Magnesium therapy in acoustic trauma

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Abstract. Acoustic trauma is one of the major causes of hearing loss and tinnitus, particularly in industrial environments. Noise-induced hearing loss (NIHL) results in direct mechanical damage as well as in indirect metabolic processes. Metabolic disorders have multiple origins: ionic, ischemic, excitotoxic and production of cochlear free radicals causing cell death, due to necrosis or apoptosis. The efficacy of magnesium, administered either to prevent or to treat NIHL has been demonstrated in several studies in animals and in humans. Magnesium, which easily crosses the hematocochlear barrier, presents neuroprotective and vasodilatory effects, and thus, is able to limit the cochlear damage. Magnesium therapy is well documented because it is usually prescribed in other pathologies. Its side effects and contraindications are few and it is cheap. This article presents also some arguments that emphasize the interest of magnesium therapy in acoustic trauma.

Key words: acoustic trauma, guinea pig, cochlea, magnesium, noise-induced hearing loss

According to 2005 estimates by the World Health Organization, 278 million people worldwide have moderate to profound hearing loss in both ears. In industrial societies, exposure to intense noise is one of the major causes of hearing loss in adults. Noise induced-hearing loss (NIHL) is the leading occupational disease, a significant cause of disability and a major cost to society. Many noisy occupations such as the military, construction, manufacturing, aviation, are concerned by NIHL. Moreover, leisure time activities can produce hazardous noise levels. In young people, exposure to loud music (during concerts or using personal stereo) involves frequently hearing threshold shift and tinnitus. In 1997, the cost of noise-induced hearing loss alone in US was estimated to be between 0.2% and 2% of the gross domestic product [1].

Traditionally, prevention of noise-induced hearing loss is based on information, reducing noise sources, and wearing hearing protection. However, when the noise levels are very intense (above 130 dB), these measures are not sufficient. Furthermore, at high exposure levels, a proportion of the sound energy may be bone conducted to the inner ear, resulting in cochlear damage despite the use of ear protection. Since attempts to cure lesions affecting the inner ear with conventional treatment have been essentially unsuccessful, there is a massive social and economic demand to develop new treatments. In humans, susceptibility to NIHL is known to be highly variable and depends upon many factors. Among them, magnesium status seems to play an important role.

Abbreviations:

DPOAE: distortion product otoacoustic emission
IHC: inner hair cell
Mg2+: magnesium
NIHL: noise-induced hearing loss
NMDA: N-methyl-D-aspartate
NO: nitric oxide
OHC: outer hair cell
PTS: permanent threshold shift
ROS: reactive oxygen species
SPL: sound pressure level
TTS: temporary threshold shift

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This observation has led to many investigations, the aim of them being to evaluate the pertinence of magnesium administration in prevention or treatment in NIHL.

**Effect of noise on the hearing**

Sound waves are transmitted via the bones of the middle ear to the fluid environment of the inner ear, where the sensory organ is developed in the cochlea. The human cochlea is a coiled tube 30-35 mm long containing three parallel chambers (figure 1A): the scala vestibuli and scala tympani, which contain perilymph, and the scala media, which contains endolymph. Conversely to the perilymph which is similar to the cerebrospinal fluid, endolymph contains a large amount of potassium (154 mM), maintained by the cells of the stria vascularis. The organ of Corti (figure 1B) is composed of supporting cells and hair cells. In humans, there are 15,000 hair cells in each cochlea, including 3,500 inner hair cells (IHCs) and 12,000 outer hair cells (OHCs). The IHCs form one row (figure 2A, B) and are the primary sensory receptors. OHCs are organized into three rows along the outer edge of the organ of Corti. The longer stereocilia of the OHCs are fixed to the tectorial membrane.

