Overview of the Neuroanatomy of Auditory Periphery and Brainstem

SCOPE

The overview in this chapter is primarily intended to provide a sufficient, if not exhaustive, foundation of the nature of the neuroanatomic organization of the structures and pathways in the auditory periphery and the brainstem. This knowledge is important because neural elements and tracts in these structures contribute to the generation of the cochlear, auditory nerve, and brainstem evoked responses we use clinically to determine the functional integrity of the peripheral and brainstem auditory system. Without this knowledge, our ability to record and interpret these responses will be less than optimal. Since structure and function are closely related, knowledge of the structural organization will help the clinician to understand the functional consequences of a structural abnormality, enabling the development of better clinical management strategies—essentially becoming a better clinician. Consistent with convention, the cochlear and auditory nerve neuroanatomy is treated as peripheral, and the brainstem includes a description starting with cochlear nucleus and including superior olivary complex, nuclei of lateral lemniscus, and inferior colliculus.

I. AUDITORY PERIPHERY: COCHLEAR AND AUDITORY NERVE NEUROANATOMY

Cochlea: Structure and Functional Implications

The mammalian cochlea in the inner can be characterized as a spiral duct with an inner membranous part (membranous labyrinth) and an outer bony part (osseous labyrinth) that is partitioned into three fluid-filled spaces, namely, the perilymph (high sodium ion [Na^+] concentration and low potassium ion [K^+] concentration) filled scala vestibuli and scala tympani, and the endolymph (high K^+ and low Na^+) filled scala media (Figure 1–1). Epithelial cells with tight junctions surrounding the membranous portion help maintain this ionic difference (Smith, 1978). The self-contained membranous scala media houses the organ of Corti that in turn sits on the basilar membrane. The basilar membrane partitions the cochlear duct into scala vestibuli and scala tympani and also forms the floor of the organ of Corti. The Reissner's membrane separates the scala media from the scala vestibuli. The hair cells and their supporting cells rest on the

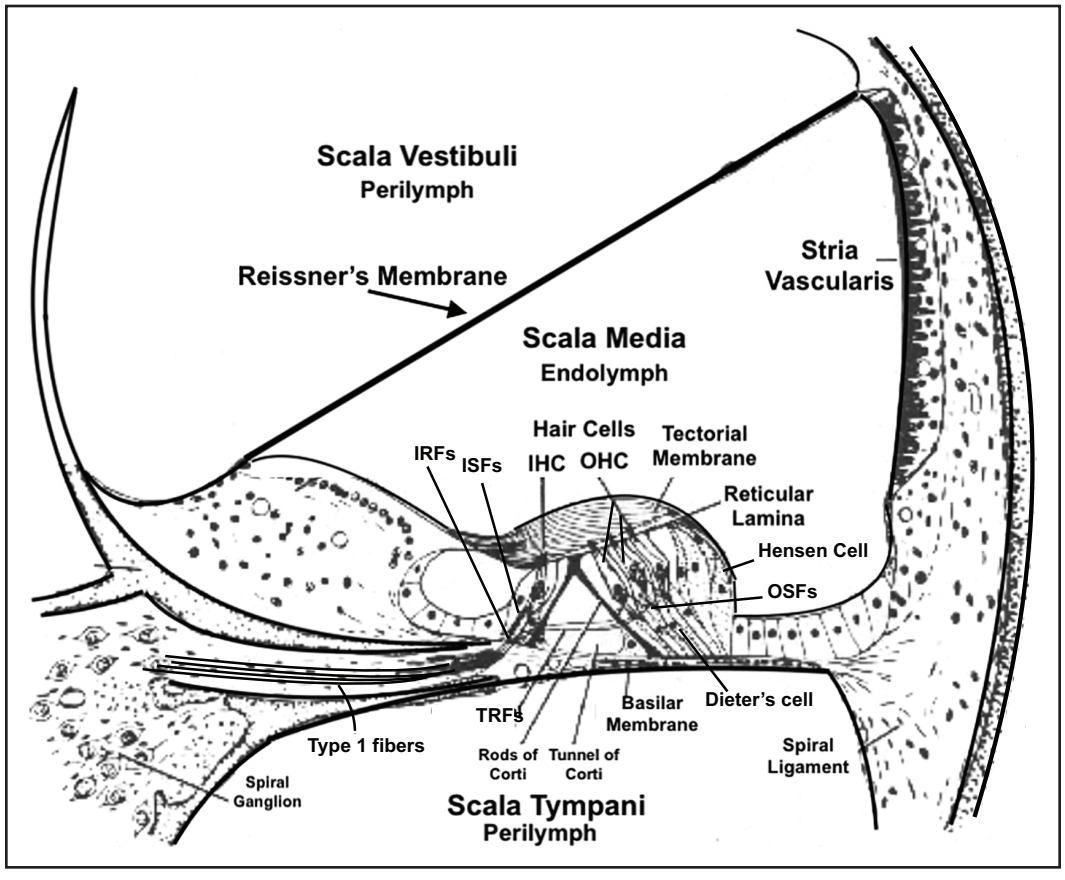

Figure 1–1. Cross-section of cochlea showing the three fluid-filled partitions (scala vestibuli, scala tympani (perilymph), and scala media (endolymph)) and the organ of Corti with outer hair cells (OHCs) and inner hair cells (IHCs), stereocilia, basilar membrane, tectorial membrane, and stria vascularis (the cochlear battery). Also shown are both the afferent fibers of the OHCs (outer spiral fibers [OSFs]) and IHCs (inner radial fibers [IRFs]) and the efferent fibers of the IHCs (inner spiral fibers [ISFs] and the OHCs (tunnel radial fibers [TRFs]). Type I myelinated fibers from the IHCs are shown coursing toward the cells in the spiral ganglion.

basilar membrane, and have an overhanging gelatinous suprastructure called the tectorial membrane (see Figure 1–1). It can be seen in Figure 1–1 that only the stereocilia of the outer hair cells (OHCs) contact the undersurface of the tectorial membrane.

