Auditory Brainstem Evoked Potentials

Clinical and Research Applications

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CONTENTS

PREFACE

I have been teaching auditory electrophysiology to graduate students and conducting research using electrophysiologic measures for over 30 years now. My complaining about the appropriateness of the available textbooks for my classes (in terms of the organization of the content, the appropriate level, the appropriate depth, and the right balance between theory and clinical applications most relevant to the students) has steadily increased over the years. Finally, I thought it was time to stop complaining and do something about it. Thus, this undertaking is an *attempt* to address my objectives and to stop my decades-long complaining. However, this attempt should not be construed as a negative reflection on several excellent resources already provided by my colleagues in the field.

This book is primarily intended to serve as a prescribed textbook for graduate-level electrophysiology course(s) for AuD and PhD students. However, its contents should also be of interest to researchers using auditory evoked potentials to complex sounds (envelope following response [EFR] and frequency following response [FFR]) to address questions relevant to the neural representation of complex sounds and how they may be altered by experience, training, and hearing impairment. The main aim is to provide an organized, coherent, sufficient, and reasonably up-to-date (but not exhaustive) account of relevant literature about the principles related to the neural bases, response characteristics, and specific clinical and research applications of the auditory evoked brainstem potentials. The goal is twofold: (a) to foster an understanding of how these measures reflect the neuroanatomical and functional organization of the auditory system from the periphery through the brainstem, and (b) to develop an appreciation for the structure-function relationship and the consequences of an impairment on this relationship that may be reflected in these measures. It is my firm belief that such knowledge integrated into the clinical practice is essential to be able to "practice at the top of your license," rather than merely be a technician. Finally, the level of technical detail presented was deliberately reduced (without filtering out important information) to encourage the reader to remain focused on learning the essentials of the relevant information. However, inquiring minds can always pursue the listed references to quench their thirst.

The contents are organized in a coherent manner by first providing a sufficient overview of the nature of the neuroanatomical organization of the structures and pathways in the auditory periphery and the brainstem (Chapter 1) followed by a review of neuronal physiology and the neural bases of auditory evoked potentials (Chapter 2). Since structure and function are closely related, knowledge of the structural organization and the neural bases of these responses will help the clinician to understand the functional consequences of a structural abnormality, enabling the development of better clinical management strategies. Chapter 3 provides a complete description of stimulus characteristics and principles of evoked potential data acquisition. This is followed by a description of the normative aspects of the auditory brainstem response (ABR) as it relates to stimulus, recording, and subject factors (Chapter 4). This knowledge is a prerequisite to set up the normative database required to interpret these responses as normal or abnormal in clinical diagnosis. A complete description of audiologic applications of the ABR for hearing screening for early identification of hearing loss and frequency-specific estimation of hearing thresholds or minimum hearing levels is provided in Chapter 5. While there is no single standard protocol for each application across clinics to date, the latest developments relevant to hearing screening and frequency-specific threshold estimation move toward the development of effective and efficient protocols that employ next-generation technology to both increase accuracy and reduce test time.

Chapter 6 examines the clinical utility of the ABR to differentiate hearing losses resulting from structural abnormalities in the conductive mechanism, sensory-to-neural transduction in the cochlea, and synaptic processing and neural transmission in the auditory nerve and brainstem. In terms of neuro-otologic applications, the use of cochlear receptor potentials (cochlear microphonic [CM] and summating potential [SP]) and the auditory nerve compound action potential (AN-CAP) to evaluate the functional integrity of the inner ear outer hair cell subsystem and the auditory nerve for differential diagnosis, and for neural function monitoring during surgeries that involve the auditory nerve and the brainstem, is examined in Chapter 7. This includes a description of the use of AN-CAP recorded directly from the auditory nerve and/or the cochlear nucleus, and the scalp-recorded ABR in intraoperative monitoring to minimize surgically induced permanent injuries, and to attempt preservation of hearing. In the next two chapters (Chapters 8 and 9), the clinical utility and research utility of the emerging brainstem evoked potentials generated by complex sounds (EFR and FFR) including speech are described. Since both these responses provide information about the nature of the temporal neural encoding of certain acoustic features important for the perception of complex sounds, they can potentially serve as effective electrophysiologic measures to evaluate the nature of degradation of these features in individuals with hearing impairment consequent to cochlear and/or retrocochlear pathologies; monitor treatment outcomes with amplification; evaluate effects of auditory retraining; and test and evaluate optimal signal processing strategies for hearing prosthetic devices. There is no substitute for sufficient hands-on experience to develop sound skills to record, analyze, and interpret the auditory brainstem responses from real people. This essential requirement not only reinforces the understanding of concepts relevant to the effects of various stimulus and recording factors on the ABR response components presented in the classroom but also facilitates learning and reinforcing practical skills necessary to accurately record and interpret the responses for optimal clinical application (Chapter 10). Finally, the accompanying online PowerPoint lectures on the PluralPlus companion website should be useful for both students and instructors in preparation of the course.