In the hearing process, the sound reaches the inner ear and the basilar membrane supporting hair cells is displaced. When the hair bundle is deflected, transduction channels are opened and K⁺ enters the hair cells. The depolarization evoked by this transduction current activates voltage-gated Ca²⁺ channels and Ca²⁺ influx. In IHCs, increased intracellular Ca²⁺ causes mobilization of synaptic vesicles and exocytotic release of glutamate at the base of the hair cells. Glutamate release modulates the activity of the auditory nerve fibers by activating specific receptors, N-methyl-D-aspartate (NMDA) and non-NMDA type. The OHCs respond quite differently to changes in membrane potential. Their membranes include a protein (prestin) which alters their conformation with the membrane potential and forces cell length changes at acoustic frequencies. This mechanism is thought to amplify and tune the mechanical responses of the basilar membrane. This amplifier activity is modulated by the efferent innervation.

This sensory system is so efficient that, near the auditory threshold, a stereocilia displacement 10,000 times lower than its diameter, may be detected. When this system is exposed to excessive noise, some damage may appear. The traumatizing noise can be a continuous noise (above 85 dB SPL, 8 hours a day for example), or an impulse noise (above 135 dB peak).

The damage mechanisms differ depending on the type of noise and are of dual origin, mechanical and metabolic. Mechanical damage develops immediately when the movements of the basilar membrane are excessive, thus inducing detachment of the hairs of the tectorial membrane, disconnection of the intercellular bridges, or even rupture of the basilar membrane [2]. Metabolic disorders appear secondarily. They have multiple origins: ionic, ischemic, excitotoxic or involving oxidative stress. They are responsible for a delayed hair cell death.

1) **Ionic origin.** The high level noise stimulation involves a massive entrance of potassium through the apical channels of the stereocilia. Moreover, mechanic damage with ruptures of the membranes lining the endolympathic spaces could involve an excessive influx of K⁺. This increased K⁺ concentration may be toxic for the hair cells [3]. The consecutive increase of intracellular Ca²⁺ overactivates a series of enzymes including phospholipases, proteases, endonucleases. The results are membrane breakdown, depolymerization of microtubules and disruption of protein synthesis.

2) **Ischemic process.** Among the many possible pathophysiological mechanisms that may contribute to noise-induced temporary or permanent threshold shifts, insufficiencies in cochlear blood flow prevail. Although the literature is inconsistent, several histological and physiological studies demonstrate signs of reduced circulation in the cochlea after noise exposure [4]. Exposure to high level noise results in a decrease of perilymphatic PO₂ and cochlear blood flow [5]. Vasoconstriction of the capillaries of the basilar membrane, spiral ligament and stria vascularis in response to noise has been reported. The capillaries of the basilar membrane, which are terminal vessels have been considered to supply oxygen to the organ of Corti. However, Lamm and Arnold [5] observed that noise-induced cochlear hypoxia preceded reduction of the cochlear blood flow. It seems that cochlear hypoxia is not brought about by a decreased delivery but reflects an increased extraction rate from cochlear fluids. In the organ of Corti, hypoxia causes injury to hair cells, a decline in the endocochlear potential and changes in ionic balance in the endolymph. It has also been shown that ischemia induces glutamate excitotoxicity and reactive oxygen species (ROS).

3) **Excitotoxicity** is a phenomenon of biochemical events, triggered by the interaction of excitatory aminoacids with ion channel-bound receptor complexes that can lead to cell death. During high-level
noise exposure, the IHCs are highly active, leading to the release of large amounts of glutamate into the synapses with the auditory fibers. The levels of glutamate in the synapses can overstimulate the glutamate receptors, specially the NMDA receptors, that involves high intracellular Ca^{2+} levels. The increase in cytosolic Ca^{2+} concentration is not only caused by an influx of extracellular Ca^{2+}, but also by the release of calcium ions from intracellular stores such as the endoplasmic reticulum or mitochondria.

Figure 1. Schematic representation of the inner ear. A) Section of the cochlea. B) Organ of Corti.
The swelling is a result of postsynaptic ion influx into the VIIIth nerve terminals that occurs due to excessive excitation [6].

