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REVIEW ARTICLE

Pharmacological agents used for treatment and prevention in noise-induced hearing loss

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Abstract Noise is a stress factor that causes auditory, psychological and physiological effects. The realization that sudden loud noises or chronic exposure to noise in social and working environments can cause hearing loss has led to increased interest in noise-induced hearing loss (NIHL). The best means of preventing primary damage is protection against noise. Since this protection is not always possible for various reasons, the use of pharmacological agents to prevent or treat NIHL should also be considered. The purpose of this study is to discuss current pharmacological protection and treatment options in the light of the literature, since no such extensive reviews have been performed to date, including agents used for protection against and treatment of NIHL. We reviewed both animal and clinical studies, and these are discussed separately for ease of comprehension. For each agent, first animal studies, then clinical studies, if available, are discussed. We also performed a two-step search of the literature. In the first step, we searched the terms "noise induced hearing loss", "treatment" and "protection" in Pubmed. Based on the results obtained, we identified the agents used for the treatment of and protection against NIHL. In the second step, we searched the names of the agents identified in the first step, together with the term "noise induced hearing loss," and reviewed the results.

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Introduction

Exposure to excessive noise is one of the most common causes of reduced hearing. Noise is a stress factor that causes auditory, psychological and physiological effects. It can also cause cellular immunity compromise, sleep disturbance and an increase in stress hormones [1]. The realization that sudden loud noises or chronic exposure to noise in social and working environments can lead to hearing loss has led to increased interest in noise-induced hearing loss (NIHL). Both genetic and environmental factors are involved in NIHL, which is a preventable health problem. The frequency and severity of noise and the type of exposure (constant, occasional, sudden or explosive) determine the degree of hearing loss, the frequencies affected and whether loss is temporary or permanent [2]. The effect of noise that damages the hearing system varies depending on the intensity and duration of exposure and individual susceptibility. The first audiological finding emerging after exposure to noise is high-frequency hearing loss. This typically manifests in notch form at around frequencies of 4000 or 6000 Hz. As hearing loss increases, compromise beginning at a range of 4000–6000 Hz spreads out to lower and higher frequencies. The highest loss with worsening auditory sensitivity commonly occurs at approximately 4000 Hz. Cochlear injury occurring in association with noise includes degeneration of hair cells, particularly the outer hair cells, progressive degeneration of supporting cells and degeneration of afferent nerve fibers. The best means of preventing primary damage is protection against noise [3]. Since this protection is not always

possible for various reasons, the use of pharmacological agents to prevent or treat NIHL should also be considered. The purpose of this study is to discuss current pharmacological protection and treatment options in the light of the literature, since no such extensive review has been performed to date, including agents used for protection against and treatment of NIHL. Animal and clinical studies are considered separately for ease of comprehension. For each agent, first animal studies, then clinical studies, if available, are discussed. We also performed a two-step search of the literature. In the first step, we searched the terms "noise induced hearing loss", "treatment" and "protection" in Pubmed. Based on the results obtained, we identified the agents used for the treatment of and protection against NIHL. In the second step, we searched the names of the agents we determined in the first step together with the term "noise induced hearing loss," and reviewed the results.

Agents used for treatment and protection

Due to the prevalence of NIHL in modern society, protection and treatment are of critical importance. Since there is yet no specific treatment for NIHL, the use of materials that protect against loud noise, such as earmuffs, still represents the primary strategy. However, the effect of these materials depends on regular and effective use. In an epidemiological study, Mrena et al. [4] reported benefit from ear protector use among military personnel but also revealed that this did not provide full protection. They suggested two possible reasons for this: insufficient protector use and protector exhibiting lower effects in field conditions than in laboratory conditions. In addition, covering the ear also obstructs environmental awareness and communication. Noise is regarded as a part of the environment in many activities and is difficult to eradicate. The development of pharmacological agents for protection against and treatment of NIHL is therefore highly important. Protection against permanent hearing loss is more urgent, although since temporary hearing loss can also have long-term effects on quality of life, the treatment of temporary loss is also important. Methods such as anti-inflammatories, antioxidants, minerals, calcium antagonists, vitamins and hemodilution agents have to date been used in the treatment of and prevention against the disease. An overview of noise-induced cochlear injury pathways and targets of the pharmacological agents mentioned in the text was summarized in Fig. 1.

Steroids

Interest in hormonal regulation of hearing physiology and sensitivity to noise has resulted in conservative strategies focusing on steroid hormones. The most studied steroids are dexamethasone and methylprednisolone. Administration route, timing and effective dose have all been investigated in various previous studies. In a study performed by Wang et al., intraperitoneal injection of 1 mg/kg dexamethasone for five consecutive days in guinea pigs exposed to 115-dB SPL white band noise provided protection against NIHL, possibly by suppressing cochlear Hes1 expression via a glucocorticoid receptor-dependent mechanism [5]. In another study; 1-, 10-, 100- and 1000-ng/ml doses of dexamethasone were administered directly into the scala tympani of guinea pigs exposed to 120-dB SPL octave band noise on the fourth day of dexamethasone administration. Direct application of dexamethasone to the inner ear was reported to be effective in protecting against NIHL [6]. Arslan et al. [7] investigated the effect of dexamethasone in the treatment of NIHL in 26 rats. These were exposed to 115-dB SPL white noise for 3 h a day for 10 days. Dexamethasone was injected at 2 mg/kg for 7 days in the first hour after noise exposure. The final hearing threshold was 5 dB, a normal hearing level, in the treated group, which was significantly better than that in the non-treated group (22.5 dB nHL). The results showed that early initiation of dexamethasone therapy is effective in the treatment of NIHL.

