

Mitigative Effects of Antioxidants in Noise Stress

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Abstract

The inevitable exposure of man and animals to noise has been aggravated by the increased use of mechanical equipment. Interrupted or continuous exposure to noise induces stress. Noise stress disrupts homeostasis resulting in a complex adaptation response, comprising physiologic mechanisms, aimed at restoring homeostasis. Noise stress exerts negative effects on the body, by inducing neuro-hormonal impairments, including behavioral, autonomic, neuroendocrine and immunological disorders, linked with increased generation of reactive oxygen species, resulting in oxidative stress. Noise exposure causes health impairment in man, and production losses in animals. Increasing distance from noise source and decreasing noise exposure time are essential for preventing noise-induced abnormalities. The administration of exogenous antioxidants in noise-induced stress, enhance the expression of endogenous antioxidant enzymes and increase their reactive oxygen specie scavenging capacity, imperative for the improvement of current prophylactic and therapeutic interventions against noise-induced stress.

Keywords: Antioxidants; Noise; Oxidative stress; Health

Introduction

Noise was derived from the Latin term 'nausea' and has been defined as unwanted sound, which is a potential hazard to communication and health [1]. Stress refers to a non-specific response of the body to unpleasant stimuli, threatening homeostasis and the integrity of the organism [2,3]. It is a state of threatened homeostasis provoked by psychological, physiological and environmental stressors [4]. Noise is measured in decibel (dB) units [1]. Wang et al. [5] reported that noise exposure is a potent stressor as it increases the levels of the stress hormone, corticosterone. Noise pollution, especially in the urban environment, is on the increase [6-8] and ranks among the environmental stressors with the highest public health impact [8]. The auditory effects include hearing impairment and permanent hearing loss due

to excessive noise exposure. The non-auditory effects include stress-related, physiological and behavioural effects.

In the central nervous system, sound proceeds in two directions; one to the auditory centre, where it is perceived and interpreted; and the other to the deep parts of brain, where it activates the autonomic nervous system and is liable for a wide range of monaural effects [9]. Noise is stressful and activates the HPA axis, resulting in the release of corticosteroid hormones from the adrenal gland into circulation, together with hearing loss and other health impairments such as headache, hypertension and coronary heart disease [2,9].

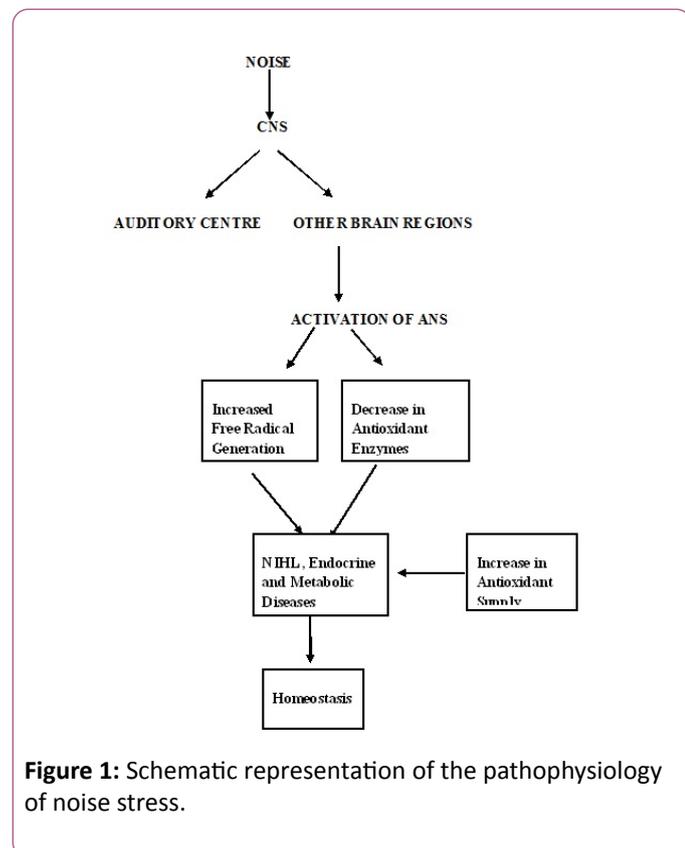
Pathophysiology of Noise Stress

Genetics has been identified to play a key role in the mechanisms of noise induced hearing loss (NIHL). It has been proven that certain patients are more vulnerable to permanent threshold shifts, based on auditory brainstem response (ABR) threshold measurements, when exposed to a similar noise experience. Loci of vulnerability to NIHL have not been identified in humans, but several mouse models have been shown to uphold NIHL (**Figure 1**) [10].