Although my initial intent was to gear the content of this book to a single course limited to the clinical and research applications of the transient auditory brainstem response (ABR), the more expanded content presented is unlikely to be covered in a single-semester course. Thus, this book can be used in a two-course sequence, wherein the first course covers the basic clinical applications (hearing screening, threshold estimation, and the use of ABR in differential diagnosis) and the second course covers the use of ABR in intraoperative monitoring, sustained brainstem responses to complex sounds and their clinical applications, and the use of sustained brainstem responses to complex sounds in research to understand the neural representation of complex sounds in normal and impaired ears.

I would like to thank the multiple reviewers (who provided helpful feedback that has made the final product better), colleagues in the profession, and graduate students who have helped shape this book. I am deeply indebted to my wife Lata Krishnan (sadly, I was not able to convince her to be a co-author) for painstakingly editing the manuscript. It was a pleasure working with the editorial staff at Plural Publishing (Christina Gunning, in particular, who was patient and helpful), and I appreciate their cooperation during times when my progress was hampered. While I have received quite a bit of help from my colleagues, all omissions and errors that persist are my own.

This book is a product developed during the isolation forced by the COVID-19 pandemic. While the isolation (which trapped me in India) forced me to work on it, encouraged on by my undergraduate classmates (AIISH batch of 1970), I do feel sad about the terrible devastation visited upon (unfortunately continuing to date and postponing a planned trip to India next week) humankind by this pandemic. I fervently hope that we come out of this soon and revert to some semblance of a normal life. Godspeed everyone.

Ravi Krishnan
West Lafayette
April, 2021

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This book is dedicated to my parents, family, mentors, colleagues, friends, and students who have all contributed to my knowledge and hopefully have instilled some wisdom in me.

"The way of devotion is not different from the way of ***knowledge or gnyaana.*** *When intelligence matures and lodges securely in the mind, it becomes* ***wisdom****. When wisdom is integrated with life and shoots out in action, it becomes* ***bhakti****. Knowledge, when it becomes fully mature, is bhakti. If it does not get transformed into bhakti,* ***such knowledge is useless tinsel****. To believe that gnyaana and bhakti,* ***knowledge and devotion, are different from each other, is ignorance****."*

