Possible Neurochemical and Neuroanatomical Bases of Age-Related Hearing Loss—Presbycusis

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ABSTRACT

Broadly speaking, age-related hearing loss is a consequence of degenerative changes in the ear or brain. Sensitivity changes in the cochlea result from the loss of sensory (hair) cells, degeneration of auditory nerve fibers (eighth cranial nerve), or reductions in the endocochlear potential resulting from atrophy of the stria vascularis and its biochemical processes normally responsible for production of endolymph. These peripheral problems residing in the inner ear are the primary causes for declines in hearing sensitivity, as reflected in the presbycusic audiogram. The other main presenting symptom for elderly listeners is an inability to perceive speech or music in the presence of background noise. This significant handicap of our aged population, in fact the number one communication deficit of our senior generation, is due not only to losses of peripheral sensitivity to sound but also to age-related neural degeneration of the central auditory system. This article gives summary highlights of recent research on uncovering the neural bases of inner ear disorders and pathologies of the central auditory system that accompany normal aging. Implications for how audiologists and otolaryngologists may improve clinical diagnoses and offer novel future treatments are pointed out.

KEYWORDS: Calcium-binding proteins, background noise, speech coding, temporal processing, auditory perception

Learning Outcomes: As a result of this activity, the reader will be able to describe new developments in neurochemical and neuroanatomical influences on hearing in older adults.

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Research of the past two decades has provided much new knowledge concerning the possible neural underpinnings of age-related sensory declines, including presbycusis. Much of this progress has come from interdisciplinary research teams, capitalizing on methodologies from hearing science and neuroscience. In this article, a general summary of what is known about the neural bases of age-related hearing loss will be given. Of necessity this will be very brief. The rest of this presentation will focus on a series of recent investigations by our Rochester team of auditory scientists and clinical researchers. This portion of the presentation will focus on the benefits of conducting parallel experimental thrusts involving human and animal model investigations. In addition, relations between speech recognition and auditory temporal processing will be emphasized, along with neuroanatomical and neurochemical experiments in animal preparations that are linked to the perceptual deficits of the human condition. One powerful aspect of this approach will be clear: progress is accelerated when repeated measures of humans and animals are carried out using different research disciplines conducting tests of the same subjects in succession.

CONCEPTUAL FRAMEWORK

When approaching the problem of understanding what biological changes take place to cause age-related sensory disorders, it is beneficial to consider at what points in the system specific deteriorations can occur. For example, in the auditory system, the effects of age can directly affect the ear or the brain (Fig. 1).[1] Influences on the ear include age-related problems of the outer, middle, or inner ears. Otolaryngologists, neuro-otologists, and facial plastic surgeons can surgically correct many problems of the outer and middle ears. Therefore, in the present article, only age-related disorders of the inner ear—the cochlea—will be treated.

Neurodegenerative changes in the brain can occur at different points in the central auditory system.[2] Because of accessibility considerations regarding surgical approaches and topography, most is known about age-related problems of the cochlear nucleus and the auditory midbrain (inferior colliculus). To complicate matters, the adult brain has an adaptive capability that was not recognized previously. Available evidence suggests that the adult mammalian brain cannot add or replace nerve cells (neurons) to compensate for those that have degenerated or died as the adult ages. However, overwhelming evidence suggests that neurons in the adult mammalian brain can rewire themselves adaptively to respond to or compensate for changing inputs. For example, in cases of hearing loss, human neuroimaging studies have shown that areas of the brain that lack input because of a high-frequency hearing loss become reinnervated by brain pathways subserving lower frequency sound information, as exemplified in human neuroimaging studies by Lockwood and colleagues.[3,4] Anatomic and chemical changes in the central auditory system that result from losses of inputs from the cochlea can be referred to as peripherally induced central changes, as displayed in Figure 1.[1]

Willott and coworkers[5] have conducted a noteworthy series of animal-model investigations demonstrating some of the central changes that result from age-related loss of high-frequency information from the cochlea. To accomplish this they use the C57 mouse strain, a strain that develops a rapid, age-related hearing loss because of declines in hair cells and auditory nerve fibers in the basal portions of the cochlea. C57 mice have a severe-to-profound high-frequency hearing loss by 6 to 8 months of age. In such studies, Willott and coworkers have observed declines in neuron numbers and regional volumes in the cochlear nucleus, which is the main target zone of the auditory division of the eighth cranial nerve.[6–9] In neurophysiological investigations of the responses of single nerve cells, they have found that portions of the auditory midbrain responsive to high-frequency sounds in young adult animals shift their sensitivity to middle and low frequencies in older C57.[5] The anatomic pathways between the cochlear nucleus and the inferior colliculus remain constant with age in these animals, suggesting some

