Feline Deafness

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KEYWORDS

• Auditory system • Brain • Cochlea • Congenital deafness • Genes • Synapse

KEY POINTS

- Cats have among the best hearing of all mammals in that they are extremely sensitive to a broad range of frequencies. The rattle of the cat's food box or the hiss of a can opening should be sufficient to summon your cat no matter where it is in the house. Failure to call your cat this way is a sign that it is ill or losing its hearing.
- The ear is a highly complex structure that is delicately balanced in terms of its biochemistry, types of receptors, ion channels, mechanical properties, and cellular organization. Minor perturbations of any component of hearing can cause loss of function.
- Sensorineural deafness is usually caused by "flawed" genes that are inherited from one or both parents. Defects can appear as a disturbance in chemistry, failure of the receptive sensory elements, or impaired biomechanics. Hearing loss can also be acquired as a result of noise trauma from industrialized environment, viral infection, or blunt trauma. To date, it is not practical to intervene and attempt to correct these forms of deafness in cats.

INTRODUCTION

The ability to hear sound is one of the fundamental ways that organisms are able to perceive the external environment. It is speculated that hearing evolved as a distance sense, a function driven by a need for animals to detect potential danger, food, or mates that could not be seen because of darkness or dense foliage. Animals have the ability to sense perturbations in the air, and in vertebrates, the internal ear is a highly developed sensory structure that enables this function. Cats have especially keen hearing.[1] Their ability to hunt, avoid predators and oncoming motor vehicles, and interact with their owners depends on their hearing. Cats with hearing loss and/or deafness are vulnerable to danger.

For terrestrial vertebrates, sound is created by vibrations in air.[2] These vibrations may be characterized by frequency (cycles per second, Hz), which is correlated to

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the sensation of pitch, the magnitude of the pressure of the vibrations (loudness), their timing (eg, onset, offset, duration, cadence), and the location. Two ears allow the extraction of important acoustic cues: the ear closer to the sound source will hear the sound sooner (interaural timing difference) and louder (interaural level difference) than the more distant ear. These binaural differences allow the brain to calculate sound location, and survival can depend on knowing if the sound comes from the right or the left. Sound arriving from the front has a different character than sound arriving from behind owing to interference by the external ear. This interference is called a head-related transfer function. The cat learns about the transfer functions so that it can also distinguish between sound in the front and back, an ability that is important to survival.

Sound is captured by the pinna, the external portion of the ear, and funneled through the ear canal to the tympanic membrane or eardrum (**Fig. 1**). The tympanic membrane is mechanically coupled to the 3 middle ear ossicles (the malleus, incus, and stapes), whose combined function is to deliver the vibrations to the fluid-filled internal ear with the same power as that delivered to the tympanic membrane. The vibrations in air become vibrations in fluid and are transmitted to the sensory hair cell receptors that reside in the organ of Corti. This mechanical signal is converted to neural signals and relayed to the brain by the cochlear (or auditory) branch of cranial nerve VIII (also known as the vestibulocochlear nerve). The brain receives and interprets these signals and the result is what we perceive as hearing.

- Mammalian hearing relies on 2 broad categories of function: mechanical and electrochemical.
- The mechanical component involves the capture of sound by the external ear and its transmission into the fluid-filled cochlea. The vibrations in the fluids mechanically stimulate different regions of the internal ear based on frequency, where these perturbations mechanically stimulate the cochlear hair cell bundle.
- The electrochemical component results from specialized cells that border the endolymphatic space and create a unique chemical environment. The endolymph has a positive potential ($\sim$80 mV) that drives K^+ into the cytoplasm of stimulated hair cells. Receptor cell responses are converted to action potentials in fibers of the cochlear nerve and conveyed to the brain. Malfunction of either of these auditory processing components results in hearing loss.
- Two types of hearing loss are identified and considered as separate entities.

"Conductive" hearing loss refers to problems of the peripheral auditory system, whereas "sensorineural" hearing loss refers to malfunction of the neuronal components of the auditory system.

- "Conductive" hearing loss results from external ear occlusion, tympanic membrane perforation, ossicular chain discontinuity or fixation, or middle ear infections. For cats, conductive hearing loss is often amenable to improvement with cleaning the external ear canal, antibiotics to clear middle ear infection, or surgical procedures to repair the tympanic membrane or ossicular function.
- "Sensorineural" hearing loss, on the other hand, can result from pathology anywhere along the auditory pathway, from the hair cell receptors to higher-order central auditory processing centers. Deafness owing to sensorineural hearing loss resembles a train wreck: it can result from many diverse causes but the outcome is always hearing loss.
- Sensorineural deafness can be classified into 2 broad classes: congenital deafness and acquired deafness.

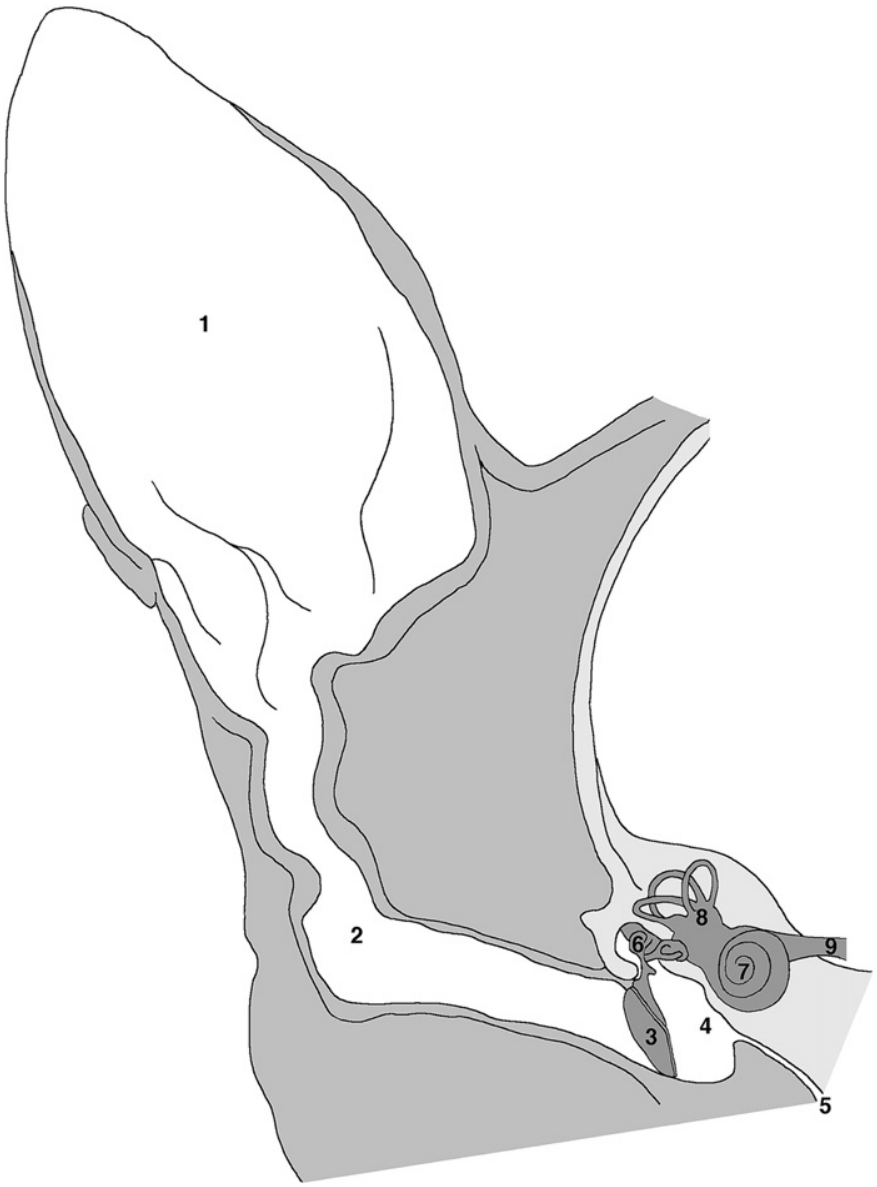

Fig. 1. Schematic drawing of the cat ear. The external ear consists of the pinna (1) and external ear canal (2) that conducts airborne sound to the tympanic membrane (3, ear drum). The tympanic membrane and 3 middle ear bones (6) occupy the middle ear space (4). These moving parts convert vibrations in air to vibrations in the inner ear (7). The middle ear space is confluent with the pharynx by way of the Eustachian tube (5). Behind the cochlea, the auditory component of the inner ear, lies the vestibular structures (8). The eighth cranial nerve, the auditory-vestibular nerve (9), conducts sensory information from the sense organ to the brain. (*Courtesy of* Catherine Connelly, Garvan Institute of Medical Research, Sydney, Australia.)

- Congenital deafness is a condition that exists at birth and often before birth, or that develops during the first month of life regardless of etiology. In humans, nearly half of the causes of deafness can be attributed to genetic abnormalities. One-third of these defects is accompanied by identified disorders in other systems, and is considered "syndromic" deafness. The remaining two-thirds, however, are isolated to hearing loss and considered "nonsyndromic."

- Acquired deafness refers to a loss of hearing that is not present at birth but develops during the animal's lifetime. The causes of acquired hearing loss can be illness (eg, meningitis), head trauma, ototoxic drugs, and exposure to loud noise. In industrialized society, cats exhibit a significant amount of "normal pathology" that is assumed to arise from street noise.[1]

GENETICS OF DEAFNESS

Considerable progress has been made in identifying the genes and genetic loci associated with mammalian deafness. The list of genes is more than 100 and an updated database of the nonsyndromic deafness genes and loci is maintained at the Hereditary Hearing Loss Homepage (http://hereditaryhearingloss.org). With the identification of hereditary deafness genes and the proteins they encode, molecular elements of basic hearing mechanisms emerge. As the function of these identified molecular elements continue to be unraveled, we can begin to understand the remarkable complexity of hearing. Multiple genes interact and express themselves at multiple loci such that rarely is a single gene responsible for the normal functioning of any system. The goal of this article was to summarize the function of some of the proteins implicated in hearing and genetic deafness while using the deaf white cat as the model (**Fig. 2**). The white cat is a good model for study because it has good low-frequency hearing like humans, and when deaf, its deafness is naturally occurring, has a genetic basis, and exhibits variable expression.

