

Cellular and molecular mechanisms involved in age-related hearing loss with focusing on oxidative stress

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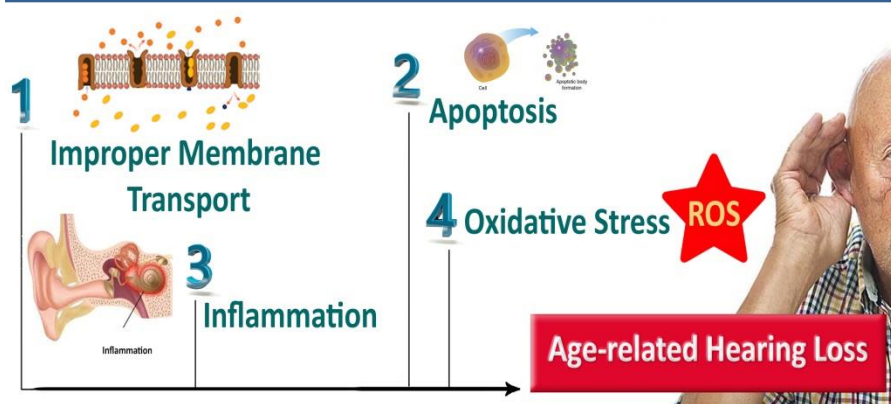
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Highlights

- ARHL is characterized by increasing age and hearing loss from low to high frequencies.
- Factors involved in ARHL are divided into two genetic and non-genetic categories.
- Inflammation, apoptosis, and oxidative stress are three main mechanisms of ARHL.

Graphical Abstract



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Abstract

Age-related hearing loss (ARHL) is a type of bilateral hearing loss that progresses from low frequencies to high frequencies with age. This disorder is classified as a multifactorial disease. Factors involved in ARHL pathology are divided into two categories of genetic and non-genetic factors. The genes involved in this disorder include three categories of genes involved in cochlear structure and function, genes correlated with oxidative stress, and mitochondrial-dependent genes. Oxidative stress, apoptosis, and inflammation are the three main causes of ARHL. Damage to hair cells induces intrinsic and extrinsic apoptosis and can therefore accelerate ARHL. Some process in cells leads to the production of high amounts of reactive oxygen species including hydrogen peroxide (H_2O_2), anion superoxide (O_2^-), and hydroxyl radical (OH). Reactive oxygen species or ROS can generally have several sources including nitric oxide synthase, NADPH oxidase, microsomal, mitochondrial, and proximal pathways. In typical conditions, ROS is produced and neutralized by antioxidant enzymes such as superoxide dismutase, catalase, and glutathione, balancing cell homeostasis. Though, the process of aging, drug treatment, and some other factors upset this homeostasis, and this causes oxidative stress and induction of ARHL in the cells of the auditory system. The aim of this study was to describe the cellular and molecular mechanisms involved in ARHL with a focus on oxidative stress.

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Introduction

Age-related hearing loss (ARHL) is a widespread disorder in the elderly and has become difficult health and social problem (1, 2). Hearing sound at high frequencies is one of the first signs of this disease. People with ARHL hear sounds slower and more unclear (3, 4). In 2012, according to the WHO report, about 360 million people suffered from hearing loss worldwide, 91% of whom were adults (5). Risk factors for ARHL include genetic and non-genetic factors. The disease is a multigenic disorder and at least 10 gene loci have been identified in animal models of the mouse for this disorder. For example, one of the loci associated with this disorder is *Ahl1*, which is located on chromosome 10 of mice and encodes an energy-dependent calcium transporter pump in the membrane that has a recessive hereditary pattern. This locus may be involved in the premature dysfunction of the organ of Corti and spiral ganglion nerve dysfunction (6, 7). In recent years, many studies have been identified on genes involved in human ARHL. The genes studied in this disease could be divided into three usual categories. Genes are involved in the function and structure of the cochlea. Genes correlated with oxidative stress. Mitochondrial-dependent genes (1).

