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"The Auditory System: Central Auditory Pathways"

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INTRODUCTION

In Chapter 17 we discussed the peripheral processing of auditory information, concluding with the discharge characteristics of auditory nerve fibers. In this chapter, we consider the processing of sound information by the central nervous system (CNS) and attempt to explain the transformations that take place between spike train activity in the 30,000 auditory nerve fibers and the perception of our rich acoustic environment.

To appreciate the difficulty of this processing task, we should reconsider the incredible versatility of our auditory capabilities. These begin with our primitive ability to detect the presence of a predator or prey in the immediate environment, independent of the illumination, direction of gaze, or wind conditions. Also we are able to use spectral and temporal variations in the acoustic energy to identify whether the intruder is close or distant, large or small, friend or foe, or a conspecific. To make such distinctions the acoustic information must be compared with stored auditory experiences, a task that requires more than the simple decoding of signals arriving on the eighth nerve. Localization of the spatial position of a sound also requires integration by CNS neurons, which must compare subtle differences in the energy arriving at the two ears. Such binaural processing, which characterizes most of our auditory pathways, is also useful for the perception of language, the highest level of human auditory processing. Here again, the raw afferent information that reaches the CNS is insufficient to account for language comprehension. Such a facility requires a stored auditory lexicon, which itself is largely independent of the specific nuances of speech sounds. A similar facility presumably underlies the understanding of complex communication signals in other species, such as whales and dolphins.

Our understanding of the CNS events that contribute to auditory detection, binaural localization, and language comprehension is rather primitive. There are, however, two organizing principles that characterize auditory, and in general terms all, sensory processing.

First, auditory information is processed by many parallel pathways. We noted in the preceding chapter that the discharge properties of the vast majority of eighth nerve fibers are quite similar, varying only in their best frequency. At the level of the cochlear nucleus where these axons terminate, this information is distributed to several subnuclei, which give rise to several ascending parallel pathways. Whereas each pathway appears to carry the full range of frequency information, each has a different set of cell types, which themselves have a variety of different inputs, targets, and response properties. From these subnuclei, and probably from subregions within each subnucleus, emanate pathways that undoubtedly transmit different kinds of information. For example, some cochlear nucleus cells drive neurons that receive inputs from both ears (binaural pathways), whereas others contribute to pathways that remain monaural as information ascends through successive levels of neural processing. There is, however, considerable "crosstalk" between these "parallel pathways," and it is unwise to consider them as completely separate.

Second, even along a particular pathway, auditory processing cannot be considered strictly serial or hierarchical. In the preceding chapter we saw that peripheral processing of sound is modified at the level of the middle ear by neural innervation of the tensor tympani and stapedius muscles and further modified at the inner ear by the olivocochlear (efferent) fibers innervating the hair cells. Similarly, at each level of the CNS, ascending information can be modified by descending information from more cephalad auditory regions. Unfortunately, how these centrifugal pathways modify afferent information is largely unknown.

In this chapter, we begin with an overview of the CNS pathways involved in hearing. Ascending pathways that originate at the eighth nerve and project toward the cerebral cortex (also called centripetal projections) will be considered first, followed by a discussion of descending (or centrifugal) projections. The general principle of tonotopic organization will then be considered, as will the anatomical and physiological properties of the major auditory regions. Equipped with this knowledge of the separate elements of the auditory system, we will discuss a few examples of auditory processing, (i.e., binaural interactions, prey localization in the mustache bat, and the middle ear and startle reflexes). Finally, we conclude with a brief section on development and plasticity in the central auditory pathways.

ORGANIZATION OF CENTRAL AUDITORY PATHWAYS

Most of our knowledge concerning the organization of nuclei and fiber tracts involved in the processing of acoustic information comes from detailed studies of the domestic cat.[14] However, the basic organization appears substantially unchanged in all mammals, and the brain-stem auditory pathways are similar in birds and reptiles as well. In some species, this phylogenetically conserved basic organization has been modified to accommodate their unique behavioral requirements. In this section, we first describe the basic organization, and then show how the brains of some animals provide unique opportunities to analyze particular aspects of acoustic processing.

Ascending Auditory Pathways

Auditory Nerve

The auditory nerve is composed of approximately 50,000 axons in the cat (approximately 30,000 in humans), of which 90 to 95% are myelinated and terminate distally on the bases of the inner hair cells. The remaining 5 to 10% are unmyelinated and transmit information from outer hair cells. These different innervation patterns suggest that inner and outer hair cells transmit different kinds of information. This assumption is supported by several facts. First, as noted in the previous chapter, the large myelinated axons are thought to innervate a single inner hair cell, whereas the unmyelinated axons contact a relatively large number of outer hair cells. Therefore, information from inner hair cells has a "private line" to the CNS, whereas information from outer hair cells shows considerable convergence. Second, information from outer hair cells is received by the brain about 1 to 2 ms later than that from inner hair cells. Finally, unless the central terminations of the unmyelinated axons ramify much more profusely and widely than those of myelinated axons, responses in CNS auditory neurons should be dominated by information from inner hair cells.

The myelinated and unmyelinated fibers gather together to form the auditory nerve that courses through the internal auditory meatus. The nerve enters the brain stem at an outgrowth of neural tissue called the acoustic tubercle. The acoustic tubercle contains the cell bodies and neuropil of

the cochlear nucleus, where all auditory nerve fibers terminate.

Cochlear Nucleus

The auditory nerve terminates in three cytoarchitectonically distinguishable subnuclei, which were named for their relative positions in the human brain. The three subnuclei, called the anteroventral, posteroventral, and dorsal cochlear nuclei, seem to have gross functional differences as well. In different species the relative size of the subnuclei varies. For example, in humans the dorsal cochlear nucleus is so small that it is almost vestigial. The current view is that all auditory

nerve terminals are excitatory to the postsynaptic cells of the cochlear nucleus, but this is not certain. The three subnuclei of the cochlear nucleus give rise to three major fiber tracts, which constitute three brain-stem pathways with apparently distinct functions.

Brain-stem Pathways

Binaural Brain-stem Pathways. One pathway originates mainly from cell bodies in the anteroventral cochlear nucleus (AVCN) and dives down into the ventral part of the brain stem to form a large fiber bundle, the *trapezoid body*, which runs across the base of the brain (Fig. 18-1) to provide

CORTEX

THALAMUS

MG

IC

MIDBRAIN

Commissure of Probst

DLL

VLL

DCN

COCHLEAR NUCLEI

PVCN

AVCN

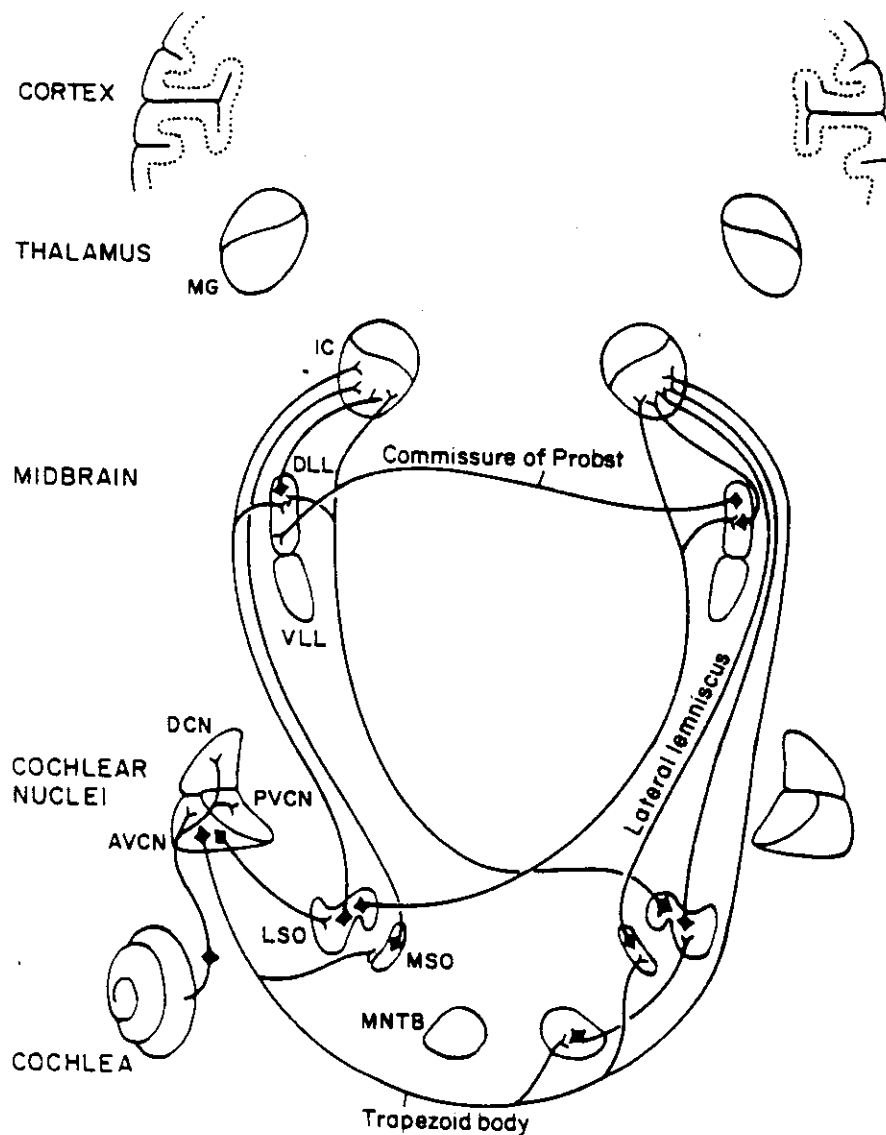Lateral lemniscus

LSO

MSO

MNTB

COCHLEA

Trapezoid body

Figure 18-1 Binaural auditory pathways in the brain stem illustrated for the left cochlear nucleus. The connections from the other cochlear nucleus would form a mirror image. AVCN = anteroventral cochlear nucleus; PVCN = posteroventral cochlear nucleus; DCN = dorsal cochlear nucleus; LSO = lateral superior olive; MSO = medial superior olive; MNTB = medial nucleus of the trapezoid body; VLL = ventral nucleus of the lateral lemniscus; DLL = dorsal nucleus of the lateral lemniscus; IC = inferior colliculus; MG = medial geniculate nucleus. (Adapted by permission from Thompson, G. *Seminars in Hearing*, Vol. 4, pp. 81-95, Thieme Medical Publishers, Inc., New York, 1983.)

the major input to the *superior olivary complex*. The input from the anteroventral cochlear nucleus has two projection sites, which can be differentiated according to their preferred auditory frequencies; one, the *medial superior olivary nucleus* (MSO), receives input predominantly from the apical and middle turns of the cochlea (i.e., lower frequencies), whereas the other, the *lateral superior olivary nucleus* (LSO), receives inputs from the middle and basal turns (i.e., higher frequencies).

The superior olivary complex is the first site for binaural interactions. Single axons from the anteroventral cochlear nucleus are thought to innervate cells at corresponding positions in both the ipsilateral and the contralateral medial superior olivary nucleus. These neurons, therefore, receive inputs from both ears. The lateral superior olivary nucleus also receives binaural input. Neurons in the anteroventral cochlear nucleus not only make excitatory connections in the ipsilateral lateral superior olivary nucleus but also send an axon across the midline in the trapezoid body to a group of large cells near the midline called the *medial nucleus or the trapezoid body* (Fig. 18-1, MNTB). From this nucleus, axons project to the ipsilateral lateral superior olive. Thus, each lateral superior olive neuron receives a direct input from the ipsilateral ear via the cochlear nucleus and an indirect input from the contralateral ear through an intervening synapse in the medial nucleus of the trapezoid body.

The major targets of axons from the medial and lateral superior olivary nuclei are the dorsal nucleus of the lateral lemniscus (Fig. 18-1, DLL) and the inferior colliculus (IC) in the midbrain. The medial superior olivary nuclei project primarily ipsilaterally while the lateral superior olivary nuclei project to both the ipsilateral and contralateral inferior colliculi as well as to the lateral lemniscal nuclei. In addition, some axons from the anteroventral cochlear nucleus, which cross in the trapezoid body, continue up to the contralateral nuclei of the lateral lemniscus or all the way to the inferior colliculus (Fig. 18-1).

Intermediate Brain-stem Pathway. The second pathway, which is relatively poorly understood, originates primarily in the posteroventral cochlear nucleus (Fig. 18-2, PVCN) with some contribution from the anteroventral cochlear nucleus. Axons from these nuclei (solid lines) travel in the *intermediate acoustic stria* to innervate both the ipsilateral and contralateral periolivary nuclei, which surround the superior olivary complex. Additional axons ascend in the contralateral lateral lemniscus to innervate the lateral lemniscal nuclei and inferior colliculus.

Monaural Brain-stem Pathway. The third pathway originates in the dorsal cochlear nucleus (DCN), whose axons course across the midline in the *dorsal acoustic stria* on the dorsal aspect of the brain stem (see Fig. 18-2). They then join the contralateral lateral lemniscus and terminate in the inferior colliculus; some also terminate in the lateral lemniscal nuclei. Thus this pathway sends information from one ear directly to the contralateral inferior colliculus.

