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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

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rats to 100 dB for 10 days, one hour daily, induced oxidative stress and histological damage in the cochlea [35].

In particular, excessive ROS levels in cochlear structures may have a relevant role in the progress of hearing loss. Of importance, like in other stress-induced otological conditions such as drug or age-related hearing loss [26], it could be suggested that ROS might be the key factor in the pathogenesis of NIHL. The accumulation of ROS in the cochlea makes the cochlea's intrinsic antioxidant defenses inadequate to neutralize ROS, leading to cochlear lipoperoxidative damage. Thus, the imbalance between ROS and the endogenous antioxidant defenses play a significant role in hair cell death and the subsequent NIHL.

In summary, considering all the revised papers, it could be hypothesized that under physiological conditions the balance between ROS generation and scavenging is highly controlled. However, when the cochlear structures face acoustic trauma, an activation of the endogenous defense systems can initially occur as an attempt to counteract cell damage, but usually the endogenous antioxidant system fails to restore redox homeostasis and the defense activity results insufficient to prevent cochlear damage.

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

Noise exposure might also induce extra-auditory effects that are generally under-estimated. Alterations in the immune and cardiovascular system, as well as in different behaviors have been reported [5,12]. In addition, the use of animal models to study the extra-auditory effects of noise has been implemented [10,36].

Although different authors found that loud noise can increase ROS in auditory structures [6,33,37], studies of the impact of noise on cellular oxidative balance in extra-auditory structures, in particular in nervous and immune systems, are limited [10,36,38].

Manikandan et al. [10] found that after acute or chronic loud noise exposure, impaired behavioral skills were found, mainly related to an oxidative imbalance, with increased hippocampal antioxidant enzymes activity in acutely exposed animals and decreased activities in chronically exposed animals. A study of Zheng and Ariizumi [39] reported that noise exposure prolonged healing of surgical wounds: while three days of noise exposure increased immune function, 28 days of exposure suppressed it. In addition, oxidative stress was increased in this group, suggesting that oxidative status might partially account for the immune suppression. Cheng et al. [40] found that just one week of moderate noise can induce oxidative stress in different mice brain regions. Finally, Cui and Li [41] reported that brain oxidative stress, together with alterations in spatial memory, was found in noise-exposed adult animals.

In summary, experimental evidences have shown that noise exposure in adulthood can induce extra-auditory effects, most in the brain and in the immune system, through the generation of an imbalance of the cellular oxidative status.

4. Noise-induced alterations on the oxidative balance of auditory and extra-auditory structures in animals exposed at early stages of development

Experimental data using developing animals exposed to noise are very limited in the bibliography. Since the auditory cortex of immature animals is more susceptible to sound-induced disturbances when compared with older animals, as suggested by Wang studies [42], exposing young subjects to noise could shed light about the critical period of development at which these animals are more vulnerable. Kim et al. [16] found that noise caused growth retardation when animals were exposed *in utero*, as well as decreased neurogenesis in the hippocampus (HC) and deterioration in spatial learning when animals became adults. Interestingly, Chang and Merzenich [17] suggested that loud levels of noise, commonly found in child-related entertainment environments, could underlie auditory and language-related delayed development.

However, any study about the oxidative balance in extra-auditory structures of animals exposed during the development was found in the literature. Therefore, it resulted relevant in our laboratory to develop a model of noise-exposed immature animals to test possible oxidative state alterations in different tissues.

We found alterations in different oxidative markers in the HC of developing animals exposed to moderate levels of noise, either through acute or sub-acute exposures, that fluctuate over time and some of which are long-lasting [14]. We hypothesized that a decrease in the levels of ROS in the HC, observed 15 days after noise exposure, may have emerged as a compensatory response of an initial noise-induced increase in antioxidant enzymes activities. Importantly, a persistent increase in the levels of the antioxidant enzyme catalase in the HC of noise-exposed animals might be involved in the further normalization of ROS values, observed after 60 days [15]. However, the decrease in SOD activity, another hippocampal antioxidant enzyme, might suggest that an oxidative imbalance could occur with the aim of stabilizing oxidative status. Interestingly, it could be postulated that even the absence of change in the hippocampal ROS levels at early times after noise exposure might be also interpreted as a result of an imbalance between oxidative markers in the HC [15].

The unexpected decrease in ROS levels found in the HC of noise-exposed developing rats could be clarified according to a report of Owusu-Ansah and Banerjee [43], who hypothesized that although having low levels of ROS would be advantageous for cell and tissue health, keeping ROS levels slightly high placed cells on alert and ready to react quickly to any threat. Therefore, although it might be thought that decreased ROS levels might be beneficial, this reduction could be actually related with the incapacity of exposed animals to manage environmental challenges. Namely, it seems that low ROS levels would not allow the cell to respond satisfactorily to the noise stimulus.

