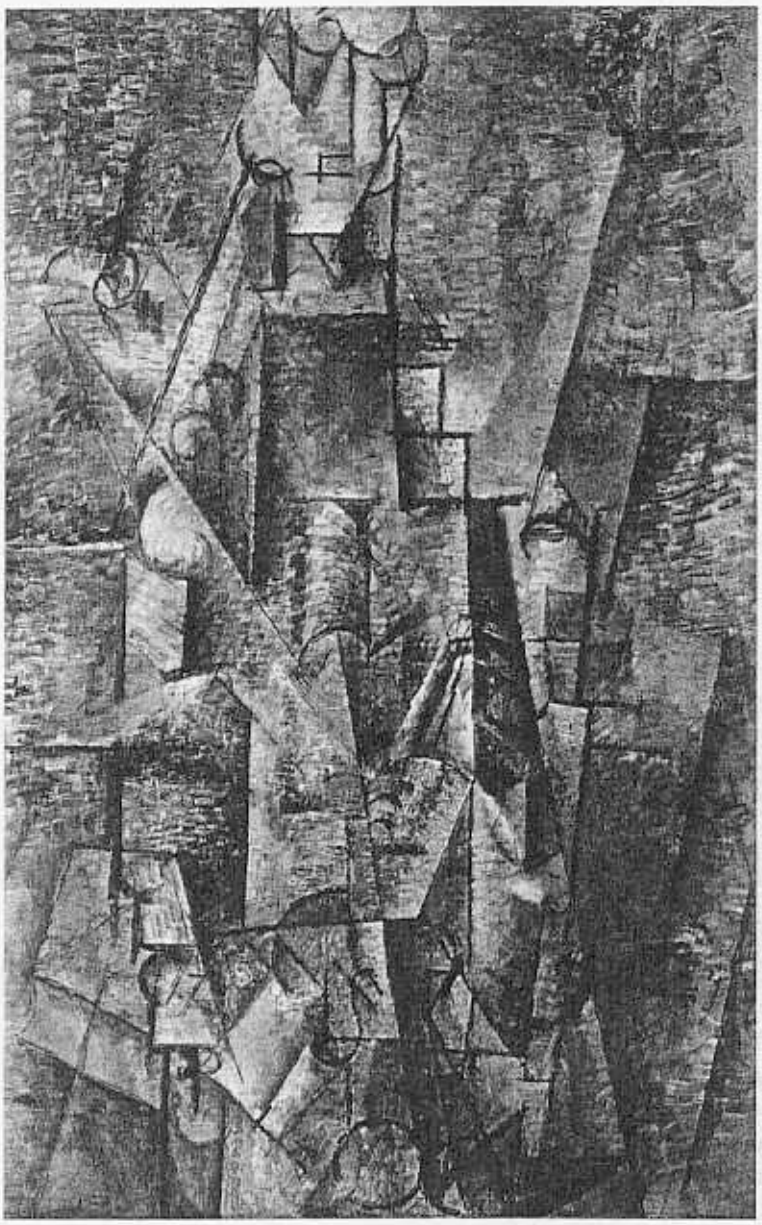
CHAPTER 7

Audition, the Body Senses, and the Chemical Senses



Man with a Clarinet by Pablo Picasso.

CHAPTER OUTLINE

One chapter was devoted to vision, but the rest of the sensory modalities must share a chapter. This unequal allocation of space reflects the relative importance of vision to our species and the relative amount of research that has been devoted to it. People often say that we have five senses: sight, hearing, smell, taste, and touch. Actually, we have more than five. For example, besides providing us with auditory information, the inner ear supplies information about head orientation and movement. And the sense of touch (more accurately, *somatosensation*) detects changes in pressure, warmth, cold, vibration, limb position, and events that damage tissue (that is, produce pain).

This chapter is divided into five major sections, which discuss audition, the vestibular system, the somatosenses, gustation, and olfaction.

Audition

For most people audition is the second most important sense. The value of verbal communication makes it even more important than vision in some respects; for example, a blind person can join others in conversation far more easily than a deaf person can. (Of course, deaf people can use sign language to converse.) Acoustic stimuli also provide information about things that are hidden from view, and our ears work just as well in the dark. This section describes the nature of the stimulus, the sensory receptors, the brain mechanisms devoted to audition, and some of the details of the physiology of auditory perception.

The Stimulus

We hear sounds, which are produced by objects that vibrate and set molecules of air into motion. When an object vibrates, its movements cause the air surrounding it alternately to condense and rarefy (pull apart), producing waves that travel away from the object at approximately 700 miles per hour. If the vibration ranges between approximately 30 and 20,000 times per second, these waves will stimulate receptive cells in our ears and will be perceived as sounds. (See ***Figure 7.1.***)

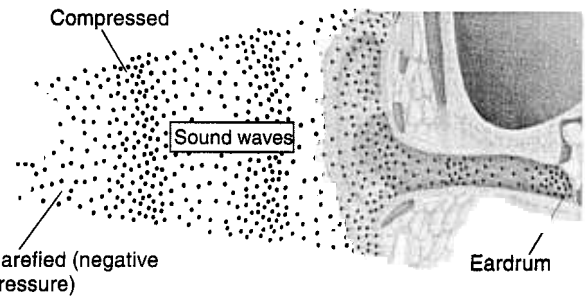


Figure 7.

Sound waves. Changes in air pressure from sound waves move the eardrum in and out. Air molecules are closer together in regions of higher pressure and farther apart in regions of lower pressure.

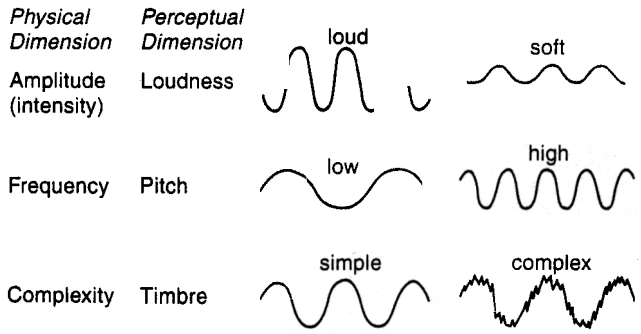


Figure 7.2

The physical and perceptual dimensions of sound waves.

In Chapter 6 we saw that light has three perceptual dimensions—hue, brightness, and saturation—that correspond to three physical dimensions. Similarly, sounds vary in their pitch, loudness, and timbre. The perceived **pitch** of an auditory stimulus is determined by the frequency of vibration, which is measured in **hertz (Hz)**, or cycles per second. (The term honors Heinrich Hertz, a nineteenth-century German physicist.) **Loudness** is a function of intensity—the degree to which the condensations and rarefactions of air differ from each other. More vigorous vibrations of an object produce more intense sound waves and hence louder ones. **Timbre** provides information about the nature of the particular sound—for example, the sound of an oboe or a train whistle. Most natural acoustic stimuli are complex, consisting of several different frequencies of vibration. The particular mixture determines the sound's timbre. (See ***Figure 7.2.***)

The eye is a *synthetic* organ (literally, "a putting together"). When two different wavelengths of light are mixed, we perceive a single color. For example, when we see a mixture of red and bluish green light, we perceive pure yellow light and cannot detect either of the two constituents. In contrast, the ear is an *analytical* organ (from *analyein*, "to undo"). When two different frequencies of sound waves are mixed, we do not perceive an intermediate tone; instead, we hear both original tones. As we will see, the ability of our auditory system to detect the individual component frequencies of a complex tone gives us the capacity to identify the nature of particular sounds, such as those of different musical instruments.

Anatomy of the Ear

Figure 7.3 shows a section through the ear and auditory canal and illustrates the apparatus of the middle and inner ear. (See ***Figure 7.3.***) Sound is funneled via the *pinna* (external ear) through the ear canal to the **tympanic membrane** (eardrum), which vibrates with the sound.

The *middle ear* consists of a hollow region behind the tympanic membrane, approximately 2 ml in volume. It contains the bones of the middle ear, called the **ossicles**, which are set into vibration by the tympanic membrane. (As we saw in Chapter 1, two of these bones evolved from part of the reptilian jaw.) The **malleus** (hammer) connects with the tympanic membrane and transmits vibrations via the **incus** (anvil) and **stapes** (stirrup) to the **cochlea**, the structure that contains the receptors. The baseplate of the stapes presses against the membrane behind the **oval window**, the opening in the bony process surrounding the cochlea. (See ***Figure 7.3.***)

The cochlea is part of the *inner ear.* It is filled with fluid; therefore, sounds transmitted through the air must be transferred into a liquid medium. This process normally is very inefficient—99.9 percent of the energy of airborne sound would be reflected away if the air impinged directly against the oval window of the cochlea. (If you have ever swum underwater, you have probably noted how quiet it is there; most of the sound arising in the air is reflected off the surface of the water.) The chain of ossicles serves as an extremely efficient means of energy transmission. The bones provide a mechanical advantage, with the baseplate of the stapes making smaller but more forceful excursions against the oval window than the tympanic membrane makes against the malleus.

The name *cochlea* comes from the Greek word *kokhlos*, or "land snail." It is indeed snail-shaped, consisting of two and three-quarters turns of a gradually tapering cylinder, 35 mm (1.37 in.) long. The cochlea is divided

pitch A perceptual dimension of sound; corresponds to the fundamental frequency.

hertz (Hz) Cycles per second.

loudness A perceptual dimension of sound; corresponds to intensity.

timbre (***tim*** *ber* or ***tamm*** *ber*) A perceptual dimension of sound; corresponds to complexity.

tympanic membrane The eardrum.

ossicle (***ahss*** *i kul*) One of the three bones of the middle ear.

malleus The "hammer"; the first of the three ossicles.

incus The "anvil"; the second of the three ossicles.

stapes (***stay*** *peez*) The "stirrup"; the last of the three ossicles.

cochlea (***cock*** *lee uh*) The snail-shaped structure of the inner ear that contains the auditory transducing mechanisms.

oval window An opening in the bone surrounding the cochlea that reveals a membrane, against which the baseplate of the stapes presses, transmitting sound vibrations into the fluid within the cochlea.

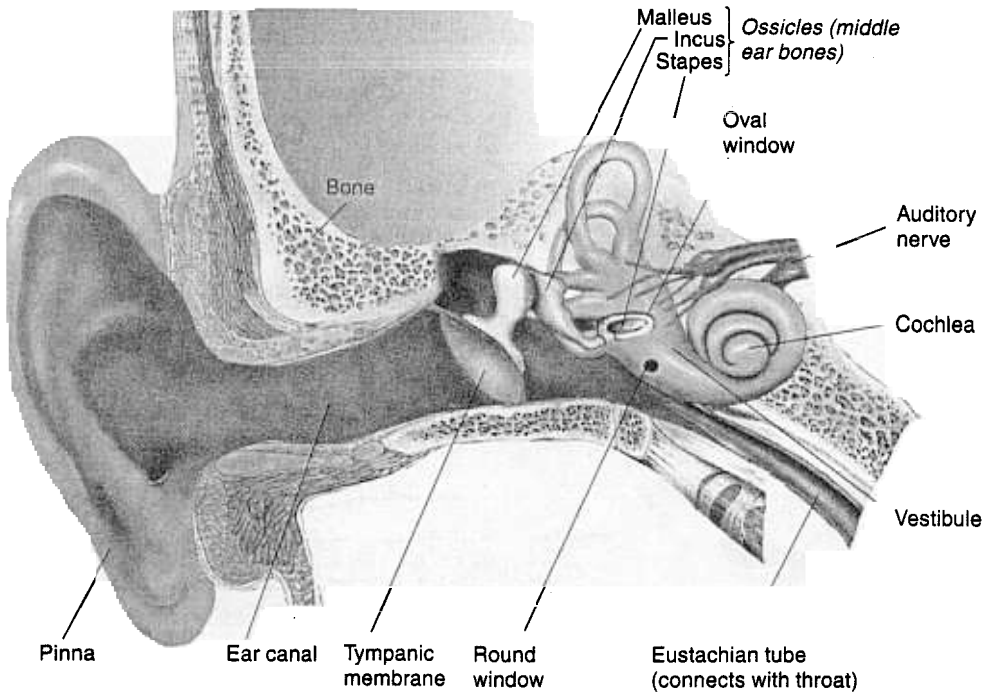


Figure 7.3
The auditory apparatus.

longitudinally into three sections, the *scala vestibuli* ("vestibular stairway"), the *scala media* ("middle stairway"), and the *scala tympani* ("tympanic stairway"), as shown in ***Figure 7.4.*** The receptive organ, known as the **organ of Corti,** consists of the *basilar membrane,* the *hair cells,* and the *tectorial membrane.* The auditory receptor cells are called **hair cells,** and they are anchored, via rod-like **Deiters's cells,** to the **basilar membrane.** The cilia of the hair cells pass through the *reticular membrane,* and the ends of some of them attach to the fairly rigid **tectorial membrane,** which projects overhead like a shelf. (See ***Figure 7.4.***) Sound waves cause the basilar membrane to move relative to the tectorial membrane, which bends the cilia of the hair cells. This bending produces receptor potentials.

Georg von Békésy—in a lifetime of brilliant studies on the cochleas of various animals, from human cadavers to elephants—found that the vibratory energy exerted on the oval window causes the basilar membrane to bend (von Békésy, 1960). Because of the physical characteristics of the basilar membrane, the portion that bends the most is determined by the frequency of the sound: High-frequency sounds cause the end nearest the oval window to bend.

Figure 7.5 shows this process in a cochlea that has been partially straightened. If the cochlea were a closed system, no vibration would be transmitted through the oval window, because liquids are essentially incompressible. However, there is a membrane-covered opening, the **round window,** that allows the fluid inside the cochlea to move back and forth. The baseplate of the stapes vibrates against the membrane behind the oval window and introduces sound waves of high or low frequency into the cochlea. The vibrations cause part of the basilar membrane to flex back and forth. Pressure changes in the fluid underneath the basilar membrane are transmitted to the membrane of the round window, which moves in and out in a manner opposite to the movements of the oval window. That is, when the baseplate of the stapes pushes in, the membrane behind the round window bulges out. As we will see in a later subsection, different frequencies of sound vibrations

organ of Corti The sensory organ on the basilar membrane that contains the auditory hair cells.

hair cell The receptive cell of the auditory apparatus.

Deiters's cell (*dye terz*) A supporting cell found in the organ of Corti; sustains the auditory hair cells.

basilar membrane (*bazz i ler*) A membrane in the cochlea of the inner ear; contains the organ of Corti.

tectorial membrane (*tek torr ee ul*) A membrane located above the basilar membrane; serves as a shelf against which the cilia of the auditory hair cells move.

round window An opening in the bone surrounding the cochlea of the inner ear that permits vibrations to be transmitted, via the oval window, into the fluid in the cochlea.

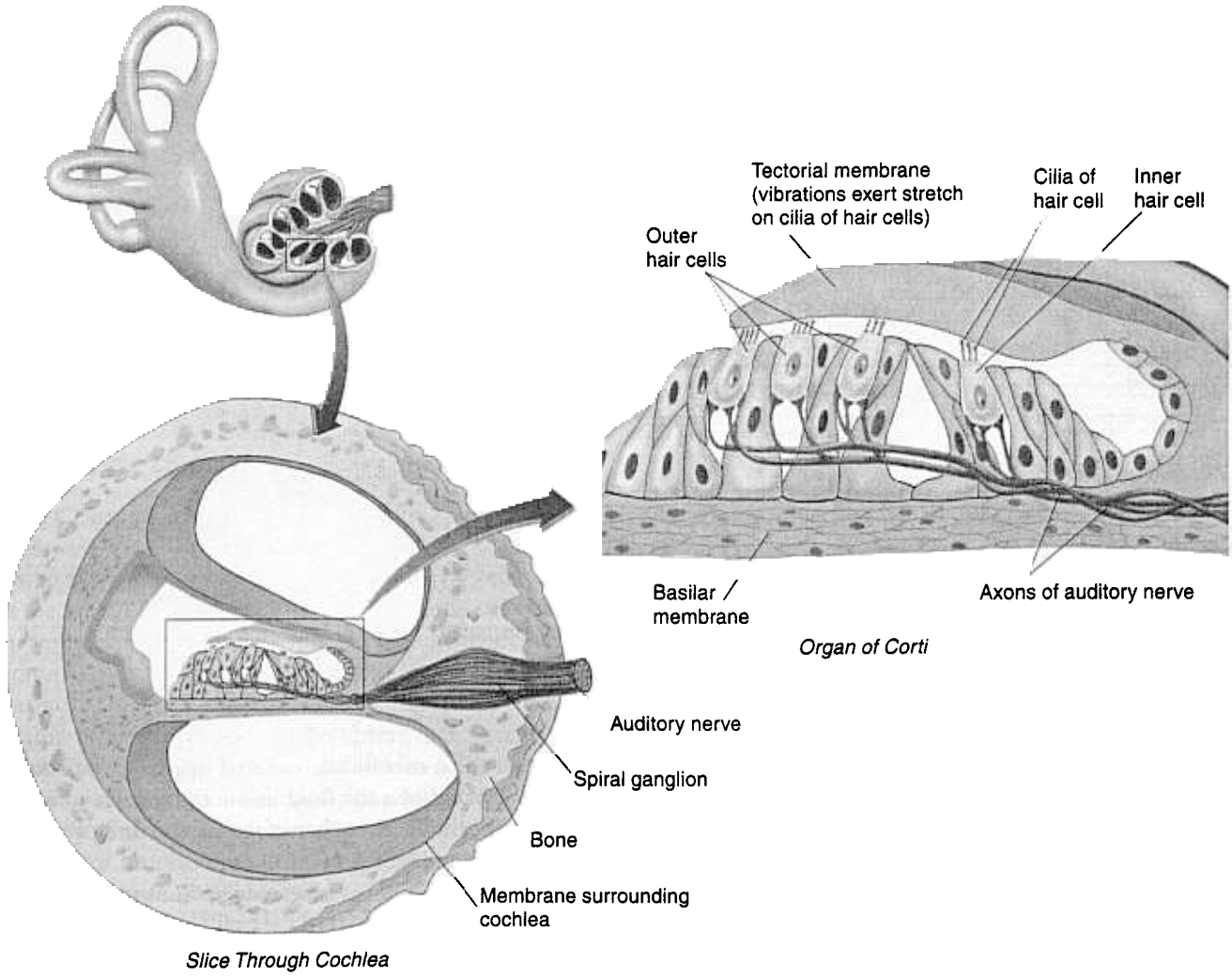


Figure 7.4

A cross section through the cochlea, showing the organ of Corti.

cause different portions of the basilar membrane to flex. (See *Figure 7.5.*)

Some people suffer from a middle ear disease that causes the bone to grow over the round window. Because their basilar membrane cannot easily flex back and forth, these people have a severe hearing loss. However, their hearing can be restored by a surgical procedure called *fenestration* ("window making"), in which a tiny hole is drilled in the bone where the round window should be.

Auditory Hair Cells and the Transduction of Auditory Information

Two types of auditory receptors, *inner* and *outer* auditory hair cells, lie on the inside and outside of the cochlear coils, respectively. Hair cells contain **cilia** ("eyelashes"), fine hairlike appendages, arranged in rows, according to height. The human cochlea contains approximately 3500 inner hair cells and 12,000 outer hair cells. The hair cells form synapses with dendrites of bipolar neurons whose axons bring auditory information to the brain. Figure 7.6 shows the appearance of the inner and outer hair cells and the reticular membrane in a photograph taken by means of a scanning electron microscope. Note the three rows of outer

cilium A hairlike appendage of a cell involved in movement or in transducing sensory information; found on the receptors in the auditory and vestibular system.

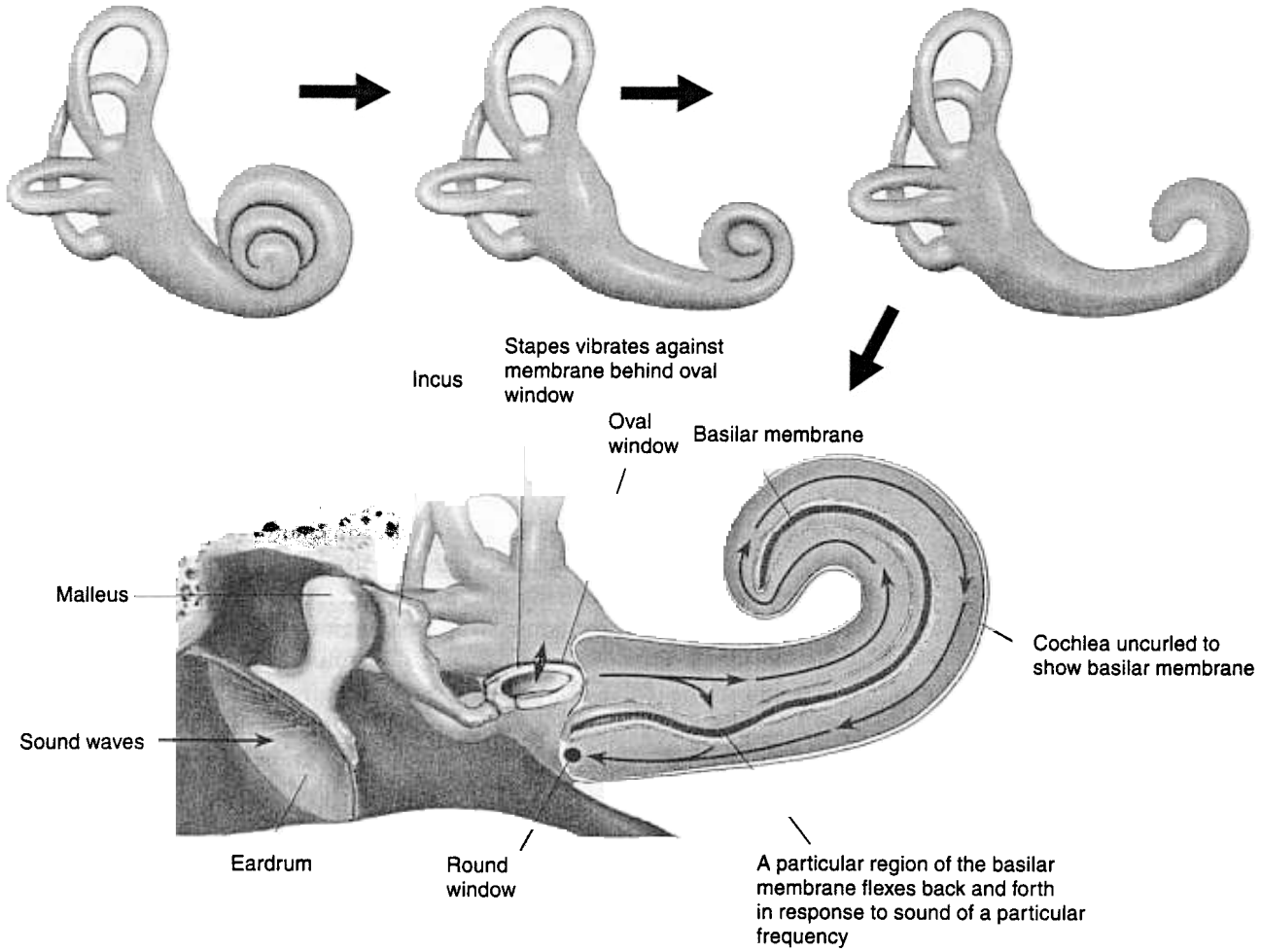


Figure 7.5

Responses to sound waves. When the stapes pushes against the membrane behind the oval window, the membrane behind the round window bulges outward. Different high-frequency and medium-frequency sound vibrations cause flexing of different portions of the basilar membrane. In contrast, low-frequency sound vibrations cause the tip of the basilar membrane to flex in synchrony with the vibrations.

hair cells on the right and the single row of inner hair cells on the left. (See *Figure 7.6.*)

Sound waves cause both the basilar membrane and the tectorial membrane to flex up and down. These movements bend the cilia of the hair cells in one direction or the other. The tips of the cilia of outer hair cells are attached directly to the tectorial membrane. The cilia of the inner hair cells do not touch the overlying tectorial membrane, but the relative movement of the two membranes causes the fluid within the cochlea to flow past them, making them bend back and forth, too.