The deaf white cat has long held a fascination to humans, attracting the attention of Charles Darwin, among others.[3,4] The product of a single autosomal dominant locus, *White* (*W*), demonstrates pleiotropic effects, including a white coat, blue iris, and deafness, all 3 of which can be attributed to an absence or abnormality of melanocytes. The correlation between white coat color, blue irises, and deafness is, however, imperfect. Thus, white cats exhibit a uniform white coat, although they can be born with a colored spot that fades with age, and they may be either unilaterally or bilaterally deaf, demonstrating varying degrees of severity, from mild to profound. Additionally, their irises are often blue because of the absence of melanin, and the likelihood of deafness has been calculated at 80% with the frequency of blue irises.[5,6]

The white, deaf phenotype has been reported in multiple species, including the mouse, dog, mink, horse, rat, Syrian hamster, alpaca, and human.[7–19] Type 2 Waardenburg syndrome most closely describes the phenotype in humans with distinctive

Fig. 2. A congenitally deaf white cat. Note the heterochromia of the irides. This particular cat is healthy with no balance deficiencies; only deafness. (*Courtesy of* Dr David K. Ryugo, Garvan Institute of Medical Research, Sydney, Australia.)

hypopigmentation of skin and hair and congenital cochleosaccule dysplasia that resembles the Scheibe deformity. Investigation of the genetic basis for distinctive coat color phenotypes represent some of the earliest mapped and characterized genetic mutations.[20] Early in embryogenesis, melanoblasts, or pigment precursor cells, migrate from the neural crest to the skin, regions of the eye, and the internal ear. Mutations affecting any step in this pathway, be it proliferation, survival, migration, or distribution of melanoblasts is often manifested as coat color variation. Genes identified in these early events of pigmentation, many of which were characterized in the mouse white-spotting mutants, include *Pax3, Mitf, Slug, Ednrb, Edn3, Sox10* and *Kit*.[21–30]

In spite of the long-standing interest in coat color and deafness, only recently has the role of melanocytes in hearing been studied. In the internal ear, melanocytes are largely observed in the stria vascularis, the vascularized epithelium responsible for secreting high levels of K^+ into the endolymph, which establishes the endocochlear potential (EP).[31] The +80 mV EP is crucial for the normal function of the auditory receptor cells. Melanocytes are the only cell type in the stria vascularis to express the potassium channel protein, KCNJ10 (Kir4.1), providing the structural basis for the rate-limiting step that establishes the EP.[32] Knockouts of the *Kcnj10* gene in mice eliminate the EP and reduce endolymph potassium concentration, with resultant deafness.[32]

The incomplete penetrance for iris color and deafness has made it challenging to interpret an individual's genetic condition by classic linkage approaches, because those who possess the particular gene will not necessarily exhibit features of the gene.[33] Reduced penetrance is thought to result from a combination of genetic, environmental, and lifestyle factors, many of which are not known. Our approach to this dilemma is to perform linkage analysis for *White* in a pedigree segregating for white coat color. Information on the mutational mechanism can be applied to the segregation of deafness in an extended pedigree to examine features associated with the incomplete penetrance for deafness (ie, the impact of homozygosity vs heterozygosity for the mutation on phenotype.) A pedigree segregating for *White* has been generated and a candidate gene approach is used by genotyping short tandem repeat loci (STRs), tightly linked to the strong candidate genes *Pax3, Mitf, Slug, Ednrb, Edn3, Sox10,* and *Kit,* previously noted as causative of hypopigmentation and deafness in other mammalian species.[21–30]

If significant linkage is not detected to a candidate gene, a whole genome scan will be performed using the newly available cat SNP chip.[34] The identified mutation will then be characterized in this extended colony and in a population genetic survey of cats (283 of registered breed, 19 mixed breed), including pigmented individuals and 34 unrelated Dominant White individuals to examine the correlation between the characterized mutation with white coat color and/or deafness.[35]

- White cats are neither necessarily deaf nor blue-eyed.
- Examination of a large white deaf colony revealed a correlation between the likelihood that an individual will be deaf and/or blue-eyed based on their genotype (homozygous or heterozygous) at *W* inferred from designed breeding studies.[36] This correlation does not mean that the relationship is causal.

A potential explanation to the reduced penetrance at the feline *W* locus has been suggested. Melanocytes can be subdivided into cutaneous and noncutaneous lineages that respond differently to KIT signaling during development.[37] Cutaneous or "classical" murine melanocytes that "color" skin and hair are highly sensitive to KIT signaling, whereas melanocytes that populate the internal ear and portions of the eye (iris and choroid) are more effectively stimulated by endothelin 3 (EDN3) or hepatocyte growth factor (HGF).[37]

KIT has recently been implicated in 2 hypopigmentation phenotypes in the cat: White Spotting (*S*), in which significant linkage has been reported to *KIT*,[38] and the glove gene.[39] The perceived lack of penetrance at *W* for deafness could be explained if *KIT* is identified as the feline *White* locus.[37] In individuals heterozygous for the mutation, some melanocytes could survive migration to the internal ear and iris, as they are less sensitive to a decrease in KIT signaling, as opposed to melanocytes destined to pigment hair, which are highly sensitive to KIT signaling. The completion of linkage analysis may provide the answer to this question of penetrance.

COCHLEAR ANATOMY AND PHYSIOLOGY

Understanding mechanisms of deafness begins with a basic knowledge of the normal anatomy and physiology of the auditory pathway. Because the auditory system is complicated, with many working parts, there are innumerable potential sources and locations where problems could arise. The first part of this review highlights structural and functional features of the peripheral and central auditory system. This background provides a context with which to review the pathophysiology of hereditary and acquired deafness.

The cochlea is a spiraled bony tube housing 3 fluid-filled chambers that spiral along its length (**Fig. 3**). Highly specialized cells within the cochlea regulate the ionic composition of these chambers. One chamber is folded back at the apex to form 2 outer chambers (scala tympani and scala vestibuli) that sandwich a middle chamber (scala media). These outer chambers are confluent at the apex and contain perilymph, a filtrate of cerebrospinal fluid of similar composition to extracellular fluid (eg, high sodium, low potassium). The middle chamber contains endolymph, a high-potassium, low-sodium fluid of similar composition to intracellular fluid. The outer wall of scala media is partially lined by the stria vascularis (see **Fig. 3**). The stria is a vascularized, multilayered epithelial structure formed by 3 different cell types: marginal, intermediate, and basal cells (**Fig. 4**). A superficial layer of marginal cells borders the endolymph. Pale-staining basal cells are linked to each other, to intermediate cells, and to fibrocytes of the spiral ligament by gap junctions. This network provides cytoplasmic confluence that allows the free diffusion of K^+ toward the marginal cells. Intermediate cells are marked by the presence of melanosomes and by deep infoldings of the plasma membrane that are matched by those of the overlying marginal cells. The resulting dense, labyrinthine membrane system of narrow compartments is filled with mitochondria and surround the penetrating capillaries that course longitudinally along the epithelium. The elaborate infoldings of membrane greatly amplify the cell surface so as to transfer K^+ into marginal cells for secretion into the endolymph.[40,41]

As a result of the differences in ionic composition between the compartments, the potential difference between endolymph and perilymph is about +80 mV. This positive potential is the largest found in the body. Because the intracellular resting potential of hair cell receptors is approximately –70 mV, the potential difference across the hair cell apex is a remarkable 150 mV. This large potential difference represents a tremendous ionic force and serves as the engine driving the mechanoelectrical transduction process of the hair cell.[42] Membrane specializations that feature gap junctions allow free passage of K^+ ions through fibrocytes and basal cells and into intermediate cells. K^+ channels and pumps transfer K^+ from intermediate cells into the intrastrial fluid and then it gets concentrated in the marginal cells. K^+ is driven into the endolymph down the K^+ concentration gradient established in the marginal cells. The cycling of K^+ through the receptor cells and back into the endolymph is key to normal cochlear function.

- Gap junctions are channels that allow rapid transport of ions and small molecules between cells. In the stria vascularis, the ion is potassium (K^+).

