Box 26–2 The Evolutionary History of Hearing Resulted in Similarities Between Groups

Mammals are not alone in possessing sensitive and frequency-selective hearing. Amphibians and reptiles, including birds, also do. It is a remarkable fact that these various groups of land vertebrates actually acquired their good hearing systems largely independently. The small, dedicated auditory receptor organ was present in the inner ear of their common ancestor. Much later, the ancestors of modern lizards, birds, and mammals each independently evolved middle-ear systems with eardrums collecting sound from the outside world. Some species, such as birds and their relatives, even evolved two groups of sensory hair cells that have a division of labor similar to that of mammalian inner and outer hair cells. Comparison of middle-ear and inner-ear structures and functions across all living vertebrate groups has revealed that they share many common features and that hearing performance is largely comparable between them. Sound amplification associated with active hair-bundle motility was already present in the very first hair cells that evolved, even before the first fishes. This amplifying system was inherited by all groups and, as described earlier, plays a critical role in improving hearing sensitivity and sharpening frequency selectivity. The greatest difference between mammals and the other groups is that the upper frequency limit of hearing is generally higher in mammals. Nonmammalian ears are limited in response to frequencies lower than about 12 to 14 kHz, whereas some mammals can hear beyond 100 kHz.

In addition to active hair-bundle motility, the second mechanism that tunes individual hair cells to specific frequencies in many nonmammalian ears is electrical in nature. In many fishes, amphibians, and birds, the membrane potential of each hair cell resonates at a particular frequency. Several factors, including alternative splicing of the mRNA encoding cochlear K^+ channels and expression of these channels' auxiliary β subunit, tune the characteristic frequency of the resonance along the tonotopic axis of the auditory organ. Whether electrical resonance contributes to frequency tuning in the ears of mammals, including humans, remains uncertain. It is plausible that mammalian hair cells use instead an interplay between somatic electromotility, which seems absent in nonmammalian species, and the micromechanical environment, including hair-bundle motility, to actively amplify and filter their inputs.

The key signatures of a Hopf bifurcation have been recognized in spontaneous mechanical oscillations of the hair bundle, in electrical oscillations of the membrane potential, and in sound-evoked vibration of the basilar membrane. It is likely that the parallel evolution of hearing organs in different groups of vertebrates resulted in several ways of benefitting from the generic properties of critical oscillation.

chemical neurotransmitter is released. An active zone is characterized by four prominent morphological features (Figure 26–16).

A presynaptic dense body or synaptic ribbon lies in the cytoplasm adjacent to the release site. This fibrillar structure may be spherical, ovoidal, or flattened, and usually measures a few hundred nanometers across. The dense body resembles the synaptic ribbon of a photoreceptor cell and represents a specialized elaboration of the smaller presynaptic densities found at many other synapses. In addition to molecular components shared with conventional synapses, ribbon synapses contain large amounts of the protein ribeye.

The presynaptic ribbon is surrounded by clear synaptic vesicles, each 35 to 40 nm in diameter, which are attached to the dense body by tenuous filaments. Between the dense body and the presynaptic cell membrane lies a striking presynaptic density that comprises several short rows of fuzzy-looking material. Within the cell membrane, rows of large particles are aligned with the strips of presynaptic density. These particles include the Ca^{2+} channels involved in the release of transmitter as well as the K^+ channels that participate in electrical resonance in nonmammalian vertebrates.

Studies of nonmammalian experimental models show that, as with most other synapses (Chapter 15), the release of transmitter by hair cells is evoked by presynaptic depolarization and requires influx of Ca^{2+} from the extracellular medium. Hair cells lack synaptotagmins 1 and 2, however, and the role of those proteins as rapid Ca^{2+} sensors has probably been assumed by the protein otoferlin, which also promotes the replenishment of synaptic vesicles. Although glutamate is the principal afferent neurotransmitter, other substances are released as well.