ARHL disorder is caused by damage and loss of spiral ganglion cells, sensory hair cells, as well as stria vascularis cells. Important mechanisms involved in ARHL include inflammation, oxidative stress, mitochondrial dysfunction, and apoptosis (8). Inflammation begins with events that eventually lead to improved damaged tissue. Like other factors, inflammation increases oxidative stress in the inner ear and consequently increases ROS, which eventually leads to apoptosis or necrosis of the inner ear cells and ARHL (9, 10). Apoptosis is the process by which caspase molecules drive cells to programmed death. This process is done in two ways, intrinsic and extrinsic. In the extrinsic pathway, stimulation of receptors on the outer membrane of the cell, through the breakdown of caspase-8, triggers the cell suicide process with the help of caspase-3. The intrinsic pathway causes the cell to commit suicide by altering the permeability of the membrane of mitochondria with the help of caspase-9 and the release of cytochrome c (11, 12). In this process, the amount of oxidative stress in the cell increases simultaneously. The role of caspase-induced apoptosis in hair cell destruction has been proven in many studies (13).

Studies on oxidative stress have shown that one of the targets of reactive oxygen species (ROS) is genomic DNA. Damage to the genome triggers the intrinsic pathway of apoptosis (14). The use of aminoglycosides has been shown to increase cellular ROS in the cytoplasm by disrupting the homeostasis of calcium between the mitochondria and endoplasmic reticulum, resulting in the release of calcium in the mitochondria and increased mitochondrial permeability, causing cell damage and death in hair cells (8, 15). Superoxide dismutase (SOD), which catalyzes the conversion of superoxide to hydrogen peroxide and oxygen, is the main part of the system of antioxidant defense *vs.* ROS. Evidence from the London ARHL cohort suggests the influence of a genetic polymorphism on the superoxide dismutase 2 (SOD2) promoter on the regulation of the SOD2 expression and correlates it to the risk of ARHL in men (16). Of course, other antioxidant molecules that can play a role in the pathophysiology of ARHL. This study aimed to describe the cellular and molecular mechanisms involved in ARHL disorder with a focus on oxidative stress.

Mechanisms involved in the age-related hearing loss

Several mechanisms are involved in ARHL. Each of these mechanisms causes hearing loss and, ultimately, presbycusis in different ways. The cases leading to this disorder are summarized in Figure 1.

The age-related immune response

The age-related immune is associated with controlling or reducing the production of proinflammatory proteins during or after the immune response. Inflammation begins with events that eventually lead to the improvement of damaged tissue. Like other factors, inflammation increases oxidative stress in the inner ear and consequently increases ROS, which ultimately leads to necrosis or apoptosis of inner ear cells and ARHL. It is now said that even a small amount of chronic inflammation is correlated with major age-related diseases (17,

18). Changes in the capillary circulation of the cochlea are one of the important factors in the development of various types of ARHL. The destruction of small vessels and stria capillaries is clearly associated with hearing loss and its occurrence. Thickening of basal laminas and retention of laminin and immunoglobulin in stria vascularis have also been reported in animal models. Experimental studies on inflammation of the inner ear have shown high levels of TNF, IL-1 β , and IL-6 in cochlear aging. IL-1 has a main role in autoimmune diseases and inflammation by activating the gene expression correlated with the acquired or innate immune response (19, 20). IL-6 is a predominant proinflammatory cytokine and marker in the inflammatory process. TNF is another important marker in inflammation. This cytokine is the central circulatory agent that is produced under pro-inflammatory conditions. NF- κ B also regulates the expression of this cytokine. After the TNF production, endothelial vascular cells begin to produce several adhesive molecules, demanding to bind to different leukocytes and trigger proinflammatory behavior. Thus, IL-1, IL-6, and TNF are cytokines that are present in most inflammatory sites and are used as targets in therapeutic interventions (17).