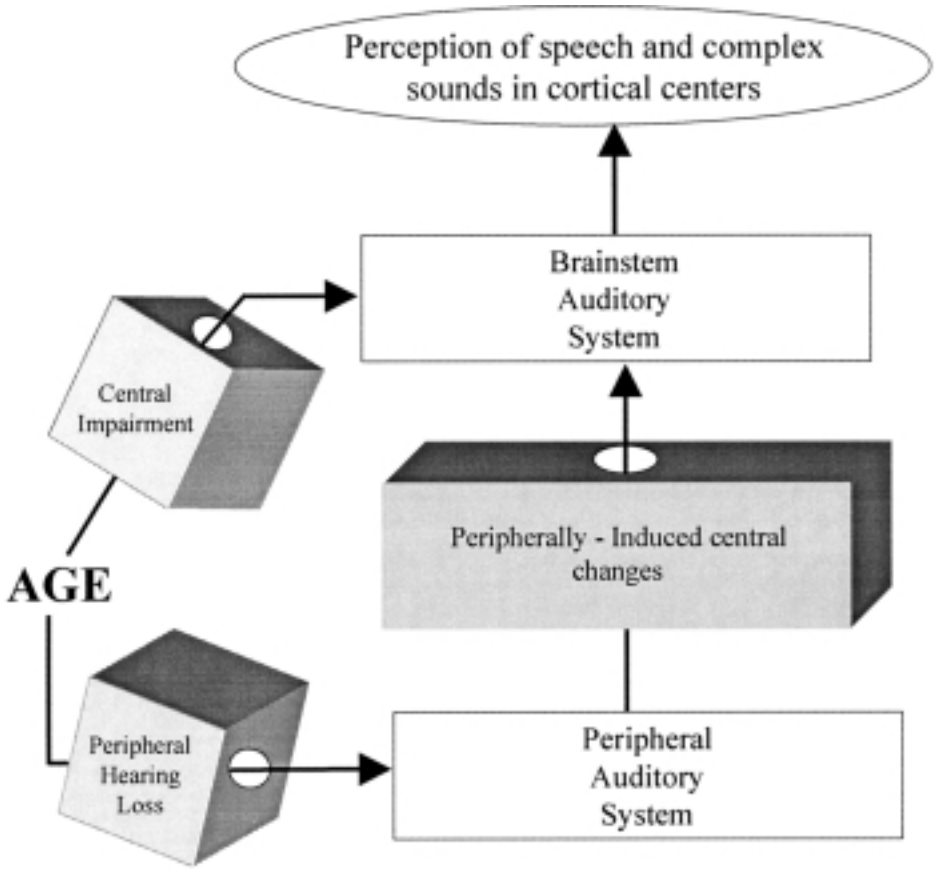

Figure 1 Aging can affect the auditory system at several levels. Age can directly affect the ear, including loss of sensory hair cells, auditory nerve fibers, and biochemical degradations affecting cochlear physiology such as degradations of the endocochlear potential necessary for proper transduction of sound into the code of the nervous system. Age also can directly impair brain functioning. This can occur in the auditory brainstem, which analyzes incoming sound information to prepare it for input to the auditory and language cortical areas where sound perception takes place. Age-related neural degeneration can take place at cortical and cognitive levels as well. Changes in the outputs of the inner ear as a function of age can induce plastic changes in the auditory brainstem and cortex that we refer to as peripherally induced central changes. These can overlap or comingle with the direct effects of aging on the central auditory system. Figure reproduced from Frisina et al,[1] with permission.

age-related hearing-loss induced rewiring at the level of the cochlear nucleus.[10] McFadden and Willott also have shown that the abilities of single neurons to encode sound location information at the level of the inferior colliculus is impaired because of age-related hearing loss.[11,12]

Experiments from other investigative teams built on the studies by Willott and coworkers using the C57 strain. For instance, Kazee and coworkers[13] and Sponger and coworkers[14] demonstrated that the number and size of synapses on principal neurons of the auditory midbrain are reduced in C57 mice, but Kazee and West demonstrated that this did not occur in CBA mice of comparable old age.[15] In an immunocytochemical investigation, O'Neill and colleagues[16] discovered that calbindin immunoreactivity in the C57 medial nucleus of the trapezoid body (MNTB) showed a statistically significant decline with age, whereas no reduction was seen in the CBA strain. The C57 decline exceeded that which could be accounted for by general neuron loss

with age in the MNTB. Calbindin is a calcium-binding protein that participates in the regulation of intracellular calcium in some nerve cells. A decline with age may indicate a decreased ability of a nerve cell to regulate calcium concentration, resulting in sickness or death of the nerve cell.

For the remainder of this article, our focus will be on the direct effects of age on the cochlea and on portions of the central auditory system and how these changes relate to the two most salient perceptual features of the elderly hearing-impaired listener: loss of sensitivity to sound and the inability to understand speech in background noise.

