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Emerging therapeutic interventions against noise-induced hearing loss

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Abstract

Introduction—Noise-induced hearing loss (NIHL) due to industrial, military, and recreational noise exposure is a major, but also potentially preventable cause of acquired hearing loss. For the United States it is estimated that 26 million people (15% of the population) between the ages of 20 and 69 have a high-frequency NIHL at a detriment to the quality of life of the affected individuals and great economic cost to society.

Areas covered—This review outlines the pathology and pathophysiology of hearing loss as seen in humans and animal models. Results from molecular studies are presented that have provided the basis for therapeutic strategies successfully applied to animals. Several compounds emerging from these studies (mostly antioxidants) are now being tested in field trials.

Expert opinion—Although no clinically applicable intervention has been approved yet, recent trials are encouraging. In order to maximize protective therapies, future work needs to apply stringent criteria for noise exposure and outcome parameters. Attention needs to be paid not only to permanent NIHL due to death of sensory cells but also to temporary effects that may show delayed consequences. Existing results combined with the search for efficacious new therapies should establish a viable treatment within a decade.

Keywords

Antioxidants; hair cells; magnesium; N-acetylcysteine; neurotrophins; noise trauma; oxidative stress; synaptopathy; vasoconstriction

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Declaration of Interest

J. Schacht is named as a co-inventor of ACEMg for treatment of hearing loss (US Patent 7,951,845 B2 to the University of Michigan), but is not involved in any trials testing this compound or any other commercial exploitation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Introduction

At least since the introduction of modern warfare and the industrial revolution, exposure to noise has been recognized as a potential cause of hearing impairment. Today, approximately 5% of the world's population suffer from noise-induced hearing loss (NIHL) acquired from industrial occupations, military duty and combat, and recreation and leisure activities. This makes NIHL the most frequent occupational disease in the US and probably worldwide[1].

Normal human conversation is conducted at around 60 decibels (dB), a logarithmic unit of sound pressure level (SPL), and the dynamic range of our auditory systems enables us to process sounds at both much lower and higher levels. However, beginning at 85 dB (~300 times the energy level of 60 dB) long or repeated exposures may result in a notable loss of hearing. This level of 85 dB and above includes some everyday sounds, for example, music on personal listening devices or emanating from small machinery such as lawnmowers. Chainsaws and other power tools may produce sound intensities of 120 dB and above, potentially causing immediate hearing damage. Firearms which are owned by around 60 million Americans can produce 140–170 dB of impact noise which, without the proper use of ear protectors, would lead to certain damage of the inner ear.

In addition to NIHL, acquired hearing loss can be of numerous other etiologies, such as the use of ototoxic medications, bacterial or viral ear infections, head injuries, and the aging process. Importantly, these effects may overlap and thereby confound investigations in both animal models and patients. In this review we will first discuss basic mechanisms underlying NIHL in well-defined experimental models as such studies provide the basis for protective strategies. We will then review progress towards a clinical management which is promising although a viable treatment to prevent or attenuate noise trauma is yet on the horizon. A comparison of this summary with an assessment written six years ago will illuminate progress made and problems still unresolved[2].

2. Pathology

2.1 Pathophysiology

The classical functional measurement of NIHL in humans is an audiogram reading of auditory thresholds. By this measure, noise-induced hearing loss (NIHL) can be divided into two subtypes, temporary and permanent hearing loss that each have specific cochlear pathology. If a noise-induced elevation of thresholds recovers completely to pre-exposure levels within hours or days, the subject experiences a temporary threshold shift (TTS). Without recovery, a permanent threshold shift (PTS) ensues which is related to the intensity and frequency of exposure. The human audiogram of noise trauma is often characterized by a sharp dip between 3 kHz and 6 kHz, within the range of speech frequency. PTS therefore generally affects speech perception and, in extreme exposure situations, may include auditory damage up to complete deafness[3].

2.2 Pathology of hair cells and auditory nerve

Auditory processing in the cochlea depends on the integrity of the sensory hair cells - inner hair cells (IHC) and outer hair cells (OHC) - and the auditory nerve connecting them to

higher centers. Animal studies suggest that TTS does not involve major overt pathology to these structures. Temporary swelling, fusion, or distortion of stereocilia, however, may impair mechanotransduction necessary for hair cell depolarization[4, 5] and reversible excitotoxic effects have been detected at IHC synapses in the form of swelling and retraction of dendrites[6, 7]. More recently, studies in a mouse model have uncovered delayed manifestations of neural degeneration of IHC synaptic ribbons and accelerated spiral ganglion cell (SGC) loss after TTS, despite the early reversibility of threshold shifts and the absence of appreciable hair cell loss[8, 9]. This observation has challenged the traditional view that degeneration of SGCs occurs exclusively as a consequence of sensory cell loss. Although longitudinal data on the impact of TTS on humans is lacking, we may soon begin to realize the impact of repeated recreational noise exposure on age-related hearing impairment.

Aside from the possibility of direct mechanical damage to the eardrum and the inner ear by high-intensity impulse noise[10], a characteristic feature of PTS is loss of cochlear hair cells (fig.1) and loss of IHC synaptic ribbons[11]. The afferent terminals of IHCs become swollen and degenerate, followed by the degeneration of the afferent fibers and SGCs. Additionally, spiral ganglion neurons display a subset of swollen satellite cells. The extent of cell damage may increase for days or weeks after the cessation of the noise exposure while degenerations of nerve fibers tends to proceed on a much slower time scale of months (in experimental animals) to years (in humans). Since sensory hair cells in mammals do not regenerate, the loss is irreversible and—at the moment and the near future—not curable.

Both animal models and human studies agree on hair cells as a target of noise trauma. Schuknecht's study of temporal bones of human subjects[12] noted that loss of OHCs at the basal turn of the cochlea was the most prominent change, while loss of IHCs was limited. However, with increasing noise intensity, destruction of IHCs followed[11]. In contrast to the vulnerability of sensory hair cells, supporting cell structures remain generally well-preserved unless under severe noise conditions.