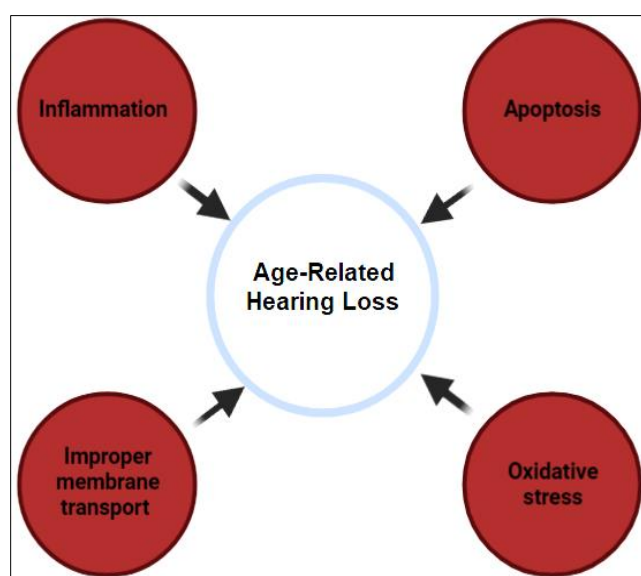


Figure 1. Mechanism of ARHL. The molecular pathways which result in ARHL.

The pathway of apoptosis

To date, studies on the process of apoptosis and its association with ARHL have been performed in mouse models, and it has been suggested that many genes associated with apoptosis change in expression with aging and hearing loss. Apoptosis and mutations in the mitochondrial DNA (mtDNA) are involved in ARHL and loss of sensory hair cells. Deletion of Bak gene, a mitochondrial pro-apoptotic gene, results in the loss of aging-associated spiral ganglion neurons; however, in c57BL/6J mice, despite these results, an over-expression of Bax and a down-regulation of cytochrome c oxidase was observed and a decrease in cochlear activity was observed in SAMP8 mice during aging. As a result, a slight increase in the expression of Bak1 apoptotic and anti-apoptotic Bcl2 genes was observed in blood samples of ARHL mice (20).

If we want to be clearer about the path of apoptosis and how it is created, we must say that this process has two general extrinsic and intrinsic pathways. The Bcl2 protein family is involved in the intrinsic apoptosis pathway. This gene family is classified into two groups: apoptotic (BAX, BAK1, and BAD) and non-apoptotic (BCLXL, BCL2). Studies in mouse models have shown increased expression in the Casp3 and Bak1 genes during the ARHL development. In a study, Tadros et al. identified over-expression of Bcl-xL and Bcl2 as a major factor in cochlear inner ear aging (13, 21). Also, according to studies and researches performed on animal models, the role of miRNA in apoptosis and its relationship with ARHL was discussed. According to these studies, miRNAs play a key role in the production and differentiation of auditory neurons. The association between aging and depletion of total miRNAs has also been demonstrated. Mice models with ARHL have been associated with

increased apoptosis of auditory cells. As a result, following these changes, an increased expression of pro-apoptotic and a decreased expression of anti-apoptotic genes was observed. Single miRNA genes can also play a prominent role in ARHL development. Its most prominent example is miR-96 with point mutations cause progressive autosomal dominance ARHL in both humans and mice (4).

Membrane transport pathway

Proper ion transport function in membranes plays an essential role in maintaining normal hearing. Ion transport is involved in the growth of hair cells, maintaining organ function, and maintaining endolymphatic potential (EP). Stria Vascularis has many mitochondria and includes marginal cells that maintain potassium-rich compounds in the cochlear duct through a unique combination of potassium pumps and channels that are necessary for keeping high intracranial potential. An example is the Na⁺K⁺ ATPase pump, which regulates low Na⁺ concentrations and high potassium levels in endolymph. ATPase levels in Stria Vascularis are said to decrease with age. Potassium exchange, which is supported by fibrocytes, shows a main action in homeostasis of inner ear. In fact, ARHL is associated with the destruction of Stria Vascularis and decreased intracochlear potential (4, 22). Mucolipins, identified as transient receptor potential channels, are a varied group of cationic carriers and are involved in mammalian sensory systems, including hearing. Mucolipins 1 and 3 are present in the lysosomes of hair cells of inner ear and help regulate calcium. In mouse models, the lack of mucolipin 1 and mucolipin 3 caused premature polygenic ARHL associated with hair cell loss (4, 23). Wolframin is a protein encoded by WSF1 that appears to be a selective large cation ion channel. Mutations in WSF1 result in a type of autosomal dominant ARHL (4). The protein structure homology models for this protein is demonstrated in Table 1. SLC7A8, or Solute Carrier Family 7 Member 8 responsible for amino acid transporter in many organs, is positioned in the inner ear and in the spiral ganglion and spiral ligament (4).