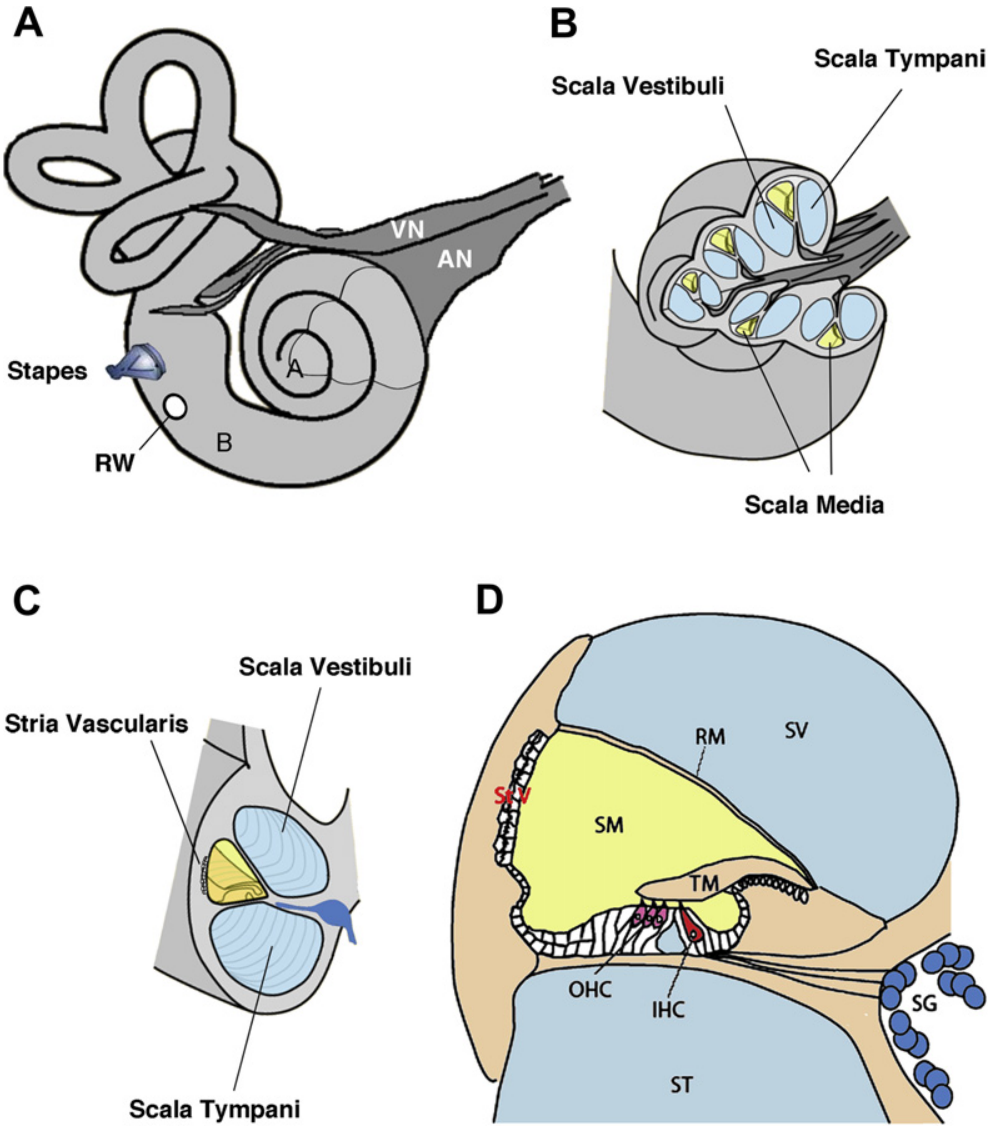

Fig. 3. Anatomy of the inner ear. (*A*) View of right hearing and balance apparatus. The cochlea is the coiled structure on the right and the semicircular canals of the vestibular system are on the left. For the cochlea, "A" indicates the apex (low frequencies) and "B" indicates the base (high frequencies). The stapes, a middle ear bone, inserts into the vestibule of the inner ear; the round window (RW) is covered by a membrane that relieves the pressure when the stapes "pistons" into the ear. The auditory (AN) and vestibular (VN) nerves bundle together to form the eighth cranial nerve. (*B*) A section of the otic capsule has been cut away (indicated in *A*) to reveal the 3 chambers of the labyrinth. The sensory organ resides in the scala media (*yellow*). (*C*) A rotated view of the cut end of a cochlear turn showing the 3 chambers, with the scala media (*yellow*) and the stria vascularis. (*D*) Enlarged diagram showing a cross-section through the scala media, emphasizing the organ of Corti and the hair cell receptors. IHC, inner hair cell; OHC, outer hair cells; RM, Reissner membrane; SG, spiral ganglion; SM, scala media; ST, scala tympani; StV, stria vascularis; SV, scala vestibuli; TM, tectorial membrane. (*Adapted from* Eisen MD, Ryugo DK. Hearing molecules: contributions from genetic deafness. Cell Mol Life Sci 2007;64(5):566–80; with permission.)

- Connexins are transmembrane proteins that form gap junction channels. Four different connexin molecules have been identified in the cochlea, including connexin 26, 30, 31, and 43.[43]
- Mutations that affect internal ear connexins result in hearing impairment and deafness.
- Mutations that affect K^+ transport result in hearing impairment and deafness.

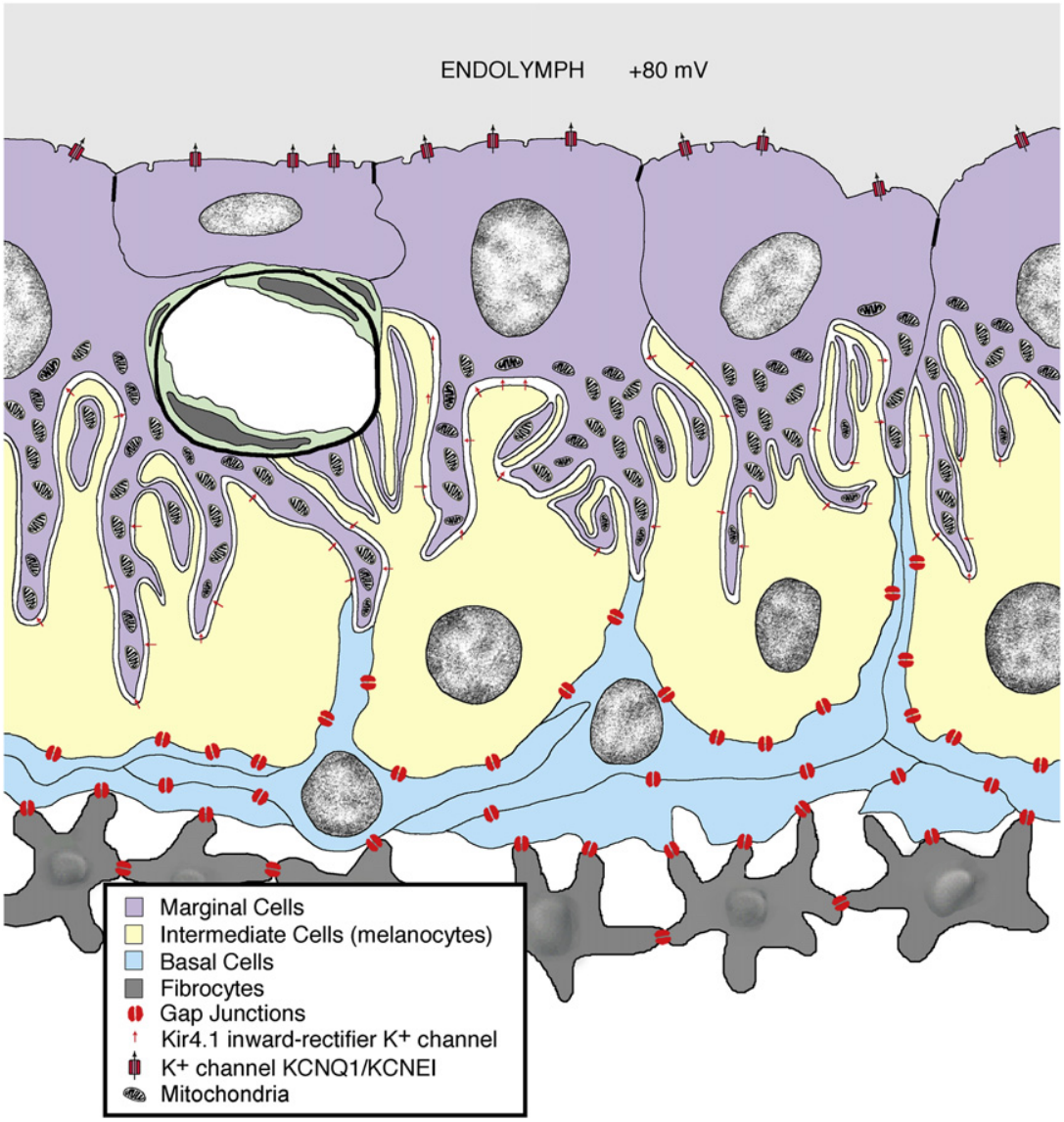

Fig. 4. Schematic drawing of the stria vascularis. Movement of K^+ ions through the gap junctions and then into the endolymph by way of ion pumps is crucial. This structure is the part of the inner ear that provides the special chemical environment that allows the system to function. (*Courtesy of* Dr David K. Ryugo, Garvan Institute of Medical Research, Sydney, Australia.)

Properties of the Cochlea

Sound vibrations are eventually delivered to the stapes, whose footplate serves as a kind of piston and imparts vibrations to the fluids of the scala vestibuli. Specializations within the cochlea decompose the mechanical stimulus of sound into its frequency components. The basilar membrane is a fibrous sheet stretched across the floor of scala media. Its width and thickness vary systematically from the base to the apex of the cochlea in that there is a continuous elasticity gradient from one end to the other. The base is narrow and thick, whereas the apex is wide and thin. This structure functions like a frequency analyzer where it resonates to high frequencies at the base and to progressively lower frequencies along toward the apex.

- The organ of Corti is the sensory organ for hearing.
- It is a multisensory structure that consists of the following:
  - Basilar membrane
  - Support cells

- Inner hair cells that are the primary sensory receptor
- Outer hair cells that modify the activity of the inner hair cells
- The tectorial membrane

The organ of Corti rests on top of the basilar membrane (**Fig. 5**). Inner hair cells synapse onto afferent endings of the myelinated cochlear nerve fibers and are primarily responsible for conveying sensory information to the brain. In contrast, outer hair cells synapse on a small number of unmyelinated cochlear nerve fibers and receive large efferent nerve endings. The outer hair cells also contain contractile machinery that responds to membrane voltage changes. The outer hair cell's function appears more involved with amplifying and manipulating the sound stimulus. Specialized supporting cells in the organ of Corti complement the hair cells and have a vital role in maintaining the integrity and function of the hair cells. A final component of the cochlea's functional apparatus is the tectorial membrane, a gelatinous ribbon of extracellular matrix attached medially and contacting the outer hair cell hair bundles.