The presynaptic apparatus of hair cells has several unusual features that underlie the signaling abilities of

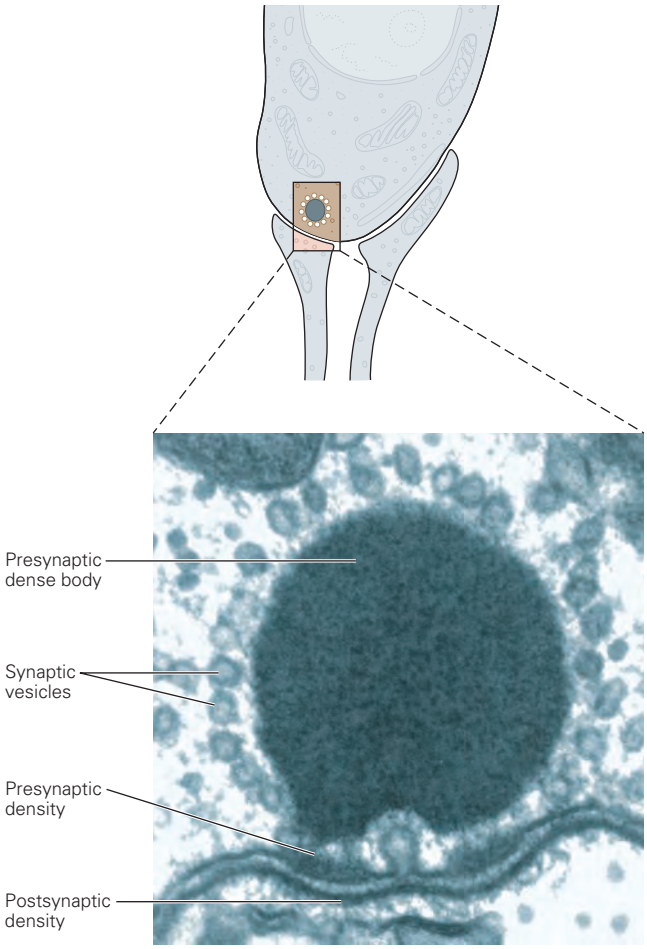

Figure 26–16 The presynaptic active zone of a hair cell. This transmission electron micrograph shows the spherical presynaptic dense body or synaptic ribbon that is characteristic of the hair cell's presynaptic active zone. It is surrounded by clear synaptic vesicles. Beneath the ribbon lies a presynaptic density, in the middle of which one vesicle is undergoing exocytosis. A modest postsynaptic density lies along the inner aspect of the plasmalemma of the afferent terminal. (Reproduced, with permission, from Jacobs and Hudspeth 1990.)

these cells. At rest, inner hair cells continuously release synaptic transmitter. The rate of transmitter release can be modulated upward or downward, depending on whether the hair cell is respectively depolarized or hyperpolarized. Consistent with this observation, some Ca^{2+} channels of hair cells are activated at the resting potential, providing a steady leak of Ca^{2+} that evokes transmitter release from unstimulated cells. Another unusual feature of the hair cell's synapses is that, like those of photoreceptors, they must be able to release neurotransmitter reliably in response to a threshold receptor potential of only 100 μV or so. This feature, too, depends on the fact that the presynaptic Ca^{2+} channels are activated at the resting potential.

Outer hair cells receive inputs from neurons in the brainstem in the form of large boutons on their basolateral surfaces (Figure 26–4). This efferent system desensitizes the cochlea by hyperpolarizing outer hair cells, which turns down the active process. The efferent terminals contain numerous clear synaptic vesicles about 50 nm in diameter, as well as a smaller number of larger, dense-core vesicles. The principal transmitter at these synapses is acetylcholine (ACh); calcitonin gene–related peptide (CGRP) also occurs in efferent terminals and may be co-released with ACh. ACh binds to nicotinic ionotropic receptors consisting of α9 and α10 subunits that have a substantial permeability to Ca^{2+} as well as to Na^+ and K^+. The Ca^{2+} that enters through these channels activates small-conductance Ca^{2+}-sensitive K^+ channels (SK channels), whose opening leads to a protracted hyperpolarization. The cytoplasm of a hair cell immediately beneath each efferent terminal holds a single cisterna of smooth endoplasmic reticulum. This structure may be involved in the reuptake of the Ca^{2+} that enters the cytoplasm in response to efferent stimulation, thus accelerating the return to the cell's resting potential.