Table 1. Homology models for Wolframin was obtained from ExPASy.

Organism	Proteome Size	Sequence Modeled	Models	Seq Coverage
Homo sapiens	20,588	16,696	40,319	
Mus musculus	21,986	18,300	41,137	
Caenorhabditis elegans	19,812	11,665	21,059	
Escherichia coli	4,392	3,565	5,914	
Arabidopsis thaliana	27,469	19,156	34,985	
Drosophila melanogaster	13,821	9,451	18,409	
Saccharomyces cerevisiae	6,050	4,373	8,030	
Schizosaccharomyces pombe	5,122	4,030	7,534	
Caulobacter vibrioides	3,720	2,858	4,858	
Mycobacterium tuberculosis	3,993	3,127	4,967	
Pseudomonas aeruginosa	5,564	4,654	8,391	
Staphylococcus aureus	2,889	2,264	3,628	
Plasmodium falciparum	5,380	3,383	6,051	

The oxidative stress pathway

Schematic of oxidative stress involved in ARHL is demonstrated in Figure 2. ROS, which is often free radicals, damage intracellular components, including the nuclear and mitochondrial genomes, and many intracellular proteins. The body develops the antioxidant system as a defense mechanism, and the inability of this system to against ROS is called oxidative stress. Phase 1 and 2 antioxidant enzymes, such as glutathione S-transferase (GST), glutathione peroxidase, N-acetyltransferase (NAT), and cytochrome P450 (CYP1A1), can counteract ROS produced in the inner ear. Thus, individuals whose genes have been deleted in their genome are at higher risk of developing ARHL (24). Mitochondria are the chief source of production of ATP in eukaryotes and the production of high amounts of it requires Na⁺K⁺ ATPase activity, which leads to the production of high amounts of ROS. These free radicals include O^{2•}, H₂O₂, and OH, which play a key role in cell signaling. Reactive oxygen species or ROS can generally have several sources, including nitric oxide synthase, NADPH oxidase, and microsomal, mitochondrial, paroxysmal pathways. The main sources of ROS production in the inner ear include mitochondria, enzymatic reactions, excessive secretion of nitric oxide (NO), neurotransmitters, and NADP oxidase 3. In usual conditions, ROS formed by mitochondria is excreted and neutralized by antioxidant enzymes such as catalase, SOD, and glutathione (GSH), balancing the homeostasis of cell. However, the aging, drugs, and exogenous factors disrupt this balance, and this imbalance is named oxidative stress (4, 25).

Because ROSs are unstable particles that react with other molecules, they destroy proteins, lipids, and DNA. ROS is mainly produced by mitochondria in mammalian cells and therefore it is said that mitochondria are the main factor in the aging process due to the source of ROS production. There is also a complex interaction between other pathways of cellular aging, including pathways in the immune response, calcium dynamics, apoptosis, and aging. ROS produced by mitochondria destroys other mitochondrial components such as mtDNA, membranes of mitochondria, and respiratory chain components, which influence the function of mitochondria. This destructive ROS eventually alters the function of the electron transfer chain and reduces the quality of ATP production. This process produces a vicious cycle called the mitochondrial clock hypothesis. This theory is because ROS produced by mitochondria causes mtDNA degradation, and because mtDNA encodes most mitochondrial proteins, a mistake in gene expression impairs the function of mitochondrial subunits. This causes ROS leakage and stimulates mitochondrial DNA damage. Thus, mutations in mtDNA increase ROS production and consequently cell destruction and apoptotic cascade, leading to cell death (25, 26). In the cochlea, ROS is produced by mechanosensory hair cells due to sensitivity to sound stimulation and is normally neutralized by the internal antioxidant mechanisms of hair cells.

