

Age-Related Hearing Loss: Unraveling the Pieces

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Age-related hearing loss (ARHL) is the most common cause of hearing loss in the world. The development of ARHL in each individual is multifactorial, involving both intrinsic and extrinsic factors. This review highlights several of the key findings in the ARHL literature and discusses future directions.

Key Words: Age-related hearing loss, presbycusis, oxidative stress, cochlear synaptopathy.

Level of Evidence: NA.

INTRODUCTION

Age-related hearing loss (ARHL), or presbycusis, is the most common cause of hearing loss and is one of the most prevalent conditions affecting the elderly globally. Estimates suggest approximately two-thirds of people over the age of 70 in the United States experience ARHL,¹ and that by 2020, over half of all people in the United States with hearing loss will be over 70 years of age.² ARHL has been shown to be independently associated with cognitive decline, dementia, depression, and loneliness^{3–6} and results in an estimated annual economic burden of over \$3 billion in medical expenditures.⁷ Although the use of hearing aids and/or cochlear implants has been shown to improve many of these associated conditions,^{5,8,9} ARHL remains significantly undertreated.^{10,11}

The development of ARHL is clearly multifactorial, involving both intrinsic and extrinsic factors. Genetics has been demonstrated to play a role, while environmental exposures accumulated throughout life are also important influences on hearing in the elderly. The natural process of aging is associated with many changes in the inner ear that have been noted in histologic studies, yet not all elderly experience ARHL. Other comorbidities may additionally influence the development or severity of presbycusis. Consequently, research on the pathophysiology of ARHL has been challenging to synthesize in

light of these interactions. In this discussion, we aim to highlight a few of the key findings in the ARHL literature and briefly discuss future directions.

Histopathology of ARHL

Schuknecht's seminal studies correlating audiogram findings in presbycusis with histopathologic findings in human cochlea initially produced four categories of presbycusis, which were later expanded to six: sensory, neural, stria (metabolic), cochlear conductive, mixed, and indeterminate. Sensory presbycusis was described as abrupt high-frequency hearing loss associated with atrophy of the basal organ of Corti. Neural presbycusis exhibited diminished word discrimination scores and relatively stable pure tone thresholds, with spiral ganglion cell loss. Strial, or metabolic, presbycusis was characterized by overall diminished pure tone thresholds in all frequencies, and associated with stria vascularis atrophy. Cochlear conductive, or mechanical, presbycusis was described as having a gradual down-sloping audiogram with no obvious histologic findings, and hypothesized to be a result of basilar membrane stiffening. Mixed presbycusis demonstrated a combination of the previously described audiograms and histologies, while indeterminate presbycusis (representing nearly 25% of all patients) did not demonstrate a consistent histologic appearance while manifesting as either flat or high-frequency loss.^{12–14}

This classification system has served as a useful framework to understand the various presentations of presbycusis, although in reality there is almost certainly significant overlap.¹⁵ The role of stria vascularis atrophy, diminished Na⁺ K⁺ ATPase function, and its effects on the endolymphatic potential (EP) have been studied and found to factor prominently in the aging cochlea. The primary function of the stria vascularis is to maintain high K⁺ concentration in the scala media, which contributes heavily to generating the EP. As Schuknecht observed, changes in the stria vascularis have been observed consistently in a subset of human histopathologic studies,¹⁴ while animal studies, particularly in gerbils, have extended this observation by demonstrating decreased Na⁺ K⁺ ATPase function and EP^{16,17} associated with aging. Mechanisms for this decline are not fully

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understood, but may be related to microvasculature changes^{18,19} and oxidative stress.²⁰