Hair Cell Anatomy, Function, and Innervation

Hair cells are polarized in that a bundle of stereocilia protrude from one end of the cell, their apex, which are composed of actin filaments (see **Fig. 5**), whereas afferent innervation occurs only at the opposite end, the base. Interconnecting links from the tip of a shorter stereocilia to the shaft of a longer neighbor, called "tip links," attach to the mechanoelectric transduction channel.[44,45] Mechanical oscillations of the basilar

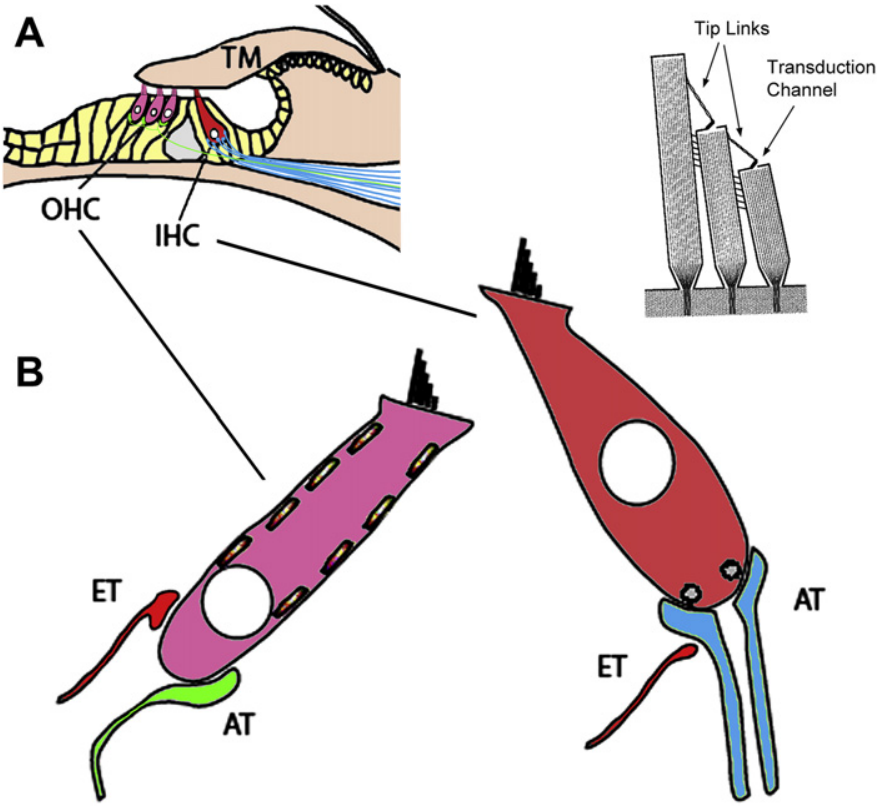

Fig. 5. Components of the organ of Corti. (*A*) The organ of Corti rests on the basilar membrane, and is composed of the sensory receptor cells (OHCs and IHCs), supporting cells (*yellow*), and the tectorial membrane (TM). (*B*) The hair cell receptors are innervated by afferent type I (*blue*) and type II (*green*) terminals, as well as by efferent (ET, *red*) terminals whose cell bodies reside in the brain stem. At the apical ends of the receptor cells are stereocilia that form part of the transduction apparatus with tip-links and channels (*upper right*). (*Adapted from* Eisen MD, Ryugo DK. Hearing molecules: contributions from genetic deafness. Cell Mol Life Sci 2007;64(5):566–80; with permission.)

membrane cause stereocilia within hair bundles to be displaced relative to each other. This displacement puts the tip links under tension and "pulls open" cation channels. Because of the high endocochlear potential, cations flow into the hair bundle and depolarize the hair cell membrane potential. Where the apical end of the cell transduces mechanical energy, the basal end releases neurotransmitter and activates afferent synapses.

The intracellular processes that respond to changes in membrane potential are distinctly different between the 2 types of auditory hair cells. Inner hair cells form afferent synapses where membrane voltage changes are converted to action potentials in myelinated cochlear nerve fibers; outer hair cells, however, contain electromotile elements within their cell membrane and generally serve as mechanical amplifiers of the sound stimuli for inner hair cells.[46]

The presynaptic machinery of inner hair cells is geared to generate graded release of neurotransmitter along their basolateral surface. Voltage-dependent Ca^{++} channels are localized with neurotransmitter release sites that open in response to membrane depolarization, which in turn results in the release of neurotransmitter. The amount of transmitter release is modulated by the magnitude of the membrane voltage change. Neurotransmitter diffuses across the synaptic cleft and binds to postsynaptic receptors on afferent dendrites of cochlear nerve fibers. This process begins the generation and propagation of action potentials along the afferent fibers.

Outer hair cells contain a contractile apparatus that responds to membrane voltage changes with contractions or elongations of the cell proper. This mechanical response appears to be conformational changes in cytoskeletal proteins of the plasma membrane wall that serve to modulate the oscillations transmitted to the inner hair cells' hair bundles. In addition to the electromotile apparatus within the outer hair cell, a system of efferent auditory feedback innervates the hair cells. Both systems work in concert to tune and amplify the sound source.[46]

The Spiral Ganglion

Spiral ganglion cells reside in Rosenthal's canal of the cochlea (**Fig. 6**). Their peripheral processes innervate the hair cell receptors, and their central processes conduct auditory information to the brain. Two types of ganglion cells have been described.[47,48]

- Type I ganglion cells are large (20–30 μm in diameter), have myelinated processes, represent 90% to 95% of the population, and innervate inner hair cells.
- Type II ganglion cells are small (15–20 μm in diameter), unmyelinated, represent the remainder of the ganglion population, and innervate exclusively outer hair cells.

Cats have approximately 50,000 ganglion cells in each ear.[49] The central axons of the spiral ganglion cells collect within the central core of the cochlea, called the modiolus, and form the cochlear nerve. The cochlear nerve joins with the vestibular nerve to form the vestibulocochlear nerve, which together, along with the facial nerve, occupies the internal acoustic meatus within the petrous portion of the temporal bone. The vestibulocochlear nerve travels toward the brainstem where the cochlear branch enters and terminates within the cochlear nucleus, whereas the vestibular branch passes beneath and around the cochlear nucleus to arch up to the vestibular nuclei.

EFFECTS OF DEAFNESS ON THE AUDITORY SYSTEM

White cats with blue eyes are undoubtedly the best-known representatives of feline deafness. Deafness in white cats has been extensively studied with a number of

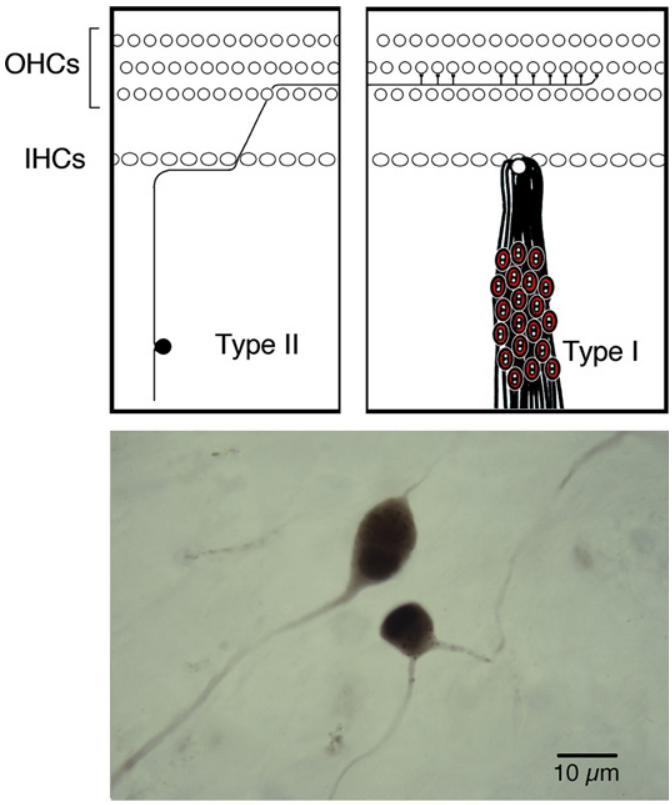

Fig. 6. Receptor innervation by ganglion cells. (*Top*) drawing that illustrates the segregated innervation of hair cells by the 2 types of spiral ganglion cells. Type II neurons represent only 5% to 10% of the population and innervate multiple outer hair cells. In contrast, type I neurons represent the remaining 90% to 95% and innervate exclusively inner hair cells. Each IHC is innervated by 10 to 20 ganglion cells. (*Bottom*) photomicrograph of representative type I and type II ganglion cells as stained by horseradish peroxidase. (*From* Kiang NY, Morest DK, Godfrey DA, et al. Stimulus coding at caudal levels of the cat's auditory nervous system. I. Response characteristics of single units. In: Moller AR, editor. Basic Mechanisms of Hearing. New York: Academic Press; 1973. p. 455–78; with permission.)

scholarly publications on the subject.[5,6,36,50] The most common cause of deafness in these cats is degeneration of the cochlea and saccule, termed cochleo-saccular degeneration (**Fig. 7**). This deafness mimics the Scheibe deformity of humans,[5,51–53] which features early postnatal onset of sensorineural hearing impairment that is transmitted in an autosomal dominant pattern with incomplete penetrance.[5,36,54–56]

- Blue-eyed white cats can have what is called cochleosaccule degeneration, causing profound deafness.
- White cats can also exhibit "spongioform" degeneration of the internal ear, also causing deafness.
- White cats are not necessarily albino cats. White cats can exhibit varying amounts of melanin, whereas albino cats have no melanin. Some white cats are deaf; albino cats are not deaf.

