Age related hearing loss- A review

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Abstract

Age-related hearing loss (ARHL), or presbycusis, is a complex degenerative sickness that influences a huge number of elderly individuals all through the world.ARHL leads to bilaterally symmetrical hearing loss resulting from the aging process. With the growing number of geriatric patients the problem of ARHL needs to be addressed. We herein present a detailed review of this disorder that is affecting the elderly population and is second only to arthritis.

Keywords: Age-related hearing loss; Cochlea;Presbycusis; Spiral ganglion neuron.

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Introduction

Populations are becoming progressively older and the degenerative processes due to aging are taking a toll on the normal organ functions [1]. Age-related hearing loss (ARHL), or presbycusis, is a complex age relateddegenerative disease that affects majority of elderly population around the globe.Itleads to bilaterally symmetrical hearing loss resulting from the aging process and is second only to arthritis (CDC, 2003)[2,3]. ARHL is also one of the most prevalent chronic problems of the aged, with approximately half of those over the age of 65 in the United States, suffering from it [4,5]. ARHL progresses slowly and may be familial [6]. ARHL has drastic effects on the social wellbeing of the patient, as it may lead to withdrawal from friends and family which may ultimately result into isolation and depression [7]. As with the growing elderly population of the world,the detailedresearch into the causes of and treatment of presbycusis is increasingly urgent.

This is evident from examples like, between 1965 and 1994, the incidence of presbycusis in people aged 50–59 increased 150% [8].Besides, in the population above 65 years it is predicted to double in the U.S. to more than 86 millionbetween the year 2000 and 2050 [9]. The prevalence of hearing loss in people older than 50 years has been estimated at 50% and in those over 80 years at 90% [10]. This makes hearing loss the most common neurosensory deficit linked with aging. Presbycusis is a complex degenerative phenomenon characterized by an

audiometric threshold shift, deterioration in speech-understanding and speech-perception difficulties in noisy environments [2]. The causes of presbycusis are not well understood. Certainly, ARHL is a reflection of the genetics of the individual (Gates et al., 1999) as well as the accumulation of noise exposures, ototoxic drugs, and disease (Hefzner et al., 2005) [3,11]. A number of factors contribute to ARHL and may include mitochondrial DNA mutation, genetic disorders, including *Ahl*, hypertension, diabetes, metabolic disease and other systemic diseases in the intrinsic aspects. Extrinsic factors include noise, ototoxic medications and diet [2].

However, ARHL may not be related to the intrinsic and extrinsic factors separately [2].ARHL not only affects the physical, cognitive and emotional activities of patients, but also their social functioning. Thereby, affecting the patients' quality of life, due tovarious psychological issues like depression, social isolation and lower self-esteem.

Schuknecht (1993) classified presbycusisinto six categories, sensory, neural, metabolic or strial, cochlear conductive, mixed and indeterminate types based on the results of audiometric tests and temporal bone pathology [2,5]. Among these six types, metabolic presbycusis is the linchpin of presbycusis types. Age-related changes also develop in the central hearing system. Functional decline of the central auditory system, because of aging, reduces speech-understanding in clamorous background and increase temporal processing deficits in gap-detection measures.

In this review, we have chosen to focus on recent works related to ARHL that has improved our understanding of the cellular and molecular mechanisms that may cause age-related loss of sensory and neural cells in the cochlea. Our goal here is to give an overview of recent progress towards understanding these phenomena.

Noise exposure and ARHL

One of the most commonly studied extrinsic factors affecting the ARHL is the exposure to damaging levels of noise. It is well known that, exposure to extremenoise can result in temporary and permanent hearing loss in both humans and animal models [12]. Longitudinal studies have highlighted that cochlear damage in youth due to exposure to loud noise leads to a severe form of presbycusis [12].In animal models, early noise exposure that only causes temporary threshold increases can cause permanent SGN loss and accelerate presbycusis [13-15]. It is believed that cochlear damage from noise exposure that causes temporary or no immediate hearing loss may, in fact, accelerate ARHL. Unfortunately, there are a number of limitations in carrying out human studies to fully understand the long haul effects of clamor presentation bringing aboutARHL. However, anatomically, the loss of SGNs is linked to early loss of synaptic terminals between inner hair cells and SGNs [14,16].