—Bharath Rathna Sri Chakravarti Rajagopalachari

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

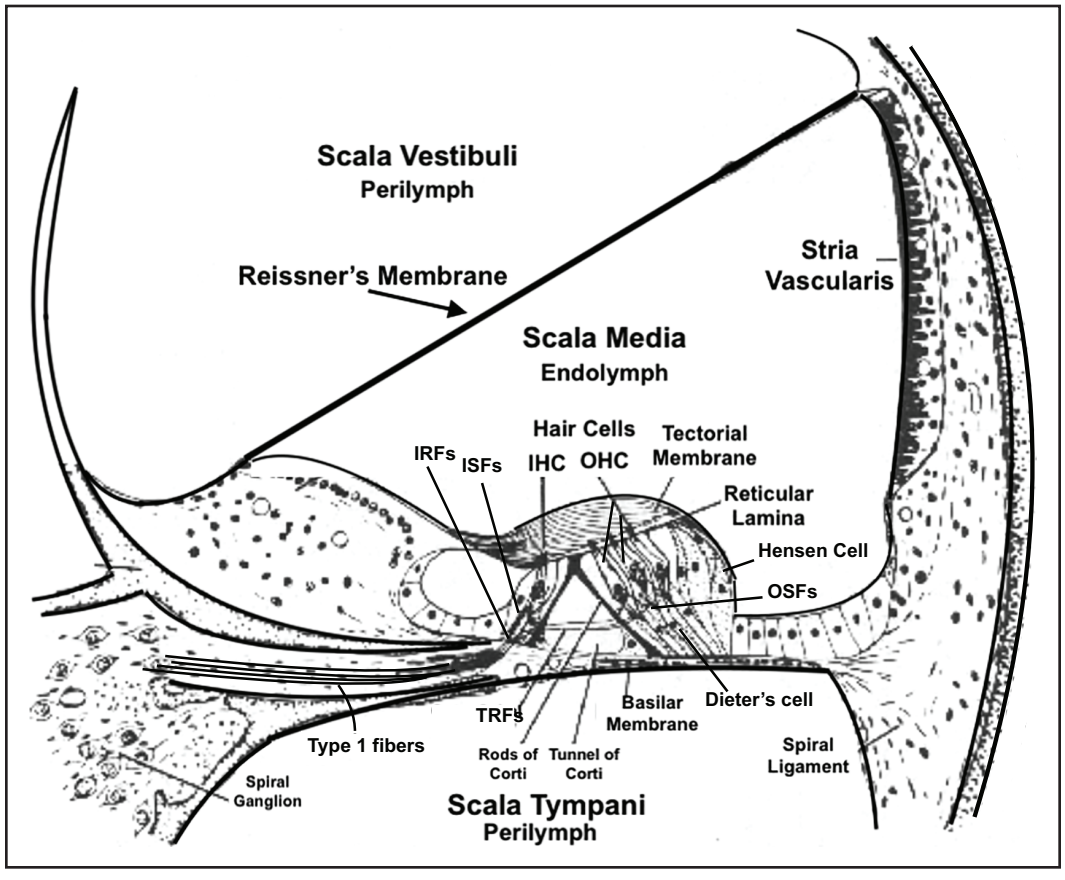

Figure 1–1. Cross-section of cochlea showing the three fluid-filled partitions (scala vestibuli, scala tympani (perilymph), and scala media (endolymph)) and the organ of Corti with outer hair cells (OHCs) and inner hair cells (IHCs), stereocilia, basilar membrane, tectorial membrane, and stria vascularis (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-

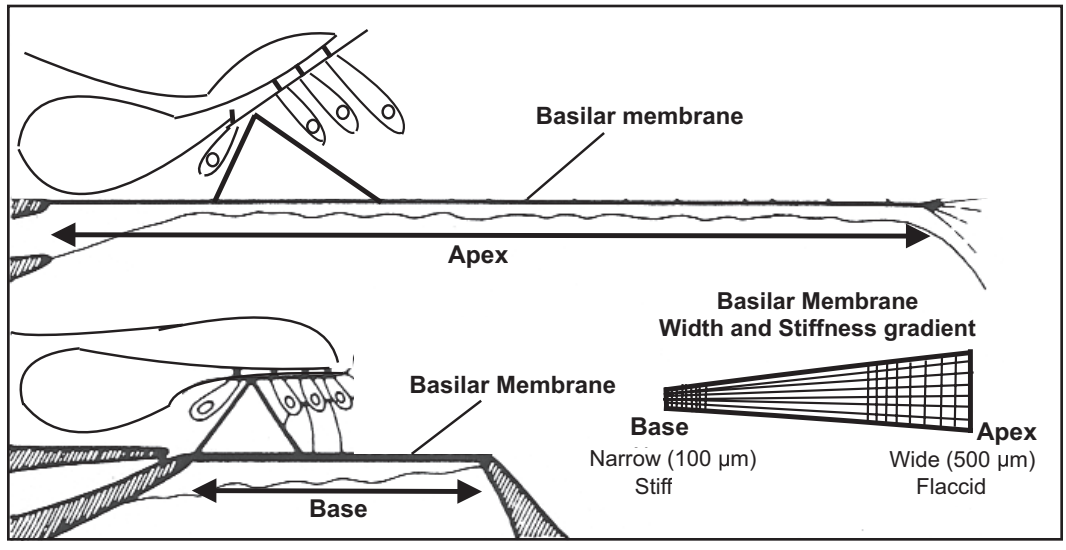

Figure 1–2. The changes in the width and stiffness of the basilar membrane from base to apex. The basilar membrane is wider at the apex and more flaccid, whereas it is narrower at the base and exhibits greater stiffness (see lower right).

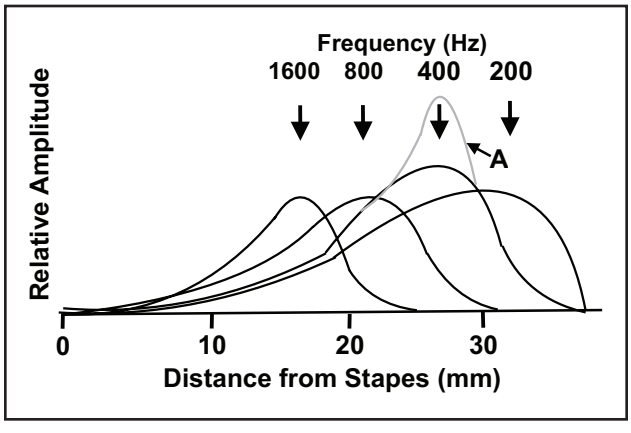

Figure 1–3. A family of Bekesy traveling wave envelopes showing frequency for place transformation. Traveling wave maxima progressively shift from apex to base (that is, to the left) as frequency is increased. Note the amplification in the maximum amplitude for 400 Hz (*arrow pointed by A*) reflecting 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.