2.3 Pathology in non-sensory tissues

Vasoconstriction and capillary loss in the spiral ligament, as well as decreased strial blood flow, have been detected in noise-exposed animals[13, 14]. These changes may transiently alter the endocochlear potential, elevating auditory threshold shifts and contributing to TTS or PTS. Severe exposures may cause permanent degeneration of the fibrocytes of the spiral limbus and spiral ligament, of which type II and IV fibrocytes are the most vulnerable[11]. Additionally, the stria vascularis may swell acutely and subsequently shrink due to loss of intermediate and marginal cells.

3. Molecular mechanisms of neurosensory damage

Essentially all information on the molecular events underlying NIHL comes from animal experimentation. The use of different animal species and noise conditions have provided a plethora of mostly consistent results, but at times also observations that are difficult to reconcile or to categorize as causal or epiphenomenal. The following sections will

summarize the most prominent current hypotheses with a focus on those that have given rise to attempts at therapeutic protection.

3.1 Oxidative stress and stress-induced pathways

The mitochondrial electron transport chain is considered a major source of reactive oxygen species (ROS) produced by all tissues including those of the cochlea. Under normal physiological conditions, 1–2% of molecular oxygen is reduced to superoxide, a free radical that can be converted to less toxic hydrogen peroxide by mitochondrial superoxide dismutase (SOD2) or proceed in a reaction chain to even more detrimental compounds such as the hydroxyl radical. Increased ROS generation in cochlear fluids and tissues, including in OHCs and the stria vascularis, by traumatic noise is well documented and other free radicals in the form of reactive nitrogen species (RNS) derived from nitric oxide (NO) are also present[15–17]. ROS may persist for 7–10 days and spread apically from the basal end of the organ of Corti, thus widening the area of damage well after an exposure has been terminated. Likewise, peroxynitrite (ONOO-), generated by the combination of NO and superoxide, has been found in the cochlea several days after noise exposure, underscoring the case for multiple oxidants contributing to hair cell death. The delayed spread of injury is an important feature of NIHL as it might provide a window of opportunity for post-exposure intervention and containment of the extent of hearing loss.

On the other hand, moderate noise exposure increased ROS in OHCs only marginally thus prompting autophagy, a cellular homeostatic response[17]. The autophagy marker LC3 was upregulated in OHCs of CBA/J mice, and the fact that only a TTS but no permanent damage was observed, suggested autophagy as a protective mechanism against NIHL. However, excessive oxidative stress, as under PTS-noise conditions, overwhelmed the beneficial potential of autophagy in OHCs and led to OHC death and NIHL[17].

Cell death in the cochlea displays features of both apoptosis and necrosis as well as necroptosis, a necrotic-like process. This assessment is based on morphological and molecular features where apoptotic cell death is actively regulated and characterized by condensed nuclei with activation of multiple cell death pathways that are primarily regulated by caspases[18–20]. In addition, noise exposure causes the release of cytochrome C and the translocation of endonuclease G in apoptotic OHCs[19–21]. Swollen nuclei, a marker of necrotic cell death, in OHCs after noise exposure indeed suggest involvement of necrosis[18]. Recent studies have added necroptosis to this spectrum in which signaling pathways like that of the receptor-interacting protein (RIP) kinases are induced, followed by caspase activation. Caspases 3, 8, and 9 have been found in OHCs with condensed nuclei after noise exposure[18, 22]. While an intervention into a cell death sequence may attenuate noise trauma, pathway interactions add a layer of complexity: inhibition of noise-induced apoptosis shifts the prevalence of OHC death to necrosis[18].

3.2 Calcium overload

Another consequence of noise exposure is an increase in free Ca^{2+} in OHCs immediately after acoustic overstimulation to which both entry through ion channels and liberation from intracellular stores might contribute[23,24]. Influx through channels may be linked to increased

endolymphatic calcium levels which increased 50-fold in the noise-exposed guinea pig. This generates a high concentration gradient driving calcium into sensory cells through voltage-gated calcium channels (VGCCs) or mechanoelectrical transduction (MET) channels[24]. Noise exposure at 110 dB to guinea pigs increased free calcium in isolated OHCs followed by OHC death and hearing loss while a non-pathologic sound level of 75 dB did not alter intracellular calcium levels[25]. Noise trauma induced by a 130 dB exposure was likewise accompanied by a sustained 60% increase in free calcium in guinea pig OHCs and a decrease in cochlear microphonics.

Calcium overload can trigger cell death in any cell type by the activation of specific calcium-dependent pathways. In addition, in IHC it can cause synaptopathy by stimulating the excessive release of glutamate neurotransmitter. The over-activation of glutamate receptors on the post-synaptic terminals can cause excitotoxicity and swelling of the nerve terminals, resulting in anatomical and functional deficits.

An involvement of calcium channels is corroborated by the fact that channel blockers attenuate NIHL. The L-type is the predominant VGCC in IHCs but is also present in OHCs[26] and under normal conditions a block of this channel reduces the calcium content of guinea pig IHCs and OHCs[27]. Furthermore, several L-type channel inhibitors (diltiazem, verapamil, nicardipine, and nimodipine) reduce the amount of hair cell loss and auditory threshold shifts following noise exposure in female ddY mice[28]. Guinea pig OHCs can likewise be protected from acute noise damage by delivery of diltiazem[29]. T-type channel blockers also offer protection. After noise exposure of C57BL/6 mice at 110 dB trimethadione protects against both TTS and PTS hearing loss and hair cell death, while ethosuximide protects against PTS[30].

3.3 Mitochondrial pathways

Mitochondrial dysfunction has been speculated to be the major mechanism of NIHL and involved in other acquired hearing pathologies as well[31]. Indispensible as the cellular energy factory they are also the major site of ROS formation. As discussed in Section 3.1, noise exposure causes ROS generation in cochlear tissues and inner ear fluids, and oxidative damage is observed in sensory cells. A related issue is transient cellular energy depletion after noise exposure.

