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Invited review

Noise exposure and oxidative balance in auditory and extra-auditory structures in adult and developing animals. Pharmacological approaches aimed to minimize its effects.

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ABSTRACT

Noise coming from urban traffic, household appliances or discotheques might be as hazardous to the health of exposed people as occupational noise, because may likewise cause hearing loss, changes in hormonal, cardiovascular and immune systems and behavioral alterations. Besides, noise can affect sleep, work performance and productivity as well as communication skills. Moreover, exposure to noise can trigger an oxidative imbalance between reactive oxygen species (ROS) and the activity of antioxidant enzymes in different structures, which can contribute to tissue damage.

In this review we systematized the information from reports concerning noise effects on cell oxidative balance in different tissues, focusing on auditory and non-auditory structures. We paid specific attention to *in vivo* studies, including results obtained in adult and developing subjects. Finally, we discussed the pharmacological strategies tested by different authors aimed to minimize the damaging effects of noise on living beings.

Contents

1. Overview

Noise coming from urban traffic, household appliances or discotheques might be as hazardous to the health of exposed people as occupational noise experimented by people working in a noisy environment [1,2]. Noise pollution has become a serious problem leading to numerous disturbances in human beings, in part due to the dramatic increase in the amount of automobiles in towns, the technological and industrial advances and the increasing number of amusement centers.

In fact, exposure to loud noise levels results problematic all around the world [3]. Although it is estimated that occupational noise causes disabling hearing loss in a proportion of 16% of adults worldwide, few data are available regarding the effects of exposure of people to noise in their daily life [4]. Therefore, even though noise exposure is a big problem in certain occupations, the general population is also increasingly exposed to noise.

Noise could be defined as a disturbing sound, in general of moderate to loud intensity, which may adversely affect living beings.

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The mechanism of noise-induced biological damage is not fully understood, but many factors may account for this damage.

Intensity, frequency and exposure time might have an influence on the effects of noise. In addition, age and health condition might differentially affect exposed subjects. Living in a noisy environment can affect people physiology and behavior, as well as sleep, work performance and peer communication [5]. Noise exposure can also produce hearing loss, mainly when it is present at high intensities [6,7]. In addition, moderate intensities of noise might induce different types of extra-auditory alterations [8–11]. Even though the effects of noise on living organisms can be reverted in the short term, they might induce long term damage, which is dangerously undervalued by the countriesí public health systems. Importantly, it has been reported that noise may display its effects either directly, through the activation of the auditory pathway or mechanical vibration of the tissues, or indirectly, through the emotional perception of sound and the subsequent impact on extra-auditory structures [5].

In humans, noise can interfere with communication, disturb sleep, cause annoyance and affect cardiac properties. Seidman and Standring [12] reported that noise exposure can affect cardiovascular and autonomic homeostasis, even under noise levels that are normally recorded in urbanized areas, leading to a reduction in quality of life. In addition, they reported that noise can modify the normal function of different tissues, especially the vascular system and the cardiac output, likely through the release of stress hormones such as catecholamines and corticosteroids. In addition, Munzel et al. [13], reported that repeated nocturnal autonomic arousals due to environmental noise may induce blood pressure enhancement and increase the risk of developing hypertension in those people exposed to loud noise levels during prolonged periods of time.

Discotheques are among the places that adolescents often visit, exposing themselves to unsafe noise levels. Moreover, the long hours spent listening to personal devices at loud intensities might also be noxious for this age group. These events have led to an increase in a plethora of noise-induced symptoms over the last few years, in particular those related with hearing loss. Unfortunately, few animal studies that focus on noise exposure in immature individuals, together with the underlying mechanisms, are available [11,14–17].