Auditory Information Flows Initially Through the Cochlear Nerve

Bipolar Neurons in the Spiral Ganglion Innervate Cochlear Hair Cells

Information flows from cochlear hair cells to neurons whose cell bodies lie in the cochlear ganglion. The central processes of these bipolar neurons form the cochlear division of the vestibulocochlear nerve (eighth cranial nerve). Because this ganglion follows a spiral course around the bony core of the cochlea, it is also called the *spiral ganglion.* Approximately 30,000 ganglion cells innervate the hair cells of each inner ear.

The afferent pathways from the human cochlea reflect the functional distinction between inner and outer hair cells. At least 90% of the spiral ganglion cells terminate on inner hair cells (Figure 26–17). Each axon contacts only a single inner hair cell, but each cell directs its output to many nerve fibers, on average nearly 10. This arrangement has three important consequences.

First, the neural information from which hearing arises originates almost entirely at inner hair cells. Second, because the output of each inner hair cell is

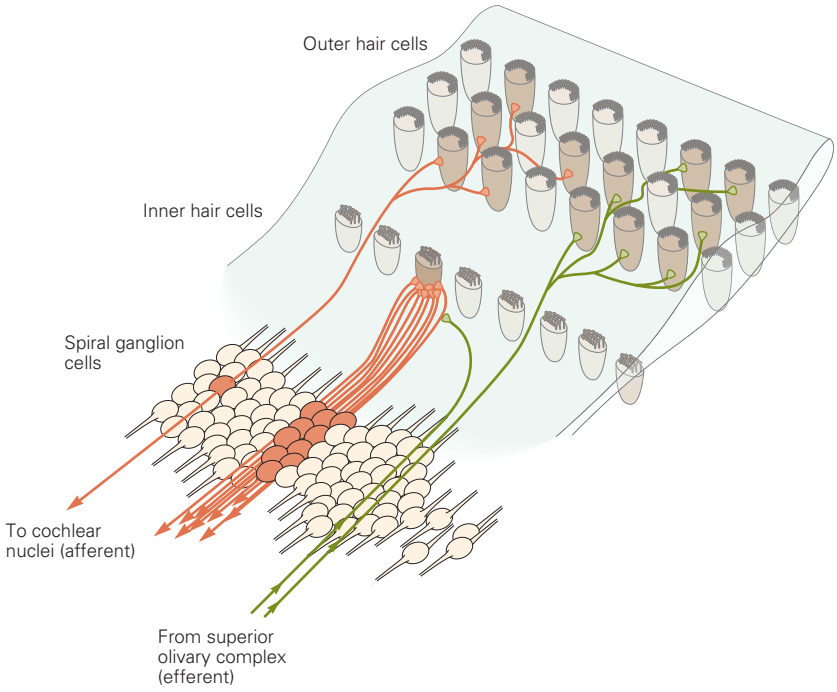

Figure 26–17 Innervation of cochlear hair cells. The great majority of sensory axons (**orange**) in the cochlea carry signals from inner hair cells, each of which constitutes the sole input to an average of 10 axons. A few sensory axons of small caliber transmit information from the outer hair cells. Efferent axons (**green**) largely innervate the outer hair cells and do so directly. In contrast, efferent innervation of inner hair cells is sparse and occurs on the sensory axon terminals. (Adapted, with permission, from Spoendlin 1974.)

sampled by many afferent nerve fibers, the information from one receptor is encoded independently in parallel channels. Third, at any point along the cochlear spiral, or at any position within the spiral ganglion, each ganglion cell responds best to stimulation at the characteristic frequency of the presynaptic hair cell. The tonotopic organization of the auditory neural pathways thus begins at the earliest possible site, immediately postsynaptic to inner hair cells.