Cilia contain a core of actin filaments surrounded by myosin filaments, and these proteins make the cilia stiff and rigid (Flock, 1977). Adjacent cilia are linked to each other by elastic filaments known as **tip links.** Each tip link is attached to the end of one cilium and to the side of an adjacent cilium. The points of attachment, known as **insertional plaques,** look dark under an electron microscope. As we will see, receptor potentials are triggered at the insertional plaques. (See *Figure 7.7.*)

Normally, tip links are slightly stretched, which means that they are under a small amount of tension. Thus,

tip link An elastic filament that attaches the tip of one cilium to the side of the adjacent cilium.

insertional plaque The point of attachment of a tip link to a cilium.

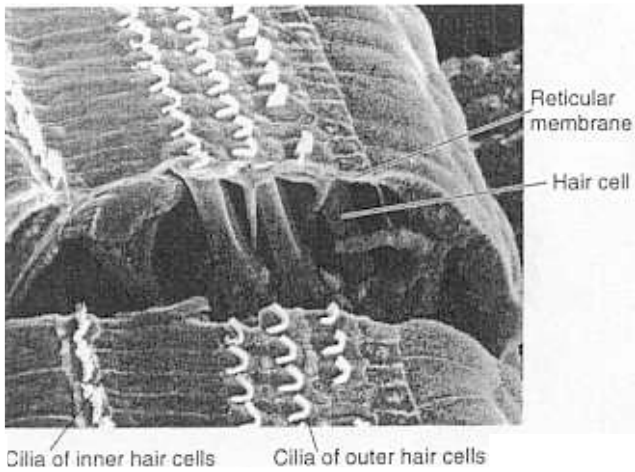


Figure 7.6

A scanning electron photomicrograph of a portion of the organ of Corti, showing the cilia of the inner and outer hair cells.
(Photomicrograph courtesy of I. Hunter-Duvar, The Hospital for Sick Children, Toronto, Ontario.)

movement of the bundle of cilia in the direction of the tallest of them further stretches these linking fibers, whereas movement in the opposite direction relaxes them. The bending of the bundle of cilia causes receptor potentials (Pickles and Corey, 1992; Hudspeth and Gillespie, 1994; Gillespie, 1995; Jaramillo, 1995). Unlike the fluid that surrounds most neurons, the fluid that surrounds the auditory hair cells is rich in potassium. Each insertional plaque contains a single cation channel. When the bundle of cilia is straight, the probability of an individual ion channel being open is approximately 10 percent. This means that a small amount of K^+ and Ca^{2+} diffuses into the cilium. When the bundle moves toward the tallest one, the increased tension on the tip links opens all the ion channels, the flow of K^+ and Ca^{2+} into the cilium increases, and the membrane depolarizes. As a result, the release of neurotransmitter by the hair cell increases. When the bundle moves in the opposite direction, toward the shortest cilium, the relaxation of the tip links allows the opened ion channels to close. The influx of K^+ and Ca^{2+} ceases, the membrane hyperpolarizes, and the release of neurotransmitter decreases. (See ***Figure 7.8.***)

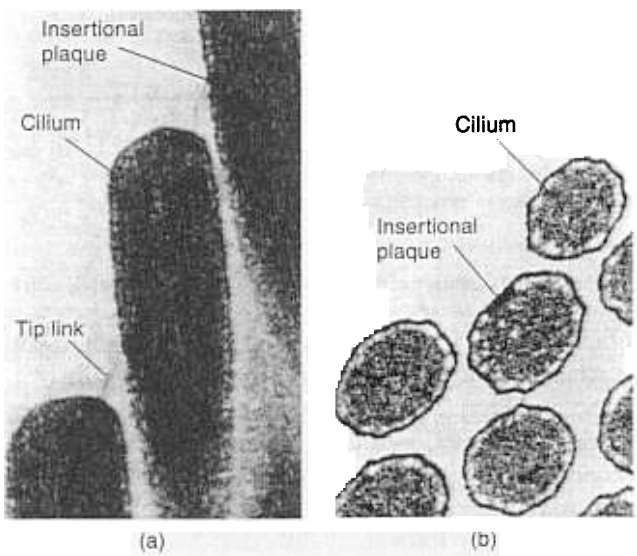


Figure 7.7

Electron micrographs of the transduction apparatus in hair cells. (a) Longitudinal section through three adjacent cilia. Tip links, elastic filaments attached to insertional plaques, link adjacent cilia. (b) A cross section through several cilia, showing an insertional plaque.
(From Hudspeth, A. J., and Gillespie, P. G. *Neuron*, 1994, *12*, 1–9.)

The location of the ion channels at the end of each tip link was revealed by use of calcium green, a calcium-sensitive fluorescent dye. Denk et al. (1995) placed tissue containing a group of hair cells in a fluid-filled chamber. They used a special scanning microscope that produced a very fine laser beam of infrared light to detect the presence of calcium in individual cilia. A micropipette located to the side of the bundle of cilia could eject or aspirate a stream of liquid, thus moving the bundle toward or away from the longest cilia. They also attached a recording microelectrode to the hair cell to record receptor potentials. (See ***Figure 7.9*** on page 208.)

Denk and his colleagues found that deflection of the bundle of cilia toward the tallest one produced a depolarization in the hair cell membrane and was accompanied by the entry of calcium. Larger displacements produced greater depolarizations and resulted in more cilia being filled with calcium. The calcium entered at the tips of the cilia and then spread through the cilia toward the body of the hair cells. Previous studies had obtained evidence suggesting that the ion channels were located near the tips of the cilia, but it had proved impossible to determine whether they were located at both ends of the tip links or only at one end. If ion channels were located at only one end of the tip links, then either the shortest or the longest cilia should not contain ion channels and thus should never be filled with calcium. However, Denk et al. found that cilia in all locations could admit calcium; therefore, the ion channels were located at both ends of the tip links. (See ***Figure 7.10*** on page 208.)

Exactly how does stretching a tip link cause an ion channel to open? Most researchers believe that the tip links are attached directly to the ion channels, and when there is a sufficient amount of tension on them, the pores of the ion channels are pulled open. In fact, Preyer et al. (1995) found that when tip links were dissolved by a special enzyme, dis-

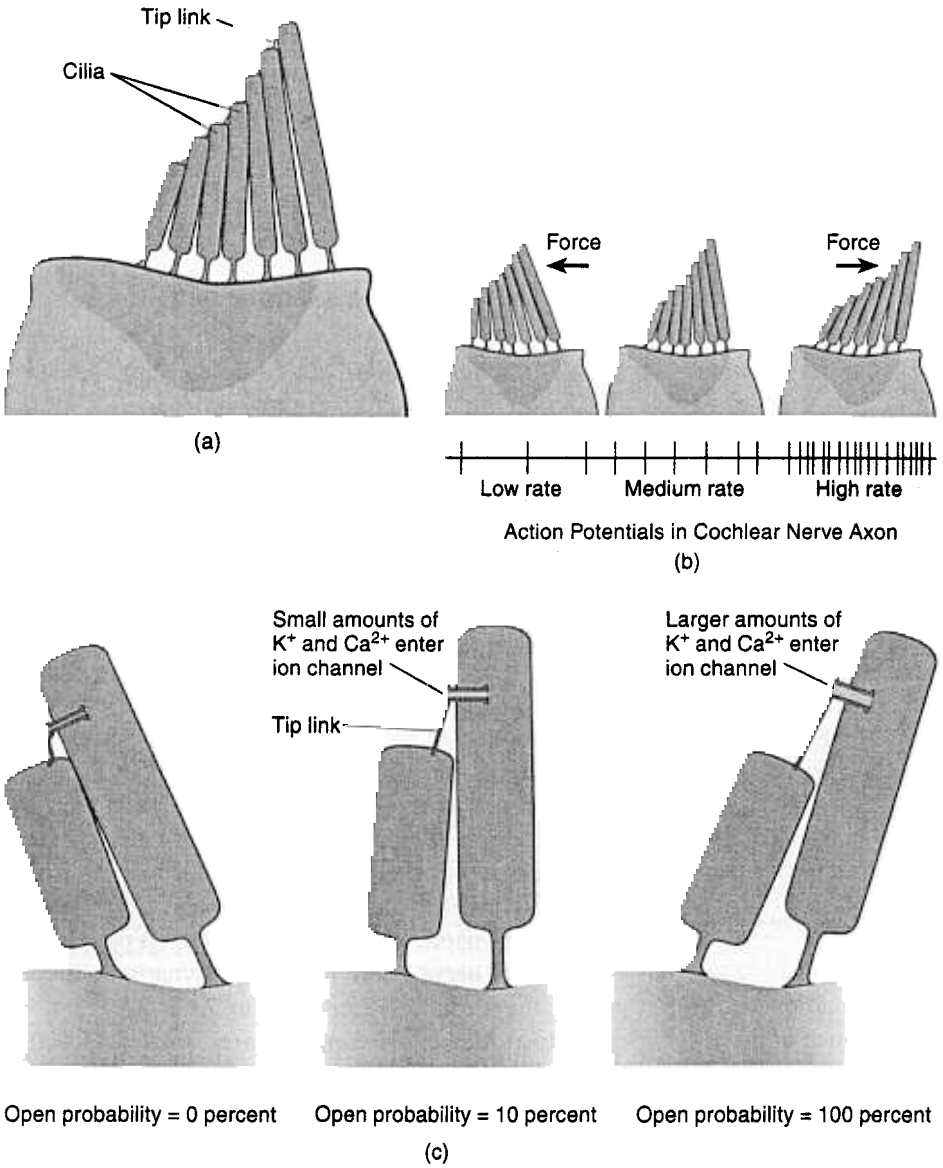


Figure 7.8

Transduction in hair cells of the inner ear. (a) Appearance of the cilia of an auditory hair cell. (b) Movement of the bundle of cilia toward the tallest one increases the firing rate of the cochlear nerve axon attached to the hair cell, while movement away from the tallest one decreases it. (c) Movement toward the tallest cilium increases tension on the tip links, which opens the ion channels and increases the influx of K^+ and Ca^{2+} ions. Movement toward the shortest cilium removes tension from the tip links, which permits the ion channels to close, stopping the influx of cations.

placement of the bundle of cilia no longer produced receptor potentials. Thus, tension on the tip links, and not simple movement of the cilia, is what opens the ion channels.

Figure 7.11 illustrates this process. It also illustrates a hypothetical explanation for the fact that the tension on the tip links is self-adjusting. For the hair cells to be maximally sensitive to movements of the bundle of cilia, the tension on the tip links must be just right. If the tension is too low, the ion channels will not open when the bundle is moved toward the longest cilium. If the tension is too high, the ion channels will always be open. Research in several laboratories (Assad and Corey, 1992; Gillespie, 1995; Jaramillo, 1995) has shown that the ion channel located on the side of a cilium contains a myosin "motor" that is capable of crawling up or down the actin filaments that run the length of the cilia. (The interaction between myosin

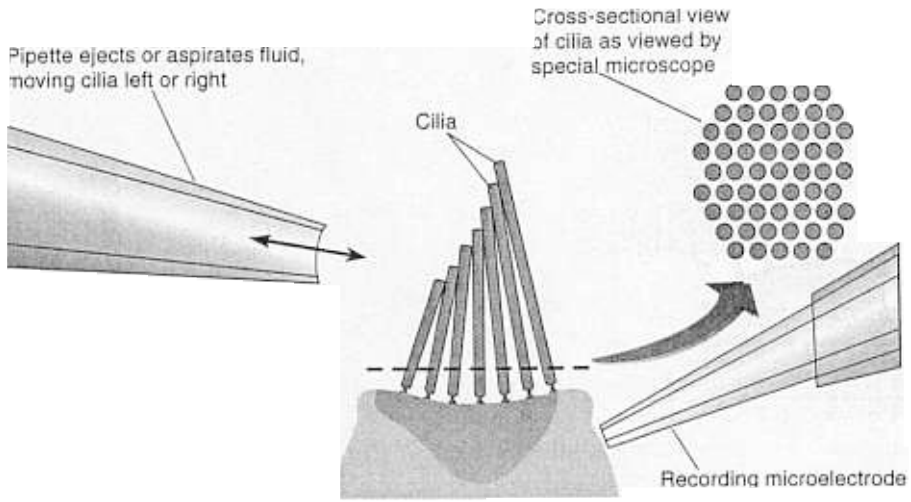


Figure 7.9

The experimental setup used by Denk et al. (1995) to detect the influx of calcium into the cilia of hair cells of the inner ear. (Adapted from Denk, W., Holt, J. R., Shepherd, G. M. G., and Corey, D. P. *Neuron*, 1995, *15*, 1311–1321.)

and actin is what provides the motive force responsible for muscular contraction. This process is described in Chapter 8.) When calcium ions enter an open ion channel, the myosin motor slides down, reducing the tension on the tip link. When the ion channel closes and calcium disappears from the cytoplasm of the cilium, the motor moves up, increasing the tension on the tip link. (See ***Figure 7.11.***)

The Auditory Pathway

Connections with the Cochlear Nerve

The organ of Corti sends auditory information to the brain by means of the **cochlear nerve**, a branch of the auditory nerve (eighth cranial nerve). The neurons that give rise to the afferent axons that travel through this nerve are of the bipolar type. Their cell bodies reside in the *cochlear nerve ganglion.* (This ganglion is also called the *spiral ganglion* because it consists of clumps of cell bodies arranged in a spiral caused by the curling of the cochlea.) These neurons have axonal processes, capable of sustaining action potentials, that protrude from both ends of the soma. The end of one process acts like a dendrite, responding with excitatory postsynaptic potentials when the neurotransmitter is released by the auditory hair cells. The excitatory postsynaptic potentials trigger action potentials in the auditory nerve axons, which form synapses with neurons in the medulla. (Refer to ***Figure 7.4.***)

Each cochlear nerve contains approximately 50,000 afferent axons. The dendrites of approximately 95 percent of these axons form synapses with the inner hair cells. Most afferent fibers make contact with only one inner hair cell, but each inner hair cell forms synapses with approximately 20 fibers (Dallos, 1992). The axons that receive information from the inner hair cells are thick and myelinated. The other 5 percent of the sensory fibers in the cochlear nerve form synapses with the much more numerous outer hair cells, at a ratio of approximately 1 fiber per 30 outer hair cells. In addition, these axons are thin and unmyelinated. Thus, although the inner hair cells represent only 29 percent of the total number of receptive cells, their connections with auditory nerves suggest that they are of primary importance in the transmission of auditory information to the central nervous system.

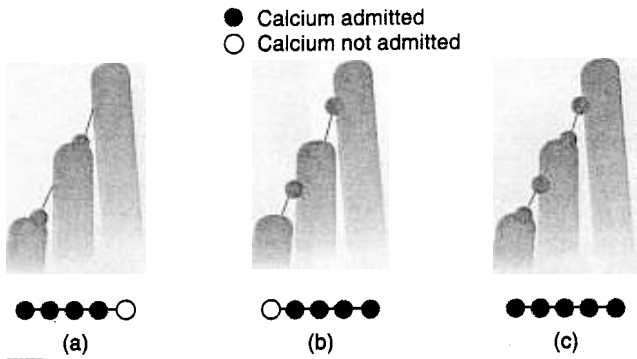


Figure 7.10

Verifying the location of ion channels in hair cells of the inner ear. If ion channels were found only at the insertional plaque located at the tip of the cilia (a) or at the side of the cilia (b), the longest or the shortest cilia should not admit calcium (indicated by the open circles). Because cilia in all locations admitted calcium, there must be an ion channel located at all insertional plaques (c). (Adapted from Denk, W., Holt, J. R., Shepherd, G. M. G., and Corey, D. P. *Neuron*, 1995, 15, 1311–1321.)

cochlear nerve The branch of the auditory nerve that transmits auditory information from the cochlea to the brain.

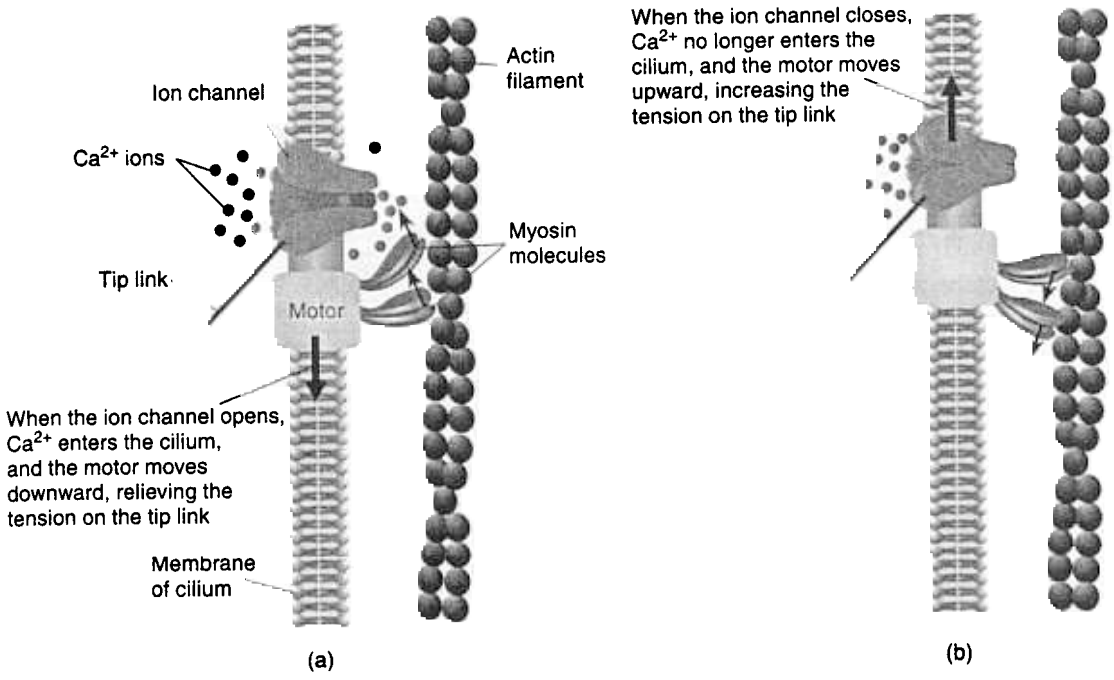


Figure 7.11

Transduction and control of the tension on the tip link. (a) Movement of the bundle of cilia toward the tallest one increases tension on the tip link, which opens the ion channels, permitting K^+ and Ca^{2+} to enter the cilia. When the ion channel is open, the entry of calcium ions causes the myosin motor to move down, reducing the tension on the tip link. (b) When the channel is closed, the disappearance of calcium causes the motor to move up, increasing the tension on the tip link. By these means tension on the tip links is regulated so that the hair cells are as sensitive as possible to sound vibrations.

(Adapted from Gillespie, P. G. *Current Opinion in Neurobiology,* 1995, *5,* 449–455 and Jaramillo, F. *Neuron,* 1995, *15,* 1227–1230.)

Physiological and behavioral studies confirm the inferences made from the synaptic connections of the two types of hair cells: The inner hair cells are necessary for normal hearing. In fact, Deol and Gluecksohn-Waelsch (1979) found that a mutant strain of mice whose cochleas contain *only* outer hair cells apparently cannot hear at all. Most investigators currently believe that the outer hair cells are primarily *effector* cells, involved in altering the mechanical characteristics of the basilar membrane and thus influencing the effects of sound vibrations on the inner hair cells. I will discuss this possibility in the section on place coding of pitch.

The cochlear nerve contains efferent axons as well as afferent ones. The source of the efferent axons is the superior olivary complex, a group of nuclei in the medulla; thus, the efferent fibers constitute the **olivocochlear bundle.** The fibers form synapses directly on outer hair cells and on the dendrites that serve the inner hair cells. The neurotransmitter at the afferent synapses appears to be an excitatory amino acid such as glutamate or aspartate. The efferent terminal buttons secrete acetylcholine, which appears to have an inhibitory effect on the hair cells.

The Central Auditory System

The anatomy of the auditory system is more complicated than that of the visual system. Rather than give a detailed verbal description of the pathways, I will refer you to *Figure 7.12.* Note that axons enter the **cochlear nucleus** of the medulla and synapse there. Most of the neurons in the cochlear nucleus send axons to the **superior olivary complex,** also located in the medulla. Axons of neurons in these nuclei pass through a large fiber bundle called the **lateral lemniscus** to the inferior colliculus, located in the

olivocochlear bundle A bundle of efferent axons that travel from the olivary complex of the medulla to the auditory hair cells on the cochlea.

cochlear nucleus One of a group of nuclei in the medulla that receive auditory information from the cochlea.

superior olivary complex A group of nuclei in the medulla; involved with auditory functions, including localization of the source of sounds.

lateral lemniscus A band of fibers running rostrally through the medulla and pons; carries fibers of the auditory system.

dorsal midbrain. Neurons there send their axons to the medial geniculate nucleus of the thalamus, which sends its axons to the auditory cortex of the temporal lobe. As you can see, there are many synapses along the way to complicate the story. Each hemisphere receives information from both ears but primarily from the contralateral one. Auditory information is relayed to the cerebellum and reticular formation as well.

If we unrolled the basilar membrane into a flat strip and followed afferent axons serving successive points along its length, we would reach successive points in the nuclei of the auditory system and ultimately successive points along the surface of the primary auditory cortex. The *basal* end of the basilar membrane (the end toward the oval window) is represented most medially in the auditory cortex, and the *apical* end is represented most laterally there. Because, as we will see, different parts of the basilar membrane respond best to different frequencies of sound, this relationship between cortex and basilar membrane is referred to as **tonotopic representation** (*tonos* means "tone," and *topos* means "place").