Transtympanic administration of methylprednisolone is also effective in the treatment of NIHL. Ozdogan et al. [8] administered intratympanic methylprednisolone following noise exposure in 16 rats. They reported a decrease in the numbers of apoptotic cells in the outer and inner hair cells of the cochlea. They concluded that intratympanic methylprednisolone injection after acoustic trauma reduces outer hair cell loss.

Tabuchi et al. [9] investigated the therapeutic time window of methylprednisolone in acoustic injury. Mice were exposed to 128-dB SPL for 4 h. The authors reported that when administered before or immediately after noise, methylprednisolone has a protective effect against acoustic injury. However, when administered 3 h after acoustic overexposure, no protective effect was observed. These findings suggest that the therapeutic time window of methylprednisolone is very short.

In contrast, studies have also reported that steroids have no otoprotective effect. Bas et al. [10] studied the effect of dexamethasone against NIHL in 32 rats exposed to 120-dB SPL noise for 4 h. The day before noise exposure and for a

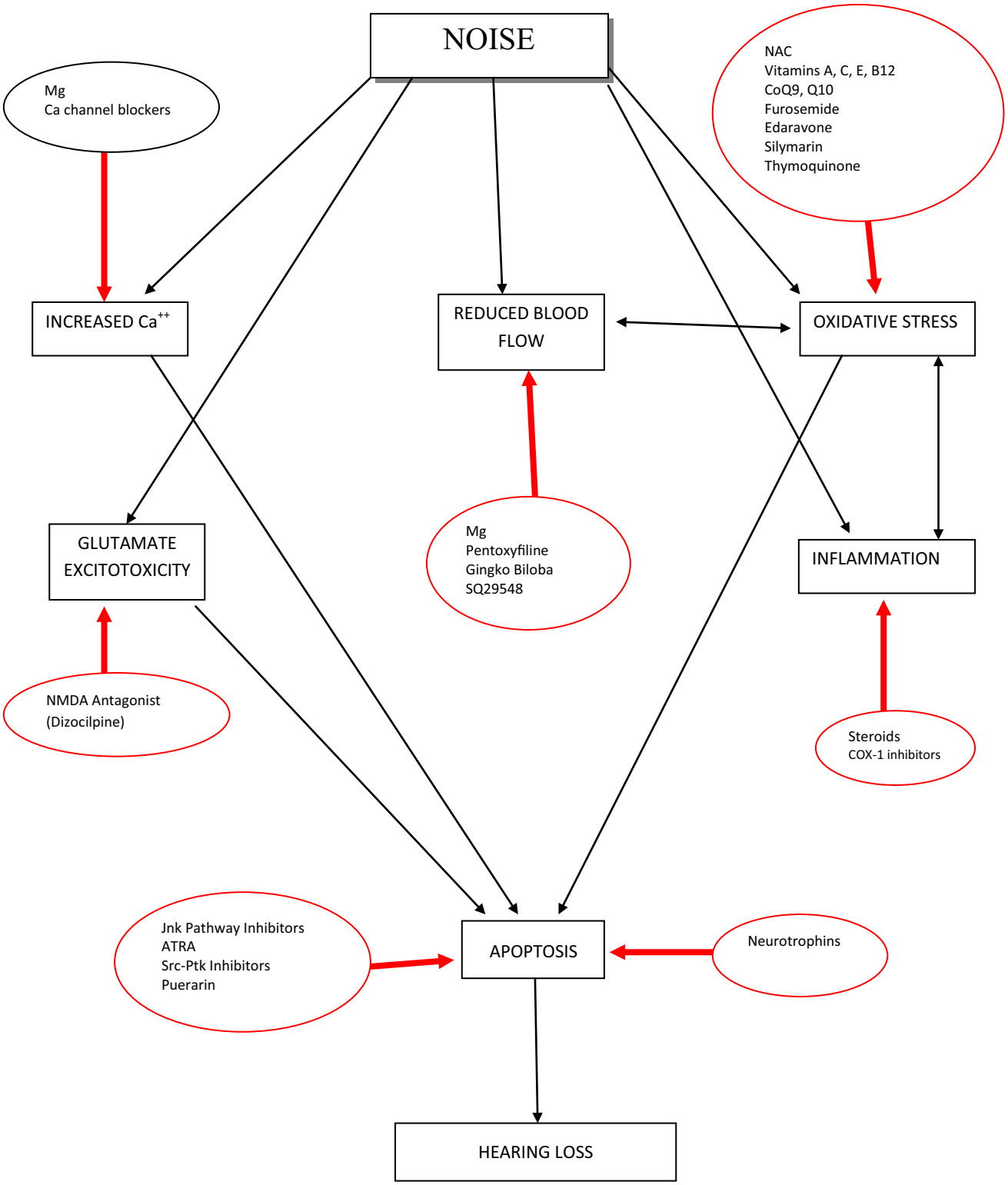

Fig. 1 An overview of noise-induced cochlear injury pathways and targets of the pharmacological agents mentioned in the text

subsequent period of 14 days, the animals were administered dexamethasone. The authors reported that dexamethasone was not effective in protecting against NIHL. In another study performed by Takahashi et al. [11] guinea pigs were exposed to 110-, 115- or 120-dB SPL noise for 10 min. Methylprednisolone was given intraperitoneally for 7 days after noise exposure. The authors concluded that methylprednisolone is not effective in the treatment of

acoustic trauma caused by exposure to 115- or 120-dB SPL, while it is effective in exposure to 110-dB SPL.

Another study investigated the intravenous application of a neurosteroid, dehydroepiandrosteronesulfate (DHEAS). Thirty-eight guinea pigs were exposed to 120- or 125-dB SPL for 10 min. DHEAS was given intravenously at 0.1 or 1 mg/kg immediately before acoustic overexposure. The authors reported that 1 mg/kg doses of DHEAS may have a protective effect against acoustic injury [12].