Relatively few cochlear ganglion cells contact outer hair cells, and each such neuron extends branching terminals to numerous outer hair cells. Although the ganglion cells that receive input from outer hair cells are known to project into the central nervous system, these neurons are so few that it is not certain whether their projections contribute significantly to the analysis of sound.

The patterns of efferent and afferent connections of cochlear hair cells are complementary. Mature inner hair cells do not receive efferent input; just beneath these cells, however, are extensive axo-axonic synaptic contacts between efferent axon terminals and the endings of afferent nerve fibers. In contrast, other efferent nerves have extensive connections with outer hair cells on their basolateral surfaces. Each outer hair cell receives input from several large efferent terminals, which fill most of the space between the cell's base and the associated supporting cell, leaving little space for afferent terminals.

Cochlear Nerve Fibers Encode Stimulus Frequency and Level

The acoustic sensitivity of axons in the cochlear nerve mirrors the connection pattern of the spiral ganglion cells to the hair cells. Each axon is most responsive to a characteristic frequency. Stimuli of lower or higher frequency also evoke responses, but only when presented at greater levels. An axon's responsiveness may be characterized by a frequency selectivity, or tuning, curve, which is V-shaped like the curves for basilar-membrane motion and hair-cell sensitivity (Figure 26–11). The tuning curves for nerve fibers with different characteristic frequencies resemble one another but are shifted along the frequency axis.

The relationship between sound level in decibels SPL and firing rate in each fiber of the cochlear nerve is approximately linear. Because of the dependence of decibel level on sound pressure, this relation implies that sound pressure is logarithmically encoded by neuronal activity. At the upper end of a fiber's dynamic range, very loud sounds saturate the response. Because an action potential and the subsequent refractory period each last almost 1 ms, the greatest sustainable firing rate is about 500 spikes per second.

Even among nerve fibers with the same characteristic frequency, the threshold of responsiveness varies from axon to axon. The most sensitive fibers, whose response thresholds extend down to approximately

0 dB SPL, characteristically have high rates of spontaneous activity and produce saturating responses for stimulation at moderate intensities, approximately 30 dB SPL. At the opposite extreme, the least sensitive afferent fibers have very little spontaneous activity and much higher thresholds, but respond in a graded fashion to levels even in excess of 100 dB SPL. The activity patterns of most fibers range between these extremes.

The afferent neurons of lowest sensitivity contact the surface of an inner hair cell nearest the axis of the cochlear spiral. The most sensitive afferent neurons, on the other hand, contact the hair cell's opposite side. The multiple innervation of each inner hair cell is therefore not redundant. Instead, the output from a given hair cell is directed into parallel channels of differing sensitivity and dynamic range.

The firing pattern of fibers in the eighth cranial nerve exhibits both phasic and tonic components. Brisk firing occurs at the onset of a tone but, as adaptation occurs, the firing rate declines to a plateau level over a few tens of milliseconds. When stimulation ceases, there is usually a transitory cessation of activity with a similar time course to that of adaptation, before gradual resumption of the spontaneous firing rate (Figure 26–18).

When a periodic stimulus such as a pure tone is presented, the firing pattern of a cochlear nerve fiber encodes information about the periodicity of the stimulus. For example, a relatively low-frequency tone at a moderate intensity might produce one spike in a nerve fiber during each cycle of stimulation. The phase of firing is also stereotyped. Each action potential might occur, for example, during the compressive phase of the stimulus. As the stimulation frequency rises, the stimuli eventually become so rapid that the nerve fiber can no longer produce action potentials on a cycle-by-cycle basis. Up to a frequency in excess of 3 kHz, however, phase-locking persists; a fiber may produce an action potential only every few cycles of the stimulus, but its firing continues to occur at a particular phase in the stimulus cycle.

