Age-Related Hearing Loss

Subjects: Pathology

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Age-related hearing impairment, also referred to as presbycusis, is the most common sensory impairment seen in the elderly. As our cochlea, the peripheral organ of hearing, ages, we tend to experience a decline in hearing and are at greater risk of cochlear sensory-neural cell degeneration and exacerbated age-related hearing impairments (e.g., gradual hearing loss, deterioration in speech comprehension, difficulty in the localization sound sources, and ringing sensations in the ears). Here, we outline recent research into major causal factors of age-related hearing loss including both extrinsic (e.g. noise and ototoxic medication), and intrinsic factors (e.g. genetic predisposition, epigenetic factors and aging).

Keywords: Age-related hearing loss ; Presbycusis ; Causal factors

1. Introduction

The clinical presentation of presbycusis, the rate of the progression, age at onset, and ultimate severity of hearing loss varies from patient to patient. Whereas the majority of elderly patients present clear hearing losses, a significant fraction of the geriatric population has almost normal hearing. This is due to intrinsic (genetic predisposition, epigenetic factors, and aging), and extrinsic factors (e.g., noise- or ototoxic drug-exposure, head trauma, cigarette smoking) that are either the sole etiology for hearing loss, or several work in synergy with the physiopathology of presbycusis[1].

2. Biological Aging on Hearing

2.1. Aging and Hearing in Healthy People

The clinical diagnosis of presbycusis is based on bilateral progressive loss of hearing starting from a high-frequency region of the hearing spectrum. Loss of hearing can begin in young adulthood, but is initially evident at 60 years for most people. Over time, the threshold elevation progresses to lower and lower frequency areas. However, presbycusis studies in humans are limited by the genetic heterogeneity and the difficulty in controlling deleterious auditory exposures over time. Despite these limitations, it has been reported that in a cohort unscreened for noise exposure, ototoxic drug exposure, and otologic disease history, presbycusis develops earlier and to a greater extent than in a highly screened cohort (without history of significant noise exposure or diseases that affect the ear)[2]. It has been suggested that the onset of hearing loss induced by biological aging is very late. Indeed, the Mabaan tribe living in the Sudanese desert retains their hearing into old age[3]. Because the hearing of the young Mabaans was the same as those of young people from other countries, the good preservation of hearing in the tribe has been attributed to their quiet living environment and generally healthy condition[4]. However, it can be argued that this difference might be caused by genetic differences between the populations. To answer this question, Goycoolea et al.[5] compared the hearing of natives of Easter Island, people living in a pre-industrial society, with those who had emigrated to Chile and spent varying amounts of time in modern society. Results showed that hearing in males that had lived or were living in Chile was significantly worse than that of males who had lived their entire lives on Easter Island, and that the poorer hearing was related to the number of years lived in modern society. Contrary to these early investigations, more recent studies showed that hearing thresholds decline with age and the rate of decline accelerates with age in presbycusis patients without noise-exposure or diseases that may affect the ear[6]. In addition, the differences of hearing thresholds between presbycusis patients with or without noise exposure are limited[7]. These results thus supported the belief that age is one of the major causal factors of ARHL.

2.2. Aging and Hearing in Animals

To study the impact of cochlear aging on hearing, animal models are a useful tool due to their short lifespan, controlled environments and diet composition, and limited genetic heterogeneity. Gerbils that grew up in quiet environments[8] showed various degrees of threshold shifts with age. The threshold shift profile was a relatively flat loss across low and mid frequencies, with the greatest losses at the higher frequencies resembling that often seen in human presbycusis[9]. These animals also showed a decline of the endocochlear potential[10][11] and reduced amplitudes of compound action

potentials of the auditory nerve[12]. Reduced amplitudes of compound action potentials in aging ears suggested asynchronous or poorly synchronized neural activity in the auditory nerve of quiet-aged gerbils[12]. Cochlear morphological examination of gerbils raised in quiet demonstrated that the most important age-related degeneration site is the stria vascularis[13]. The stria vascularis is essential for maintaining the endocochlear potential which is the main driving force for the transmission of sound signals from the ear to the brain. The degeneration of marginal and intermediate cells of the stria vascularis began in both the base and apex of the cochlea, extending to the mid-cochlear regions as age increased. In addition, there was a loss of Na-K-ATPase[14] and losses of the strial capillary area in aged animals[15]. Certainly, more work with other species aged in quiet is needed in this area. However, existing data from quiet-aged gerbils make it clear that in gerbils, cochlear aging impacts specifically the stria vascularis and probably the neural structures.

3. Genetic Predispositions

Presbycusis shows a clear familial association. Heritability studies of presbycusis in humans have estimated that 25% to 75% of the variance in this pathology has a genetic component[1][16][17]. Genetic polymorphisms in the genes coding detoxification enzymes, such as glutathion S-transferase (*GSTM1* and the *GSTT1* null genotypes) and N-acetyltransferase 2 (*NAT2*6A*)[18][19][20] were reported to be linked to ARHL. SOD2 promoter variants (−38C > G) of the SOD2 gene encoding a ubiquitous mitochondrial superoxide dismutase enzyme (MnSOD) may link to the ARHL risk in men[21]. The main function of uncoupling protein 2 (UCP2) is the control of mitochondria-derived oxygen species (ROS) [22]. In a Japanese population, *UCP2* Ala55Val polymorphisms exhibited a significant association with ARHL[23].

An increased individual susceptibility to ARHL may rely on single nucleotide polymorphisms in the grainyhead-like 2 gene (*GRHL2*), nonsyndromic sensorineural deafness type *5 (DFNA5)* and potassium voltage-gated channel subfamily q Member 4 (*KCNQ4)* genes, whose mutations are responsible for DFNA28, DFNA2, and DFNA5, respectively[24][25][26], but also in the glutamate metabotrophic receptor 7 gene (*GRM7, e.g.,* OMIM ID: 604101)*[27][28]*. Finally, a common mtDNA 4977-bp deletion was frequently found in presbycusic patients[24].