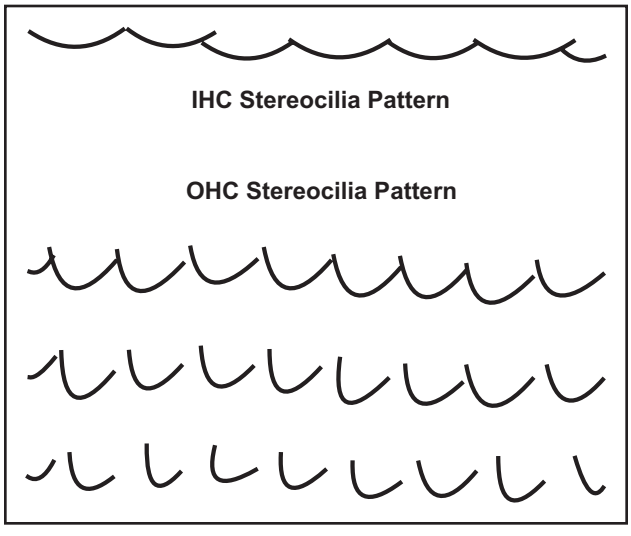

Figure 1–4. Stereocilia pattern for the inner hair cells (IHCs) and outer hair cells (OHCs) in a surface view of the normal organ of Corti. The crescent pattern for the single row of IHC stereocilia (*top*) and the V or W pattern for the three rows of OHC stereocilia (*bottom*) are clearly evident. Top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

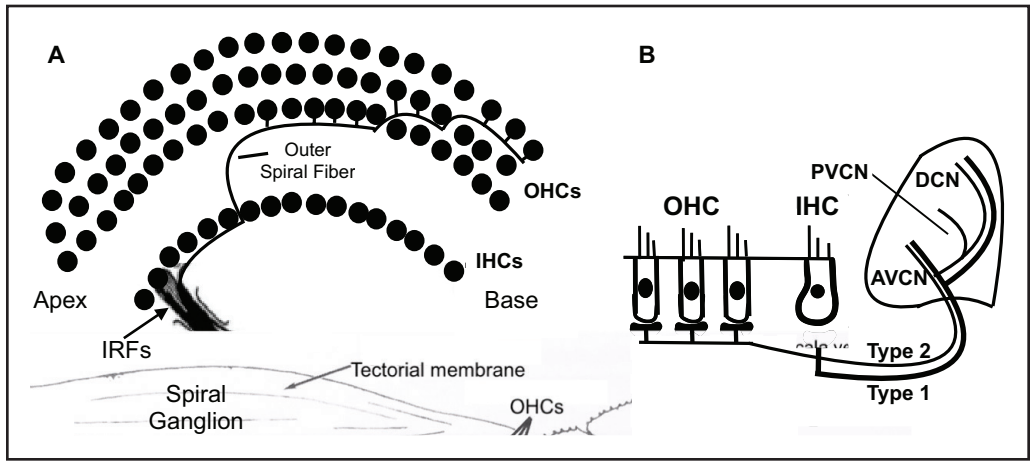

Figure 1–5. Afferent innervation pattern of the outer hair cells (OHCs) and inner hair cells (IHCs). Panel A illustrates the afferent innervation pattern of the cochlear OHCs and IHCs. Panel B shows the nature of the afferent synapses on the IHCs and OHCs.