Deaf white cats show an absence of melanocytes,[57] whereas albinos have a normal distribution of melanocytes but lack the enzyme tyrosinase and so are incapable of producing melanin pigment.[58] Although albino cats are not deaf, they exhibit abnormal auditory evoked brainstem responses (ABR) at least when compared with pigmented cats.[59] Although ABR thresholds, peak shapes, and peak latencies can vary considerably from laboratory to laboratory,[60–62] there is a distinct loss of sensitivity in albino

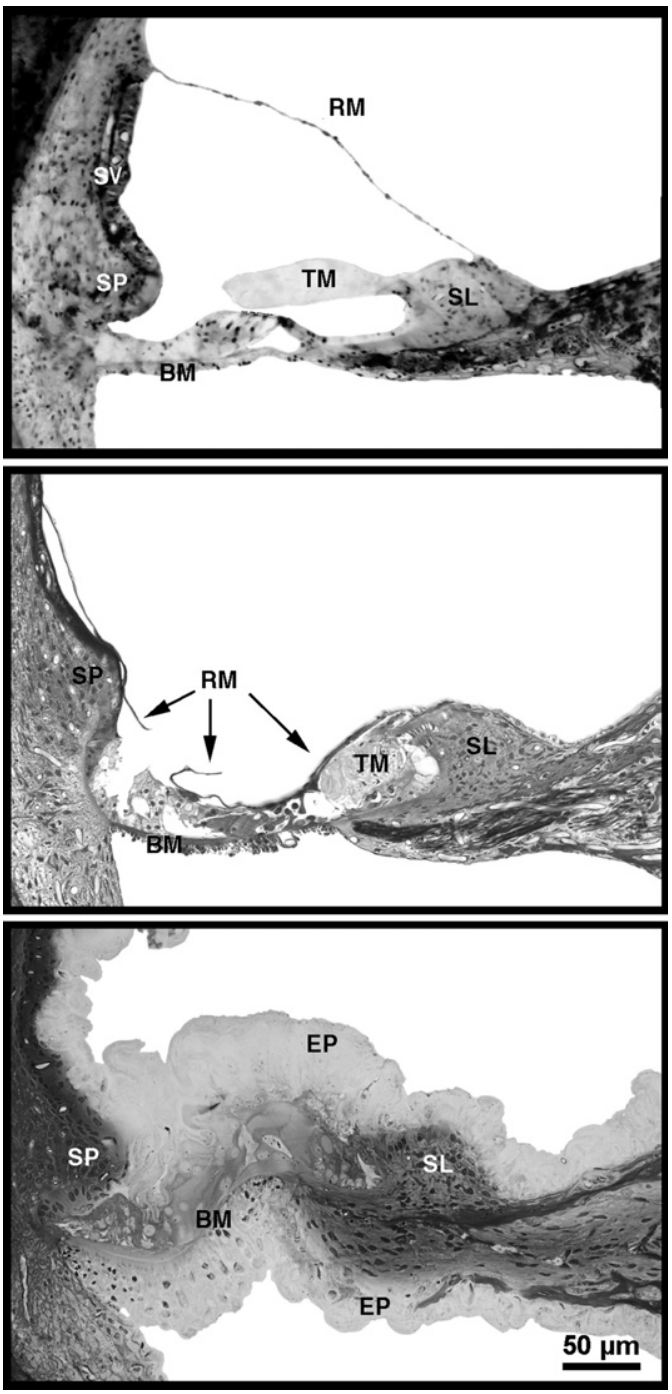

Fig. 7. Photomicrographs of organ of Corti in cats with normal hearing (*top*); cats deafened by the collapse of Reissner membrane, thinning of the stria vascularis, and obliteration of the sensory epithelium (*middle*); and cats deafened by spongioform hypertrophy that destroys the organ of Corti (*bottom*).[65] Scale bar equals 50 μm. BM, basilar membrane; EP, epithelium; RM, Reissner membrane; SL, spiral limbus; SP, spiral prominence; SV, stria vascularis; TM, tectorial membrane. (*From* Ryugo DK, Cahill HB, Rose LS, et al. Separate forms of pathology in the cochlea of congenitally deaf white cats. Hear Res 2003;181:73–84, with permission.)

cats. The underlying causes of these variations are unknown but definite atrophic changes in the auditory pathway occur as a result of pigment-related alterations of internal ear development.[63]

The appearance of the internal ear of deaf cats is strikingly different from that of hearing cats. Cats were given hearing tests when they were 30 days postnatal. At

this age, cats with normal hearing stabilize their pinna reflex, orient appropriately to sounds in space, and learn to differentiate between sounds.[64] Moreover, mesenchyme has cleared from the middle ear and the external ear canal is open to the tympanic membrane.[65] Deafness is indicated by a failure to elicit a sound-evoked brain response and is coupled to cochlear pathology. Deafness in white cats was correlated with 2 types of structural abnormalities. The more common form resembled that previously reported[5,6,66,67] in which the Reissner membrane is collapsed on the organ of Corti and the scala media is obliterated (middle panel, see **Fig. 7**). The collapse occurs during the first 10 postnatal days. The stria vascularis is present but is distinctly thinner than normal (compare top and middle panel, see **Fig. 7**). By the time the external ear canal opens (after the third postnatal week), kittens that are completely unresponsive to acoustic stimulation have no scala media on histologic examination. In older deaf cats, the organ of Corti is virtually unrecognizable.

The other form of cochlear pathology in white cats featured a proliferation of cells throughout the cochlear spiral (bottom panel, see **Fig. 7**). There was a hypertrophy of Reissner membrane such that it became highly irregular and folded, eventually filling the scala media.[65] The supporting cells of the organ of Corti and epithelial cells of the basilar membrane hypertrophied as well. The basilar membrane was buckled, the tunnel of Corti never attained its characteristic triangular shape, hair cells did not differentiate, and the stria vascularis was obscured. Overall, the tissue exhibited a "spongiform" appearance.

Spiral ganglion cells have their cell bodies in the peripheral auditory system, but extend their central terminations into the central auditory system. The survival of these ganglion neurons is dependent on the health of the organ of Corti because they undergo degeneration that is associated with hair cell loss and sensorineural deafness.[68–72] In congenitally deaf white cats, there is a gradual loss of spiral ganglion cells with age with about half the ganglion cell population surviving after a year (**Fig. 8**). Several studies have addressed the effects of intracochlear electrical stimulation on spiral ganglion cell survival following neonatal deafness because of the importance these cells play in the outcome of cochlear implants. The actual benefits of electrical stimulation are still subject of debate because of conflicting outcomes.[73–80]

TRANS-SYNAPTIC CHANGES IN THE AUDITORY PATHWAY: COCHLEAR NUCLEUS

Afferent activity is essential for the normal development and maintenance of the central auditory system in mammals. Reductions of cochlear nerve input to the brain have been produced by drugs, nerve section or cochlear ablation, and noise trauma. These measures produce dramatic changes in the structure and function of the central auditory pathway.[81–90] Are the pathologic changes attributable to the side effects of experimental manipulations, missing sensory receptors, absent cochlear nerve activity, or deafness regardless of cause? Does auditory enrichment have an opposing effect on brain structure and function as compared with auditory deprivation? To better understand the "nurture" component of brain development, we need to establish baseline features for the normal central auditory system as well as for the hearing impaired system.

Electrophysiological recordings from cochlear nerve fibers of pigmented cats with normal hearing provided standard tuning curves and thresholds.[67] These cats also exhibited normal startle and orientation responses to hand claps presented behind them. In contrast, deaf white cats exhibit no such behavioral responses, no sound-evoked spike activity, and greatly reduced spontaneous activity. The sampling of fibers was based on intracellular penetration, so we did not bias our results by

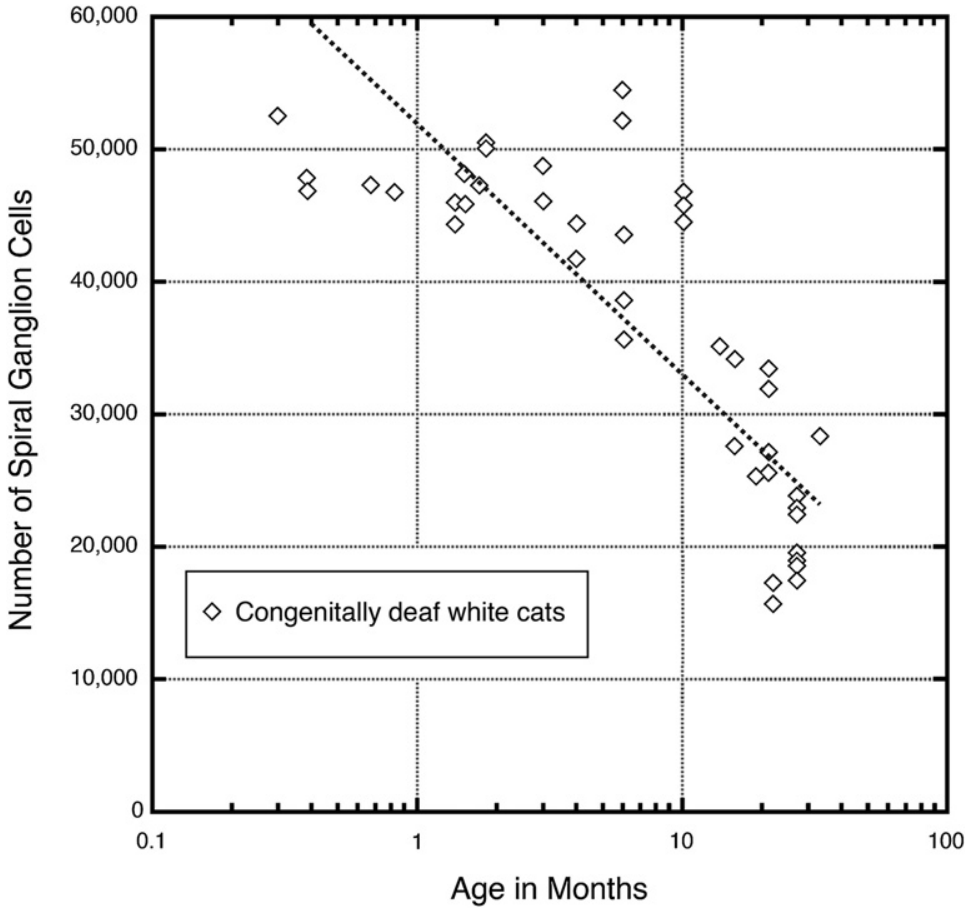

Fig. 8. Plot of spiral ganglion cell loss over time as determined for congenitally deaf white cats. (*Data from* Mair IW. Hereditary deafness in the white cat. Acta Otolaryngol Suppl 1973;314:1–48; and Chen I, Limb CJ, Ryugo DK. The effect of cochlear implant-mediated electrical stimulation on spiral ganglion cells in congenitally deaf white cats. J Assoc Res Otolaryngol 2010;11:587–603.)

searching for the presence of "extracellular" action potentials. The sudden potential drop from 0 to –40 mV indicated that the recording tip of the electrode was "inside" an individual cochlear nerve fiber,[91,92] so fibers with near zero spontaneous activity were not missed.

Activity and Structure

Roughly 60% of cochlear nerve fibers exhibit high levels of spontaneous spike discharges (40–100 spikes per second) in normal hearing cats. It is no wonder that neural activity exerts an influence on cellular morphology. Sensorineural hearing loss results in a loss of activity whose effect on target cell size in the cochlear nucleus can vary among the different cell types.[93–95] The cochlear nucleus is not a homogeneous structure. A number of different neuron populations have been described that are associated with different classes of cochlear nerve endings.[96–99] The idea has been suggested that the relationship between inputs and cell morphology defines the neuron's response to sound.[100,101] What has emerged over the years is the notion that neuron classes can be defined by shared physiologic response properties, morphologic characteristics, and synaptic inputs, and that they form different cell populations that have separate outputs to higher centers. These divergent circuits process different features of sound but converge again at a "central processor" to produce a percept of the auditory signal.

