Research Advances on Stria Vascularis Dysfunction and Age-Related Hearing Loss

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Abstract

Age-related hearing loss (ARHL) is a common sensory disorder in humans caused by inner ear abnormalities. The stria vascularis (SV) is a major cochlear structure that can degenerate independently and affect hearing. This article aims to review the research progress on the relationship between the stria vascularis and age-related hearing loss, focusing on literature regarding age-related hearing loss caused by the stria vascularis under different etiologies, including reactive oxygen species and inflammation, vascular injury, mitochondrial dysfunction, gene deletion, among others. It attempts to explore its mechanisms at the cellular and molecular biology levels.

Full Text

Research Progress on Vascular Stria Dysfunction and Age-Related Hearing Loss

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Abstract

Age-related hearing loss (ARHL) is a common sensory disorder in humans caused by abnormalities in the inner ear. The stria vascularis (SV) is a major cochlear structure that can degenerate independently and affect hearing. This article aims to review research progress on the relationship between the stria vascularis and age-related hearing loss, focusing on literature concerning ARHL caused by stria vascularis dysfunction under various etiologies, including reactive oxygen species and inflammation, vascular injury, mitochondrial dysfunction, and gene deletion. We attempt to explore the underlying mechanisms at the cellular and molecular biological level.

Keywords: age-related hearing loss; stria vascularis; vascular damage; ROS; Na+/K+-ATPase

1. Age-Related Hearing Loss

Age-related hearing loss (ARHL), also known as presbycusis, refers to the gradual onset of auditory system dysfunction with increasing age, affecting more than 10% of the world' s population. It ranks as the second most common disease among elderly individuals and represents the third most prevalent condition globally [1-4]. ARHL is a progressive, irreversible, and symmetrical bilateral sensorineural hearing loss that initially affects high frequencies, with the affected frequency range gradually expanding to lower frequencies as age increases, eventually developing into full-frequency hearing loss [5,6].

By 2050, the global number of people with mild to complete hearing impairment is projected to increase to 2.45 billion, with the vast majority being age-related hearing loss [7]. Presbycusis also leads to social withdrawal, depression, anxiety, cognitive decline, and dementia in elderly individuals [8]. Degenerative changes in the inner ear of elderly humans and other mammals occur among sensory hair cells, spiral ganglion neurons (SGNs), and cells of the stria vascularis and spiral ligament [9-11].

2. Stria Vascularis

2.1 Physiology of the Stria Vascularis

The stria vascularis (SV) is a highly vascularized tissue lining the medial aspect of the cochlear lateral wall, composed of three main cell types: marginal cells (MC), intermediate cells (IC), and basal cells (BC), each performing specific functions. Additionally, the SV contains a specialized differentiated capillary network—the blood-labyrinth barrier (BLB)—whose structure includes endothelial cells (ECs), basement membrane (BM), pericytes (PCs), and perivascular resident macrophage-like melanocytes (PVM/Ms). During development, the cellular layers of the SV originate from different cell lineages: marginal cells derive from otic epithelium, while basal cells form from otic mesenchyme after the establishment of marginal and intermediate cell layers [12,13].

Marginal cells form the innermost layer of the stria vascularis through tight junctions, are exposed to endolymph, and are responsible for the active transport of potassium and other substances into the endolymph. The intermediate cell layer includes the BLB and contains abundant Kir4.1 ion channels that facilitate K+ transport. The basal cell layer connects with spiral ligament fibrocytes through connexins, responsible for recycling potassium and other molecules from perilymph and controlling ion influx into the SV, preventing ion leakage between cochlear compartments [15].