Studies have shown that mice deficient in a gene Xp21.2, mapped in the dystrophin gene locus, is more vulnerable to NIHL, compared to control mice. Schick et al. [11] proved that escalation in noise sensitivity occurs at lower frequencies in vasodilator-stimulated phosphoprotein -/- mice. Fairfield et al. [12] studied the relationship of NIHL and the function of heat-shock protein (HSP), molecules that enhance the survival of cells in response to stress, and heat shock factor-1 (HSF1), the key transcription factor that regulates HSPs expression in stress in mice. They reported that HSF1 mice have more hearing loss than normal mice, given the same noise exposure. Morita et al. [13] studied the gene Ahl3, located in the 14-Mb region on the mouse chromosome 17 and its function in NIHL. They discovered a resistance to NIHL after prolonged noise exposure in mice, when the wild type Ahl3 allele was present, signifying a genetic variation in vulnerability to NIHL [9].

Acoustic trauma can instigate mechanical disruption of the cochlea and may initiate permanent hearing loss [9]. Lurie et al. [14] described graduated degrees of acoustic trauma in guinea pigs, commencing with stripping of mesothelial cells

under the basilar membrane, progressing to disruption of external hair cells and ultimately, separation of the organ of Corti from the basilar membrane as the duration of exposure increases. Oxidative stress has been acknowledged to play a key role in the initiation of noise-related health impairments [3].



Public Health Significance of Noise

Noise-induced hearing loss has global implications, with 10 million adults and 5.2 million children in the US, and 250 million people world-wide having a noise-induced hearing loss greater than 25 dB; a clinically significant hearing loss [9]. Additionally, occupational noise accounts for 16% of the disabling hearing loss in adults world-wide, resulting in decreased economic production [15]. Nocturnal environmental noise also provokes measurable metabolic and endocrine perturbations, including secretion of adrenaline, noradrenaline, cortisol, increased heart rate and arterial blood pressure, and increased motility. While asleep, these biological responses to noise are mostly unnoticed [16-18]. Data confirm that exposure to traffic noise, not specifically at night, is associated with increased incidence of diabetes mellitus [19], hypertension [20], stroke among the elderly [21], and mortality from coronary heart disease [15,18,20,22].

According to WHO [8], noise causes health damage every day estimated at 4 million dollars. Moreover, psychoneurotic and psychosomatic complaints are also observed due to noise exposures [23]. Zheng and Ariizumi [24] reported that noise exposure prolongs healing of surgical wounds; while three days of noise exposure increases immune function, but 28

days of its exposure suppresses immune function. In addition, oxidative stress increases in rats subjected to 28 days of noise stress, suggesting that oxidative status partially accounts for the immune suppression [25]. In farm animals, noise directly affects reproductive physiology and energy consumption [26]. Noise may also have indirect effects on population dynamics through changes in habitat use, courtship and mating, reproduction and parental care [27]. Pigs exposed to 90 dB prolonged or intermittent noise resulted in decrease in growth [28]. When poultry is exposed to intermittent loud noise, egg laying and growth rate decreases while mortality increases [29]. Losses have been reported from mink farms in the form of premature births, insufficient lactation and females kill their offspring in connection with exposure to sonic booms [30]. In cattle, exposure to a high-intensity noise (105 dB) results in decrease feed consumption (appetite reduction), milk yield and effectiveness of the milk ejection reflex [31].

Noise-induced hearing loss is the greatest cause of sensory disability [8], affecting up to 1 in 6 of the population. It is estimated that approximately 20% of the burden is generated from excessive noise exposure in occupational and leisure settings [32]. Sustained exposure to sound pressure levels greater than 85 dB, or sudden exposure to impulse noise leads to irreversible damage to the sensory structures of the cochlea. Once damaged, the mammalian sensory hair cells do not regenerate, and the loss of hearing is permanent [8].