Clinical studies

Zhou et al. [13] investigated the effectiveness of early transtympanic injection of methylprednisolone. In that clinical study, 53 patients with NIHL whose treatment was delayed, were divided into two groups. The control group was administered conventional steroid treatment in the form of methylprednisolone (125 mg i.v. for the first day, followed by 32 mg per day p.o. for 5 days, 16 mg per day for 2 days and 8 mg per day for another 2 days), naftidrofuryl (200 mg p.o.t.i.d.), diazepam (5 mg p.o.t.i.d.), and low-molecular-weight heparin (0.4 ml s.c.b.i.d.) or low-molecular-weight dextran (500 ml i.v.q.d.), while the study group received the same steroid therapy with additional transtympanic steroid injection. The authors prepared a solution consisting of 40 mg methylprednisolone dissolved in 1 ml of sodium bicarbonate. The patients received 0.4 ml of this solution for 4 days. A total of 51.9 % of the patients in the TR group exhibited a ≥15-dB HL improvement in pure-tone average, compared with 23.1 % of the patients in the control group at 8-week follow-up audiogram. The differences between the two groups were statistically significant. The authors concluded that additional transtympanic injection increases the effect of systemic steroid therapy.

N-acetyl cysteine

Since free oxygen radicals and the effect of oxidative stress are important in the pathogenesis of the disease, the idea arose that antioxidants might be effective in treatment. Degeneration can be prevented if free radicals and reactive oxygen species in the cochlea can be eliminated. One of the most important antioxidants in the body is glutathione (GSH), which reacts directly with oxidants and inhibits oxidation of molecules. GSH plays an important role in NIHL. Yamasoba et al. [14] studied the effect of GSH in NIHL. Eight guinea pigs received daily injections of an inhibitor of GSH synthesis or a cysteine prodrug while being exposed to 102-dB SPL, 3 h per day for 5 days. They found that inhibition of GSH made the cochlea more susceptible to noise-induced damage and that restoration of GSH attenuated noise-induced cochlear damage. Similarly, Ohinata et al. [15] described GSH as an important factor in the restriction of cochlear damage in acoustic injury.

N-acetyl cysteine (NAC) deacetylates to cysteine in the liver or local tissue and neutralizes the effect of noise via several mechanisms. NAC inhibits cell death pathways, provides a substrate for GSH synthesis in cochlea, and acts as free radical scavenger [16, 17]. Due to these affects, studies have investigated NAC in terms of the treatment and prevention of NIHL. NAC has been found to be more effective against permanent threshold shift (PTS) than transient threshold shift (TTS). This difference is based on the mechanism of action of NAC. NAC is more effective against the causes of PTS such as hair cell and neuronal loss caused by GSH depletion and oxidative stress [16].

Kashani et al. [18] investigated the efficacy of NAC against NIHL in rabbits. They divided 24 rabbits into four groups; a control group, a noise and saline group, a noise and NAC group and a NAC only group. NAC was administered by intraperitoneal injection 3 days before and 3 days after noise exposure. ABR was performed 1 h and 14 days after noise. Mean 49-dB SPL temporary and 23.9-dB SPL permanent hearing threshold shifts were observed in the noise and saline group rabbits. In the group receiving NAC, mean 31.5-dB SPL temporary and 10.7-dB SPL permanent thresholds shift was observed. In conclusion, the application of NAC provided adequate protection against NIHL at all the frequencies investigated.

Lu et al. [19] studied the effect of NAC in NIHL when combined with disodium 2,4-disulfophenyl-*N*-*tert*-butylnitrone (HPN-07), a free radical spin trap reagent. In that study, rats were exposed to 115-dB SPL noise for 1 h. A NAC/HPN-07 combination was administered 1 h after noise exposure and continued for 2 days. The authors described this combination as a promising pharmacological treatment for PTS and TTS. It also protected cochlear sensory cells and against afferent neuritis. The time of administration of NAC was also found to be important. In a study by Lorito et al. [20] 40 rats were exposed to 105-dB SPL noise. They were then divided into four groups and treated with different NAC administration schemes. One of the groups received a single injection before noise exposure, another group received a single injection 24 h after exposure and another group received four injections over 48 h with a single injection dosage of 375 mg/kg. The effect of NAC was reported to vary depending on the timing of drug administration. The best protection was observed when NAC was administered after noise exposure. Other animal studies have suggested that oral administration of NAC is as effective as intraperitoneal injection. Choi et al. [21] studied the therapeutic effect of orally administrated NAC on acute NIHL using 30 chinchillas exposed to 105-dB SPL octave band noise. The

drugs were administered 4 h after noise exposure and twice daily thereafter for 2 days. Similarly, Bielefeld et al. [22] studied the protective effect against NIHL of NAC administered through different routes in chinchillas. They suggested that NAC has a protective effect against noise not only at low doses, but also when given via the oral route. Some studies, however, have failed to show a protective effect of NAC, for reasons that are yet unclear [23].

Clinical studies

The effect of NAC on NIHL has also been investigated in clinical studies. In one such study by Ge et al. [24] 223 out of 363 volunteers received oral administration of NAC before noise exposure. Routine audiometric evaluation and ABR testing were performed. The authors concluded that oral administration of NAC has a protective effect against NIHL. Lindblad et al. [25] studied the effect of NAC when given after exposure. Eleven healthy volunteers received 200 mg of NAC four times after gun shooting sessions. The threshold shifts were smaller in both groups but when compared to 23 healthy controls, they found that NAC exhibited a protective effect in the cochlea. The most striking finding they concluded was that the non-linearity of the cochlea was practically unchanged in the NAC-group throughout the study. Doosti et al. [17] studied the effect of NAC in preventing NIHL in male textile workers. NAC was administered orally to 16 subjects at 1200 mg/day for 14 days. Comparison of mean of change of threshold after exposure showed significant change between NAC administered group and control group. They found that for each dB increase in before hearing threshold, the estimated after thresholds decreased by 2.86 for NAC at 4 kHz, 2.54 at 6 kHz and 2.34 at 16 kHz. The authors concluded that NAC can reduce noise-induced TTS in workers exposed to occupational noise. Similar results were reported by Lin et al. [26] since they used the same dose and same period of administration of NAC. They studied with male workers who had been employed for at least 1 year in a steel manufacturing company. They found that, for all participants exposed to noise, the mean TTS was 2.77 dB after placebo, and 2.45 dB after NAC. In contrast to those studies, Kramer et al. [27] observed no positive effect of NAC in NIHL. They administered a single 900 mg dose of NAC to volunteers before visiting a nightclub, but observed no significant effect of NAC.