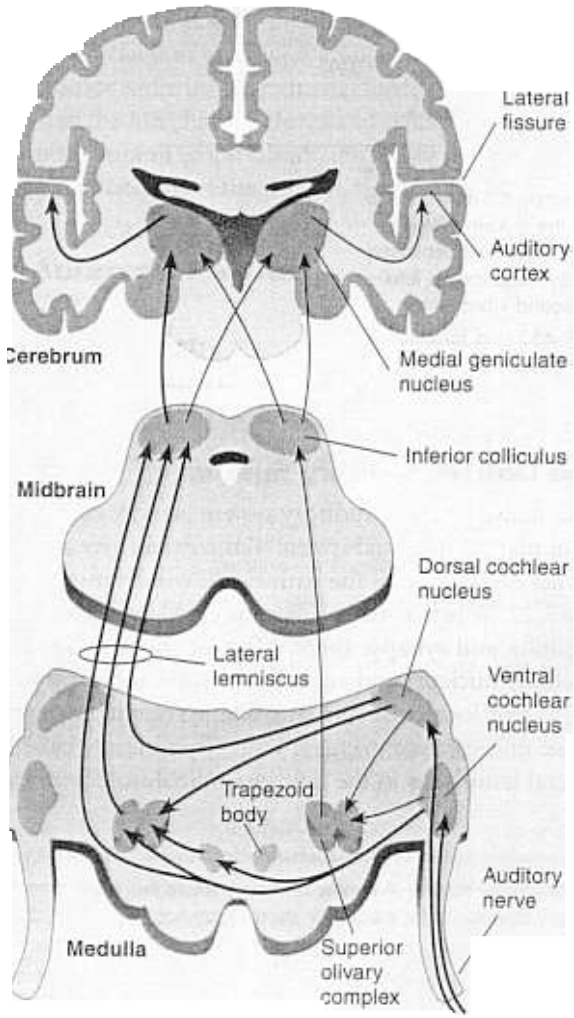


Figure 7.12
The pathway of the auditory system. The major pathways are indicated by heavy arrows.

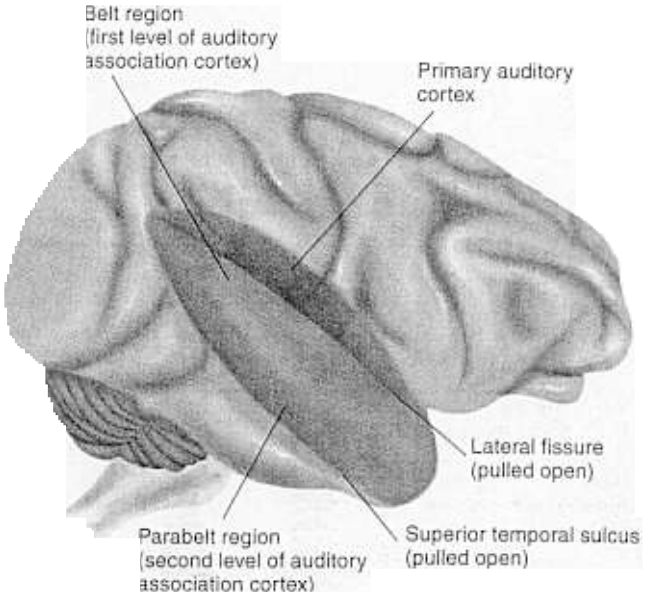


Figure 7.13
A lateral view of the monkey brain, showing the location of the primary auditory cortex, the belt region (first level of auditory association cortex), and the parabelt region (second level of auditory association cortex). The temporal lobe has been pulled down to expose the cortex on the upper and lower banks of the lateral fissure, and the superior temporal sulcus has been pulled apart. (Adapted from Kaas, J. H., Hackett, T. A., and Tramo, M. J. *Current Opinion in Neurobiology*, 1999, *9*, 164–170.)

As we saw in Chapter 3, the primary auditory cortex lies hidden on the upper bank of the lateral fissure. The primary auditory cortex actually consists of three regions, each of which receives a separate tonotopic map of auditory information from the ventral division from the medial geniculate nucleus (Kaas, Hackett, and Tramo, 1999). The first level of auditory association cortex, the **belt region,** surrounds the primary auditory cortex, much as the extrastriate cortex surrounds the primary visual (striate) cortex. The belt region receives information from both the primary auditory cortex and the dorsal and medial divisions of the medial geniculate nucleus. The second level of auditory association cortex, the **parabelt region,** receives information from the belt region and from the divisions of the medial geniculate nucleus that project to the belt region. The two major regions of the auditory association cortex, the belt and the parabelt, can themselves be further subdivided—into a dozen or more subregions. (See ***Figure 7.13.***)

Perception of Pitch

As we have seen, the perceptual dimension of pitch corresponds to the physical dimension of frequency. The cochlea detects frequency by two means: moderate to high frequencies by place coding and low frequencies by rate coding. These two types of coding are described next.

Place Coding

The work of von Békésy has shown us that because of the mechanical construction of the cochlea and basilar membrane, acoustic stimuli of different frequencies cause different parts of the basilar membrane to flex back and forth. Figure 7.14 illustrates the amount of deformation along the length of the basilar membrane produced by stimulation with tones of various frequencies. Note that higher frequencies produce more displacement at the basal end of the membrane (the end closest to the stapes). (See *Figure 7.14.*)

These results suggest that at least some frequencies of sound waves are detected by means of a **place code.** In this context a code represents a means by which neurons can represent information. Thus, if neurons at one end of the basilar membrane are excited by higher frequencies and those at the other end by lower frequencies, we can say that the frequency of the sound is *coded* by the particular neurons that are active. In turn, the firing of particular axons in the cochlear nerve tells the brain about the presence of particular frequencies of sound.

Evidence for place coding of pitch comes from several sources. High doses of the antibiotic drugs kanamycin and neomycin produce degeneration of the auditory hair cells. Damage to auditory hair cells begins at the basal end of the cochlea and progresses toward the apical end; this pattern can be verified by killing experimental animals after dosing them with the antibiotic for varying amounts of time. Longer exposures to the drug are associated with increased progress of hair cell damage down the basilar membrane. Stebbins et al. (1969) found that the progressive death of hair cells induced by an antibiotic closely parallels a progressive hearing loss: The highest frequencies are the first to go, and the lowest are the last.

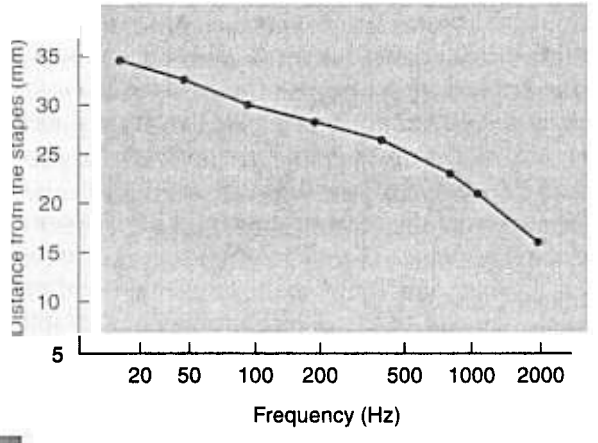


Figure 7.14

Anatomical coding of pitch. Stimuli of different frequencies maximally deform different regions of the basilar membrane.

(From von Békésy, G. *Journal of the Acoustical Society of America,* 1949, *21,* 233–245.)

Good evidence for place coding of pitch (at least, in humans) comes from the effectiveness of cochlear implants. **Cochlear implants** are devices used to restore hearing in people with deafness caused by damage to the hair cells. The external part of a cochlear implant consists of a microphone and a miniaturized electronic signal processor. The internal part contains a very thin, flexible array of electrodes, which the surgeon carefully inserts into the cochlea in such a way that it follows the snail-like curl and ends up resting along the entire length of the basilar membrane. Each electrode in the array stimulates a different part of the basilar membrane. Information from the signal processor is passed to the electrodes by means of flat coils of wire, implanted under the skin.

The primary purpose of a cochlear implant is to restore a person's ability to understand speech. Because most of the important acoustical information in speech is contained in frequencies too high to be accurately represented by a rate code, the multichannel electrode was developed in an attempt to duplicate the place coding of pitch on the basilar membrane (Loeb, 1990). When different regions of the basilar membrane are stimulated, the person perceives sounds with different pitches. The signal processor in the external device analyzes the sounds detected by the microphone and sends separate signals to the appropriate portions of the basilar membrane. This device can work well; some people with cochlear implants can understand speech well enough to use a telephone.

The work of von Békésy indicated that although the basilar membrane codes for frequency along its length, the coding

tonotopic representation (*tonn oh top ik*) A topographically organized mapping of different frequencies of sound that are represented in a particular region of the brain.

belt region The first level of auditory association cortex; surrounds the primary auditory cortex.

parabelt region The second level of auditory association cortex; surrounds the belt region.

place code The system by which information about different frequencies is coded by different locations on the basilar membrane.

cochlear implant An electronic device surgically implanted in the inner ear that can enable a deaf person to hear.

was not very specific. His studies, and those of investigators who followed him, indicated that a given frequency causes a large region of the basilar membrane to be deformed. This finding contrasted with the observation that people can detect changes in frequency of only 2 or 3 Hz.

The reason for this discrepancy is now clear. Because of technical limitations, von Békésy had to observe the cochleas of animals that were no longer living or, at best, cochleas that had been damaged by the procedure necessary to make the measurements. More recently, investigators have used much more sensitive—and less damaging—procedures to observe movements of the basilar membrane in response to different frequencies of sound. It appears that the point of maximum vibration of the basilar membrane to a particular frequency is very precisely localized—but only when the cells in the organ of Corti are alive and healthy (Evans, 1992; Ruggero, 1992; Narayan et al, 1998).

The fact that the tuning characteristics of the basilar membrane change when the cells in the organ of Corti die suggests that these cells somehow affect the mechanical properties of the basilar membrane. We now know that the outer hair cells are responsible for this selective tuning, but we do not understand yet exactly how they accomplish this feat. As I mentioned earlier, outer hair cells not only are sensory transducers but are also contractile elements: They contain actin and myosin filaments, just as muscle fibers do. When these cells are exposed to an electrical current, or when acetylcholine is placed on them, they contract by up to 10 percent of their length (Brownell et al., 1985; Zenner, Zimmermann, and Schmitt, 1985). Because the tips of their cilia are embedded in the tectorial membrane, contraction would affect the mechanical characteristics of the basilar membrane—and, consequently, the response properties of the inner hair cells. Kemp (1978) discovered that when brief sounds are presented to a normal cochlea, it produces a sound itself, which can be detected with a microphone. Presumably, this sound is produced by contraction of the outer hair cells. Most investigators believe that the signals that cause contraction of the outer hair cells come partly from the olivocochlear bundle and partly from local circuits of neurons within the organ of Corti.

Rate Coding

We have seen that the frequency of a sound can be detected by place coding. However, the lowest frequencies do not appear to be accounted for in this manner. Kiang (1965) was unable to find any cells that responded best to frequencies of less than 200 Hz. How, then, can animals distinguish low frequencies? It appears that lower frequencies are detected by neurons that fire in synchrony to the movements of the apical end of the basilar membrane. Thus, lower frequencies are detected by means of **rate coding.**

The most convincing evidence of rate coding of pitch comes from studies of people with cochlear implants. Pijl and Schwartz (1995a, 1995b) found that stimulation of a single electrode with pulses of electricity produced sensations of pitch that were proportional to the frequency of the stimulation. In fact, the subjects could even recognize familiar tunes produced by modulating the pulse frequency. (The subjects had become deaf later in life, after already having learned to recognize the tunes.) As we would expect, the subjects' perceptions were best when the tip of the basilar membrane was stimulated, and only low frequencies could be distinguished by this method.

Perception of Loudness

The cochlea is an extremely sensitive organ. Wilska (1935) used an ingenious procedure to estimate the smallest vibration needed to produce a perceptible sound. He glued a small wooden rod to a volunteer's tympanic membrane (temporarily, of course) and made the rod vibrate longitudinally by means of an electromagnetic coil that could be energized with alternating current. He could vary the frequency and intensity of the current, which consequently changed the perceived pitch and loudness of the stimulus. He found that subjects could detect a sound even when the eardrum was vibrated over a distance less than the diameter of a hydrogen atom—showing that the auditory system is very sensitive. Thus, in very quiet environments a young, healthy ear is limited in its ability to detect sounds in the air by the masking noise of blood rushing through the cranial blood vessels rather than by the sensitivity of the auditory system itself. More recent studies using modern instruments (reviewed by Hudspeth, 1983) have essentially confirmed Wilska's measurements. The softest sounds that can be detected appear to move the tip of the hair cells between 1 and 100 picometers (pm; trillionths of a meter). They achieve their maximum response when the tips are moved 100 nm (Corwin and Warchol, 1991).

The axons of the cochlear nerve appear to inform the brain of the loudness of a stimulus by altering their rate of firing. Louder sounds produce more intense vibrations of the eardrum and ossicles, which produce a more intense shearing force on the cilia of the auditory hair cells. As a result, these cells release more neurotransmitter, producing

rate code The system by which information about different frequencies is coded by the rate of firing of neurons in the auditory system.

a higher rate of firing by the cochlear nerve axons. This explanation seems simple for the axons involved in place coding of pitch; in this case pitch is signaled by which neurons fire, and loudness is signaled by their rate of firing. However, the neurons in the apex of the basilar membrane that signal the lowest frequencies do so by their rate of firing. If they fire more frequently, they signal a higher pitch. Therefore, most investigators believe that the loudness of low-frequency sounds is signaled by the *number* of axons arising from these neurons that are active at a given time.

Perception of Timbre

Although laboratory investigations of the auditory system often employ pure sine waves as stimuli, these waves are seldom encountered outside the laboratory. Instead, we hear sounds with a rich mixture of frequencies—sounds of complex timbre. For example, consider the sound of a clarinet playing a particular note. If we hear it, we can easily say that it is a clarinet and not a flute or a violin. The reason we can do so is that these three instruments produce sounds of different timbre, which our auditory system can distinguish.

Figure 7.15 shows the waveform from a clarinet playing a steady note (*top*). The shape of the waveform repeats itself regularly at the **fundamental frequency**, which corresponds to the perceived pitch of the note. A Fourier analysis of the waveform shows that it actually consists of a series of sine waves that includes the fundamental frequency and many **overtones**, multiples of the fundamental frequency. Different instruments produce overtones with different intensities. (See ***Figure 7.15.***) Electronic synthesizers simulate the sounds of real instruments by producing a series of overtones of the proper intensities, mixing them, and passing them through a loudspeaker.

When the basilar membrane is stimulated by the sound of a clarinet, different portions respond to each of the overtones. This response produces a unique anatomically coded pattern of activity in the cochlear nerve, which is subsequently identified by circuits in the auditory association cortex.

Actually, the recognition of complex sounds is not quite that simple. Figure 7.15 shows the analysis of a *sustained* sound of a clarinet. But most sounds (including those produced by a clarinet) are dynamic; that is, their beginning, middle, and end are different from each other. The beginning of a note played on a clarinet (the *attack*) contains frequencies that appear and disappear in a few milliseconds. And at the end of the note (the *decay*), some harmonics disappear before others. If we are to recognize different sounds, the auditory cortex must analyze a complex sequence of multiple frequencies that appear, change in amplitude, and disappear. And when you consider the fact that we can listen to an orchestra and identify several instruments that are playing simultaneously, you can appreciate the complexity of the analysis performed by the auditory system. We will revisit this process later in this chapter.

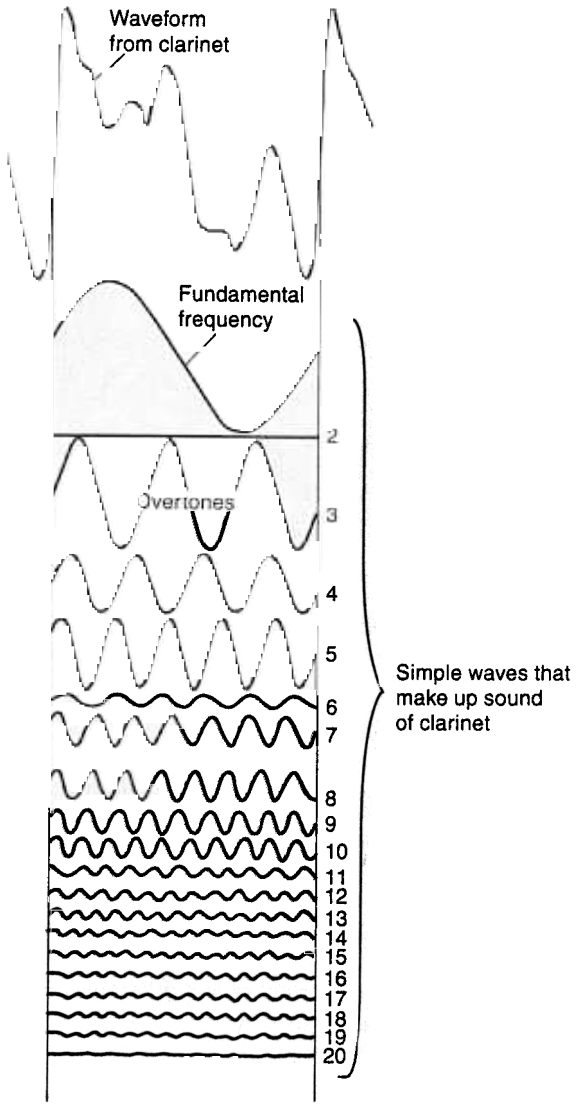


Figure 7.15

The shape of a sound wave from a clarinet (*top*) and the individual frequencies into which it can be analyzed.

(Reprinted from *Stereo Review*, copyright © 1977 by Diamandis Communications Inc.)

fundamental frequency The lowest, and usually most intense, frequency of a complex sound; most often perceived as the sound's basic pitch.

overtone The frequency of complex tones that occurs at multiples of the fundamental frequency.

Perception of Spatial Location

So far, I have discussed coding of pitch, loudness, and timbre only (the last of which is actually a complex frequency analysis). The auditory system also responds to other qualities of acoustic stimuli. For example, our ears are very good at determining whether the source of a sound is to the right or left of us. Two separate physiological mechanisms detect the location of sound sources: We use phase differences for low frequencies (less than approximately 3000 Hz) and intensity differences for high frequencies. In addition, we use another mechanism—analysis of timbre—to determine whether the source of a sound is in front of us or behind us.

Localization by Means of Arrival Time and Phase Differences

If we are blindfolded, we can still determine with rather good accuracy the location of a stimulus that emits a click. We do so because neurons respond selectively to different *arrival times* of the sound waves at the left and right ears. If the source of the click is to the right or left of the midline, the sound pressure wave will reach one ear sooner and initiate action potentials there first. Only if the stimulus is straight ahead will the ears be stimulated simultaneously. Many neurons in the auditory system respond to sounds presented to either ear. Some of these neurons, especially those in the superior olivary complex of the medulla, respond according to the difference in arrival times of sound waves produced by clicks presented *binaurally* (that is, to both ears). Their response rates reflect differences as small as a fraction of a millisecond.

Of course, we can hear continuous sounds as well as clicks, and we can also perceive the location of their source. We detect the source of continuous low-pitched sounds by means of phase differences. **Phase differences** refer to the simultaneous arrival, at each ear, of different portions (phases) of the oscillating sound wave. For example, if we assume that sound travels at 700 miles per hour through the air, adjacent cycles of a 1000-Hz tone are 12.3 inches apart. Thus, if the source of the sound is located to one side of the head, one eardrum is pulled out while the other is pushed in. The movement of the eardrums will reverse, or be 180° *out of phase.* If the source were located directly in front of the head, the movements would be perfectly in phase (0° out of phase). (See ***Figure 7.16.***) Because some auditory neurons respond only when the eardrums (and thus the bending of the basilar membrane) are at least somewhat out of phase, neurons in the superior olivary complex in the brain are able to use the information they provide to detect the source of a continuous sound.

A possible mechanism to explain the ability of the nervous system to detect very short delays in the arrival times of two signals was first proposed by Jeffress (1948). He suggested that neurons received information from two sets of axons coming from the two ears. Each neuron served as a *coincidence detector;* it responded only if it received signals simultaneously from synapses belonging to both sets of axons. If a signal reached the two ears simultaneously, neurons in the middle of the array would fire. However, if the signal reached one ear before the other, then neurons farther away from the "early" ear would be stimulated. (See ***Figure 7.17.***)

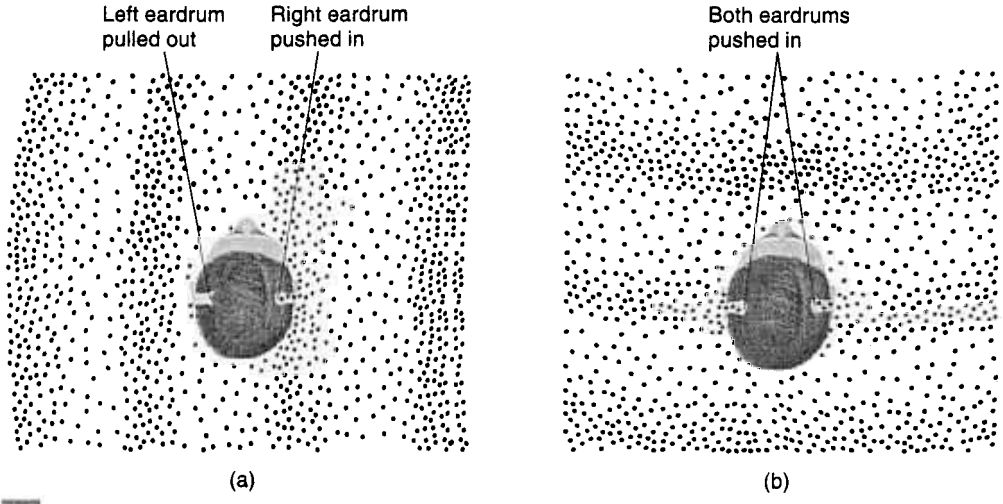


Figure 7.16

Localizing the source of low-frequency and medium-frequency sounds through phase differences. (a) Source of a 1000-Hz tone to the right. The pressure waves on each eardrum are out of phase; one eardrum is pushed in while the other is pushed out. (b) Source of a sound directly in front. The vibrations of the eardrums are synchronized (in phase).

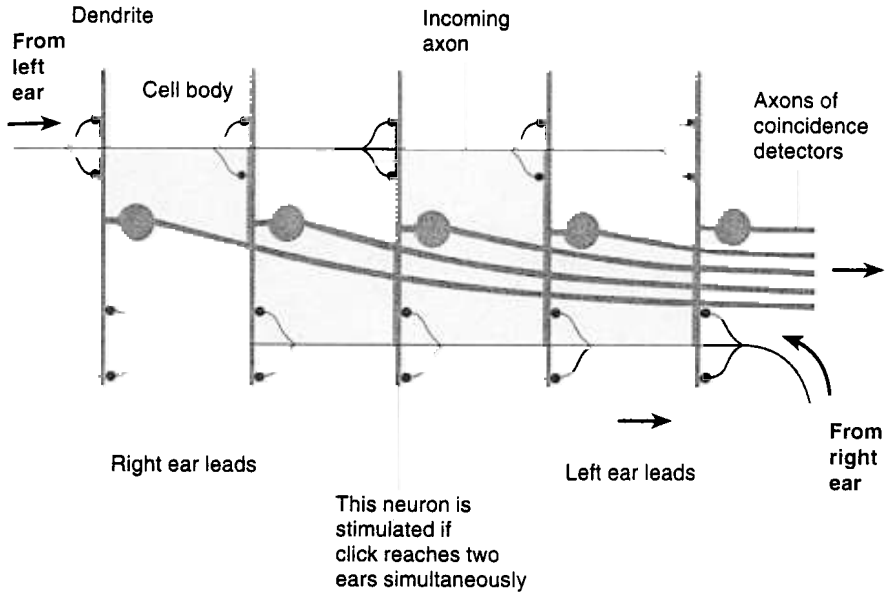


Figure 7.17

A model of a coincidence detector that can determine differences in arrival times at each ear of an auditory stimulus.