Pathology of hair cells and SGNs in AHL

Humansand animals with ARHL typically present with the degeneration and death of multiple cell types. Lamentably, it is hard to comprehend if the pathology of hair cells and SGNs are associated [16]. The common perspective has for some time been that age-related loss of SGNs happens as a result of hair cell loss, synaptic loss, or both. SGNs do begin to die after mechanical or chemical damage of hair cells, although the rate is species specific. This led to the hypothesis that SGNs rely on hair cells for trophic support [17,18]. In any case, SGN loss can likewise happen without harm or demise of hair cells [19-21]. Subsequently, it is vague, in creatures with hair cell and SGN loss, if SGN loss happens in parallel to or as a result of hair cell death. An indisputable response to that question has demonstrated hard to discover.

Molecular mechanisms of ARHL

Oxidative stress pathways

A number of studies have focused on the hypothesis that age-related mitochondrial dysfunction is an underlying pathology that can cause or hasten ARHL [5]. These are based on the fact that that many genetic condition-sassociated with hearing loss also impair mitochondrial function, and maternally inherited mutations of the mitochondrial genome can cause deafness [22–25]. The cell normally keeps a balance betweenreactive oxygen species (ROS)andantioxidants [26]. This homeostasis degenerate with aging, leading to the higher ROS levels, which results in a variety of age-associated maladies, including ARHL [27]. Studies are available that have searched for, but not yet identified, genetic variants in ROS signaling genes that are associated with presbycusis [28,29]. Be that as it may, animal models vulnerable to oxidative stress display a range of aging related phenotypes, and the results suggest the cochlea is, forobscurereasons, hypersensitive to ROS induced mitochondrial damage [23]. For example, premature presbycusis in mice missing the gene encoding Cu/Zn superoxide dismutase 1 (SOD1) [30,31]. Similarly, mice deficient for glutathione peroxidase have shown evidence of accelerated ARHL and are more sensitive to noise induced hearing loss (NIHL) [32].

These studies show the sensitivityof the cochlea to ROS,thus encouraging many scientists touse exogenous antioxidants to prevent or ameliorate presbycusis with varied results [5]. The aftereffects of some studies have demonstrated clear advantage given by antioxidant treatment [33,34], yet others demonstrate no impact [35,36]. These studies use different techniques and thus there is no clear data on the dose the antioxidants also there is no clear mode of delivery [5]. Altogether, the researchtill date proposes thatoxidative imbalance does contribute to presbycusis, but also indicates that antioxidant therapy is not a magic elixir that willcounteractor treatARHL.

Cell death pathways

A lot of the harm brought about byROS produced in the mitochondria occurs in the immediate environment. It is understood that,deletions of mitochondrial DNA are more common in presbycusispatients than those with normal hearing [37]. Some have conjectured that harm to mitochondrial DNA leads to decreases in energy production that can ultimately cause cell death. Various methodologies have been utilized by specialists endeavoring to break down the impact of mutating mitochondrial DNA on aging and cochlear function. There are examples as suggested by few groups who have generated mice that fail to produce a specific DNA polymerase that is required for repair of mutations in mitochondrial DNA. These mice accumulate mitochondrial mutations more rapidly than wild-type mice. Interestingly, these mice also develop premature hearing loss [38,39]. By contrast, mice subjected to caloric restriction, which slows the age-related decline of mitochondrial function, have delayed presbycusis [40,41].

These findings lend credence to the idea that the cell death that causes presbycusis results from accumulated damage to mitochondria.

Numerous research groups have labored to determine if active or passive mechanisms of cell death occur in the cochleae of those with presbycusis.Recognizing distinctive types of cell deaths are regularly convoluted, particularly in vivo and in matured subjects. Not surprisingly, researchers have found evidence of both necrosis and programmed cell death in aging cochleae. Multiple lines of evidence suggest that the damage and stress to hair cells and spiral ganglion cells results in programmed cell death. For instance, TUNEL staining has been used repeatedly to show DNA fragmentation in hair cells and SGNs from aged animals [40,42]. A few endeavors to assesscell death mechanisms in the cochlea utilized qPCR and microarray technologies to analyze presbycusis-associated gene expression changes in the cochlea. Together, they have found that numerous apoptosis-related genes have altered expression in aged cochleae [39,43].

