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Noise Induced Hearing Loss: The Role of Oxidative Stress

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ABSTRACT

Introduction: Noise-induced hearing loss (NIHL) is a relevant source of hearing disability affecting the general population, and accounts for about 16% of all the reported cases of disabling hearing loss in the adult population worldwide. NIHL can follow workplace-related and recreational noise exposure, and can be influenced by individual factors such as age, sex, genetic predisposition and socio-economic factors.

Objectives: The aim of this paper is to provide a quick overview of the principal findings in noise induced hearing loss, focusing on the role of oxidative stress and antioxidant intervention.

Review: Oxidative stress plays a central role in leading to a condition of NIHL. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) largely participate in cellular mechanisms that underlie mainly the outer hair cell death after noise exposure and lead to sensorineural hearing loss. The beneficial effects of antioxidant supplementation have been demonstrated by several experimental studies in animals, while the observed results in humans are mixed.

Conclusion: NIHL still represents a widespread condition among the general population; with a higher prevalence in developing countries among workers, and in developed countries among young adults exposed to leisure noise. Extensive literature confirms that increasing antioxidant levels in the organ of Corti may be an appropriate approach towards understanding NIHL in humans by increasing the endogenous antioxidant response or by administering antioxidant molecules systemically or locally.

KEY WORDS: Noise-induced hearing loss (NIHL); Oxidative stress; Sensorineural.

ABBREVIATIONS: NIHL: Noise-induced hearing loss; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; WHO: World Health Organization.

INTRODUCTION

Noise-induced hearing loss (NIHL) is a relevant source of hearing disability among the general population, and accounts for about 16% of all the disabling hearing loss conditions in the adult population worldwide.¹ NIHL, due to military, industrial and recreational noise exposure, can be influenced by individual factors such as age, sex, hereditary condition and socio-economic factors.

NIHL is one of the most commonly reported occupational disorders in Europe and in the rest of the world; it accounts for between 7 and 21% of the hearing loss cases^{1,2} and represents a significant health problem in workplaces with severe economic consequences. Studies on hearing in different type of workers, suggest that hearing loss due to workplace noise was a significant problem in the 1960s and early 1970s, while it is of less importance in the current time due to improved regulation and the use of protective equipment.³ This does not apply to developing countries, where exposure to high levels of noise at work still represents a serious problem.

Recreational noise exposure, often overlooked in the past, is widely diffused among

teenagers and young adults. The World Health Organization (WHO) estimates that 1.1 billion young people worldwide could be at a risk of hearing loss due to unsafe listening practices, and nearly half of all the individuals aged between 12 and 35 years old, are exposed to unsafe levels of sound on account of the use of personal audio devices and about 40% of them are exposed to potentially damaging sound levels at clubs, discotheques and bars.⁴ According to a report from the European Union, the widespread participation in electronic games, even at an early age, and the increased use of earphones resulted in an estimated 31% increase in all cases of youth hearing loss between 2005-2006 and 1988-1994 (Safe EU). From the available data, it appears that many countries cannot control the phenomenon of recreational noise exposure.⁵

There are many audiological definitions of NIHL; the most commonly accepted one involves high-frequency hearing loss due to an exposure to a frequency range between 3 and 6 kHz.⁶

Impulse Noise

Impulse noise is probably more damaging towards hearing than continuous noise and is of utmost importance in NIHL. Exposure to impulse noise among metal and military workers has been shown to cause a significant hearing loss, mainly for the higher frequencies (3-8 kHz), although it is not definite whether impulse noise is more damaging to hearing than continuous noise.⁷⁻⁹ Zhou and Salvi exposed 12 adult guinea pigs to a series of 40 pairs of impulse noise at the intensity of 168 dB sound-pressure level (SPL) and reported that intensive impulse noise resulted in the apoptosis of cochlear hair cells that initiated between the end of basal turn and the beginning of second turn, and spread to the basal and third turn along the basilar membrane. The authors reported an increased expression of p53 apoptotic protein in damaged hair cells, not only in the central damaged area, but also in the basal turn and the third turn, demonstrating that p53 may play an important role in leading to impulse noise induced-hair cell apoptosis.¹⁰

The Role of Oxidative Stress in the Pathophysiology of NIHL

The pathophysiological basis of NIHL has been extensively

studied; factors leading to hearing loss after noise exposure include direct mechanical trauma, oxidative stress, metabolic exhaustion, ischemia and ionic imbalance in the inner ear fluids.¹¹