INNER EAR PATHOLOGIES

There are actually several cochlear pathologies that contribute to age-related hearing problems, several of which were categorized by Schuknecht in his pioneering work.[17–19] Loss of inner and outer hair cells starting in the basal turn of the cochlea can play a role, although correlations between hair cell loss and elevations in hearing sensitivity are often weak. Loss of outer hair cells generally occurs first in age-related hearing loss and in drug-, fever- and environmentally induced hearing impairment. Outer hair cells play a crucial role in amplifying sounds so as to give the normal adult auditory system its exquisite sensitivity. Outer hair cells, of which there are generally three rows in humans, also contribute to cochlear nonlinearities, some of which are under efferent control via central auditory feedback circuits. Many of these cochlear nonlinearities and efferent system functions play roles in reduction of responses of the auditory system to background noise. Inner hair cells compose the beginnings of the neural channels through which specific sound information is broken down into frequency bands (cochlear frequency analysis) and then carried to the brain in an organized manner. The inner hair cells survive longer in an age-related sense than do outer hair cells. Yet, in very old mammals, including homo sapiens, inner hair cell losses in both the cochlear base and the apex can become significant.

A better predictor of age-dependent frequency-specific hearing deficits is the loss of spiral ganglion cells (neural cell bodies of the auditory nerve). Hearing scientists have found that these neuronal age-related declines are more closely related to physiological measures of cochlear output, such as the compound action potential recorded near the round window, than are hair cell losses. Another significant cause of age-related sensitivity reductions of the cochlea is deterioration of the endolymphatic potential, which originates in the blood vessel-rich organ on the outer wall of the cochlear duct known as the stria vascularis. The gerbil animal model used by Schmiedt,[20,21] Schulte and Adams,[22] and Schulte and Schmiedt[23] has shown that the stria vascularis, and its enzymatic system for producing endolymph, degenerate with age. This degeneration occurs even in animals that have been raised in quiet environments and is tightly correlated to elevations in auditory nerve fiber thresholds.[24] Degenerative changes in the stria vascularis of old gerbils, particularly in the cochlear base and apex, resemble those that have been reported for the base and apex of the old human cochlea.[25]

SPEECH PROCESSING DECLINES AND AUDITORY BRAINSTEM DEFICITS

A series of interrelated experiments by the Rochester auditory research group sheds light on how anatomic and chemical deficits of the brainstem may underlie perceptual problems associated with human presbycusis. Some provocative initial studies suggested that some speech perception problems of the elderly human may relate to an age-related temporal processing deficit. In fact, a generalized neural slowing, manifesting itself as increases in reaction times and reduced sensory processing in general, may exist in elderly listeners.[26,27] To shed new light on this hypothesis, Frisina and Frisina[28] tested groups of young and old adult human listeners on a variety of speech recognition tasks in quiet and background noise. Old subjects were classified into different hearing

loss groups based on traditional audiometric criteria, including a group of old subjects who did not differ significantly from young adults in their hearing abilities in quiet for pure tones (up to 6 kHz) and speech. A main finding of this investigation was that despite audiometric sensitivity equivalence, the old normal hearing subjects (the golden ears) still had significantly worse speech recognition problems in background noise relative to their younger counterparts. Another noteworthy finding was that old subjects of all degrees of presbycusic hearing loss were more effective at using semantic context than were young subjects. This was determined in part by comparing relative benefits of high-predictability performance versus low predictability performance on the speech perception in noise (SPIN) test.[29] One interpretation of these findings is that the old subjects had unimpaired cognitive processing capabilities, consistent with their good use of semantic context, but impaired subcortical neural processing mechanisms that were interfering with their speech perception capabilities in background noise situations.

Frisina and colleagues went on to examine cerebral blood flow activity in these two groups of audiometrically normal subjects using positron emission tomography methodologies.[1] They monitored brain blood flow while young and old adult subjects performed the SPIN task, with various levels of background noise present. They found that in both young and old adult subjects, the addition of background noise significantly increased the blood flow in midbrain, (thalamic and cerebellar areas of the brainstem) relative to activity levels for speech presented in quiet. In contrast, auditory cortical blood flow levels remained similar in quiet versus background noise speech perception situations. The main aging effect was an increase in blood flow in young adult subjects in the midbrain and thalamic regions of the brainstem, relative to old subjects for identical listening situations in background noise.

Using Frisina and Frisina's groups of young and elderly adult subjects with normal audiometric sensitivity in quiet, Snell[30] demonstrated that the old listeners have auditory temporal processing deficits not present in the young adult group. In psychoacoustic gap experiments using different carrier frequencies and a variety of other gap parameters, Snell and colleagues always found systematic differences in gap thresholds between the young adult and elderly subject groups who had normal audiometric sensitivity.[31] These age-linked temporal processing declines are similar to those observed psychoacoustically by Fitzgibbons and Gordon-Salant.[32] Walton and colleagues[33] performed an auditory brainstem response (ABR) forward masking study using the same two groups of subjects. They employed an ABR forward masking gap paradigm in which a pure-tone masker preceded a pure-tone probe of the same frequency. They varied the temporal gap width to see how much of a gap was needed to allow for recovery of the probe tone amplitude relative to the unmasked probe response amplitude. Exemplary findings are given in Figure 2. Note that for short gap widths, old listeners needed a longer gap width for recovery of the probe response.

