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REVIEW

Sensorineural hearing loss and endothelial dysfunction due to oxidative stress: Is there a connection?

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Abstract

Sensorineural hearing loss (SNHL) is a common disorder that affects millions of people in the world. Hearing loss has many different presentations, ranging in severity from mild to profound, including low and high pitch patterns, and can affect people of any age. SNHL is caused by loss of cochlear hair cells or neurons and this damage is irreversible.

Over the last decades, researchers have identified reactive oxygen species (ROS) as the major factor mediating hearing loss, either directly by causing metabolic damage or indirectly by inducing apoptosis in inner ear sensory cells (hair cells or spiral ganglion neurons). Moreover, recent observations also link oxidative stress to further damage in the inner ear caused by endothelial dysfunction in the cochlear microcirculation.

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Introduction

In mammals, loss of cochlear hair cells is irreversible and leads to permanent sensorineural hearing impairment, a condition that significantly reduces quality of life. Hair cell loss may results from several conditions such as aging, exposure to noise, infectious diseases and use of ototoxic drugs such as cisplatin and aminoglycosides [1,2,3]. Several lines of evidence show that oxidative stress can play a relevant role in the pathogenesis and development of inner ear diseases [1, 2, 3, 4]. At cellular level, inner ear damage is mostly initiated and mediated by reactive oxygen species (ROS) that may induce cell damage (apoptosis or necrosis) because of their direct oxidizing effects on cellular macromolecules such as lipids, proteins and DNA. ROS include superoxide anion (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), hypochlorous acid (HOCl), NO, and peroxynitrite ($ONOO^-$) [1,2,3,4]. As shown by recent data, oxidative stress not only directly mediates metabolic cellular damages in the inner ear sensory cells, but may also cause further damage by inducing endothelial dysfunction in inner ear microcirculation [5,6].

Endothelial dysfunction: a possible role in the pathogenesis of SNHL

There is rising evidence that endothelium is at major risk of ROS-induced lesions and this damage is most evident in microcirculation. The role of endothelial cells (ECs) in microcirculation is crucial because they control and regulate: a) the maintenance of blood in a fluid state, as ECs normally inhibit coagulation at multiple stages; b) the exchange of fluid and macromolecules between blood and tissues, mainly at the capillary level; c) local blood flow, as ECs interact with smooth muscle cells to control the vascular tone; d) the inflammatory response through the expression

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of adhesion molecules, as well as the release of chemokines that promote capture and transmigration of blood leukocytes into tissues; e) the immune surveillance, as ECs express high levels of class I and II major histocompatibility complex (MHC) [7, 8-16].

Endothelial dysfunction is defined by the failure of ECs to perform their activities. ECs injury or death that results from endothelial dysfunction most often occurs as thrombosis, inadequate perfusion, vascular leak, and inflammation.

The role of oxidative stress in endothelial dysfunction has been already investigated. It has been reported that high concentrations of circulating ROS (especially hydrogen peroxide, H_2O_2) may induce apoptosis or sudden death of ECs. In "in vitro" models of oxidative stress it has been shown that, at low concentrations, H_2O_2 may increase expression of ICAM-1 (Inter-Cellular Adhesion Molecule 1) and MHC class I molecules, but not of vascular cell adhesion molecule-1 (VCAM-1); these responses occur without evidence of cellular irreversible injury. Instead, higher amounts of H_2O_2 can cause ECs apoptosis or, at the highest doses, sudden death of cultured ECs [7, 17].

Moreover, ROS also mediate the induced intracellular damage in ECs [7]. ECs apoptosis may be triggered by ROS through a common pathway involving activation of apoptosis signalling kinase 1 (ASK1) and c-Jun N-terminal kinase (JNK), resulting in cleavage and activation of a cytosolic member of the Bcl-2 gene family and a cytochrome c mitochondrial release reaction. In human ECs, the most relevant pathway for generating ROS is catalyzed by the phagocyte oxidase complex [7]; ECs also express NADPH dependent oxidase (Nox) complexes. Rather than contribute to oxidative stress, endogenous ECs systems for ROS generation normally have physiological signal functions, generating "second messengers" that regulate ECs growth/proliferation, ECs barrier function, vasorelaxation, and vascular remodeling [7,18]. However, increasing evidence supports the hypothesis that excessive oxidative stress can significantly contribute to ECs dysfunction and then to pathogenesis and progression of vascular diseases such as hypertension, atherosclerosis, cardiac hypertrophy, and heart failure [7, 18, 19] as well as microvascular disease [7]. These observations could also be relevant to explain the pathogenesis of some inner ear disorders.