Auditory Forebrain Projections. As indicated in Figures 18-1 and 18-2, the three brain-stem pathways converge at the inferior colliculi, which communicate with each other via their commissure. From there, information ascends ipsilaterally in the *brachium of the inferior colliculus* to the main thalamic auditory area, the *medial geniculate body*. Axons from the medial geniculate body terminate in the ipsilateral temporal regions of the cerebral cortex. In lower mammals the auditory areas are primarily on the lateral surface of the cortex; in primates, they are buried in the lateral fissure on the superior aspect of the superior temporal gyrus. Cortical auditory regions in the two hemispheres are interconnected through the corpus callosum.

Descending Auditory Pathways

Sensory processing is often described as a hierarchical process with specific functions attributed to specific neural structures. This model is particularly inappropriate for describing auditory processing. The transmission of information from lower to higher structures is dramatically influenced by information flowing in the opposite direction. As was pointed out in Chapter 17, these descending influences are evident from the very beginning of auditory information processing, including the middle ear and inner ear.

Four major descending pathways are shown in Figure 18-3. At the brain-stem level, the periolivary nuclei project to both the ipsilateral and contralateral inner ear. This *olivocochlear pathway* is composed of two relatively distinct components. One component originates in cell bodies lying lateral to the medial superior olivary nucleus and sends axons ipsilaterally to synapse on the distal dendrites of spiral ganglion cells just under the inner hair cells. The second originates in cell bodies situated in olivary and periolivary nuclei medial to the medial superior olive. It provides axons that synapse primarily on the base of contralateral outer hair cells. The functions of the olivocochlear projections were discussed in the previous chapter. A second descending system
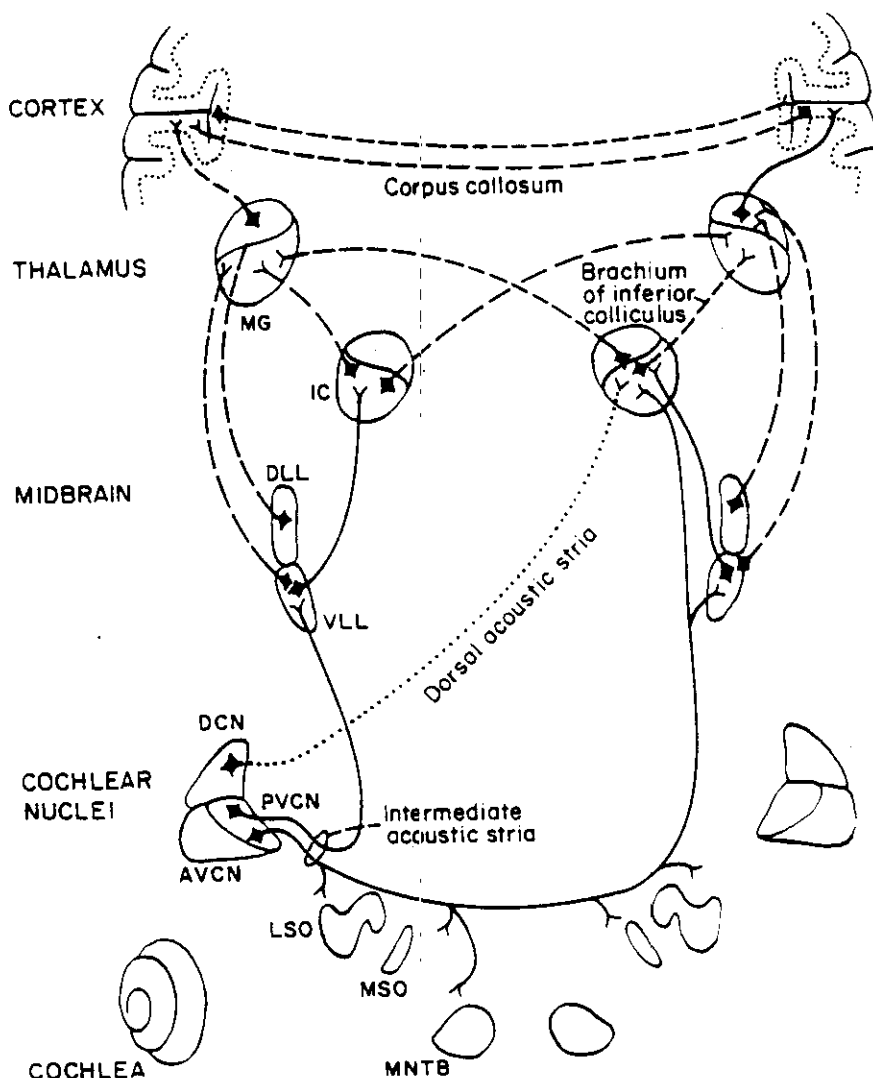
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Figure 18–2 Connections of the intermediate brain-stem pathway (solid lines) and monaural brain-stem pathway (dotted line). As in Figure 18–1, only projections from one side are shown. Forebrain auditory pathways are dashed (abbreviations as in Fig. 18–1). (Adapted with permission from Thompson. G. *Seminars in Hearing.* Vol. 4. pp. 81–95. Thieme Medical Publishers. Inc.. New York. 1983.)

originates in the periolivary nuclei but ends in the cochlear nucleus. Cell groups situated lateral to the medial superior olive send axons primarily to the ipsilateral cochlear nucleus, whereas cells medial to the medial superior olive terminate mainly in the contralateral cochlear nucleus. A third descending pathway originates in the inferior colliculus and lateral lemniscal nuclei. The lateral lemniscal nuclei project to the superior olivary complex and the cochlear nucleus; the inferior colliculus projects to a variety of brain-stem auditory structures, such as the superior olivary complex, as well as some regions that are not considered part of the primary auditory pathways, such as certain pontine nuclei which transmit auditory information to the cerebellum and superior colliculus (see Chap. 20). Last, the auditory cortex

gives rise to at least two descending pathways. Axons descend to the divisions of the medial geniculate nucleus from which ascending cortical connections originate. Other cortical cells project to the ipsilateral inferior colliculus.

Summary

This discussion of the major connections of the central auditory pathways serves to illustrate two points. First, the ascending auditory pathways consist of multiple independent, parallel processing networks that extract, encode, and transmit information about different aspects of the acoustic energy reaching the two ears. Second, the descending pathways allow each structure up to and

including the cerebral cortex to modulate the information in the ascending pathways.

TONOTOPIC ORGANIZATION

In Chapter 17 we noted that peripheral auditory processing is governed by the principle that micromechanical properties of the inner ear transform sound energy into a unique pattern of hair cell excitation. Hair cells in the apical cochlea respond best to low frequencies, basal hair cells prefer high frequencies, and cells in the middle of the cochlea prefer intermediate frequencies. Since this *place code* is a major factor in the discrimination of sounds of different spectral content, we might expect that the spatial encoding of frequency would be retained in the central auditory pathways.

Indeed, when Rose and colleagues[33] played pure tones to a cat, they discovered that each neuron of the cochlear nucleus was excited optimally by a single frequency (its *best frequency*), and that within each subdivision of the cochlear nucleus the best frequencies were organized in a regular order; neighboring cells preferred similar but slightly different frequencies. Figure 18–4 shows one of their recording electrode tracks through part of the cochlear nucleus and identifies the best frequencies of the neurons that were encountered. Within each subnucleus (e.g., Dc), best frequencies were encountered in a descending ordered
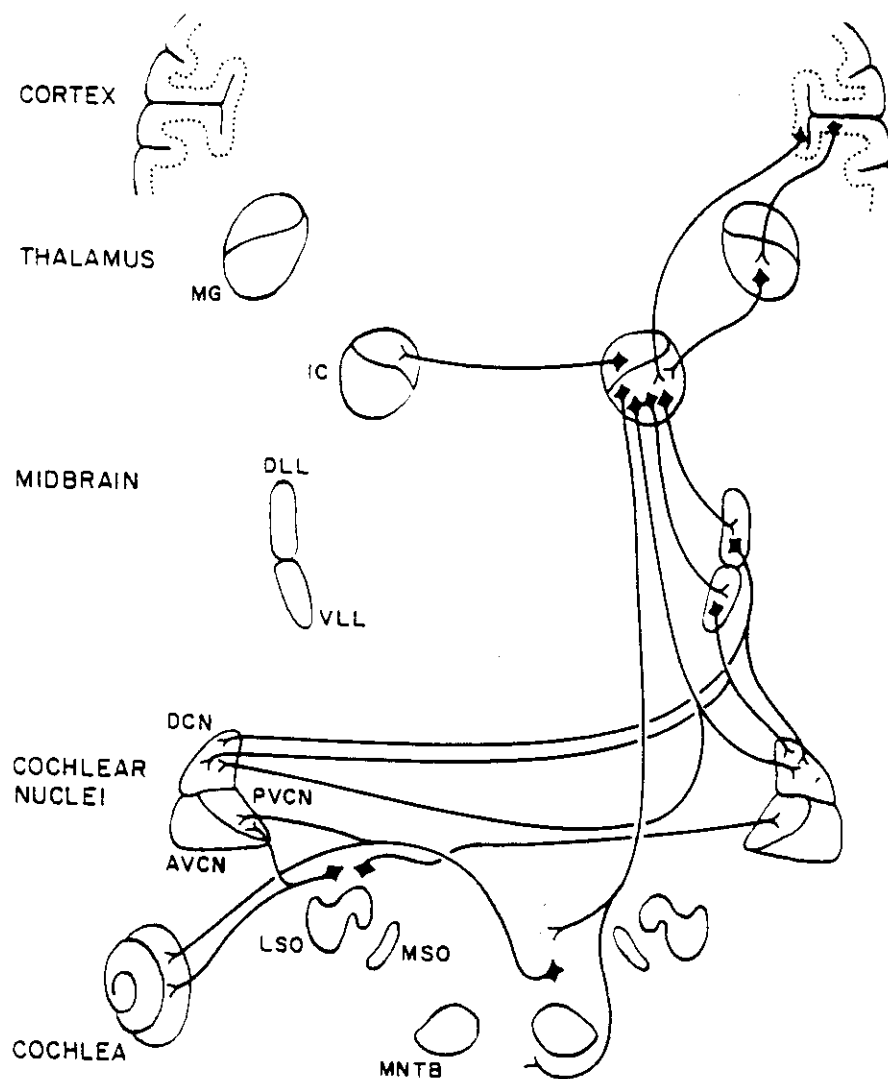

Figure 18–3 The major descending auditory pathways for one side of the brain (abbreviations as in Fig. 18–1). (Adapted with permission from Thompson, G. *Seminars in Hearing*, Vol. 4, pp. 81–95. Thieme Medical Publishers, Inc., New York, 1983.)
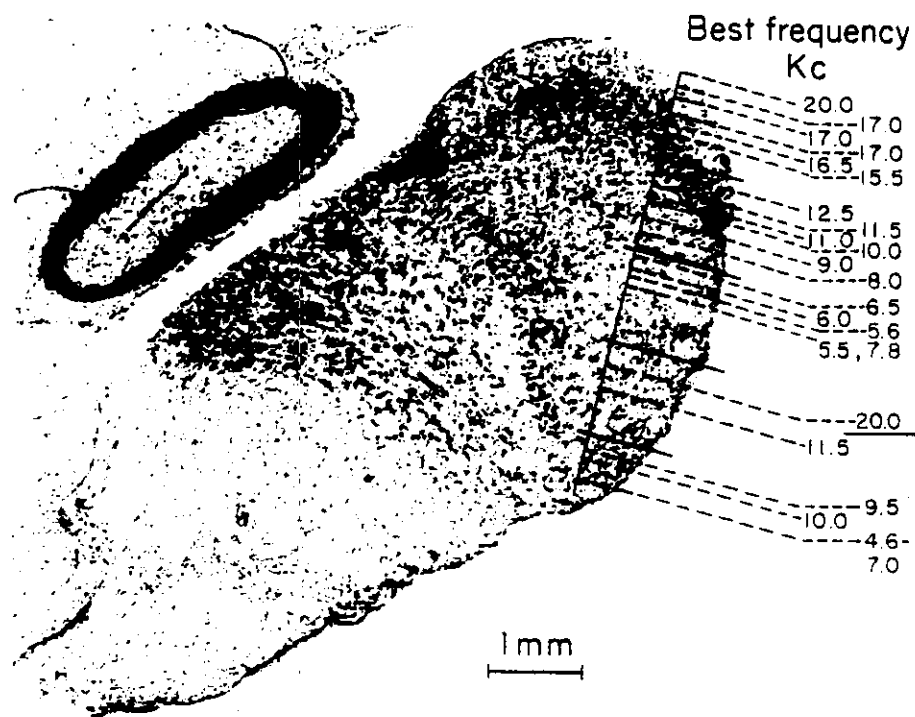
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Figure 18—4 Sagittal section through the cochlear nucleus of the cat showing an electrical penetration through the dorsal cochlear nucleus (Dc) and posteroventral cochlear nucleus (Pv). The best frequency (in kHz) of neurons encountered at successive points along the electrode tract are indicated to the right. Note that there is a systematic decrease in best frequencies until the electrode enters Pv, at which point a new decreasing sequence begins. (From Rose J.E. et al., *Bull. Johns Hopkins Hosp.* 104:211–251, 1959.)

sequence; as the electrode tip crossed the boundary into another subnuclear region (e.g., Pv), there was an abrupt change in frequency and the beginning of a new ordered sequence. This classical experiment showed that within each region of the cochlear nucleus there is an orderly representation of the cochlea.