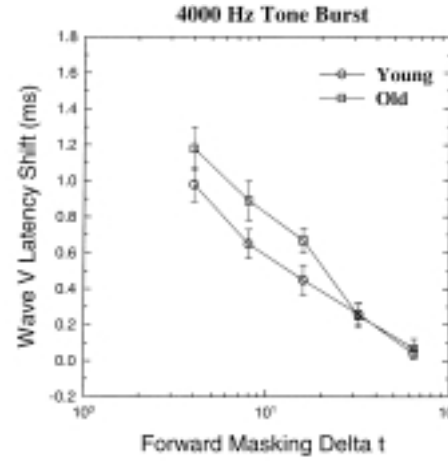

Figure 2 Human ABR Wave V latency shifts, re: unmasked latencies, are plotted as a function of the forward masking gap (abscissa). The carrier frequency of the masker and probe was 4 kHz. The data points represent mean data for the young adult (N = 10) and old subjects (N = 10), and the error bars represent one standard deviation. Response latencies are similar for long gaps between the masker and the probe tones. However, for short gaps, the response of the old subjects is significantly time delayed relative to that of the young subjects. Figure reproduced from Walton et al,[36] with permission.

Yet for long gap widths, no difference was detected. This temporal processing deficit manifested in wave V of the ABR suggests an age-related brainstem temporal processing problem for humans.

To relate these human findings to animal model experiments, it was next necessary to determine if animals had an age-related auditory temporal processing deficit (analogous to the human psychoacoustic data) and, if so, whether this could be linked to a brainstem neurophysiological problem (comparable to the human ABR temporal coding deficit). The Rochester group pursued this by investigating auditory age-related temporal processing abilities in rodents by employing behavioral paradigms. Ison and coworkers, using an inhibition of startle response behavioral assay, demonstrated that CBA mice have declining temporal processing (acoustic gap) abilities as they age.[34] CBA mice have a slowly progressive, relatively flat, mild hearing loss with age. These auditory temporal processing declines started in middle age and continued into old age (+2 years).

The next challenge was to explore the existence of possible biological correlates of perceptual gap detection in neural circuitry of the mouse auditory brainstem. If such neural correlates exist, it would be possible to investigate whether they decline with age in any way resembling the age-related human and animal temporal processing perceptual deficits. Walton and colleagues investigated this by measuring CBA young adult mouse temporal processing capabilities behaviorally and then by making single neuron recordings in the inferior colliculus of the same mouse strain.[35] Indeed, they discovered that many single neurons displayed auditory gap encoding capabilities that were very similar to the behavioral gap coding abilities of these mice, as shown here in Figure 3. Neurons in the auditory midbrain of unanesthetized mice can be broadly classified into transient and sustained neurons. Transient neurons give a response at the beginning of a sound and then subside their spike (action potential) activity as the sound remains on. Sustained neurons maintain a significant level of spike activity for the entire duration of a sound. Both types of neurons were capable of responding to gaps in sounds in ways resembling the behavioral data.

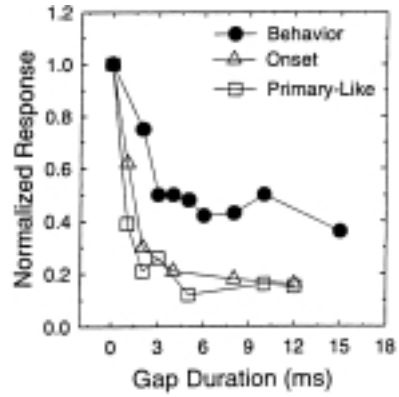

Figure 3 Behavioral measurements of auditory temporal processing are similar to the responses of single neurons in the auditory midbrain of the unanesthetized mouse. This graph displays the mean acoustic startle response results, plotted as filled circles (N = 5 CBA mice). The open symbols show normalized gap functions for transient (triangles, Onset) neurons (N = 13), and for sustained (squares, Primary-Like) neurons (N = 3) measured in the inferior colliculus of the same animals for which the behavior was measured. The behavioral and single neuron data were normalized (value of 1) to responses when no gap was present. Figure reproduced from Walton et al[35] (Fig. 12), with permission.