Periodicity in neuronal firing enhances the information about the stimulus frequency. Any pure tone of sufficient level evokes firing in numerous cochlear nerve fibers. Those fibers whose characteristic frequency coincides with the frequency of the stimulus respond at the lowest stimulus level, but respond still more briskly for stimuli of moderate intensity. Other nerve fibers with characteristic frequencies further from the stimulus also respond, although less vigorously. Regardless of their characteristic frequencies, however, all the responsive fibers may display phase

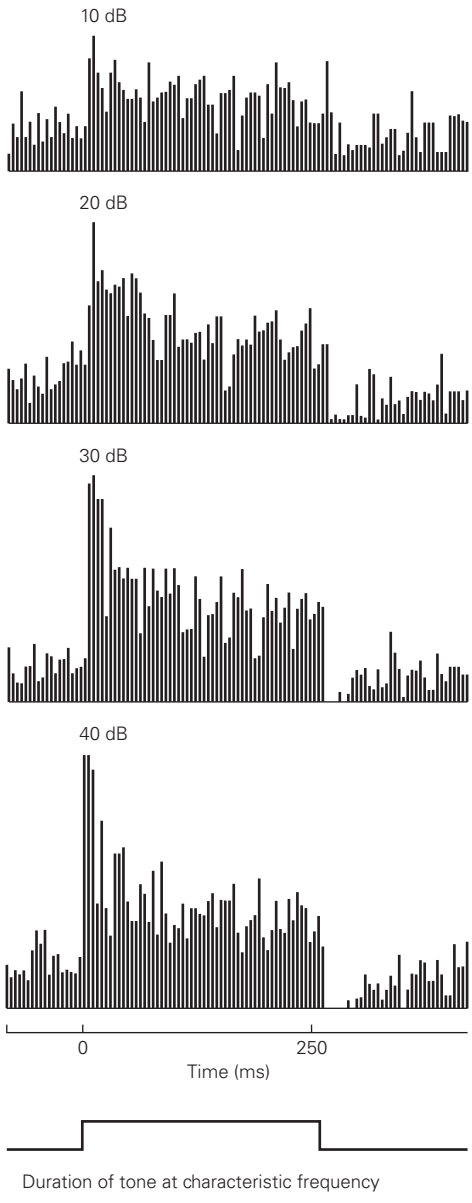

Figure 26–18 The firing pattern of a cochlear nerve fiber. A cochlear nerve fiber is stimulated for somewhat more than 250 ms with a tone burst at about 5 kHz, the cell's characteristic frequency. After a quiet period, the stimulus is repeated. Histograms show the average response patterns of the fiber as a function of stimulus level. The sample period is divided into discrete temporal bins, and the number of spikes occurring in each bin is displayed. An initial, phasic increase in firing is correlated with the onset of the stimulus. The discharge continues during the remainder of the stimulus during adaptation, but decreases following termination. This pattern is evident when the stimulus is 20 dB or more above threshold. Activity gradually returns to baseline during the interval between stimuli. (Adapted, with permission, from Kiang 1965.)

locking: Each tends to fire during a particular part of the stimulus cycle.

The central nervous system can therefore gain information about stimulus frequency in two ways. First, there is a *place code*: The fibers are arrayed in a tonotopic map in which the position is related to characteristic frequency. Second, there is a *frequency code*: The phase-locked firing of the fiber provides information about the frequency of the stimulus, at least for frequencies below 3 kHz.