Some genes associated with ARHL have also been identified in mice, including age-related hearing loss gene 1 (*Ahl1*), localized in chromosome 10, *Ahl2[29]* on chromosome 5 (associated with early-onset hearing loss when combined with a homozygous disease allele at the *Ahl1* locus), and *Ahl3* on chromosome 17[30]. The Ahl candidate region contains several interesting candidate genes, including genes encoding gap-junction proteins and several collagens. Mouse strains exhibiting ARHL are also more sensitive to noise-induced hearing loss than are other strains. Collectively, polymorphisms in some monogenic deafness-causing genes, neurotransmitter-related genes, and genes involved in detoxification of oxidative stress and mitochondrial function are clearly associated with ARHL.

4. Epigenetic Factors

Traditionally, genetics and adult lifestyle factors are considered to be among the main determinants of aging-associated pathological conditions. Accumulating evidence, however, suggests that epigenetic factors may contribute to these conditions[31][32]. The term epigenetics is defined as a change in phenotype that is not caused by a change in DNA sequence[33]. Epigenetic regulation of gene expression may change over time due to environmental exposures in common complex traits. The two most well understood mechanisms of epigenetic alterations that lead to these phenotypic changes are DNA methylation and histone modifications.

4.1. DNA Methylation

Age-related changes in DNA methylation include global hypomethylation and region-specific hypermethylation[34]. In the cochlea, the first evidence showing that involvement of aberrant DNA methylation in presbycusis came from a study focused on the gap junction protein b-2 (GJB2), in the cochlea of mimetic aging rats. In this study, Wu et al.[35] showed that hypermethylation of the promoter region of GJB2 gene resulted in connexin 26 down-regulation and an increased risk for presbycusis. Furthermore, Xu et al. [36] reported that hypermethylation of hearing-loss genes such as solute carrier family 26 member 4 (*SLC26A4*, DFNB4) and purinergic receptor P2X 2 (*P2RX2*, DFNA41) resulted in an increased risk for presbycusis in men. In addition, reduced expression of P2RX2, KCNQ5, ERBB3, and SOCS3 genes through DNA hypermethylation in elderly women was associated with presbycusis[37]. More recently, Bouzid et al. demonstrated that hypermethylation of CpG site in the cadherin-23 (*CDH23*) gene is likely to be associated with presbycusis in elderly women[37]. These results implicate complex pathogenic mechanisms underlying ARHL.

4.2. Histone Modification

Histone proteins including H1/H5, H2A, H2B, H3, and H4 are the chief proteins of chromatin and play an important role in maintaining the shape and structure of a nucleosome. In the last few years, the role of histone modifications in aging and age-related diseases has emerged. Watanabe and Bloch[38] investigated the modification of histones in the aged cochlea of mice using immunohistochemistry. Acetylated histone H3 was detected in the spiral ganglion cells and the organ of Corti of young cochlea, but not in those of aged cochlea. Conversely, dimethylatedhistone H3 was detected in the aged group, but not in the young group. The degeneration was severest in the spira lganglion cells and the organ of Corti of the basal turn. These results suggested that histone modifications may be involved in cochlear aging regulation.

5. Environmental Factors

The complexity of etiological factors for presbycusis begins with the number of environmental risk factors, such as occupational or leisure noise, ototoxic medication (aminoglycoside, cisplatin, salicylate, loop diuretics…), cigarette smoking, and alcohol abuse[39]. However, to date, it is not clear whether these environmental factors produce some kind of early onset and/or accelerated progression of cochlear aging or whether they act on specific pathophysiological mechanisms. In this part of our review, we will focus on the two most-studied environmental factors: noise exposure and ototoxic medication.

5.1. Noise Exposure

A retrospective clinical study from a large cohort of men in the Framingham Heart Study observed that in ears with presumed cochlear damage from previous noise exposure, subsequent progression of ARHL was exacerbated at frequencies outside the original noise-induced hearing loss[40]. These observations suggest an age-noise interaction that exacerbates age-related hearing loss in previously noise-damaged ears.

Increasing evidence from animal aging models indicates that early noise exposure renders the inner ears significantly more vulnerable to aging and may have an impact on the onset and/or progression of ARHL[41][42][43]. Indeed, Kujawa and Liberman[41] found that noise exposure in young CBA/CaJ mice, an inbred mouse strain used as “good hearing” mouse model, could trigger progressive neuronal loss and exacerbate the ARHL. Furthermore, Fernandez et al.[43] showed that interactions between noise and aging might require an acute synaptopathy to accelerate cochlear aging. In addition, repeated exposure to a short duration sound (1 h/110 dB SPL) over a long period also led to an early onset of ARHL (at six months of age) in Wistar rats when compared to non-exposed rats in which the onset of ARHL was around 12 months of age[44][45]. Although the long-term effects of early noise exposure on the aging ear are poorly understood, these clinical and experimental results indicate that noise exposure may modify the onset and/or progression of ARHL, particularly for neural presbycusis.

5.2. Ototoxic Medications

To date, the influence of other environmental risk factors such as ototoxic medications, cigarette smoking, or alcohol abuse on ARHL is less clear and often controversial. Recently, a large longitudinal cohort study (n = 3753) aimed at elucidating the association of ototoxic medications exposure with the risk of developing hearing loss during the 10-year follow-up period demonstrated that ototoxicity-age interactions may also exacerbate age-related hearing loss in older adults[46].

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