The stria vascularis generates hearing function by maintaining the endocochlear potential, which is essential for the hair cell transduction process. First, ion

transporters in the stria vascularis actively circulate potassium ions (K+) between endolymph in the scala media and perilymph in the tympanic membrane. This maintains endolymph in a high-potassium (157 mM), low-sodium (1.3 mM) state, in sharp contrast to the low-potassium (4.2-6.0 mM), high-sodium (141-148 mM) state of perilymph [14,15]. This contrast generates a potential difference of +80-100 mV between cochlear lymphatic fluids, known as the endocochlear potential [16]. When sound waves stimulate mechano-gated K+ channels in hair cell stereocilia, these channels allow potassium influx and hair cell depolarization [17]. Subsequently, voltage-dependent Ca2+ channels are activated, permitting Ca2+ influx and neurotransmitter release, generating signals transmitted to the brain [16,18]. Once hair cells depolarize, K+ exits the hair cells and is absorbed by fibrocytes in the spiral ligament [19]. Tight junction proteins such as claudin-11 then transport K+ into the SV, where ion channels like Kir4.1 return K+ to the endolymph. This K+ cycling ensures normal hearing function.

2.2 The Cochlear Blood-Labyrinth Barrier in the Stria Vascularis

The stria vascularis contains the cochlear blood-labyrinth barrier (BLB), which controls the entry of ions, fluids, and nutrients from blood circulation into the stria vascularis through tight junctions, membrane barriers, and chemical mechanisms [20].

The BLB contains approximately 1,220-1,300 pericytes (PCs) with numerous foot processes that closely adhere to capillary walls in the stria vascularis and embed within the basement membrane [21]. PCs are rich in desmin, an intermediate filament protein that enhances the physical elasticity of the capillary network and strengthens the mechanical integrity of the cellular framework [22]. RT-qPCR and immunohistochemistry results indicate that vascular endothelial growth factor isoform A165 (VEGFA165) is particularly important for pericyte function. Since pericytes play a critical role in maintaining stria vascularis integrity, VEGFA165 may represent a therapeutic target for preventing hearing loss caused by SV damage [23]. Other potential targets include Zona Occludens-1 (ZO-1) and VE-cadherin, which are tight junction proteins expressed by pericytes and are associated with BLB endothelial cell integrity [24].

Most perspectives hold that perivascular resident macrophage-like melanocytes (PVM/Ms) in the blood-labyrinth barrier also play a role in stria vascularis function [25]. PVM/Ms originate from cochlear neural crest melanocytes and migrate to the cochlear stria vascularis during development [26]. PVM/Ms possess melanocyte characteristics because they contain abundant melanin and express melanocyte marker proteins such as glutathione S-transferase $ 4(*Gat* $4) and Kir4.1, the latter being a marker protein for intermediate cells [27]. Melanin can maintain tissue homeostasis by buffering calcium, scavenging heavy metals, foreign proteins, and lipids, and promoting antioxidant activity [28].

3. Role of the Stria Vascularis in Age-Related Hearing Loss

As previously described, the endocochlear potential is generated by stria vascularis cells and serves as the energy source for conduction currents and sound signal amplification [29]. Potassium ions in endolymph continuously cycle back to the spiral ligament and stria vascularis after passing through hair cells, then return to endolymph [30,31]. This current drive powers the outer hair cells' electromotility [32], which acts like an amplifier that can boost sound signals by 50-70 dB in the cochlear base (high-frequency region) and approximately 20 dB in the cochlear apex (low-frequency region). Therefore, loss of conduction current and cochlear potential differentially affects high-frequency hearing most severely, and the most prominent clinical manifestation of age-related hearing loss is high-frequency hearing loss. This suggests that stria vascularis dysfunction may be an important factor in presbycusis.

Natalia Trpchevska et al. conducted a genome-wide association meta-analysis of 723,266 European individuals, highlighting the role of the stria vascularis in hearing loss. When analyzing gene enrichment in spiral ganglion neurons (SGNs) and cochlear lateral wall cells (stria vascularis cells), LDSC (linear regression analysis) revealed that spindle cells of the stria vascularis and root cells of the external sulcus participate in the pathogenesis of age-related hearing loss, while MAGMA (gene and pathway analysis) emphasized that stria vascularis basal cells also contribute to the process [33].