The timing and synchrony of this processing is crucial because continuity is what unifies sounds into a coherent stream. We describe one circuit involved in acoustic

"timing" to illustrate this idea. Brain changes caused by peripheral hearing loss must be mediated, at least in part, by cochlear nerve fibers and their interactions in the cochlear nucleus. Because the cochlear nucleus is the gateway to the central auditory system, any corruption of signal processing that occurs there will be felt at higher centers. The pathophysiology manifest at the cochlear nucleus will indicate where else in the auditory system defects might appear.

At the termination of the ascending branch of each cochlear nerve fiber is a prominent axosomatic terminal ending that is distinguished by its large size and complex arborization around the postsynaptic cell body (**Fig. 9**). This distinctive class of synaptic ending is called an endbulb.[99,102,103] Interestingly, in every land vertebrate examined, cochlear nerve fibers terminate in the cochlear nucleus with an endbulb.[104] The evolutionary conservation and large size emphasize its importance to auditory processing. The numerous synaptic release sites that embrace the cell body of a spherical bushy cell suggest a fail-safe transmission from nerve fiber to brain cell, exactly the relationship necessary to preserve timing in the auditory signal. Recall that the ability to localize the source of a sound depends on 2 ears: the ear closer to the source hears the sound sooner and louder than the far ear. The difference in time of arrival and loudness between the 2 ears provides the cues for sound localization. The endbulb and its postsynaptic neuron form the start of the brain circuit that encodes timing.

It had been observed that endbulb morphology was distinctly related to the spontaneous discharge rate (SR) and threshold of the cochlear nerve fiber in normal-hearing cats. Those endbulbs arising from fibers with low activity exhibit smaller but more highly complex arborizations in comparison with those fibers of high activity.[105] This activity-related difference in endbulb morphology is subtle and required fractal analysis to provide conclusive evidence of this variation. In the cats with hearing loss, analysis revealed endbulb size and branching complexity to be correlated with hearing sensitivity and fiber activity (**Fig. 10**).

Endbulb Synapses

Differences in endbulb branching complexity were observed as a reflection of hearing status. Endbulb synapses were then examined with the aid of an electron microscope because synapses represent the crucial functional unit. Cochlear nerve synapses from normal-hearing cats have been well described,[106,107] so they will be only briefly

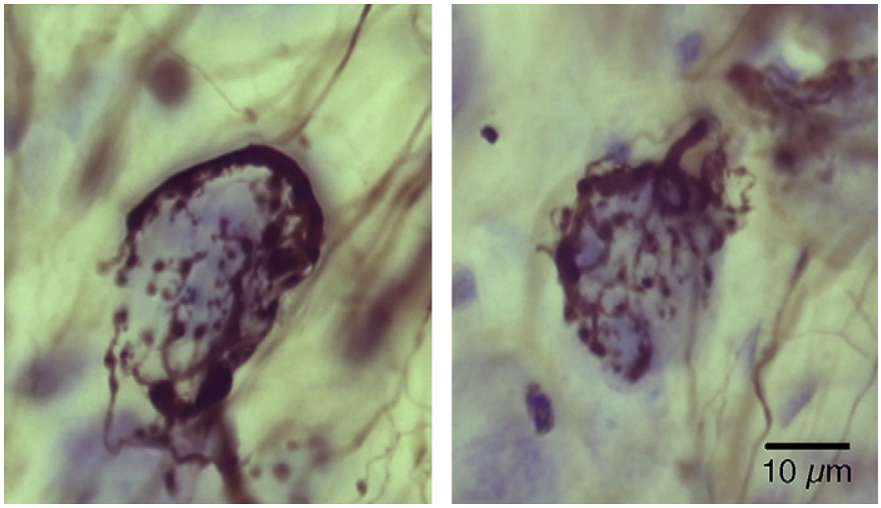

Fig. 9. Photomicrographs of typical endbulbs stained by horseradish peroxidase in the cochlear nucleus of the cat. Note their large size and elaborate branching pattern. A cell body is nestled within the grasp of the endbulb arborization. (*Courtesy of* Dr David K. Ryugo, Garvan Institute of Medical Research, Sydney, Australia.)

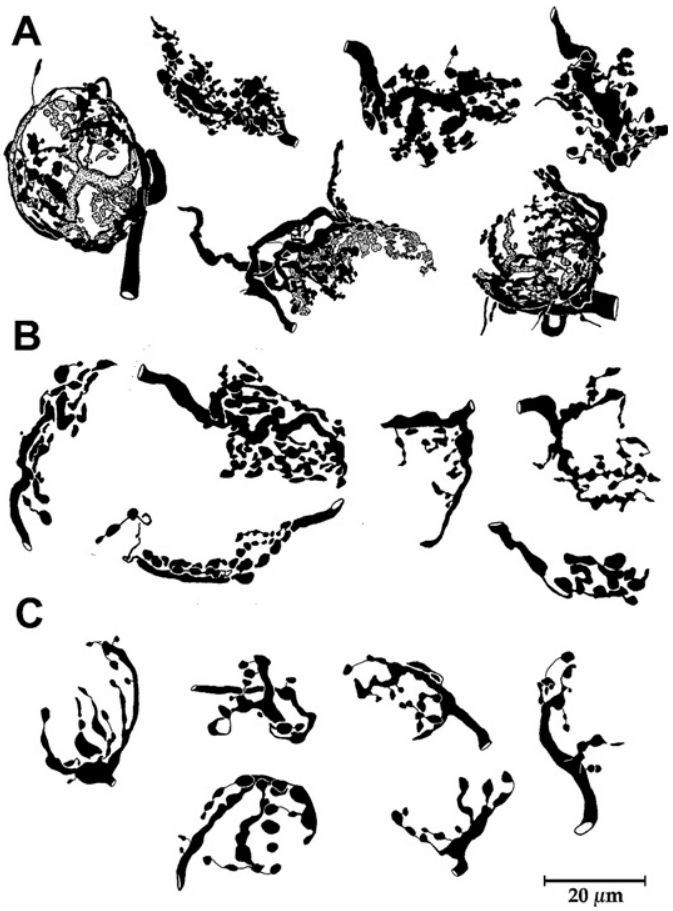

Fig. 10. Camera lucida drawings of endbulbs from normal-hearing cat (*A*), white cat with 50 dB hearing loss (*B*), and congenitally deaf white cat (*C*). Note that the complexity of the shape of endbulbs diminishes with hearing loss. (*From* Ryugo DK, Rosenbaum BT, Kim PJ, et al. Single unit recordings in the auditory nerve of congenitally deaf white cats: morphologic correlates in the cochlea and cochlear nucleus. J Comp Neurol 1998;397:532–48; with permission.)

mentioned for comparison purposes with those of the white cats. Transmitter release sites form around discrete postsynaptic densities, where the postsynaptic membrane bulges into the presynaptic endbulb to form a dome (**Fig. 11**). Clear, round synaptic vesicles are scattered throughout the endbulb cytoplasm but are concentrated around the release sites. A normal endbulb may have up to 2000 individual presynaptic release sites,[108] which oppose round-to-oval membrane thickenings called the postsynaptic density (PSD). These membrane specializations contain transmitter receptors and are distributed relatively uniformly beneath the overlying endbulb.

In contrast, synapses from totally deaf white cats appear distinctly different. Presynaptic vesicle density is distinctly increased and postsynaptic densities are thicker and considerably expanded (**Fig. 12**). Reconstructing the postsynaptic membrane, which lays beneath the presynaptic endbulb, demonstrated PSD hypertrophy by its expansion over the surface of the neuron. Synapses of partially deaf cats (eg, those with elevated thresholds), however, seemed to represent a transition between normal and deaf synapses.[67]

TRANS-SYNAPTIC CHANGES IN THE AUDITORY PATHWAY: SUPERIOR OLIVARY COMPLEX

The medial superior olive (MSO) is the first site in the central auditory pathway where convergence of neural information from the 2 ears occurs (**Fig. 13**). The convergence arises from the cochlear nucleus neurons that are the recipients of endbulb synapses.

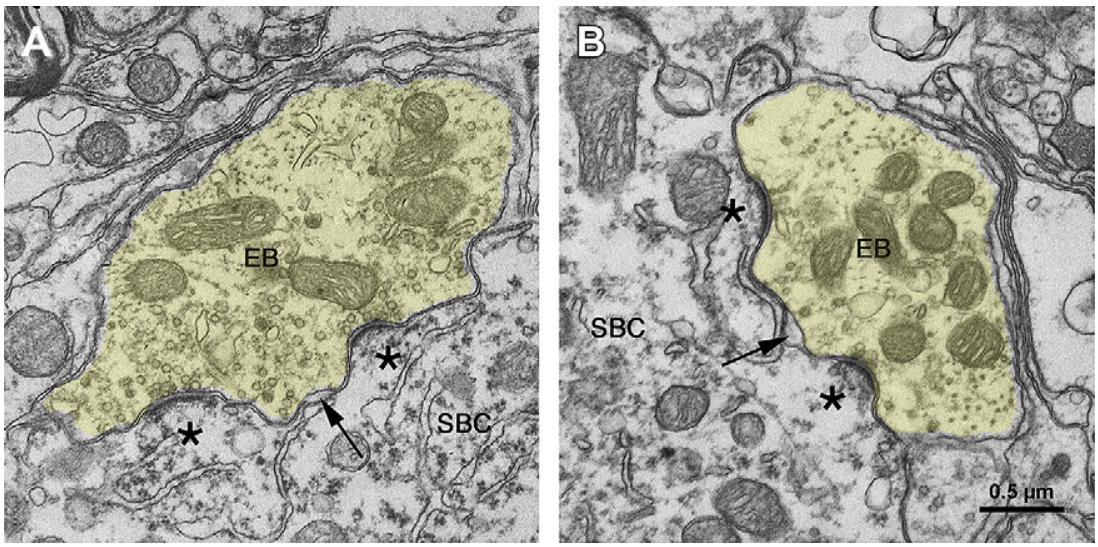

Fig. 11. Electron micrographs through synapses of endbulbs (EB) from cats with normal hearing.[134] The endbulb (*yellow*) forms synapses opposite dome-shaped postsynaptic densities (*asterisk*) and round synaptic vesicles accumulate along the presynaptic membrane. Cisternae (*arrow*) form between the membrane of the endbulb and that of the postsynaptic spherical bushy cell (SBC); these intermembraneous channels may serve as "gutters" to facilitate transmitter diffusion away from the synapse. Scale bar equals 0.5 μm. (*From* O'Neil JN, Limb CJ, Baker CA, et al. Bilateral effects of unilateral cochlear implantation in congenitally deaf cats. J Comp Neurol 2010;518:2382–404, with permission.)