A major energy expenditure of cochlear tissues is the maintenance of ionic gradients across cell membranes. In order to sustain the necessary level of ATP, cochlear blood flow must provide an adequate supply of oxygen and nutrients. However, high-intensity noise exposure decreases capillary blood flow and causes local vasoconstriction[32, 33]. The resulting ischemia reduces ATP levels within the inner ear, including the lateral wall structures which are responsible for upholding the endocochlear potential[19, 34–36]. Consequently, a reduction of ATP levels in the cochlea is associated with noise-induced permanent hearing loss[19, 34, 35]. Conversely, maintenance of ATP levels by supplying creatine as an energy source attenuates temporary and permanent NIHL in guinea pigs[37]. Creatine kinase, the enzyme required for the utilization of creatine as an ATP buffer, is abundant in the stria vascularis; hence, creatine treatment may maintain the endocochlear potential by supplying ATP for ionic pumps[38].

A potential pathway from ATP depletion to cell death may involve the downstream actions of adenosine monophosphate-activated protein kinase (AMPK). As a homeostatic energy sensor AMPK reacts to negative fluctuations of the AMP:ATP ratio by switching off energy-consuming activities and turning on energy-generating pathways[39]. While the activation of AMPK to phospho-AMPK initially is an adaptive response to cellular stress, its sustained activation in a noise-dependent manner has a detrimental effect on sensory hair cells[40], similar to responses in other cellular stress models, including ischemia-reperfusion, hypoxia, and stroke[41, 42]. The prolonged elevation of phospho-AMPK activates c-Jun N-terminal kinase (JNK), upregulates pro-apoptotic Bim and subsequent apoptotic cell death pathways known to be involved in NIHL[18, 43, 44]. Consequently, inhibition of AMPK activation by siRNA silencing or the specific pharmacological inhibitor dorsomorphin attenuates NIHL and cochlear synaptopathy[40]. In addition, silencing LKB1, a kinase upstream of AMPKα, also protects against these pathologies[40].

4. Pharmaceutical intervention in animal models

The wide array of presumed mechanisms of NIHL has suggested the notion of a convergence of many factors leading to cell death. Consequently, a wide array of agents has been tested for their protective efficacy in animals, including antioxidants, adenosine receptor antagonists, calcium-channel blockers, NMDA receptor antagonists, and inhibitors of apoptotic signaling. This list is not nearly exhaustive. By the year 2005 at least 28 drugs had already been tested[45].

4.1.1 Antioxidants and related compounds

Antioxidants, such as glutathione (GSH)[46, 47], D-methionine[48], ebselen[49], resveratrol[50], ascorbic acid[51, 52], and water-soluble coenzyme Q10[53], all attenuated NIHL in animal models when applied prior to noise exposure. Treatments up to 3 days after exposure were also able to attenuate NIHL to some degree, particularly A1 adenosine receptor agonists[54], ferulic acid[55], D-methionine[48], or the combined administration of the ROS and RNS scavengers salicylate and trolox[56]. Among antioxidants, N-acetylcysteine (NAC) has probably been the most extensively evaluated for reducing noise trauma under a variety of conditions, animal models, and dosages[57]. The diverse experimental parameters preclude direct comparisons of individual studies and make it difficult to establish a single efficacious treatment modus[58, 59]. However, NAC has exhibited protective effects not only when given prior to noise[60, 61] but it also rescued from NIHL after exposure[62]. In surprising contrast, some studies failed to see protection by NAC[63, 64].

4.1.2 Neurotrophic factors

Another successful line of protection utilized neurotrophins but the efficacy of neurotrophic factors varied with the individual compound and the dose administered[65–68]. Direct injection of glial cell line-derived neurotrophic factor (GDNF) into the guinea pig cochlea provided protection in a dose-dependent manner, although the highest doses of GDNF actually increased susceptibility to noise[65]. The efficacy of GDNF may reside in its ability to reduce free radical generation, as well as modulate intracellular Ca^{2+} through induction of calcium binding proteins, and interference with apoptotic factors[66].

4.1.3 Calcium-channel blockers

As outlined in more detail in Section 3.2, protection against calcium overload has successfully been employed to prevent NIHL. Blockade of L-type voltage-gated Ca^{2+} channels protected against NIHL in mice[28] and in guinea pigs[29], and blockade of T-type voltage-gated Ca^{2+} channels was effective in mice[30]. Also consistent with a contribution of calcium-mediated events in hair cell damage, application of the calcineurin inhibitor FK506 attenuated NIHL in guinea pigs[69].

4.1.4 Vasodilators

Magnesium can exert multiple actions on a cell; it may reduce calcium influx and block apoptosis in hair cells, but can also limit ischemia by promoting vasodilation of cochlear arterioles[70]. In early experiments, noise caused significantly greater hearing loss in rats when fed a magnesium-deficient rather than a magnesium-enriched diet[71]. Additionally, long-term administration of magnesium after exposure to impulse noise improved hearing thresholds in guinea pigs[70]. Further, intense noise induced vasoconstriction via formation of the lipid peroxidation product 8-iso-PGF2α in the cochlea[72], and this reduction of cochlear blood flow was reversed by a specific antagonist[33], offering another approach for protection.

4.1.5 Glutamate antagonists

Also in the armamentarium against NIHL is regulation of glutamate excitotoxicity. Application of a glutamate antagonist reduced the dendritic damage from subsequent noise trauma[73]. An NMDA receptor antagonist, MK-801, also offered some protection against NIHL[60, 74]. Interestingly, magnesium, discussed above in the context of vasoconstriction, may also act on excitotoxic events as magnesium deficiency may lead to an increased release of glutamate via exocytosis and overstimulation of NMDA receptors on the auditory nerve[75].