The ***basilar membrane***, attached medially to the osseous spiral lamina and laterally to the spiral ligament, extends from the base to the apex of the cochlea (about 35 mm) where the perilymphatic spaces communicate via the helicotrema. The change in the *stiffness gradient* (resulting from the relatively denser network of radial and longitudinal fibers underneath the basilar membrane in the base, and relatively sparse network of these fibers in the apex [Figure 1–2, bottom right]) and the membrane width, going from narrow at the base (100 μM) to wide (500 μM) at the apex (see Figure 1–2), contribute significantly to the frequency for place transformation. That is, the traveling wave generated by the back-and-forth motion of the stapes in the oval window upon sound stimulation progresses in an apical direction, with its envelope gradually reaching a maximum at a place determined by the frequency of the stimulus and quickly decreasing in amplitude thereafter (Figure 1–3). The location of the peak of the displacement shifts to the left (toward the base of the cochlea) with increasing frequency. It should be noted here that von Bekesy's (1960) experiments were on cadavers using high stimulus levels; therefore, the displace-

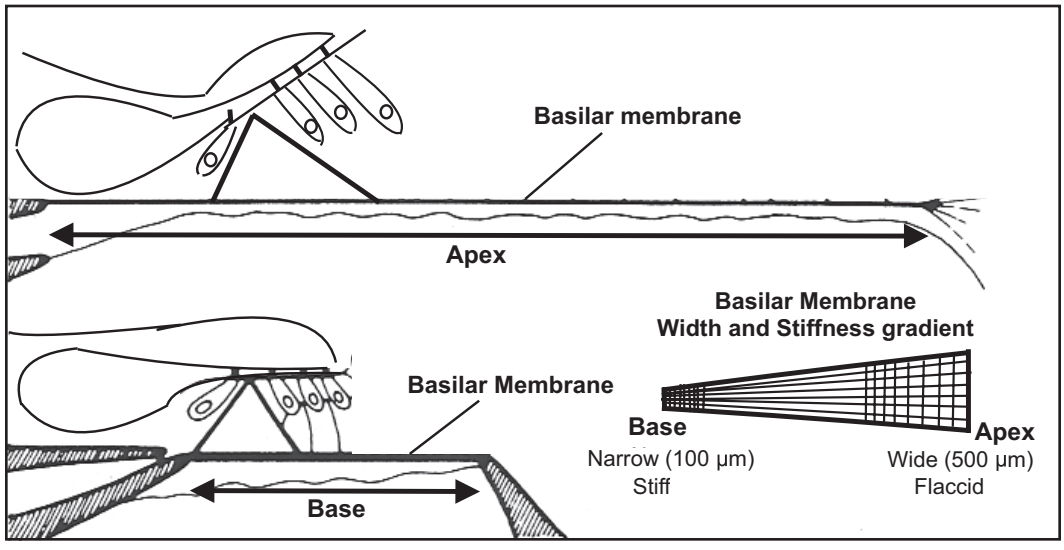

Figure 1–2. The changes in the width and stiffness of the basilar membrane from base to apex. The basilar membrane is wider at the apex and more flaccid, whereas it is narrower at the base and exhibits greater stiffness (see lower right).

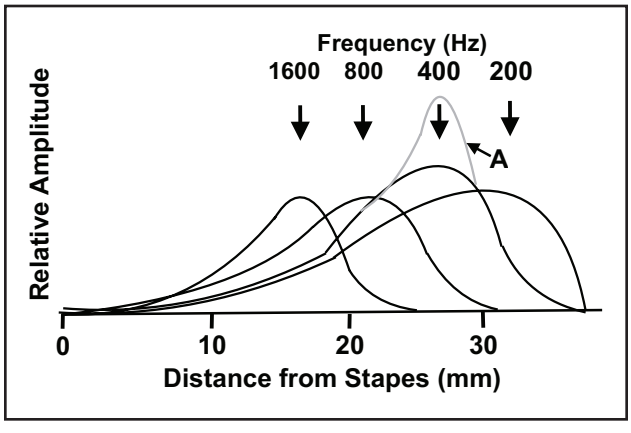

Figure 1–3. A family of Bekesy traveling wave envelopes showing frequency for place transformation. Traveling wave maxima progressively shift from apex to base (that is, to the left) as frequency is increased. Note the amplification in the maximum amplitude for 400 Hz (*arrow pointed by A*) reflecting cochlear amplification using the active process. The frequency corresponding to each traveling wave is identified at the top. Traveling waves approximately reflect data from G. von Bekesy, 1960, *Experiments in Hearing*. New York, NY: McGraw-Hill, Figure 11.49.