Furthermore, it is essential to emphasize that besides the traditional role of ROS as hazardous by-products, these species can trigger various physiological reaction cascades. Particularly, ROS are required in different signaling pathways to act as second messengers [44]. Therefore, low ROS levels can be certainly harmful because ROS are essential for the organism [45]. Interestingly, it should be also considered that low ROS levels generated by a high endogenous antioxidant capacity may raise compensatory mechanisms that might repair or rescue the cell [46]. Indeed, it could be postulated that the oxidative imbalance observed in noise-exposed immature animals, derived from a combination of low ROS levels and increased antioxidant enzymes activities, could underlie the behavioral disturbances observed later in life [10,14,15]. Moreover, even an early increase in ROS levels observed in different models, added to a subsequent increase/decrease in antioxidant compounds levels, support the hypothesis of the damaging effects of an oxidative imbalance [20,21,47].

In summary, it seems that noise-induced damage in brain regions of developing animals might involve changes in the cellular oxidative status that are opposite to those observed in adult animals, suggesting that possible neutralizing pharmacological strategies should differ depending on the stage of the development.

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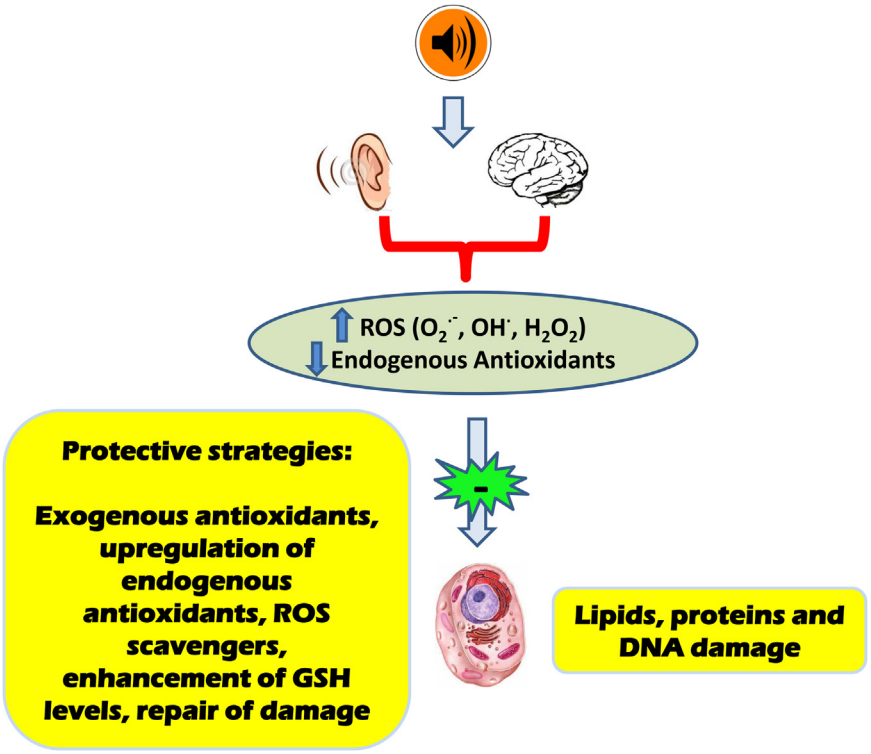

Fig. 1. Schematic representation of the effects of noise on oxidative balance in auditory and extra-auditory tissues, indicating the point in which antioxidants compounds might interfere.

Table 1
Summary of protective agents proved to counteract noise-induced hearing loss in different animal models and the probable mechanism of action.

Antioxidant	Mechanism	Reference
Mannitol	Upregulation of antioxidant enzymes	Yamasoba et al. [33]
Trolox	Antioxidant	Yamashita et al. [34]
Salicylates	Repair oxidative stress injury to mitochondria	Kopke et al. [50]
Acetyl-L-carnitine	Enhances GSH levels	Kopke et al. [50]
N-acetylcysteine	Enhances GSH levels	Kopke et al. [4]
Vitamins A,C and E	ROS scavengers	Le Prell et al. [37]
CoQ10	ROS scavenger	Fetoni et al. [7]
Inhaled hydrogen gas	ROS scavenger	Kurioka et al. [27]
Hydrogen-saturated saline	ROS scavenger	Chen et al. [53]
Renexin	Antioxidant	Park et al. [54]
Rosuvastatin	Upregulation of antioxidant defenses	Ersoy et al. [51] Koc et al. [52]
Rosmarinic acid	ROS scavenger	Fetoni et al. [35]
Orientin	Antioxidant	Wang et al. [55]