Although different experimental conditions make it difficult to compare individual studies and to clearly identify an effective treatment model, NAC has been shown to exhibit a protective effect when administered before noise and maintained after it [28–30]. The use of NAC has been confirmed to be effective against NIHL when applied before or shortly after exposure to noise in a number of studies. Administration of NAC may therefore become a confirmed treatment modality against NIHL in the near future.

Magnesium

Magnesium is thought to have a protective effect against acoustic trauma. The efficiency of magnesium depends on its neuroprotective and vasodilator effects in reducing reactive oxygen species. Magnesium therapy is already well documented in other diseases due to its low cost, fewer side effects, and rare contraindications [31]. Magnesium prevents apoptosis in hair cells by reducing calcium flow into the cell. In addition, it reduces ischemia by causing vasodilatation in the cochlear arterioles. Xiong et al. [32] investigated the relationship between concentrations of magnesium in the cochlea and NIHL. They used energy dispersive X-ray analysis to measure magnesium in the cochlea of 90 guinea pigs exposed to noise. They observed a negative correlation between cochlea magnesium content and hearing loss. Yıldırım et al. [33] investigated the effect of magnesium in the prevention of NIHL. Thirty-nine guinea pigs were exposed to noise for 16 h per day for 10 days. The subjects received 39 mmol/l $MgCl_2$ which were administered orally, starting from 15 days before noise exposure. Oral magnesium therapy was reported to be effective in the prevention of cochlear damage in NIHL. In another study, Abaamrane et al. [34] evaluated the efficacy of long-term administration of magnesium in NIHL. Guinea pigs were exposed to gunshot noise (170-dB SPL peak) and received subcutaneous injection of 35 mg $MgSO_4$ for 3 days and were also given drinking water supplemented with 3.7 g $MgCl_2$ for 1 month. The results were compared with those for methylprednisolone and a placebo. The most effective treatment option was 1-month magnesium therapy. Recovery was accelerated with methylprednisolone therapy, although this exhibited only moderate final efficacy. The authors suggested that the use of magnesium for 1 month is effective and safe in humans for protection against NIHL.

Clinical studies

Attias et al. suggested in two separate clinical studies that oral administration of magnesium aspartate provides significant protection against both PTS and TTS in humans. In the first study [35], 300 healthy subjects receiving basic military training for 2 months received an additional drink containing either 167 mg magnesium aspartate or a placebo on a daily basis. The authors suggested that long-term additional intake of oral magnesium reduced PTS with no notable side effects. In their second study [36], they

investigated the effect of magnesium on TTS in 20 human subjects. All subjects were exposed monaurally to 90 dB SL white noise, for 10-min duration. They received 122 mg magnesium aspartate dissolved in drinking juice for 10 days. The mean audiometric temporary threshold shifts and TTS incidence was found to be smaller in Mg group. The authors again reported that magnesium provides significant protection against TTS with no side effects. They therefore concluded that higher blood levels of magnesium have a protective effect against NIHL.

Calcium blockers

Excessive calcium flow into the cell leads to cell death. Calcium flow into the cell in the central nervous system takes place through calcium channels. Inhibitors of these channels protect against neural cell damage. While calcium irregularity is a commonly accepted cause of noise injury, calcium blockers may be useful in protection against or treatment of NIHL. The effectiveness of L-type and T-type calcium canal blockers differs. Uemaetomari et al. [37] investigated which type of calcium channel is responsible for acoustic injury of the cochlea. Mice were exposed to 128 dB SPL for 4 h, and L-type or T-type calcium channel blockers were administered immediately before acoustic overexposure. The L-type calcium channel blockers diltiazem, verapamil, nicardipine and nimodipine were found to exhibit a protective effect on hair cells against noise trauma. Similar results were reported by Heinrich et al. [38], who studied the effect of diltiazem in protection of the outer hair cells in acoustic exposure. Forty-two guinea pigs were used in that study, and diltiazem was administered at 75 mg/kg before, after or both before and after noise trauma. Administration of diltiazem before and after noise trauma was observed to exhibit some degree of protective effect on outer hair cells. Controversially, Boettcher [39] administered 30 mg/kg/day diltiazem for 3 days to gerbils, which were then exposed to 90-dB SPL for 20 min. In another experiment, the same doses of diltiazem were given intraperitoneally for 3 days to gerbils before exposure to noise. Drug administration was continued during the noise. Administration of diltiazem did not affect TTS or PTS. The authors suggested that diltiazem has no protective effect against NIHL.

In another study, Boettcher et al. [40] studied the effect of nimodipine on NIHL. Gerbils received 10 mg/kg nimodipine or placebo subcutaneously and were exposed to 102 or 107 dB noise. Nimodipine was reported to exhibit no protective effect against noise exposure. Similar results for nimodipine have been reported by Kansu et al. [41] from a study involving 18 guinea pigs. These received a single dose of 3 mg/kg nimodipine intraperitoneally. Nimodipine was observed to provide no protection against noise.