Having established a correspondence between single-neuron coding and behavioral processing of sound gaps, Walton and coworkers went on to see if single neurons in the inferior colliculus of unanesthetized CBA mice diminished their gap coding abilities as a function of age.[36] Samples of many neurons from young adult CBA mice, compared with comparable samples from old CBA mice, showed that there were more neurons in young adult mice that had short gap thresholds (1 msec) than there were in older mice (Fig. 4). Old animals had some neurons with short gap thresholds, but the distribution of gap thresholds was skewed toward longer gap durations in the old animals. In addition, on the average, neurons in old animals tended to give less vigorous responses (in terms of number of spikes) than neurons from young adult animals did, as presented in Figure 5. These neurophysiological age-related deficits are in contrast to responses

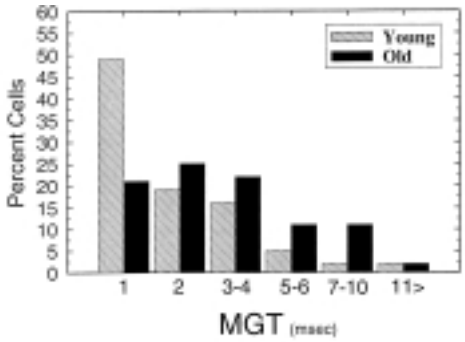

Figure 4 Inferior colliculus neurons from old animals (filled bars, N = 108) tend to have longer minimum gap thresholds (MGT) than do single neurons from young adult animals (hatched bars, N = 78). Some neurons in old animals can still encode short gaps (1 msec), but most need longer gap durations to give a threshold response. Figure reproduced from Walton et al[36] (Fig. 8), with permission.

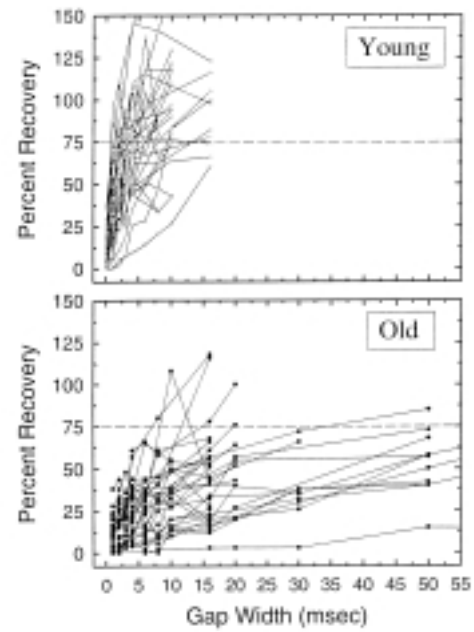

Figure 5 For a given gap width, neurons from old CBA mice tend to give smaller responses than do neurons from young adult mice. The ordinate on this graph gives the response to the gap relative to the response to the onset of a wideband noise stimulus. If the gap response equals the response of the noise burst, then the response is tabulated as 100%. If the gap response exceeds the onset response, then it is tabulated as greater than 100% (facilitated). Note that it was rare to encounter a single neuron that had facilitated responses in an old mouse. In addition, for a given gap width (plotted on the abscissa), responses from old animals tend to be below those from young adult mice. Figure reproduced from Walton et al[36] (Fig. 9), with permission.

to more simple sounds, which do not show significant changes with age at the level of the mouse auditory midbrain.[37,38]

At the conclusion of Walton's single neuron physiological experiments, a central nervous system (CNS) anatomic marker/tracer known as horseradish peroxidase (HRP) was injected into the auditory midbrain. Frisina and coworkers[39] examined the recording sites for Walton's experiments and found the HRP injections to be centered in the dorsomedial area of the inferior colliculus, as presented in Figure 6. It was then possible to start searching for neural correlates or causes of the neurophysiological temporal processing declines reported by Walton and coworkers. Frisina et al[40] examined the input to this region of the dorsomedial inferior colliculus by examining the location of neural cell bodies retrogradely labeled with HRP in the same mice in which the temporal processing experiments were performed. Major input areas to this region of the inferior colliculus came from the contralateral cochlear nucleus, the ipsilateral superior olivary complex, and, bilaterally, the nuclei of the lateral lemniscus. These investigators went on to see if these inputs change with age, and they found that some declined and others stayed the same. For example, inputs from all three divisions of the contralateral cochlear nucleus manifested statistically significant reductions with age, with the most dramatic declines from the young adult to the middle-aged group (16 to 18 months).[1,2] In contrast, other inputs, for example those from the ipsilateral superior olivary complex and the nuclei of the lateral lemniscus, remained constant with age.

Pursuing the theme of identification of possible neural correlates or etiologies of the neurophysiologically demonstrated auditory temporal processing deficit at the level of the inferior colliculus of CBA mice, Zettel and colleagues[41] explored the presence of calcium-binding proteins in the dorsomedial inferior colliculus. Calcium excitotoxicity is a prominent candidate for age-linked neural degeneration and death in the mammalian brain.