The perceptionsthat caloric restriction results in reduced TUNEL positive cells and mutation of mitochondrial DNA polymerase results in an increased number of TUNEL positive cells indicate that programmed cell death has a role in cochlear decline [40,44]. Likewise, mice that overexpress the human X-linked inhibitor of apoptosis (XIAP) protein have less hearing loss than wild-type siblings. Consistently, fewer hair cells died in mice with excess XIAP [45].

While microscopic analysis showed that dying hair cells in the cochleae of older mice typically appeared to be undergoing apoptotic death, there was also evidence of some cells undergoing necrotic death. As might be expected, these authors found expression of molecular markers consistent with caspase-dependent and caspase-independent cell death [46]. By contrast, one group found that neither overexpression of the pro-apoptotic protein BCL2 nor deletion of the gene encoding that protein affected AHL [47].

However, Someya et al. 2009,found that mice with a deletion of the pro-apoptotic gene *Bak* are resistant to age-related hearing loss and SGN death [48]. In general, it gives the idea that specifictypes of programmed cell death may contribute to age-related loss of cochlear function. However, it's not clear those other forms of cell deaths are not relevant. Additional work is required to elucidate the role of non-apoptotic cell death and to describe the apoptotic pathway functioning in hair cells and SGNs further.

Calcium signaling pathways

The changes in the calcium homeostasis havemore than once been recommended asa contributor to age-related impairment of neuronal function [49-51]. This is also evident by the low hearing thresholds in elderly women on channel blockers [52]. In this way, proposingthat calcium regulation contributes to ARHL [5]. Hair cells and SGNs have several types of calcium channels; including L- and T-type voltage-gated calcium channels [53-55]. The T-type, or low-voltage, calcium channel family is comprised of three members (Cav3.1, Cav3.2, and Cav3.3), based on their main pore-forming alpha subunits, a1G, a1H, and a1I, respectively [56]. The a1G and a1I subunits are weakly expressed in OHCs and IHCs and moderately expressed in SGNs.

The a1H subunit is highly expressed in SGNs and absent from OHCs and IHCs [55]. Intriguingly, one group recently reported a noteworthydelay of ARHLand preservation of SGNs in mice missing the gene encoding the $Ca_v3.2$ T-type calcium channel [5]. Furthermore,they showed that wild-type mice treated with T-type calcium channel inhibitors had significant preservation of hearing thresholds and SGNs, when contrasted with untreated controls[57]. These T-type calcium channel inhibitors can likewiseavertNIHL [58]. Together, these discoveries emphatically propose that extra research to consider the connectionbetween calcium signaling and hearing loss is warranted. Research into the potential therapeutic value of T-type calcium channel inhibitors is ongoing[5].

Other Pathways

Unmistakably ARHL is a muddled issue. What's more, is connected with various causes or etiologies. Accordingly, numerous differentmechanisms have been implicated as contributors to ARHL, but have not been studied extensively. These areas, described below, may prove to be fruitful avenues for future endeavors to characterize and prevent ARHL.

Glucocorticoid signaling pathways

The role of glucocorticoid signaling was initially proposed when Bao et al. 2005,showed that deletion of the β2 subunit of nAChRbrought on quickened ARHL connected with SGN degeneration [59]. Ensuing work in other research facilities demonstrated thataged mice, but not young mice, lacking high-affinity nicotinic receptors were shieldedfrom NIHL. This insurance was brought about by an age-related increase of corticosterone and activation of glucocorticoid signaling pathways, not a disruption of efferent cholinergic transmission. Curiously, incessant rise ofsystemic corticosterone levels resulted in the extensive SGN loss, indicating there is a delicate

balance of glucocorticoid signaling required for proper cochlear homeostasis [58]. So also,loss of NFκB, which can function as a key component in the glucocorticoid signaling pathway, in mice caused premature SGN loss [60].