In order to achieve a tonotopic organization in the cochlear nucleus each point on the cochlea must be represented as a two-dimensional sheet of neural tissue. This organization is illustrated in Figure 18–5. Several ganglion cells receive input from each position along the cochlea. This information can then be distributed to a laminar, sheet-

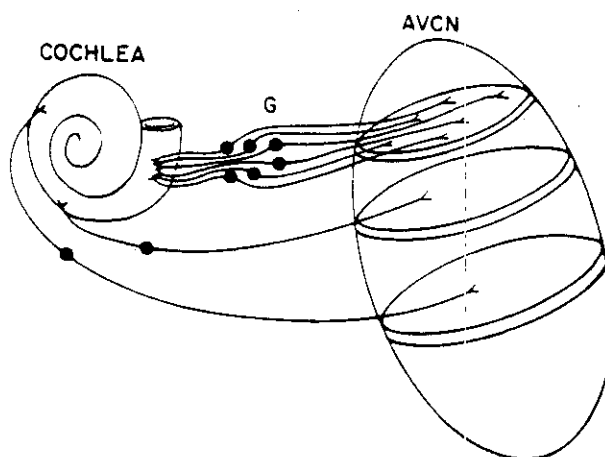Figure 18—5 Schematic of the topographic projection of points on the cochlea to the anteroventral cochlear nucleus (AVCN). Each region of the cochlea is innervated by many spiral ganglion cells (G) whose central axons terminate as a sheet in the cochlear nucleus, forming an isofrequency lamina. These isofrequency lamina are stacked in order of their cochlear innervation to form a tonotopic organization.

7.

like area at the level of the cochlear nucleus. These "isotrequency lamina" are then stacked to form the complete tonotopic representation of the cochlea.

The principle that the receptor surface is spatially "mapped" onto different areas of the brain is not unique to the auditory system. The same organizational principle has been seen in the somatosensory system (where it is called somatotopic organization; see Chap. 15) and will be seen in the visual system (where it is called retinotopic organization; see Chap. 20). In the auditory system the orderly anatomical arrangement of neurons according to their best frequencies is called *tonotopic organization*. Tonotopic organization has now been demonstrated in each of the auditory nuclei from the cochlear nucleus to the cerebral cortex and in a large variety of species, including both vertebrates and invertebrates. For vertebrates with elongated cochleas, such as reptiles, birds, and mammals, the following rules seem to govern the organization.

1. Connections between auditory nuclei are always in tonotopic register, regardless of whether the connections are ascending, descending, or at the same levels of the neuroaxis (i.e., corticocortical connections) and irrespective of their sign (excitatory or inhibitory).

2. When an auditory region is subdivided into subnuclei, each contains an entire tonotopic organization. For example, each subregion of the auditory cortex has a complete representation of the cochlea.

3. In binaurally activated areas, such as the medial superior olive, the tonotopic representation of each ear is in register so that each neuron is most sensitive to the same frequency played to either ear.

4. Although the frequency range varies from species to species, the basic tonotopic map is the same within a class of vertebrates and is virtually identical for individuals of the same species. Often, the similarity of maps between animals of the same species is so precise that a formula that predicts the best frequency of a neuron on the basis of its anatomical location can be accurate to within 200 to 300 Hz.[*]

Each frequency does not necessarily have an equal anatomical representation. Within a structure, the actual number of neurons devoted to a given frequency depends on the number of receptors responding to that frequency. When an animal is specialized to use a particular frequency band, both the cochlea and the central nervous system have a relatively larger amount of tissue

devoted to that band, and the neural representation actually becomes magnified as one ascends the central pathways to the auditory cortex. For example, the mustache bat uses biosonar to navigate, and its auditory system is specialized to use 60-kHz echoes for this behavior. Its cochlea has a specialized region of high receptor density to encode this frequency. This region accounts for about 20% of the cochlea, but its central representation covers almost 50% of the auditory cortex. Although this is an extreme example, it is likely that other species that utilize specific frequencies for behavioral adaptations also show a neural "magnification factor" as one ascends the auditory pathways. A similar phenomenon characterizes other sensory systems. For example, the fovea has an increased representation in the central visual pathways (Chap. 20) as do the perioral regions and tips of the digits in the central somatosensory pathways (Chap. 15).

THE COCHLEAR NUCLEUS

As the cochlear nerve enters the brain, each axon divides into two main branches; one courses anterior to terminate in the *anteroventral* subdivision of the cochlear nucleus. The other branch runs posterior through the posteroventral subdivision where it usually synapses via en passant synapses and short collaterals. Most of these axons finally terminate in the *dorsal cochlear nucleus*. The tonotopic organization of each subdivision of the cochlear nucleus is established by the branching patterns of entering auditory nerve axons. Low-frequency fibers enter ventrally and branch immediately, whereas high-frequency fibers enter dorsally and branch later. The transmitter used by auditory nerve terminals has not been unequivocally identified; it is probably an excitatory amino acid, an aspartate-like compound.

While we describe the cochlear nucleus as being composed of three main subdivisions, several investigators have further subdivided each region on the basis of cell types or other anatomical features. In addition, there are marked variations between species in the relative sizes of each division.

To appreciate the contribution of the cochlear nucleus to auditory processing, we must briefly review the discharge properties of its inputs from the auditory nerve as revealed by several analysis techniques (Fig. 18–6). The discharge patterns of the vast majority of eighth nerve axons differ only in their best frequency. Most axons have a high

rate of spontaneous activity (Fig. 18–6A) and sharp excitatory tuning curves (Fig. 18–6B). Those responding to frequencies below 5 to 6 kHz preserve the temporal characteristics of the stimulus by phase-locking (Fig. 18–6F). Rate-intensity func-

tions at a neuron's best frequency are usually monotonic and saturate at 30 to 40 dB above threshold (Fig. 18–6D). The temporal response characteristics of an auditory nerve axon to a tone burst are obtained by repeating a stimulus many times and grouping the action potentials into sequential time bins. The action potentials in each time bin are then added for all the stimuli to produce a post-stimulus-time-histogram (PSTH). The typical form of a PSTH for an auditory nerve fiber is shown in Figure 18–6C. Finally, one can determine the entire frequency "response area" (or frequency "receptive field," analogous to somatosensory and visual receptive fields; see Chaps. 15 and 20) of an auditory neuron by plotting its discharge rate as a function of frequency at a number of stimulus intensities. Such a plot, characteristic of all auditory primary afferents, is shown in Figure 18–6E.

In contrast to the similarities in the discharge properties of primary auditory afferents, cochlear nucleus neurons display a wide variety of response properties. For example, Figure 18–7 compares PSTHs in the auditory nerve with those found in the cochlear nucleus. Some cochlear nucleus responses are virtually identical to those of the nerve fibers (lowest cell), whereas others respond only to the onset of sound (second cell),
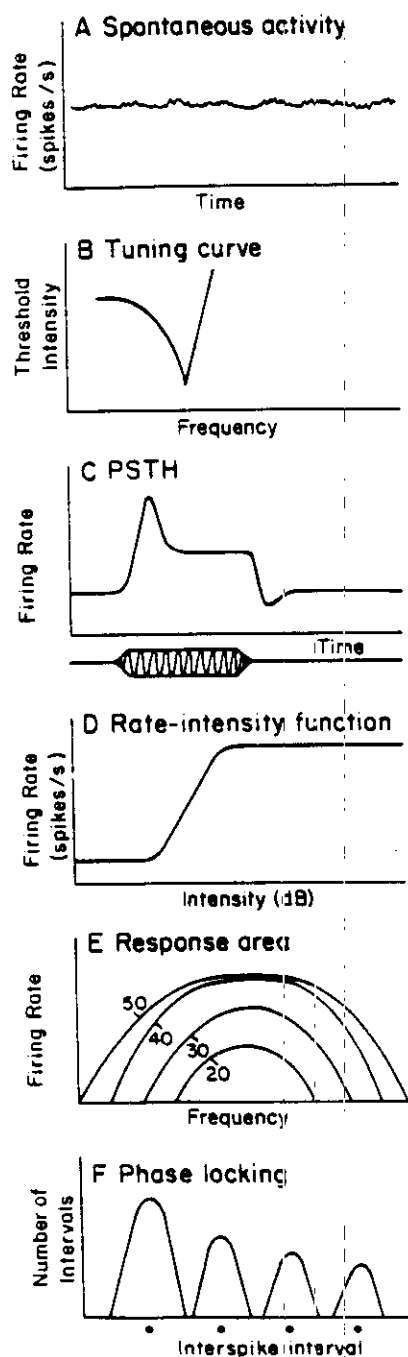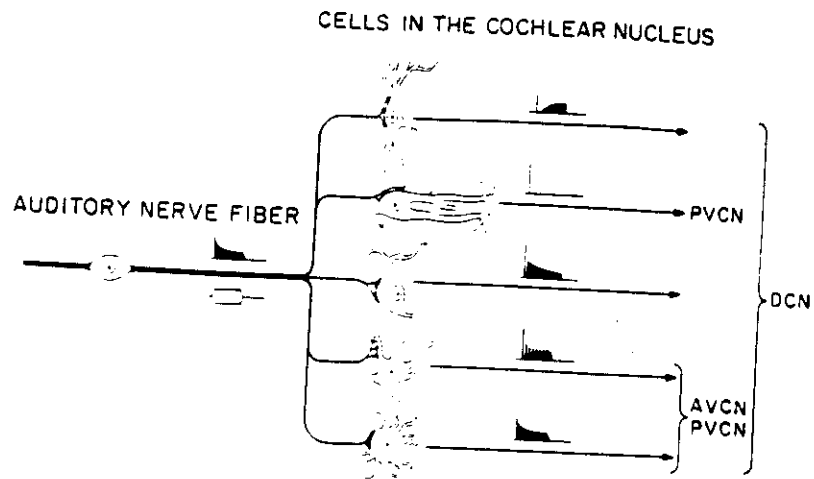

A Spontaneous activity

B Tuning curve

C PSTH

D Rate-intensity function

E Response area

F Phase locking

Figure 18–6 Typical analyses used to describe the response patterns of auditory neurons to simple acoustic stimuli. A. Spontaneous activity in the absence of acoustic stimuli. B. A tuning curve that plots the threshold for an increase in activity above the spontaneous rate as a function of the frequency of a pure tone acoustic stimulus. Each neuron has a "best frequency," indicated by the tip of the tuning curve; at higher or lower frequencies a louder stimulus is required to elicit a response. C. Post-stimulus time histogram (PSTH) shows the pattern of discharge rate as a function of time. A PSTH typically is constructed by repeating a short pure-tone stimulus (shown under graph) many times and averaging the number of discharges in successive time bins following stimulus onset. The typical auditory nerve response pattern (called primary-like) shows an initial high rate of activity immediately after stimulus onset, a decreased, steady rate which is maintained until the stimulus is turned off, and a brief period of inhibition at stimulus offset before the activity returns to spontaneous discharge rate. D. A rate-intensity function plots firing rate as a function of the intensity of a pure tone stimulus. Most auditory nerve fibers have monotonic rate-intensity functions as shown here. E. Average discharge rate is plotted as a function of stimulus frequency. The family of curves represent different stimulus intensities from 20 to 50 dB. F. Phase-locking of auditory nerve fibers can be seen by plotting the number of times that each interspike interval occurs against the interval between each pair of spikes. Note that discharges tend to be spaced at the period of the tone or at multiples thereof, which are indicated by dots on the abscissa.

CELLS IN THE COCHLEAR NUCLEUS

Figure 18–7 Relationship of responses in the cochlear nucleus to morphologically identified cell types. The discharge pattern of an auditory nerve fiber (solid PSTH) to a moderate intensity, short (25–50 ms) tone burst (envelope below PSTH) at the fiber's best frequency is compared to various response patterns elicited by the same burst in the dorsal cochlear nucleus (DCN) and the cell morphologies to which the responses are believed to correspond. AVCN = anteroventral cochlear nuclei; PVCN = posteroventral cochlear nuclei. (From Kiang, N. Y.-S. In Tower, D., ed. *The Nervous System.* Vol. 3. *Human Communication and Its Disorders,* pp. 81–96. New York, Raven Press, 1975 with permission.)

and still others show distinct temporal patterns of excitation and inhibition (first and third cells). These differences in the response properties of cochlear nucleus neurons are associated with particular subdivisions and with cell types with unique morphologies.¹⁸

Anteroventral Nucleus

The anteroventral subdivision of the cochlear nucleus contains two cell types that can be differentiated morphologically. One type is large, round or globular-shaped, with a few short, stubby dendrites that branch repeatedly. These are usually called "bushy cells" or spherical cells. The second type is large and stellate with several tapering dendrites of medium length.

The responses of bushy cells to tone bursts are strikingly similar to those described for auditory nerve fibers and, therefore, are called "primary-like" responses (see Fig. 18–7, lowest cell). A tone elicits a large initial response followed by a decline to a steady-state firing rate for the duration of the tone; when the tone is turned off, there is a short period of inhibition. These cells exhibit phase-locking, monotonic rate-intensity functions with a dynamic range of 20 to 40 dB, and tuning curves resembling those of auditory nerve fibers. The only consistent difference between the responses of auditory nerve fibers and bushy cells is that the latter often show "inhibitory sidebands"—that is, inhibition of spontaneous activity when tones are presented at frequencies and intensities adjacent to the excitatory tuning curve. Therefore, at this level, there is some integration of the events occurring in surrounding cells.

