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Development and Prevention of Noise-induced Hearing Loss: The Role of Oxidative Stress and Antioxidants

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ABSTRACT

Exposure to industrial, military, and other occupational noises can cause noise-induced hearing loss (NIHL), which poses significant health risks for workers but is also potentially preventable. Currently, there is no effective treatment for NIHL, as mammalian cochlear hair cells cannot regenerate once damaged. Therefore, preventing hair cell death or implementing early therapeutic intervention is essential for preserving hearing function. NIHL is a complex condition that results from multiple pathophysiological changes. Recent studies on cochlear cellular structures have revealed promising strategies for NIHL prevention through the development of protective pharmacological agents. Reduced cochlear blood flow, inflammation, and oxidative stress are recognized as key mechanisms contributing to NIHL, with oxidative stress playing a particularly critical role. This research aimed to investigate the link between oxidative stress and the onset of NIHL, as well as to explore the potential of endogenous and exogenous antioxidant defense mechanisms in its prevention.

KEYWORDS: *Noise, Noise-induced hearing loss, Oxidative Stress, Antioxidants*

INTRODUCTION

The word *noise* originates from the Latin term *nausea* and refers to an unwanted, unpleasant, and unexpected sound. More specifically, noise can be described as an inappropriate sound occurring at the wrong place or time. It arises from various sources, including occupational, environmental, and recreational activities [1]. Globally, noise is recognized as one of the most widespread environmental pollutants particularly in occupational settings and presents significant risks to both physical and mental health [2]. The biological effects of noise exposure are generally classified into two categories: auditory and non-auditory effects [3]. Non-auditory effects arise when noise acts as a stressor, triggering physiological and behavioral responses. Auditory effects result from repeated or prolonged noise exposure, which can damage the hair cells in the cochlea and lead to noise-induced hearing loss (NIHL) [4,5].

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Occupational noise-induced hearing loss (ONIHL) remains one of the most prevalent work-related illnesses globally [6]. Despite the implementation of national and international regulations and protective standards, its worldwide prevalence continues to be high [7]. According to the World Health Organization, occupational noise exposure accounts for approximately 16% of adult hearing disabilities globally [8,9]. In the United States, nearly 22 million workers are exposed to hazardous noise levels annually, while in the United Kingdom, this figure is around 1.7 million. In China, more than 10 million workers are exposed to harmful noise levels, with a pooled ONIHL prevalence of 21.3% [10]. In Iran, recent statistics indicate that two million workers are exposed to noise levels exceeding permissible occupational limits [11], and a recent meta-analysis reported a pooled ONIHL prevalence of 34.69% [12]. However, there are currently no available data regarding the economic burden of ONIHL in Iran. The economic burden of occupational noise-induced hearing loss (ONIHL) on society is substantial and continues to grow. For example, the annual financial cost attributed to hearing loss in the United States is estimated at approximately $242.2 million [13]. Beyond economic implications, ONIHL significantly diminishes quality of life, impairs functional capacity, and affects individuals' social and occupational relationships [7,14]. The high prevalence of ONIHL reflects the widespread exposure to hazardous noise across various industries and workplaces.

Despite existing preventive regulations, there is currently no effective treatment for noise-induced hearing loss (NIHL), as cochlear hair cells in mammals cannot regenerate. However, recent research into the cellular and molecular mechanisms underlying NIHL has identified potential avenues for pharmaceutical prevention. This study aimed to review existing literature on NIHL and its pathophysiological mechanisms, with the goal of advancing our understanding of underlying biological processes and informing the development of novel therapeutic strategies.

A BRIEF REVIEW OF THE STRUCTURE OF THE EAR

The ear has three parts: outer, middle, and inner ears. The outer ear, the most external part, encompasses the auricle and the ear canal. The middle ear has three components: the tympanic cavity, eustachian tube, and mastoid cells. The tympanic cavity (the primary component of the middle ear) is a tiny chamber that is predominantly covered by the tympanic membrane and contains the ossicles (malleus, incus, and stapes) of the middle ear [15]. The inner ear is divided into two parts: the bony and membranous labyrinth. The membranous labyrinth is within the bony labyrinth and includes three sections: semicircular canals, utricle and saccule, and cochlea. The cochlea is a system of coiled tubes, forming a spiral of approximately 2.5 turns [16]. If the cochlea is uncoiled into a strip, one terminus is referred to as the base (near the oval and round windows), and the other terminus as the apex [17]. There are three canals within the cochlea: the vestibular canal, cochlear duct, and tympanic canal, which are separated by the basilar membrane and Reissner's membrane. The vestibular and tympanic canals (outer canals) are filled with an incompressible fluid named perilymph, which has an ionic composition identical to that of the extracellular fluid. The cochlear duct (inner canal) is filled with endolymph, which has a composition similar to that of intracellular fluid (high K^+ and low Na^+ concentrations) [18]. The vestibular canal terminates in the oval window, whereas the tympanic canal terminates in the round window. The organ of Corti, which contains hair cells, nerve endings, and supporting cells, is located in the basilar membrane. Hair cells are organized into one row of inner hair cells and three to five rows of outer hair cells. The stereocilia on the inner hair cells follow a linear pattern, while those on the outer hair cells form patterns resembling the letters "V" or "W" [19]. The organ of Corti is covered by a gelatinous and fibrous structure called the tectorial membrane, which is anchored on one side to the limbus and connected to the tallest stereocilia of the outer hair cells on the other side. When the basilar membrane moves up and down, it creates a relative motion between the tectorial membrane and the organ of Corti, resulting in the deflection of hair cells [20].