In vitro dissection of temporal bone tissue from patients with presbycusis revealed stria vascularis atrophy, BM thickening, increased immunoglobulin, and laminin deposition [34]. Similar findings were observed in aged animals: in young C57BL/6 mice, PVM/Ms had prominent long foot processes and were tightly connected to stria vascularis capillaries; however, in aged mice, PVM/Ms foot processes became shorter, and in 21-month-old mice, PVM/Ms were flattened and deformed with reduced contact with capillaries [21]. Aged C57BL/6 mice also showed significantly reduced distribution density of PCs and PVM/Ms in the stria vascularis, reduced PC organelles, vacuolated appearance, separation from ECs, and accompanying obvious morphological changes in the stria vascularis [21].

Carraro et al. [35] developed a local corrosion casting method to further study the inner ear vascular system. Observation of the SV in presbycusis mice revealed obvious abnormalities in the stria vascularis at the basal turn, but normal vessels in the spiral ligament, indicating that early age-related hearing loss lesions begin at the SV level. Studies have shown that when hair cells are damaged or even completely absent, the morphology and function of the stria vascularis can remain normal, and its ability to generate and maintain the endocochlear potential is not affected by hair cell loss [36]. However, when the cochlear stria vascularis cannot develop normally, the cochlea cannot generate a normal endocochlear potential, outer hair cells undergo progressive apoptosis, and hearing is completely lost [37]. One study also found that downregulation of BKCa chan-

nel function in cochlear stria vascularis pericytes in a D-galactose-induced aging guinea pig model may lead to pericyte diastolic dysfunction, thereby affecting the permeability of the stria vascularis blood-labyrinth barrier and causing age-related hearing loss [38]. These findings all demonstrate the crucial role of the stria vascularis in age-related hearing loss.

4. Mechanisms of Stria Vascularis Dysfunction

4.1 Reactive Oxygen Species and Inflammation

Reactive oxygen species (ROS) are metabolic byproducts of oxygen, including peroxides, superoxides, and hydroxyl radicals. Under special conditions (such as UV or heat exposure), ROS levels increase dramatically, potentially causing severe damage to cellular structures in a process known as oxidative stress [39]. Oxidative stress can lead to increased oxygen free radicals and other reactive oxygen species within cells, which can activate inflammatory responses, causing inflammatory cell infiltration and release of inflammatory mediators. Inflammatory response is a non-specific immune reaction produced by the body in response to stimuli such as infection and tissue damage [40].

Within the stria vascularis, mitochondrial aerobic metabolism produces large amounts of ATP to maintain Na+/K+-ATPase activity while simultaneously generating ROS. With age, ROS-induced damage accumulates in the stria vascularis, causing mitochondrial DNA mutations [41]. Research has found that reduced expression of antioxidant enzymes leads to stria vascularis atrophy and SGCs degeneration, accelerating hearing dysfunction [42]. For example, copper/zinc superoxide dismutase (SOD1) is an antioxidant metalloenzyme that catalyzes the dismutation of superoxide anion radicals into oxygen and hydrogen peroxide, protecting cells from superoxide and hydroxyl radical damage. SOD1 deficiency affects mouse hearing, while SOD1 overexpression reduces age-related hearing loss by decreasing free radical damage to cochlear cells [42]. Additionally, catalase and glutathione peroxidase in the stria vascularis can reduce the occurrence of age-related hearing loss [43].

Previous literature indicates that inflammation in the auditory system may be one cause of ARHL [44,45]. The cochlear lateral wall, where the stria vascularis and spiral ligament reside, is a common site of inflammation [46], likely due to the permeability of the stria vascularis blood-labyrinth barrier. Perivascular resident macrophage-like melanocytes (PVM/Ms) in the blood-labyrinth barrier release pro-inflammatory factors through the tight junction barrier [47]. When inflammatory cytokines induce inflammatory/immune responses, PVM/Ms control barrier permeability, making these cells crucial for regulating inflammation in the auditory system.

4.2 Na+/K+-ATPase and Mitochondrial Activity

Na+/K+-ATPase, also known as the sodium-potassium pump or sodium pump, is a special class of proteins on the cell membrane that can decompose ATP

to generate energy and use this energy to actively transport Na+ and K+ ions. The primary function of Na+/K+-ATPase is to regulate the concentration gradient of K+ and Na+ ions across the cell membrane and maintain normal ionic environments.