The striking similarity of neuronal responses in the anteroventral cochlear nucleus to those of the auditory nerve can be understood by considering the morphology of auditory nerve terminals. Auditory nerve fibers provide 2 to 4 large calyx-type endings onto the soma and primary dendrites of the bushy cells. These *end bulbs of Held* provide input from one or only a few hair cells. In vitro experiments using tissue slices containing the auditory nerve root and the cochlear nucleus indicate that bushy cells fire one action potential for each spike in the nerve up to very high rates of simulation;²⁰ therefore, the synapse is extremely secure.

The second cell type of the anteroventral cochlear nucleus also has response characteristics similar to those of eighth nerve fibers, except that it discharges rhythmically after the initial transient portion of the PSTH (Fig. 18–7, 4th trace). This discharge pattern, which has been called a "chopper" response, is often associated with stellate cells.²¹⁻²³

It should not be concluded that *no* integration occurs in the anteroventral cochlear nucleus. Both primary-like and chopper cells receive several other synaptic connections that include GABAergic and noradrenergic inputs, which are presumed to be inhibitory; a cholinergic input; and probably other peptidergic inputs.²⁴ The sources of most of these other inputs have not been identified and their roles in information processing remain obscure.

Posteroventral Nucleus

The most common type of neuron in the posteroventral subdivision of the cochlear nucleus responds best to the *onset* of a stimulus. Thus, it

faithfully phase-locks to low frequencies or rapid clicks (below 1 kHz) but responds only to the onset of a higher frequency tone. The neural network responsible for the dramatic cessation of activity in these neurons following the onset of a stimulus is not known, but must include only one or two interneurons since the response is inhibited very rapidly. These cells also often have broad tuning curves, suggesting that they receive inputs from cells located over considerable distances along the cochlea. Altogether, their response characteristics suggest that they can faithfully code rapid temporal changes in a complex acoustic stimulus or in the envelope of a complex stimulus. These response characteristics have been attributed to a cell whose soma and dendritic morphology resemble an octopus (Fig. 18-7, second cell): thus, it is called an *octopus cell*.

Other response types similar to those described in the anteroventral cochlear nucleus (i.e., chopper cells and primary-like cells) also exist in the posteroventral cochlear nucleus, but the cellular morphology associated with these responses is unknown.[50, 34]
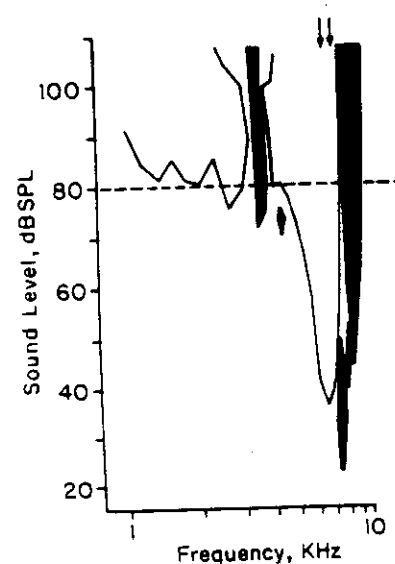

Figure 18–8 Complex tuning curve typical of one type of cell in the dorsal cochlear nucleus. Black areas show frequency-intensity combinations that are excitatory. Enclosed white areas show frequency-intensity combinations that inhibit spontaneous activity. The dotted horizontal line at 80 dB SPL is described in the text. (After Young, E.D. In Berlin, C.I., ed. *Hearing Science*, pp. 423–460, College Hill Press, 1984.)

Dorsal Nucleus

The dorsal cochlear nucleus is the most complex of the cochlear subnuclei. It has been subdivided into a number of regions with heterogeneous cell morphologies and, as noted above, receives descending inputs from a variety of other brain-stem regions including the inferior colliculus.

The response patterns of cells in the dorsal cochlear nucleus show a considerable variety, including the simple pattern characteristic of primary afferents and each of the other patterns shown in Figure 18-7. A consideration of the inhibitory responses further complicates the number of possible patterns.[29] For example, Figure 18–8 shows the inhibitory and excitatory regions for a neuron in the dorsal cochlear nucleus. At moderate sound pressure intensities (80 dB; dashed line), the cell is inhibited by low frequencies. Then, as the frequency is increased it is excited, then inhibited again, and then excited again as the frequency is raised further. At higher or lower intensities, the response pattern is different. Furthermore, responses of dorsal cochlear nucleus cells are dramatically altered by barbiturate anesthesia,[30] further complicating our understanding of information processing in this region.

UTILITY OF BINAURAL INFORMATION

In all the structures discussed so far, neural discharge has been influenced by either one ear or the other. Beginning with the superior olive, however, many neurons are influenced by stimuli delivered to both ears. Before examining such discharge patterns, it is helpful to consider the use we make of our binaural capabilities in order to better understand the binaural responses of neurons.

Binaural hearing allows us to perform two well-known auditory feats. First, we can localize sound in space. Binaural hearing is essential for the localization of a brief sound that varies in position around the horizontal meridian (measured in degrees azimuth). Some animals, such as the barn owl, also can use binaural cues to localize the position of a sound in three-dimensional space. Second, we can attend selectively to sound emanating from a particular location, such as the conversation of one person in a crowded, noisy room (the "cocktail party effect"). Both these feats are accomplished by using either differences in the timing or differences in the intensity of the sounds reaching the two ears.

Interaural time differences occur because sound

travels relatively slowly and there is a finite distance between the ears. The speed of sound in air is 340 m/s and the diameter of the human head is about 17.5 cm. Thus, a sound emanating from the 90-degree azimuth (along a line intersecting the ears) reaches the far ear approximately 660 μs after it reaches the near ear. For sound positions between 0 (the sagittal midline plane) and 90 degrees, the time differences will be proportionally less. This timing difference provides two related binaural signals. First, the onset of stimulation of the two ears will occur at slightly different times; this is important when sound undergoes an abrupt change in frequency or intensity. Second, a constant sound emanating from a single source will be phase-delayed to the far ear. For example, at the 90-degree azimuth, a pure tone of 500 Hz will be shifted in phase by about 120 degrees, and a tone of 740 Hz by about 180 degrees. Thus, for a steady, complex sound, different frequency components will be shifted in phase by different amounts even though the interaural time delay is constant. Interaural time delays are significant only at lower frequencies (less than 2 kHz).

Interaural sound pressure (or intensity) differences occur at higher sound frequencies because part of the sound energy is reflected when its wavelength is short compared to the size of the head; that is, the head is said to cast a "sound shadow." Therefore, when the sound source is displaced to one side of the head, the sound intensity at the far ear is less than that at the near ear. In other words, the spectral properties of complex sounds will differ at the two ears. In humans, interaural intensity differences can be as much as 20 dB at frequencies above 5 kHz. Below about 1 kHz, interaural intensity differences are quite small or nonexistent.

Thus, interaural time differences provide effective spatial information about low frequency sound components, whereas interaural intensity differences provide information about high frequency components. This dichotomy is called the *duplex theory* of sound localization.

The timing or intensity of sounds at the two ears depend not only on the location of the sound source but also on the position of the head and pinna. Thus, the activity of neurons associated with the neck and pinna musculature ultimately must influence the responses of neurons with binaural sensitivities.

SUPERIOR OLIVARY COMPLEX

The superior olivary complex consists of the medial and lateral superior olivary nuclei and the medial nucleus of the trapezoid body. The more diffusely organized periolivary nuclei are poorly understood and will not be considered in this chapter. Since the superior olivary nuclei are the first regions of the central auditory pathways to receive substantial input from both ears, they are thought to play an important role in sound localization and binaural processing. Both their anatomical organization and the response characteristics of their neurons are consistent with this suggestion.

Medial Superior Olive

The neurons of the medial superior olive lie in a thin sheet that is oriented dorsoventrally and rostrocaudally in the ventral brain stem. In cross section, this nucleus appears as a stack of loosely aligned cells (Fig. 18–9C). The major cell type has a bipolar dendritic tree; one dendrite extends toward the midline, and the other extends toward the lateral surface of the brain stem. Axons from the ipsilateral anteroventral cochlear nucleus innervate the lateral dendrites, whereas axons from the contralateral anteroventral cochlear nucleus cross the midline in the trapezoid body to terminate on the medial dendrites (Fig. 18–9A). In the mammal, it is not known whether a neuron in the anteroventral cochlear nucleus sends a collateral to each medial superior olive, but such a pattern does exist in the bird.[31]

Binaurally responsive cells are designated by two letters according to the sign of their responses (excitatory, E; inhibitory, I). The first letter is the sign of the response produced by stimulation of the contralateral ear, and the second is the sign produced by stimulation of the ipsilateral ear. Thus, an IE cell is inhibited by the contralateral ear and excited by the ipsilateral ear. Most cells in the medial superior olive are of the EE type. Their excitatory best frequency is the same for stimulation of either ear.

When tested with monaural stimuli, neurons in the medial olivary nucleus have primary-like responses similar to those in the anteroventral cochlear nucleus. Binaural stimulation, however, reveals that they also are sensitive to differences in the time at which sound arrives at the two ears. Figure 18–10 shows how the average discharge rate of a cell in the medial superior olive varies when a pure tone at the cell's best frequency is first presented to one ear and then is delayed by varying amounts before being delivered to the other ear. The highest discharge rate for this cell
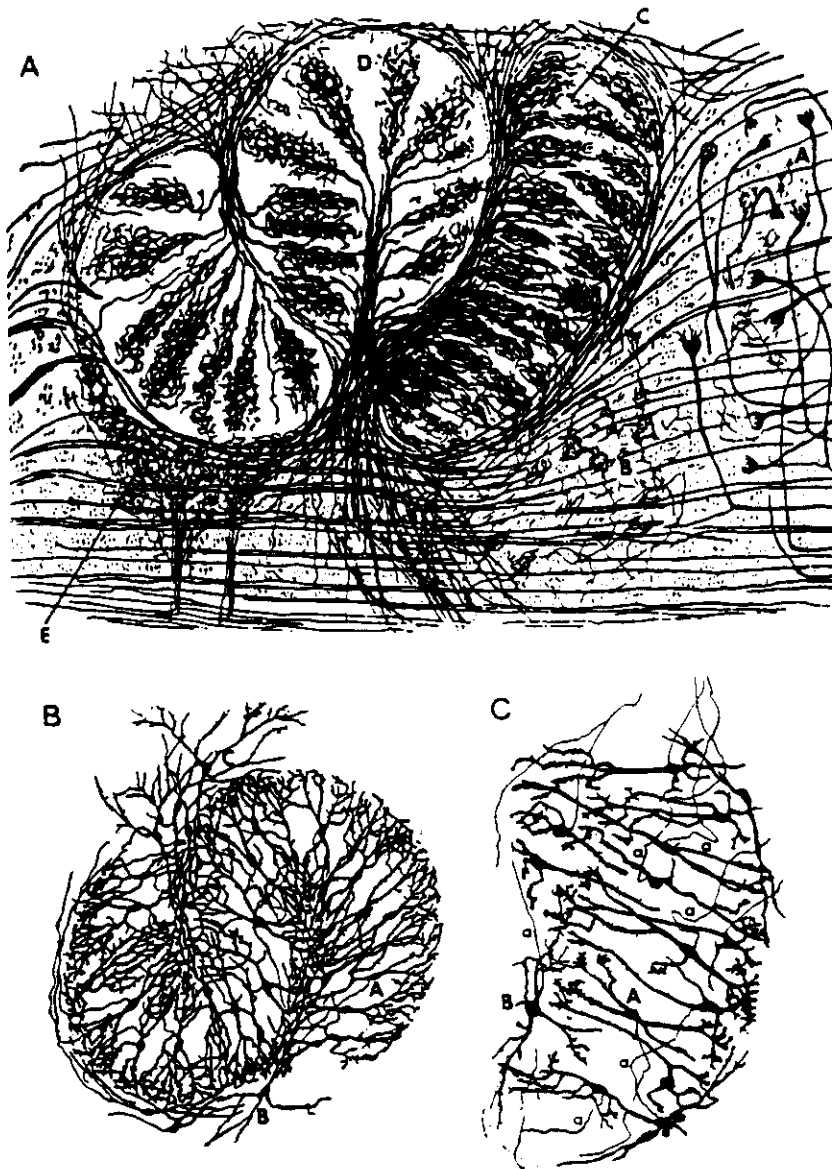
Figure 18-9 Ramon y Cajal's (1909) classical Golgi illustrations of the afferent axonal plexus *(A)*, and of cell types in lateral *(B)* and medial *(C)* superior olivary nuclei of young kittens. Abbreviations in *A*: A = medial nucleus of trapezoid body (note calyces of Held); B = periolivary cell region; C = medial superior olivary nucleus; D = lateral superior olivary nucleus; E = lateral nucleus of trapezoid body; F = fibers of trapezoid body. In *B* and *C*. capital letters identify different cell types and *a* identifies axons.

resulted when the stimulus to one ear occurred about 0.5 ms or 1.5 ms later than the stimulus to the other. Delaying one stimulus was more effective than presenting both simultaneously or presenting the stimulus monaurally, even at an increased sound intensity. Finally, when the two ears were stimulated at the least favorable delay, the response was *less* than when the contralateral ear was stimulated alone. Different cells are responsive to different *characteristic delays* between stimuli presented to the two ears. Since an auditory stimulus reaches the two ears at different times whenever a sound comes from anywhere

off the midline plane (i.e., off the 0-degree azimuth), neurons with different characteristic delays are thought to code the position of sound. When the temporal difference in binaural stimuli matches the characteristic delay of a neuron in the medial superior olive, a large response will occur; other neurons with different characteristic delays will be less active or inhibited.