4.1.6 Steroid hormones

Steroids are extensively being used in clinical practice and their benefits and safety are well established. In animal models, direct administration of dexamethasone into the inner ear and intravenous administration of dehydro-epiandrosterone each lessened NIHL[76, 77]. However, the therapeutic time window was very short and another study did not confirm a positive effect of dexamethasone[78]. The hormone estradiol may also be involved in a protective circuit, acting through estrogen receptor (ER)β, as well as by interaction with BDNF. In support, the ERβ-selective agonist 2,3-bis(4-hydroxyphenyl)-proprionitrile attenuated noise trauma in mice while, conversely, ERβ knock-out mice had an enhanced sensitivity to noise exposure[79].

4.1.7 Anti-apoptotic agents

Finally, therapy with anti-apoptotic agents is another potential strategy, and several animal studies document protection against or enhanced recovery from NIHL by blocking apoptotic cascades, such as the MAP kinase (MAPK)-c-Jun-N-terminal kinase (JNK) pathway. Local administration of a JNK-inhibitor into the inner ear protected against NIHL[44], and round-window administration restored hearing when given as much as 12 hours after noise

exposure[80]. Retinoic acid, which is an active metabolite of vitamin A and functions as a potent inhibitor of the JNK pathway, also protected from NIHL after oral administration to mice[81]. However, inhibition of apoptosis with the pan-caspase inhibitor ZVAD reduced hair cell apoptosis, but shifted the prevalence of OHC death to necrotic-like cell death. Conversely, administration of the necrosis inhibitor necrostatin-1 (Nec-1) diminished noise-induced RIP3 induction and necrotic hair cell death, but increased apoptotic hair cell death[18], suggesting that prevention of NIHL requires a multi-pronged approach.

4.2 Limitations of animal studies

Although results from animal studies have been promising for the attenuation of NIHL, the discrepancies between evaluations of potential protectants in different studies (e.g. for N-acetylcysteine or dexamethasone) present an important caveat in the translation of such experiments into the clinic. Success and failure in animal studies may be owed to specific experimental conditions and animal species. As a case in point, noise-induced hair cell loss is frequency-related in humans and in some animal models, such as the guinea pig and chinchilla; however, in mice and rats, hair cell susceptibility follows a base-to-apex pattern where basal hair cells are much more easily damaged than the apical cells. Importantly, the properties of noise exposure vary considerably between studies in terms of intensity, duration, band width, and use of continuous or impulse noise. A given protective regimen may be suitable for one exposure paradigm but not for another and It would therefore be prudent for translational studies to confirm potential effects of protective compounds in at least two animal species and several noise conditions.

In addition, it is important to note that a physiologically significant impact on auditory performance in humans requires a shift of above 10 dB. A hearing loss or improvement in hearing below this threshold will have a marginal impact in everyday life, if any. Compounds providing “statistically significant” but small-scale protection might prove a principle, but it remains to be established in clinical trials whether such compounds would provide a physiologically relevant protection. It is therefore prudent for translational studies to confirm potential effects of protective compounds in at least two animal species and several noise conditions before going to clinical trials.

5. Human studies

The success of animal studies suggests that pharmacological protection against noise trauma is possible in principle. In the design of clinical trials on noise-induced hearing loss, however, there is an ethical question of exposing subjects to potentially damaging conditions, notably PTS. Therefore, some trials have evaluated potential protectants under TTS conditions with noise exposures thought to leave no permanent damage in the auditory system. However, new evidence from animal experimentation[8] has raised the prospect that a seemingly innocuous exposure in youth may lead to an aggravated age-related hearing loss. Another approach to avoid an ethical dilemma are military or industrial settings where noise trauma due to machinery or combat operations was deemed inevitable despite hearing protection. Utilizing those two scenarios, several treatments have been tested prospectively on TTS and PTS, and post-traumatic on potential PTS. Finally, accidental noise trauma is

another condition where treatments can be tested although a baseline audiogram or a control group might not be available.

5.1 Confounding variables in NIHL

Before we discuss success and failure of human trials it is important to stress that human trials might face confounding factors that might not be obvious in inbred animal species. Nevertheless, even in laboratory experiments different strains (of mice, mostly) react differently to noise exposure indicating that genetic variations influence the outcome of noise trauma and, by extension, of protective therapies. The nutritional state might likewise influence the severity of responses to noise, as might other disease or lifestyle variables.

5.1.1 Genetics—Genetic variations in human populations influence both the responses to noise exposure and the potential effectiveness of protection (see 5.2). Considering the likely mechanisms of NIHL, it is not surprising that susceptibility to noise is frequently linked to traits that regulate cochlear redox homeostasis. Polymorphisms influencing the outcome of noise exposure have been identified for:

Glutathione S-transferase (GST): In a population of 58 steel factory workers those with GST null genotypes in GSTT1 and GSTM1, and GSTP1 suffered more noise-induced TTS during their shift[82].

Superoxide dismutase 2 (SOD2; Mn-SOD): Two studies have linked single nucleotide polymorphisms in this enzyme to enhanced NIHL. One study was based on a screen of 200 participants in Taiwan[83]. The other took audiometric data from 2400 Han Chinese workers and compared the genotypes of the 10% most susceptible and the 10% most resistant individuals[84].

Heat shock proteins (HSP): Single nucleotide polymorphisms in HSP70 were associated with enhanced susceptibility to noise in 349 Taiwanese workers[85].

PCDH15 and MYH14: In contrast to GST, SOD and HSP, these genes are not directly involved in antioxidant and homeostatic defenses. PCDH is a member of the cadherin superfamily serving in stereocilia function and mutated in Usher Type IF. MYH14 is a non-muscle myosin heavy chain and mutations may cause autosomal dominant hearing loss. A gene association study in two independent populations, a Polish and a Swedish cohort, revealed a significant association of these two genes with susceptibility to NIHL[86].