Sensorineural Hearing Loss Is Common but Is Amenable to Treatment

Whether mild or profound, most deafness falls into the category of *sensorineural hearing loss,* often misnamed "nerve deafness." Although hearing loss can result from direct damage to the eighth cranial nerve, for example from an acoustic neuroma, deafness stems primarily from the loss of cochlear hair cells and their afferent fibers.

The 16,000 hair cells in each human cochlea are not replaced by cell division but must last a lifetime. However, in amphibians and birds, supporting cells can be induced to divide and their progeny to produce new hair cells. In the zebrafish and in birds, some hair cell populations are regenerated continually by the activity of stem or supporting cells. Researchers have recently succeeded in replenishing mammalian hair cells in vitro. Until we understand how hair cells can be restored to the organ of Corti, however, we must cope with hearing loss.

The past few decades have brought remarkable advances in our ability to treat deafness. For the majority of patients who have significant residual hearing, hearing aids can amplify sounds to a level sufficient to activate the surviving hair cells. A modern aid is custom-tailored to compensate for each individual's hearing loss, so that the device amplifies sounds at frequencies to which the wearer is least sensitive, while providing little or no enhancement to those that can still be heard well.

When most or all of a person's cochlear hair cells have degenerated, no amount of amplification can assist hearing. However, a degree of hearing can be restored by bypassing the damaged organ of Corti with a cochlear prosthesis or implant. A user wears a compact unit that picks up sounds, separates their frequency components, and forwards electronic signals representing these constituents along separate wires to small antennae situated just behind the auricle. The signals are then transmitted transdermally to receiving antennae implanted in the temporal bone. From there, fine wires bear the signals to appropriate electrodes implanted as an array in the cochlea at various positions along the scala tympani. Activation of the electrodes excites action potentials in any nearby axons that have survived the degeneration of the hair cells (Figure 26–19).

The cochlear prosthesis takes advantage of the tonotopic representation of stimulus frequency along the cochlea—the *place code* (Figure 26–11 and Chapter 28). The axons innervating each segment of the cochlea are concerned with a specific, narrow range of frequencies. Each electrode in a prosthesis can excite a cluster of nerve fibers that represent similar frequencies. The stimulated neurons then forward their outputs along the eighth nerve to the central nervous system, where these signals are interpreted as a sound of the frequency represented at that position on the basilar membrane. An array of approximately 20 electrodes can mimic a complex sound by appropriately stimulating several clusters of neurons.

The number of implanted cochlear prostheses worldwide is now approaching 350,000. Their effectiveness, however, varies widely from person to person. In the best outcome, an individual can, under quiet conditions, understand speech nearly as well as a normally hearing person and can even conduct telephone conversations. At the other extreme are patients who derive little benefit from prostheses, presumably because of extensive degeneration of the nerve fibers near the electrode array. Most patients find their prostheses of great value. Even if hearing is not completely restored, the devices help in lip reading and alert patients to noises in the environment.

Hearing loss is often accompanied by another distressing symptom, *tinnitus*, or "ringing in the ears." By interfering with concentration and disrupting sleep, tinnitus can exasperate, depress, and even madden its victims. Because on rare occasions tinnitus stems from lesions to the auditory pathways, such as acoustic neuromas, it is important in neurological diagnosis to exclude such causes. Most tinnitus, however, is idiopathic: Its cause is uncertain. More and more studies implicate stress as an important factor. Some drugs also trigger the condition; antimalarial drugs related to quinine and aspirin at the high dosages used in the treatment of rheumatoid arthritis are notorious for this. Often, however, tinnitus occurs at high frequencies to which a damaged ear is no longer sensitive. In these instances, tinnitus may reflect hypersensitivity in the deafferented central nervous system, a phenomenon analogous to phantom limb pain (Chapter 20).