The effect of T-type calcium canal blockers is clearer than that of L-type blockers. Shen et al. [42] investigated the effect of the antiepileptic T-type calcium channel blockers trimethadione and ethosuximide. Forty-four mice were exposed to 110-dB SPL for 30 min. Trimethadione was used at a dose of 200 mg/kg/day, and ethosuximide at 1.5 mg/kg/day. The authors suggested that administration of trimethadione prior to noise exposure reduced NIHL. Administration of both trimethadione and ethosuximide after noise exposure was reported to be effective in NIHL.

Clinical studies

Maurer et al. [43] investigated the effect of diltiazem in preventing acoustic trauma during middle ear surgery in their clinical study involving 100 patients. The results indicated only a small postoperative hearing loss after ear surgery. Diltiazem was found to have a minimal and statistically insignificant protective effect against noise injury.

Vitamins

The antioxidants vitamins A, C and E can protect the inner ear against noise trauma by creating a synergistic effect with magnesium [44]. McFadden et al. [45] investigated the effect of dietary vitamin C supplementation on NIHL. Before exposure to 114-dB SPL octave band noise for 6 h, guinea pigs were fed with normal, supplemented or deficient levels of ascorbate for 35 days. The lowest level of PTS was observed in the animals receiving the highest levels of dietary ascorbate. The authors suggested that high levels of vitamin C reduce susceptibility to NIHL. In another study by Fischer et al. [46] 48 guinea pigs were fed with low or high doses of ascorbic acid for 7 days. The authors found that administration of high doses of ascorbic acid reduces hearing impairment and protects the cochlea against noise trauma.

Hou et al. [47] studied the protective effect of vitamin E on NIHL. Thirty-two out of 48 guinea pigs were exposed to 100-dB SPL for 8 h per day for three consecutive days. These received 10 or 50 mg/kg vitamin E daily by intraperitoneal injection starting from 3 days before noise exposure, during the three noise exposure days and for a further 3 days after exposure. They concluded that vitamin E has some preventive effect against NIHL.

Clinical studies

Kapoor et al. [48] investigated 40 male workers at an army base workshop. To evaluate the effect of supplementation

of vitamin E, 400 mg/day was given to the volunteers after breakfast. They showed that Vitamin E supplementation decreased the oxidative stress by reducing blood MDA levels and increasing the antioxidative enzyme activity of SOD while maintaining the plasma total antioxidant status. Vitamin E supplementation helps in controlling the impact of intense noise on hearing at frequencies 0.25, 0.5, and 1.0 kHz. They concluded that it is possible that the protection in vitamin E-supplemented group may have been obtained if Vitamin E supplementation was started weeks before the study. Vitamin E was observed to reduce oxidative stress caused by noise exposure, thus resulting in protection against NIHL.

Vitamin B_{12} is a nutrient that affects hearing physiology and sensitivity to noise. Gok et al. [49] investigated levels of vitamins A, E, B_{12} and folic acid in subjects working in a local hydroelectric power station and suffering from NIHL. They determined lower vitamin B_{12} levels in patients with NIHL, while levels of vitamin A, E and folic acid were not lower. Shemesh et al. [50] measured serum levels of vitamin B_{12} in 113 army personnel exposed to military noise. Vitamin B_{12} deficiency was observed in 47 % of patients suffering from tinnitus and NIHL. These findings showed that vitamin B_{12} deficiency is related to dysfunction of the auditory pathway. Quaranta et al. [51] studied the effects of supra-physiological vitamin B_{12} administration on NIHL in 20 young volunteers. They reported a decreased noise-related temporary threshold in patients with serum concentrations of vitamin B_{12} greater than 2350 pg/ml. They suggested that elevated plasma vitamin B_{12} levels may reduce the risk of NIHL.

Neurotrophins

Neurotrophins are proteins which control several of aspects of the survival, development, and functions of neurons. These have also been used as another protective agent against NIHL. Aarnisalo et al. [52] suggested that an intrascalar glial cell line derived neurotrophic factor (GDNF) therapy reduces apoptosis in spiral ganglion neurons and the brain stem. Local use of GDNF was reported to be useful in protecting cochlear neurons from degeneration after noise trauma. Shoji et al. [53] investigated the differential protective effects of neurotrophins. In that study, guinea pigs were exposed to 115-dB SPL and received neurotrophic factor-3(NT-3) or brain derived neurotrophic factor (BDNF)via the scala tympani at doses of 1 or 10 μg/ml. Animals receiving 10 μg/ml NT-3 exhibited a significant increase in outer hair cell survival and a decrease in ABR threshold shift. Animals treated with BDNF exhibited no functional or histological protection. The authors suggested that the effectiveness of neurotrophic factor varies depending on individual characteristics and the dose administered. Shoji et al. [54] investigated the dose-dependent effect of GDNF in noise-exposed guinea pigs. They reported that direct injection of GDNF into the guinea pig cochlea provides dose-dependent conservation. At a dose of 1 ng/ml, no protection was observed. At doses of 10 ng/ml, however, significant hair cell protection was observed, while at 100 ng/ml, this protection was even greater, and bilateral. High doses of GDNF (1 μg/ml) increased sensitivity to noise. That study concluded that GDNF can protect the inner ear against NIHL at certain concentrations. Keithley et al. [55] investigated the effect of local application of GDNF to the ear before and after noise. Guinea pigs were exposed to 120-dB SPL for 2 h. GDNF was applied to the cochlea though the round window membrane just before acoustic trauma, or 2, 4 or 6 h after trauma. GDNF therapy before acoustic trauma or 2 h after trauma was reported to be effective, but not administration 4 or 6 h after trauma. This indicated that early administration of GDNF can prevent cochlear sensory cell damage and hearing loss in NIHL.