In fact, that is exactly how the mechanism works. Carr and Konishi (1989, 1990) obtained anatomical evidence in support of Jeffress's hypothesis from the brain of the barn owl, a nocturnal bird that can detect very accurately the source of a sound (such as that made by an unfortunate mouse). Figure 7.18 shows a drawing of the distribution of the branches of two axons, one from each ear, projecting to the nucleus laminaris, the barn owl analog of the mammalian medial superior olive. As you can see, axons from the ipsilateral and contralateral ears penetrate the nucleus from opposite directions; therefore, dorsally located neurons within the nucleus are stimulated by sounds that first reach the contralateral ear. (Compare *Figures 7.17* and *7.18.*) Carr and Konishi recorded from single units within the nucleus and found that the response characteristics of the neurons located there were perfectly consistent with these anatomical facts.

Localization by Means of Intensity Differences

The auditory system cannot readily detect binaural phase differences of high-frequency stimuli; the differences in phases of such rapid sine waves are just too short to be measured by the neurons. However, high-frequency stimuli that occur to the right or left of the midline stimulate the ears unequally. The head absorbs high frequencies, producing a "sonic shadow," so the ear closest to the source of the sound receives the most intense stimulation. Some neurons in the auditory system respond differentially to binaural stimuli of different intensity in each ear, which means that they provide information that can be used to detect the source of tones of high frequency.

The neurons that detect binaural differences in loudness are located in the superior olivary complex. But whereas neurons that detect binaural differences in phase or arrival time are located in the *medial* superior olivary complex, these neurons are located in the *lateral* superior olivary complex. Information from both sets of neurons is sent to other levels of the auditory system.

Localization by Means of Timbre

We just saw that left–right localization of the source of a high- and low-frequency sounds is accomplished by two different mechanisms. But how can we determine whether the source of a sound is in front of us or behind us? One answer is that we can turn our heads, thus transforming the discrimination into a left–right decision. But we have another means by which we can distinguish front from back: analysis of timbre. This method involves a part of the auditory system that I have not said much about: the external ear (pinna). If you look at someone's external ear, you will see that it contains several folds and ridges. Most of the sound waves that we hear bounce off the folds and ridges of the pinna before they enter the ear canal. This process changes the nature of the sounds that we hear. Depending on the angle at which the sound waves strike these folds and ridges, different frequencies will be enhanced or attenuated. In other words, the pattern of reflections will change with the location of the source of the sound, which will alter the timbre of the sound that is perceived. Sounds coming from behind the head will sound different from those coming from above the head or in front of it.

People's ears differ in shape; thus, the changes in the timbre of a sound coming from different locations will

phase difference The difference in arrival times of sound waves at each of the eardrums.

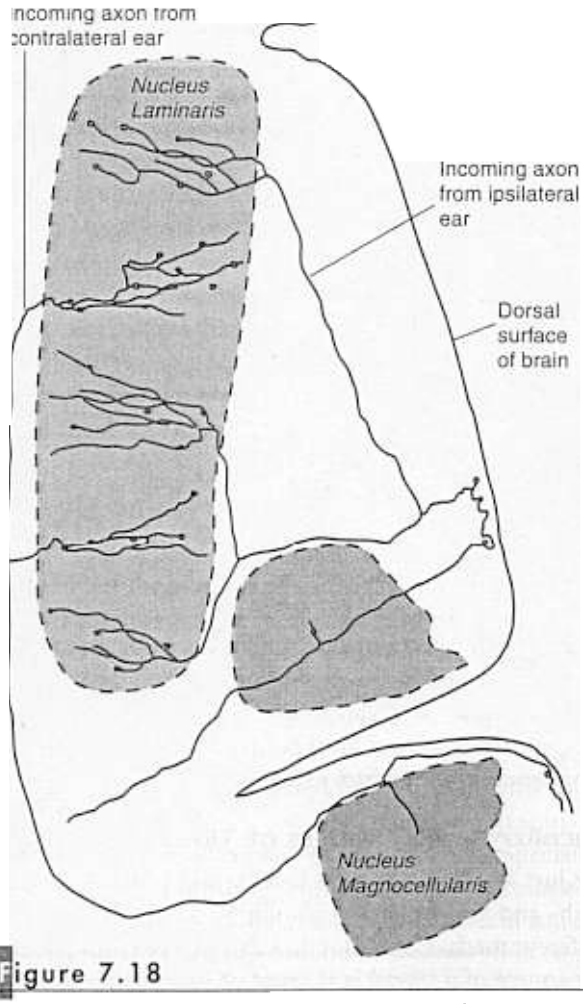


Figure 7.18

Evidence for a coincidence detector in the brain of a barn owl. Compare the branches of the axons with those of Figure 7.17. The drawing was prepared from microscopic examination of sections of stained tissue.

(Adapted from Carr, C. E., and Konishi, M. *Proceedings of the National Academy of Sciences, USA,* 1989, *85,* 8311–8315.)

also differ from person to person. This means that each individual must learn to recognize the subtle changes in the timbre of sounds that originate in locations in front of or behind the head. The neural circuits that accomplish this task are not genetically programmed—they must be acquired as a result of experience.

Behavioral Functions of the Auditory System

Hearing has three primary functions: to detect sounds, to determine the location of their sources, and to recognize the identity of these sources—and thus their meaning and relevance to us (Heffner and Heffner, 1990; Yost, 1991). Let us consider the third function: recognizing the identity of a sound source. Unless you are in a completely silent location, pay attention to what you can hear. Right now, I am sitting in an office and can hear the sound of a fan in a computer, the tapping of the keys as I write this, the footsteps of someone passing outside the door, and the voices of some people talking in the hallway. How can I recognize these sources? The axons in my cochlear nerve contain a constantly changing pattern of activity corresponding to the constantly changing mixtures of frequencies that strike my eardrums. Somehow, the auditory system of my brain recognizes particular patterns that belong to particular sources, and I perceive each of them as independent entities.

The task of the auditory system in identifying sound sources, then, is one of *pattern recognition.* The auditory system must recognize that particular patterns of constantly changing activity belong to different sound sources. And as we saw, few patterns are simple mixtures of fixed frequencies. For example, the notes played on a clarinet have a characteristic attack and decay. And notes of different pitches produce different patterns of activity in our cochlear nerve—yet we recognize each of the notes as belonging to a clarinet. Needless to say, we are far from understanding how this pattern recognition works.

Although the subcortical components of the auditory system are often referred to as "relay nuclei," it is clear that these nuclei do much more than passively transmit information from the cochlear nerve to the auditory cortex. For example, as we saw earlier in this chapter, the superior olivary complex contains circuits that analyze the location of sound sources according to arrival time (or phase differences) and intensity differences.

Pattern recognition, however, appears to be accomplished by circuits of neurons in the auditory cortex. We know a little bit about the types of analyses that the auditory cortex accomplishes. Various studies (Whitfield and Evans, 1965; Saitoh, Maruyama, and Kudoh, 1981) have found neurons in the auditory cortex that respond only to the onset or cessation of a sound (or to both), to changes in pitch or intensity (sometimes only to changes in one direction), or to complex stimuli that contain a variety of frequencies. Winter and Funkenstein (1971) found neurons in the auditory cortex of the squirrel monkey that responded specifically to the vocalizations made by members of this species. McKenna, Weinberger, and Diamond (1989) found that when they presented a series of different tones, some neurons in the primary auditory cortex responded to a particular frequency only in a particular context; for example, they would respond if the tone were the last in a series but not if it were the first. Rauschecker, Tian, and Hauser (1995) found that neurons in the auditory association cortex of rhesus monkeys responded much better to sound mixtures than to pure tones. Thus, neurons in the auditory cortex encode rather complex fea-

tures. Because data are scanty so far, we have no real conception of the coding mechanism that the brain uses for these changes or even of precisely what features are coded.

However the analysis of auditory information is accomplished, it is clear that the circuits that perform this analysis must receive accurate information. For example, recognition of complex sounds such as those found in speech requires that the timing of changes in the components of these sounds be preserved all the way to the auditory cortex. In fact, the neurons that convey information to the auditory cortex contain special features that permit them to conduct this information rapidly and accurately (Trussell, 1999). Their axons contain special low-threshold voltage-gated potassium channels that produce very short action potentials. Their terminal buttons are large and release large amounts of glutamate, and the postsynaptic membrane contains neurotransmitter-dependent ion channels that act unusually rapidly; thus, these synapses produce very strong EPSPs. The terminal buttons form synapses with the somatic membrane of the postsynaptic neurons, which minimizes the distance between the synapses and the axon—and also the delay in conducting information to the axon of the postsynaptic neuron.

Bilateral lesions of the auditory cortex in monkeys cause an almost total hearing loss, which eventually shows some recovery (Heffner and Heffner, 1990). The animals' ability to localize sounds is severely disrupted; they can eventually learn to discriminate a sound coming from the left or right from one coming from the center, but they are unable to walk toward the source of the sound. Thus, their sound localizing ability does not translate into useful behavior (Heffner and Heffner, 1990). In addition, lesions of the left auditory cortex disrupt the animals' ability to discriminate the vocalizations made by other members of this species.

As we saw in Chapter 6, lesions of the visual association cortex in humans can produce visual agnosias—the inability to recognize objects even though the visual acuity may be good. Similarly, lesions of the auditory association cortex can produce auditory agnosias, the inability to comprehend the meaning of sounds even though the individuals are not deaf. If the lesion occurs in the left hemisphere, the person will sustain a particular form of language disorder. If it occurs in the right hemisphere, the person will be unable to recognize the nature or location of nonspeech sounds. Because of the importance of audition to language, these topics are discussed in much more detail in Chapter 16.

interim summary

The receptive organ for audition is the organ of Corti, located on the basilar membrane. When sound strikes the tympanic membrane, it sets the ossicles into motion, and the baseplate of the stapes pushes against the membrane behind the oval window. Pressure changes thus applied to the fluid within the cochlea cause a portion of the basilar membrane to flex, causing the basilar membrane to move laterally with respect to the tectorial membrane that overhangs it. This movement pulls directly on the cilia of the outer hair cells and causes movements in the fluid within the cochlea, which, in turn, causes the cilia of the inner hair cells to wave back and forth. These mechanical forces open potassium channels in the tips of the hair cells and thus produce receptor potentials.

The hair cells form synapses with the dendrites of the bipolar neurons whose axons give rise to the cochlear branch of the eighth cranial nerve. The central auditory system involves several brain stem nuclei, including the cochlear nuclei, superior olivary complexes, and inferior colliculi. The medial geniculate nucleus relays auditory information to the primary auditory cortex on the medial surface of the temporal lobe. The primary auditory cortex contains three separate tonotopic representations of auditory information and is surrounded by two levels of auditory association cortex: the belt region and the parabelt region.

Pitch is encoded by two means. High-frequency sounds cause the base of the basilar membrane (near the oval window) to flex; low-frequency sounds cause the apex (opposite end) to flex. Because high and low frequencies thus stimulate different groups of auditory hair cells, frequency is encoded anatomically. The lowest frequencies cause the apex of the basilar membrane to flex back and forth in time with the acoustic vibrations. The outer hair cells act as motive elements rather than as sensory transducers, contracting in response to activity of the efferent axons and modifying the mechanical properties of the basilar membrane.

The auditory system is analytical in its operation. That is, it can discriminate between sounds with different timbres by detecting the individual overtones that constitute the sounds and producing unique patterns of neural firing in the auditory system.

Left–right localization is performed by analyzing binaural differences in arrival time, in phase relations, and in intensity. The location of sources of brief sounds (such as clicks) and sounds of frequencies below approximately 3000 Hz is detected by neurons in the medial superior olivary complex, which respond most vigorously when one ear receives the click first or when the phase of a sine wave received by one ear leads that received by the other. The location of sources of high-frequency sounds is detected by neurons in the lateral superior olivary complex, which respond most vigorously when one organ of Corti is stimulated

more intensely than the other. Front–back localization of sounds can be accomplished by turning the head or by subtle differences in the timbre of sounds coming from different directions. The folds and ridges in the external ear (pinna) reflect different frequencies into the ear canal, changing the timbre of the sound according to the location of its source.

To recognize the source of sounds, the auditory system must recognize the constantly changing patterns of activity received from the axons in the cochlear nerve. Studies have found neurons in the auditory cortex that respond to complex stimuli, such as ascending or descending pitches, series of tones, combinations of two or more tones, or even species-specific vocalizations. Bilateral lesions of the auditory cortex of monkeys produce severe impairments in hearing, and lesions of the left auditory cortex impair the ability to discriminate the vocalizations of other monkeys.

Vestibular System

The vestibular system has two components: the vestibular sacs and the semicircular canals. They represent the second and third components of the *labyrinths* of the inner ear. (We just studied the first component, the cochlea.) The **vestibular sacs** respond to the force of gravity and inform the brain about the head's orientation. The **semicircular canals** respond to angular acceleration—changes in the rotation of the head—but not to steady rotation. They also respond (but rather weakly) to changes in position or to linear acceleration.

The functions of the vestibular system include balance, maintenance of the head in an upright position, and adjustment of eye movement to compensate for head movements. Vestibular stimulation does not produce any readily definable sensation; certain low-frequency stimulation of the vestibular sacs can produce nausea, and stimulation of the semicircular canals can produce dizziness and rhythmic eye movements (*nystagmus*). However, we are not directly aware of the information received from these organs. This section describes the vestibular system: the vestibular apparatus, the receptor cells, and the vestibular pathway in the brain.

Anatomy of the Vestibular Apparatus

Figure 7.19 shows the labyrinths of the inner ear, which include the cochlea, the semicircular canals, and the two vestibular sacs: the **utricle** ("little pouch") and the **saccule** ("little sack"). (See ***Figure 7.19.***) The semicircular canals approximate the three major planes of the head: sagittal, transverse, and horizontal. Receptors in each canal respond maximally to angular acceleration in one plane. The semicircular canal consists of a membranous canal floating within a bony one; the membranous canal contains a fluid called *endolymph*. An enlargement called the **ampulla** contains the organ in which the sensory receptors reside. The sensory receptors are hair cells similar to those found in the cochlea. Their cilia are embedded in a gelatinous mass called the **cupula**, which blocks part of the ampulla. (See ***Figure 7.19.***)

To explain the effects of angular acceleration on the semicircular canals, I will first describe an "experiment." If we place a glass of water on the exact center of a turntable and then start the turntable spinning, the water in the glass will, at first, remain stationary (the glass will move with respect to the water it contains). Eventually, however, the water will begin rotating with the container. If we then stop the turntable, the water will continue spinning for a while because of its inertia.

The semicircular canals operate on the same principle. The endolymph within these canals, like the water in the glass, resists movement when the head begins to rotate. This inertial resistance pushes the endolymph against the cupula, causing it to bend, until the fluid begins to move at the same speed as the head. If the head rotation is then stopped, the endolymph, still circulating through the canal, pushes the cupula the other way. Angular acceleration is thus translated into bending of the cupula, which exerts a shearing force on the cilia of the hair cells. (Of course, unlike the glass of water in my example, we do not normally spin around in circles; the semicircular canals measure very slight and very brief rotations of the head.)

The vestibular sacs (the utricle and saccule) work very differently. These organs are roughly circular, and each contains a patch of receptive tissue. The receptive tissue is located on the "floor" of the utricle and on the "wall" of the saccule when the head is in an upright position. The receptive tissue, like that of the semicircular canals and cochlea,

vestibular sac One of a set of two receptor organs in each inner ear that detects changes in the tilt of the head.

semicircular canal One of the three ringlike structures of the vestibular apparatus that detect changes in head rotation.

utricle (*you trih kul*) One of the vestibular sacs.

saccule (*sak yule*) One of the vestibular sacs.

ampulla (*am pull uh*) An enlargement in a semicircular canal; contains the cupula and the crista.

cupula (*kew pew luh*) A gelatinous mass found in the ampulla of the semicircular canals; moves in response to the flow of the fluid in the canals.

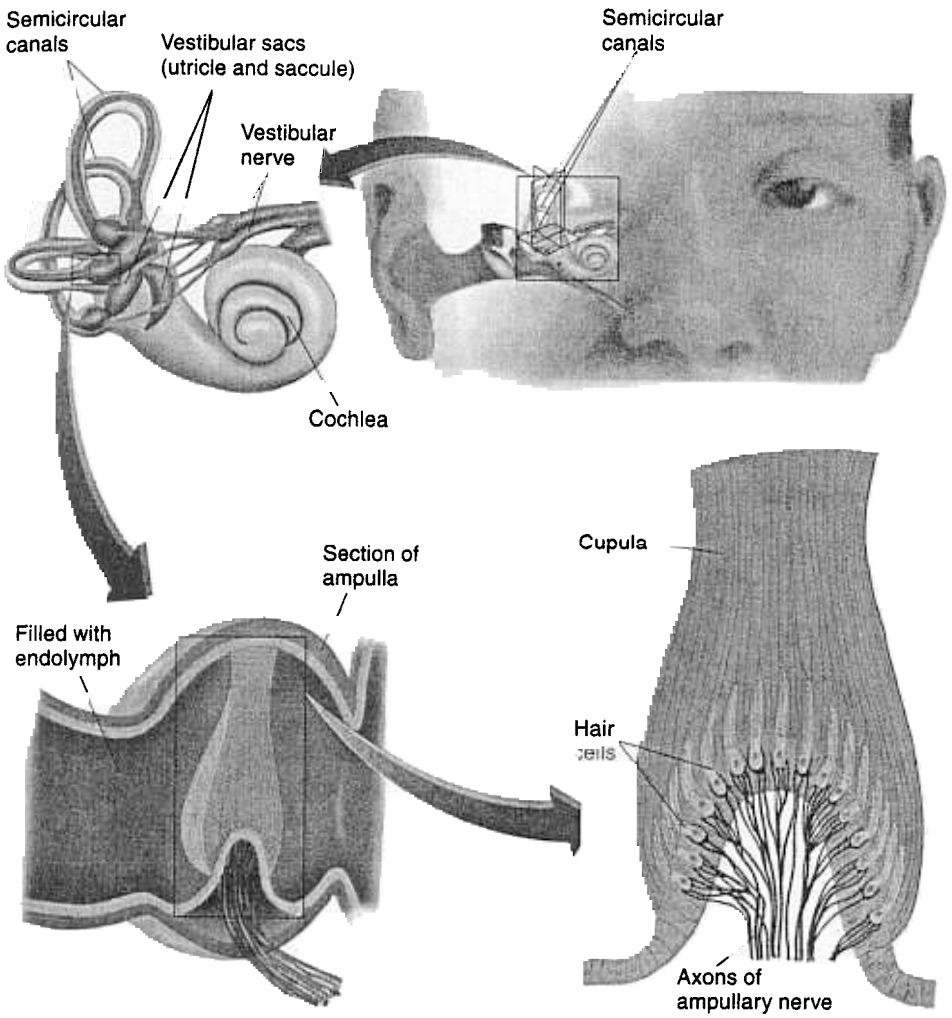


Figure 7.19
The receptive organ of the semicircular canals.

contains hair cells. The cilia of these receptors are embedded in an overlying gelatinous mass, which contains something rather unusual: *otoconia,* which are small crystals of calcium carbonate. (See ***Figure 7.20.***) The weight of the crystals causes the gelatinous mass to shift in position as the orientation of the head changes. Thus, movement produces a shearing force on the cilia of the receptive hair cells.

The Receptor Cells

The hair cells of the semicircular canal and vestibular sacs are similar in appearance. Each hair cell contains several cilia, graduated in length from short to long. These hair cells resemble the auditory hair cells found in the cochlea, and their transduction mechanism is also similar: A shearing force of the cilia opens ion channels, and the entry of potassium ions depolarizes the ciliary membrane. Figure 7.21 shows two views of a hair cell of a bullfrog saccule made by a scanning electron microscope. (See ***Figure 7.21.***)

The Vestibular Pathway

The vestibular and cochlear nerves constitute the two branches of the eighth cranial nerve (auditory nerve). The bipolar cell bodies that give rise to the afferent axons of the vestibular nerve are located in the **vestibular ganglion,** which appears as a nodule on the vestibular nerve.

Most of the axons of the vestibular nerve synapse within the vestibular nuclei in the medulla, but some axons travel directly to the cerebellum. Neurons of the vestibular nuclei send their axons to the cerebellum, spinal cord, medulla, and pons. There also appear to be vestibular projections to the temporal cortex, but the precise pathways have not been determined. Most investigators believe that the cortical

vestibular ganglion A nodule on the vestibular nerve that contains the cell bodies of the bipolar neurons that convey vestibular information to the brain.

projections are responsible for feelings of dizziness; the activity of projections to the lower brain stem can produce the nausea and vomiting that accompany motion sickness. Projections to brain stem nuclei controlling neck muscles are clearly involved in maintaining an upright position of the head.

Perhaps the most interesting connections are those to the cranial nerve nuclei (third, fourth, and sixth) that control the eye muscles. As we walk or (especially) run, the head is jarred quite a bit. The vestibular system exerts direct control on eye movement, to compensate for the sudden head movements. This process, called the *vestibulo-ocular reflex*, maintains a fairly steady retinal image. Test this reflex yourself: Look at a distant object and hit yourself (gently) on the side of the head. Note that your image of the world jumps a bit, but not too much. People who have suffered vestibular damage and who lack the vestibulo-ocular reflex have difficulty seeing anything while walking or running. Everything becomes a blur of movement.

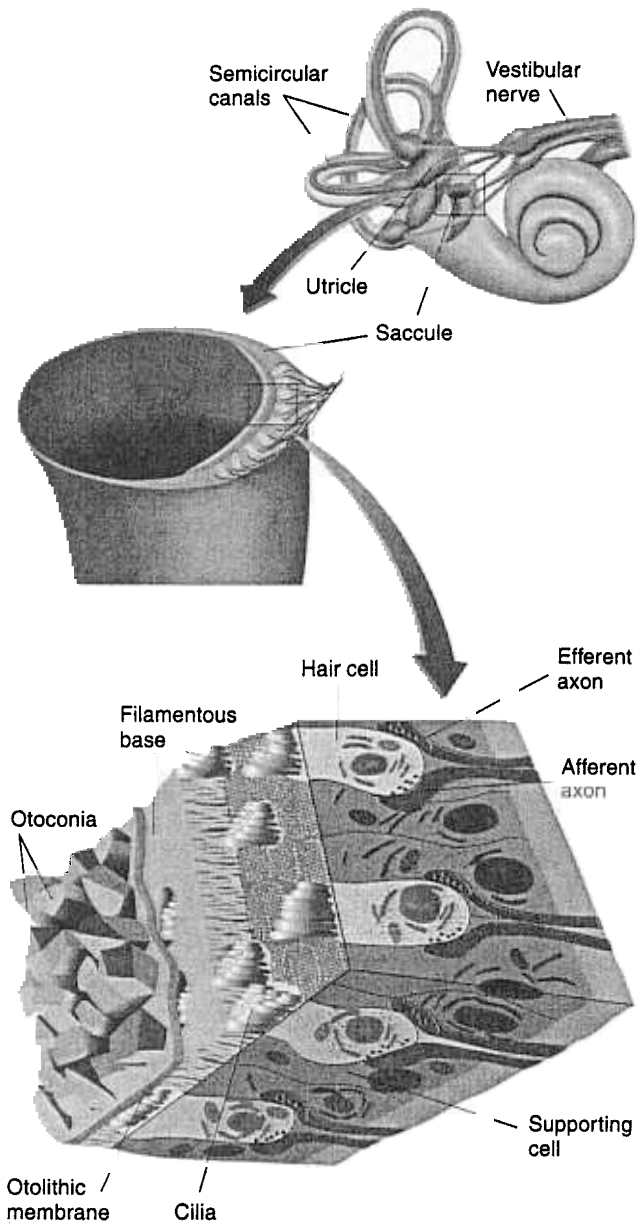


Figure 7.20
The receptive tissue of the vestibular sacs: the utricle and the saccule.