4) Oxidative stress. It has been demonstrated that an increase of ROS is involved in noise trauma [7, 8]. At least three important ROS are generated in the reduction of \( \text{O}_2 \) to \( \text{H}_2\text{O} \): superoxide anion \((\text{O}_2^\cdot)\), hydrogen peroxide \((\text{H}_2\text{O}_2)\) and hydroxyl radicals \((\text{OH}^\cdot)\). The production of nitric oxide (NO) during noise exposure may increase ROS-induced damage by converting relatively benign free radicals to much more active and destructive species (peroxynitrite). Direct evidence of ROS ototoxicity has been demonstrated in isolated outer hair cells and following infusion into the perilymphatic space in the cochlea [9]. ROS ototoxicity is believed to be associated with deleterious cellular effects at multiple sites including lipid peroxidation, DNA strand breaks, alterations in carbohydrate and protein structures and trigger the expression of cell death genes, leading to necrosis or apoptosis. Oxidants are also initiators in intracellular cell death signalling pathways that may lead to apoptosis. The noise-induced ROS formation may occur with a delay of 7-10 days following exposure [10].

Irrespective, these mechanisms can lead to cell death which may be more or less rapid, due to necrosis or apoptosis [11]. Recent studies have revealed that these two types of cell death exist following exposure to intense noise and that apoptosis appears extremely rapidly after the noise stress [12].

Then, after intense noise exposure, a more or less extended hair cell loss could be observed (figure 2C), OHCs being more susceptible than IHCs. The appearance of lesions can be studied more depth using scanning electron microscopy (figure 2D). Abnormal ciliated tufts can be observed, with partly fused hairs and broken interciliary bridges. The stereocilia often appear as floppy and bent due to a degradation of cytoskeleton protein.
Mammalian hair cell loss and damage have always been considered irreversible, although hair cell regeneration has been shown to occur under certain circumstances [13].

Clinically, the intense noise exposure could involve hypoacusis (the auditory threshold increases), often tinnitus (abnormal perception of a ringing that does not exist) or hyperacusis (unusual hypersensitivity induced by exposure to sound). The hypoacusis could be transitory (temporary threshold shift, TTS) or definitive (permanent threshold shift, PTS). TTS results from damage of the stereocilia which is not too severe to prevent repair of these structures.

**Magnesium and NIHL**

Individual susceptibility to noise seems to play an important factor determining the eventual NIHL. For the last few years, researchers and clinicians have demonstrated the influence of magnesium in the susceptibility to recover following acoustic trauma. NIHL of guinea pigs with varying Mg2+ intake was found to increase with decreasing Mg2+ content of the drinking water while the Mg2+ content of the food was low and constant. In the group of Mg-deficient guinea pigs, the hearing threshold shift after 10 days of continuous noise exposure was negatively correlated to the Mg2+ content of the perilymph [14]. Coherent results were obtained in rats [15]. Similarly, electrocochleographic measurements of the auditory threshold shifts induced by impulses noises [16] showed that deficient animals are slightly more susceptible to this type of noise. This susceptibility is less remarkable than after exposure to a continuous noise for a long duration, as observed in the previous experiments. After exposure to continuous noise, up to 75% of the variance of PTS [17] in guinea pigs could be explained by the level of perilymph Mg2+. The increased susceptibility to NIHL with Mg2+ deficit has not been only demonstrated in animal experiments: in a retrospective study in humans, subjective threshold shifts across frequencies of 3, 4 and 5 kHz were negatively correlated to serum magnesium [18]. This finding was the first indication that magnesium status in humans may be one of the factors determining variations in sensitivity to noise-induced hearing loss. Günther et al. [19] reported that NIHL observed in 24 Israeli Air Force pilots was negatively correlated to serum Mg2+ concentration. However, Walden et al. [20] have explored the susceptibility of soldiers to NIHL but they failed to demonstrate any correlation between audiometric index and body magnesium.