The principal neurons of the MSO are aligned in a vertical sheet with its diametrically opposed bipolar dendrites facing medially and laterally.[109] Excitatory inputs are segregated such that ipsilateral input innervates lateral dendrites in the ipsilateral MSO and medial dendrites of the contralateral MSO.[110,111] These neurons have a proposed function as a "coincidence detector" for processing interaural timing differences (ITD).[112] In addition, inhibitory inputs to the MSO arise from the medial (MNTB) and lateral

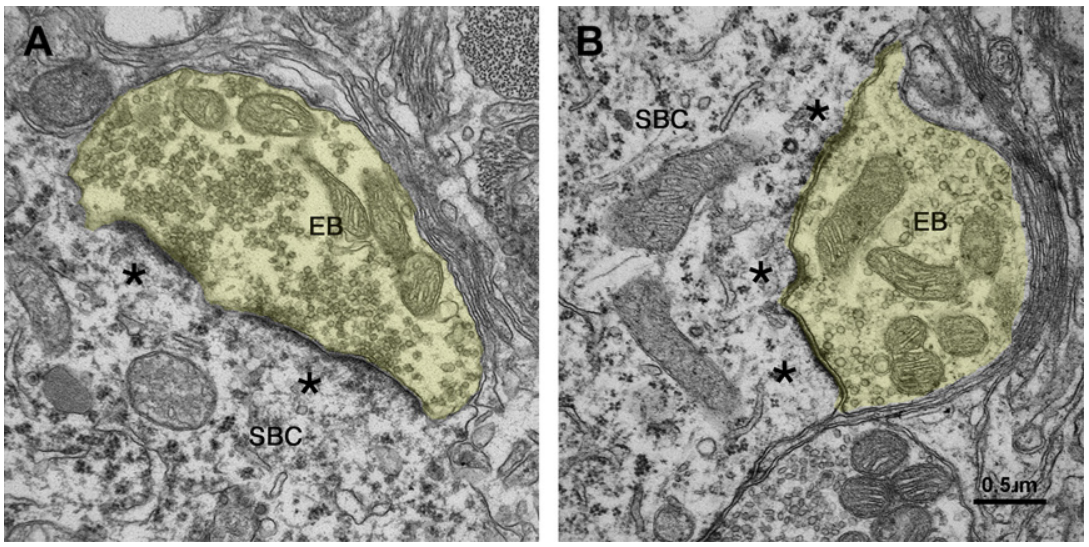

Fig. 12. Electron micrographs through synapses of endbulbs (EB) of congenitally deaf cats.[135] The postsynaptic densities of these synapses have hypertrophied (*asterisk*) and become more flattened. Synaptic vesicles have proliferated in the endbulb (*yellow*) cytoplasm and intermembraneous channels have disappeared. The scale bar equals 0.5 μm. (*From* O'Neil JN, Limb CJ, Baker CA, et al. Bilateral effects of unilateral cochlear implantation in congenitally deaf cats. J Comp Neurol 2010;518:2382–404, with permission.)

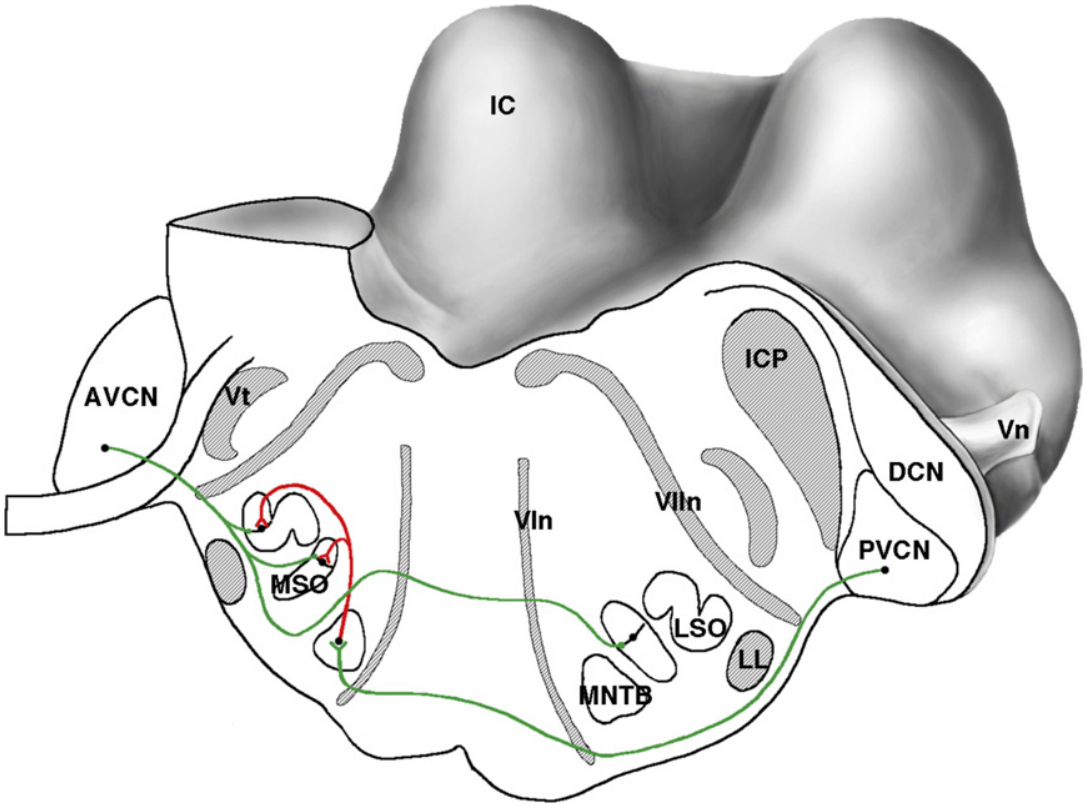

Fig. 13. Caudal-lateral view of the cat brain stem where the cut surface passes through the superior olivary complex. The cut is angled so that it also passes through different parts of the cochlear nucleus on the left and right. The excitatory path from the spherical bushy cells of the left anteroventral cochlear nucleus (AVCN) initiates processing of interaural timing differences in the medial superior olive (MSO) and interaural level differences in the lateral superior olive (LSO). The excitatory path from globular bushy cells of the right posteroventral cochlear nucleus (PVCN) initiates the processing of interaural level differences, and its target is the medial nucleus of the trapezoid body (MNTB). The output of the MNTB is inhibitory (*red*) and it terminates in the MSO and LSO. AVCN, anteroventral cochlear nucleus; DCN, dorsal cochlear nucleus; IC, inferior colliculus; ICP, inferior cerebellar peduncle; LL, lateral lemniscus; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; VIn, abducens (sixth) nerve root; VIIn, facial (seventh) nerve root; Vn, trigeminal (fifth) cranial nerve; Vt, spinal trigeminal tract. (*Courtesy of* Catherine Connelly, Garvan Institute of Medical Research, Sydney, Australia.)

nucleus of the trapezoid body (LNTB), are confined to the cell bodies of MSO neurons, and function to adjust the output signal of MSO neurons to higher centers.[113,114]

Congenital deafness causes a bilateral disruption in the spatially segregated inputs to the MSO principal neurons such that inhibitory input at the cell body is significantly reduced compared with what is observed in hearing animals.[90,111] This change in axosomatic inhibition was manifest by a loss of staining for gephyrin, an anchoring protein for the glycine receptor,[111] and the migration of terminals containing flattened and pleomorphic synaptic vesicles (indicative of inhibitory synapses) away from the cell body.[90] Excitatory inputs to the dendrites were severely shrunken[90] and the dendrites themselves atrophied.[115]

TRANS-SYNAPTIC CHANGES IN THE AUDITORY PATHWAY: INFERIOR COLLICULUS

The inferior colliculus (IC) is a complex, tonotopically organized nucleus of the midbrain receiving auditory inputs from many ascending brainstem sources including

both cochlear nuclei, superior olivary complex, and nuclei of the lateral lemniscus, as well as descending inputs from the auditory cortex and superior colliculus.[116–118] It is a large bilateral nucleus. A rudimentary tonotopic organization within the IC has been shown to exist in long-term deafened animals.[119,120] This organization is evident even in congenitally deaf animals, implying that a blueprint for connections is in place and can develop even without the benefit of hearing.[121]

Acute deafness did not increase temporal dispersion in spike timing to trains of electric pulse stimulation in the cochlear nerve nor impair ITD sensitivity.[122,123] Congenital deafness, however, did reduce ITD sensitivity in the responses of IC units. Single-cell recordings in the IC showed that half as many neurons in the congenitally deaf cat showed ITD sensitivity to electrical stimulation when compared with the acutely deafened animals. In neurons that showed ITD tuning, they were found to be broad and variable.[124] The synaptic changes that disrupt the electrophysiological response properties are a reflection of neuronal response profiles that arise from lower structures in the pathway.[125–128] Collectively, the data imply that ITD discrimination is a highly demanding process and that even with near perfect synapse restoration, the task is sufficiently difficult that perhaps only complete restoration of synapses will enable the full return of function.

