Pathophysiology, Immunosenescence and Inflammaging of Presbyacusis

Subjects: Otorhinolaryngology

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Age-related hearing loss (ARHL), or presbyacusis, is a type of sensorineural hearing loss that primarily affects the elderly. However, the age of onset, rate of decline, and severity of hearing loss vary widely. As a result of ageing, the immune system can become defective, leading to the accumulation of unresolved inflammatory processes in the body. Various stimuli can sustain inflammaging, including pathogens, cell debris, nutrients, and gut microbiota.

Keywords: age-related hearing loss ; presbyacusis ; immunosenescence ; inflammaging ; chronic inflammation

1. Introduction

Age-related hearing loss (ARHL), or presbyacusis, is a type of sensorineural hearing loss that primarily affects the elderly [1]. However, the age of onset, rate of decline, and severity of hearing loss vary widely.

ARHL is the most common sensory disorder, with a high economic impact [2][3]. The World Health Organization (WHO) estimates that by 2050, 2.5 billion people, predominantly over 60, will be living with some degree of hearing loss [4][5]. Despite the high prevalence of this sensory disorder, there is a paucity of both preventative and treatment strategies other than prosthetic devices (hearing aids and cochlear implants).

Presbyacusis typically presents as bilateral, progressive, and irreversible [6][7]. The increasing prevalence of presbyacusis may be attributable to environmental factors, notably noise exposure and the rise in metabolic diseases [8][9][10].

This sensory disorder can be characterised by reduced hearing sensitivity and speech understanding in background noise, slowed central processing of acoustic information, and impaired localisation of sound sources [7]. Hearing loss affects high frequencies initially and eventually spreads to lower frequencies involved in speech understanding [7]. Untreated hearing impairment contributes to social isolation, loss of self-esteem, depression, and cognitive decline [11][12][13]. Even mild levels of hearing loss increase the long-term risk of cognitive decline and dementia [14].

ARHL has a complex pathophysiology linked to genetic risk factors that determine the rate and extent of cochlear degeneration. However, the severity of the hearing loss is also influenced by previous otological diseases, chronic illnesses, cumulative noise exposure, use of ototoxic drugs, and lifestyle [15]. Moreover, this condition has been associated with numerous comorbidities, including dementia, frailty, Alzheimer's disease, and type II diabetes [16][17][18][19][20]. A common trait of these disorders is chronic inflammation in target organs [21]. More recently, changes in gut microbiota have been linked to systemic inflammation affecting multiple organ systems, including the brain and the inner ear [22][23][24].

2. Pathophysiology of Age-Related Hearing Loss

Age-related hearing loss has mixed aetiology [7] and is likely a cumulative result of genetic and epigenetic factors [8][25][26][27] and environmental stressors [28]. Otological diseases, chronic exposure to noise, smoking, or exposure to ototoxic drugs can contribute to the development of ARHL [29][30]. Other factors include diet, gender, comorbidities, and lifestyle [20][31].

Reduced vascularisation in the cochlea, cumulative oxidative stress (OS), low-grade cochlear inflammation, impaired mitochondrial quality control, and mitochondrial DNA damage play a critical role in developing ARHL [8][32]. Age-related degenerative changes in the cochlea can lead to a loss of sensory hair cells and primary auditory neurons, damage to cochlear lateral wall tissues (stria vascularis and spiral ligament), and reduced vascularisation [29][33]. Post-mortem histological studies in the human cochlea have revealed sensory hair cell loss in the organ of Corti (OoC), degenerative

changes in the auditory nerve, atrophy of the stria vascularis (SV), and loss of fibrocytes in the spiral ligament (SL) [20][34][35][36]. More recent studies have demonstrated a loss of auditory nerve afferent fibres in the cochlea and synapses between the inner hair cells and type I afferent fibres [37][38]. The ageing process also negatively affects the central auditory pathways [20]. Based on predominant histopathological findings and differences in pure-tone audiometric testing, Schuknetcht et al. proposed classifying ARHL into sensory, neural, strial, and cochlear conductive types [34][35][39]. Many people with ARHL likely have a mixed pathology, but in some cases, the cause of ARHL cannot be determined by histological evaluation of cochlear tissues [40].

At present, ARHL has not been fully reproduced in animal models. However, these models are often used to delineate human pathophysiology, as clinical studies are challenging due to cochlear localisation deep in the temporal bone, precluding histological and high-resolution imaging studies [20]. In animal studies, vascular changes include reduced capillary network and narrowing of the vascular lumen in the SV [41][42][43]. The secretory epithelium of the SV is responsible for maintaining the high potassium (K^+) content of the endolymph and generation of the endocochlear potential (EP), which drives sensory transduction in the cochlea [44][45][46]. The SV typically deteriorates in the mid-cochlear to apical regions and is associated with reduced expression levels and activity of sodium-potassium pumps (Na-K-2Cl cotransporter NKCC1 and Na^+, K^+-ATPase), which leads to reduced EP [47][48][49][50][51][52][53][54]. Reduced activity of sodium-potassium pumps and decreased EP have been demonstrated in ageing gerbils raised in quiet and ageing mice [44][55].

The mouse is a robust and reliable mammalian model for ageing research, and the use of inbred mouse strains was instrumental in investigating the genetics of ARHL. For example, the commonly used C57BL/6 mouse strain develops progressive high-frequency hearing loss caused by a mutation of the cadherin 23 (*Cdh23*) gene, which encodes a component of the stereocilial tip-link required for gating of the mechanoelectrical transducer (MET) channel in sensory hair cells [56].