Since we use interaural time differences to localize low frequencies, neurons in the medial superior olive seem uniquely suited to participate in low frequency sound localization. Generally, animals that have a low auditory frequency range
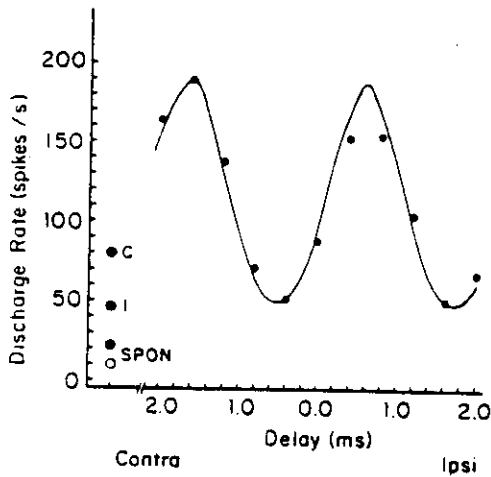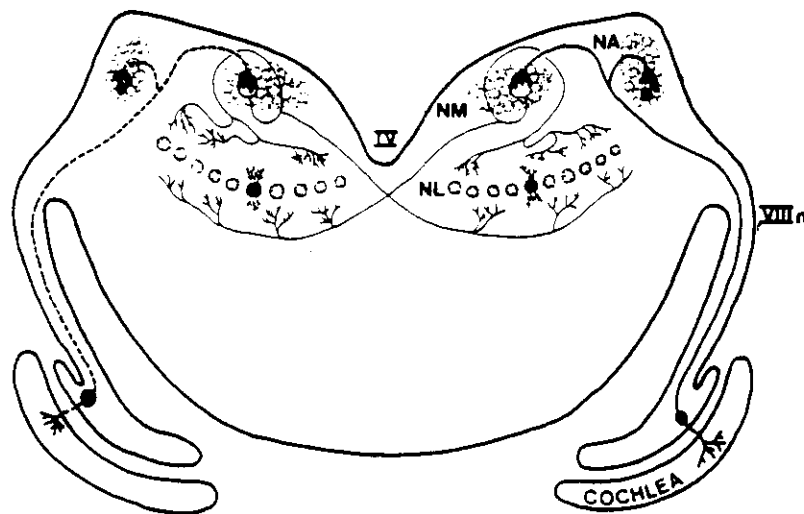
Figure 18–10 Discharge rate of a cell in the medial superior olive of the dog as a function of the interaural delay of a 444.5 Hz stimulus presented to both ears at 70 dB SPL. Points at the left indicate response to monaural contralateral stimulation (C), monaural ipsilateral stimulation (I), and no stimulation (SPON). Note that the unit's discharge rate is a periodic function of the interaural delay, with the maximum rate occurring when the stimulus to the ipsilateral ear is delayed approximately 600 μs or that to the contralateral ear is delayed about 1.5 ms. (After Goldberg, J. M.; Brown, P. B. J. Neurophysiol. 32:613–636, 1969.)

have a large medial superior olive, whereas those that hear predominantly high frequencies have a small one.

The avian nucleus laminaris, which is believed to be the homologue of the mammalian medial superior olive, has a unique anatomical organization that apparently causes interaural time differ-

ences to be represented topographically. As shown in Figure 18–11, the nucleus laminaris is a sheet of neurons, each of which has a distinct bipolar dendritic configuration; one dendritic tree extends dorsally and one ventrally. The dorsal dendrites receive input from the ipsilateral ear, and the ventral dendrites receive input from the contralateral ear. As seen in Figure 18–11, the ipsilateral input reaches the dorsal dendrites across the sheet of cells at the same time (all ipsilateral axons from the nucleus magnocellularis [NM] have the same length). In contrast, an axon from the contralateral NM innervates the ventral dendrites sequentially via short axon collaterals, such that the most lateral cell in the nucleus laminaris will be excited approximately 30 μs after the most medial cell. This anatomical arrangement of afferents could provide the substrate for differential stimulation of nucleus laminaris cells as a function of the position of a sound source in the contralateral hemifield. When a sound emanates from the midline, medial cells in the nucleus laminaris receive coincident dorsal and ventral activation. When a sound is moved to the 90-degree azimuth, the delay in the sound waves reaching the ear farthest from the sound source will be matched by the delay of action potentials from the ear closest to the sound source. Under these circumstances, coincident activation will occur only on the lateral neurons of the nucleus laminaris contralateral to the sound source. Thus, each sound location will produce a coincident arrival of action potentials to the dorsal and ventral processes at only one location in the contralateral nucleus laminaris.

Figure 18–11 Schematic diagram of primary auditory pathways in the avian brain stem. Auditory nerve fibers (VIIIn) terminate in the nucleus angularis (NA) and nucleus magnocellularis (NM). Axons from NM, the avian homologue of the mammalian anteroventral cochlear nucleus, terminate bilaterally in the nucleus laminaris (NL). Note that the terminal arborizations of these axons on the two sides of the brain differ. The ipsilateral axon is the same length across the mediolateral extent of NL while the contralateral axon forms a serial delay-line from medial to lateral.

Lateral Superior Olive and Medial Nucleus of the Trapezoid Body

We will consider these two nuclei together because they appear to constitute one functional system in the mammalian brain.

The medial nucleus of the trapezoid body serves primarily as a high-fidelity relay nucleus between the contralateral anteroventral cochlear nucleus and the lateral superior olive. The response properties of its neurons seem virtually identical to those of anteroventral cochlear nucleus neurons; that is, they have V-shaped frequency tuning curves and primary-like or chopper type PSTHs (recall Fig. 18–7). This dominance of the cochlear nucleus input on responses in the medial nucleus of the trapezoid body is probably due to the fact that axons from the anteroventral cochlear nucleus are of extremely large diameter (i.e., rapidly conducting) and terminate in huge calyces that envelope the postsynaptic neuron (see Fig. 18–9A).

The postsynaptic neurons in the medial nucleus of the trapezoid body, in turn, send their axons to the ipsilateral lateral superior olive, where they make inhibitory synapses using glycine as the neurotransmitter.[4] In addition to this inhibitory input from the contralateral ear, most cells of the lateral superior olive also receive an excitatory input from the same frequency region of the ipsilateral anteroventral cochlear nucleus. Therefore, lateral superior olive neurons are of the IE type. Neurons in the lateral superior olive are extremely sensitive to the intensity differences of sounds presented to the two ears. Figure 18–12A shows that the response of an IE cell increases dramatically as ipsilateral sound intensity is increased (0 curve). When tones of the same frequency are delivered at increasing intensity to the contralateral ear, the rate-intensity curves become less steep and reach lower maximum values, reflecting the increased contralateral inhibition. By varying the frequency of the tone applied to the contralateral ear while the ipsilateral ear is being stimulated at its best frequency, investigators have shown that the best frequency of the inhibitory input is identical to that of the excitatory.[5,38] Since the discharge rates of lateral olivary neurons are exquisitely sensitive to small differences in sound intensity between the two ears but rather insensitive to absolute intensities of sound delivered to the two ears (Fig. 18–12B), the discharge rates of lateral superior olivary neurons seem to encode the location of a sound source rather than its absolute intensity.

The superior olivary complex seems to be the level of the auditory system at which information
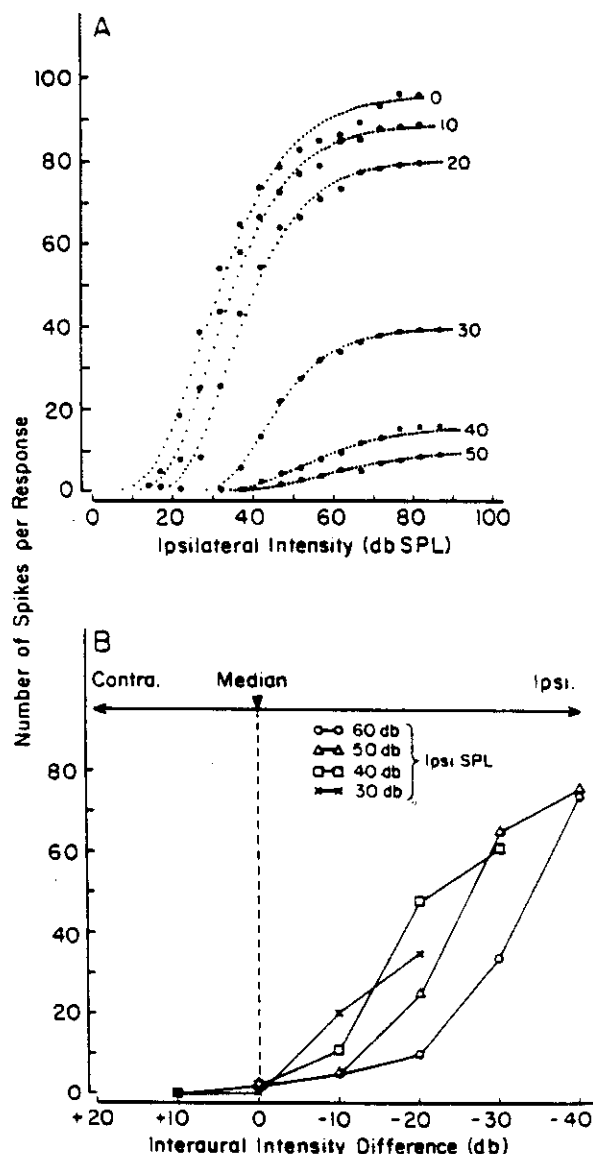

Figure 18–12 Family of binaural intensity functions for an IE cell in the lateral superior olivary nucleus of the cat showing sensitivity to interaural intensity differences. A. Each function was generated by presenting a contralateral tone at the characteristic frequency of the neuron (31.0 kHz) at the fixed intensity indicated and then varying the intensity of the simultaneously presented ipsilateral tone of the same frequency. Function marked 0 is for monaural ipsilateral stimulation. For any given level of stimulus to the ipsilateral (excitatory) ear (on abscissa), the response declines with increases in the level of the stimulus to the contralateral (inhibitory) ear. B. Data in A have been replotted to show variation in response as a function of interaural intensity difference (contralateral intensity relative to ipsilateral intensity) at different levels of the ipsilateral stimulus. The horizontal line at the top of the figure indicates the broad azimuthal ranges corresponding to the interaural intensity differences. (Data from Boudreau, J. C., Tsuchitani, C. In Neff, W. D., ed. *Contributions to Sensory Physiology.* Vol. 4, pp. 143–213. New York. Academic Press. 1970.)

is distributed to the contralateral side of the brain. In this respect, the superior olivary complex functions somewhat like the optic chiasm. Lesions of the superior olive entirely eliminate the ability to localize sounds, while lesions above this level (lateral lemniscus, inferior colliculus, medial geniculate or auditory cortex) disrupt sound localization only in the opposite hemifield.[18]

NUCLEI OF THE LATERAL LEMNISCUS

The dorsal and ventral nuclei of the lateral lemniscus are embedded in the ascending and descending axons of the lateral lemniscus. These nuclei, which are not well studied,[14] belong to two different ascending pathways. The major sources of afferent input to the dorsal nucleus are the nuclei belonging to the ventral binaural system, including the ipsilateral medial superior olive, both lateral superior olives, and the contralateral anteroventral cochlear nucleus. The response properties of dorsal nucleus cells reflect all of these inputs. In addition, they respond best to binaural stimuli. Ventral nucleus cells, on the other hand, receive their major afferent input from the contralateral ventral cochlear nucleus and respond accordingly. The dorsal and ventral nuclei project to many common nuclei, including the medial geniculate, the midbrain reticular formation, and the superior colliculus. One difference is that the dorsal nucleus projects to both inferior colliculi, whereas the ventral nucleus does not project to the contralateral inferior colliculus.

INFERIOR COLLICULUS

The inferior colliculus serves as the major integration and transmission relay for information ascending in the central auditory pathways. Because it is more accessible than other brain-stem auditory nuclei, it has received the most experimental attention. This attention, however, has revealed it to be an immensely complicated area, which has been divided into 10 or more subdivisions on the basis of morphological criteria.[26] Here, we distinguish just the three traditional subdivisions and consider only the physiological properties of cells in the largest subdivision, the *central nucleus*. These cells have sharp tuning curves, display increasing responses over a range of 20–40 dB above threshold, and show relatively poor phase locking. However, there is considerable variability. For example, some cells exhibit very broad tuning curves while others have unusually sharp tuning curves.