MECHANISM OF NIHL

NIHL is a multifaceted auditory impairment resulting from the interaction of environmental and genetic elements, which determine an individual's sensitivity to noise. Noise is the most significant environmental factor involved in NIHL [13]. While various theories have been proposed to explain NIHL, its exact pathogenesis remains incompletely understood [21]. Generally, noise can damage the inner ear through physical forces generated by sound waves or molecular alterations affecting inner ear cell or neuron function [22]. In other words, cochlear damage due to noise exposure reflects both mechanical and metabolic injuries. Mechanical damage directly affects the cellular and intracellular structures of the organ of Corti, while metabolic injury

results from disruptions to the processes vital for maintaining inner ear homeostasis [23].

Mechanical Damage

It is widely believed that mechanical damage to the cochlea is the primary pathological change associated with NIHL when noise intensity is exceptionally high. When high-level noise reaches the inner ear, it causes severe fluctuations in the endolymph and perilymph of the organ of Corti, resulting in extreme stretching and compression of the basilar and tectorial membranes. This can cause the stereocilia of inner and outer hair cells to detach from the tectorial membrane, making it difficult for hair cells to receive vibrational stimuli effectively. Additionally, the vibrations in the lymphatic fluids can separate hair cells from the basilar membrane, disrupting ribbon synapses. This disruption prevents the remaining synapses from maintaining optimal function, ultimately compromising the capability of hair cells to encode auditory signals [24].

Metabolic Injury

While mechanical injury leads to structural damage in cells, metabolic injury arises from a series of interrelated pathophysiological changes [25]. The cochlea depends on aerobic metabolism, requiring oxygen to generate energy for its cells [8]. This energy production occurs within the mitochondria via the electron transport chain, which involves a sequence of reactions where electrons are transferred between carriers to produce adenosine triphosphate (ATP), the energy source of cells [26]. During this process, superoxide anions ($O_2^{\bullet-}$) are generated as unwanted byproducts.

Exposure to high levels of noise forces mitochondria to generate large quantities of energy, leading to excessive production of $O_2^{\bullet-}$ [25, 27]. These $O_2^{\bullet-}$ then participate in subsequent reactions, producing harmful molecules such as hydrogen peroxide (H_2O_2), hydroxyl radicals (OH•), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl) [28]. The enzyme superoxide dismutase (SOD) facilitates the conversion of $O_2^{\bullet-}$ into H_2O_2 and water [29].

The cochlea receives blood from two microvascular networks: the lateral wall and the spiral ganglion neurons [30]. Noise exposure increases the metabolic demands of cochlear cells and tissues, which require higher energy for ion pumping and homeostasis maintenance. This heightened metabolic activity boosts mitochondrial respiration [31]. In a majority of tissues, increased metabolism is accompanied by an increase in blood flow to deliver more oxygen to stressed cells. However, in the cochlea, exposure to high sound levels leads to a reduction in blood flow [32]. Reduced oxygen delivery (ischemia) disrupts mitochondrial phosphorylation and leads to higher production of $O_2^{\bullet-}$. After ischemia, the restoring blood flow (reperfusion) can worsen the generation of $O_2^{\bullet-}$ [33].

The ion balance, critical for normal hearing, is highly susceptible to disruption due to noise exposure. Excessive noise stimulation of hair cells causes abnormal ion flux through the ion channels in the cell membrane [25]. Calcium, a crucial ion for inner ear function, is usually present in low concentrations in hair cells and spiral ganglion neurons under normal conditions. However, in response to noise, calcium levels rise significantly, leading to the release of neurotransmitters from hair cells, which convert mechanical signals into electrical signals [34]. Excessive glutamate neurotransmitter release can result in excitotoxicity [25]. Excitotoxicity refers to the toxic effects of excitatory neurotransmitters, such as glutamate, wherein prolonged or excessive activation of glutamate receptors triggers a neurotoxic cascade, ultimately leading to neuronal dysfunction and cell death [35].