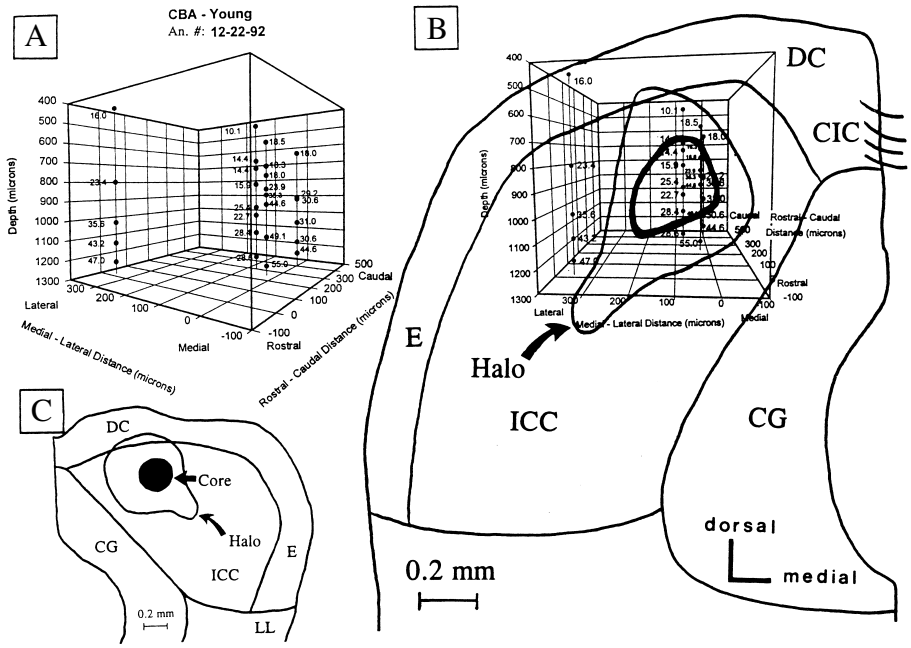

Figure 6 Injections of a CNS marker or tracer (HRP) allowed precise localization of neurophysiological recording sites in the IC of young and old CBA mice. It also allowed for tracing of connections of this neural region with other parts of the central auditory system that provide inputs to this region and receive outputs from this region. (a) Example of a physiological map from one young adult animal represented in a three-dimensional (3-D) graphic format. The sound frequency to which each single neuron was most sensitive is given in kilohertz. The graph is rotated so as to provide a vantage point where many neuron locations are visible. All axes are in arbitrary micron units (i.e., the 0 points of the axes are arbitrary and do not correspond to the center of the HRP injection site). Note that the frequencies to which the neurons are most sensitive increase as one moves deeper in the IC. (b) Correspondence of the physiological map (rotated to a paracoronal plane) and the neuroanatomical cytoarchitectonics. The dense core of the HRP injection site has a **bold** border, and its halo has a thin border (arrow). Injection sites were placed in dorsomedial IC. The 3-D physiological data are calibrated to the coronal, anatomic section at the 300-μm rostral-caudal plane (i.e., at the injection site center) both anatomically and physiologically. (c) Camera lucida drawing of the dense core (straight arrow) and halo (curved arrow) of the center of the injection site in dorsomedial IC from another animal. Chromagen: DAB; counterstain: cresyl violet; section thickness: 60 μm. Figure reproduced from Frisina et al[28] (Fig. 1), with permission.

Calcium-binding proteins such as calbindin and calretinin play key roles in governing the intracellular concentrations of calcium in certain CNS neurons. Zettel and coworkers found that calbindin declined and calretinin increased with age in the dorsomedial inferior colliculus for CBAs, as displayed in Figure 7.[41] In a parallel experiment in C57 mice, they found that calbindin declined but calretinin remained unchanged in old animals.[41] This suggested that the calretinin upregulation might be activity dependent, whereas the decline in calbindin might be a more general consequence of aging because it occurred in animals that had hearing (CBA) as well as those that were deaf (C57). Zettel et al[42] tested this hypothesis by deafening CBAs when they were young adults (with kanamycin injections into the cochlea), letting them mature to 2 years of age and then examining their brains for the presence of calretinin in the dorsomedial inferior colliculus. Indeed, they found that the upregulation of calretinin observed for the normal, aged CBAs was not present in those deafened from birth.

Caspary and colleagues have made multidisciplinary investigations of age-related changes in inhibitory neurotransmitters in the auditory midbrain of rats.[43] Gamma aminobutyric acid (GABA), a primary in-