Stria vascularis cells, hair cells, and neurons all contain high concentrations of mitochondria [48,49] and Na+/K+-ATPase [50] because inner ear cells require energy to maintain the endocochlear potential generated by the stria vascularis, assist outer hair cell motility, conduct synaptic activity, and maintain spontaneous firing of auditory neurons in SGNs.

Observations of the stria vascularis and spiral ligament in aged gerbils found reduced Na+/K+-ATPase activity, stria vascularis functional degeneration, and decreased blood flow [51]. In aged CBA/CaJ mice, Na+/K+-ATPase expression decreased by 80% with concurrent stria vascularis atrophy [50]. Additionally, patients with hearing loss due to presbycusis also showed significantly reduced Na+/K+-ATPase activity in the stria vascularis, though this change could also result from overall stria vascularis atrophy in the cochlea [52]. It can be hypothesized that reduced Na/K-ATPase expression leads to stria vascularis atrophy, though this question still requires experimental resolution.

Lyu et al. observed damaged mitochondria in aged SV with disorganized, malformed cristae and reduced cytochrome c oxidase (COX) levels, indicating mitochondrial morphological damage and dysfunction [53]. Spicer suggested that oxidative damage to mitochondria in stria vascularis cells leads to reduced ATP production, which in turn decreases Na+/K+-ATPase activity, thereby affecting normal stria vascularis function, reducing endocochlear potential, and elevating auditory thresholds [38].

4.3 Vascular Injury

Due to the cochlea' s single arterial supply system with few collateral vessels, when the SV's single artery is blocked, the SV can only receive blood supply from adjacent branch arterioles. This special structure and compensatory collateral system make the cochlea highly sensitive to vascular changes [54].

Diabetes and hyperlipidemia are common health problems that emerge with aging, and numerous studies have long demonstrated causal relationships between diabetes, hyperlipidemia, and age-related hearing loss [55]. The underlying mechanisms are closely related to vascular degeneration caused by hyperglycemia and hyperlipidemia [56-59]. Clinical studies have found that the cochlear vasculature changes in diabetic patients, including basement membrane thickening, significant vascular wall dilation, SV atrophy, and loss of hair cells and SGNs [60], leading to mild to severe hearing loss [61,62]. Lee et al. demonstrated in a diabetic mouse model that diabetes causes SGN apoptosis, mitochondrial damage, and SV thickness atrophy, though no significant differences were observed in inner hair cells (IHCs) or outer hair cells (OHCs) [63]. Nguyen PTT' s research proved that diabetes worsens ARHL in diabetic ApoE KO male

mice through apoptosis of SGNs and cells in the SV [64].

Hyperlipidemia increases blood viscosity and damages blood vessels [65]. Increased plasma lipids produce lipid deposits in small arteries near the cochlea, damaging cochlear nerve cells and subsequently blocking auditory signals sent to the brain. Elevated cholesterol levels cause arterial wall sclerosis and luminal narrowing, and ischemic injury to the cochlea also leads to structural and functional destruction of the stria vascularis [66]. Additionally, ROS increases dramatically under dyslipidemia conditions, causing mitochondrial dysfunction and apoptosis [67,68].

Homocysteine (HCY) is a sulfur-containing amino acid that serves as an intermediate product of methionine metabolism. When homocysteine concentration increases, the superoxides and peroxides it forms can cause capillary endothelial cell damage and low-density lipoprotein oxidation, leading to persistent vascular smooth muscle contraction and hypoxia, resulting in atherosclerosis [69]. The dense capillary network of the SV makes it particularly vulnerable to damage in hyperhomocysteinemia [70]. A large US cross-sectional study analyzed possible correlations between serum folate, vitamin B12, and homocysteine levels and ARHL. Results indicated that individuals with elevated serum homocysteine and reduced serum folate had higher risk of ARHL. The pathological causes have been studied in mouse models, which found that elevated homocysteine levels caused by dietary folate deficiency lead to damage in SGNs, SV, and spiral ligament, including increased oxidative load and apoptosis [71].