Because Mg2+ deficiency increases the susceptibility to NIHL, several studies have been conducted in animal or in human to point out the possible interest of a prophylactic efficacy of the magnesium. Joachims et al. [15] observed that guinea pigs with physiologically high Mg2+ levels, exposed to a single shot impulse or a series of impulses, had significantly smaller threshold increases as compared to physiologically low Mg2+ animals. Scheibe et al. [21] showed that oral magnesium supplementation significantly reduces TTS and PTS in guinea pigs subjected to a series of impulses (2280 x 167 dB SPL). The mean PTS was found to correlate negatively with the total Mg2+ concentration of perilymph and plasma. Conversely, they did not observe any significant effect on PTS following exposure to a gunshot noise (187 dB SPL). More recently, Attias et al. [22] have explored the activity of the outer hair cells in guinea pig, by mean of otoacoustic emission, after impulse noise exposure. The thresholds were less significantly affected by noise exposure and the audition recovery was faster in the animals supplemented in Mg2+. In human, preventive administration of magnesium has been also shown to be effective on hearing loss related to noise. Attias et al. [23] tested the prophylactic effect of magnesium in human subjects exposed to hazardous noise. The study was carried out on 300 young, normal-hearing recruits who underwent 2 months of basic military training. This training included repeated exposures to high levels of impulse noises while using earplugs. The subjects received daily an additional drink containing either 167 mg magnesium aspartate or a placebo. The NIHL was significantly more frequent and more severe in the placebo group (28.5% in the right ear) than in the magnesium group (11.2%). Moreover, the severity of the NIHL was negatively correlated to the magnesium content of red and mononuclear cells. The additional intake of magnesium was not accompanied by any notable side effect, such as gastrointestinal symptoms, dizziness or headache. These prophylactic effects in human were confirmed by Attias et al. [24] after temporary threshold shifts. Subjects were exposed to a white 90 dB SL noise during 10 min. This exposure appeared to be sufficient to produce TTS without PTS. Compared to a placebo, the preventive oral intake of magnesium (122 mg Mg2+ aspartate during 10 days) provided significant protection against TTS. A negative correlation between the blood magnesium levels and the TTS was also noted.
How does magnesium therapy work?

Magnesium is the fourth most important cation in the body and the second most important intracellular cation. It activates approximately some hundred enzyme systems, including most of the enzymes involved in energetic metabolism. Thus, magnesium plays an essential role in the regulation of most cellular functions. However, it is recognized that magnesium status in humans is often deficient. In the recent French study su.vi.max (the “supplementation en vitamines et mineraux antioxidants” study) concerning 5,448 subjects, it was shown that 77 per cent of women and 72 per cent of men had dietary magnesium intakes lower than recommended dietary allowances [20]. It has been known for a long time that stress situations influence magnesium content. Mild physical or psychological stress increase plasma Mg2+, while prolonged severe or chronic stress decreases it [30]. This observation is also true for noise induced stress. Exposure to acute noise stress is able to induce an increase of circulating magnesium, and a subsequently increased excretion of this cation in urine, which suggests that chronic exposure to noise, could facilitate depletion of the whole-body magnesium content [31]. Moreover, catecholamines, increased by noise stress [32] or Mg2+ deficiency, induce lipolysis by a β-adrenergic effect. The increase of free fatty acids within the adipocytes causes an increased formation of undissociated Mg2+ soaps, thus reducing intracellular concentrations of free Mg2+. It seems that it may be a vicious circle involving Mg2+ deficiency and noise stress.

Scheibe et al. [33] were the first to study in the same animal the correlation between the plasma, perilymph and cerebrospinal magnesium contents. Conversely to the blood brain barrier, the blood perilymph barrier is not able to concentrate Mg2+ taken up from plasma. Also, the perilymph Mg2+ concentration correlates well with the plasma level and a Mg2+ deficiency affects perilymph content.