ment patterns shown here reflect only the passive physical response minus the cochlear active processes (also referred to as the cochlear amplifier associated with the outer hair cell subsystem) that further improve sensitivity and frequency selectivity substantially. The effects of the active process are illustrated by the larger and sharper peak of the basilar membrane displacement for the 400-Hz traveling wave (arrow A in Figure 1–3). The electromotility (length changes in the OHCs with stimulation) is thought to supply the mechanical feedback process that amplifies low-level sound (Brownell, Bader, Bertrand, & de Ribaupierre, 1985; Dallos, 1992). The cochlear amplification derived from the electromotility of OHCs increases the sensitivity to soft sounds by 40 to 60 dB (Dallos, 1992, 2008). The electromotility, thought to produce the cochlear amplification of OHCs, is presumably driven by prestin, a motor protein expressed in the mammalian OHCs. Cochlear amplification is essential for normal hearing in adult animals. The property of frequency for place transformation becomes particularly relevant when we later discuss considerations of specific stimulus properties to obtain cochlear place-specific responses to estimate audiogram-like hearing thresholds using the auditory brainstem response (ABR).

The ***organ of Corti*** sits on the basilar membrane and consists of two structurally and functionally distinct receptor cells (OHCs and inner hair cells [IHCs]), lateral support cells (Hensen's cells), and vertical alignment cells (Deiters' cells,

phalangeal processes of the Dieters' cells and the reticular lamina) (see Figure 1–1), and the afferent and efferent fibers with distinct innervation patterns for each receptor type. The highly vascular stria vascularis on the outer wall of the scala media serves to power the metabolic processes involved in the +80-mV endolymphatic potential needed to mediate the transduction mechanisms of the hair cell and is also involved in recovering the K^+ expelled during transduction (Wangemann, 2002).

The test tube–shaped **OHCs** (9,000–12,000 in number and arranged in three to five rows along the length of the cochlea) are located on the lateral portion of the outer pillar of Corti, slanted toward the outer pillar (see Figure 1–2). The six to seven rows of stereocilia on the apex of each OHC are arranged in a V or W pattern (Figure 1–4, bottom), with the tallest ones on the most lateral row (toward the outer wall). The length of the OHC stereocilia also increases along the longitudinal axis of the cochlear partition (from about 2 μm in the base to about 8 μm in the apex). In addition, the height of the OHC increases from about 10 μm in the base to about 80 μm in the apex. Both physical changes in the OHCs are thought to contribute to the cochlear frequency for place transformation —the taller hair cells with their longer stereocilia in the apical regions are more selective to low frequencies. The stereocilia are cross-linked, both within each row and between rows (Pickles, Comis, & Osborne, 1984), which aids in the opening and closing of potassium channels at the tip of the stereocilia to facilitate excitation and inhibition of the hair cells, respectively.

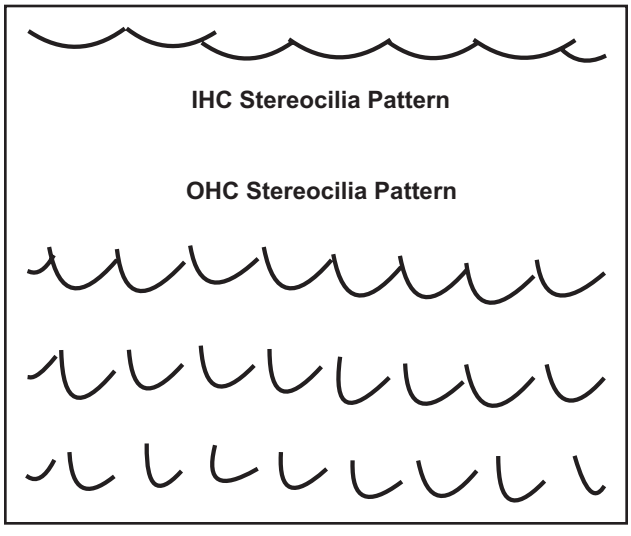

Figure 1–4. Stereocilia pattern for the inner hair cells (IHCs) and outer hair cells (OHCs) in a surface view of the normal organ of Corti. The crescent pattern for the single row of IHC stereocilia (*top*) and the V or W pattern for the three rows of OHC stereocilia (*bottom*) are clearly evident. Top in each is the modiolar side, and the bottom is the outer wall side.

The flask-shaped, relatively bigger single row of **IHCs** (about 3,000–4,000 in number) are located on the medial side of the inner pillar of Corti (see Figure 1–2), again slanted toward the inner pillar of Corti. Unlike the OHCs, the height and the length of the IHCs and their stereocilia remain unchanged along the longitudinal axis of the cochlear partition. The two to four rows of stereocilia on the top of each IHC form a crescent shape (Figure 1–4, top). Like the OHCs, the stereocilia of the IHCs have similar cross-links.