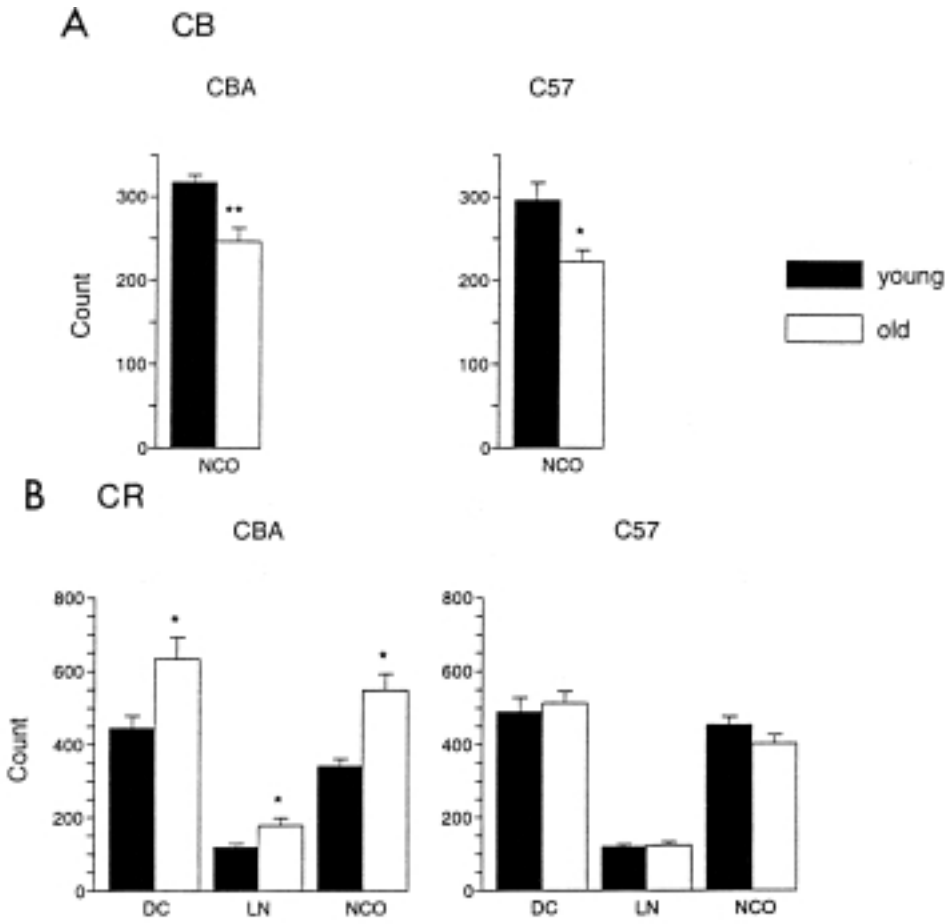

Figure 7 Aged CBA mice that have mild-to-moderate peripheral hearing losses in old age show auditory temporal processing deficits measured behaviorally and neurophysiologically. In the dorsomedial region of the inferior colliculus (DC, LN, NCO), where single neurons display temporal processing degradations, the presence of calbindin (CB) decreases with age, whereas calretinin (CR) is upregulated as animals reach old age. (A) The average number of CB+ neurons in the NCO of young adult versus old CBA and C57 mice. CB+ neurons decline significantly with age in both mouse strains. (B) The mean number of CR+ neurons in young adult versus old CBA mice significantly increases with age in CBA mice, but not in C57 mice that are deaf in old age. Error bars denote the standard error of the mean. *$p < 0.05$, **$p < 0.01$. Figure reproduced from Zettel et al[41] (Fig. 12), with permission.

hibitory neurotransmitter in the brainstem auditory system, is particularly prominent in nerve endings and neurons in the inferior colliculus, especially its central nucleus. It is likely that this inhibitory neurotransmitter plays a crucial role in various facets of auditory functioning such as space coding, temporal processing, and discrimination of signals from background noise. Caspary and associates[44] examined inferior colliculus neuron immunolabeling against GABA in young adult (2 to 7 months) and old (18 to 29 months) Fischer-344 rats. Quantitative analyses revealed that in the ventrolateral inferior colliculus (high-frequency region) the number of labeled neurons decreased by 36% in old animals. Biochemical experiments measured the basal (resting) and K^+-evoked efflux of GABA. Inferior colliculus tissue from old rats showed statistically significant declines in both basal and K^+-evoked release of GABA compared with young adults. As a control, release of excitatory transmitters, such as glutamate and aspartate; other endogenous amino acids; and the

inhibitory neurotransmitter acetylcholine was measured and found not to change with age.

Caspary's group went on to demonstrate an age-related reduction in GABAb receptor binding in the rat inferior colliculus.[45] Using quantitative receptor autoradiography, decreases were found in the inferior colliculus, whereas no age-related changes were observed in the nearby cerebellum. These inferior colliculus effects were observed despite no change in its cross-sectional area with age. They then demonstrated that GABAb receptor binding goes down in old animals. In contrast, GABAa receptor counts increased with age, probably as a partial compensation for the GABAb.[46]