Cochlear synaptopathy

The pathophysiology of both age-related and noise-induced hearing loss has also traditionally been thought to be associated with primary degeneration of outer hair cells, with secondary deafferentation-associated degeneration of the spiral ganglion cells and nerve fibers.^{21,22} However, recent observations of neural degeneration in the absence of hair cell injury have resulted in a paradigm shift in the understanding of the mechanisms by which presbycusis may develop. The work of Kujawa and Liberman in animal models using immunostaining have revealed a loss of cochlear synapses, termed cochlear synaptopathy, with delayed spiral ganglion cell degeneration which occurs in the absence of hair cell loss.^{23–25} Similarly, in preserved human temporal bones, it has been observed that spiral ganglion cell counts decrease throughout life despite normal hair cell populations,²⁶ while cochlear dissection and immunostaining of fresh human temporal bones less than 12 hours post-mortem suggest a role for cochlear synaptopathy in the aging ear.²⁷ While the mechanism of this injury is not fully understood, it has been postulated that glutamate excitotoxicity resulting in swelling of the nerve terminals may play a role,^{23,28} particularly in the setting of noise-induced hearing loss.

Early detection of cochlear synaptopathy has proven to be difficult as standard audiometric testing involves pure tone thresholds, which tend to reflect hair cell function and are relatively insensitive to neural injury.¹⁴ Given the current inability to directly measure cochlear synaptopathy in vivo, efforts are currently underway to assess alternative metrics which indirectly assess early injury. Auditory brainstem response (ABR) is one technique which is currently under investigation, and there is early evidence that diminished wave I amplitude with normal thresholds may be an indication of early cochlear synaptopathy.^{23,25} Additionally, it has been noted that this cochlear synaptopathy may preferentially affect acoustic nerve fibers which have low spontaneous discharge rates, a finding that may explain the poor hearing-in-noise performance of patients with ARHL.^{25,29} As a result, hearing-in-noise testing may also provide another diagnostic modality by which early injury can be detected; unfortunately, this cannot be tested in animal models. Finally, electrocochleography has also been reported as a potential tool by which cochlear synaptopathy may be detected in early hearing loss. Those at higher risk for hearing loss demonstrated an elevated SP/AP ratio, reflecting a selective neural injury which may represent cochlear synaptopathy, although this hypothesis is currently unable to be validated.³⁰

Oxidative stress

Oxidative damage from reactive oxygen species (ROS) has been a frequent field of investigation for many diseases. Mitochondria have been implicated as a major source of ROS, which has led to a theory of aging

which is driven largely by mutations in mitochondrial DNA resulting from accumulation of ROS over time.³¹ Given the high metabolic demands of the stria vascularis, oxidative stress has long been considered a major factor in the histopathologic changes noted previously.³² Accelerated hearing loss, stria vascularis atrophy and spiral ganglion degeneration were noted in a transgenic mouse model which had decreased expression of an important antioxidant enzyme.³³ In contrast, overexpression of the same enzyme did not demonstrate a protective effect on presbycusis,³³ suggesting the presence of other unmeasured influencing factors. Interestingly, in another aging mouse model, an oxidative imbalance was noted to be heavily concentrated in the hair cells and spiral ganglion cells while sparing the stria vascularis,³⁴ raising the possibility for a broader role for oxidative stress involving “sensory” and “neural” causes of presbycusis in addition to the hypothesized effect on the stria vascularis. In human studies, plasma levels of detectable ROS have also been demonstrated to be positively associated with increased pure tone thresholds.³⁵

A recent report using a mouse model of presbycusis has provided evidence for a protective effect of exercise, possibly via an anti-inflammatory pathway.³⁶ Animals which exercised displayed delayed declines in certain hearing thresholds, greater hair cell survival, and increased spiral ganglion neuron density compared to controls. Additionally, exercise was associated with greater number of capillaries in the apical regions of the cochlea. Gene expression studies demonstrated significant decreases in expression of several inflammatory genes with exercise, suggesting an important link between microvasculature changes and chronic inflammation resulting in long-term histologic changes.