OXIDATIVE STRESS AND CELLULAR DAMAGE

Cell damage, dysfunction, or death can result from oxidative stress, which occurs when the balance between oxidants and antioxidants is disrupted. Under normal conditions, endogenous antioxidants provide sufficient protection against environmental oxidant attacks. However, continuous exposure to environmental oxidants, such as noise, hastens antioxidant depletion, shifting the balance toward insufficiency and oxidative stress [36].

As previously mentioned, excessive acoustic stimulation triggers metabolic shifts in the cochlea, including the generation of reactive oxygen species (ROS) such as $O_2^{\bullet-}$, H_2O_2, and OH•. ROS are oxygen-derived molecules that either act as free radicals themselves or readily produce free radicals [37]. A free radical is an atom or molecule with one or more unpaired electrons in its outer orbital, making it highly reactive. Free radicals achieve stability by acquiring electrons from other molecules, thereby oxidizing them. In biological systems, this process damages cellular components (nucleic acids, proteins, and lipids), resulting in oxidative damage [38, 39]. Under normal physiological

conditions, ROS produced by mitochondria are neutralized by endogenous antioxidant mechanisms, maintaining inner ear homeostasis [34, 40]. The imbalance between ROS production and antioxidant defense mechanisms leads to a condition known as oxidative stress [41].

Lipid Peroxidation

The cell or organelle membrane is particularly susceptible to damage caused by ROS, a process known as lipid peroxidation [42]. Lipid peroxidation may be characterized as the oxidative degradation of lipids containing carbon–carbon double bonds. Since membranes form the foundation of organelles like mitochondria and the plasma membrane, lipid peroxidation severely compromises cell function and survival. By attacking unsaturated fatty acids in the phospholipid bilayers of biological membranes—which are essential for their critical property of fluidity—lipid peroxidation affects the biophysical characteristics of the membranes. It alters membrane properties such as fluidity and electrical resistance, limits protein mobility within the membrane, and deactivates ion pumps crucial for ionic homeostasis. Moreover, lipid peroxidation generates harmful intermediates, such as aldehydes (e.g., malondialdehyde), which function as bioactive molecules under physiological and pathological conditions. These compounds influence signal transduction, gene expression, and cell proliferation [43]. Lipid peroxidation is self-perpetuating and may contribute to sustained cellular damage even after noise exposure ends [33].

DNA Damage

Free radicals cause DNA alterations through various mechanisms, including base destruction; single- or double-strand breaks; purine and pyrimidine nucleotide modifications; mutations, deletions, and substitutions; and cross-linking with proteins [44].

Protein Damage

ROS can fragment peptide chains, alter protein charges, and oxidize specific amino acids, thereby damaging these macromolecules [45]

ANTIOXIDANT DEFENSE SYSTEM

The antioxidant defense systems of living organisms utilize diverse strategies based on antioxidant molecules to counteract the effects of free radicals and oxidative stress [28]. Antioxidants are reducing agents present both intracellularly and extracellularly that can react with free radical species and regulate their production. They constitute the body's primary defense mechanism against free radicals, playing a crucial role in neutralizing them and maintaining the equilibrium between oxidation and reduction reactions [46].

Endogenous Antioxidants

An extensive network of intracellular and extracellular antioxidants operates with diverse functions in each defense area. Superoxide dismutases (SODs) represent the primary defense against $O_2^{\bullet-}$ toxicity, catalyzing the conversion of $O_2^{\bullet-}$ to H_2O_2 and H_2O, thereby limiting the availability of $O_2^{\bullet-}$. H_2O_2 H_2O_2 is subsequently converted into water by catalase and glutathione peroxidase (GPx). However, in the presence of Fe^{2+}, H_2O_2 may produce hydroxyl radicals $(OH^{\bullet})$ via the Fenton reaction. Consequently, SOD activity may exhibit dual and opposing effects. Primarily, when coordinated with catalase and GPx, it functions as an antioxidant enzyme by neutralizing H_2O_2 to prevent its accumulation. Second, SOD may function as a pro-oxidant because excessive H_2O_2 can lead to ROS overproduction and cellular toxicity. Therefore, reduced SOD activity is associated with a significant risk of oxidative stress. It has been postulated that the antioxidant properties of SOD under various pathophysiological conditions are beneficial in protecting the immune system [47]. Mitochondrial SOD is an antioxidant enzyme that plays an essential protective role in preventing Noise-induced damage to the cochlea by reducing ROS levels [27]. The absence of this enzyme renders young mice susceptible to noise-induced hearing loss (NIHL) [48].