Oxidative stress plays a central role towards causing NIHL. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) largely participate in cellular mechanisms that underlie mainly outer hair cell death after noise exposure and lead to sensorineural hearing loss.¹²⁻¹⁴ ROS are produced by mitochondria, cytochrome p450 metabolism, microsomes, nitric oxide synthase and other inflammation-related processes. Cells are equipped with endogenous defense systems that can detoxify ROS; oxidative stress conditions are the result of the disruption of intracellular redox homeostasis. A schematic of the effects of noise exposure on hair cells is shown in Figure 1.¹⁵

The overproduction of free radicals is highly toxic and triggers a complex mechanism of damage due to the peroxidation of membrane lipids, denaturation of cellular proteins, damage of DNA and cell death in several pathological conditions such as mutagenesis, carcinogenesis, aging, neurodegenerative and inflammatory diseases.¹⁶ The imbalance between ROS and RNS and intrinsic antioxidant defenses is the main element underlying hair cell death through either apoptosis or necrosis in NIHL¹⁷ and ischaemia-reperfusion.¹⁸ Following the noise exposure, the mitochondria increases aerobic respiration and utilizes larger quantities of oxygen, thus generating larger amounts of superoxide and other ROS, and has been proven to induce a temporary reduction in the cochlear blood flow. Types and description of damages induced by noise exposure in the inner ear are summarized in Table 1.¹⁸

Noise exposure damages inner ear structures, such as the outer and inner hair cells and stria vascularis, inducing peroxidation of membrane lipids, particularly in the mitochondria, and production of malondialdehyde and isoprostanes, two potent vasoconstrictors that ignite hypoxic injury. Additionally, 4-hydroxy-2-noneal (4-HNE), observed in mammalian outer hair cells, is a strong inducer of apoptosis produced by lipid peroxidation. Finally, the TUNEL assay showed the fragmentation of nuclear and mitochondrial DNA that leads to cell death through 1) the activation of the intrinsic pathway of apoptosis, of caspases and protease cascades that trigger the mechanism of DNA

Table 1. Types and Description of Damages Induced by Noise exposure in the Inner ear.³⁸

Types of noise-induced damages	Description of noise-induced damages
Mechanical damage	Disruption of Reissner’s membrane and basilar membrane, loss of stereocilia bundles, disruption of subcellular organelles, damage of the inner and outer hair cells, injury of stria vascularis and spiral ganglion cells, and destruction of the lateral walls of the outer hair cells
Neural degeneration	Degeneration of cochlear nerve peripheral terminals on the inner hair cells, spiral ganglion cells, and the cell bodies of cochlear nerve afferents, and synaptic degeneration in the central auditory system, especially in the dorsal cochlear nucleus
Metabolic damages	Decreased cochlear blood flow leading to cochlear ischemia-reperfusion injury, mitochondrial damage, oxidative stress, and cell death by producing free radicals

damage^{19,20}; and 2) an extrinsic pathway involving MAPK-JNK complex.²¹

The Role of Antioxidant Agents in NIHL

Several experimental studies have shown the beneficial effects of antioxidant supplementation in animals, while results in humans are mixed. At an experimental level, 3 relevant molecules worth discussing are Coenzyme Q10, N-acetylcysteine and D-methionine. Coenzyme Q10 (CoQ10), also known as ubiquinone, is a vitamin-like, lipid-soluble antioxidant that acts as a mobile electron carrier within the mitochondrial electron transfer chain. The therapeutic potential of CoQ10 is limited by its poor bio-availability in the aqueous media. In a recent paper, Fetoni et al demonstrated that a soluble formulation of CoQ10, called Q-ter, significantly reduced mitochondrial damage, lipid peroxidation and oxidative damage of cellular proteins induced by oxidative stress and decreased signs of apoptosis²²; the recorded data was concordant with the observations in papers by the same author in which they evaluated systemic *versus* trans-tympanic modality.^{23,24} Also, in a pilot prospective study, which was randomized and double-blinded, the authors showed a significant hearing protection in a group of young volunteers that received ob-Q 200 mg once a day for 7 days before exposure to white noise at 90 dB HL for 15 minutes.¹⁴ In humans, the antioxidant role of Q-ter in hearing loss has been evaluated in the treatment of presbycusis, with limited effects.²⁵