TRANS-SYNAPTIC CHANGES IN THE AUDITORY PATHWAY: AUDITORY CORTEX

The end point of stimulus coding along the auditory pathway presumably occurs in the auditory areas of the cerebral cortex. Acoustic features, such as distance, location,

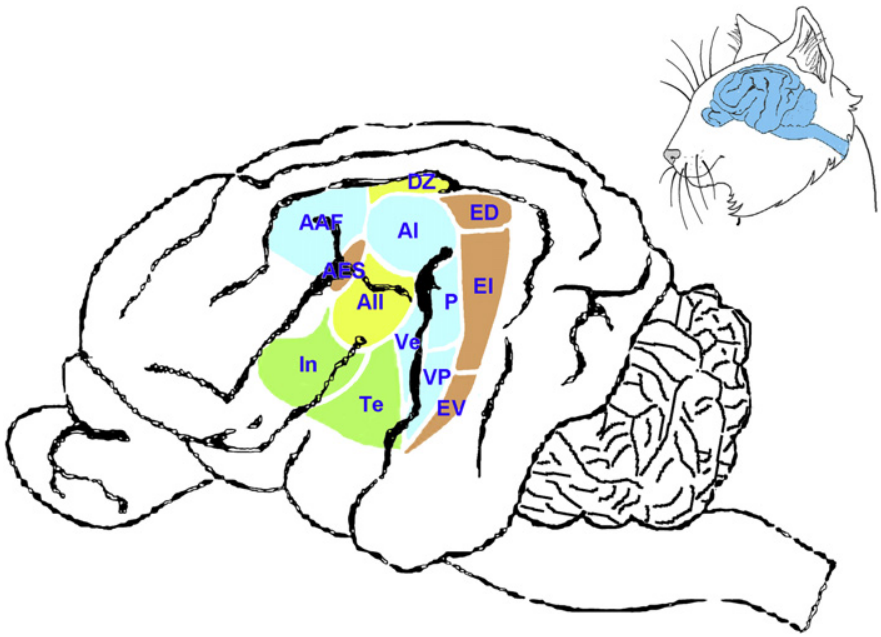

Fig. 14. Side view of cat brain. The inset (*upper right*) illustrates the position of the brain relative to the head. The gyral patterns of the cortex are fairly reproducible across individual cats but they are not identical; thus, they are not reliable markers for cortical function. The many auditory areas reflect the complex processing involved in creating sound awareness. AAF, anterior auditory field; AES, anterior ectosylvian sulcus area; AI, primary auditory cortex; AII, secondary auditory cortex; DZ, dorsal auditory zone; ED, posterior ectosylvian gyrus; EI, posterior ectosylvian gyrus, intermediate part; EV, posterior ectosylvian gyrus, ventral part; in, insular cortex; P, auditory cortex, posterior area; Te, temporal cortex; Ve, auditory cortex, ventral area; VP, auditory cortex, ventral posterior area. (*Courtesy of* David K. Ryugo, Garvan Institute of Medical Research, Sydney, Australia; *data from* Winer JA, Lee CC. The distributed auditory cortex. Hear Res 2007;229:3–13.)

pitch, motion, and significance, are carried by the auditory stream and become unified into a single percept. This unity is coordinated by a system of multiple auditory areas that are fed by the parallel sets of ascending pathways. Hierarchically processed acoustic events are distributed across the different cortical areas and assembled for cognitive interpretation (**Fig. 14**). The number and complexity of cortical areas is testament to the computational demands on hearing.[129] Not surprisingly, congenital deafness leads to functional and morphologic abnormalities along the auditory pathway, including auditory cortex.[130,131] The repair of these defects, fortunately, can be achieved through the timely restoration of normal activity in the auditory system.[132–134]

SUMMARY

In summary, hearing is a vital sense in the everyday life of cats. It enables them to be constantly aware of their environment, especially when vision is insufficient. Hearing loss represents a huge disadvantage to them, and there are many possible sources of this disability. Deafness can be a result of genetic mutation, disease, industrial noise, ototoxic chemicals, or trauma. Any of these sources could cause abnormalities in sensory transduction in the ear that lead to brain pathology in structure, chemistry, synaptic transmission, or perceptual dysfunction owing to fouled circuits. Regardless of the cause, sensorineural deafness produces change in many parts of the nervous system that in general, cannot be treated, but contribute to the pathology.

GLOSSARY

ABR: ABR is the acronym for a sound-evoked auditory brainstem response. It is a noninvasive means of assessing auditory responses of the brain as recorded from the scalp. Because of the relatively large distance from recording site to brain, the response must be averaged over 500 to 1000 stimulus presentations.

Action potential, membrane potential: Action potential refers to a rapid change in electrical potential that is measured between the inside and outside of a nerve or muscle cell when stimulated. It is the common unit of communication between nerve cells.

Afferent: Afferent is a term used to describe individual neurons, systems of neurons, or parts of neurons that convey information toward another neuron or into the central nervous system.

Arborization: Arborization is a term used to describe a “treelike” appearance of certain neuron outgrowths, either an axon or its termination or the shape of dendritic branching.

Autosomal dominant locus: Autosome refers to any chromosome that is not a sex-determining chromosome (eg, not X and not Y). Two copies of every gene are located on a chromosome and tend to work together; when one gene overpowers the other, it is said to be dominant. The locus refers to the gene’s specific location on an identified chromosome.

Axosomatic: Axosomatic refers to the relationship between an incoming synaptic terminal and the postsynaptic target, where “axo” refers to the incoming presynaptic structure and “somatic” indicates the postsynaptic cell body or soma. In this case, the axon terminal forms a synapse on the cell body of the target neuron. Axodendritic describes the case in which an incoming axon terminal synapses on the dendrite. And so on.

Candidate gene approach: The candidate gene approach focuses on associations between genetic variation within specified genes of interest and phenotypic expression of disease state or trait.

Central auditory system: The central auditory system is that part of the hearing system that resides within the brain. It is composed of many neuronal structures that are linked together by axonal pathways to form an integrated system. Its normal function is to convert the physical attributes of sound into conscious perceptions of auditory meaning.

Cochleosaccule dysplasia: Cochleosaccule dysplasia is pathology of the saccule (vestibular sensory organ) and cochlea (hearing organ). The dysplasia is characterized by a collapse of the saccular membrane and Reissner membrane, respectively, onto the sensory epithelium.

Efferent: Efferent is the term used to describe individual neurons, systems of neurons, or parts of neurons that convey information away from its origin, as away from the cell body or away from the central nervous system.

Endolymph, endolymphatic space, endocochlear potential: Endolymph is the specialized fluid of the inner ear that bathes the organ of Corti. It is contained within the endolymphatic space, which is equivalent to the cochlear duct. Its special high potassium content endows it with a positive potential (approximately +80 mV) relative to ground; the potential is called the endocochlear potential.

Gap junctions: Gap junctions are membrane specializations between 2 cells that allow electrical coupling and the passage of ions and small molecules. These specializations underlie electrical synapses.

Gloving: The gloving gene is implicated in the white feet of pigmented cats.

Interaural time disparity: Interaural time disparity refers to the circumstance in which a sound located away from the listener's midline arrives at the closer ear before it arrives at the farther ear. The difference in time of arrival is computed by the brain to inform the organism where along the horizontal plane, with respect to the head, the sound originated.

KIT: Kit is a gene that is involved in the production of melanocytes, blood cells, mast cells, and stem cells. Mutations of this gene are known to cause white coat color.

Knockouts: Knockouts or gene knockouts refer to a genetically engineered mouse in which a gene has been inactivated or deleted ("knocked out").

Linkage: Linkage is the tendency of genes that are located near each other on a chromosome to be inherited together. The probability of such an occurrence is calculated by testing if the 2 loci are linked compared with observing the same traits purely by chance.

Melanocytes: Melanocytes are neural-crest–derived, melanin-producing cells found mainly in the epidermis but also in eyes, ears, and meninges.

Mesenchyme: Mesenchyme refers to cells of mesodermal origin that are capable of developing into connective tissue, blood, or endothelial tissue.

Myelinated: Myelin is an insulating sheath around individual axons formed by the tight wrapping of cell membrane of oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system.

Peripheral auditory system: The peripheral auditory system is that part of the hearing apparatus that resides in the cochlea (or inner ear).

Pitch: Pitch is related to the frequency of sound vibrations and is an attribute of auditory sensation whereby sounds may be ordered from low to high.

Pleiotropic effects: Pleiotropic refers to having multiple effects from a single gene.

Pleomorphic synaptic vesicles: Pleomorphic synaptic vesicles is the term used to describe the circumstance in which synaptic vesicles in aldehyde-preserved tissue, when examined with an electron microscope, exhibit a variety of shapes from round to oval to flattened. This variety of vesicle shapes is inferred to indicate inhibitory action at the associated synapse.

Potential difference: Potential difference refers to the voltage difference between 2 points. In the case of endolymph and perilymph, it reflects the differential distribution of Na+, K+, and Cl– within 2 closed compartments.

Receptor cell: Receptor cells are specialized to convert energy in the form of light, chemical, or mechanical into neural signals.

Spongiform: Spongiform is an adjective used to describe the spongelike appearance of a pathologic overgrowth of cells in the cochlea.

Spontaneous discharge rate: Spontaneous discharge rate refers to the situation in which a neuron gives rise to action potentials in the absence of experimenter-delivered stimulation.

Stereocilia: Stereocilia are specialized microvilli that form on the top surface of auditory and vestibular sensory receptor cells. Deformation of the stereocilia in one direction opens ion channels, whereas deformation in the opposite direction closes them.

Synapse: The synapse is a structure at the point of communication between 2 neurons where chemical or electrical signals can be passed.

Syndromic deafness, nonsyndromic deafness: Syndromic deafness refers to hearing loss that is associated with other distinctive medical conditions; nonsyndromic deafness occurs by itself.

Tonotopic: Tonotopic is a term used to describe the systematic organization of frequency across an auditory structure, where there is a progression of frequency representation from low to high.

W: The primary gene responsible for white color. It is dominant over other colors, so white cats can be either Ww or WW. Cats that are ww express pigmentation patterns determined by other genes.

Waardenburg syndrome: Waardenburg syndrome is a group of inherited conditions passed down through families that involve deafness and pale skin, hair, and eye color.

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