The exact manner by which Mg2+ affects the susceptibility to noise-induced hearing loss is still unknown, but several mechanisms could be evoked. The first mechanism concerns its interaction with Ca2+ exchanges. Free extracellular Mg2+ influences the Ca2+ channels and contributes to preserve membrane polarization [34, 35]. The influx of calcium is reduced by an increase in free extracellular Mg2+. In addition, it affects the activation of voltage-dependent Ca2+ and K+ channels at the membrane [36, 37]. It is possible that, for reduced Mg2+ deficiency, the Mg2+ concentration at the hair cell membrane decreases, leading to an overall increase in membrane permeability. This causes an increase in the intracellular calcium, while K+ decreases by passive flow diffusion. Consequently the decreased electrolyte gradients induce greater transport activity with regard to these ions and an increase in the energetic turnover of the cell [37]. A lasting increase in the intracellular Ca2+ can lead to cell energy depletion, finally leading to the death of the cell.

A second mechanism that could explain the magnesium efficacy on NIHL implies cochlear microcirculation. A decreased Mg2+ intake was found to be associated with the reduction of the blood microcirculation of the inner ear by increasing the secretion of catecholamines and prostaglandins, which augments the risk of energy depletion in the hair cells following noise exposure [19]. This is aggravated by the fact that the blood flow in vessels supplying the cochlea is reduced to 70% after noise exposure [38]. Recently, more direct support was provided by Scheibe et al. [39]. Cochlear ischemia induced hearing loss was aggravated in animals with physiologically low Mg2+ compared with high Mg2+ ones. Furthermore, Mg2+ improves cochlea blood viscosity. The direct measurement of the cochlear blood flow
Figure 3. Influence of the dose (upper figure) and the administration delay (lower figure) of magnesium therapy after NIHL in guinea pigs (adapted from Scheibe et al. [26]).
with a Laser Doppler flowmeter [40] confirms that a preventive dietary magnesium supplement protects the inner ear against noise-induced impairment of the blood flow. It has been demonstrated in several studies that an increase in extracellular magnesium induces a dose-dependent vasodilatation of the arterioles, precapillary sphincters and venules. In addition, magnesium reduces the constriction of the microvessels induced by vasoconstrictor substances [41]. Vasodilatation by magnesium is probably caused by reducing Ca²⁺ influx and the competitive inhibition of Mg²⁺ to Ca²⁺ at binding sites of the myosin light chain kinase regulated protein calmodulin [42]. Other mechanisms could explain the effect of Mg²⁺ on the cochlear microcirculation. An acute noise stress exposure, as well a Mg²⁺ deficient states, increases the release of catecholamines, particularly noradrenaline, which limits the cochlear blood flow [43]. Hypomagnesaemia results in a reduced endothelial NO release. In this way, hypomagnesaemia can induce vasoconstriction [44]. At least, magnesium reduces the production of endothelin and attenuates its vasoconstrictive effect [45]. The endothelin contributes to the cochlear microcirculation disorder caused by noise [46]. Not only does magnesium combat ischemia, but it is also thought to prevent cell damage caused by hypoxia. König et al. [47] noted a protective effect of magnesium (and of MK801, a selective NMDA receptor antagonist) on hypoxia-induced hair cell loss in vitro. In addition, a high magnesium concentration attenuated the hypoxia/ischemia-induced disruption of mitochondrial membrane potential, a critical event in triggering cell death [48]. This mechanism is supported by the observation that an increase in the extracellular magnesium concentration led to a decrease in hypoxia induced apoptosis by maintaining the normal ratio of Bax to Bcl-2 proteins involved in determining the survival of cells or their death [49].