Afferent Innervation of the Cochlea

The cell bodies of the afferent neurons form the spiral ganglion located in the central core of the cochlear spiral called the modiolus. The peripheral portion of the afferent bipolar neurons enters the cochlea through the habenula perforata and synapses at the base of each hair cell. The peripheral portions innervating the OHCs, called the outer spiral fibers (OSFs), enter the cochlea through the habenula perforata in the osseous spiral lamina and cross along the floor of the tunnel of Corti toward the OHCs. As they spiral around the cochlea in an apical-to-basal direction, each OSF synapses with 10 to 15 OHCs (starting with the OHCs in the inner row, then the middle row, and finally the outermost row—see Figure 1–5). Thus, the output of many OHCs converges on one OSF, suggesting integration of information from many OHCs spread across the cochlear partition. These unmyelinated OSFs are also referred to as Type II fibers (smaller diameter and slower conducting) and form only about 5% to 10% (Spoendlin, 1978) of the 30,000 auditory nerve fibers in humans. While the peripheral fibers innervating the IHCs follow a similar path from the spiral ganglion, the innervation pattern is very different (see Figure 1–5). The peripheral portion of

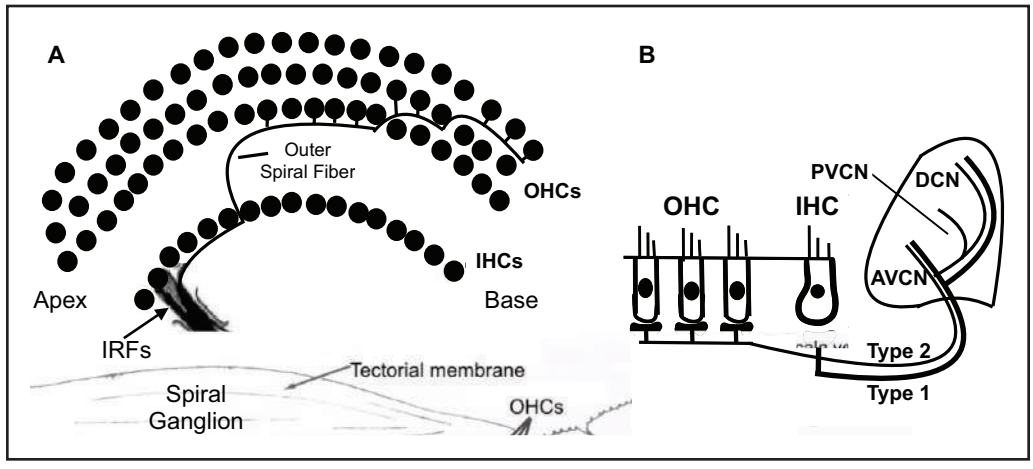

Figure 1–5. Afferent innervation pattern of the outer hair cells (OHCs) and inner hair cells (IHCs). Panel A illustrates the afferent innervation pattern of the cochlear OHCs and IHCs. Panel B shows the nature of the afferent synapses on the IHCs and OHCs.

the fibers innervating the IHCs is called the inner radial fiber (IRF). Unlike the OSF, these myelinated fibers, called Type I fibers (larger diameter and faster conducting), enter the cochlea through the habenula perforata (as many as 20 fibers through each radial canal, travel radially and synapse the nearest IHC at its base). Unlike each OSF, each IRF innervates only one IHC. However, as many as 30 IRFs innervate one IHC, thus providing a diverging output from one IHC. These IRFs form 90% to 95% of the total number of afferents in the auditory nerve.

Formation of the Auditory Nerve

The central axons of the spiral ganglion cells twist to form the auditory nerve bundle, and along with the central axons of the vestibular branch form the VIII cranial nerve (Figure 1–6, left panel). The VIII cranial nerve exits the temporal bone via the internal auditory meatus and enters the brainstem at the lateral aspect of the pontomedullary junction and bifurcates into an anterior and a posterior branch. The anterior branch courses anteriorly and terminates in the neurons forming the anterior ventral cochlear nucleus (AVCN). The posterior branch sends off collaterals to innervate neurons in the posterior ventral cochlear nucleus (PVCN) as it proceeds posterodorsally to terminate in the neurons of the dorsal cochlear nucleus (DCN) (Figure 1–6, right panel). The individual fibers forming the auditory nerve are organized systematically such that apical (low-frequency cochlear regions) fibers are toward the core, and basal (high-frequency cochlear regions) are increasingly on the surface of the auditory nerve bundle. This orderly arrangement representing cochlear place (and therefore frequency) provides the framework for the development of tonotopic organization at the terminal points of the auditory nerve in the cochlear nucleus (see Figure 1–6, right panel—see the frequency arrangement, **L** [low], **M** [mid], and **H** [high], in the AVCN).

II. NEUROANATOMY OF THE AUDITORY BRAINSTEM

Salient Features of Organization of Brainstem Structures and Pathways

For the purpose of discussion here, the auditory brainstem extends from the medullary-level cochlear nucleus to the midbrain-level inferior colliculus, including the caudal pontine–level superior olivary complex (SOC) and nuclei of the lateral lemniscus, and the midbrain inferior colliculus (Figure 1–7, left panel). The neuroanatomic organization of each nucleus along the auditory brainstem