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

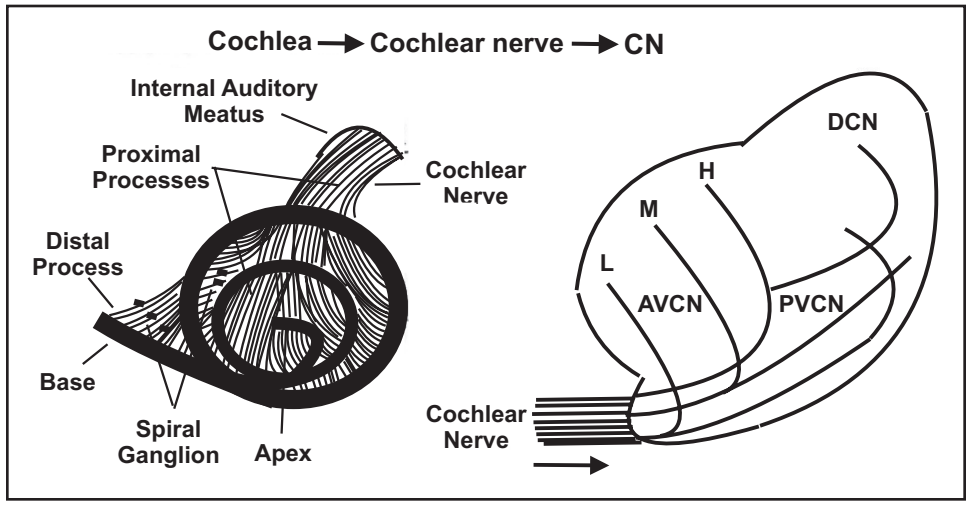

Figure 1–6. Origin and termination of the auditory nerve in the subdivisions of cochlear nucleus. Innervation and exit of the cochlear nerve from the cochlea are shown on the left. Course and termination points of the auditory nerve in the cochlear nucleus are shown on the right. Distal and proximal 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.

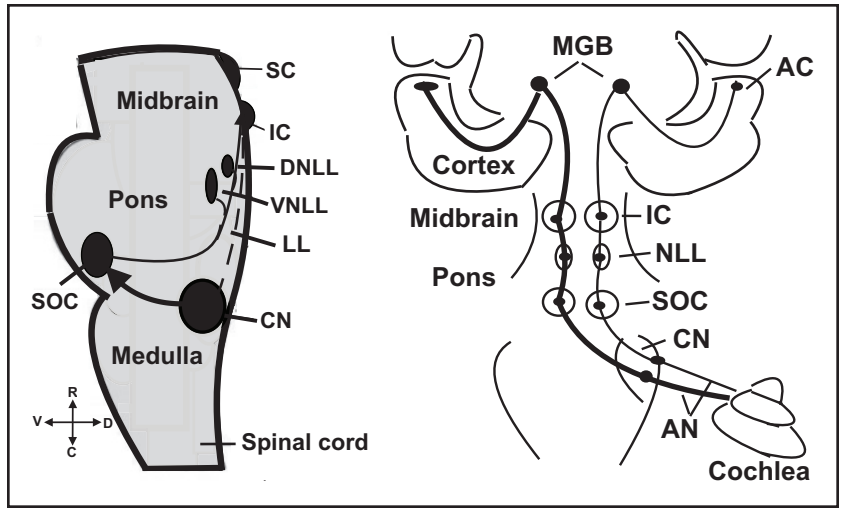

Figure 1–7. Schematic lateral view of the brainstem and midbrain showing auditory nuclei along the brainstem and their anatomic levels. Nuclei identified are cochlear nucleus (CN) and superior olivary complex (SOC) at the medullary and pontine levels; ventral nucleus of lateral lemniscus (VNLL) and dorsal 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

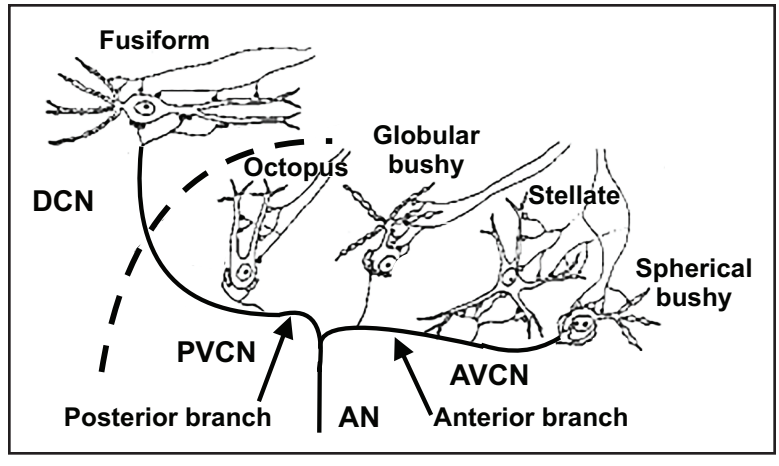

Figure 1–8. Auditory nerve bifurcation into an anterior and posterior branch in the cochlear nucleus (CN) and prominent cell types in anterior ventral cochlear nucleus (AVCN), posterior ventral cochlear nucleus (PVCN), and dorsal cochlear nucleus (DCN). Note the large calyx of Held–type synapses engulfing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