N-acetylcysteine (NAC) is a derivative of cysteine that acts as an augmenter of the antioxidant glutathione reserves in the body; *in vivo* studies have shown that NAC acts as a scavenger of ROS, but its main antioxidant activity is derived from being a precursor of cysteine, which is itself a precursor in the formation of glutathione. In addition, NAC protects against mitochondrial damage and reduces glutamate excitotoxicity both in outer hair cells and dendrites of the afferent neurons.¹⁹

D-methionine is a D-isomer of methionine that can be reversibly oxidized in the oxidation-reduction process and acts 1) by increasing the intracellular levels of glutathione in the mitochondrial models of acoustic trauma and aminoglycosidic damage and 2) as a scavenger for cisplatin damage. However, the use of D-methionine, similar to all the molecules with a ROS scavenging mechanism, is controversial due to the risk of limiting the systemic antineoplastic activity (Figure 1).^{21,26}

Other Factors that Affect NIHL

Other factors may have an impact on NIHL. Population studies show that men are more likely to experience hearing loss following noise exposure than women; genetic factors also play an important role. Moreover, social-economic background and ethnicity have been reported to play a role in NIHL.^{27,28}

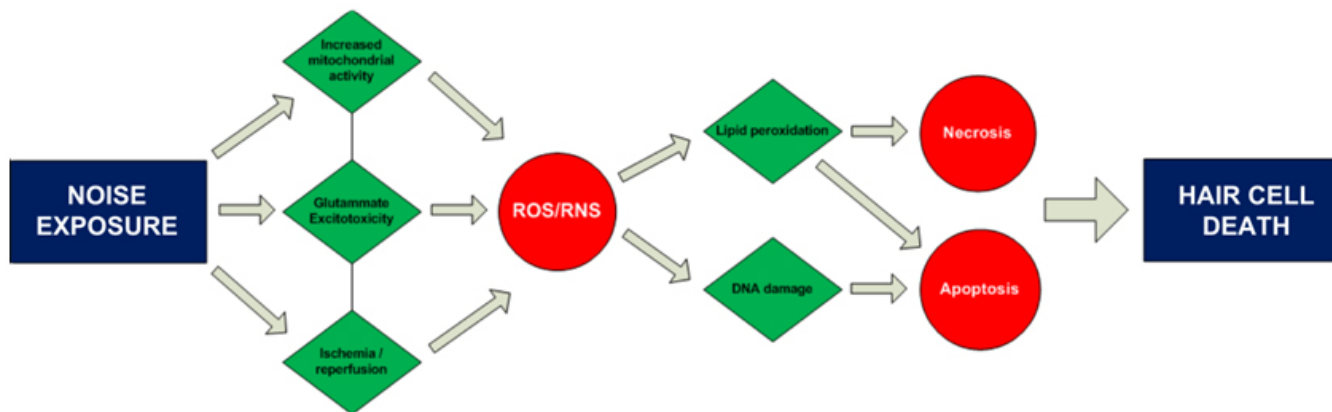
Smoking, coronary heart disease, diabetes, high blood pressure and other risk factors which could lead to heart disease, such as elevated levels of cholesterol, seemed to facilitate hearing damage following noise exposure, due to their impact on microcirculation in the organ of Corti.²⁹

Exposure to chemicals and certain ototoxic medications may cause hearing loss³⁰ and tinnitus^{31,32}; authors reported that concurrent vibration^{33,34} may enhance the harmful effects of noise on hearing. Noisy leisure activities, especially the use of firearms, can also lead to hearing loss, while leisure noise from other sources appears to have a small effect on hearing loss in population studies, but may still be harmful at the individual level if the exposure is high enough.³⁵⁻³⁷

CONCLUSION

NIHL still represents a widespread condition among the general population; with a higher prevalence in developing countries

Figure 1: Schematics of the Effects of Noise Exposure on Hair Cells. The Imbalance between ROS and RNS and Intrinsic Antioxidant Defenses Following Noise Exposure leads to Hair Cell Death through either Apoptosis or Necrosis.



for work-related noise exposure, and in developed countries for leisure noise. Workers with a higher risk of developing NIHL are found in the engineering industry, building and construction, agriculture and in the armed forces. Nearly half of all the individuals aged between 12 and 35 years old are exposed to unsafe levels of recreational noise. Antioxidant administration have been demonstrated to play a significant role in animal models, especially when administered in high dosage before, during and after noise exposure; mixed results have been reported in human studies. Extensive literature confirms that increased levels of antioxidant molecules in the organ of Corti may play a significant role against NIHL in humans; this may be obtained by increasing the endogenous antioxidant response or by administering antioxidant molecules systemically or locally.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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