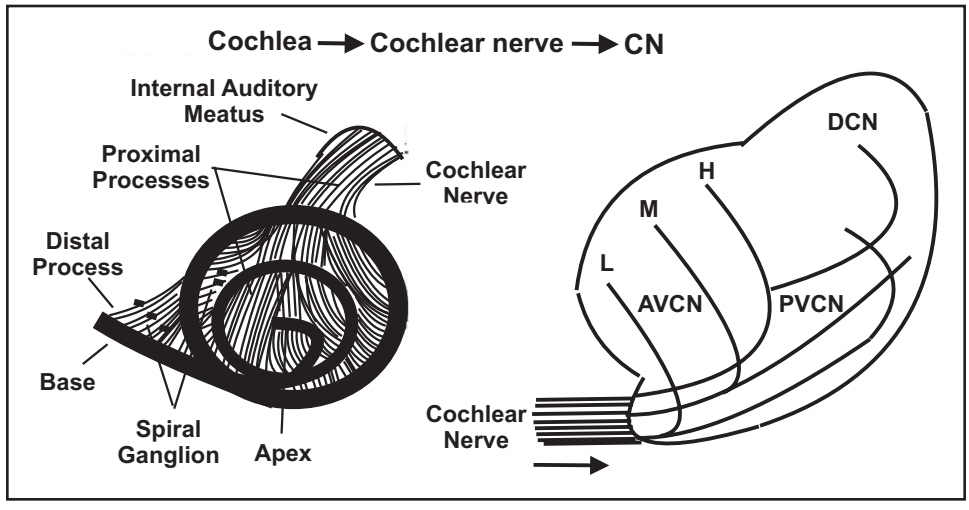

Figure 1–6. Origin and termination of the auditory nerve in the subdivisions of cochlear nucleus. Innervation and exit of the cochlear nerve from the cochlea are shown on the left. Course and termination points of the auditory nerve in the cochlear nucleus are shown on the right. Distal and proximal portions originating from the cochlear spiral (*left*) of the afferent fibers are identified. The bifurcation of the auditory nerve fibers into anterior and posterior branches is also illustrated.

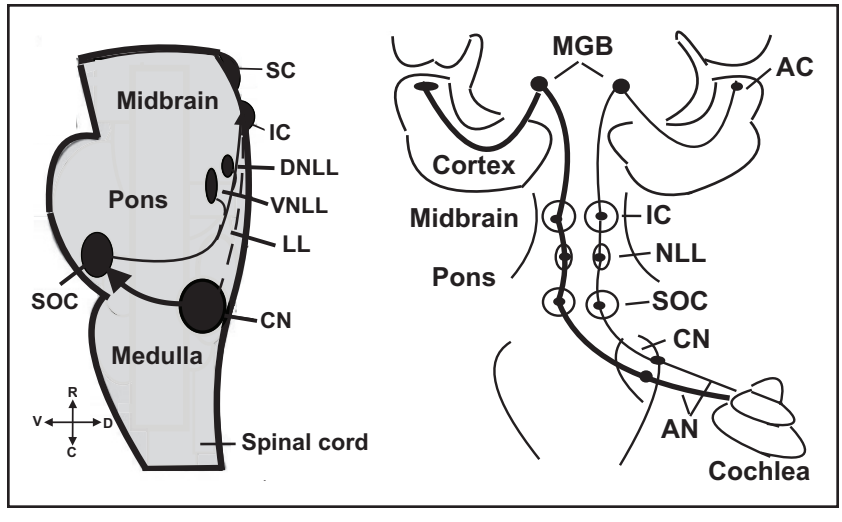

Figure 1–7. Schematic lateral view of the brainstem and midbrain showing auditory nuclei along the brainstem and their anatomic levels. Nuclei identified are cochlear nucleus (CN) and superior olivary complex (SOC) at the medullary and pontine levels; ventral nucleus of lateral lemniscus (VNLL) and dorsal nucleus of lateral lemniscus (DNLL) at the rostral pontine level; ascending lateral lemniscus (LL) fibers through the brainstem; and inferior colliculus (IC) at the midbrain level; the superior colliculus (SC), the visual midbrain nucleus, is also identified.

shares certain characteristics that include bilateral structures, contralateral dominant afferent pathways (Figure 1–7, right panel), core (with exquisite representation of the cochlear frequency map-tonotopic organization) and belt (nontonotopic, multisensory, efferent recipients) subdivisions,

efferent pathways, and the presence of binaural neurons past the cochlear nucleus. The following description of the neuroanatomic organization of each brainstem structure includes information about location, subdivisions, cell types, inputs, outputs, and orientation of the tonotopic map. The intent here is to provide an introduction to the neuroanatomic organization of nuclei and tracts along the auditory pathway(s) in the brainstem.

Cochlear Nucleus (CN)

Location: The cochlear nucleus (CN) is located on the dorsolateral aspect of the pontomedullary junction proximal to the root entry zone of the auditory nerve (see Figure 1–7, left panel).

Subdivisions: It is a rather complex nucleus with a broad diversity in cell types that forces consideration of division into multiple subdivisions (Adams, 1986; Brawer, Morest, & Kane, 1974; Cant, 1992; Moore & Osen, 1979; Osen, 1969). However, the scope here is to consider just the two main subdivisions—ventral cochlear nucleus (VCN) and DCN. The VCN is further subdivided (see Figure 1–6, right panel) into an AVCN and a PVCN.

Cell types: The anterior portion of AVCN contains large spherical bushy cells (the principal cell type here with short bushy dendrites) and medium-sized stellate or multipolar cells. The posterior portion of the AVCN contains small spherical bushy cells, globular bushy cells, and large stellate cells. These large stellate cells are also found in the anterior PVCN. The posterior PVCN is characterized by the presence of octopus cells. The cell types in the laminar DCN include stellate, fusiform, granule, and giant cells. These morphologically distinct cell types (Figure 1–8) also show different response properties, suggesting differences in their functional roles (Young et al., 1988).