An important epidemiologic observation has been the significant impact of race on hearing outcomes and its suggested connection to oxidative stress. It has consistently been noted that the risk of presbycusis is reduced in black individuals compared to white individuals,¹⁰ and recent analysis indicates that darker skin color is positively associated with improved hearing, independent of ethnicity.³⁷ In mice studies comparing albinos to otherwise identical pigmented counterparts, a higher proportion of albinos demonstrated decreased EP as well as reduced stria thickness.³⁸ It is hypothesized that melanin may act as a chelator of metals, ions, and oxidative radicals, thereby reducing the accumulated effects of oxidative stress that leads to ARHL.³⁹

Genetics of ARHL

While environmental risk factors for hearing loss (including but not limited to noise, chemical exposure, tobacco, alcohol, ototoxic medications) have been well studied,⁴⁰ it has been more challenging to tease apart the genetic influences on ARHL. Twin studies have estimated a heritability of 40 to 47%,^{41,42} while the Framingham analysis estimated 31 to 38%,⁴³ suggesting that both genes and environment play important roles. Not surprisingly, the influence of environment increases with age as individuals are exposed to more external

stimuli which may exacerbate the natural course of presbycusis.⁴¹ This interaction of genetics and environmental factors certainly complicates our ability to separate each individual contributor to ARHL but remains an area of significant interest.

As discussed previously, there has been significant interest in the role of ROS in ARHL. Mitochondria are the major source of ROS, and it has been postulated that mitochondrial DNA mutations may hasten the oxidative damage sustained by the cochlea. Several human studies have attempted to investigate the association between common mitochondrial mutations and ARHL. The most common mitochondrial deletion, known as mtDNA4977 or the common deletion (CD), has been shown to be associated with hearing loss^{44–46} in human temporal bone studies. Further quantification of CD has suggested a correlation between levels of CD in the cochlear tissue and severity of hearing loss,⁴⁷ although this finding was unable to be repeated in a separate study.⁴⁸ One of the genes located in the CD is the cytochrome c oxidase subunit 3 (COX 3), a vital component of the electron transport chain in mitochondria, and a deficiency of COX3 has been noted in human temporal bones of patients with presbycusis.⁴⁹ Additionally, it has also been observed that temporal bones of patients with ARHL with the CD also demonstrate narrowed vasculature, leading to the hypothesis that diminished vascular supply to the inner ear may compound rates of mitochondrial mutation.⁴⁶

In recent years, genome-wide association studies (GWAS) have attempted to identify single nucleotide polymorphisms (SNP) which may be associated with ARHL, although given the polygenic nature of the condition, it has been difficult to consistently identify genes of interest.⁵⁰ One GWAS study in a European population of 834 cases and 834 controls identified significant variants located in GRM7, a gene encoding a metabotropic glutamate receptor which was found in spiral ganglion cells as well as inner and outer hair cells.⁵¹ These variants were later studied in a separate American population of 687 individuals of European descent and found to have significant effects on pure tone thresholds as well as speech reception thresholds, but not hearing-in-noise testing.⁵² A separate GWAS of a genetically isolated Finnish population similarly identified a significant SNP directly downstream of the GRM7 locus.⁵³ In light of the recent findings of cochlear synaptopathy and the postulated mechanism of glutamate toxicity, GRM7 may be of particular interest for further study. The same study of the Finnish population also identified a SNP involving the gene encoding IQGAP2, a cochlear GTPase found to play a role in cadherin-mediated adhesion. Given the role of cadherins in maintaining hair cell function and their implicated role in several syndromes characterized by hearing loss,⁵⁴ this may also be another promising direction for future investigation.