Also, ROS, which is caused by excessive stimulation of sound and ototoxic drugs disrupts the antioxidant defense mechanisms of hair cells and leads to ROS accumulation and eventually cell dysfunction, including lipid peroxidation, polysaccharide depolymerization, and nuclear degradation. Other consequences of increased ROS accumulation can be disruption of cochlear blood flow and destruction of supporting structures and nerve fibers. These destructive changes are also seen in stria vascularis. Calcium is another essential messenger in the cochlea. Elevated intracellular Ca²⁺ leads to increased ROS production, glutamate, and NO. Glutamate is the neurotransmitter of auditory neurons type I. The function of glutamate is limited to rapid and efficient absorption and metabolism, and as long as its secretion is not excessive, it cannot cause excitotoxic damage to neurons and damage to adjacent cells. NO also acts as a neurotransmitter and in some cases as a neurotoxin. In this way, it could act as a free radical alone or combine with anion superoxide to create peroxynitrite. RNSs, like ROSs in the cochlea, cause cell dysfunction and ultimately stimulate apoptosis and cell death. RNSs are produced by combining superoxide and nitric oxide. Nitric oxide is also created by induced nitric oxide synthase, a vital enzyme (26, 27).

In cochlear aging, the need for energy production is met by oxidative phosphorylation. Also, in the cochlea and during the aging process, two important events, including the reduction of cochlear blood flow and vascular conduction, cause the production of free radicals. It is also said that mtDNA is sensitive to oxidative

damage due to the lack of protective proteins such as histones. Mutations in mitochondrial DNA, which include point mutations, deletions, and insertions, accumulate and spread through cell division, leading to age-related diseases. The main role of mtDNA is to regulate mitochondrial biological activity. Oxidative damage to mtDNA hair cells disrupts mitochondrial regulation and ultimately stimulates apoptosis. Stimulation of the apoptotic pathway by oxidative stress and ROS accumulation is a decrease in Bcl-2 protein expression. Members of the Bcl-2 protein family are present upstream of caspase and act as a checkpoint in regulating apoptosis. Bcl-2 is primarily present in the outer membrane of the mitochondria, whose function is to prevent the secretion of cytochrome c and to prevent the activation of the apoptotic pathway. According to studies by Cunningham et al., this protein is present in the outer ear hair cells of mice (28, 29).

In addition, Bcl-2 high expression reduces the caspase-9 activation and consequently inhibits the activity of the apoptotic pathway. Therefore, excessive production of ROS reduces the expression of Bcl-2 and therefore oxidative stress stimulates the apoptotic pathway. Creatine is also one of the substances that is effective in preventing hearing damage. Creatine is essential for maintaining the energy required by the cell during the process of the auditory. It also plays a role in reducing the production of ROS in the mitochondria, increasing and surviving the potential of the inner membrane of the mitochondria. In addition, the accumulation of ROS in hair cells inhibits the enzymatic activity of creatine kinase and ultimately leads to an imbalance in creatine phosphorylation. Finally, the p53 (nuclear transcription factor) is said to be activated by oxidative DNA damage, leading to apoptosis and cell loss. Thus, due to oxidative damage to DNA caused by mitochondrial-derived ROS, in the cochlear tissue of the aged ear and other tissues, p53 is transferred to the mitochondria and activates Bak, resulting in hair cell apoptosis (25, 30).