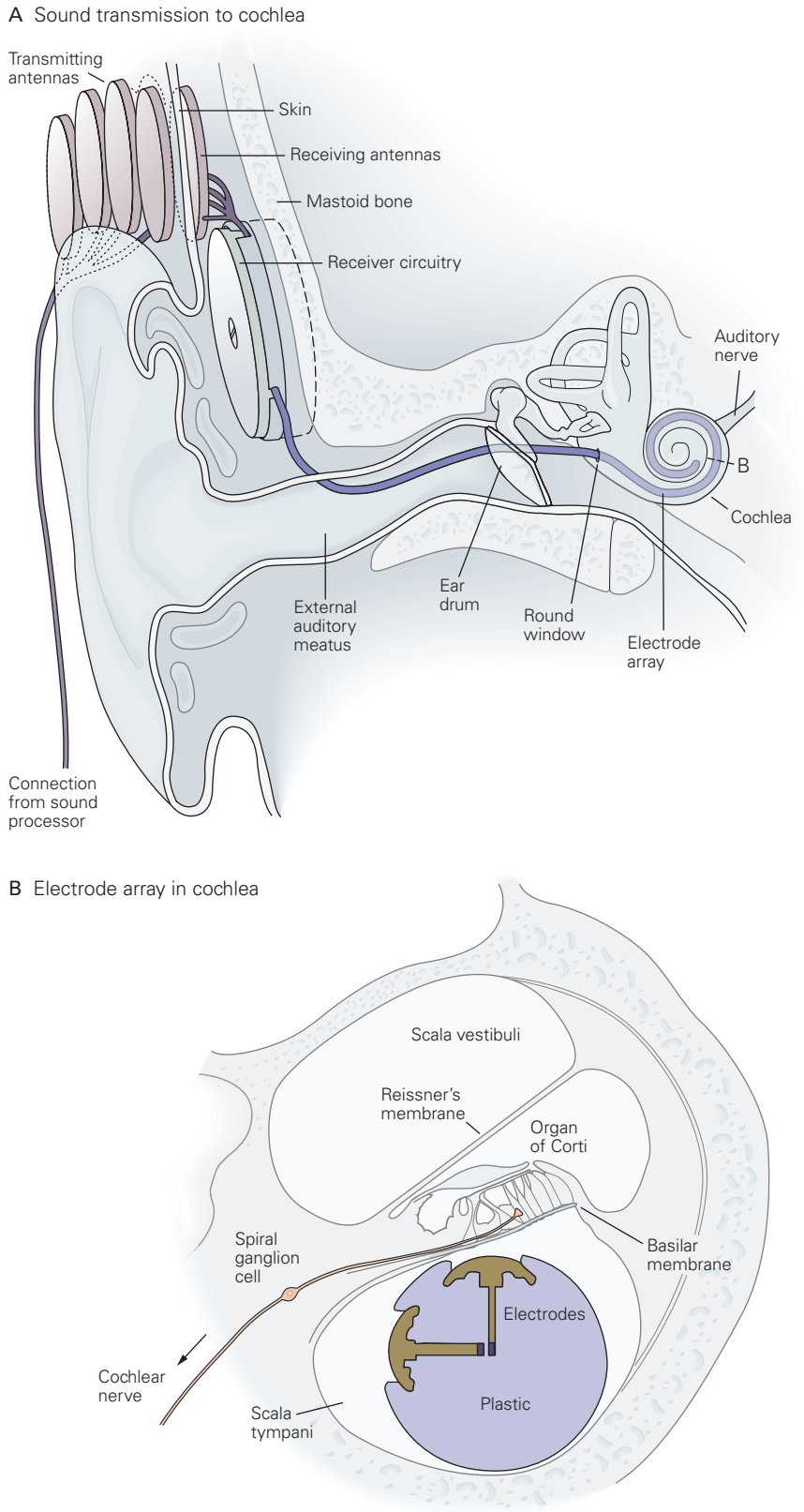

Figure 26–19 A cochlear prosthesis. (Reproduced, with permission, from Loeb et al. 1983.)