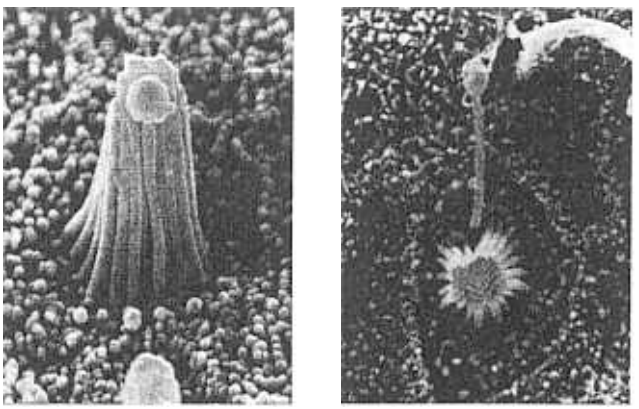


Figure 7.21
(a) Oblique view of a normal bundle of vestibular hair cells. (b) Top view of a bundle of hair cells from which the longest has been detached.
(From Hudspeth, A. J., and Jacobs, R. *Proceedings of the National Academy of Sciences, USA*, 1979, *76*, 1506–1509.)

interim summary

The semicircular canals are filled with fluid. When the head begins rotating or comes to rest after rotation, inertia causes the fluid to push the cupula to one side or the other. This movement exerts a shearing force on the cupula, the organ containing the vestibular hair cells. The vestibular sacs contain a patch of receptive tissue that contains hair cells whose cilia are embedded in a gelatinous mass. The weight of the otoconia in the gelatinous mass shifts when the head tilts, causing a shearing force on some of the cilia of the hair cells.

Each hair cell contains one long cilium and several shorter ones. These cells form synapses with dendrites of bipolar neurons whose axons travel through the vestibular nerve. The receptors also receive efferent terminal buttons from neurons located in the cerebellum and medulla, but the function of these connections is not known. Vestibular information is received by the vestibular nuclei

in the medulla, which relay it on to the cerebellum, spinal cord, medulla, pons, and temporal cortex. These pathways are responsible for control of posture, head movements, eye movements, and the puzzling phenomenon of motion sickness.

Somatosenses

The somatosenses provide information about what is happening on the surface of our body and inside it. The **cutaneous senses** (skin senses) include several submodalities commonly referred to as *touch*. **Kinesthesia** provides information about body position and movement and arises from receptors in joints, tendons, and muscles. The muscle receptors are discussed in this section and in Chapter 8. The **organic senses** arise from receptors in and around the internal organs, providing us with unpleasant sensations, such as stomachaches or gallbladder attacks, or pleasurable ones, such as those provided by a warm drink on a cold winter day. Because the cutaneous senses are the most studied of the somatosenses, both perceptually and physiologically, I will devote most of my discussion to them.

The Stimuli

The cutaneous senses respond to several different types of stimuli: pressure, vibration, heating, cooling, and events that cause tissue damage (and hence pain). Feelings of pressure are caused by mechanical deformation of the skin. Vibration is produced in the laboratory or clinic by tuning forks or mechanical devices, but it more commonly occurs when we move our fingers across a rough surface. Thus, we use vibration sensitivity to judge an object's roughness. Obviously, sensations of warmth and coolness are produced by objects that change skin temperature from normal. Sensations of pain can be caused by many different types of stimuli, but it appears that most cause at least some tissue damage.

Kinesthesia is provided by stretch receptors in skeletal muscles that report changes in muscle length to the central nervous system and by stretch receptors in tendons that measure the force being exerted by the muscles. Receptors within joints between adjacent bones respond to the magnitude and direction of limb movement. Muscle length detectors, located within the muscles, do not give rise to conscious sensations; their information is used to control movement. These receptors will be discussed separately in Chapter 8.

Additional information about the internal organs is provided by receptors in the linings of muscles, outer layers of the gastrointestinal system and other internal organs, and linings of the abdominal and thoracic cavities. Many of these tissues are sensitive only to stretch and do not report sensations when cut, burned, or crushed. In addition, the stomach and esophagus are responsive to heat and cold and to some chemicals.

Anatomy of the Skin and Its Receptive Organs

The skin is a complex and vital organ of the body—one that we tend to take for granted. We cannot survive without it; extensive skin burns are fatal. Our cells, which must be bathed by a warm fluid, are protected from the hostile environment by the skin's outer layers. The skin participates in thermoregulation by producing sweat, thus cooling the body, or by restricting its circulation of blood, thus conserving heat. Its appearance varies widely across the body, from mucous membrane to hairy skin to the smooth, hairless skin of the palms and the soles of the feet.

Skin consists of subcutaneous tissue, dermis, and epidermis and contains various receptors scattered throughout these layers. Figure 7.22 shows cross sections through hairy and **glabrous skin** (hairless skin, found on our fingertips and palms and on the bottoms of our toes and feet). Hairy skin contains unencapsulated (free) nerve endings; **Ruffini corpuscles**, which respond to indentation of the skin; and **Pacinian corpuscles**, which respond to rapid vibrations. Pacinian corpuscles are the largest sensory end organs in the body. Their size, approximately 0.5 × 1.0 mm, makes them visible to the naked eye. They consist of up to seventy onionlike layers wrapped around the dendrite of a single myelinated axon. Free nerve endings, which detect painful stimuli and changes in temperature, are found just below the surface of the skin. Other free nerve endings are found in a basketwork around the base of hair follicles and around the emergence of hair shafts from the skin. These fibers detect movement of hairs. (See ***Figure 7.22.***)

cutaneous sense (*kew **tane** ee us*) One of the somatosenses; includes sensitivity to stimuli that involve the skin.

kinesthesia Perception of the body's own movements.

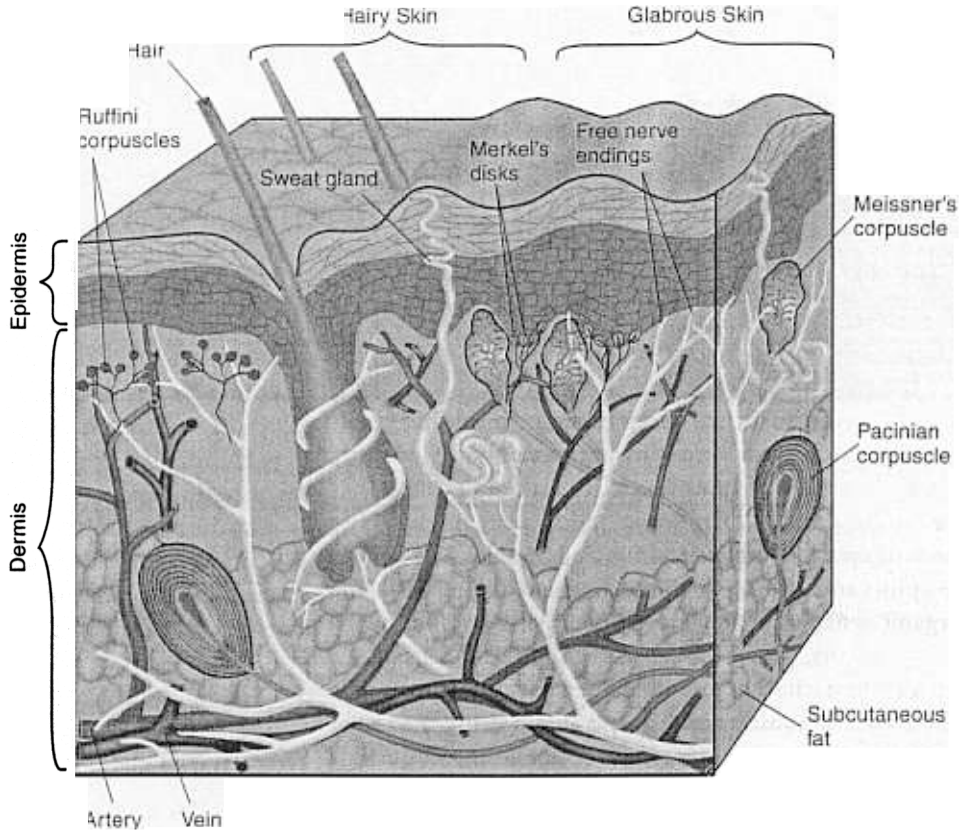
organic sense A sense modality that arises from receptors located within the inner organs of the body.

glabrous skin (*glab russ*) Skin that does not contain hair; found on the palms and the soles of the feet.

Ruffini corpuscle A vibration-sensitive organ located in hairy skin.

Pacinian corpuscle (*pa **chin** ee un*) A specialized, encapsulated somatosensory nerve ending that detects mechanical stimuli, especially vibrations.

Figure 7.22
Cutaneous receptors.



Glabrous skin contains a more complex mixture of free nerve endings and axons that terminate within specialized end organs (Iggo and Andres, 1982). The increased complexity reflects the fact that we use the palms of our hands and the inside surfaces of our fingers to explore the environment actively: We use them to hold and touch objects. In contrast, the rest of our body most often contacts the environment passively; that is, other things come into contact with it.

Glabrous skin, like hairy skin, contains free nerve endings, Ruffini corpuscles, and Pacinian corpuscles. (Pacinian corpuscles are also found in the joints and in various internal organs.) Glabrous skin also contains **Meissner's corpuscles,** which are found in *papillae* ("nipples"), small elevations of the dermis that project up into the epidermis. These end organs are innervated by between two and six axons. They respond to low-frequency vibration or to brief taps on the skin. **Merkel's disks,** which respond to indentation of the skin, are found at the base of the epidermis, in the same general locations as Meissner's corpuscles, adjacent to sweat ducts. (See ***Figure 7.22.***)

The *mechanoreceptors* in the skin (that is, those receptors that respond to mechanical stimulation) can be divided into four categories, depending on the size of their receptive field in the skin, and the speed with which they adapt to a constant stimulus. (The process of adaptation is described in the next subsection.) Glabrous skin, with its increased cutaneous sensitivity, contains receptors with the smallest receptive fields: Meissner's corpuscles and Merkel's disks. (See ***Table 7.1.***)

Perception of Cutaneous Stimulation

The three most important qualities of cutaneous stimulation are touch, temperature, and pain. These qualities are described in the sections that follow.

Touch

Sensitivity to pressure and vibration is caused by movement of the skin. The best-studied receptor is the Pacinian corpuscle, which primarily detects vibration. When the corpuscle is bent relative to the axon, the membrane becomes depolarized. If the threshold of excitation is exceeded, an

Meissner's corpuscle The touch-sensitive end organs located in the papillae, small elevations of the dermis that project up into the epidermis.

Merkel's disk The touch-sensitive end organs found at the base of the epidermis, adjacent to sweat ducts.

Table 7.1
Categories of mechanoreceptors in glabrous skin

Speed of Adaptation	Size of Receptive Field	Identity of Receptor
slow	small, sharp borders	Merkel's disk
slow	large, diffuse borders	Ruffini corpuscles
rapid	small, sharp borders	Meissner's corpuscles
rapid	large, diffuse borders	Pacinian corpuscles

action potential is produced at the first node of Ranvier. Loewenstein and Mendelson (1965) have shown that the layers of the corpuscle alter the mechanical characteristics of the organ, so the axon responds briefly when the intact organ is bent and again when it is released. Thus, this receptor is sensitive to vibration but not to steady pressure.

The bending of the tip of the nerve ending in a Pacinian corpuscle appears to produce a receptor potential by opening ion channels in the membrane. These channels appear to be anchored to protein filaments beneath the membrane and have long carbohydrate chains attached to them. When a mechanical stimulus changes the shape of the nerve ending, tension is exerted on the carbohydrate chains, pulling the channel open. (See *Figure 7.23.*) Most investigators believe that the encapsulated endings serve only to modify the physical stimulus transduced by the axons that enter them.

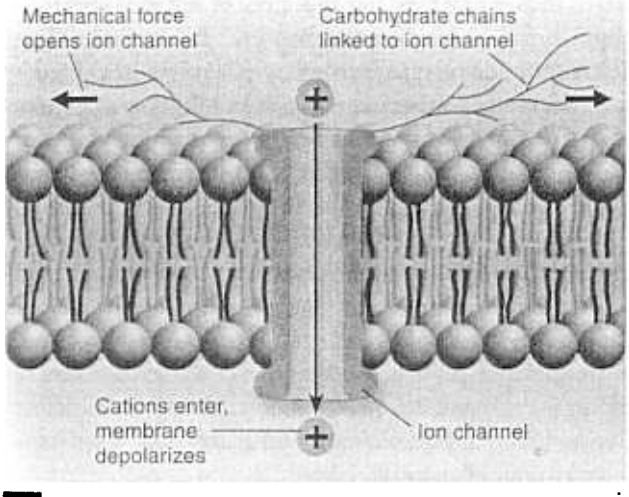


Figure 7.23
A hypothetical explanation of transduction of somatosensory information. Mechanical force on carbohydrate chains linked to ion channels opens the channels, permitting the entry of cations, which depolarizes the membrane potential.

■ **Adaptation** Investigators have known for a long time that a moderate, constant stimulus applied to the skin fails to produce any sensation after it has been present for a while. For example, we not only ignore the pressure of a wristwatch, but we cannot feel it at all if we keep our arm still (assuming that the band is not painfully tight). Physiological studies have shown that the reason for the lack of sensation is the absence of receptor firing; the receptors adapt to a constant stimulus.

This adaptation is not caused by "fatigue" of physical or chemical processes within the receptor. Instead, adaptation occurs because of the physical construction of the skin and the cutaneous sensory organs. Nafe and Wagoner (1941) recorded the sensations reported by human subjects as a stimulus weight gradually moved downward, deforming the skin. Pressure was reported until the weight finally stopped moving. When the weight was increased, pressure was reported until downward movement stopped again. Pressure sensations were also briefly recorded when the weight was removed, while the surface of the skin regained its normal shape. (You may have noticed that when you first take your hat off, it feels for a few moments as if you were still wearing it.)

■ **Responsiveness to Moving Stimuli** A moderate, constant, nondamaging stimulus is rarely of any importance to an organism, so this adaptation mechanism is useful. Our cutaneous senses are used much more often to analyze shapes and textures of stimulus objects moving with respect to the surface of the skin. Sometimes, the object itself moves; but more often, we do the moving ourselves.

If I placed an object in your palm and asked you to keep your hand still, you would have a great deal of difficulty recognizing the object by touch alone. If I said you could now move your hand, you would manipulate the object, letting its surface slide across your palm and the pads of your fingers. You would be able to describe its three-dimensional shape, hardness, texture, slipperiness, and so on. Obviously,

your motor system must cooperate, and you need kinesthetic sensation from your muscles and joints, besides the cutaneous information. If you squeeze the object and feel a lot of well-localized pressure in return, it is hard. If you feel a less intense, more diffuse pressure in return, it is soft. If it produces vibrations as it moves over the ridges on your fingers, it is rough. If very little effort is needed to move the object while pressing it against your skin, it is slippery. If it does not produce vibrations as it moves across your skin, but moves in a jerky fashion, and if it takes effort to remove your fingers from its surface, it is sticky. Thus, our somatosenses work dynamically with the motor system to provide useful information about the nature of objects that come into contact with our skin.

Temperature

Feelings of warmth and coolness are relative, not absolute (except at the extremes). There is a temperature level that, for a particular region of skin, will produce a sensation of temperature neutrality—neither warmth nor coolness. This neutral point is not an absolute value but depends on the prior history of thermal stimulation of that area. If the temperature of a region of skin is raised by a few degrees, the initial feeling of warmth is replaced by one of neutrality. If the skin temperature is lowered to its initial value, it now feels cool. Thus, increases in temperature lower the sensitivity of warmth receptors and raise the sensitivity of cold receptors. The converse holds for decreases in skin temperature. This adaptation to ambient temperature can be demonstrated easily by placing one hand in a bucket of warm water and the other in a bucket of cool water until some adaptation has taken place. If you then simultaneously immerse both hands in water at room temperature, it will feel warm to one hand and cool to the other.

There are two types of thermal receptors: one that responds to warmth and one that responds to coolness. (As we will see in the next section, another category of cutaneous receptor responds to intense heat and gives rise to a sensation of pain.) The transduction of temperature changes into the rate of axonal firing is not yet understood. Spray (1986) suggested that the sodium-potassium pump may be responsible for sensory transduction in coolness receptors. A drop in temperature would slow the action of the pump, which would permit sodium to accumulate in the free nerve ending and depolarize its membrane. In support of this suggestion he found that *ouabain*, a toxin that inactivates the sodium-potassium pump, produced a brief burst of activity in cold-receptive fibers in the skin of a frog. After that burst, the fibers became unresponsive to temperature changes. Obviously, detectors of warmth must operate by a different mechanism.

An ingenious experiment by Bazett et al. (1932) showed long ago that receptors for warmth and coolness lie at different depths in the skin. The investigators lifted the prepuce (foreskin) of uncircumcised males with dull fishhooks. They applied thermal stimuli on one side of the folded skin and recorded the rate at which the temperature changes were transmitted through the skin by placing small temperature sensors on the opposite side. They then correlated these observations with verbal reports of warmth and coolness. The investigators concluded that coolness receptors were close to the skin and that warmth receptors were located deeper in the tissue. (This experiment shows the extremities to which scientists will go to obtain information—pun intended.)

Pain

The story of pain is quite different from that of temperature and pressure; the analysis of this sensation is extremely difficult. It is obvious that our awareness of pain and our emotional reaction to it are controlled by mechanisms within the brain. For example, we can have a tooth removed painlessly under hypnosis, which has no effect on the sensitivity of pain receptors. Stimuli that produce pain also tend to trigger species-typical escape and withdrawal responses. Subjectively, these stimuli *hurt*, and we try hard to avoid them. However, sometimes we are better off ignoring pain and getting on with other tasks. In fact, our brains possess mechanisms that can reduce pain, partly through the action of the endogenous opioids. These mechanisms are described in more detail in a later section of this chapter.

Pain reception, like thermosensation, is accomplished by the networks of free nerve endings in the skin. There appear to be at least three types of pain receptors (usually referred to as *nociceptors*, or "detectors of noxious stimuli"). High-threshold mechanoreceptors are free-nerve endings that respond to intense pressure, which might be caused by something striking, stretching, or pinching the skin. A second type of free nerve ending appears to respond to extremes of heat, to acids, and to the presence of *capsaicin*, the active ingredient in chile peppers. (Note that we say that chile peppers make food taste "hot.") This type of fiber contains *capsaicin receptors*, ionotropic receptors that contain a cation channel (Kress and Zeilhofer, 1999). What the natural ligand for this receptor is, and why it also responds to heat and acids, is not yet known. Presumably, this receptor is responsible for pain produced by burning of the skin and also for pain caused by inflammation, which is reduced by applying a cold compress.

Another type of nociceptive fiber contains receptors that are sensitive to ATP (Burnstock and Wood, 1996). These receptors are ionotropic and control channels that admit sodium and calcium ions. You will recall that ATP is produced by mitochondria and serves as an energy source for the cell's metabolic processes. ATP is also released when

the blood supply to a region of the body is disrupted (a condition called *ischemia,* which occurs during the spasms of blood vessels that cause angina or migraine) or when a muscle is damaged. It is also released by rapidly growing tumors. Thus, these nociceptors may be at least partly responsible for the pain caused by angina, migraine, damage to muscles, and cancer.

The Somatosensory Pathways

Somatosensory axons from the skin, muscles, or internal organs enter the central nervous system via spinal nerves. Those located in the face and head primarily enter through the trigeminal nerve (fifth cranial nerve). The cell bodies of the unipolar neurons are located in the dorsal root ganglia and cranial nerve ganglia. Axons that convey precisely localized information, such as fine touch, ascend through the *dorsal columns* in the white matter of the spinal cord to nuclei in the lower medulla. From there axons cross the brain and ascend through the *medial lemniscus* to the *ventral posterior nuclei of the thalamus,* the relay nuclei for somatosensation. Axons from the thalamus project to the primary somatosensory cortex, which in turn sends axons to the secondary somatosensory cortex. In contrast, axons that convey poorly localized information, such as pain or temperature, form synapses with other neurons as soon as they enter the spinal cord. The axons of these neurons cross to the other side of the spinal cord and ascend through the *spinothalamic tract* to the ventral posterior nuclei of the thalamus. (See ***Figure 7.24.***)

Recall from Chapter 6 that the primary visual cortex contains columns of cells, each of which responds to particular features, such as orientation, ocular dominance, or spatial frequency. Within these columns are blobs that contain cells that respond to particular colors. The somatosensory cortex also has a columnar arrangement; in fact, cortical columns were discovered there by Mountcastle (1957) before they were found in the visual and auditory cortex. Within a column neurons respond to a particular type of stimulus (for example, temperature or pressure) applied to a particular part of the body.

Dykes (1983) has reviewed research indicating that the primary and secondary somatosensory cortical areas are divided into at least five (and perhaps as many as ten) different maps of the body surface. Within each map, cells respond to a particular submodality of somatosensory receptors. So far, separate areas have been identified that respond to slowly adapting cutaneous receptors, rapidly adapting cutaneous receptors, receptors that detect changes in muscle length, receptors located in the joints, and Pacinian corpuscles.

As you learned in Chapter 6, the extrastriate cortex consists of several subareas, each of which contains an independent representation of the visual field. For example, one area responds specifically to color and form, and another responds to movement. The somatosensory cortex appears to follow a similar scheme: Each cortical map of the body contains neurons that respond to a specific submodality of stimulation. Undoubtedly, further investigations will provide more accurate functional maps of the cortical subareas of both of these sensory systems.