Most cells in the central nucleus of a variety of species are excited by contralateral stimuli. In the best studied animal, the cat, about 25% of the cells respond exclusively to stimuli delivered to the contralateral ear, and the other 75% are binaural. Of the latter, the majority with best frequencies above 3 kHz are excited by the contralateral ear and inhibited by the ipsilateral ear (EI); the majority with low best frequencies are excited by both ears (EE).[14] The relative proportions of the two cell types vary widely between species, according to the frequency range of their hearing. Thus, most rodents have a higher proportion of EI units, whereas the kangaroo rat, which has excellent low-frequency hearing, has a higher proportion of EE units.

Two kinds of evidence indicate that EE cells code the absolute temporal delay of stimuli reaching the two ears rather than the phase relationship between stimuli. First, the characteristic delay is independent of frequency.[28] Second, a characteristic delay can be demonstrated by adjusting the delay between noise bursts presented to the two ears; in this situation the characteristic delay reflects the delay between noise bursts rather than the relative phase shift, which varies as a function of frequency.[14] EE neurons respond best when stimulation of the ipsilateral ear lags that of the contralateral ear, which is the situation that occurs when a sound is in the contralateral hemifield. These neurons respond not only to the initial time disparity produced by the onset of sound but also to ongoing time disparities produced by a continuous sound located on one side of the head.

EI cells in the inferior colliculus behave like IE cells in the lateral superior olive (LSO). That is, almost all EI cells in the inferior colliculus are completely suppressed if the ipsilateral stimulus is of equal or greater intensity than the contralateral stimulus. Therefore, like the EE cells discussed above, EI cells respond when a sound source is in the contralateral hemifield, where it is louder to the contralateral ear.

To localize the rustling sound of its prey (e.g., mice) while it is perched or in midflight, the barn owl uses both interaural time and intensity differences.[20] The inferior colliculus of the barn owl contains neurons that respond selectively to stimuli emanating from specific spatial locations in the contralateral hemifield and are relatively unresponsive to signals from any other location (Fig. 18–13). These space-specific neurons respond only when both the interaural time and interaural in-
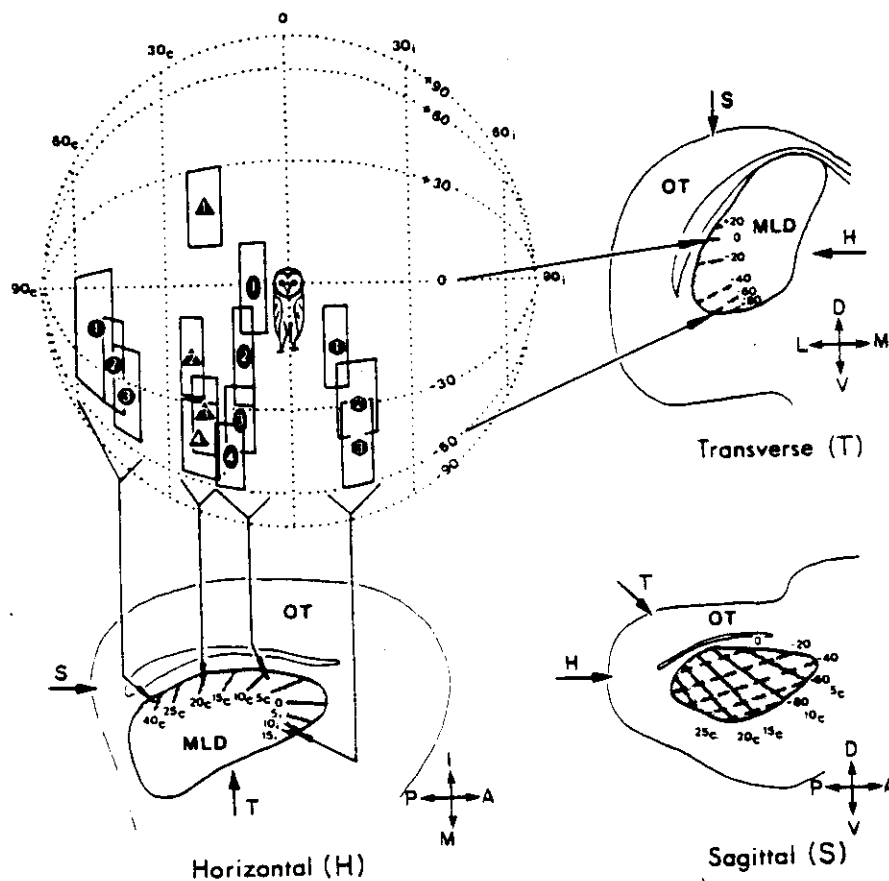
Figure 18–13 A neural map of auditory space in the inferior colliculus of the barn owl. The coordinates of auditory space are depicted as a globe surrounding the owl. Projected onto the globe are the best spatial locations for auditory stimuli (solid-line rectangles) for 14 units recorded in four separate penetrations. Neurons identified by the same symbol (diamond, hexagon, etc.) were recorded on the same penetration in an order indicated by the numbers. Locations of the four penetrations are indicated in the horizontal section by solid arrows. The transverse, horizontal, and sagittal sections through MLD (the avian inferior colliculus) illustrate the spatial map (stippled portion) topography. Isoazimuth contours, based on field centers, are shown as solid lines; isoelevation contours are represented by dashed lines. On each section, arrows identified as S, H, or T indicate planes of the other two sections. Solid, crossed arrows to the lower right of each section indicate directions: A = anterior; D = dorsal; L = lateral; M = medial; P = posterior; V = ventral; OT = optic tectum. (From Knudsen, E. I.; Konishi, M. *Science* 200:795–797. Copyright 1978 by the AAAS.)

tensity differences are appropriate for the particular location. Space-specific neurons are distributed so that the inferior colliculus has a topographical representation of all positions in the owl's auditory space. Successive cells encountered on an electrode penetration prefer progressively adjacent positions in auditory space (see Fig. 18–13). As a stimulus is moved from the midline plane to the 90-degree azimuth, neurons at progressively more posterior positions in the inferior colliculus are activated, and as the stimulus is elevated, progressively more dorsal neurons are excited.

The inferior colliculus is the main source of sensory input to the auditory forebrain, which is thought to be responsible for the conscious perception of sounds. The auditory forebrain is composed of thalamic regions receiving auditory input and the cortical areas with which they are reciprocally connected. This organization has been investigated most thoroughly in the cat.

In addition to serving as the major hub for ascending and descending auditory information, the inferior col-

liculus also delivers auditory information to structures outside of the main auditory pathways. Such structures include the deep layers of the superior colliculus, which also receive directional information from the visual system (see Chap. 20), and the pontine nuclei, which transmit auditory information to the cerebellum.

MEDIAL GENICULATE BODY

The medial geniculate body is the major thalamic relay for ascending auditory information (recall Fig. 18–2). It is usually subdivided into three main divisions (ventral, medial, and dorsal), each of which has a different cytoarchitecture and different auditory and nonauditory inputs.[*]

The *ventral division*, which is the most thoroughly studied division, has neuronal discharge characteristics that are similar to those of the auditory nuclei that have already been discussed. Most neurons have sharp tuning curves, firing rates that increase monotonically with increasing stimulus intensity, and binaural inputs (either EE or EI). Most respond primarily to the onset of a

pure tone, which suggests that they are more sensitive to dynamic than static acoustic information. Therefore, the ventral division faithfully transmits the frequency, intensity, and binaural characteristics of the acoustic stimulation.

A strict tonotopic organization is also preserved in the ventral division, which seems to result from the laminar organization of its cells and its dendrites, as shown in Figure 18-14. Morest[*] suggested that each lamina represented an isofrequency band whose elements exhibit little overlap with neighboring bands. Single neuron recording studies have confirmed this suggestion. The major ascending input to the ventral nucleus is from the central nucleus of the ipsilateral superior colliculus.

The *dorsal division* is a heterogeneous group of as many as 10 subnuclei with vague boundaries. The response patterns of its neurons are equally

Figure 18-14 A transverse section of the ventral division of the cat medial geniculate. The section was stained by the Golgi method to show cell bodies and dendrites. Note the laminar appearance with the dendrites oriented parallel to the lamina. The lamina form isofrequency sheets, and the tonotopic organization is perpendicular to the lamina. (From Morest, D. K. J. Anat. 98:611–630, 1964, with permission of Cambridge University Press.)

diverse. Although many can be driven by acoustic stimuli, their responses tend to be more irregular, their latencies more variable, and their tuning curves broader than those of neurons in the ventral division.[*] A consequence of the broad tuning is that the tonotopic organization is imprecise. Nevertheless, a complete frequency representation is repeated several times within this division. The activity of many cells are inhibited only by auditory stimulation. Also, the activity of some cells is influenced by other sensory modalities, particularly somesthetic. Their variable auditory responses and responses to other sensory modalities reflect the fact that inputs to these cells originate from the area surrounding the central nucleus of the inferior colliculus and from nonauditory areas of the midbrain tegmentum and cortex.

The auditory responses of neurons in the *medial division* are also diverse. Response latencies range from 7 to 70 ms, both broad and sharp tuning can be found, and all combinations of binaural interactions are observed. Many neurons have two distinguishing characteristics: (1) they are maximally excited by sounds of a particular intensity and suppressed by more intense sounds, and (2) they continue to respond for the duration of an auditory stimulus rather than only to its onset.[*] These characteristics suggest that neurons of the medial division signal the relative intensity and duration of an auditory stimulus rather than its spectral and temporal content. Finally, many medial division neurons are polysensory.

The medial division receives its auditory input from regions surrounding the superior olivary nucleus or the lateral lemniscal nuclei. It also receives a variety of other sensory and nonsensory inputs (for example, from the spinothalamic tract, vestibular nuclei, superior colliculus, and thalamic reticular nuclei).[*]

AUDITORY CORTEX

Woolsey[*] and his colleagues first mapped the auditory areas in the cat cerebral cortex by describing the cortical areas where electrical stimulation of the auditory nerve produced evoked potentials (a similar strategy is described for the visual system; see Chap. 20). Figure 18-15A shows Woolsey's summary, indicating five tonotopically organized cortical regions (AI, AII, SF, EP, and Ins) with other auditory responsive" areas surrounding them. The tonotopic organization of each subdivision is indicated grossly by B, for the representation of the basal (high-frequency) cochlea, and A, for the apical (low-frequency) region. In-

termediate frequencies are also represented. More recent studies based on single unit data and anatomical connections (Fig. 18–15 B, C) suggest four tonotopically organized cortical auditory areas (A, AI, P, and VP), again surrounded by a belt of "auditory responsive cortex."

The auditory cortex in primates, although not as well studied, has essentially similar features.[4]

The primary auditory cortex is buried in the depths of the Sylvian fissure on the superior aspect of the temporal gyrus. It has a tonotopic organization with low frequencies represented rostrally, and high frequencies caudally. The auditory cortex of humans can be distinguished by its densely packed, small cells in layer IV. Both clinical observations and modern imaging techniques indicate that high frequencies are represented deep in the Sylvian fissure, whereas lower frequencies are located more toward the top of the temporal gyrus.[4, 32]

When microelectrodes are driven through the cat auditory cortex perpendicular to its surface, each neuron encountered has a similar best frequency. Thus, like other sensory cortices (see Chaps. 15 and 20), there is a columnar organization of certain stimulus attributes, in this case frequency. If the microelectrode is driven perpendicular to the frequency columns and parallel to the cortical surface, the best frequencies either increase or decrease progressively until the boundary between one cortical area and another is reached. At the boundary, the orderly progression stops and may reverse. If the electrode moves along a frequency column but parallel to the cortical surface, similar best frequencies are again recorded, indicating that a band of cortex oriented perpendicular to the tonotopic progression receives input from the same place on the cochlea; i.e., it is an isofrequency band.