Inputs: All Type I and II fibers of the auditory nerve form the afferent inputs to the subdivisions of the CN (Raphael & Altschuler, 2003; Robertson, 1984; Ryugo, 1992). As described earlier, the AN bifurcates upon entering the CN into an anterior and a posterior branch. The anterior branch courses anteriorly and terminates in the AVCN. The posterior branch courses posteriorly and dorsally sending collateral terminals to the PVCN and continuing on to terminate in the DCN (see Figures 1–6, right panel, and Figure 1–8). While the trajectory of AN inputs to the CN from all portions of the cochlea are similar, the location of bifurcation in the CN systematically moves from ventral for fibers innervating the apical cochlear regions to dorsal for fibers innervating the basal cochlear regions

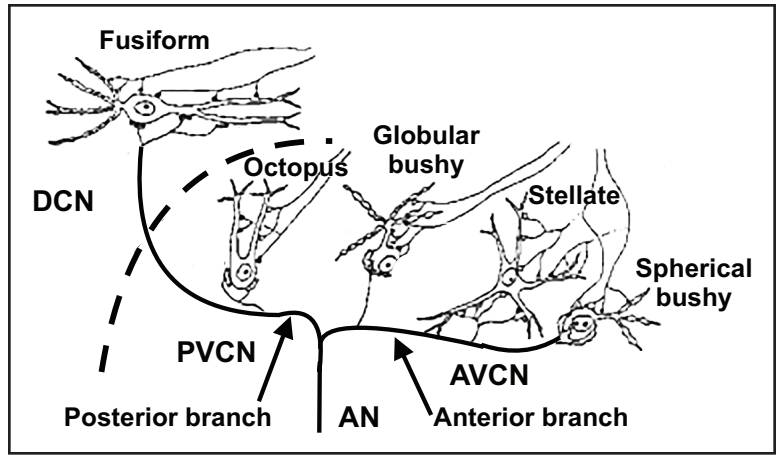

Figure 1–8. Auditory nerve bifurcation into an anterior and posterior branch in the cochlear nucleus (CN) and prominent cell types in anterior ventral cochlear nucleus (AVCN), posterior ventral cochlear nucleus (PVCN), and dorsal cochlear nucleus (DCN). Note the large calyx of Held–type synapses engulfing the soma of the spherical and globular bushy cells.

(Lorente de No, 1933). This pattern sets up the dorsal, high-frequency and ventral, low-frequency tonotopic map in each of the three subdivisions of the CN. While the AVCN receives several intrinsic and extrinsic inhibitory inputs, what is characteristic here are the large excitatory end bulb of Held synapses between the anterior branch of the auditory nerve and the spherical and globular bushy cells in AVCN. These complex synapses provide a coordinated release of neurotransmitter onto these CN cells. It should be noted here that the globular cells in comparison have relatively smaller synapses. The auditory nerve innervates the fusiform cells in the DCN on their basal dendrites and not the soma.

Outputs: The ipsilateral and the dominant contralateral outputs of the three subdivisions of the CN are carried by three major pathways, each primarily dedicated to one of the three subdivisions (Figure 1–9) The largest of the three, the ventral acoustic stria (VAS) or the trapezoid body (TB), carries excitatory outputs from the spherical bushy cells in the AVCN and runs along the ventral portion of the brainstem and projects to the ipsilateral medial superior olive (MSO) via the lateral dendrites, and the contralateral MSO via the medial dendrites (Cant, 1992). The contralateral input to the lateral superior olive (LSO) originates in the globular cell region of the AVCN, which projects excitatory outputs via the TB to the contralateral medial nucleus of the trapezoid body (MNTB) using the giant calyx of Held synapse that almost engulfs the MNTB. The calyx of Held allows the principal neurons in the MNTB to provide a well-timed and sustained inhibition to the LSO as well as to many other auditory nuclei (i.e., provides the contralateral inhibitory input to the binaural neurons in the LSO). The MNTB in turn projects an inhibitory input to the medial side of the ipsilateral LSO. The TB fibers from the multipolar cell regions (primarily PVCN) also ascend as the lateral lemniscus along the contralateral brainstem and send out collaterals to the ventral (VNLL) and dorsal nuclei of the lateral lemniscus (DNLL) before terminating in the central nucleus of the inferior colliculus (CNIC). The larger multipolar cells in the PVCN project only to the contralateral CN via the intermediate acoustic stria (IAS). Octopus cells in the PVCN project to the periolivary region in the SOC