Role of Oxidative Stress in Mechanism of Noise Stress

Oxidative stress is a state of amplified generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which exceeds the scavenging competence of the antioxidant systems in the body. The shift in the balance between oxidants and antioxidants in favour of oxidants is termed oxidative stress [33]. Noise stress instigates increased ROS and RNS generation, which are capable of breaching lipid and protein molecules and damaging DNA; triggering loss of function and cell death following noise exposure [4,34]. The ROS additionally trigger apoptosis by activating proapoptotic mitogen activated protein (MAP) kinase-signalling pathways [9]. Oxidative destruction has been connected with ROS-induced diseases [35]. Noise induced hearing loss may occur largely due to oxidative stress [36]. Exposure to noise has been proven to cause an initial boost in cochlear blood flow. Within a short period of time, there is an abrupt decline in cochlear circulation, evidenced by an aggregation of erythrocytes, capillary vasoconstriction, and stasis. This extreme metabolic activity and decreased cochlear blood flow from noise exposure alters cellular redox states and instigates the formation of ROS [37,38]. ROS may also be generated by diverse mechanisms. *In vivo*, they may be formed as a by-product of mitochondrial respiration. The ROS include the superoxide ion (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH^-), hypochlorite (OCl^-), and nitric oxide (NO^-) [3]. In excess, ROS damages cellular DNA, proteins, and lipids, as well as up-regulate apoptotic pathways, resulting in cell death, irreparable damage to eloquent hearing structures

and other health correlated conditions, such as cardiovascular diseases, diabetes mellitus and sleep disturbances [39].

Antioxidants

The body has numerous mechanisms to neutralise oxidative stress by producing antioxidants, which are either naturally produced *in situ* (endogenous) or supplied externally through foods and/or supplements (exogenous). Antioxidants are molecules that scavenge ROS/RNS and transform them to less dangerous molecules. They preclude and repair damages caused by ROS/RON [3].

Endogenous antioxidant compounds are categorised as enzymatic antioxidants and non-enzymatic (metabolic and nutrient) antioxidants. The major enzymatic antioxidants comprise superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione reductase (GRx) [40]. The catalytic activity of these enzymes permit the transformation of superoxide anion into hydrogen peroxide (H₂O₂) and water, thereby mitigating the harmful effects of ROS [33]. SOD catalyses the dismutation of superoxide to H₂O₂, and it is the first defense against ROS [41]. Catalase catalyses the breakdown of H₂O₂ to water and oxygen, and also plays a role in oxidative defense of the animal tissue by catalysing the reduction of hydrogen and lipid peroxides. This prevents oxidative damage in cell membranes. Increased activity of SOD results in increased production of H₂O₂; and thus, a simultaneous rise in GPx and CAT activities is required for protection against heat stress-induced ROS [3-4]. Trace elements such as selenium (Se), zinc (Zn), copper (Cu) and manganese (Mn) perform important catalytic role in the enzymatic activity of GPx and SOD (Zn, Mn, Cu) [41]. Exogenous nutrient antioxidants are not produced in the body, but are provided via foods or supplements [42]. They comprise vitamin E, trace elements (Se, Mn, Zn), flavonoids, carotenoids, omega-3 and omega-6 fatty acids [43].

Mechanism of action of antioxidants

Antioxidants are compounds or systems that delay autooxidation by inhibiting formation of free radicals or by interrupting propagation of free radicals by one of the following mechanisms; scavenging species that initiate peroxidation, chelating metal ions such that they are unable to generate reactive species or decompose lipid peroxides, breaking the autoxidative chain reaction and/or reducing localized oxygen concentrations [44].

Antioxidants are molecules that can neutralize free radicals by accepting or donating electron(s) to eliminate the unpaired condition of the radical [42]. The antioxidant molecules may directly react with the reactive radicals and destroy them, while they may become new free radicals which are less active, longer-lived and less dangerous than those radicals they have neutralised. They may be neutralized by other antioxidants or other mechanisms to terminate their radical status [45].