A. Transmitting antennas receive electrical signals from a sound processor, located behind the subject's auricle or on the frame of his eyeglasses, and transmit them across the skin to receiving antennas implanted subdermally behind the auricle. The signals are then conveyed in a fine cable (**dark purple**) to an electrode array in the cochlea.

B. This cross section of the cochlea shows the placement of pairs of electrodes in the scala tympani. A portion of the extracellular current passed between an electrode pair is intercepted by nearby cochlear nerve fibers, which are thus excited and send action potentials to the brain.

Highlights

1. Hearing begins with capture of sound by the ear. Mechanical energy captured by the outer ear flows through the middle ear to the cochlea, where it causes the elastic basilar membrane to oscillate.
2. The basilar membrane supports the receptor organ of the inner ear—the organ of Corti, an epithelial strip that contains approximately 16,000 mechanosensory hair cells. Hair cells transduce basilar-membrane vibrations into receptor potentials that cause sensory neurons to fire.
3. The frequency components of a sound stimulus are detected at different locations along the basilar membrane by different hair cells, following a tonotopic map. Mechanical gradients of the basilar membrane contribute to frequency analysis by the cochlea. In addition, each hair cell is tuned at a characteristic frequency according to its morphological, mechanical, and electrical properties, which vary continuously along the tonotopic axis of the cochlea.
4. Hair cells operate much more quickly than do other sensory receptors, which allows them to respond to sound frequencies beyond 100 kHz in some mammalian species. Accordingly, the mechanoelectrical transduction channels in the hair cell are activated directly by mechanical strain.
5. Each hair cell projects from its apical surface a tuft of cylindrical stereocilia—the hair bundle, which works as a mechanical antenna that vibrates in response to sound stimuli. The transduction channels occur at the stereociliary tips. Their open probability is modulated by tension changes in tip links that interconnect neighboring stereocilia.
6. Uniquely among sensory receptors, hair cells amplify their inputs to enhance their sensitivity, sharpen their frequency selectivity, and widen the range of stimulus levels that they can detect. Two forms of cellular motility contribute to this active process. First, receptor potentials evoke length changes of the somata of outer hair cells, a biological analog of piezoelectricity called electromotility. Second, the hair bundle—the mechanosensory antenna of the hair cell—can vibrate autonomously.
7. The ear not only receives sound but also emits sound called otoacoustic emissions. Spontaneous and evoked otoacoustic emissions result from the cochlea's active amplification processes.
8. The cochlea does not work as a high-fidelity sound receiver; instead, it introduces conspicuous distortions that contribute to sound perception. The auditory nonlinearity originates in the cochlea, which amplifies preferentially weak sound stimuli, and constitutes a hallmark of sensitive hearing that is used to screen hearing deficits in newborns.
9. A large variety of experimental observations at the level of a single hair bundle, of the basilar membrane, and in psychoacoustics are readily explained if the cochlea contains active mechanical modules that each operate on the verge of an oscillatory instability—the Hopf bifurcation. The Hopf bifurcation provides a general principle of auditory detection that simplifies our understanding of hearing.
10. The evolutionary history of hearing reveals that the various groups of land vertebrates acquired their hearing systems largely independently, but that their sensitivity and frequency selectivity are similar. In particular, both mammalian and nonmammalian ears benefit from mechanical amplification of sound inputs and show otoacoustic emissions. Mammals most notably differ from other groups in that their hearing range extends to frequencies beyond 12 to 14 kHz.
11. Analysis of the genetic forms of deafness has provided information on dozens of proteins key to the function of the hair cell, in particular those responsible for mechanoelectrical transduction and for synaptic transmission between hair cells and fibers of the auditory nerve. Although these genes may serve as potential targets for future therapies, sensorineural hearing loss is currently treated mostly with hearing aids or cochlear prostheses. New strategies, such as hair-cell replenishment via stem-cell differentiation or optogenetic stimulation of the spiral ganglion, provide promising avenues for research on hearing restoration.

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