Elevated auditory thresholds in ARHL typically result from degeneration and loss of outer hair cells within the OoC. The loss of hair cells progresses from the basal turn of the cochlea (high-frequency region) to the apical turn (low-frequency region) [32]. Degenerative changes also affect synaptic networks between the inner hair cells and afferent auditory nerve fibres, which leads to reduced speech understanding in background noise [57][58][59].

3. Immunosenescence and Inflammaging

Immunosenescence is an age-dependent development of immune dysfunction that involves lymphoid organ remodelling, leading to reduced capacity to control inflammatory cytokines during and after the immune response. Immunosenescence can lead to chronic inflammation in ageing tissues, frequent infections, autoimmune diseases, and cancer due to impaired immune surveillance [21][60][61][62][63][64].

Inflammaging is a relatively new concept described as age-related, low-grade systemic inflammation that may not directly link to microbial infection [32][65]. Various stimuli, including cell debris, nutrients, and gut microbiota, can sustain inflammaging [66]. This sterile or pathogen-driven inflammation increases morbidity and mortality in the elderly [21][67][68]. As a result of ageing, the immune system becomes defective (immunosenescence), leading to the accumulation of unresolved inflammatory processes impacting otherwise healthy organ systems [69]. As a result, inflammaging can contribute to a spectrum of disorders such as Parkinson's and Alzheimer's disease, type II diabetes, and cardiovascular disease [70][71][72][73][74][75][76][77][78][79][80][81][82]. However, inflammaging is not a physiological or expected outcome of ageing; instead, a tell-tale of accelerated ageing [66].

Sensorineural hearing loss has also been linked with chronic inflammation [83][84][85]. Despite the historical belief that the cochlea is an immune-privileged organ [86], more recent studies have shown that the cochlea is vulnerable to systemic inflammation [22][87]. Cochlear microcirculation is controlled by tight junctions connecting vascular endothelial cells, forming the blood-labyrinth barrier (BLB) in the lateral wall [88]. The BLB plays a role in preventing pathogen infiltration, maintaining ion homeostasis, and transporting nutrients to the cochlea [89]. Pericytes and perivascular resident macrophage-like melanocytes (PVM/M) represent the second line of support for the BLB. Local inflammation activates PVM/M in the cochlea and thus increases the permeability of the BLB [90]. Furthermore, PVM/M can release proinflammatory cytokines through the tight-junction barrier [90] and increase the permeability of the BLB to the bacterial metabolite lipopolysaccharide (LPS) [88][91]. Similarly, acoustic trauma [88][92][93] and hypoxia [94] can also increase the permeability of the BLB, resulting in cochlear inflammation that predominantly affects the lateral wall tissues (SV and SL) [21][84]. It was shown that vascular cell senescence is a key factor in the breakdown of the blood-brain barrier (BBB) [95], which is

physiologically and structurally equivalent to the BLB of the inner ear [22]. This suggests that vascular cell senescence may also affect the integrity and permeability of the BLB.

Inflammation has been identified in multiple preclinical and population health studies as a pathophysiological mechanism contributing to ARHL [85]. For example, in the “Hertfordshire Ageing Study”, Verschuur et al. described a progressive increase in the expression of markers associated with systemic inflammation (interleukin-6, C-reactive protein, white blood cell, and neutrophil counts) in subjects with ARHL, which correlated with the elevation in hearing thresholds [63][96]. That study concluded that low-grade inflammation is at the foundation of ARHL. In the English Longitudinal Study of Ageing, Lassale et al. also demonstrated an association between white blood cell counts and age-related hearing impairment [97]. Other studies revealed changes in the number and morphology of macrophages in the ageing cochlea [98][99]. Activated macrophages were present in the lateral wall and auditory nerve and were more abundant in the cochlear basal turn of the older donors [99]. Based on these studies, an ongoing ASPREE-HEARING study was designed to investigate the benefits of low dosages of the anti-inflammatory agent aspirin on the progression of ARHL [100]. The rationale for this research is that aspirin is an inflammation resolution mediator [101], as it decreases the levels of proinflammatory mediators, including TNF-α, IL-6, and thromboxane B2 (TXB2) [102][103][104].

Preclinical studies have shown that in ageing C57BL/6J mice, the resident macrophages in the basilar membrane of the OoC change morphologically in response to sensory cell degeneration, indicating their activation [105]. This finding is consistent with the up-regulation of genes linked with immune and inflammatory responses in older murine cochleae [106]. Using next-generation sequencing, Su and collaborators [106] revealed multiple immune and inflammatory transcriptomic changes during cochlear ageing. The TNF signalling pathway, toll-like receptor signalling pathway, Jak-STAT signalling pathway, and NF-kB signalling pathway featured prominently among up-regulated genes in aged mice [106].

A senescence-associated secretory phenotype (SASP) is one of the possible factors contributing to inflammaging and associated changes in the central nervous system (CNS). It has been established that cells change their phenotype to senescence as a preventative measure for malignancies; however, these cells accumulate within tissues as the body ages [107]. Even though these cells are growth-arrested, they are still metabolically active and change protein expression primarily due to DNA damage [108]. SASP promotes local inflammation via the secretion of cytokines, chemokines, reactive oxygen and nitrogen species, and growth factors [107]. Proliferative cells of the CNS, such as endothelial and glial cells, can adopt SASP, leading to low-grade chronic inflammation in the ageing brain [109]. It was proposed that the permeability of the BBB might be affected by the build-up of SASP cells [95][110][111].

Despite the similarities between the BBB and the BLB, this aspect of senescence has yet to be established for the BLB and ARHL.

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