Endothelial dysfunction and inner ear: experimental data

Only few experimental data are presently available about endothelial dysfunction and pathogenesis of inner ear disease, mostly guinea pigs and rats. Guo et al. described inner ear histopathological changes related to endothelial dysfunction [20]. They detected hair cell loss (mainly at the cochlear basal turn), thickening of vascular intima, and lumen stenosis of the spiral modiolar artery in the cochlea of apolipoprotein E gene deficient mice, in which impairment of endothelial function is caused by increased production of superoxide radical (O_2-) and reduced endothelial NO synthase activity [20]. Also, Gloddlek et al., in a guinea pig model, advanced the hypothesis that microvascular inner ear disease could be related to EC damages, as disrupted ECs promote the onset of a local vasculitis by secreting pro-inflammatory cytokines like IL-1, IL-6 or TNF-alpha in addition to expressing of adhesion molecules [21]. The persistence of these immunopathological mechanisms may lead to microvascular stenosis and/or atresia with consequent inner ear ischemic damages in experimental conditions [21].

In another guinea pig model, Selivanova et al. also reported a reduced expression of VEGF (Vascular Endothelial Growth Factor), a mitogen for endothelial cells specifically promoting angiogenesis and vascular permeability of endothelial cells), after intense noise exposure (70 db SPL / 1 hour), in all cell types of the organ of Corti, including those of the stria vascularis [22].

Endothelial dysfunction and inner ear: present clinical evidences

Recent literature reports link endothelial dysfunction to some inner ear diseases including sudden sensorineural hearing loss, tinnitus and presbycusis.

Sudden Sensorineural Hearing Loss (SSNHL). The two most accredited hypotheses for the pathogenesis of SSNHL are the vascular and the viral one [23, 24]. Quaranta et al. and Haubner et al. investigated the role of endothelial dysfunction in the inner ear

microcirculation, detecting an increased expression of circulating adhesion molecules (VCAM-1) in patients affected by sudden sensorineural hearing loss, thus confirming the existence of an endothelial dysfunction and supporting the vascular involvement in SSNHL pathogenesis [5, 6].

Moreover, Merchant et al. (2008) advance the hypothesis that in SSNHL circulating cytokines could be responsible for inner ear damage. According to a stress response hypothesis, they state that SSNHL may be the result of abnormal activation of cellular stress pathways within the cochlea, involving transcription factors such as nuclear factor-κ B (NFκ B) [24]. Pathological activation of NFκ B may induce production of inflammatory cytokines and other stress-related proteins that can disrupt the homeostatic balance of cells and tissues, accounting for the sudden onset of SSNHL. NFκ B is present in significant amounts in specific cochlear tissues such as the supporting cells of the organ of Corti, the spiral limbus, the spiral ligament and the stria vascularis [24].

Tinnitus. Neri et al. observed that oxidative stress markers (such as malondialdehyde, 4-hydroxynonenal, myeloperoxidase, glutathione peroxidase, nitric oxide, L-arginine, L-ornitine, thrombomodulin and von Willebrand factor) are increased and nitric oxide production reduced in brain circulation reflux blood of patients with acute tinnitus. The authors state that these oxidative stress conditions are able to cause a general cerebro-vascular endothelial dysfunction, which also induce a dysfunction of the inner ear microcirculation [25].

Presbycusis. Several molecular cascades are thought to be involved in age-related hearing loss, and the current consensus is that oxidative stress is one of its core mechanisms [26]. Studies of the aging cochlea showed a decrease of antioxidant defences such as glutathione level in the auditory nerve or antioxidant enzymes in the organ of Corti (hair cells) and spiral ganglion neurons. Significant loss of hair cells and spiral ganglion neurons, as well as a systematic degeneration of endothelial cells of the stria vascularis, has been experimentally observed in mice lacking superoxide dismutase [27-32].

Conclusions

Sensorineural hearing loss results from injury to the sensory components (i.e. hair cells) or neuronal components (i.e. auditory nerve cells) of the inner ear. It is already clear that oxidative stress, characterized by an increase in reactive oxygen species (ROS) and consequent damage to intracellular biochemical processes, represents an important factor in the pathophysiology of several types of sensorineural hearing loss, including presbycusis, noise trauma, and drug-induced hearing loss.

Nonetheless, recent evidence also suggests that, in some conditions (such as sudden sensorineural hearing loss, tinnitus and presbycusis), oxidative stress may cause further damage by inducing endothelial dysfunction within inner ear microcirculation. Further studies are required to better clarify this point since experimental data are still limited. So far, the only few evidences available on animal models (rats and guinea pigs) suggest an involvement of endothelial dysfunction in the pathogenesis of inner ear disease. Presently, clinical evidences are also weak. If the pathophysiological mechanisms will be explained in more details, inner ear endothelial dysfunction could also represent a new and very interesting therapeutic target.

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