5.1.2 Nutrition and nutritional supplements—Adequate nutrition is a prerequisite for good health and coping with stress and disease. Preservation of hearing and resistance to noise are no exceptions. Data from the National Health and Nutrition Examination Survey[87] documented a significant relationship between dietary quality and auditory sensitivity at high frequencies. In addition, the data suggested a benefit of healthy diets for a noise-exposed population.

Specifically, an adequate supply of vitamins appears essential. Several studies found positive correlations between better auditory thresholds and self-reported intake of vitamin C,

vitamin E, retinol (vitamin A analog), riboflavin (vitamin B2), niacin (vitamin B3). Also, diets high in beta-carotene, magnesium, or lycopene (a carotenoid antioxidant) are associated with better preservation of hearing[88–90]. Conversely, vitamin deficiencies might aggravate noise-induced hearing loss and tinnitus. Army personnel with NIHL or NIHL with tinnitus had lower vitamin B12 levels than normal hearing subjects[91].

5.1.3 Smoking—Smoking is another controllable parameter that may influence NIHL. Smokers have a higher risk of developing high-frequency hearing loss than non-smokers with a similar occupational noise exposure[92, 93]. The interaction may be related to a dual insult to mitochondria, since animal experiments have documented that exposure to cigarette smoke leads to the generation of oxidative stress by affecting mitochondrial function[94].

5.2 Pharmacological protection

Of the myriad compounds effective in protecting animals from noise trauma, only a few have been tested in human trials. Most of these studies have employed drugs related to antioxidant defenses and cell death pathways, some of which have already been established as beneficial in other medical contexts. While the results are not uniformly positive, evidence points to the potential to attenuate NIHL.

5.2.1 N-acetyl cysteine

Prospective study on TTS in a leisure setting: An early study with N-acetylcysteine (NAC) could not confirm its efficacy. Thirty-two young attendees of a night club received either 900 mg oral NAC or a placebo. After two hours at a noise level of 93–103 dBA the resulting TTS was small and similar in both groups[95].

Prospective study of TTS in an industrial setting: A double-blind cross-over study with 53 workers employed at a steel manufacturing plant (daily noise levels 88.4–89.4 dB) found “significantly reduced TTS” in the groups receiving 1200 mg NAC per day for the 14-day trial period[96]. However, the difference in TTS was not significant in the population overall but emerged when the participants were subdivided based on the genetic polymorphisms of glutathione S-transferase (GST; see section 5.1.1). Only the subgroup with null genotypes in both GSTT1 and GSTM1 had profited from NAC. Even then, the protection was not remarkable (3.1 ± 3.1 dB on placebo versus 1.2 ± 3.6 dB on NAC, at 3, 4, and 6 kHz). The result can be taken as a suggestion of a potential benefit of NAC but also points to genetics as an important modulator of noise trauma.

Prospective study on TTS in a military setting: More complex auditory functions than only audiogram or otoacoustic emissions were included in an analysis of hearing in military personnel after a shooting exercise and revealed protection of the cochlea by NAC[97]. Thresholds were minimally elevated by shooting. However, psycho-acoustical modulation transfer functions (thresholds for brief tones in modulated noise) revealed a highly significant decrease in cochlear non-linearity after the noise exposure in 23 control subjects while no changes were seen in the NAC-group of 11 subjects. The NAC treatment consisted of 4× 200 mg NAC, taken at various times after exposure.

Prospective study on potential PTS in a military setting: Likewise, a randomized trial of 566 military subjects on weapons training had differentiated outcomes depending on the analyses used[98]. There were no differences in the primary outcomes, threshold shifts and percent of adverse events, between the placebo group and NAC (a total daily dose of 2700 mg NAC for each of the first 13 days of training followed by three days of 1800 mg). However, additional analyses revealed significant differences in threshold shifts when handedness (trigger hand) of the shooters was taken into account.

Blast trauma: It is informative in this context to compare NIHL to blast trauma and the resulting mild traumatic brain injury (mTBI), a frequent injury in combat. The sequelae of blast trauma are highly complex and hearing loss may only be one of its manifestations. Due to the unpredictability of battlefield explosions, blast injuries can only be addressed after the trauma has occurred. In a double-blind, placebo-controlled study in an active war zone[99] NAC treatment was begun within 24 hours after an injury. Following a 4-gram loading dose, subjects were given 4 g NAC daily for 4 days, then 3 g daily, leading to a significantly improved resolution of symptoms associated with blast exposure mTBI such as dizziness, hearing loss, headache, memory loss, sleep disturbances, and neurocognitive dysfunction at a 7-day endpoint.

5.2.2 Magnesium—

Magnesium has long drawn attention for human trials given the reports on noise-induced and Mg-attenuated vasoconstriction (see sections 2.3 and 4) and its relative non-toxicity.

Prospective studies on PTS in military settings: As early as 1987 a significant correlation was found between noise-induced hearing loss and serum magnesium concentrations in 24 air force pilots[71]. As a consequence, daily oral magnesium supplementation of 167 mg Mg-aspartate was tested in a double-blind placebo-controlled fashion during a 2-months period of military training[71, 100]. During this time, the recruits were exposed to 420 firearm shots each at a level of ~140 dB after accounting for attenuation by ear plugs. The incidence of PTS (>25 dB at 4 kHz/6 kHz and or 8 kHz) was approximately twice as high in the placebo group than in the Mg group (11%). It is important to note that the degree of PTS was low in subjects with high serum Mg^{2+} levels and higher in subjects with low serum Mg^{2+} levels, regardless of treatment. This observation again points to the influences of genetics and physiology (here the tendency of hypomagnesemia) on susceptibility to noise trauma.