Sex-specific hormones pathways

Numerous scientists have discoveredsex-specific differences in ARHL in humans and animal models [61]. Additionally, estrogen has neuro-protectiveimpacts in numerous frameworks [62]. In 2006, the researchers discovered that post-menopausal women using progestin for hormone replacement therapy had hearing loss more frequently than women using other or no treatments [63]. Similarly, combination hormone replacement therapy, using estrogen and progestin, was found to increase the incidence of ARHL [64].

However, the exact mechanisms, by which progestin impacts cochlear function are unclear [5]. However, this case highlights the fact that our listening to framework can be entirely delicate to strikes which don't harm other organic capacities [5].

Stress response signaling pathways

The role of stress response proteins in maintaining cochlear function was first identified in studies of NIHL[5]. These studies revealed that mice missing *heat-shock factor 1* (*Hsf1*) are less ready to recuperate from clamor impelled cochlear harmthan control mice [65,66]. A role for universal stress response proteins in ARHL was seen in recent works that demonstrated that the stress response proteins HSP70 and HSP110 are upregulated in the cochleae of control mice (CBA/N), as compared to mice that are prone to ARHL (DBA/2J)[5]. Curiously, some authors likewise demonstrated thataddition of geranylgeranylacetone, which induces HSP expression in the cochlea, to the diet of AHL sensitive mice prevented hearing loss, in spite of the fact that the protection was limited to the cochlear apices [67].

Glutamate signaling pathways

The genetic basis of ARHL may also be linked to glutamate signaling as a potential cause. In particular, variations inGRM7, the gene encoding metabotropic glutamate receptor type 7, have been linkedwith susceptibility to ARHL [68]. In spite of the fact that the precise systems are obscure, the authors demonstrated that GRM7 is expressed in SGNs and hair cells and postulate that the causative alleles ultimately result in glutamate toxicity similar to that previously seen in SGN explants [69,5].

Stem cells

Preliminary studies utilizing stem cells to ameliorate the degree of ARHL have likewise been finished. Once stem cells are localized to the cochlea, they could be stimulated with local growth factors to encourage differentiation into either hair cells or lateral wall cells [70].

Conclusions

A number of animal models of presbycusis have been developed to allow detailed study of disease progression and causes. Recent studies in the animal models have adequately uncoverednumerous cellular and molecular mechanisms that contribute to ARHL. Unmistakably commotion presentation isthat noise exposure is a critical environmental factor and that genetic aberrations can predispose one to age-related cochlear damage and dysfunction. Likewise, there is little uncertainty that damage to mitochondria and their ensuingdysfunction are often forerunnersto eventual disease phenotypes. Also, calcium signaling, glucocorticoid signaling, sex-specific hormones, and stress response pathways can addto presbycusis. However, it is hazy if thesesignaling pathways are all around requiredpresbycusis. Future studies are vital, that depend on more nitty gritty examination, including cell-type-specific transgenic models, genomic, and proteomic techniques, to ensure the most definite understanding and compelling medications for ARHL.

Advancement of viable procedures forprevention of peripheral ARHL requires a comprehensionmechanisms underlying the age-related cochlear changes. But the human studies have certain restrictions inherent in humans (genetic heterogeneity, duration of time for the onset and progression of ARHL, difficulty in controlling deleterious auditory exposures), a comprehension of themechanisms of ARHL (as well as possible points of intervention) are best achieved with animal models of aging, in spite of the constraints of animal models of aging. The challenge with the commonly-used animal models of aging is determining the extent to which the animal model aspects of human auditory aging and identifying the aspects of the animal model that cannot be generalized to the common human ARHL patient. Since research centeranimals are maintained in controlled environments, they are presented to few, assuming any, of the natural dangers that can influence the course of human ARHL, including: high-level noise, disease pathogens, medications, and others. In addition, numerous animal models are inbred strains, limiting the genetic heterogeneity of the models and making it more likely that they can be generalized to only a fraction of the

diverse human population. Moreover, the lifespan of animal and humans have gigantic distinction.

The treatment options for ARHL are the use of hearing aids. However, fewer older adults are using hearing aids.And thus therole of dissemination of healthcare information to the geriatric population is very important, especially in resource limited settings and the agencies working in this field for the spread of healthcare information should work really hard [71-83]. The enhanced screening and intervention programs to identify older adults who would benefit from amplification are needed to improve hearing in the elderly population.

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