Neuropilin-1 (Nrp1) is a transmembrane receptor active during cardiovascular and neuronal development [72]. Nrp1 is associated with the neuropilin/semaphorin 3A (Semaphorin3A, Sema3a) signaling pathway, where Sema3a acts as a ligand for Nrp1. This pathway affects vascular endothelial growth factor and axonal development, being essential for normal development of inner ear neurons and the stria vascularis [73]. Nrp1 knockout mice develop abnormal inner ear microvasculature and neurons, including gradually reduced SGCs density and dilated stria vascularis vessels. Pezhman Salehi et al. constructed inner ear-specific Nrp1 conditional knockout (Nrp CKO) mice. At postnatal day 5, Nrp1 CKO mice began showing disorganized spiral ligament and dilated SV, but normal SGNs density and presynaptic ribbon counts. Four-month-old Nrp1 CKO mice showed expanded SV vessels in outer hair cell regions, reduced SGNs density, and decreased presynaptic ribbons. Additionally, compared to 2-month-old mice, 4-month-old and 1-month-old Nrp1 CKO mice showed elevated hearing thresholds across frequencies from 32 to 2 kHz. These data indicate that conditional loss of inner ear Nrp1 causes progressive hearing loss in mice [73].

4.4 Genetic Defects

Many genes play important roles in the growth and development of the stria vascularis. MED12 is a member of the multiprotein mediator complex expressed in

blood vessels [74]. Molecular genetics studies have shown that MED12 germline mutations can cause familial genetic diseases, with some patients exhibiting abnormal vascular structures (such as aneurysms) [75], suggesting a role for MED12 in vascular development [76]. Teng-wei Huang et al. found that the Med12 gene maintains stria vascularis integrity by regulating expression of ZO-1, Ecad, and Cx31 [77]. Additionally, Med12 deletion alters cell adhesion between basal cells and spiral ligament, thereby hindering normal endolymph production and ultimately causing dysfunction in hair cell sound transduction [77].

Microphthalmia-associated transcription factor (MITF-M) is a key gene for melanocyte proliferation and differentiation [78]. Mitf-M gene mutations cause a series of phenotypic changes in multiple species, particularly in pigment cells, leading to ocular pigment loss and microphthalmia. Loss of human Mitf-M gene expression causes Waardenburg syndrome type II, which presents with congenital cataracts and sensorineural deafness [79]. Animal models in pigs and mice have shown that lack of Mitf-M gene prevents melanocytes from migrating to the cochlear stria vascularis, thereby affecting endocochlear potential generation and causing hair cell damage [80].

ApoE is a lipid-binding protein that serves as the primary lipid and cholesterol carrier in the central nervous system, responsible for lipid and cholesterol transport and metabolism [81]. ApoE-KO mice show functional and morphological changes in the inner ear [82], possibly because ApoE regulates intracellular glutamate content and REDOX balance by affecting expression of membrane transporter genes Slc7a8 and Slc6a19, making cochlear hair cells in ApoE-KO mice susceptible to apoptosis [82]. In ApoE-KO mice, atherosclerosis is found not only in systemic large arteries but also in small arteries such as those in the cochlear stria vascularis [83,84]. These pathological changes may contribute to the hearing loss found in ApoE-KO mice [85].

The Slc26a gene is responsible for outer hair cell electromotility, and knockout or damage causes severe hearing loss [86]. T. Ito et al.' s results showed that progressive irreversible hearing loss in Slc26a-deficient mice is primarily caused by degeneration and functional loss of the stria vascularis [87].

Conclusion

The stria vascularis is crucial for hearing. It strictly regulates the ionic composition of cochlear endolymph, generates the cochlear potential required for sound transduction, and protects the cochlea by providing immune surveillance and maintaining the BLB. Although the cochlea is small, fragile, and encased in bone deep within the skull—making it difficult to dissect and study—current research has preliminarily explored mechanisms by which stria vascularis damage leads to age-related hearing loss, such as mitochondrial damage, altered vascular environment, and gene deletion, providing numerous references for targeting the stria vascularis to prevent presbycusis. With the development of microimaging techniques and improvements in molecular biology experimental methods, more

approaches are available to fully understand the role of the stria vascularis in the pathogenesis of age-related hearing loss, which is expected to contribute to future prevention, early diagnosis, and long-term treatment of presbycusis.

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