Due to the complexity of ARHL, there has been increasing interest in GWAS studies in the mouse model. Compared to human studies, mouse studies have the advantage of controlling for environmental exposure, improved replicability, and greater genetic contribution to

hearing traits. The development of a population of mouse strains designed for use in complex traits, referred to as the Hybrid Mouse Diversity Panel (HMDP), has allowed greater resolution of genetic mapping in the study of ARHL.^{55,56} Baseline ABR threshold phenotypes of 100 HMDP strains have recently been reported in the literature⁵⁷ and demonstrated substantial inter-strain variability at each of six frequencies. GWAS performed on the HMDP comparing strains for each of the six frequencies demonstrated several significant loci, suggesting a role for frequency-specific genetic contributions as well as loci which contributed to hearing across all frequencies.⁵⁸ A new technique permitting meta-analysis of mouse GWAS studies involving heterogeneous populations identified several novel loci which previously were not recognized in prior studies, as well as reconfirming several known loci involved in ARHL.⁵⁹ Additional studies involving the HMDP are currently underway and are likely to continue to identify loci of interest for future investigation. Continued improvements in the field of genomic studies carry significant promise in revealing the genetic architecture of ARHL and its interaction with the environment.

Future Directions

Traditionally, treatment options have been limited to hearing aids and cochlear implantation. Recent findings may open the door for new pathways for treatment, particularly if earlier detection is possible. Given the potential role of oxidative stress in ARHL, there has been significant interest in clinical trials investigating molecules which target oxidative stress pathways, several of which are in Phase III trials.⁶⁰ Lifestyle modifications may also have a role in delaying presbycusis. As discussed previously, exercise has been shown to improve both the histologic and functional findings of hearing loss.³⁶ Dietary supplementation of antioxidants and vitamins have been studied in animal models of ARHL with mixed results. While some have reported an otoprotective benefit with vitamin E, vitamin C, and calorie restriction,⁶¹ others have reported no differences in either hearing outcomes or histopathology.⁶²

Human studies of dietary influences on hearing outcomes have similarly demonstrated mixed results, and are additionally fraught with confounders. Antioxidants have been shown to potentially be helpful in the setting of noise-induced and drug-induced hearing loss, and response is also much more easily assessed. However, in the setting of presbycusis, there is no acute insult resulting in hearing loss, making hearing outcomes of dietary supplementation more challenging to assess. A cross-sectional study of human adults correlating hearing and self-reported diet suggested an association between higher carbohydrate, vitamin C, vitamin E, riboflavin, magnesium, and lycopene ingestion with lower pure-tone thresholds and larger otoacoustic emissions,⁶³ while another cross-sectional investigation of the relationship between hearing thresholds and the Healthy Eating Index (an overall assessment of an individual's compliance with general dietary recommendations) suggested that overall healthier eating was associated with improved high-frequency thresholds.⁶⁴ Further illustrating

the complex interplay of factors influencing hearing, it was demonstrated that individuals who had a significant noise exposure history experienced a greater hearing benefit from healthier eating than those without.⁶⁴

The discovery of cochlear synaptopathy has prompted investigation of a separate pathway of therapeutics. Neurotrophins which have demonstrated the ability to neuronal survival and dendritic sprouting have been of particular interest. In a guinea pig model of noise-induced hearing loss, brain-derived neurotrophic factor and neurotrophin-3 were applied to the round window following significant noise exposure. Those treated with neurotrophins were found to exhibit reduced levels of cochlear synaptopathy on immunohistochemistry as well as preserved ABR, providing strong evidence for a protective role.⁶⁵ Overexpression of neurotrophin-3 in a mouse model interestingly did not prevent the occurrence of synapse loss immediately following acoustic trauma, but did promote synapse recovery after several weeks; in contrast, control animals demonstrated progressive synapse loss.⁶⁶ Similar studies in animal models of ARHL should be conducted to confirm benefit of these neurotrophic factors.

CONCLUSION

ARHL is one of the most common conditions affecting the elderly, and its incidence is projected to continue to increase as the population ages. It represents a common terminal condition with a multitude of both extrinsic and intrinsic factors variably influencing each individual throughout life. Recent findings have changed the understanding of the pathophysiology of ARHL and have forced a reconsideration of the sequence of events by which hearing loss in the elderly develops. Early detection and prevention of ARHL may be the most successful therapeutic strategy, and future research should focus on long-term strategies by which this may be achieved.

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