Prospective study on TTS in a military setting: A subsequent study by the same group[100] tested the efficacy of magnesium supplementation on 20 volunteers who were exposed for 10 days monaurally to 90 dB SL white noise for 10 minutes per day. In the magnesium-supplemented group, higher Mg^{2+} blood levels were associated with some protection from TTS. However, the correlation was relatively small ($r = 0.36$) and serum Mg^{2+} levels in placebo subjects were not reported.

5.2.3 Other agents

‘Supra-physiological’ vitamin B_{12}: As discussed in section 5.1.2, Vitamin B_{12} is one of the nutrients that influence auditory performance and sensitivity to noise. In a prospective

double-blind study on potential TTS[101], 20 subjects were injected cyanocobalamin or placebo for 10 days. Threshold shifts were assessed 1 hour after a 10-minute monaural exposure to a continuous narrowband noise masker centered at 3 kHz at 112 dB SPL. The vitamin treatment achieved blood vitamin B_{12} concentrations that were up to 10-fold higher than the normal range and afforded significant protection. It is not clear how vitamin B_{12} interacts with noise exposure; it may be involved in stabilizing neural activity, possibly reducing the excitatory effects of excess noise stimulation.

Anti-apoptotic agents: AM-111, an anti-apoptotic cell-permeable JNK ligand, was tested on 11 subjects that had sustained exposure to firecrackers[102]. The victims were treated within 24 hours or less in a double-blind, randomized parallel-dose trial in which two different dosages were administered intratympanically. There was no placebo group for ethical reasons of withholding a potentially beneficial treatment. Thirty days after treatment there was no difference between the two dosage groups. However, their overall recovery was judged to have exceeded a spontaneous recovery as would have been observed (based on clinical experience) in untreated patients following acute noise trauma. By the same argument, analysis of hearing recovery rates on a patient-by-patient basis suggested that AM-111 had a marked therapeutic effect in at least two cases.

Prednisolone & piracetam: Prednisolone, a corticosteroid primarily used in anti-inflammatory therapy and piracetam, a widely approved nootropic agent and presumed cognitive enhancer, were injected into 52 subjects who had been exposed to gunshot impulse noise at military training sessions[103]. Placebos were not administered but groups were analyzed by onset of therapy after the trauma. Improvement of auditory thresholds correlated with the delay in treatment and ranged from a 69% recovery rate among patients treated within the first hour to a 13% recovery in the group with a 24-hour delay. The final threshold shifts were also significantly lower in the early treatment groups.

5.3 Currently registered clinical trials

In addition to the above studies, several clinical trials are currently underway or anticipated. Table 1 lists those registered on ClinicalTrials.gov, a service of the U.S. National Institutes of Health. The table is not necessarily complete as registration is not compulsory, for example, for trials in countries outside the United States. The treatments under investigation are generally again based on successful animal experimentation and results from previous trials. Six of the seven agents are antioxidants (see section 4). In addition, N-acetylcysteine and magnesium haven been the subject of field tests before, as has prednisolone (see section 5.2). Details of the studies such as subject selection, dosing regimen, exposure parameters and outcome measures can be accessed under the NCT identifier number.

5.4 Unknown risks of pharmacological protection

While adequate nutrition is essential for the maintenance of auditory acuity (see section 5.1.2), chronic or excess consumption of antioxidant or vitamin supplements may not only be detrimental to hearing but may also be associated with an increased risk of cancer and mortality.

Vitamins A and D—Two population-based surveys with over 2000 participants each confirmed the generally positive effects of a balanced diet and vitamin intake but singled out high retinol (a vitamin A analog) intake[88] and high serum levels of vitamin D[89] as associated with worse hearing.

β-carotene, vitamin A, and vitamin E—Meta-analyses of clinical trials found β-carotene, vitamin A, and vitamin E correlated with increased overall mortality[104, 105]. In addition, β-carotene was found to be potentially associated with an increased risk of cancer in smokers[106].

While these are important caveats in deciding the composition of therapeutic regimens, we might have to distinguish between acute treatment and chronic exposures. A short-term administration of antioxidants or vitamins should still be a safe protection against drug- and noise-induced hearing loss. However, the hazards of a chronic program of nutritional supplements remain unknown.

6. A new paradigm: The hidden hearing loss of cochlear synaptopathy

Some of the clinical studies discussed in section 5 noted defects in secondary outcome measures without significant threshold changes in the audiograms. Such deficits in auditory processing indicate that the measurement of thresholds is insufficient to detect subtle forms of cochlear damage. Such “hidden hearing loss”[107] can represent faulty neural output and manifest, for example, as impaired speech perception. In both animals and humans, physiological evidence for hidden hearing loss can be gained by a detailed analysis of auditory brain stem response (ABR) to sound stimuli. While the ABR thresholds—just as the audiogram thresholds—may be normal, the stimulus-dependent amplitude of ABR waves and their latencies might be affected.

Recent studies using these measures have revealed deafferentation of hair cell-to-auditory nerve fiber connections in mice subjected to mild acoustic trauma that only resulted in a TTS[8, 108]. This pathology might represent an early event in response to noise and an additional contributing factor to NIHL, while not negating the importance of hair cell loss in permanent NIHL. Interestingly, the phenomenon of cochlear synaptopathy is not limited to NIHL but may also exist in aminoglycoside ototoxicity[109] and age-related hearing loss[110].

A potential mechanism of cochlear synaptopathy is suggested by experiments[9, 111] demonstrating that the cell-derived neurotrophin NT-3 is crucial for the maintenance of adult cochlear hair cell synapses in the mouse. In specific support of a critical role in NIHL, overexpression of NT-3 promoted the regeneration of ribbon synapses and the recovery of auditory responses after acoustic trauma. Furthermore, local round-window delivery of NT-3 24 hours after noise trauma also regenerated cochlear synapses and function.

7. Conclusion

Animal models have given convincing insights into the pathology and mechanisms of NIHL. Calcium overload and mitochondrial dysfunction with reduced energy production and enhanced formation of free radicals might give rise to pathways of apoptosis, necrosis or

necroptosis in auditory sensory cells. More subtle but potentially equally important injury can occur to hair cell-auditory nerve connections causing hidden hearing loss.

