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Current Concepts of the Mechanisms in Age-Related Hearing Loss

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Commentary

Age-related hearing loss (AHL), also known as presbycusis, is one of the most prevalent chronic degenerative conditions; it progresses with age and affects tens of millions of the elderly worldwide. It is characterized by a decline in auditory function, which is reflected by higher hearing thresholds and poor frequency resolution [1], resulting in the inability to understand words and making it difficult to understand everyday language. The primary pathology of AHL includes the loss of sensory hair cells and spiral ganglion neurons, and strial atrophy [2], in addition to degeneration of the central auditory pathways. AHL is caused by the interaction of multiple factors and shows large variations in the onset and extent of hearing loss. These multiple factors complicate the interpretation of basic and clinical research in AHL [3]. Human epidemiological studies have identified four risk factor categories for AHL, including cochlear aging (individual age), environment (occupational and leisure noise exposure, ototoxic medications, socioeconomic status), genetic predisposition (sex, race, specific genetic loci/genes), and health comorbidities (hypertension, diabetes, stroke, cigarette smoking) [4-6]. Genetic investigation has identified several putative gene associations, including with genes related to antioxidant defense systems, such as glutathione S-transferase and atherosclerosis.

It has been postulated that reactive oxygen species (ROS) play a major role in the degeneration of cochlear cells during aging [7,8]. Oxidative stress in the cochlea may result in enhanced hypoxia owing to a poor cochlear blood supply in atherosclerosis, which could be accelerated by genetic and comorbid factors.

Mitochondria are believed to be a major source of ROS [9-11]. ROS generated inside the mitochondria can damage nuclear DNA, mitochondrial DNA (mtDNA), membranes, and proteins, and further, accumulate such damage. In particular, the level of a 4977-bp deletion in mtDNA, known as the "common ageing deletion", increases with age in human temporal bones [12-15]. *Polg* knockin mice, which were created by introducing a two-base substitution, lost the ability to proofread mtDNA defects and showed an early onset of AHL with severe degeneration of spiral ganglion and cochlear nucleus neurons [16,17]. These findings indicate that the accumulation of mtDNA mutations during aging leads to mitochondrial dysfunction, an associated impairment of energy metabolism, and degeneration of the cochlea and central auditory pathway.

Multiple antioxidant enzymes scavenge ROS and control their damaging effects, including superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase. These antioxidant defense systems may also be influenced by the genetic background including race, and the level of some antioxidant enzymes have been shown to decrease during aging. For example, Mice lacking SOD1 were shown to have accelerated age-related cochlear hair cell loss, reduced thickness of the stria vascularis, and severe degeneration of spiral ganglion neurons [16,17]. These findings indicate that an age-related decline in the cochlear antioxidant defence systems can lead to an age-related increase in ROS and also play a pivotal role in the development of AHL.

In fact, supplementation of the following antioxidants slows AHL in mice and rats: vitamin E and C plus melatonin or lazaroid; lecithin; a mixture of L-cysteine-glutathione mixed disulfide, ribose-cysteine, NW-nitro-L-arginine methyl ester, vitamin B12, folate, and ascorbic acid; α-lipoic acid and coenzyme Q_{10}; and N-acetyl-L-cysteine [8,18-20]. Further, compared to age-matched controls, C57BL/6 mice that received caloric restriction (CR) retained normal hearing and showed no obvious cochlear degeneration and a significant reduction in the number of terminal deoxynucleotidyl transferase dUTP nick end labeling-positive and cleaved caspase-3-positive cells among the spiral ganglion cells. DNA microarray analysis revealed that CR downregulated the expression of 24 apoptotic genes, including *Bak* and *Bim*, suggesting that CR could prevent apoptosis of cochlear cells [21]. Oxidative stress from paraquat induced Bak expression and apoptosis in primary cochlear cells, which was ameliorated in Bak-deficient cells [8]. These results suggested that AHL was caused by oxidative stress-induced Bak-dependent apoptosis. Furthermore, CR failed to reduce oxidative DNA damage and prevent AHL in C57B/6 mice lacking Sirt3, a mitochondrial deacetylase [22]. In response to CR, Sirt3 was deacetylated and it in turn activated mitochondrial isocitrate dehydrogenase 2, leading to increased NADPH levels and an increased ratio of reduced-to-oxidized glutathione in the mitochondria. These findings indicated that the beneficial effects of CR were mediated by ROS-antioxidant systems and that Sirt3 is essential for upregulating the cochlear mitochondrial glutathione antioxidant defence system during CR.

Taken together, the putative AHL mechanism is that the cumulative effects of oxidative stress result in the accumulation of mtDNA mutations/deletions and the decline of mitochondrial function, and that these progressively induce Bak-dependent apoptosis of cochlear cells. AHL may be delayed or prevented by supplementary antioxidants or CR. Large clinical trials are needed to verify if AHL can be delayed or prevented in humans and to clarify the molecular mechanism of AHL.

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