As we saw in Chapter 6, damage to the visual association cortex can cause visual agnosia, and as we saw earlier in this chapter, damage to the auditory association cortex can cause

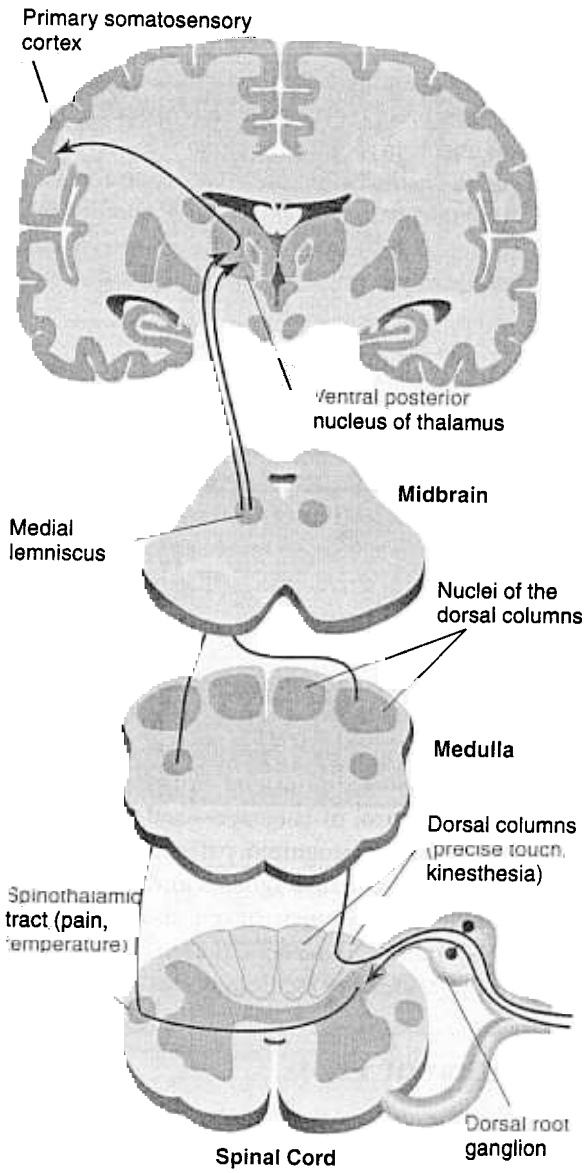


Figure 7.24

The somatosensory pathways from the spinal cord to the somatosensory cortex. Note that precisely localized information (such as fine touch) and imprecisely localized information (such as pain and temperature) are transmitted by different pathways.

auditory agnosia. You will not be surprised to learn that damage to the somatosensory association cortex can cause tactile agnosia. For example, Reed, Caselli, and Farah (1996) described patient E. C., a woman with left parietal lobe damage who was unable to recognize common objects by touch. For example, the patient identified a pine cone as a brush, a ribbon as a rubber band, and a snail shell as a bottle cap. The deficit was not due to a simple loss of tactile sensitivity; the patient was still sensitive to light touch and to warm and cold objects, and she could easily discriminate objects by their size, weight, and roughness.

Nakamura et al. (1998) described patient M. T., who had a different type of tactile agnosia. Patient M. T. had bilateral lesions of the angular gyrus, a region of the parietal lobe surrounding the caudal end of the lateral fissure. This patient, like patient E. C., had normal tactile sensitivity, but he could not identify objects by touch. However, unlike patient E. C., he could *draw* objects that he touched even though he could not recognize what they are. (See ***Figure 7.25.***) The fact that he could draw the objects means that his ability to perceive three-dimensional objects by touch must have been intact. However, the brain damage prevented the information analyzed by the somatosensory association cortex to be transmitted to parts of the brain responsible for control of language—and for consciousness. As you may have recognized, patient E. C.'s deficit resembles apperceptive visual agnosia and patient M. T.'s deficit resembles associative visual agnosia (both described in Chapter 6). Indeed, these deficits are referred to as apperceptive and associative tactile agnosias.

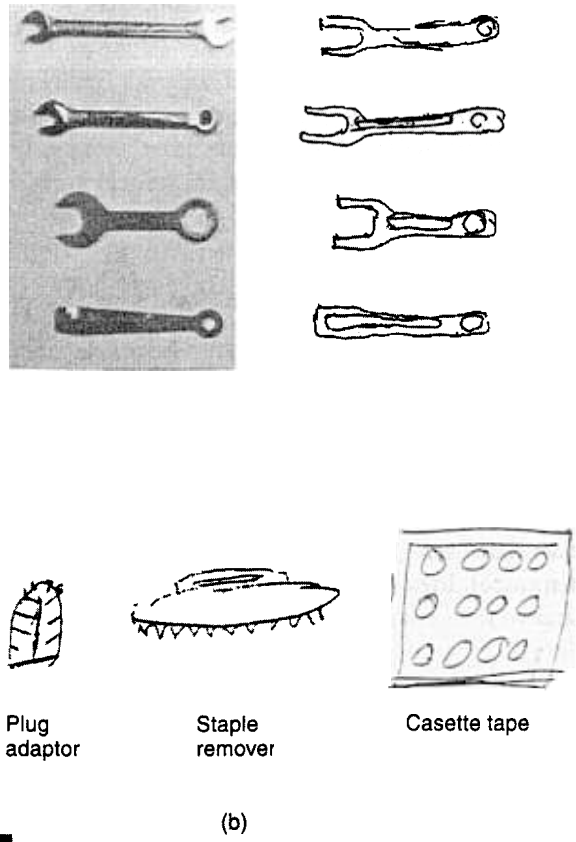


Figure 7.25

Tactile agnosia. (a) Drawings of wrenches felt but not seen by M. T., a patient with associative tactile agnosia. Although the patient did not recognize the objects as wrenches, he was able to draw them accurately. (b) Drawings of objects felt but not seen by E. C., a patient with apperceptive tactile agnosia. The patient could neither recognize the objects by touch nor draw them accurately.

(From Nakamura, J., Endo, K., Sumida, T., and Hasegawa, T. *Cortex,* 1998, *34,* 375–388, and Reed, C. L., Caselli, R. J., and Farah, M. J. *Brain,* 1996, *119,* 875–888. Reprinted by permission of Masson S.P.A. and Oxford University Press.)

Perception of Pain

Pain is a curious phenomenon. It is more than a mere sensation; it can be defined only by some sort of withdrawal reaction or, in humans, by verbal report. Pain can be modified by opiates, by hypnosis, by the administration of pharmacologically inert sugar pills, by emotions, and even by other forms of stimulation, such as acupuncture. Recent research efforts have made remarkable progress in discovering the physiological bases of these phenomena.

We might reasonably ask *why* we experience pain. The answer is that in most cases pain serves a constructive role. For example, people who have congenital insensitivity to pain suffer an abnormally large number of injuries, such as cuts and burns. One woman did not make the shifts in posture that we normally do when our joints start to ache. As a consequence, she suffered damage to the spine that ultimately resulted in death. Other people have died from ruptured appendixes and ensuing abdominal infections that they did not feel (Sternbach, 1968). I am sure that a person who is passing a kidney stone would not find much comfort in the fact that pain does more good than ill; but pain is, nevertheless, very important to our existence.

Some environmental events diminish the perception of pain. For example, Beecher (1959) noted that many wounded American soldiers back from the battle at Anzio, Italy, during World War II reported that they felt no pain from their wounds; they did not even want medication. It would appear that their perception of pain was diminished by the relief they felt from surviving such an ordeal. There are other instances in which people still report the perception of pain but are not bothered by it. Some tranquilizers have this effect, and damage to parts of the brain does, too.

Several studies have found that painful stimuli activate the anterior cingulate cortex, a region of limbic cortex on the medial side of the cerebral hemispheres. One study suggests that this region is involved not with pure percep-

tion of pain, but with the emotional reaction that painful stimuli cause—with the *aversiveness* of pain. Rainville et al. (1997) produced pain sensations in human subjects by having them put their arms in ice water. Under one condition they used hypnosis to diminish the unpleasantness of the pain. The hypnosis worked; the subjects said the pain was less unpleasant, even though it was still as intense. Meanwhile, the investigators used a PET scanner to measure regional activation of the brain. They found that the painful stimulus increased the activity of both the primary somatosensory cortex and the anterior cingulate cortex. When the subjects were hypnotized and less sensitive to the pain, the activity of the anterior cingulate cortex decreased—but the activity of the primary somatosensory cortex remained high. Presumably, the primary somatosensory cortex is involved in the perception of pain, and the anterior cingulate cortex is involved in its aversiveness. (See ***Figure 7.26.***)

A particularly interesting form of pain sensation occurs after a limb has been amputated. After the limb is gone, up to 70 percent of amputees report that they feel as though the missing limb still existed and that it often hurts. This phenomenon is referred to as the **phantom limb** (Melzak, 1992). People with phantom limbs report that the limb feels very real, and they often say that if they try to reach out with it, it feels as though it were responding. Sometimes, they perceive it as sticking out, and they may feel compelled to avoid knocking it against the side of a doorframe or sleeping in a position that would make it come between them and the mattress. People have reported all sorts of sensations in phantom limbs, including pain, pressure, warmth, cold, wetness, itching, sweatiness, and prickliness.

The classic explanation for phantom limbs has been activity of the sensory axons belonging to the amputated limb. Presumably, this activity is interpreted by the nervous system as coming from the missing limb. When nerves are cut and connections cannot be reestablished between the proximal and distal portions, the cut ends of the proximal portions form nodules known as *neuromas.* The treatment for phantom pain has been to cut the nerves above these neuromas, to cut the dorsal roots that bring the afferent information from these nerves into the spinal cord, or to make lesions in somatosensory pathways in the spinal cord, thalamus, or cerebral cortex. Sometimes these procedures work for a while, but often the pain returns.

Melzak suggested that the phantom limb sensation is inherent in the organization of the parietal cortex. As we saw in Chapter 3, the parietal cortex is involved in our awareness of our own bodies. Indeed, people with lesions of the parietal lobe (especially in the right hemisphere) have been known to push their own leg out of bed, believing that it actually belongs to someone else. Melzak reports that some people who were born with missing limbs nevertheless experience phantom limb sensations, which would suggest that our brains are genetically programmed to provide sensations for all four limbs.

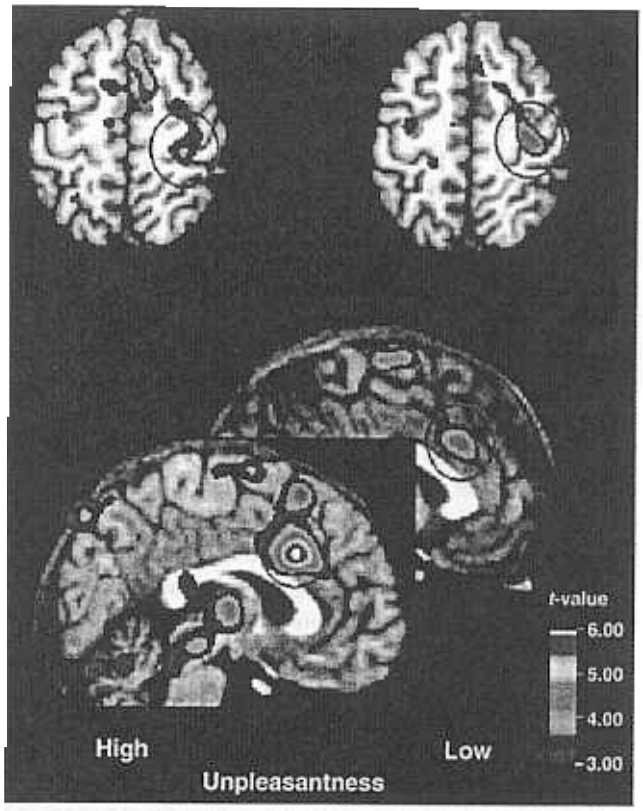


Figure 7.26

PET scans showing brain regions that respond to sensory and emotional components of pain. (*Top:*) Dorsal views of the brain. Activation of the primary somatosensory cortex (circled in red) by a painful stimulus was not affected by hypnotically induced analgesia, indicating that this region responded to the sensory components of painful stimulation. (*Bottom:*) Midsagittal views of the brain. The anterior cingulate cortex (circled in red) showed much less activation when a painful stimulus was presented during hypnotically induced analgesia.

(From Rainville, P., Duncan, G. H., Price, D. D., Carrier, B. and Bushnell, M. C. *Science,* 1997, *277,* 968–971.)

Endogenous Modification of Pain Sensitivity

For many years investigators have known that perception of pain can be modified by environmental stimuli. Recent work, beginning in the 1970s, has revealed the existence of neural circuits whose activity can produce analgesia. A

phantom limb Sensations that appear to originate in a limb that has been amputated.

variety of environmental stimuli can activate these analgesia-producing circuits. Most of these stimuli cause the release of the endogenous opioids, which were described in Chapter 4.

Electrical stimulation of particular locations within the brain can cause analgesia, which can even be profound enough to serve as an anesthetic for surgery in rats (Reynolds, 1969). The most effective locations appear to be within the periaqueductal gray matter and in the rostroventral medulla. For example, Mayer and Liebeskind (1974) reported that electrical stimulation of the periaqueductal gray matter produced analgesia in rats equivalent to that produced by at least 10 milligrams (mg) of morphine per kilogram of body weight, which is a large dose. The technique has even found an application in reducing severe, chronic pain in humans: Fine wires are surgically implanted in parts of the central nervous system and attached to a radio-controlled device that permits the patient to administer electrical stimulation when necessary (Kumar, Wyant, and Nath, 1990).

Analgesic brain stimulation apparently triggers the neural mechanisms that reduce pain, primarily by causing endogenous opioids to be released. Basbaum and Fields (1978, 1984), who summarized their work and that of others, proposed a neural circuit that mediates opiate-induced analgesia. Basically, they proposed the following: Endogenous opioids (released by environmental stimuli or administered as a drug) stimulate opiate receptors on neurons in the periaqueductal gray matter. Because the effect of opiates appears to be inhibitory (Nicoll, Alger, and Nicoll, 1980), Basbaum and Fields proposed that the neurons that contain opiate receptors are themselves inhibitory interneurons. Thus, the administration of opiates activates the neurons on which these interneurons synapse. (See *Figure 7.27.*)

Neurons in the periaqueductal gray matter send axons to the **nucleus raphe magnus,** located in the medulla. The neurons in this nucleus send axons to the dorsal horn of the spinal cord gray matter; destruction of these axons eliminates analgesia induced by an injection of morphine. The inhibitory effects of these neurons apparently involve one or two interneurons in the spinal cord. (See *Figure 7.27.*)

Pain sensitivity can be regulated by direct neural connections, as well as by secretion of the endogenous opioids. The periaqueductal gray matter receives inputs from the frontal cortex, amygdala, and hypothalamus (Beitz, 1982; Mantyh, 1983). These inputs permit learning and emotional reactions to affect an animal's responsiveness to pain even without the secretion of opioids.

Biological Significance of Analgesia

It appears that a considerable amount of neural circuitry is devoted to reducing the intensity of pain. What functions do these circuits perform? When an animal encounters a noxious stimulus, it usually stops what it is doing and engages in withdrawal or escape behaviors. Obviously, these responses are quite appropriate. However, they are sometimes counterproductive. For example, if an animal sustains a wound that causes chronic pain, a tendency to engage in withdrawal responses will interfere with its performance of everyday activities, such as obtaining food. Thus, chronic, unavoidable pain would best be diminished.

Another useful function of analgesia is the suppression of pain during important behaviors such as fighting or

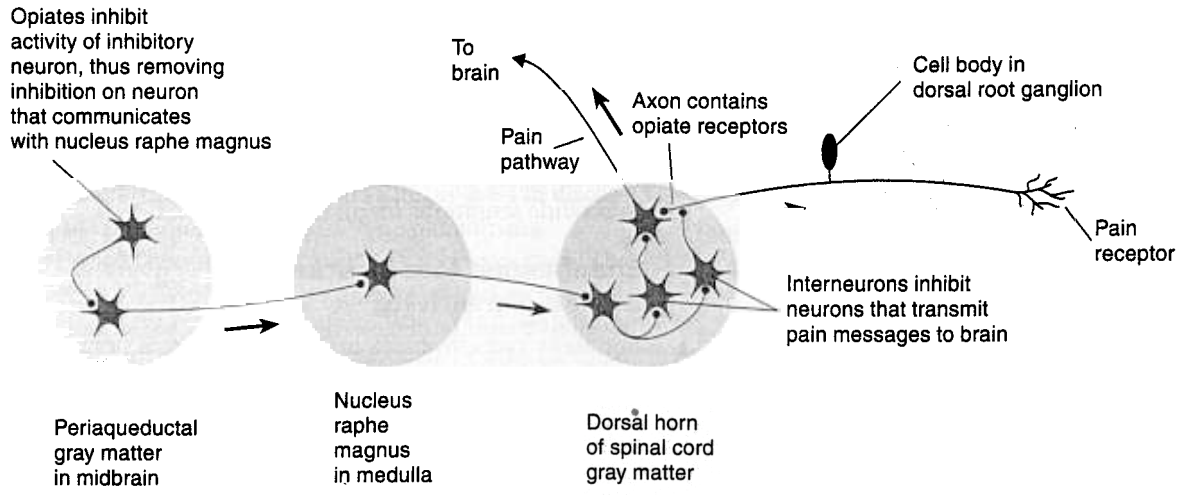


Figure 7.27

The neural circuit that mediates opiate-induced analgesia, as hypothesized by Basbaum and Fields (1978).

mating. For example, males fighting for access to females during mating season will fail to pass on their genes if pain elicits withdrawal responses that interfere with fighting. As we will see, these conditions *do* diminish pain.

First, let us consider the effects of unavoidable pain. Several experiments have shown that analgesia can be produced by the application of painful stimuli or even by the presence of nonpainful stimuli that have been paired with painful ones (that is, through classically conditioned analgesia). For example, Maier, Drugan, and Grau (1982) administered inescapable shocks to rats' tails or administered shocks that the animals could learn to escape by making a response. Although both groups of animals received the same amount of shock, only those that received *inescapable* shocks showed analgesia. That is, when their pain sensitivity was tested, it was found to be lower than that of control subjects. The analgesia was abolished by administration of naloxone, which indicates that it was mediated by the release of endogenous opioids. The results make good sense, biologically. If pain is escapable, it serves to motivate the animal to make appropriate responses. If it occurs whatever the animal does, then a reduction in pain sensitivity is in the animal's best interest. Defeat by another animal of the same species or exposure to the sound or smell of a predator all have been reported to produce analgesia (Kavaliers, 1985; Lester and Fanselow, 1985; Hendrie, 1991).

Pain can be reduced by stimulating regions other than those that hurt. For example, people often rub or scratch the area around a wound, in an apparent attempt to diminish the severity of the pain. And as you know, acupuncturists insert needles into various parts of the body to reduce pain. The needle is usually then rotated, thus stimulating axons and nerve endings in the vicinity. Often, the region that is stimulated is far removed from the region that becomes less sensitive to pain.

Several experimental studies have shown that acupuncture does, indeed, produce analgesia (Mann et al., 1973; Gaw, Chang, and Shaw, 1975). Mayer, Price, Rafii, and Barber (1976) reported that the analgesic effects of acupuncture could be blocked by naloxone. However, when pain was reduced by hypnotic suggestion, naloxone had no effect. Thus, acupuncture, but not hypnosis, appears to cause analgesia through the release of endogenous opioids.

Although pain reduction produced by acupuncture may be more effective if a person believes that it will work, belief in its efficacy is not the only reason this procedure works. Many studies have demonstrated that acupuncture reduces the reaction of laboratory animals to pain, where "belief" can certainly not be an issue. Lee and Beitz (1992) reported that acupuncture that was able to reduce an animal's sensitivity to painful stimuli also reduced the production of Fos protein in somatosensory neurons in the dorsal horn of the spinal cord. (You will recall from Chapter 5 that the production of Fos protein in neurons indicates that they have been activated.)

There is evidence that engaging in behaviors that are important to survival also reduces sensitivity to pain. For example, Komisaruk and Larsson (1971) found that gentle probing of a rat's vagina with a glass rod produced analgesia. Such probing also increases the activity of neurons in the periaqueductal gray matter and decreases the responsiveness of neurons in the ventrobasal thalamus to painful stimulation (Komisaruk and Steinman, 1987). The phenomenon also occurs in humans; Whipple and Komisaruk (1988) found that self-administered vaginal stimulation reduces sensitivity to painful stimuli but not to neutral tactile stimuli. Presumably, copulation triggers analgesic mechanisms. The adaptive significance of this phenomenon is clear: Painful stimuli encountered during the course of copulation are less likely to cause the behavior to be interrupted; thus, the chances of pregnancy are increased.

As we saw in Chapter 4, pain can also be reduced, at least in some people, by administering a pharmacologically inert placebo. When some people take a medication that they believe will reduce pain, it triggers the release of endogenous opioids. This effect is eliminated by the opiate receptor-blocker naloxone (Levine, Gordon, and Fields, 1979). Thus, for some people a placebo is not pharmacologically inert. The placebo effect is probably mediated through connections of the frontal cortex with the periaqueductal gray matter.

interim summary

Cutaneous sensory information is provided by specialized receptors in the skin. Pacinian corpuscles provide information about vibration. Ruffini corpuscles, similar to Pacinian corpuscles but considerably smaller, respond to indentation of the skin. Meissner's corpuscles, found in papillae and innervated by several axons, respond to low-frequency vibration or to brief taps on the skin. Merkel's disks, also found in papillae, consist of single, flattened dendritic endings next to specialized epithelial cells. These receptors respond to pressure. Painful stimuli and changes in temperature are detected by free nerve endings.

Our somatosensory system is most sensitive to changes in mechanical stimuli. Unless the skin is moving, we do not

nucleus raphe magnus A nucleus of the raphe that contains serotonin-secreting neurons that project to the dorsal gray matter of the spinal cord and is involved in analgesia produced by opiates.

detect nonpainful stimuli, because the receptors adapt to constant mechanical pressure. Temperature receptors also adapt; moderate changes in skin temperature are soon perceived as neutral, and deviations above or below this temperature are perceived as warmth or coolness. Transduction in temperature receptors might be accomplished by changes in the rate of the sodium-potassium pump. There are at least three different types of pain receptors: high-threshold mechanoreceptors; fibers with capsaicin receptors, which detect extremes of heat, acids, and the presence of capsaicin (and, undoubtedly, a yet-undiscovered natural ligand); and fibers with receptors sensitive to ATP, which is released during ischemia, after muscle damage, and by rapidly growing tumors.

Precise, well-localized somatosensory information is conveyed by a pathway through the dorsal columns and their nuclei and the medial lemniscus, connecting the dorsal column nuclei with the ventral posterior nuclei of the thalamus. Information about pain and temperature ascends the spinal cord through the spinothalamic system. Organic sensibility reaches the central nervous system by means of axons that travel through nerves of the autonomic nervous system.

The neurons in the primary somatosensory cortex are topographically arranged, according to the part of the body from which they receive sensory information (somatotopic representation). Columns within the somatosensory cortex respond to a particular type of stimulus from a particular region of the body. Recent studies have shown that different types of somatosensory receptors send their information to separate areas of the somatosensory cortex.

Pain perception is not a simple function of stimulation of pain receptors; it is a complex phenomenon with a sensory component and an emotional component that can be modified by experience and the immediate environment. A PET study using hypnotic analgesia suggests that the anterior cingulate cortex may be involved in the emotional component of pain. The phantom limb phenomenon, which often is accompanied by phantom pain, appears to be inherent in the organization of the parietal lobe.

Just as we have mechanisms to perceive pain, we have mechanisms to reduce it—to produce analgesia. Under the appropriate circumstances neurons in the periaqueductal gray matter are stimulated through synaptic connections with the frontal cortex, amygdala, and hypothalamus. In addition, some neurosecretory cells in the brain release enkephalins, a class of endogenous opioids. These neuromodulators activate receptors on neurons in the periaqueductal gray matter and provide additional stimulation of neurons in this region. Connections from the periaqueductal gray matter to the nucleus raphe magnus of the medulla activate serotonergic neurons located there. These neurons send axons to the dorsal horn of the spinal cord gray matter, where they inhibit the transmission of pain information to the brain. In humans chronic pain is sometimes treated by implanting electrodes in the periaqueductal gray matter or the thalamus and permitting the patients to stimulate the brain through these electrodes when the pain becomes severe.