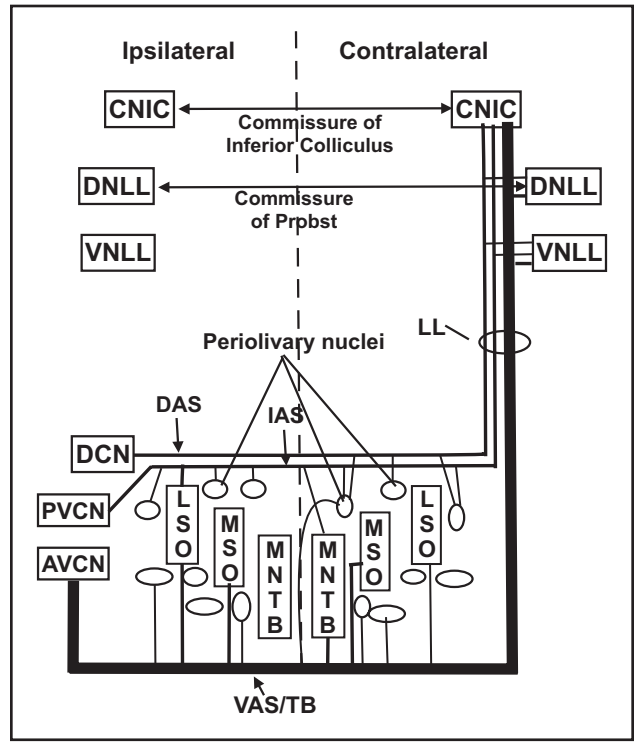

Figure 1–9. Outputs of the subdivisions (anterior ventral cochlear nucleus [AVCN], posterior ventral cochlear nucleus [PVCN], and dorsal cochlear nucleus [DCN]) of the cochlear nucleus. Three major output pathways are the dorsal acoustic stria (DAS) from the DCN; intermediate acoustic stria (IAS) from the PVCN; and the ventral acoustic stria (VAS) or trapezoid body (TB). Targets include lateral superior olive (LSO), medial superior olive (MSO), and medial nucleus of the trapezoid body (MNTB) in the superior olivary complex (SOC); ventral and dorsal nuclei of lateral lemniscus (VNLL and DNLL); and the central nucleus of inferior colliculus (CNIC). All of these fibers together form the lateral lemniscus as they ascend from the CN to the CNIC.

and to the contralateral VNLL (Warr, 1982). Finally, the dorsal acoustic stria (DAS) carries information from the DCN (fusiform and giant cells) to the contralateral CNIC bypassing the SOC (Warr, 1982).

Tonotopic Organization: Refers to the spatial representation of the cochlear frequency map in a given three-dimensional nucleus. In each of the three subdivisions of the cochlear nucleus, neurons tuned to low frequencies are in the ventral portion, and neurons tuned to progressively higher frequencies are located in progressively dorsal regions as you track along a ventral-to-dorsal direction (Figure 1–10).

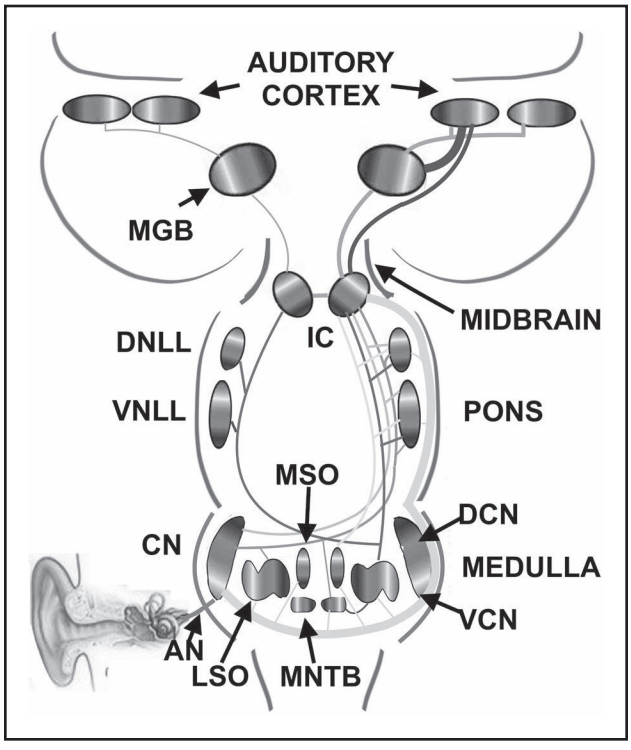

Figure 1–10. Nuclei along the ascending (*lighter lines*) and descending (*darker lines*) auditory pathways showing the orientation of the tonotopic maps in each nucleus (*low frequency: lighter color; high frequency: darker color*).

Superior Olivary Complex (SOC)

Location: The SOC is a nuclear mass located on the ventral portion of the caudal pons, medial and ventral to the CN, and represents the first point of information convergence from the two ears (see Figure 1–10). The human SOC has about 5,871 neurons (LSO: 1,980 neurons; MSO: 3,891 neurons with no well-defined MNTB) (Hilbig, Beil, Hilbig, Call, & Bidman, 2009).

Subdivisions: The SOC is divided into three subdivisions, the most lateral and S-shaped structure, the LSO; the banana-shaped structure, medial and slightly dorsal to the LSO, the MSO; and the most medial and ventral subdivision, the MNTB (see Figure 1–10). The MNTB neurons are embedded in the TB fibers. The LSO and the MSO are thought to be a single functional unit. However, given that the MNTB is almost nonexistent in humans (Masterton, Thompson, Bechtold, & RoBards, 1975), its role in the binaural processing of interaural intensity cues for localization is doubted—at least in humans. While the LSO/MNTB is specialized for processing interaural intensity differences, the MSO is specialized to process interaural time differences relevant for sound localization in the horizontal plane. The size of the MSO varies with head size (smaller heads, smaller MSO and more dominant LSO) and appears to indicate the relative usefulness of interaural cues for localization in each animal (Hilbig et al., 2009; Masterton et al., 1975). Except for humans, the LSO is the most prominent and well-differentiated nucleus in most other species. Like a belt around the three main subdivisions are neurons that are collectively called the periolivary nuclei that are thought to be part of the efferent system (Hilbig et al., 2009).