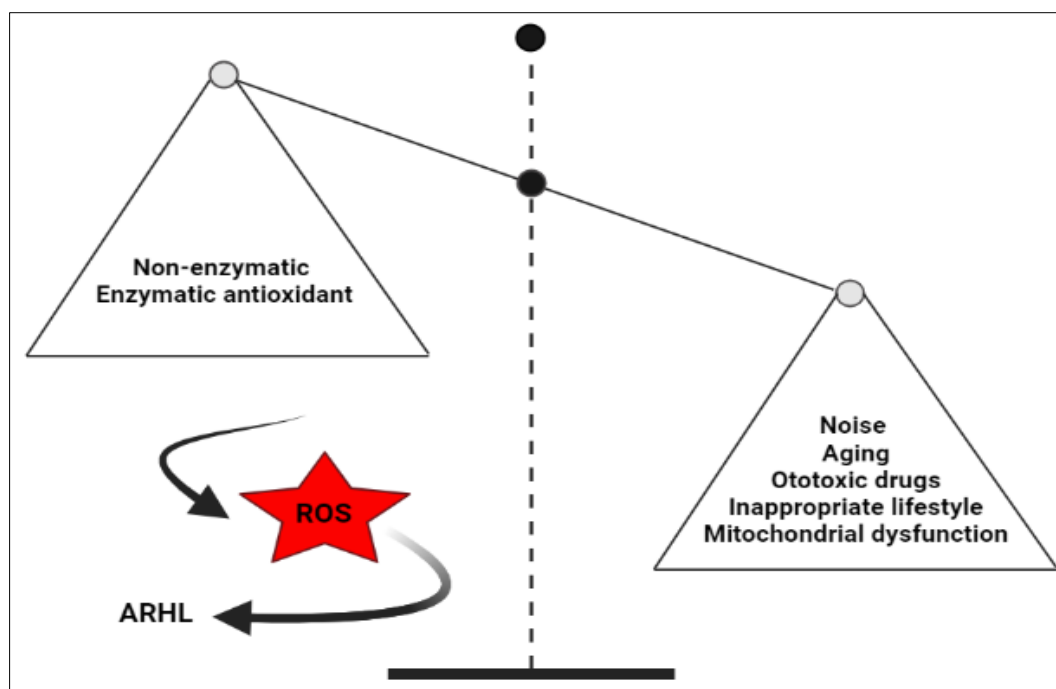


Figure 2. Schematic of oxidative stress involved in ARHL. An imbalance between ROS and antioxidants leads to oxidative stress and ARHL.

GSTP1, GSTM1, GSTT1, NAT, and CYP1A1 are among the genes involved in ROS production and cell damage. Polymorphisms in each of these genes, known as phase I and II enzymes, detoxifying and antioxidant, cause cell damage. GSTs are antioxidant enzymes involved in the combination of an extensive variety of electrophilic matters with glutathione, which facilitate the deactivation of toxic substrates and have a key role in antioxidant defense in the adult cochlea. Decreased glutathione and GST activity causes susceptibility to cell damage. At lower levels of glutathione, the cochlea is prone to loud noise and the aminoglycoside stimulates

damage. Carriers of the GSTM1 gene displayed a lower degree of hearing loss than those with the gene. This was not true for the GSTT1 gene. The GSTM1 gene is an antioxidant enzyme found in mammalian cochlea and is responsible for protecting human capillary cells from cell damage associated with aging and noise. The next polymorphism in the GSTP1 gene is involved in the replacement of valine with isoleucine, and this change leads to the development of ARHL (31). The GSTM1 and GSTT1 genetic polymorphisms involve the deletion of 20 bp, which ultimately leads to a loss of functional activity around a combination of metabolites and specific enzymes (24).

Cytochrome P450A1 is a member of the cytochrome P450 gene family positioned on chromosome 15 and is one of the main phase I enzymes and has a vital role in the metabolism of endogenous and exogenous substances and the activation of polycyclic aromatic hydrocarbons (PAH) and converts them to carcinogens. This gene is involved in the detoxification and excretion of harmful substances by oxidizing some substances such as steroids, fatty acids, and xenobiotics. Other genes in the CYP family include aryl hydrocarbon hydroxylase (AHH), which includes mononucleotide polymorphisms related to the substitution of thymine to cytosine at position 3801 and the 3' untranslated region of CYP1A1. Another related polymorphism of this gene is rs1048943, which is located downstream of Exon 7 and causes a mutation in the exchange of isoleucine to valine in the catalytic area of the protein and ultimately enhances the function of the enzyme (24, 32).