5. Pharmacological strategies aimed to counteract oxidative stress in order to protect against noise-induced damage

In the last few years, authors made efforts in the research of strategies to prevent or reverse noise-induced alterations, mainly aimed to neutralize oxidative imbalance. Considering the ROS theory of noise damage, the endogenous antioxidant systems may not be sufficient to counteract excessive noise effects (Fig. 1). Therefore, implementation of an antioxidant exogenous treatment after acoustic trauma might be proposed [48]. In Table 1 we summarize the different compounds found in the literature that were proved as protective agents against noise-induced hearing loss.

Physiologically, different and redundant antioxidant endogenous systems of defense exist in the cell, capable to counteract oxidative stress, comprising enzymatic (superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase) and non-enzymatic systems (GSH, vitamins and micronutrients) [26].

The benefits of the use of ROS scavengers for the treatment of ROS-induced cochlear damage are controversial [24,49]. Nevertheless, reduction of structural and functional noise or stress-induced pathologies in the auditory pathway in animal models has been reported: different compounds such as mannitol [32], trolox [33], acetyl-L-carnitine combined with *N*-acetylcysteine [50], salicylates or vitamins A,C and E [36], *N*-acetylcysteine [4], *Ocimum sanctum* -a medicinal herb popularly known as basil- [28], are capable of attenuating cochlear oxidative damage following hearing loss [26].

As noise pollution became more intense over the last few years, several authors persisted in investigating possible strategies to protect cells from oxidative stress, using conventional and non conventional compounds with antioxidant potency.

For example, Fetoni et al. [7] found that NIHL can be reversed by a treatment with a natural antioxidant, CoQ10, by preventing cochlear oxidative stress through the decrease in $O_2^{\bullet-}$ production and lipid peroxidation.

Rosuvastatin, a lipid-lowering agent, has demonstrated to have antioxidant properties. Ersoy et al. [51] reported that this agent induced a decrease of oxidative stress in the brain of adult rats exposed to noise for 20 days. The upregulation of the antioxidant defenses and the subsequent prevention of tissue damage undertaken by rosuvastatin in rats exposed to noise were confirmed by Koc et al. [52].

Interestingly, a non conventional ROS scavenger, inhaled hydrogen gas, was reported by Kurioka et al. [27] as therapeutically effective in the prevention of noise-induced oxidative damage in cochlear hair cells. Moreover, Chen et al. [53] reported that hearing loss and the underlying oxidative stress triggered after exposure to 130 dB for 1 h were prevented through the use of hydrogen-saturated saline, which is capable of scavenging the $OH^{\bullet}$ radical.

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Renexin, a compound obtained from cilostazol and ginkgo biloba extract, has been shown to have antioxidant properties [54]. The permanent hearing loss induced by exposure of adult mice to 110 dB of noise for 1 h was completely prevented after the treatment with this compound.

Rosmarinic acid, a polyphenol compound commonly found in culinary herbs, was able to ameliorate the auditory function and limit the loss of cochlear hair cells damaged by noise exposure, as well as to counteract the noise-induced increase in lipid peroxidation and $O_2^{\bullet -}$ production, according to results of Fetoni et al. [34].

Finally, orientin (luteolin-8-C-glucoside), a phenolic compound found abundantly in millet and in the juice and peel of passion fruit, was capable of reducing brain oxidative stress markers and increasing antioxidant enzymes, as well as to improve spatial learning and memory acquisition of the passive avoidance response that were altered after moderate noise exposure [55].

In summary, it might be hypothesized that an antioxidant strategy could be faced to prevent, at least in part, auditory and extra-auditory noise-induced damage when adult animals were exposed. No data are available regarding the use of protective strategies in developing animals exposed to noise.

6. Conclusions

As observed in the studies reviewed here, the last several years have brought major progress in the understanding of noise-induced cochlear damage, especially regarding the ROS-mediated mechanism. It might be postulated that the oxidative imbalance between ROS and the endogenous antioxidant system can help determining the fate of the affected cells.

The search for new strategies of prevention in noise-exposed animals might contribute to find a way to improve the quality of life of people exposed daily to loud noise levels.

Finally, considering the potential differences between the oxidative mechanisms triggered at different developmental ages and in view of the increment of noise exposure among the youth population, more attention should be put to the research of strategies that could be effective in preventing noise-induced auditory and extra-auditory damage, linked to oxidative balance, mainly in developing subjects.

Conflicts of interest

Authors state that there are no conflicts of interest.

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