Several challenges of the environment can enhance the production of reactive oxygen species (ROS) in different tissues, which may overcome the endogenous antioxidant defenses, leading to oxidative stress [18–21]. As defined by Halliwell [22], ROS are unstable molecular species that contain one or more unpaired electrons, which make them highly reactive. This author also explains that ROS are continuously generated during aerobic respiration as by-products of redox reactions and that appropriate ROS levels are vital to regulate several signaling pathways. However, an imbalance between the production of ROS and the endogenous antioxidant defense system might lead to a potentially toxic increase in ROS levels that can induce cell damage. This ROS increase might stimulate a ROS reaction chain that can, in turn, stimulate the production of other ROS, such as hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet -}$) or hydroxyl radicals ($OH^{\bullet}$), generating a subsequent oxidative damage to cellular lipids and proteins, as well as mitochondrial and nuclear genome mutations, leading finally to cellular death [22–26].

It has been reported that either loud noise exposure of short duration or moderate intensity noise exposure of longer duration can irreversibly injure the auditory system via oxidative stress. Kurioka et al. [27] recently reported that loud noise exposure might induce an increase in mitochondrial ROS production and cause excitotoxicity, leading to hair cell death in the organ of Corti. Nevertheless, noise-induced production of ROS may not be limited to the cochlea. It has been reported that noise can induce changes in ROS levels and in the endogenous ROS antioxidant enzymes in the brain [10,14,28]. A significant increase in the antioxidant enzymes activities observed after noise exposure in different tissues might denote that an earlier increase in ROS production was triggered, indicating that the brain antioxidant defense system is capable of being activated in response to excessive generation of ROS [28].

In summary, it has been reported that exposure to different intensities of noise may cause auditory and extra-auditory alterations. Moreover, exposure to noise -mainly in mature organisms- can enhance production of ROS and trigger oxidative stress in different tissues, which can contribute to cellular damage. Unfortunately, although many countriesí health systems are aware of the problem of the increased occurrence of noise exposures at high intensities, mainly in children and adolescents, well-performed human randomized controlled trials destined to test substances capable of preventing noise-induced effects remain scarce.

In this review we present an updated compilation of reports concerning noise effects on cell oxidative balance in different tissues, focusing on auditory and non-auditory structures, including both results obtained in adult subjects as well as data obtained in our laboratory with developing animals exposed to noise. In addition, considering that ROS increase might be responsible of noise-induced alterations in different structures, some reports evidencing protective effects of different antioxidant substances on tissues affected by noise were analyzed.

2. Noise-induced alterations on the oxidative balance of auditory structures in animals exposed in adulthood

Noise is among the environmental agents that most frequently cause hearing loss, being oxidative stress one of the proposed mechanisms of noise-induced hearing loss (NIHL), a condition that develops progressively over a long period of time as a consequence of exposure to continuous or intermittent loud noise. There is a consensus that loud noise exposure might affect the cochlea and its function through ROS generation, which may induce hair cells death. In addition, a continuous exposure might generate more damage in comparison with intermittent noise exposure of similar intensity.

It has been reported by several authors that the harmful effects of noise exposure could be mediated by the increase in ROS levels [29]. Seidman and Standring [12] postulated that the intense cochlear metabolic activity induced by noise exposure may be a decisive factor in eliciting hearing loss, inducing an alteration of cellular redox state and leading to the formation of ROS. It is important to highlight that younger people have more risk of developing NIHL, as they are more commonly exposed to loud noise levels at concerts and discotheques as well as through portable digital devices [2]. Ohlemiller et al. [30] found that ROS cochlear levels were significantly high 1 h after exposure to 110 dB noise and persisted even after the stimulus was removed. Moreover, Tamura et al. [5] reported that exposure to broadband noise induced damage to hair cells, producing an increase of oxidative stress in the organ of Corti in the inner ear, resulting in NIHL in a rodent animal model. In addition, it has been shown that in the stria vascularis, ROS levels were increased after noise exposure [31], $OH^{\bullet}$ radicals increased in the cochlea [30], H_2O_2 induced cell damage to the inner ear *in vitro* [32], the endogenous antioxidant GSH increased in the lateral wall [33] and GSH peroxidase activity increased after noise exposure in hair cells [34]. Also, Fetoni et al. [7] observed that decreased levels of coenzyme Q (CoQ), an endogenous ROS scavenger, can lead to the inactivation of respiratory chain enzymes inducing a positive feedback loop, in which lower antioxidant enzymes activities induced an increment in ROS production. Moreover, exposure of