A therapeutic intervention into noise-induced hearing loss is possible. Several classes of drugs appear particularly effective (antioxidants, anti-apoptotic agents, steroids) and some of these have been and will be tested in industrial, military and leisure settings. Intriguingly, considerably more drugs than those currently listed in registered trials are suggested by animal studies. Compounds to be considered would include additional antioxidants mentioned in section 3.1, neurotrophic factors, calcium-channel blockers, or steroids which already have a place in the clinic. Whether such drugs will eventually be viable therapeutics against NIHL in humans remains to be established in further translational studies that would more rigorously test their efficacy, dosing, and the best route of administration.

Caveats also apply. First, a single treatment may not protect in all cases of NIHL but its efficacy may depend on the type, duration, and intensity of noise exposure. Second, genetics and the physiological (nutritional) state of subjects are confounding factors that are capable of influencing the outcome of therapeutic interventions and may necessitate a more targeted approach. Nevertheless, the outlook is promising and a viable clinical treatment should be available in the near future.

Expert opinion

The last decade has brought impressive progress in understanding NIHL and the feasibility of its prevention. However, in order to proceed and optimize potential treatments close attention must be paid to several open issues in both animal experimentation and translation.

Comparable test conditions and standards of protection must be established. Comparisons of studies from different laboratories are difficult because of variations in animal models, exposure and test parameters. Animal models primarily use continuous noise of different characteristics as the stimulus while in industrial, military, and recreational settings impulse noise predominates. Treatments efficacious against one form of noise might not protect against the other and prospective drugs should be tested for their efficacy under different conditions. Furthermore, pharmacokinetic evaluations are largely missing, making a compound’s efficacy (or lack thereof) and the extent to which noise trauma can be influenced difficult to quantify.

In this context, we should pay more attention to the notion of “significant” effects of protective drugs. A reduction of hearing loss of 5 or 10 dB can be statistically significant and prove a principle but would not improve the quality of life of the affected individual. More robust results are needed to warrant clinical trials.

Combination treatment may provide enhanced protection. It has rarely been tested whether protection might be more effective when a combination of agents were to target different molecular mechanisms. It might be promising, for example, to use complementary therapies to modulate oxidative stress as an early event with apoptosis/necrosis inhibitors to combat later sequels. Other combinations can be gleaned from the list of potentially protective

agents that aim at diverse events such as excitotoxicity, blood flow, calcium overload, and neurotrophic or hormonal control mechanisms.

It is insufficient to rely on pure-tome audiograms as an outcome measure. Some forms of auditory damage (e.g., “hidden hearing loss”) will escape simple audiometric tests, and protective strategies may have to be subjected to more sophisticated audiological assessments. Some of the clinical studies discussed in section 5 already noted defects in secondary outcome measures without significant threshold changes in pure-tone audiograms.

We also must be more concerned about TTS which has in the past been considered innocuous. This assumption is now being called into question by the demonstration of cochlear synaptopathy in TTS with potential consequences for later accelerated hearing loss. We do not have data to know whether any magnitude of TTS will have late-life consequences or whether a threshold for late-life damage exists. Volunteers in TTS experiments have a right to know. The development of preventive or rescue treatment even for TTS is indicated.

Genetics of susceptibility to NIHL is a confounding variable and need to be tackled now that genetic screening has entered the analytical mainstream. As some clinical trials have already shown, protective therapies might be effective only in subsets of the population and treatments eventually will have to be tailored to genetic variants. Furthermore, genetic predisposition to noise trauma raises the question whether we have the ethical duty to exclude sensitive individuals from hazardous environments or test conditions.

Improved post-hoc treatments are essential. Most research so far has focused on intervention prior to exposure. However, the need for medications effective after trauma is obvious from the battlefield and also from recreational exposures when patients present with auditory problems after the fact. Both animal studies and field trials suggest that a “window of rescue” exists. Although there might be overlap with drugs that work prospectively, different drugs might be more efficacious for post-hoc rescue. This question has yet to be addressed.

Finally, compliance and safety might be an issue in long-term prevention. Compliance issues are well documented for the use of ear protectors and similar issues might arise for drug administration. Approaches need to be explored how individuals can best be motivated to take a daily pill and how compliance can be monitored. Safety of drugs has been established only for short treatments in both animals and humans but there is little information on the long-term effects even of common nutritional supplements. These need to be monitored, in particular in view of studies that suggest morbidity and mortality associated with excess vitamin intake.

Overall, the outlook for an intervention in NIHL is positive. Successful animal models and encouraging initial clinical trials have confirmed the proof-of-principle that NIHL can be prevented or at least attenuated. With attention to unresolved issues and fine-tuning of translational research, the next decade should see protective treatments enter the clinic.

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Highlights

- The classical pathology of NIHL is destruction of auditory hair cells and degeneration of spiral ganglion cells.
- Based on the molecular mechanisms of NIHL, therapeutic protection has successfully been developed in animal models.
- Human trials to protect against noise trauma are promising but current results remain tentative.
- Synaptopathy has emerged as an early event in NIHL and neurotrophins are potential rescue agents.