Connections of Auditory Cortex

The organization of the auditory areas of the cat cortex has been extensively studied by a combination of microelectrode recording and anatomical techniques.[12, 13, 22, 23, 46] Although cortical organization may be somewhat different in primates, the
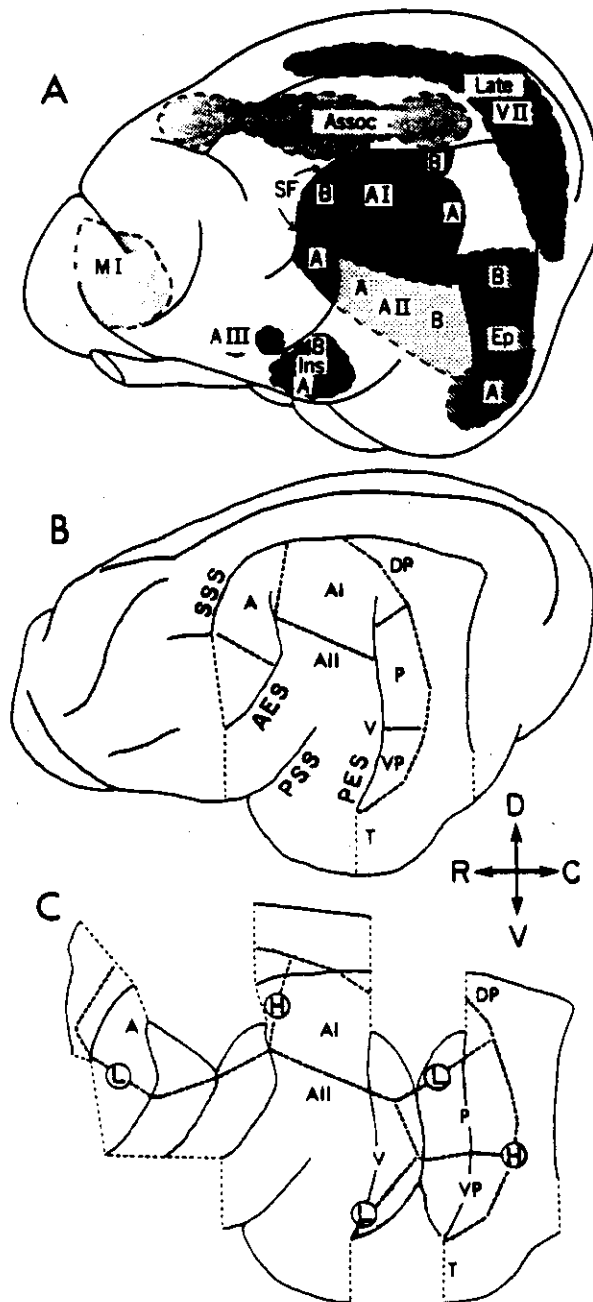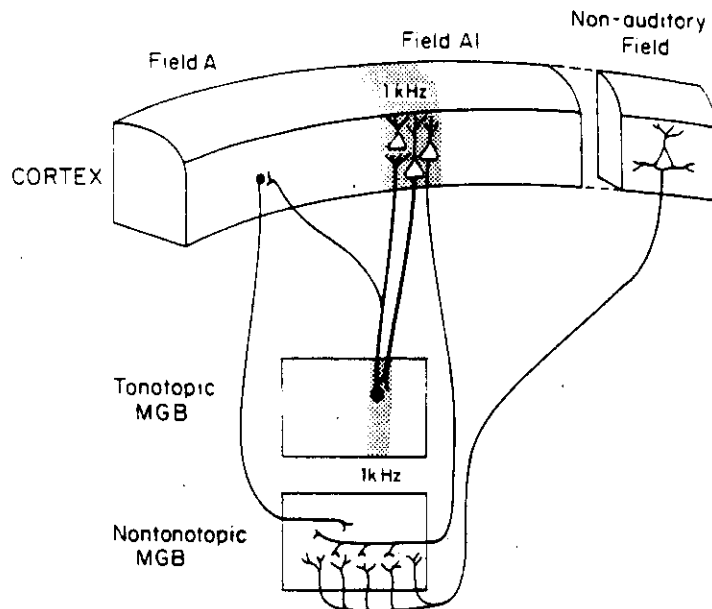

Figure 18–15 Auditory cortical fields in the left hemisphere of the cat. A. Summary diagram showing five tonotopically organized cortical regions: SF, AI, AII, EP, and Ins. The tonotopic organization of each area is indicated by A, representing apex (low frequency) of the cochlea, and B, representing base (high frequency) of the cochlea. Other regions that respond to sound but are not tonotopically organized are also shown. B and C show more recent parcellation of tonotopic cortical regions based on microelectrode recording and anatomical connections. Four tonotopic regions are defined: A, AI, VP, and P. In C the sulcus and the tonotopic organization of each area are shown, from high (H) to low (L) frequency. (From Imig, T. J.; Reale, R. A.; Brugge, J. F.; Morel, A.; Adrian, H. O. In Lepore, F.; Ptito, M.; and Jasper, H. H., eds. In Two Hemispheres—One Brain: Functions of the Corpus Callosum, pp. 103–115. New York, A. R. Liss, 1986.)

Figure 18–16 Schematic diagram showing patterns of connections between cortical auditory fields and both tonotopically and nontonotopically organized areas of the medial geniculate nucleus (MGB). Note the heavy reciprocal point-to-point connections between A1 and the same frequency region of the tonotopic MGB, the sparser projection from the tonotopic MGB to field A, and the diffuse projections of A, A1, and the nonauditory field to the nontonotopic MGB.

main principles are similar. In the cat, each of the four tonotopic cortical areas receives a major input from a subregion of the tonotopically organized ventral division of the medial geniculate body. This input presumably confers the tonotopic organization on the cortical areas. Each cortical area, in turn, sends a point-to-point projection back to the same thalamic region from which it received its frequency-specific innervation. These connections, therefore, form a frequency-specific geniculocorticogeniculate loop. In addition to its major cortical projection, each tonotopic region of the thalamus sends a minor projection to one or more of the other cortical auditory areas. Each cortical area also is reciprocally connected with one or more nontonotopic areas in the medial or dorsal division of the medial geniculate body. Figure 18–16 illustrates these complex feed-forward and feedback connections. For example, a 1-kHz region of the cortical field A1 makes a point-to-point reciprocal connection with a 1-kHz area in the ventral division of the medial geniculate body, which also has a minor projection to field A. The nontonotopic areas of the thalamus also project to the A1 cortical fields, but this projection is more diffuse, as is the reciprocal corticothalamic projection. Each cortical region also connects reciprocally with its homotopic area in the opposite hemisphere, with one or two other areas of the opposite hemisphere, and with all the other tonotopic areas in the same hemisphere. Like the thalamic connections, one or two of these connections are very strong and precisely tonotopic while others are more sparse and diffuse.

Recently, the functional organization of auditory cortex has been further elucidated by the discovery of "binaural bands" that extend parallel to the tonotopic gradient (perpendicular to each isofrequency band). If an electrode penetration is run perpendicular to an isofrequency band, the response of each neuron to contralateral ear stimulation may be enhanced by stimulation of the ipsilateral ear. If an electrode penetration is run adjacent to the first track, the responses of these cells to contralateral ear stimulation are suppressed by ipsilateral ear stimuli (Fig. 18–17). These *summation* and *suppression bands* are reminiscent of the ocular dominance columns in the visual cortex (Chap. 20). Concomitant anatomical studies show that cells in bands that receive dense projections from the opposite cortex display summation and that cells in interposed bands, which receive projections from the same hemisphere, show binaural suppression (see Fig. 18–17).

In summary, the anatomical and physiological organization of the cat auditory cortex suggests that multiple pathways emerge from separate areas of the thalamus to reciprocally innervate separate regions of their auditory cortex, and that each pathway processes different types of information. However, although each pathway has its own unique, dominant connections, each also communicates with the others.

Organization of Bat Auditory Cortex

The idea of separate cortical areas, each processing different functionally related signals, has
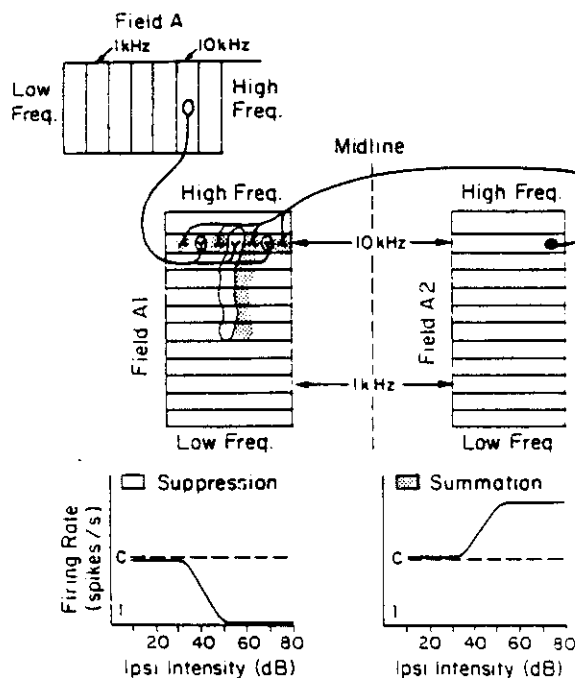
Figure 18–17 Schematic representation of cortico-cortical connections thought to be responsible for binaural summation (shaded) and binaural suppression (unshaded) bands in cerebral cortex. The 10-kHz band of field A1 on the left side receives alternating projections from the 10-kHz region of field A1 on the right side and the 10-kHz region of the ipsilateral field A. This pattern is repeated for each frequency (not shown here). The two lowest graphs show the responses of neurons in the shaded (right) and unshaded (left) regions. In each graph the response to contralateral stimulation alone is indicated by C; ipsilateral stimulation alone elicits no excitatory response. When the contralateral stimulus is paired with an ipsilateral stimulus, the response depends on the intensity of the ipsilateral stimulus. Increasing ipsilateral stimulus intensity causes a decreased response for "suppression" neurons in the unshaded regions and an increased response for "summation" neurons in the shaded regions.

been best revealed by making use of the unique prev-locating system of the mustache bat.³⁸ ³⁹ During flight, the mustache bat emits a series of highly directional, ultrahigh-frequency, echo locating pulses. Each pulse is composed of harmonically related constant frequency portions followed by a short, frequency-modulated (FM) component. The second harmonic at 61 to 63 kHz is the most intense part of the vocalization. Obstacles or prey (flying insects) in the path of the bat cause a reflection (echo) of the biosonar pulse. This echo has several interesting properties, which the bat is able to detect. For example, the delay between the pulse and the echo is proportional to the distance of the object. The echo also contains

slightly different frequency components than the vocalizations because of a Doppler shift caused by the bat and target (e.g., insect) moving at different velocities. If the bat is closing in on his target, the echos will contain slightly higher frequencies than the pulse; if he is flying away from the target, the echos will be at slightly lower frequencies.

The mustache bat's auditory system has several specializations that allow it to optimize its tracking performance. Although its total frequency range is from around 7 to 120 kHz, about 30% of its primary auditory cortex is tuned to the narrow band of sounds between 61 and 63 kHz, the range that is crucial for the detection of the most intense part of its vocalizations. Second, another cortical area contains neurons whose responses depend on the precise frequency difference of the pulse and the echo (i.e., on the Doppler shift). Neurons sensitive to different Doppler shifts are topographically organized so as to represent systematic changes in the relative velocities of the bat and its target. Finally, neurons in a third area are differentially sensitive to the delay between the FM portions of the pulse and echo. These neurons respond poorly to the FM portions of either signal alone, but when the FM portion of the pulse is paired with the FM part of the echo at a particular delay, a vigorous response occurs. Thus, this area seems to contain neurons that respond to targets at specific distances.

Based on their work in the bat, Suga and his colleagues³⁹ ⁴⁰ have proposed four rules for cortical processing: (1) cortical neurons are specialized for processing different parameters of a complex acoustic stimulus; (2) neurons specialized for processing different parameters are clustered in separate areas; (3) within the clusters, different neurons respond best to different values of the parameter and are arranged topographically according to systematic variations in the parameter; and (4) the components of an auditory signal that are most important to the organism have an expanded cortical representation. It is not yet known whether these rules provide general principles for auditory cortical organization in other mammals.

Lesion Studies of Auditory Cortex

Over the past 50 years, many investigators have attempted to determine the role of auditory cortex by removing it and examining the resulting deficits in behavior. This approach has allowed us to draw important conclusions about the functional importance of different regions. However, it must be

remembered that all ablation studies are plagued by certain shortcomings. First, studies that destroy part of the brain test the capabilities of an animal *without* that brain area rather than the function of that area per se. Second, the deficit could be due to an absence of appropriate sensory integration but might equally well be due to deficits in sensory-motor integration, motivational factors, or purely motor capabilities. Whereas the latter deficit is relatively easy to demonstrate, the others are more difficult to dissociate from purely sensory dysfunction. Third, lesions of a given brain area produce effects beyond the tissue that was damaged. Other areas of the brain receiving direct, secondary, or tertiary connections from the lesioned area also will be affected. For example, regions supplying afferents to the damaged area will undergo some degree of *retrograde degeneration*, and the targets of the lesioned area may undergo *anterograde transneuronal atrophy* or cell loss. In addition, sprouting of terminals from other afferents to the damaged area may occur. Finally, it is difficult to remove specific auditory cortical regions without damaging neighboring ones. In view of these caveats, behavioral deficits produced by lesions serve only to implicate a region in the regulation of the affected behavior. Nevertheless, it is of interest to examine those behaviors that are disrupted by lesions of auditory cortex.

In general, after removal of the entire auditory cortex, animals can still learn simple frequency and intensity discriminations but are unable to identify the position of a particular stimulus within a more complex pattern (e.g., distinguish a tone burst pattern of high-low-high frequencies from one containing low-high-low frequencies). Cortical lesions also disrupt tasks that require temporal discriminations such as determining the number of tone bursts in a series or distinguishing acoustic stimuli of barely different durations.[2] Finally, cortical lesions affect behaviors based on stimuli delivered to the contralateral ear more than those to the ipsilateral ear. Although humans who have suffered unilateral cortical damage exhibit some improvement with time after the lesion, a moderate hearing loss in the opposite ear remains. In monkeys, bilateral lesions of the auditory cortex also produce a persistent 30- to 40-dB hearing loss of the middle frequencies.[1]

The anatomical and physiological data presented above suggest that the primary auditory cortex is involved in the localization of sound in the opposite hemifield. This suspicion has recently been confirmed by experiments in which cats were trained to localize the precise position of sound

emanating from one of seven speakers positioned within ± 90 degrees of the midline plane.[16, 17] Unilateral lesions of the entire auditory cortex permanently disrupted the cat's ability to choose the correct speaker in the contralateral hemifield, although localization in the ipsilateral hemifield was unaffected. Furthermore, cats with removals of A1 cortex along isofrequency strips (for example, between 6 and 12 kHz) could not localize stimuli at those frequencies in the contralateral hemifield, whereas sound localization was normal at other frequencies. These experiments reveal that the ability to accurately localize sound requires an intact primary auditory cortex on the opposite side of the brain, and that this involvement is frequency specific. Sound location seems to be independently represented within each frequency representation of primary auditory cortex.