Treatment and management of age-related hearing loss

The ARHL prevention is a new approach in recent research. Over the years, many efforts have been made to prevent/slow its onset or progression, which has essentially included strengthening their antioxidant defenses. Other efforts that have been reported to be effective include the treatment of animals with blockers of calcium channel, statins, geranylgeranylacetone heat shock protein, cochlear vasodilator, electrical stimulation to restore the cochlear potential, salicylate therapy, calorie restriction, and anti-apoptotic therapies (26). It is said that the genetic background and physiological status of individuals are complex factors that have a role in the success of therapeutic interventions. Keeping away noise and other risk factors such as diabetes, ototoxic drugs, heart disease, and high blood pressure could avoid damage to cochlear hair cells and consequently reduce the influences of ARHL. However, this is not always possible and treatment methods for ARHL are still not available. The complexity of the mechanisms of all types of ARHL, including sensory, neural, and strial makes it impossible to use simple audiometric tests. Another required challenge is the targeted drugs delivery, including nanocarriers, to enhance the effectiveness of drugs in cochlear therapies. Finally, the constant question is the concern about the dangers of long-term drug use; While short-term treatment of vitamins and antioxidants is safer. Antioxidant supplements include vitamins A, E, C, B12, coenzyme Q10, ginseng, STS, D-methionine, Alpha-lipoic acid, NAC, Amifostin, Ebselen, Flunarizine. Analysis of clinical trials displays that long-term use of vitamin A, beta-carotene, and other vitamins is correlated with total mortality (33-35).

Other treatments that may be effective in ARHL include gene therapy and stem cell therapy. In the last decade, many attempts have been made to regenerate functional hair cells and spiral ganglion neurons using mature stem cells, induced pluripotent stem cells, and embryonic stem cells in the elderly inner ear (20). If we want to point out ways to improve hearing loss, we can say that this can be done by tools and methods. How to use these tools and methods depends on the severity of the disease and also its effectiveness in different people. There are a number of tools and aids to improve hearing. For example, hearing aids are electronic devices that can be used by placing them on the back or front of the ear. These instruments make the sounds louder. Cochlear implants are small electronic instruments that are surgically implanted in the inner ear. When hearing loss is acute, the doctor may recommend cochlear implants for one or both ears. There are other methods as well, such as a bone-anchored hearing system, hearing aids, and lipreading practice. But the most commonly suggested method is the hearing aid prosthesis and cochlear implant, which are able to improve hearing to an acceptable level and give the person the ability to understand speech in calm environments. However, these tools do not work properly in crowded environments (36-39).

Conclusion

Age-related hearing loss is one of the most common hearing disorders, especially in the aged population. The disorder involves the central auditory pathway, the afferent spiral ganglion neurons, the stria vascularis, and the hair cells of the organ of Corti. Numerous studies show that accumulation of reactive oxygen species, mitochondrial genome damage, and decreased antioxidant activity are associated with cochlear aging and ARHL. Enzymes that are involved in the oxidative stress pathway can reduce the risk of developing this disease by functioning properly and overcoming excess ROS. Successful treatment interventions depend on factors such as genetic background, physiological status, avoidance of noise, some underlying diseases such as diabetes, heart disease, and hypertension, and the use of ototoxic drugs. Many activities have been done to prevent or slow down ARHL disorder, mainly by strengthening their antioxidant defenses with antioxidants. Other efforts have been reported in this field, including the treatment of animals with calcium channel blockers, heat shock inducers, statins, salicylate therapy, cochlear vasodilators, electrical stimulation, and anti-apoptotic therapies. These approaches can be promising effective treatments for ARHL in the future.

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