Neurotrophine-3 (NT-3) protects the spiral ganglions against neuronal loss. Diao et al. [56] studied the protective effect of the nitric oxide synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME) in acoustic trauma when applied with or without NT-3. L-NAME was administered intraperitoneally, while NT-3 was delivered to the scala tympani. They reported that a combination of NT-3 and L-NAME can provide additional protection against acoustic trauma compared to L-NAME alone.

Clinical studies

The application of human mesenchymal stem cells (hMSC) after NHIL protects the inner ear. Local application of stem cells to the ear can cause irreversible damage. In a study by Choi et al. [57], hMSC was harvested from the bone marrow of the iliac crest of healthy volunteers. Rat cochlea damaged by noise and 4×10 cells of hMSC were given via intravenous injection. Homing of some hMSC to the cochlea with degenerated inner hair cells was documented, and this migration was accompanied by the expression of BDNF.

Dizocilpine (MK-801)

Regulation of glutamate excitotoxicity is another means of protecting against NIHL. The administration of glutamate antagonists reduces dendritic injury and prevents noise trauma. MK-801 is a highly potent and selective, non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist which has been shown to prevent hair cell damage. Chen et al. [58] reported that MK-801 exhibited significant protection against PTS induced by noise trauma.

In order to observe the conservative effect of MK-801 versus TTS or PTS in acoustic trauma, Diao et al. [59] studied 20 guinea pigs exposed to 110-dB SPL octave band noise for 3 h and another 20 guinea pigs exposed to 115-dB SPL octave band noise for 5 h. They concluded that MK-801 protects against PTS but not TTS in acoustic trauma by preventing vacuole degeneration in inner hair cells and afferent dendrites. Xia et al. [60] reported that MK-801 can alleviate the damage caused by noise trauma by altered NMDAR-mediated calcium influx. Duan et al. [61] investigated the effect of MK-801 in NIHL in guinea pigs exposed to 105 dB SPL for 24 h. MK-801 in 1 mg/kg doses was injected intraperitoneally immediately before noise trauma. They reported complete protection at 8 and 12 kHz and partial protection at 1 and 4 kHz.

Coenzyme Q9 and Q10

Coenzyme Q10 (CoQ10) is a member of the mitochondrial respiratory chain which inhibits lipid peroxidation, increases ATP production and removes reactive oxygen species (ROS), thus protecting against oxidative stress-induced apoptosis. The water-soluble formulation of Coenzyme Q10 known as multicomposite CoQ10-terclatrate (Q-ter) has better bioavailability. Fetoni et al. [62] investigated guinea pigs exposed to 120-dB SPL for 1 h. Both Q-10 and Q-ter were given intraperitoneally 1 h before noise exposure and once daily for 3 days. Treatment reduced the number of apoptotic cells. The decrease in apoptosis and improvement in hearing was greater in animals treated with Q-ter. The authors suggested that Q-ter has a greater ability to prevent oxidative damage than that of CoQ10.

In a study intended to show the efficacy of antioxidants in the treatment of NIHL in mice, Fetoni et al. [63] investigated hearing function, cochlear oxidative damage, morphological changes in the hearing cortex and cochlear structure and CoQ9 and CoQ10 levels. They observed hearing loss and injury in hair cells and spiral ganglia because of noise-related oxidative damage. That study also reported that acoustic trauma increased dendritic morphology and reduced pyramidal neuron 2–3–5–6 levels in the hearing cortex, and that the systematic administration of Q-ter reduced oxidative cochlear injury, cortical dendritic damage and hearing loss. They concluded that antioxidant therapy improved hearing physiology and auditory morphology by regulating noise-related oxidative imbalance in the cochlea. Similar results were observed by Hirose et al. [64]. They also used guinea pigs exposed to 130-dB SPL for 3 h and administered water-soluble CoQ-10 intraperitoneally 2 h before noise exposure. They observed that the numbers of lost outer hair cells and the ABR threshold shifts were significantly lower in the animals treated with CoQ-10.

The effectiveness of systemic and transtympanic administration of Q-ter was compared in another animal study, by Fetoni et al. [65]. The authors used rats exposed to 120-dB SPL acoustic trauma for 60 min and receiving systemic or transtympanic Q-ter. They found that Q-ter administration significantly reduced NIHL, and similar degrees of protection were observed via the transtympanic and systemic routes.

Clinical studies

Staffa et al. [66] studied the effect of oral administration of Q-ter in another clinical study. Thirty volunteers were exposed to 90-dB SPL narrow band noise for 10 min. The recovery time was recorded for each subject. Eighteen subjects were administered Q-ter, after which a second test was administered. The mean recovery time was 31.60 min in Q-ter group which was significantly smaller compared to control subjects. Oral administration of 160 mg of Q-ter caused faster recovery after noise exposure.

Antiapoptotic agents

Antiapoptotic agents represent another treatment modality. Jun-N-terminal kinase (JNK) is a member of the mitogen activated protein kinase (MAPK) family. In animal studies, these agents have been shown to have a protective or therapeutic effect against NIHL by obstructing apoptotic cascades, including MAP kinase-c-JNK. Nagashima et al. [67] exposed mice to 110-dB SPL for 1 h. As noise exposure increased the level of phospho-JNK in the spiral ligament, eliminating activation of the JNK signal pathway was effective in protecting against NIHL. Wang et al. [68, 69] investigated the effect of the MAP kinase signaling pathway in acoustic trauma and indicated that this is involved in acoustic trauma-induced hair cell loss. They further suggested that blocking this signal pathway may be beneficial in protecting the organ of Corti. Local application of JNK inhibitor into the scala tympani of the guinea pig cochlea has a protective effect against NIHL.

Ahn et al. [70] evaluated the role of all-trans retinoic acid (ATRA), an active metabolite of vitamin A, in preserving hearing in mice exposed to noise. Mice were exposed to 122-dB SPL for 3 h per day for three consecutive days. They were fed 1 mg/kg of ATRA for 2 days before and during 3 days of noise exposure. That study concluded that ATRA can protect mice against NIHL through inhibition of the JNK pathway.