Exogenous Antioxidants

Since no effective treatment for NIHL has yet been identified, and mammalian cochlear hair cells lack regenerative capabilities, it is crucial to prevent hair cell death or intervene therapeutically in the early stages of NIHL to preserve hearing. Identifying antioxidants as potential preventive agents has emerged as a novel approach in neurodegenerative diseases, including NIHL. This concept is supported by studies on therapeutic strategies targeting excessive free radical production.

Observational studies have investigated the effects of various vitamins, minerals, and compounds—both individually and in combination including vitamins B_{12}, C, and E; magnesium; N-acetylcysteine (NAC); alpha-lipoic acid; zinc gluconate; *gi*; and beta-carotene [49–53]. Experimental research has also examined the protective effects of numerous antioxidant supplements

in preventing hearing loss in animal models, such as resveratrol [54]; vitamins E and C; magnesium [55]; ascorbic acid [56]; NAC [57]; statins [58]; myricetin [4]; vitamin E; ferulic acid; coenzyme Q_{10} [8]; metformin [59]; caffeic acid [60]; rosmarinic acid [61]; pioglitazone [62]; *Ginkgo biloba* [63, 64]; quercetin [65]; D-methionine [66]; and other compounds. Previous reviews have explored the association between hearing loss and vitamins/antioxidants. Jung et al. found that deficiencies in nutritional factors (vitamins A, C, E, and zinc) led to increased hearing loss [67]. Furthermore, Abbasi et al. demonstrated that using vitamin B_{12}, folic acid, and NAC as antioxidants can prevent occupational noise-induced hearing loss (ONIHL) [68]. A meta-analysis investigating NAC's therapeutic effects on sensorineural hearing loss revealed that NAC improved hearing test results in cases of sudden hearing loss but did not prevent NIHL [69].

Although the pathogenesis of NIHL has not been fully elucidated, the currently accepted mechanism suggests that noise-induced damage to the organ of Corti results from excessive production of reactive oxygen species (ROS) [70]. ROS are generated in the cochlea immediately following noise exposure [71], and their formation continues for up to two weeks post-exposure—peaking 7 to 10 days after exposure—leading to prolonged responses and hair cell death [33, 72]. Consequently, the use of antioxidants is expected to mitigate NIHL [68].

NOISE CHARACTERISTICS INFLUENCING NIHL

As previously mentioned, NIHL is a complex form of hearing loss arising from the combined effects of personal (genetic and acquired) and environmental factors [73]. Personal factors—including health-related behaviors (such as use of hearing protection, tobacco use, and alcohol intake) and health conditions (such as hypertension and hyperlipidemia)—may influence noise sensitivity [74, 75]. Environmental factors include noise, vibration, heat, chemicals (e.g., organic solvents, heavy metals), ototoxic drugs, infections, nutritional disorders, smoking, hypertension, cholesterol levels, and possibly pigments, all of which have been implicated in the development of NIHL [76]. Undoubtedly, noise is the most critical environmental factor involved in NIHL [13]. Noise-induced damage largely depends on its acoustic properties, including intensity, exposure duration, frequency content, and bandwidth. Frequency characteristics (e.g., intermittence, tonality, roughness, etc.) cause greater disturbance compared to steady-state noise of the same intensity [77]. Therefore, evaluating the adverse health effects of noise solely based on intensity is inadequate, as even low-level noise has been shown to cause pathophysiological effects that disrupt auditory function [78]

ADDITIONAL FACTORS INFLUENCING NIHL

Various other factors may contribute to the development of NIHL. Studies indicate that males are more susceptible to hearing loss than females, partly due to their higher representation in industrial occupations. Additionally, socioeconomic background and ethnicity also play roles in NIHL susceptibility [79, 80]. Some individuals exhibit a higher genetic predisposition to NIHL, reflecting diverse genetic backgrounds [81]. Smoking, coronary artery disease, diabetes, hypertension, high cholesterol, and exposure to vibration may exacerbate hearing damage following noise exposure [82, 83]. Moreover, combined exposure to chemicals and nanoparticles has been implicated in the development of NIHL [5, 84, 85].

CONCLUSION

Traditionally, the prevention of NIHL has relied on the use of hearing protection devices and the control of noise emission. However, increased understanding of the cellular and biochemical basis of NIHL has led to the development of new preventive strategies. Among these, given that the most widely accepted mechanism of NIHL involves the overproduction of reactive oxygen species (ROS) in the organ of Corti, the use of antioxidants to neutralize ROS and inhibit cell death appears to be the most rational approach.

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