Other areas of the auditory cortex and surrounding auditory association areas have received relatively little attention. Physiological investigations reveal a variety of responses to acoustic as well as to other sensory stimuli, but these responses often are dramatically influenced by anesthesia and other "state" variables. Behavioral studies have also failed to yield a coherent picture of functional roles for these regions.

MOTOR CONSEQUENCES OF AUDITORY STIMULI: AUDITORY REFLEXES

Acoustic Middle Ear Reflex

As discussed in Chapter 17, contraction of the two muscles in the middle ear, the stapedius and the tensor tympani, limits movement of the tympanic membrane and the stapes, thereby damping the transmission of sound by the inner ear. This *middle ear reflex* protects the inner ear from intense sounds and attenuates loud sounds to improve discrimination. In addition, contraction of the middle ear muscles occurs prior to vocalizations in humans, probably to attenuate the low-frequency components of our own vocalizations so that our own speech is more intelligible. Contraction of the middle ear muscles is always bilateral and can be evoked by acoustic stimulation of either ear. Thus, in its bilateral action, the acoustic middle ear reflex resembles the pupillary light reflex (see Chap. 19). Finally, this reflex is useful clinically to separate peripheral from central dysfunction.

The neuronal pathways involved in the middle ear reflex involve a three- or four-neuron circuit from the cochlea to the motor neurons in the facial

and trigeminal nuclei, which innervate the stape-
dius and tensor tympani muscles, respectively.
The principal components of this pathway are (1)
primary auditory nerve fibers, (2) neurons in the
ventral cochlear nucleus, (3) neurons in or around
both superior olivary nuclei, and (4) the motor
nuclei of the facial (VII) and trigeminal (V) nerves.
In addition to these direct pathways, there are
longer latency pathways involving brain-stem au-
ditory nuclei and the reticular formation and/or
the red nucleus, which, in turn, project to the
motor nuclei of V and VII. The relative roles of
the direct and indirect pathways are unknown.

Acoustic Startle Reflex

Another important auditory reflex is the acoustic
startle response, which usually causes us to react
to a loud sound. Activation of the startle reflex
produces a short latency motor response that trav-
els down the spinal cord, beginning with muscle
contraction in the neck and shoulders and culmi-
nating with contraction of muscles in the distal
segments of the forelimbs and legs. In rats, the
reflex time from the onset of the acoustic stimulus
to electromyographic responses in the hindlimbs
is only 7 to 8 ms. The descending input, which
elicits the motor response, involves projections
from the primary auditory neurons to the ventral
cochlear nucleus and then to the contralateral
lateral lemniscal nuclei. Neurons in or near the
lateral lemniscal nuclei project into the caudal
portion of the pontine reticular formation, which
sends axons down the reticulospinal tract to in-
nervate spinal interneurons and occasionally mo-
tor neurons directly. Like the middle ear reflex,
therefore, the startle reflex can involve a direct
pathway of as few as four or five neurons. At each
level, from the cochlear nucleus to the motor
neurons, the direct pathway can be influenced by
inputs from other neural networks. Indeed, the
startle reflex can be modified by a variety of factors
such as learning, state of the animal, or other
"competing" sensory events. The startle reflex also
produces a chain of autonomic responses whose
neural substrate is largely unknown.

DEVELOPMENT AND PLASTICITY OF THE CENTRAL AUDITORY SYSTEM

Several properties of the auditory system make
it well suited for understanding the factors that
regulate both normal neuronal development and
neural plasticity. First, the coding properties of

auditory neurons can be precisely and quantita-
tively described on the basis of sound frequency,
sound intensity, and binaural interactions. Sec-
ond, the cell bodies that represent successive lev-
els of processing (e.g., cochlear nucleus, superior
olive, inferior colliculus) are spatially segregated,
making them individually accessible. Third, there
is an extensive literature on the normal develop-
ment of both peripheral and central structures
with which to compare the results of experimental
manipulations.[11, 35, 45]

The age at which individuals begin responding
to sound varies considerably from species to spe-
cies. Some animals, such as humans, guinea pigs,
and precocial birds, begin responding in utero or
in ovo. For example, the human fetus responds to
loud sounds by the beginning of the third trimes-
ter (25–26 weeks). Other species, such as most
carnivores, rodents, and altricial birds, do not
respond until after birth. Mice and rats, for ex-
ample, first respond about 10 to 12 days after
birth. Electrical stimulation of the auditory nerve
can evoke cortical responses before sound-elicited
responses are obtained. Therefore, the onset of
auditory function is dependent on peripheral mat-
uration, rather than the establishment of CNS
connections.

Very soon after central connections are estab-
lished, peripheral maturation can be documented
by several observations. First, the cochlear micro-
phonic response can be elicited by very loud,
relatively low-frequency stimuli. Within 1 to 2 days
an eighth nerve compound action potential can be
recorded. As the middle and inner ear mature,
response thresholds recorded from the auditory
nerve or cerebral cortex decrease, and responses
can be obtained to a broader range of frequencies.
Tuning curves become progressively sharper over
this same period, indicating that the ontogeny of
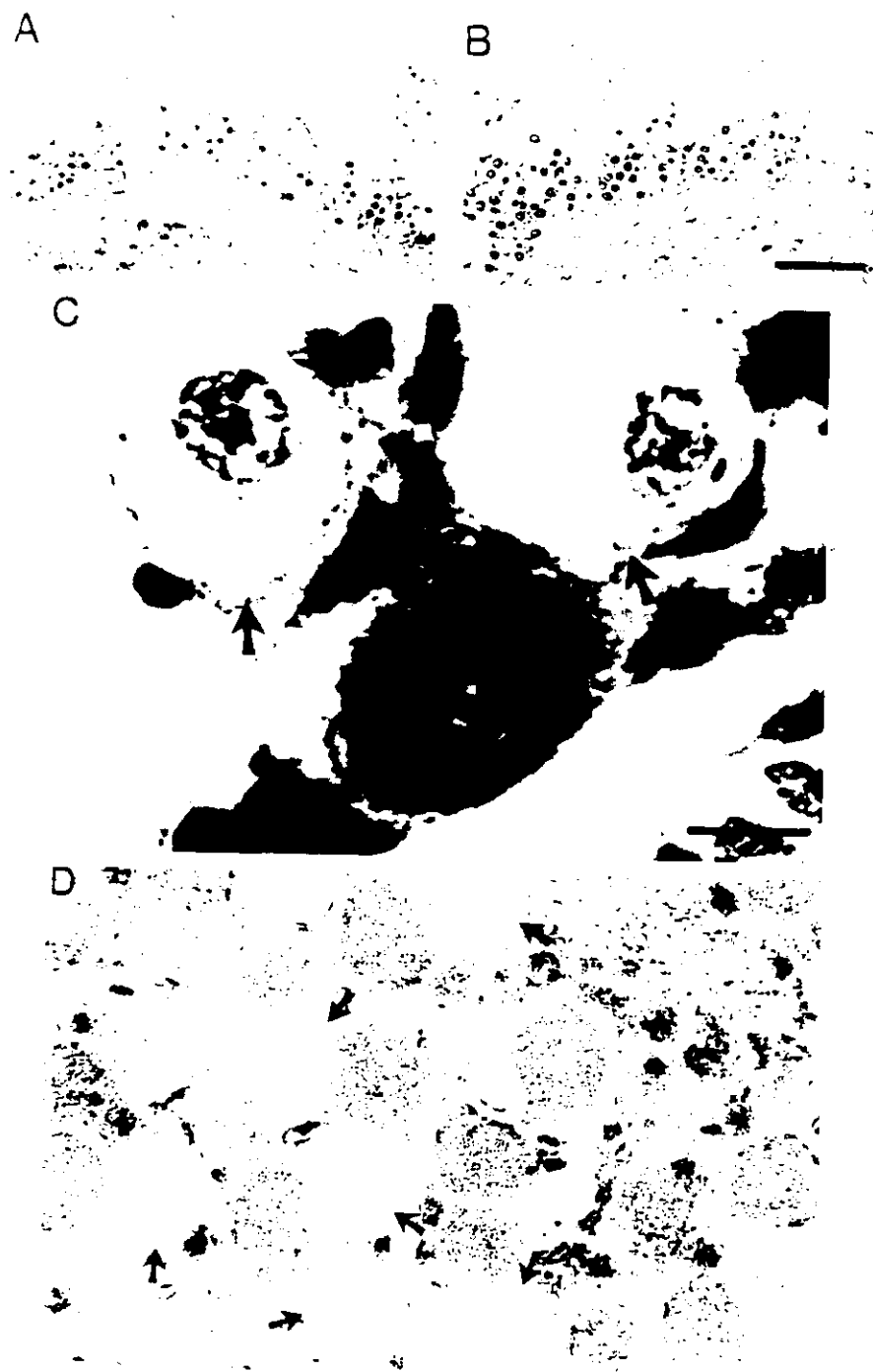frequency selectivity is due primarily to peripheral
maturation.

Subtle changes in physiological properties also
can be attributed to CNS maturation. For example,
response latency decreases with CNS myelination.
Also, as synapses mature, neurons are better able
to follow rapidly repeating stimuli. In addition,
immature tuning curves recorded from CNS neu-
rons are, in part, due to the maturation of CNS
connectivity.[34] In contrast, the topographic repre-
sentation of frequency is established prior to the
age at which auditory responses can first be de-
tected. For example, IE neurons in the neonatal
gerbil lateral superior olive have matching excita-
tory and inhibitory best frequencies.[38]

It is clear that normal input from the inner ear
is required for normal maturation at all levels of

the auditory system. For example, Levi-Montalcini[21] showed that removal of the embryonic anlagen of the inner ear (the otocyst) in the chick results in severe cell loss in the maturing cochlear nuclei. This loss is correlated with the age at which auditory nerve activity first elicits postsynaptic responses in the CNS.[15] Similarly,

removal of the cochlea or silencing the electrical activity of the auditory nerve of neonatal chicks can cause a large number of CNS changes, including cell death, decreased protein synthesis, cell atrophy, alterations of enzyme activity, and dendritic atrophy.[1,17] Figure 18–18 shows examples of the trophic influence of the inner ear on cochlear

A

B

Figure 18–18 Photomicrographs showing rapid changes in the nucleus magnocellularis (NM) of the chick (avian homologue of the mammalian anteroventral cochlear nucleus; see Fig. 18–11) following destruction of the cochlea. A and B are low-magnification views of NM on the ipsilateral side (A) and contralateral side (B) of the brain just two days following the removal of the cochlea; approximately half of the ipsilateral neurons are gone or exhibit very pale staining. Scale bar = 0.2 mm. C. High-power view of the ipsilateral side showing that neurons in the process of transneuronal degeneration (arrows) have lost cytoplasmic staining for Nissl substance, indicating a severe depletion of cytoplasmic RNA. Scale bar = 10 mm. D. In this animal ³H-leucine was injected one half hour prior to death to study protein synthesis by NM neurons following elimination of eighth nerve activity three hours earlier. The cells without black silver grains (arrows) have already ceased protein synthesis and will degenerate. (A–C from Born, D. E.; Rubel, E. W. J. Comp. Neurol. 231:435–445, 1985. D Reprinted with permission from Born, D. E.; Rubel, E. W. J. Neurosci. 8:901–919, 1988 Pergamon Press plc.)

C

D

nucleus cells. The low-power photomicrographs (Fig. 18–18A,B) show considerable neuron loss in the cochlear nucleus (NM in Fig. 18–11) ipsilateral to inner ear removal in neonatal chicks. The cells that are destined to degenerate can be identified by loss of staining within 24 hours (Fig. 18–18C) and by reduced protein synthesis (cells without black grains over cytoplasm in Fig. 18–18D) within 3 to 6 hours after elimination of auditory nerve activity. Similar dramatic effects of peripheral manipulations on CNS auditory pathway development also have been shown in neonatal rats, mice, gerbils, and cats. In some cases, neonatal rearing with a conductive hearing loss of 30 to 40 dB produces atrophy of cells in the brain-stem auditory nuclei, presumably because of the reduction of afferent activity during development.[42]

Peripheral influences on auditory system development are not limited to anatomical atrophy in the brain-stem auditory nuclei. Changing the balance of inputs from the two ears can cause marked physiological alterations. For example, stimulation of the ipsilateral ear, which normally produces inhibition of inferior colliculus neurons, produces excitatory responses if the contralateral ear is removed soon after birth.[28]

These and other examples of peripheral influences on the structure and function of the auditory system are most clearly demonstrable in the immature organism. Similar manipulations on adult animals produce either less dramatic or no effects. There seems to be a restricted period during development, beginning at the time of synapse formation, when the establishment of normal mature central pathways depends critically on the amount or pattern of synaptic activity. An understanding of the biological basis of these critical or sensitive periods which also have been demonstrated for vision (see Chap. 20) will emerge through examining how the genome of the developing neuron is expressed and how expression can be modified by changes in the ionic fluxes that occur in the environment of developing neurons.

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