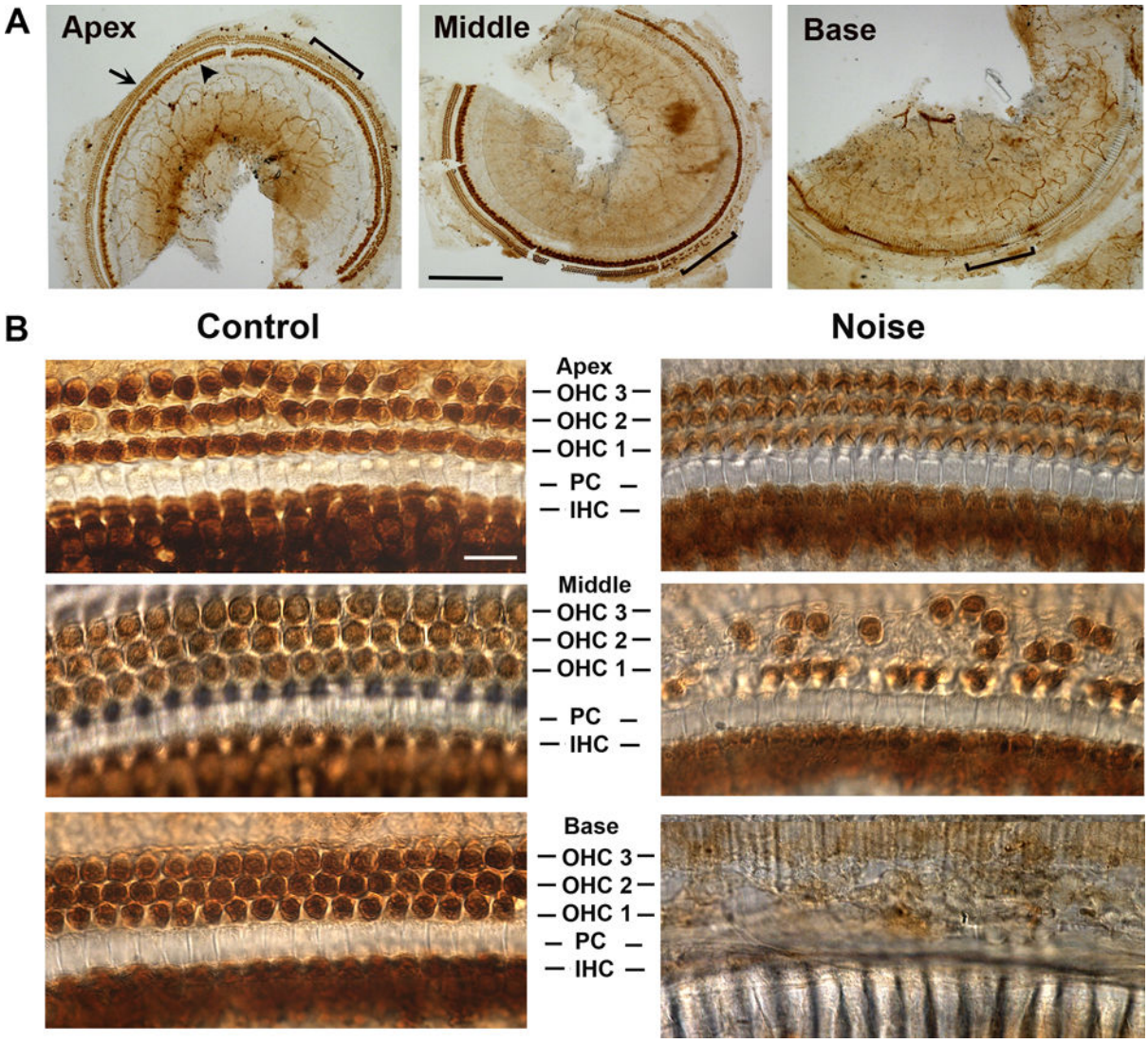

Figure 1.

Hair cell loss in the cochlea of 12-week-old male CBA/J mice exposed to noise calibrated to yield PTS (broadband noise at 108 dB SPL for 2 h) assessed two weeks after the exposure. (a) A surface preparation of the cochlea was immunolabeled for Myosin VII and then stained with DAB. Images were taken along the entire length of the cochlear epithelium from the apex to the base. Staining outlines the outer hair cells (arrow in panel 'Apex') and the region of inner hair cells (arrowhead). The bracketed areas are shown in higher magnification in panel B ('Noise'). Scale bar = 100 μm. (b) The comparison of corresponding images on the left and right illustrates the base-to-apex pattern of hair cell loss. Controls without noise exposure reveal three rows of intact outer hair cells (OHC), one row of inner hair cells (IHC) and pillar cells (PC). Following noise exposure, hair cells remain largely intact in the apex, sporadic losses occur in the middle segment, and complete destruction of the hair cells is evident in the base. Scale bar = 10 μm.

Table 1

Clinical Trials on Noise-induced Hearing Loss in the NIH Registry

Compound(s)	Class	Sponsor	Study Phase & NCT Identifier	Scheduled Completion	Results
N-acetylcysteine	Antioxidant	National Taiwan University Hospital, Taipei, Taiwan	Phase 2 NCT00552786	Completed March 2008	Lin et al., Hear. Res. 269:42–47, 2010
AuraQuell, ACEMg (Magnesium, ascorbate, α-tocopherol, β-carotene)	Antioxidants, vasodilator	University of Michigan, Ann Arbor, Michigan, USA	Phase 2NCT00808470	Completed Dec 2013	No results posted
SPI-1005 (ebselen)	Antioxidant	Sound Pharmaceuticals Inc, Seattle, Washington, USA	Phase 2 NCT01444846	Completed March 2014	No results posted
EPI-743 (p-benzoquinone analog)	Mitochondrial redox modulator	Edison Pharmaceuticals Inc, Mountain View, California, USA	Phase 2ANCT02257983	Completed Feb 2016	No results posted
d-methionine	Antioxidant	MetAmor Inc,Glen Gardner, New Jersey, USA	Phase 3NCT01345474 NCT02903355	December 2017	Recruiting
Zonisamide, methylprednisolone	Anticonvulsant, anti-inflammatory	Washington University School of Medicine, St. Louis, Missouri, USA	Phase 1/2NCT02049073	January 2020	Study not yet open
N-acetylcysteine plus magnesium	Antioxidant, vasodilator	University Hospital Antwerp, Antwerp, Belgium	Phase unknown NCT01727492	Unknown	Unknown

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