The Src protein tyrosine kinase (PTK) cascade is able to initiate apoptosis through metabolic and mechanical

effects in cochlea hair cells. Harris et al. [71] compared the effect of the Src-PTK inhibitors KX1-004, KX1-005 and KX1-174 in chinchillas exposed to 106 dB SPL for 4 h. The drugs were applied directly to the round window at a dose of 30 µl. The authors concluded that round window administration of all Src-PTK inhibitors provided protection against noise, but that the most effective drug was KX1-004. Bielefeld et al. [72] compared the protective effects of NAC and KX1-004. A 325 mg/kg dose of NAC was delivered intraperitoneally, while 50 mg/kg of KX1-004 was administered subcutaneously. Noise exposure consisted of 100-dB SPL for 6 h/day for 4 days. Animals treated with NAC and KX1-004 exhibited less TTS at days 1 and 21 without any significant side effects. The authors suggested that the protective effect of KX1-004 is similar to that of NAC at a relatively lower concentration.

D-Methionine

The effect of administration of D-methionine before and after noise exposure has also been investigated. The protective effect of D-methionine against NIHL was investigated by Claussen et al. [73]. In that study, a 2-day regimen comprising five doses of D-methionine injection was administered to three groups of five chinchillas each exposed to 115-dB SPL for 6 h. Intraperitoneal administration of D-methionine 3 days prior to noise exposure significantly protected against noise-induced ABR threshold shift and OHC loss. Lo et al. [74] investigated the dose-dependent effect of D-methionine in NIHL. One hour after exposure to continuous broadband white noise at 105-dB SPL for 6 h, guinea pigs were treated five times at 12-h intervals with 200, 400, or 600 mg/kg D-methionine. The level of rescue from noise-induced PTS following treatment with 200, 400, or 600 mg/kg D-methionine was observed to be dose-dependent, and treatment with D-methionine at 600 mg/kg achieved a complete rescue response.

Clinical studies

The protective effect of oral administration of D-methionine tablets against NIHL was evaluated in a clinical study by Ge et al. [75]. 113 out of 203 volunteers received oral administration of D-methionine tablets before noise exposure. Routine audiometric evaluation and ABR were performed before and after noise exposure. The experimental group exhibited significant hearing impairment on the first and seventh days after noise exposure. The authors suggested that D-methionine tablets are effective in protection against NIHL.

Other drugs

Tamir et al. [28] investigated the effect of loop diuretic furosemide in NIHL. Mice were exposed to 115-dB SPL for 3.5 h. Furosemide was injected intraperitoneally at doses of 100 mg/kg. The authors reported that furosemide exhibits a protective effect against NIHL by reducing the endocochlear potential in the scala media, resulting in a reduction in free radical formation.

The protective effect of another antioxidant substance, edaravone, was investigated by Gao et al. [76]. Guinea pigs were exposed to 110-dB SPL for 4 days. After the first day of noise exposure, edaravone or edaravone solid lipid nanoparticles (SLN) were administered by intratympanic or intravenous injection. Threshold shift and ROS generation were lower in the treated animals. Edaravone and particularly edaravone-SLN exhibited a marked protective effect against NIHL.

Another study investigated the effect of silymarin, an antioxidant flavonoid complex derived from herb milk thistle. Silymarin was injected intraperitoneally into guinea pigs for 6 days. The animals were exposed to 120-dB SPL for 6 h. The threshold shift of the treated animals decreased significantly. The authors suggested that silymarin has a protective effect against both temporary and permanent NIHL [77].

Another isoflavonoid extracted from *Pueraria lobota*, puerarin, was investigated by Qu et al. [78]. Mice were exposed to 110-dB SPL for 8 h per day for 14 days. Ten minutes before noise exposure, mice received a single intraperitoneal injection of 200 mg/kg puerarin. The authors suggested that puerarin is effective against NIHL by regulating the expression of protein kinase Cy and GABAB receptor.

Kansu et al. investigated the protective effect of the vasodilator drug pentoxifylline on the cochlea after acoustic overexposure [41]. Eighteen guinea pigs were administered a single shot of pentoxifylline intraperitoneally at a dose of 150 mg/kg. The histological findings and ABR recordings were near-normal in animals treated with pentoxifylline. The authors suggested that pentoxifylline has a potent protective effect against noise.

Thymoquinone is a phytochemical compound found in *Nigella sativa* which exhibits antioxidant, anticonvulsant and analgesic effects. The effect of thymoquinone against NIHL was investigated by Aksoy et al. [79]. Thirty-two rats were included in that study. The experimental group animals were exposed to 105-dB SPL for 4 h. Thymoquinone was shown to exhibit a reparative effect against NIHL, rather than a preventive one.

Xiong et al. [80] compared the protective effects of ALA, vitamin E and radix astragalin acoustic trauma.

Vitamin E at 100 mg/kg, ALA at 200 mg/kg and radix astragali at 6000 mg/kg were administered intragastrically to 50 guinea pigs 24 h before and 72 h after noise exposure. Vitamin E, ALA and radix astragali significantly reduced malondialdehyde concentrations, ABR deficiency and hair cell damage. The effects of ALA and radix astragali were both better than that of vitamin E, but there was no significant difference between ALA and radix astragal.