Using immunogold electron microscopy techniques, Helfert and coworkers[47] quantitatively compared alterations in the organization of GABA+ and GABA− terminals and synapses in the rat inferior colliculus. They discovered that the density of both types of terminals and synapses went down by 24 to 33% in old animals relative to young adults, with the range reduced by 9% if the densities were age corrected for overall shrinkage of the auditory midbrain. Because these declines were similar for GABA+ and GABA− synapses, it appears that excitatory and inhibitory inputs decline proportionately with age, avoiding an age-related imbalance. Following this, Milbrandt and coworkers[48] examined the GABAa receptor subunit composition and discovered that this is altered with age in the rat inferior colliculus such that enhanced responses to GABA can take place. Specifically, as the animals age, the gamma-1 protein subunit *increased* and the alpha-1 subunit *decreased*.[49] They also found an age-related increase in GABA-mediated chloride influx, which is functionally consistent with these changes in subunit composition. If subunit redistributions occur for excitatory synapses, enhancing their potency, then the relative balance of excitation and inhibition could be maintained with age to help preserve normal functioning of the auditory midbrain in the face of other age-related structural and neurochemical declines, such as those involving GABAb receptors. The main conclusion is that there are *reductions* in most aspects of GABA biochemistry in the rat inferior colliculus, including concentration of GABA, its receptors, and its activity levels.

SUMMARY AND FUTURE DIRECTIONS

Hearing science and auditory neuroscience potentially have much to offer the practicing audiologist and otolaryngologist. As more is discovered about which levels of the auditory system are deleteriously affected by age and age-related insults or pathologies, better ways of diagnosing different types of presbycusic deficits in clinical settings will be forthcoming. Not only should information from scientific investigations improve diagnoses of presbycusis but also, on the treatment side of the equation, differential diagnosis of varieties of presbycusis will be more tightly linked to alternative and novel treatments. For example, prescription of hearing aids will differ for an elderly person who has a significant end-organ sensitivity impairment versus an old person with primarily a temporal processing deficit resulting from neuropathology of the auditory brainstem. As auditory neuroscientific investigations proceed in molecular biological directions, it is possible that some of the sensorineural atrophy characteristic of the inner ear or brain may be corrected through biochemical interventions or gene therapy approaches. For example, in birds, cochlear hair cells grow back after damage. In fact, they reconnect with surviving auditory nerve fibers and carry information to the brain that is very similar to that of an undamaged auditory system. The biochemical and molecular genetic sequence of events that underlie this regenerative hearing restoration process in birds may someday be applicable for regenerating hair cells in the presbycusic ear and repairing damage to neural circuitry in the old auditory brainstem.

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ABBREVIATIONS

ABR	auditory brainstem response
C57	strain of mouse that develops a severe-to-profound high-frequency hearing loss by 6 to 8 months of age
CBA	strain of mouse that loses its hearing slowly with age
CG	central gray (periaqueductal gray)
CIC	commissure of the IC
CNS	central nervous system
DC	dorsal cortex of IC
DAB	diaminobenzidine
E	external nucleus of IC
GABA	gamma aminobutyric acid
HRP	horseradish peroxidase
IC	inferior colliculus
ICC	central nucleus of IC
LL	lateral lemniscus
LN	lateral nucleus of IC
MNTB	medial nucleus of the trapezoid body of the superior olivary complex
NCO	nucleus of the commissure of IC
SPIN	speech perception in noise test

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ARTICLE ONE
SELF-ASSESSMENT QUESTIONS

1. Age-related hearing loss, presbycusis, results from
   A. age changes in the brain
   B. age changes in the liver
   C. age changes in the brain resulting from distorted inputs from the aging ear
   D. age changes in the ear
   E. answers A, C, and D

2. The inability of aged persons to correctly perceive speech in background noise is *not* due to
   A. loss of hair cells in the ear
   B. reductions in certain brainstem auditory pathways
   C. neurochemical changes in the brain with age
   D. birth order
   E. history of noise exposure and other ototoxic agents

3. The adult brain is surprisingly plastic or adaptive in the following way:
   A. Neurons in the brain can reconnect, depending on changing inputs.
   B. When neurons of the brain or spinal cord die, they grow back naturally.
   C. When hair cells of the ear are destroyed by ototoxic agents, they regenerate in mammals, including humans.
   D. When spiral ganglion cells die in humans or monkeys, they grow back spontaneously and reconnect to hair cells.
   E. Auditory nerve fibers regenerate following acoustic neuroma surgery.

4. Which of the following is *not* a true statement concerning the functional organization of the cochlea?
   A. In most mammals, there is one row of inner hair cells and three rows of outer hair cells.
   B. Outer hair cells have actin filaments and can change their shape for different levels of sound, like small muscles.
   C. During aging, outer hair cells are lost first in the base of the cochlea; only later do inner hair cells disappear.
   D. Inner hair cells are the main channels through which we hear, and outer hair cells improve sensitivity of our hearing for certain sounds.
   E. In mammals, the cochlea is a straight, air-filled cavity.

5. Animal model experiments suggest that the following changes take place in the auditory brainstem with age:
   A. The number of neurons that encode short time gaps in sounds declines.
   B. Certain neural pathways become diminished.
   C. Certain parts of the auditory system are taken over by the visual and somatosensory systems.
   D. For the typical high-frequency hearing loss characteristic of presbycusis, parts of the brain normally used for high frequencies get taken over for processing of middle frequencies.
   E. A, B, and D are correct.