Cell types: In the MSO, there are essentially three types of principal cells: bipolar disc-shaped cells oriented in a rostrocaudal direction, multipolar cells with a distributed dendritic tree, and marginal cells along the medial and lateral surface with dendrites covering the MSO surface. The orientation of the principal disc-shaped cells allows for binaural inputs to project to the MSO laterally from the ipsilateral CN and medially from the contralateral CN. The prominent LSO cell types include disc-shaped principal cells (referred to as elongate fusiform cells) similar in orientation to the MSO principal cells, and multipolar cells that span the cell surface but with no clear orientation of the dendrites. The predominant cell type in the MNTB is the principal globular cell. In addition, multipolar cells and elongate fusiform cells are found in the MNTB.

Inputs: The afferent inputs to the MSO, LSO, and MNTB are primarily the outputs of the AVCN described in the CN output section (Figure 1–11, bottom portion). To refresh, the MSOs receive binaural excitatory inputs from the AVCN spherical cells with the lateral dendrites carrying the ipsilateral inputs and the medial dendrites carrying the contralateral inputs. The MSO marginal cells receive inhibitory inputs from the MNTB and excitatory inputs from the CN, similar to the MSO. In contrast, the LSO receives excitatory ipsilateral inputs laterally from the spherical bushy cells in AVCN and contralateral inhibitory inputs through the ipsilateral MNTB, which converts the excitatory inputs it receives from the globular bushy cells in

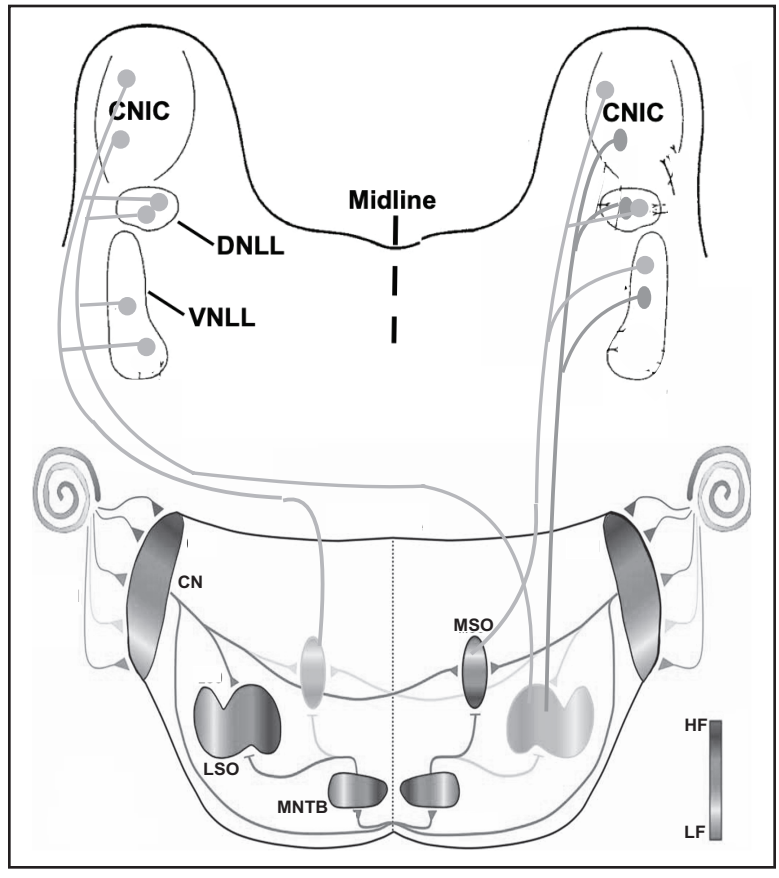

Figure 1–11. Binaural inputs from the cochlear nucleus to the lateral superior olive (LSO) and medial superior olive (MSO) (*bottom*), and outputs to higher brainstem nuclei from LSO and MSO.

the contralateral AVCN. The MNTB synapse is a very large secure calyx of Held synapse.

Outputs: The outputs of the MSO principal and marginal cells on each side ascend ipsilaterally via the lateral lemniscus (Figure 1–11, top portion) sending out collaterals to the DNLL before terminating in the CNIC. Unlike the MSO, the outputs from each LSO project bilaterally along the lateral lemniscus to the CNIC. The outputs to the ipsilateral CNIC are inhibitory (Saint Marie, Ostapoff, Morest, & Wenthold, 1989), and the outputs to the contralateral CNIC are excitatory. Collaterals along the way are also projected to both the DNLL and the VNLL. The MNTB primarily projects to the LSO on the same side; however, it is likely that collaterals send projections to VNLL and IC (Kuwabara, DiCaprio, & Zook, 1991). Although the organization of nuclei and tracts are similar across animal models, there are individual differences in the projection strengths and targets.

Tonotopic organization: While the MSO, LSO, and MNTB are tonotopically organized, it is likely that the MSO is low-frequency biased and the LSO is high-frequency biased to optimally process interaural time and intensity differences, respectively. In the MSO, low frequencies are represented in the dorsal part and high frequencies are represented in the ventral part. In both the LSO and the MNTB, low frequencies are represented in the lateral portion and high frequencies are represented in the medial portion (see Figures 1–10 and 1–11). In addition, for each frequency region, it is likely that an orthogonal spatial map exists in the SOC to represent interaural differences and therefore the location of the sound source in the horizontal plane.