The effect of non-steroidal anti-inflammatory drugs depends on inhibition of cyclooxygenase (COX), lipoxygenase (LOX), or both. Hoshino et al. [81] studied the effects of non-steroidal anti-inflammatory drugs on the functional recovery of the cochlea after acoustic injury. They used indomethacin (COX-1 inhibitor), meloxicam, SC58125, and CAY10404 (COX-2 inhibitors) and nordihydroguaiaretic acid (LOX inhibitor). Mice were exposed to 128-dB SPL for 4 h and received one of these drugs for 2 weeks. ABR was performed before and after acoustic overexposure. COX-1 and LOX inhibitors exhibited protective effects against acoustic injury. In contrast, COX-2 inhibitors exhibited no noticeable effect on acoustic injury. Similar results for celecoxib were reported by Pourbakht [82]. In that study, five guinea pigs were treated with 50 mg/kg doses of celecoxib for 3 days before exposure to 102-dB SPL for 3 h. ABR was performed before and 1 h after acoustic overexposure. Celecoxib was observed to have no protective effect against NIHL.

Gavriel et al. [83] investigated the effectiveness of leupeptin, a member of the calcium activated protease family, in the treatment of NIHL. Sixteen ears of eight rats were exposed to noise caused by ten M16 gunshots. Immediately after noise exposure, leupeptin was administered to the middle ear cavities through polyethylene tubes for four consecutive days. Eight days after exposure, the threshold shifts in the experimental ears were significantly lower. The authors suggested that leupeptin administered to the middle ear cavity was effective in reducing NIHL.

Gingko biloba extract increases blood circulation, scavenges free radicals and exhibits an antagonistic effect against platelet activating factor. Lee et al. [84] investigated the effect of gingko biloba on NIHL. Mice were exposed to 110-dB SPL for 1 h. The mice in the experimental group were fed 3, 6 or 12 mg/kg of gingko biloba for 7 days before noise exposure. At all doses, more rapid recovery was observed in ABR in mice fed with gingko biloba at 16 kHz. At the other frequencies, no significant difference in hearing recovery was observed. The authors concluded that gingko biloba had a partial effect on temporary hearing threshold shift after noise.

Noise exposure increases the production of an 8-iso-prostoglandin F2alpha (8-iso-PGF2 alpha), a marker of reactive oxygen species and a potent vasoconstrictor, in the cochlea. Noise-induced reductions in cochlear blood flow may depend on the production of 8-iso-PGF2alpha. Reduced cochlear blood flow resulting from vasoconstriction due to noise trauma can be prevented with the administration of an 8-iso-PGF2alpha antagonist, SQ29548 [85].

Clinical studies

Alpha-lipoic acid (ALA) is an essential cofactor for mitochondrial enzymes. It also exhibits antioxidant effects and acts as a potent free radical scavenger. The effect of ALA on NIHL was evaluated by Quaranta et al. [86]. They reported that a single dose 600 mg of ALA did not induce TTS, while administration of ALA for 10 days resulted in significant protection especially at 6 kHz. In addition, TEOAE amplitude change after noise exposure was lower for this group. They concluded that administration of a short course of ALA may have a protective effect against TTS in humans.

Combinations

Since multiple pathophysiological factors are involved in NIHL, combinations of drugs targeting multiple pathways simultaneously have also been studied. Cascella et al. [87] investigated the efficacy of Acuval 400®, a novel agent, alone or in combination with CoQ-10 in protecting against NIHL. Acuval 400® is a food supplement multivitamin containing various vitamins (A, E, B_1, B_2, B_6 and B_{12}), L-arginine, ginkgo biloba and minerals such as magnesium, selenium and zinc, as well as small amounts of Coenzyme Q10 (0.31 g/100 g). Fifty-five rats were used. The drugs were administered orally 24 and 2 h before noise exposure, and then daily for 3 days. At low frequencies, animals treated with only Acuval® exhibited similar threshold shifts to those of the controls. At higher frequencies, the effect of Acuval® was more pronounced. Combination treatment was found to exhibit protective effects at all frequencies. The authors suggested that Acuval 400® is effective in providing protection from NIHL. Furthermore, a combination of Acuval 400® and CoQ-10 is more effective than Acuval 400® alone.

Bao et al. [88] investigated the prophylactic and therapeutic effect of drug combinations against NIHL. As the effect of T-type calcium channel blockers and steroids had been shown in previous studies, they used combinations of calcium channel blockers and steroids. T-type calcium channel blockers ethosuximide, zonisamide and the steroids dexamethasone and methylprednisolone were employed. Mice were exposed to 110-dB SPL for 30 min. The drugs were administered 2 h prior to noise exposure or 24 h after noise via intraperitoneal injection. The

combination of zonisamide and methylprednisolone exhibited significant protective effects and synergy when administered before noise exposure. Controversially, combinations of ethosuximide and methylprednisolone or ethosuximide and dexamethasone exhibited no synergistic effect against NIHL when administered after noise exposure.

Psillasetald [89] investigated the effect of a combination of steroid and the nootropic agent piracetam in 52 military personnel exposed to weapon noise. The treatment consisted of intravenous injection of 25 mg prednisolone and eight ampules of piracetam for 10 days. Hearing recovery was significantly better in the subjects who received the drug within the first hour of noise exposure. Starting this combination in the early period was shown to be effective against NIHL.

Conclusion

Noise-induced hearing loss is one of the most common causes of hearing loss. While most focus has been on protective materials in prevention against NIHL, these are insufficiently effective due to various difficulties involved in their use. Pharmacological agents are therefore important in protection against NIHL and in treating resultant hearing loss.

While early treatment is of unquestionable importance, no definitive treatment modality has yet been established. Our review of the literature shows that the most commonly used agents for the treatment of NIHL are steroids. These have also been reported to be effective against NIHL in most studies. Research also suggests the effectiveness of antioxidants, especially NAC. Clinical studies of NAC suggest that it is useful in protecting against and in the treatment of NIHL. Studies have also described the usefulness of magnesium in the treatment of and protection against NIHL. Although the effectiveness of other agents has been reported in animal studies, the number of clinical studies is insufficient. Further studies are needed to determine the practical use of these agents.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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