Analgesia occurs when it is important for an animal to continue a behavior that would tend to be inhibited by pain—for example, mating or fighting. In addition, inescapable pain activates brain mechanisms that produce analgesia, but escapable pain does not. This distinction makes sense: If the pain is escapable, its sensation should not be blunted but should serve to motivate the animal's efforts to escape. Because the endogenous opioids are found in several regions of the brain that are apparently not involved in pain perception, these neuromodulators undoubtedly serve functions besides analgesia. The fact that many people have chosen to self-administer opiates extracted from the opium poppy attests to its potency as a reinforcer of behavior.

Analgesia can also be produced by stimulating regions other than those that hurt, which is the basis for acupuncture. This phenomenon can be demonstrated in laboratory animals, which suggests that it has a physiological basis. The administration of a placebo can also produce analgesia. Because this effect is blocked by naloxone, it must involve the release of endogenous opioids.

Gustation

The stimuli we have encountered so far produce receptor potentials by imparting physical energy: thermal, photic (involving light), or kinetic. However, the stimuli received by the last two senses to be studied—gustation and olfaction—interact with their receptors chemically. This section discusses the first of them: gustation.

The Stimuli

Gustation is clearly related to eating; this sense modality helps us to determine the nature of things we put in our mouths. For a substance to be tasted, molecules of it must dissolve in the saliva and stimulate the taste receptors on the tongue. Tastes of different substances vary, but much less than we generally realize. There are only four qualities of taste: *bitterness, sourness, sweetness,* and *saltiness.* (As we will see later, researchers have suggested that there may also be two other taste qualities.) Flavor, as opposed to taste, is a composite of olfaction and gustation. Much of the flavor

of a steak depends on its odor; to an *anosmic* person (one who lacks the sense of smell) or to a person whose nostrils are stopped up, an onion tastes like an apple, and a steak tastes like salty cardboard.

Most vertebrates possess gustatory systems that respond to all four taste qualities. (An exception is the cat family; lions, tigers, leopards, and house cats do not detect sweetness—but then, none of the food they normally eat is sweet.) Clearly, sweetness receptors are food detectors. Most sweet-tasting foods, such as fruits and some vegetables, are safe to eat (Ramirez, 1990). Saltiness receptors detect the presence of sodium chloride. In some environments inadequate amounts of this mineral are obtained from the usual source of food, so sodium chloride detectors help the animal to detect its presence. Injuries that cause bleeding deplete an organism of its supply of sodium rapidly, so the ability to find it quickly can be critical.

Most species of animals will readily ingest substances that taste sweet or somewhat salty. However, they will tend to avoid substances that taste sour or bitter. Because of bacterial activity, many foods become acidic when they spoil. The acidity tastes sour and causes an avoidance reaction. (Of course, we have learned to make highly preferred mixtures of sweet and sour, such as lemonade.) Bitterness is almost universally avoided and cannot easily be improved by adding some sweetness. Many plants produce poisonous alkaloids, which protect them from being eaten by animals. Alkaloids taste bitter; thus, the bitterness receptor undoubtedly serves to warn animals away from these chemicals.

Anatomy of the Taste Buds and Gustatory Cells

The tongue, palate, pharynx, and larynx contain approximately 10,000 taste buds. Most of these receptive organs are arranged around *papillae,* small protuberances of the tongue. *Fungiform papillae,* located on the anterior two-thirds of the tongue, contain up to eight taste buds, along with receptors for pressure, touch, and temperature. *Foliate papillae* consist of up to eight parallel folds along each edge of the back of the tongue. Approximately 1300 taste buds are located in these folds. *Circumvallate papillae,* arranged in an inverted V on the posterior third of the tongue, contain approximately 250 taste buds. They are shaped like little plateaus surrounded by moatlike trenches. Taste buds consist of groups of twenty to fifty receptor cells, specialized neurons arranged somewhat like the segments of an orange. Cilia are located at the end of each cell and project through the opening of the taste bud (the pore) into the saliva that coats the tongue. Tight junctions between adjacent taste cells prevent substances in the saliva from diffusing freely into the taste bud itself. Figure 7.28 shows the appearance of a circumvallate papilla; a cross section through the surrounding trench contains a taste bud. (See *Figure 7.28.*)

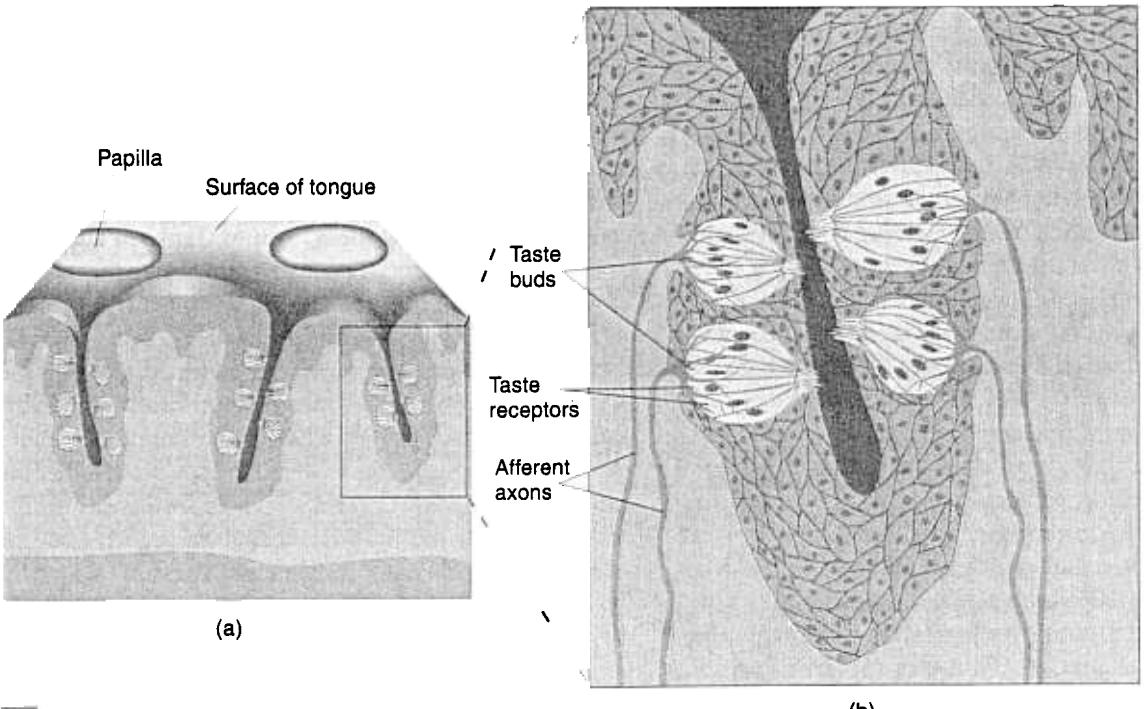


Figure 7.28

The tongue. (a) Papillae on the surface of the tongue. (b) Taste buds.

Taste receptors form synapses with dendrites of sensory neurons that convey gustatory information to the brain. The receptors have a life span of only ten days. They quickly wear out, being directly exposed to a rather hostile environment. As they degenerate, they are replaced by newly developed cells; the afferent dendrite is passed on to the new cell (Beidler, 1970).

Perception of Gustatory Information

Transduction of taste is similar to the chemical transmission that takes place at synapses: The tasted molecule binds with the receptor and produces changes in membrane permeability that cause receptor potentials. Different substances bind with different types of receptors, producing different taste sensations. In this section I will describe what we know about the nature of the molecules with particular tastes and the receptors that detect their presence. I should note that in some cases researchers have found that more than one type of receptor detects a particular taste and that different types of receptors may be found in different species. Thus, the following description, and the information in Figure 7.29, should be seen as representative rather than definitive.

To taste salty, a substance must ionize. Although the best stimulus for saltiness receptors is sodium chloride (NaCl), a variety of salts containing metallic cations (such as Na^+, K^+, and Li^+) with a small anion (such as Cl^-, Br^-, SO_4^{2-}, or NO_3^-) taste salty. The receptor for saltiness seems to be a simple sodium channel. When present in the saliva, sodium enters the taste cell and depolarizes it, triggering action potentials that cause the cell to release neurotransmitter (Avenet and Lindemann, 1989; Kinnamon and Cummings, 1992). (See ***Figure 7.29a.***) The best evidence that sodium channels are involved is the fact that amiloride, a drug that is known to block sodium channels, prevents sodium chloride from activating taste cells and decreases sensations of saltiness. However, the drug does not completely block these sensations in humans, so most investigators believe that more than one type of receptor is involved (Schiffman, Lockhead, and Maes, 1983; Ossebaard, Polet, and Smith, 1997).

Sourness receptors appear to respond to the hydrogen ions present in acidic solutions. However, because the sourness of a particular acid is not simply a function of the concentration of hydrogen ions, the anions must have an effect, as well. The reason for this anion effect is not yet known. Kinnamon, Dionne, and Beam (1988) suggest that sourness is detected by sites on potassium channels in the membrane of taste cell cilia. These channels are normally open, permitting K^+ to flow out of the cell. Hydrogen ions bind with these sites and close the channels. Their closure prevents this outward current and depolarizes the membrane, producing action potentials. (See ***Figure 7.29b.***)

Bitter and sweet substances are more difficult to characterize. The typical stimulus for bitterness is a plant alkaloid such as quinine; for sweetness it is a sugar such as glucose or fructose. The fact that some molecules elicit both sensations suggests that bitterness and sweetness receptors may be similar. For example, the Seville orange rind contains a glycoside (complex sugar) that tastes extremely bitter; the addition of a hydrogen ion to the molecule makes it taste intensely sweet (Horowitz and Gentili, 1974). Some amino acids taste sweet. Indeed, the commercial sweetener aspartame consists simply of two amino acids: aspartate and phenylalanine.

The structure of molecules that taste bitter appears to include a hydrophobic residue—that is, a region that is repelled by the presence of water. Especially bitter substances also have a region with a positive charge (Kurihara et al., 1994). The bitterness receptors are coupled with a G protein called **gustducin,** which is very similar in structure to *transducin,* the G protein involved in transduction of photic information in the retina (McLaughlin et al., 1993). When a bitter molecule binds with the receptor, gustducin activates phosphodiesterase, an enzyme that destroys cyclic AMP. Thus, detection of a bitter-tasting molecule by the receptor causes a decrease in intracellular cyclic AMP. In taste receptor cells, as in photoreceptors, it appears that potassium channels in the body of the taste receptor cell are normally held open by the action of cyclic AMP, which permits a constant efflux of K^+ cations. Thus, a fall in the level of cyclic AMP causes potassium channels to close, and the membrane depolarizes. (See ***Figure 7.29c.***)

Most molecules that taste sweet have a hydrogen ion situated 0.3 nm from a site that will accept a hydrogen ion. Presumably, the sweetness receptor has sites that match these. Sweetness receptors, like bitterness receptors, appear to be coupled to gustducin. Wong, Gannon, and Margolskee (1996) produced a mutation in mice using genetic engineering techniques that permit investigators to "knock out" a particular gene—in this case the gene responsible for the production of gustducin. As expected, the mice did not respond to bitter substances. But in addition, they failed to respond to sweet substances. (They did respond to sour and salty substances.) The binding of sweet-tasting molecules with their receptors causes an increase in the level of cyclic AMP in the cell. This second messenger causes calcium channels to open, and the subsequent in-

gustducin (*gust doo sin*) A G protein that plays a vital role in the transduction of sweetness and bitterness.

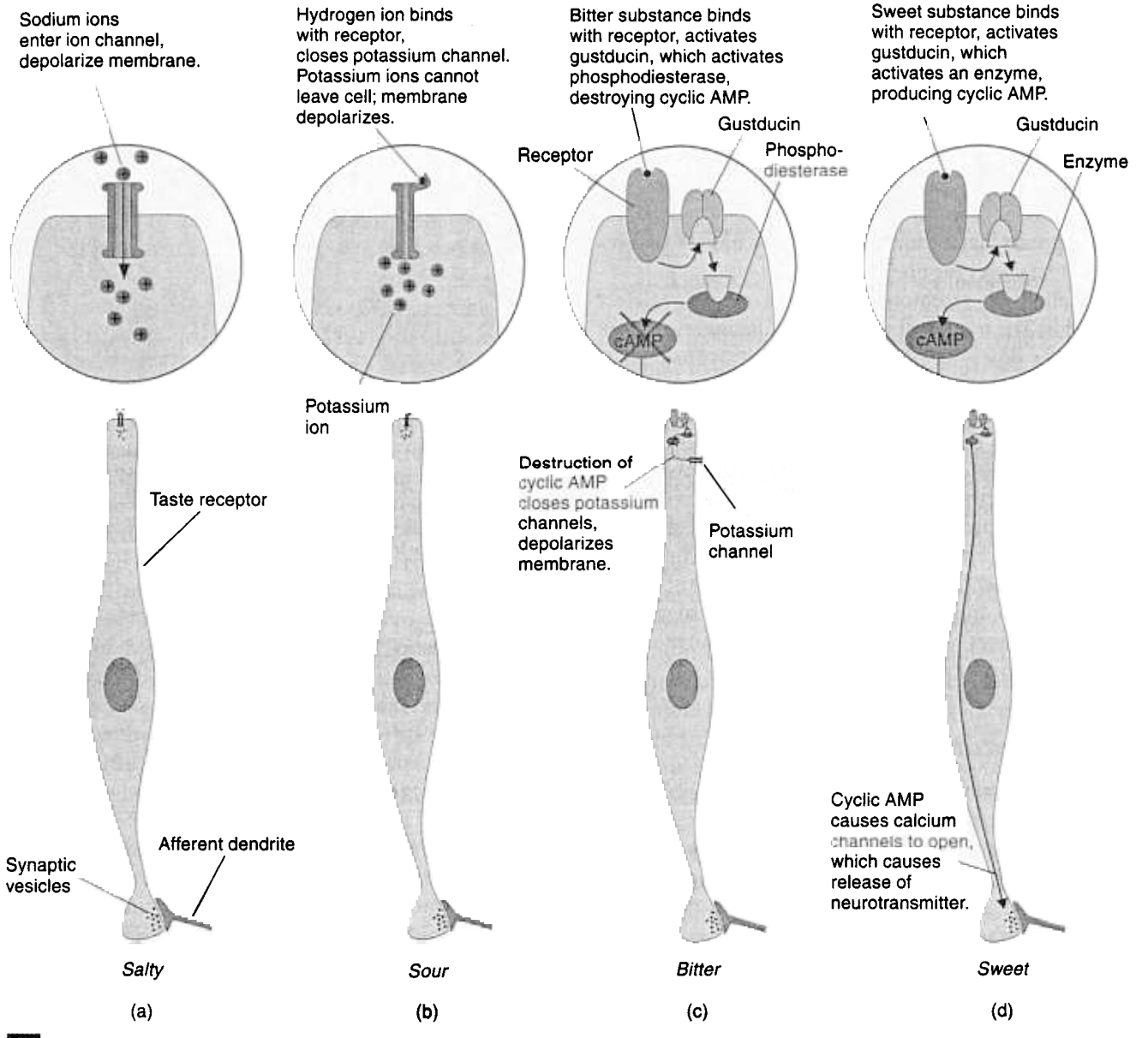


Figure 7.29

Transduction of taste information. (a) Salty taste. (b) Sour taste. (c) Bitter taste. (d) Sweet taste.

flux of calcium causes the cell to release its neurotransmitter (Lindemann, 1996). (See *Figure 7.29d.*)

Researchers have proposed two other taste qualities: umami and fatty acids. **Umami,** a Japanese word that means "good taste," refers to the taste of monosodium glutamate (MSG), a substance often used as a flavor enhancer in Asian cuisine (Kurihara, 1987; Scott and Plata-Salaman, 1991). MSG is present in meats, cheeses, and some vegetables. There is good evidence that the umami receptor exists in several species, but the existence of this taste quality is still not universally accepted in humans. Chaudhari et al. (1996) suggest that a specialized metabotropic glutamate receptor (mGluR4) may be responsible for detecting the taste of glutamate. The investigators found this receptor in taste buds but not in other parts of the tongue. They also reported that rats did not distinguish the taste of MSG from that of a ligand for this receptor, L-AP4. Activation of the mGluR4 receptor appears to close a cation channel, thus depolarizing the membrane (Bigiani et al., 1997).

Fats (triglycerides) consist of three fatty acids molecules joined to a molecule of glycerol, a carbohydrate. Because a

umami (*oo mah mee*) The taste sensation produced by glutamate.

gram of fat contains almost twice as many calories as a gram of protein or carbohydrate, it seems reasonable that there could have been natural selection for receptors that identify fat. The fact that people show such strong preference for foods that are rich in fat suggests that we can detect the presence of this compound. However, until fairly recently, most investigators believed that we identify fats by their texture or "mouth feel" and perhaps by their odor. Now it appears that the tongue may indeed possess taste receptors that detect the presence of fats.

Actually, these receptors, if they exist, appear to detect fatty acids. The tongue contains *lingual lipase*, an enzyme that breaks down fat molecules into their constituents (Lohse et al., 1997). Furthermore, the apical membranes of taste buds contain fatty-acid transporters, molecules that permit the entry of fatty acids into the cell (Fukuwatari et al., 1997). Gilbertson et al. (1997), using the patch-clamp method to record from individual taste cells, found that the presence of fatty acids closes a potassium channel that is normally open, depolarizing the membrane. Only essential fatty acids—those that must be obtained from an animal's diet—had this effect, suggesting that the receptors identify the fats that are nutritionally the most important.

The Gustatory Pathway

Gustatory information is transmitted through cranial nerves 7, 9, and 10. Information from the anterior part of the tongue travels through the **chorda tympani**, a branch of the seventh cranial nerve (facial nerve). Taste receptors in the posterior part of the tongue send information through the lingual (tongue) branch of the ninth cranial nerve (glossopharyngeal nerve); the tenth cranial nerve (vagus nerve) carries information from receptors of the palate and epiglottis. The chorda tympani gets its name because it passes through the middle ear just beneath the tympanic membrane. Because of its convenient location, it is accessible to a recording or stimulating electrode. Investigators have even recorded from this nerve during the course of human ear operations.

The first relay station for taste is the **nucleus of the solitary tract**, located in the medulla. In primates the taste-sensitive neurons of this nucleus send their axons to the ventral posteromedial thalamic nucleus, a nucleus that also receives somatosensory information received from the trigeminal nerve (Beckstead, Morse, and Norgren, 1980). Thalamic taste-sensitive neurons send their axons to the primary gustatory cortex, which is located in the frontal insular and opercular cortex (Pritchard et al., 1986). Neurons in this region project to the secondary gustatory cortex, located in the caudolateral orbitofrontal cortex (Rolls, Yaxley, and Sienkiewicz, 1990). Unlike most other sense modalities, taste is ipsilaterally represented in the brain—that is, the right side of the tongue projects to the right side of the brain, and the left projects to the left. (See ***Figure 7.30.***)

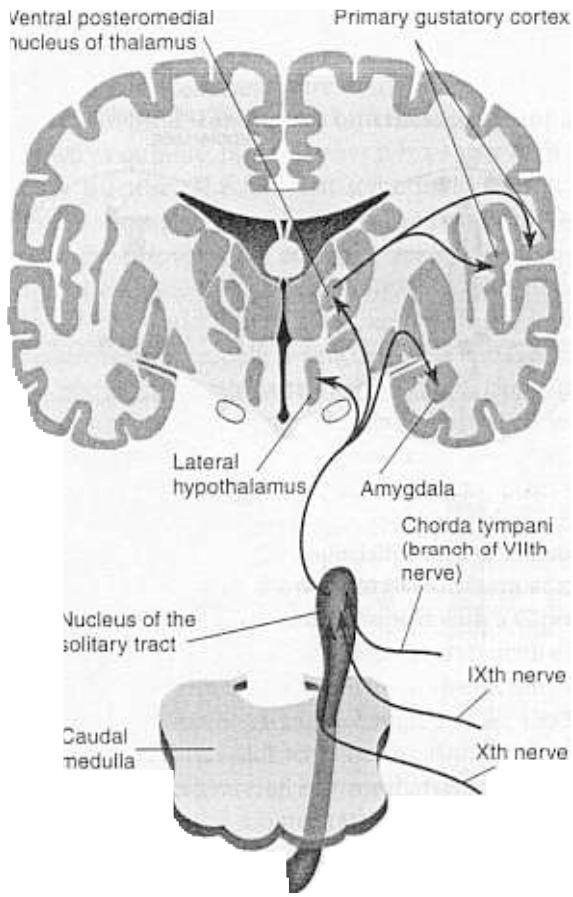


Figure 7.30
Neural pathways of the gustatory system.

Gustatory information also reaches the amygdala and the hypothalamus and adjacent basal forebrain (Nauta, 1964; Russchen, Amaral, and Price, 1986). Many investigators believe that the hypothalamic pathway plays a role in mediating the reinforcing effects of sweet and salty tastes. In fact, some neurons in the hypothalamus respond to sweet stimuli only when the animal is hungry (Rolls et al., 1986). I will discuss this phenomenon in more detail in Chapter 14.

chorda tympani A branch of the facial nerve that passes beneath the eardrum; conveys taste information from the anterior part of the tongue and controls the secretion of some salivary glands.

nucleus of the solitary tract A nucleus of the medulla that receives information from visceral organs and from the gustatory system.

Neural Coding of Taste

Almost all fibers in the chorda tympani respond to more than one taste quality, and many respond to changes in temperature as well. However, most show a preference for one of the four qualities (sweet, salty, sour, or bitter). Figure 7.31 shows the average responses of fibers in the rat chorda tympani and glossopharyngeal nerve to sucrose (S), NaCl (N), HCl (H), quinine (Q), and water (W), as recorded by Nowlis and Frank (1977). (See ***Figure 7.31.***)

Scott and his colleagues (Scott et al., 1991; Smith-Swintosky, Plata-Salaman, and Scott, 1991) operated on monkeys, attaching devices that permitted them to record the activity of single neurons in the primary gustatory cortex while the animals were awake and alert. Slightly over 3 percent of the cells they found responded to taste. Others responded to movement of the mouth or to various somatosensory stimuli. Many cells did not respond to any of the stimuli that the investigators tried.

Although the distribution of the taste-sensitive neurons in the nucleus of the solitary tract and the gustatory thalamus resembles that found on the surface of the tongue (Beckstead, Morse, and Norgren, 1980; Scott et al., 1986), their distribution in the gustatory cortex appears to be unsystematic. However, the investigators did find clusters of neurons with similar response characteristics, which suggests that like other regions of sensory cortex, the gustatory cortex may be organized in columns. They found two major groups of taste-sensitive neurons: sweet and salty. They found cells that were responsive to sour and bitter also, but the responses were less distinct. They noted that the minimum concentrations of salty, sweet, sour, and bitter substances that produced responses in these neurons were very close to the minimum concentrations of these substances that human subjects can detect. Recording in the secondary gustatory cortex, Rolls and his colleagues (reviewed by Rolls, 1995a) found both narrowly and broadly tuned neurons responding to single taste qualities or to several of them.

interim summary

Taste receptors detect only a few sensory qualities: bitterness, sourness, sweetness, saltiness, and, perhaps, umami and fatty acids. Bitter foods often contain plant alkaloids, many of which are poisonous. Sour foods have usually undergone bacterial fermentation, which can produce toxins. On the other hand, sweet foods (such as fruits) are usually nutritious and safe to eat, and salty foods contain an essential cation: sodium. The fact that people in affluent cultures today tend to ingest excessive amounts of sweet and salty foods suggests that these taste qualities are naturally reinforcing.