The third potential mechanism explaining the Mg²⁺ efficiency, involves excitotoxicity. The magnesium apparently enhances the survival capability of the cochlear afferents, reducing the effect of glutamate-induced inner hair cell damage [50]. Magnesium is able to modulate the opening of Na⁺/Ca²⁺ channels of the NMDA receptors [51, 52]. The blockade of the NMDA receptors by Mg²⁺ is voltage-dependent, but extracellular Mg²⁺ behaves as a non-competitive NMDA antagonist, without the side effects presented by the other non-competitive NMDA antagonists [53]. In the hearing process, if Mg²⁺ is low, an excess of Ca²⁺ could enter into the hair cells. In turn, more glutamate would then be produced in response to this Ca²⁺ influx. Increased glutamate would also greatly increase the activity of the NMDA receptor, which is also operating with low magnesium. With the double insult of high glutamate and low Mg²⁺, a flood of Ca²⁺ could go through the NMDA channels into the nerve cell, which energetic system could be compromise.

Furthermore, magnesium reduces free radical production. Two mechanisms have been suggested [54]: It may directly inhibit free radical production or it may facilitate scavenging of free radicals. Afanas’ev et al. [55] owed that Mg inhibits reduced NADPH oxidase, an enzyme that produces superoxide radicals. The effect of magnesium was comparable to other metals (such as copper) that are usually considered excellent inhibitors of free radical generation by reduced NADP oxidase. This same study found that although magnesium does facilitate free radical scavenging, it does so only at a minimal level compared with other scavengers. Thus, the mechanism for magnesium attenuation of free radicals may be through inhibition of free radical production. Magnesium also protects endothelial cells against cytotoxicity of radicals [56].

In summary, magnesium could act at different levels of the noise-induced hearing loss process. Conversely to other therapeutic agents used after NIHL (i.e. corticosteroids), it easily crosses the perilymph blood barrier and reaches the organ of Corti. Thus, by its neuroprotective and vasodilatory effect, magnesium administration presents a prophylactic and a therapeutic efficiency in NIHL.

Clinical relevance of magnesium therapy

Magnesium has been used for many years on eclampsia in human. Because Mg²⁺ deficiency could be involved in several pathologies [57], the interest of magnesium therapy is now increasing. It is also prescribed in various diseases as cardiovascular, neuropsychiatric disorders or in anaesthesiology [58]. More generally about the inner ear pathologies, the deficiency of magnesium is a relevant predisposing risk factor for the development of otoacoustic toxicity induced by various causes [59].

In clinical trials, it has been shown that Mg²⁺ improves hearing recovery in cases of idiopathic sudden hearing loss [60]. In all these studies the side effects of the magnesium therapy appeared to be limited. Nausea and headache have been described in patients with serum Mg²⁺ level above 1.8 mmol/L. Toxicity involving bradycardia or hypotension can occur with a serum level above 2.2 mmol/L. Thus, magnesium therapy with recommended dosage
appears to be safe with few contraindications in spite of severe renal failure [61]. This therapy could also be easily and rapidly applied after traumatizing noise exposure. In some countries like in France, the recommended treatment in human after severe noise-induced hearing loss consists of placement in a silent environment, injection of glucocorticoid, associated or not with vasodilator substances, hyperbaric oxygenotherapy or normovolemic hemodilution. The mechanisms underlying the therapeutic effect of glucocorticoids are still speculative [62]. They could act by suppressing the expression of cytokines, by modulating the function of several transcription factors such as the nuclear factor-kappaB (that has a protective role in the central nervous system), by inhibiting NO synthase or increasing the putative anti-apoptotic Bcl2-gene expression.

The association of different treatments (i.e. glucocorticoid and magnesium) could also present a great interest, provide they act at different levels of the cellular death process. The benefits of such an association need to be elucidated with further experiments.

**Conclusion**

By its neuroprotective and vasodilatory effects, magnesium has the potency to prevent, as well to limit, hearing loss after noise exposure. Because it is safe, cheap and commonly available, this treatment could easily be applied either to improve the recovery after noise-induced hearing loss, or to prevent noise-induced hearing loss in subjects exposed to a noisy environment.

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**References**


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