Another important function of antioxidants is to regulate ROS-related enzymes. Antioxidants may decrease the cellular level of ROS either by inhibiting the activities or expression of ROS-generating enzymes such as NAD(P)H oxidase and xanthine oxidase (XO), or by enhancing the activities and expressions of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase [46].

Role of antioxidants in ameliorating noise stress

Increasing distance from noise source and decreasing noise exposure time is essential for preventing noise induced abnormalities. However, the ameliorative effects of antioxidants for the treatment of structural and functional noise stress-induced pathologies in the auditory pathway is imperative and have been reported: compounds such as mannitol [47], salicylates or vitamins A, C and E [48], N-acetylcysteine [49], trolox [50], acetyl-L-carnitine combined with N-acetylcysteine [51] and *Ocimum sanctum*—a medicinal herb popularly known as basil, attenuates cochlear oxidative damage following hearing loss [52]. Fetoni et al. [53] reported that NIHL can be reversed by treatment with a natural antioxidant, CoQ10, which prevents cochlear oxidative stress through the decrease in O₂•⁻ production and lipid peroxidation.

Rosuvastatin, a lipid-lowering agent, has been verified to have antioxidant properties. Ersoy et al. [54] reported that this agent decreases oxidative stress in the brain of adult rats, exposed to noise for 20 days. The up-regulation of the antioxidant defenses and the subsequent prevention of tissue damage undertaken by rosuvastatin in rats subjected to noise was confirmed by Koc et al. [55]. It is also worthy of note that inhaled hydrogen gas was reported by Kurioka et al. [56] to be therapeutically effective in the deterrence of noise-induced oxidative damage in cochlear hair cells. In addition, Chen et al. [57] reported that hearing loss and the underlying oxidative stress, triggered after exposure to 130 dB for 1 h was prevented through the use of hydrogen-saturated saline, which is capable of scavenging the OH• radical. Renexin, a derivative from cilostazol and Ginkgo biloba extract, has been shown to possess antioxidant properties [58]. The irreversible hearing loss induced by exposure of adult mice to 110 dB of noise for 1 h was entirely prevented after the treatment with this compound. Rosmarinic acid, a polyphenol compound, commonly derived from culinary herbs, was able to mitigate the auditory function and assuage the loss of cochlear hair cells damaged by noise exposure, and also attenuated the noise-induced increase in lipid peroxidation and O₂•⁻ production [48]. The phenolic compound orientin, abundant in millet and juice of passion fruit, reduces brain oxidative stress markers and increases activities of antioxidant enzymes. It also improves spatial learning and memory acquisition of the passive avoidance response, altered after moderate noise exposure [5]. Administration of inositol, ascorbic acid and tocopherol has been used to enhance the non-specific body resistance to noise stress [59]. *Emblica officinalis* possesses antioxidant properties, effective against noise stress-induced

behavioural changes in Wistar rats [2]. Srinivasan et al. [60] reported the neuroprotective effects of *Indigofera tinctoria* on noise stress affects Wistar rat brain. Tualang honey was also reported to improve memory performance and decrease depressive-like behaviour in rats exposed to loud noise stress [61]. Seidman et al. [62] demonstrated the protective effect of resveratrol against noise-induced hearing loss. Melatonin has also been shown to attenuate noise stress-induced gastro-intestinal motility disorders, gastric stress ulcer and oxidative stress in rats [4]. These reports show that antioxidants are potential agents and may be beneficial in the improvement of the current prophylactic and therapeutic interventions against noise-induced stress.

Conclusion

Noise stress exerts negative effects on the body, which are mediated by stress-induced neurochemical and hormonal anomalies. These reactions may be behavioural, autonomic, neuroendocrine and immunological; often linked with increased generation of free radicals and subsequently, oxidative stress. Increasing distance from noise source and decreasing noise exposure time is essential for preventing noise induced abnormalities. The advocacy for the administration of exogenous antioxidants to mitigate noise-induced stress is attributed to their ability to enhance the expression of endogenous antioxidant enzymes alongside their free radical scavenging capacity which is imperative for the improvement of current prophylactic and therapeutic interventions against noise-induced stress.

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