Saltiness receptors appear to be simple sodium channels. Sourness receptors appear to detect the presence of hydrogen ions, which closes potassium channels located on the cilia and depolarizes the membrane of the cell. Both bitter and sweet tastes are detected by receptors bound to gustducin, a G protein. The structure of molecules that taste bitter appears to include a hydrophobic residue, and some also have a region with a positive charge. Bitter molecules activate phosphodiesterase, which destroys cyclic AMP and closes potassium channels, thus depolarizing the membrane of the cell. Most molecules that taste sweet have a hydrogen ion situated 0.3 nm from a site that will accept a hydrogen ion. Sweet molecules *increase* cyclic AMP levels, which opens calcium channels and thus causes the release of the neurotransmitter. The taste of glutamate (umami) is detected by a particular metabolic glutamate

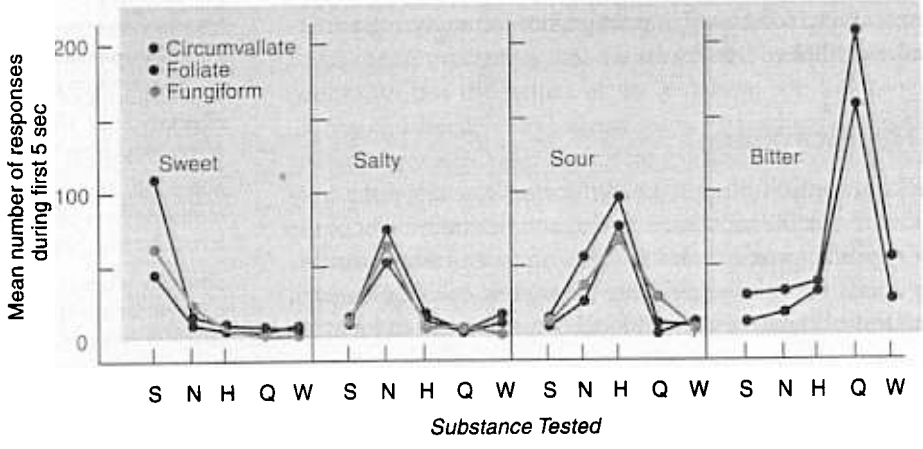


Figure 7.31

Mean number of responses recorded from axons in rat chorda tympani and glossopharyngeal nerve during the first 5 seconds after the application of sugar (S), NaCl (N), HCl (H), quinine (Q), and water (W). The response characteristics of the axons are categorized as sweet, salty, sour, or bitter. (From Nowlis, G. H., and Frank, M., in *Olfaction and Taste 6*, edited by J. Le Magnen and P. MacLeod. Washington, DC: Information Retrieval, 1977.)

receptor (mGluR4). Fats, an important component of the diet, may also be tasted, at least indirectly. The tongue contains an enzyme that converts some of the fat in the mouth to fatty acids, which appear to be transported into taste cells, where they stimulate specialized receptors.

Gustatory information from the anterior part of the tongue travels through the chorda tympani, a branch of the facial nerve. The posterior part of the tongue sends gustatory information through the glossopharyngeal nerve, and the palate and epiglottis send gustatory information through the vagus nerve. Gustatory information is received by the nucleus of the solitary tract (located in the medulla) and is relayed by the ventral posteromedial thalamus to the primary gustatory cortex in the opercular and insular areas. The caudolateral orbitofrontal cortex contains the secondary gustatory cortex. Gustatory information is also sent to the amygdala, hypothalamus, and basal forebrain.

Olfaction

Olfaction, the second chemical sense, helps us to identify food and avoid food that has spoiled and is unfit to eat. It helps the members of many species to track prey or detect predators and to identify friends, foes, and receptive mates. For humans olfaction is the most enigmatic of all sensory modalities. Odors have a peculiar ability to evoke memories, often vague ones that seem to have occurred in the distant past—a phenomenon that Marcel Proust vividly described in his book *Remembrance of Things Past.* Although people can discriminate among many thousands of different odors, we lack a good vocabulary to describe them. It is relatively easy to describe sights we have seen or sounds we have heard, but the description of an odor is difficult. At best, we can say that it smells like something else. Thus, the olfactory system appears to be specialized for *identifying things,* not for analyzing particular qualities.

The Stimulus

The stimulus for odor (known formally as *odorants*) consists of volatile substances having a molecular weight in the range of approximately 15 to 300. Almost all odorous compounds are lipid soluble and of organic origin. However, many substances that meet these criteria have no odor at all, so we still have much to learn about the nature of odorants.

Anatomy of the Olfactory Apparatus

Our 50 million olfactory receptor cells reside within two patches of mucous membrane (the **olfactory epithelium**), each having an area of about 1 square inch. The olfactory epithelium is located at the top of the nasal cavity, as shown in ***Figure 7.32.*** Less than 10 percent of the air that enters the nostrils reaches the olfactory epithelium; a sniff is needed to sweep air upward into the nasal cavity so that it reaches the olfactory receptors.

The inset in Figure 7.32 illustrates a group of olfactory receptor cells, along with their supporting cells. (See ***inset, Figure 7.32.***) Olfactory receptor cells are bipolar neurons whose cell bodies lie within the olfactory mucosa that lines the *cribriform plate,* a bone at the base of the rostral part of the brain. There is a constant turnover of olfactory receptor cells, as there is of gustatory receptor cells; their life cycle is approximately 60 days. The cells send a process toward the surface of the mucosa, which divides into 10 to 20 cilia that penetrate the layer of mucus. Odorous molecules must dissolve in the mucus and stimulate receptor molecules on the olfactory cilia. The axons of olfactory receptor cells enter the skull through small holes in the cribriform ("perforated") plate. The olfactory mucosa also contains free nerve endings of trigeminal nerve axons; these nerve endings presumably mediate sensations of pain that can be produced by sniffing some irritating chemicals, such as ammonia.

The **olfactory bulbs** lie at the base of the brain on the ends of the stalklike olfactory tracts. Each olfactory receptor cell sends a single axon into the olfactory bulb, where it forms synapses with dendrites of **mitral cells** (named for their resemblance to a bishop's miter). These synapses take place in the complex axonal and dendritic arborizations called **olfactory glomeruli** (from *glomus,* "ball"). There are approximately 10,000 glomeruli, each of which receives input from a bundle of approximately 2000 axons. The axons of the mitral cells travel to the rest of the brain through

olfactory epithelium The epithelial tissue of the nasal sinus that covers the cribriform plate; contains the cilia of the olfactory receptors.

olfactory bulb The protrusion at the end of the olfactory tract; receives input from the olfactory receptors.

mitral cell A neuron located in the olfactory bulb that receives information from olfactory receptors; axons of mitral cells bring information to the rest of the brain.

olfactory glomerulus (*glow* ***mare*** *you luss*) A bundle of dendrites of mitral cells and the associated terminal buttons of the axons of olfactory receptors.

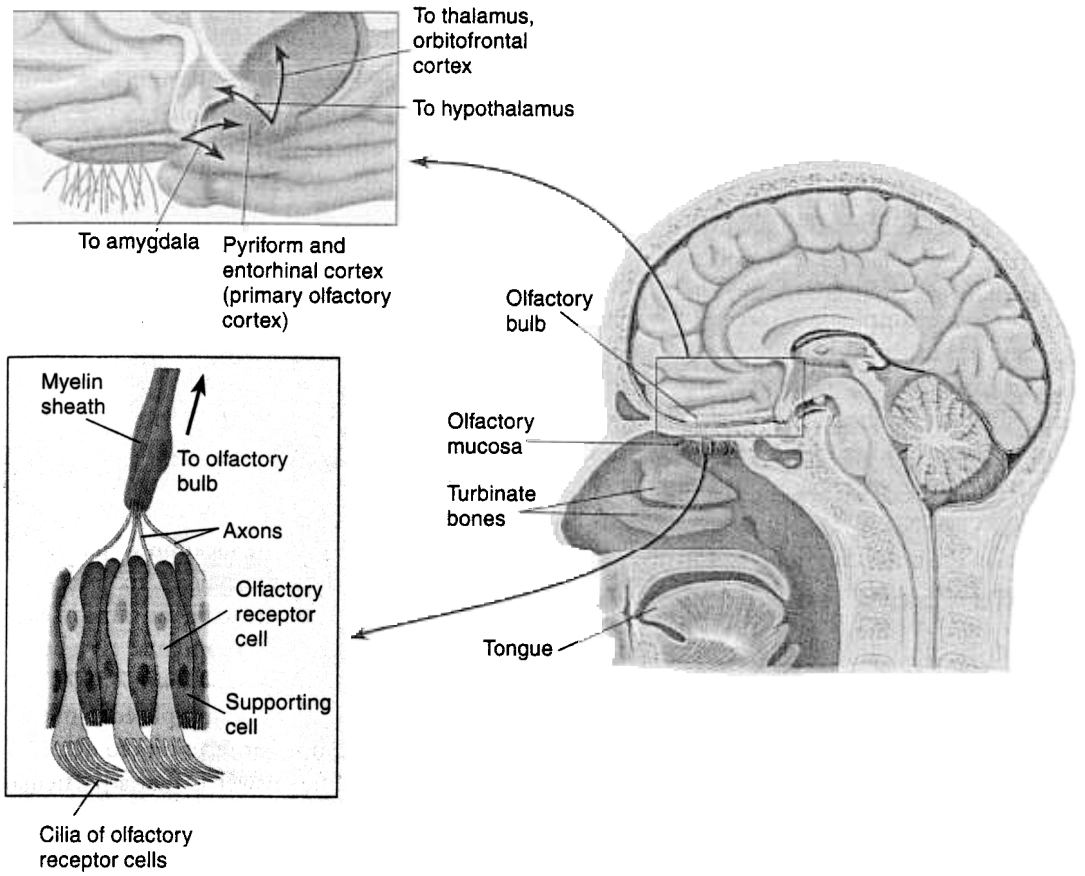


Figure 7.32
The olfactory system.

the olfactory tracts. Some of these axons terminate in other regions of the ipsilateral forebrain; others cross the brain and terminate in the contralateral olfactory bulb.

Olfactory tract axons project directly to the amygdala and to two regions of the limbic cortex: the pyriform cortex and the entorhinal cortex. (See ***Figure 7.32.***) The amygdala sends olfactory information to the hypothalamus, the entorhinal cortex sends it to the hippocampus, and the pyriform cortex sends it to the hypothalamus and to the orbitofrontal cortex, via the dorsomedial nucleus of the thalamus (Buck, 1996; Shipley and Ennis, 1996). As you may recall, the orbitofrontal cortex also receives gustatory information; thus, it may be involved in the combining of taste and olfaction into flavor. The hypothalamus also receives a considerable amount of olfactory information, which is probably important for the acceptance or rejection of food and for the olfactory control of reproductive processes seen in many species of mammals.

Most mammals have another organ that responds to chemicals in the environment: the *vomeronasal organ.* Because it plays an important role in animals' responses to pheromones, chemicals produced by other animals that affect reproductive physiology and behavior, its structure and function are described in Chapter 10.

Efferent fibers from several locations in the brain enter the olfactory bulbs. These include acetylcholinergic, noradrenergic, dopaminergic, and serotonergic inputs (Shipley and Ennis, 1996). As we shall see in Chapter 10, the noradrenergic input appears to be involved in olfactory memories, particularly those involved in reproduction.

Transduction of Olfactory Information

For many years researchers have recognized that olfactory cilia contain receptors that are stimulated by molecules of odorants, but the nature of the receptors was unknown. Jones and Reed (1989) identified a particular G protein, which they called G_{olf}. This protein is able to activate an enzyme that catalyzes the synthesis of cyclic AMP, which, in turn, can open sodium channels and depolarize the membrane of the olfactory cell (Nakamura and Gold, 1987; Firestein, Zufall, and Shepherd, 1991; Menco et al., 1992).

As we saw in Chapter 2, G proteins serve as the link between metabotropic receptors and ion channels: When a

ligand binds with a metabotropic receptor, the G protein either opens ion channels directly or does so indirectly, by triggering the production of a second messenger. The discovery of G_{olf} suggested that olfactory cilia contained odorant receptors linked to this G protein. Indeed, Buck and Axel (1991) used molecular genetics techniques and discovered a family of genes that code for a family of olfactory receptor proteins. So far, olfactory receptor genes have been isolated in more than twelve species of vertebrates, including mammals, birds, and amphibians (Mombaerts, 1999). In humans there appear to be between five hundred and one thousand different receptors, each sensitive to different odorants (Ressler, Sullivan, and Buck, 1994a). Thus, molecules of odorant bind with receptors, and the G proteins coupled to these receptors open sodium channels and produce depolarizing receptor potentials.

Perception of Specific Odors

For many years recognition of specific odors has been an enigma. Humans can recognize up to ten thousand different odorants, and other animals can probably recognize even more of them (Shepherd, 1994). Even if we have several hundred (or even one thousand) different olfactory receptors, that leaves many odors unaccounted for. And every year, chemists synthesize new chemicals, many with odors unlike those that anyone has previously detected. How can we use a relatively small number of receptors to detect so many different odorants?

Before I answer this question, we should look more closely at the relation between receptors, olfactory neurons, and the glomeruli to which the axons of these neurons project. First, the cilia of each olfactory neuron contain only one type of receptor (Nef et al., 1992; Vassar, Ngai, and Axel, 1993). As we saw, each glomerulus receives information from approximately two thousand different olfactory receptor cells. Using in situ hybridization methods to identify particular receptor proteins in individual cells, Ressler, Sullivan, and Buck (1994) discovered that although a given glomerulus receives information from approximately two thousand different olfactory receptor cells, each of these cells contains the same type of receptor molecule. Thus, there are as many types of glomeruli as there are types of receptor molecules. Furthermore, the location of particular types of glomeruli (defined by the type of receptor that sends information to them) appears to be the same in each of the olfactory bulbs in a given animal and may even be the same from one animal to another. (See ***Figure 7.33.***)

Now let's get back to the question I just posed: How can we use a relatively small number of receptors to detect so many different odorants? The answer is that a particular odorant binds to more than one receptor. Thus, because a given glomerulus receives information from only one type of receptor, different odorants produce different *patterns* of activity in different glomeruli. Recognizing a particular

Figure 7.33

Details of the connections of olfactory receptor cells with the glomeruli of the olfactory bulb. Each glomerulus receives information from only one type of receptor cell. Olfactory receptor cells of different colors contain different types of receptor molecules.

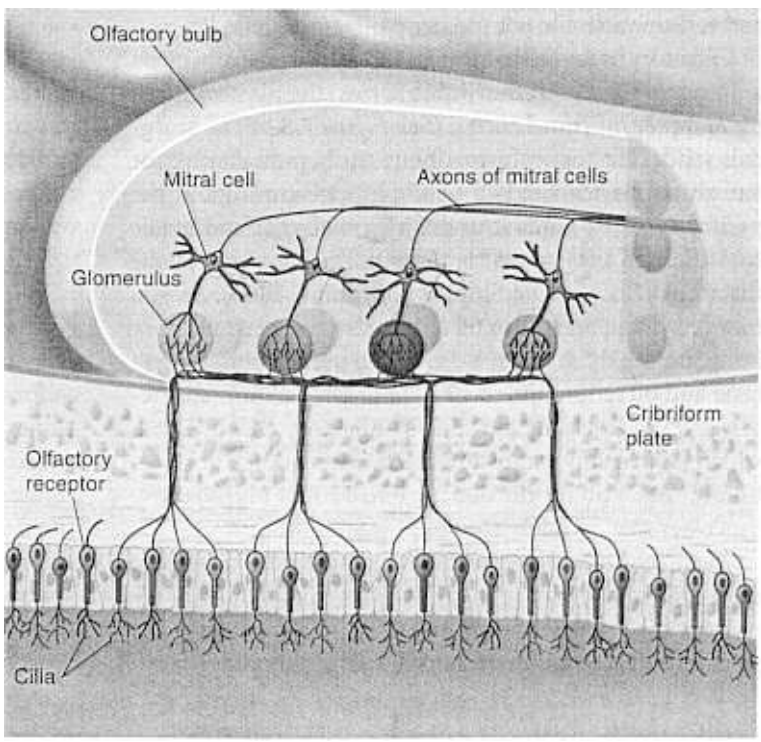


Figure 7.34

A hypothetical explanation of coding of olfactory information. Different odorant molecules attach to different combinations of receptor molecules. (Activated receptor molecules are shown in blue.) Unique patterns of activation represent particular odorants.

(Adapted from Malnic, B., Hirono, J, Sato, T., and Buck, L. B. *Cell*, 1999, *96*, 713–723.)

odor, then, is a matter of recognizing a particular pattern of activity in the glomeruli. The task of chemical recognition is transformed into a task of spatial recognition.

Figure 7.34 illustrates this process (Malnic et al., 1999). The left side of the figure shows the shapes of eight hypothetical odorants. The right side shows four hypothetical odorant receptor molecules. If a portion of the odorant molecule fits the binding site of the receptor molecule, it will activate it and stimulate the olfactory neuron. As you can see, each odorant molecule fits the binding site of at least one of the receptors, and in most cases fits more than one of them. Notice also that the *pattern* of receptors activated by each of the eight odorants is different, which means that if we know which pattern of receptors is activated, we know which odorant is present. Presumably, the brain recognizes particular odors by recognizing different patterns of activation in the olfactory bulbs. (See ***Figure 7.34.***) Of course, even though a particular odorant might bind with several different types of receptor molecules, it might not bind equally well with each of them. For it example, it might bind very well with one receptor molecule, moderately with another, weakly with another, and so on.

Rubin and Katz (1999) obtained evidence to support this model. Figure 7.35 shows the patterns of activity in the olfactory bulbs produced by exposing the olfactory mucosa to three different odorants, pentanal, butanal, and propanal. The molecular structures of these odorants is shown to the right. The patterns were obtained by means of computerized optical analysis of the exposed surface of the olfactory bulbs. The small spots of color represent individual glomeruli; the larger spots are groups of adjacent glomeruli. As you can see, the three odorants produced different patterns of activity. (See ***Figure 7.35.***)

Just how the brain recognizes these patterns is not yet known. The task is obviously complex. Cain (1988) noted that although most odors are produced by mixtures of many different chemicals, we identify odors as belonging to particular objects. For example, the smells of coffee,

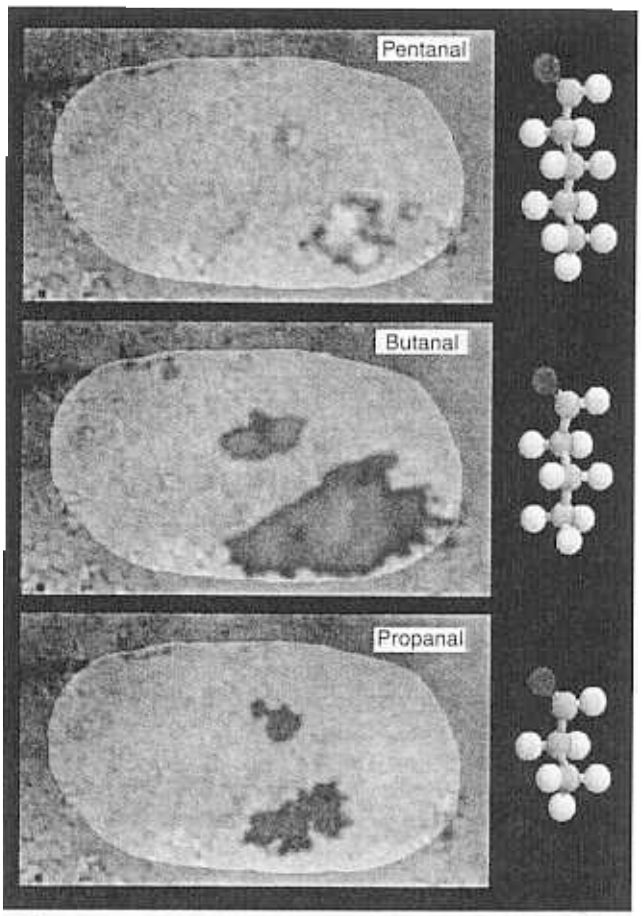


Figure 7.35

Patterns of activation of glomeruli in the rat olfactory bulb produced by exposure of the olfactory mucosa to three different odorants.

(From Rubin, B. D., and Katz, L. C. *Neuron*, 1999, *23*, 499–511 Copyright 1999 Cell Press.)

fried bacon, and cigarette smoke are each made of up to several hundred different types of molecules. Although each of these odors is a mixture, we recognize them as being unique—we do not detect the individual components. However, if the smells of coffee, fried bacon, and cigarette smoke are mixed together (as they might be at a breakfast counter that permits smoking), we still recognize all three odors, even though each one of them is itself a mixture!

Another consideration is that animals whose olfactory bulbs are mostly destroyed can still discriminate between different odors (Lu and Slotnick, 1998). Clearly, a portion of the pattern of activation in the olfactory bulbs still provides enough information for the animals to perform olfactory discriminations. Whether the odors still smell the same to the animals after the surgery (that is, whether the destruction of part of the pattern changes the way particular odorants are perceived) is an unanswered question.

interim summary

The olfactory receptors consist of bipolar neurons located in the olfactory epithelium that lines the roof of the nasal sinuses, on the bone that underlies the frontal lobes. The receptors send processes toward the surface of the mucosa, which divide into cilia. The membranes of these cilia contain receptors that detect aromatic molecules dissolved in the air that sweeps past the olfactory mucosa. The axons of the olfactory receptors pass through the perforations of the cribriform plate into the olfactory bulbs, where they form synapses in the glomeruli with the dendrites of the mitral cells. These neurons send axons through the olfactory tracts to the brain, principally to the amygdala, the pyriform cortex, and the entorhinal cortex. The hippocampus, hypothalamus, and orbitofrontal cortex receive olfactory information indirectly.

Aromatic molecules produce membrane potentials by interacting with a newly discovered family of receptor molecules, which may number up to one thousand. These receptors are coupled to a special G protein, G_{olf}. This protein catalyzes the synthesis of cyclic AMP, which opens sodium channels and depolarizes the membrane. Each glomerulus receives information from only one type of olfactory receptor. This means that the task of detecting different odors is a spatial one; the brain recognizes odors by means of the patterns of activity created in the glomeruli.

suggestedreadings

Audition

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Hildebrand, J. G., and Shepherd, G. M. Mechanisms of olfactory discrimination: Converging evidence for common principles across phyla. *Annual Review of Neuroscience,* 1997, *20,* 595–632.

suggestedwebsites

Somatosensory Pathways

http://thalamus.wustl.edu/course/body.html

This site contains a tutorial on somatosensory pathways and a variety of images that would be useful for lectures on touch and pain.

Relief of Pain and Suffering

http://www.library.ucla.edu/libraries/biomed/his/PainExhibit/

The measurement and treatment of pain is the focus of this site. Topics covered on the site include pain measurement, analgesia and anesthesia, and the phantom limb phenomenon.