesterase has been discovered that is found predominantly in olfactory sensory neurons (Yan et al., 1995, Proc. Natl. Acad. Sci. 10:9677). The enzyme is activated by Ca^{2+}. What do you think this enzyme does, and why do you think it is regulated by calcium? (Hint: Study the response and recovery animations in the **Conceptual Insights** module on signaling pathways.)