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Emerging treatments for noise-induced hearing loss

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Abstract

Introduction—Approximately 5% of the population worldwide suffer from industrial, military, or recreational noise-induced hearing loss (NIHL) at great economic cost and detriment to the quality of life of affected individuals. This review discusses pharmacological strategies to attenuate NIHL that have been developed in animal models and that are now beginning to be tested in field trials.

Areas covered—The review describes the epidemiology, pathology and pathophysiology of NIHL in experimental animals and human. The underlying molecular mechanisms of damage are then discussed as a basis for therapeutic approaches to ameliorate the loss of auditory function. Finally, studies in military, industrial, and recreational settings are evaluated. Literature was searched employing the terms “noise-induced hearing loss” and “noise trauma”.

Expert opinion—NIHL, in principle, can be prevented. With the current pace of development, oral drugs to protect against NIHL should be available within the next 5 to 10 years. Positive results from ongoing trials combined with additional laboratory tests might accelerate the time from the bench to clinical treatment.

Keywords

noise-induced hearing loss; hair cells; permanent hearing loss; pharmacological protection; temporary hearing loss

1. Noise-induced hearing loss (NIHL) - Background

1.1 Pathology and pathophysiology of hearing deficits

Approximately 10% of the population worldwide suffer from hearing loss and about half of these cases can be attributed to auditory damage caused by exposure to intense noise [1]. Noise trauma can result in two types of injury to the inner ear, depending on the intensity and duration of the exposure: transient attenuation of hearing acuity, a so-called 'temporary threshold shift' (TTS), or a permanent threshold shift (PTS). There is growing evidence that different physiological processes might underlie the two manifestations of noise exposure, although some overlap is also possible. Unless specifically mentioned otherwise, NIHL in this review refers to the permanent form of hearing loss.

Since hearing after a TTS generally recovers within 24–48 hours [2], TTS has not received much attention as a potential problem in the past. However, recent studies are bound to change this notion. In a mouse model, TTS at young ages accelerated age-rated hearing loss,

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even though the hearing thresholds were completely restored shortly after the TTS [3]. Thus, the self-inflicted recreational noise damage of the current generation might exacerbate age-related hearing loss [4] and diminish quality of life in the future. Longitudinal data on the impact of TTS on humans, however, are lacking.

In PTS, the audiogram is frequently characterized by a sharp dip between 3 kHz and 6 kHz. If a hearing loss is mild (15 to 20 dB), it might not be noticed in everyday life, as it may only cause difficulty in discriminating speech from background noise, but is generally not noticed in one-on-one conversations. More severe noise exposure will affect speech perception and may also expand the range of auditory damage up to complete deafness [5].

The auditory sensory cells (hair cells) contained in the organ of Corti of the cochlea are responsible for the transduction of acoustic input into nerve impulses. Of the two types of hair cells, the inner hair cells are considered the primary transducers and are innervated by more than 90% of the auditory afferent nerve fibers. Outer hair cells mostly receive efferent innervation and serve to enhance the sensitivity to sound stimulation. Several types of supporting cells and auxiliary structures such as the stria vascularis and spiral ligament are critical in maintaining the structural organization and homeostasis of cochlea. When only the outer hair cells are missing, hearing thresholds tend to increase to 40 to 60 dB [6]. An additional loss of inner hair cells will lead to even higher threshold shifts up to complete deafness.

The characteristic pathological feature of NIHL is the loss of hair cells. In temporal bones of human subjects that had been exposed to chronic occupational noise for about 30 years, loss of outer hair cells at the basal turn was the most prominent change, while loss of inner hair cells was limited [7]. Degeneration of the auditory nerve corresponded with loss of outer hair cells [8], although loss of nerve fibers tends to be slow following the insult to the hair cells. Animal models confirm that the outer hair cells are a primary pathological target in acute NIHL (fig. 1), generally followed by destruction of inner hair cells with greater noise exposure [9]. With sufficiently high intensity and duration of noise, not only the hair cells but the entire organ of Corti may be disrupted [10].

A crucial aspect of hair cell loss due to any cause (noise, ototoxic medications, age) is the inability of mammalian sensory cells to regenerate [11]. Prevention of their loss or early rescue after an insult are, therefore, the only current options to ameliorate noise-induced damage.

1.2 Mechanisms of cell damage

Research on NIHL using animals models has produced two basic theories for the underlying cause [12]. One is that intense noise can damage the cochlea mechanically by vibrating the organ of Corti beyond its structural limits [13], the second is that metabolic stress triggers hair cell death [12,14]. These two theories are not mutually exclusive and different mechanisms may operate at higher and lower intensities of noise exposure, respectively. Although an exact threshold is not known, exposures beyond 130 dB may have a significant mechanical component [15].

Current theories of metabolic damage center on the formation of reactive oxygen species (free radicals, ROS) evoked by excessive noise stimulation, followed by activation of apoptotic signaling pathways to cell death. ROS emerge immediately after noise exposure [16] and persist for 7–10 days thereafter, spreading apically from the basal end of the organ of Corti, thus widening the area of damage [17]. This delayed spread of injury is an important feature of noise-induced hearing loss as it might provide a “window of opportunity” for post-exposure intervention and containment of the extent of hearing loss. In

addition to ROS, free radicals in the form of reactive nitrogen species (RNS) derived from nitric oxide (NO) are also present [18]. Peroxynitrite (ONOO-), generated by the combination of NO and ROS, has been found in the cochlea several days after noise exposure [17], underscoring the case for oxidant stress contributing hair cell death.

Another consequence of noise exposure is an increase of free Ca^{2+} in outer hair cells immediately after acoustic overstimulation [19] to which both entry through ion channels and liberation from intracellular stores might contribute. A link between elevated Ca^{2+} levels in the cochlea and ROS production (causative or consequential) is possible, but not proven, as Ca^{2+} overload can also trigger apoptotic and necrotic cell death pathways independent of ROS formation [20]. For example, calcineurin, a Ca^{2+}/calmodulin-dependent protein phosphatase, is activated after noise exposure [21] and can, in turn, activate mitochondria-mediated cell death pathways via the Bcl-2-associated death promoter (BAD) in outer hair cells of mice [22].

Another factor associated with excessive noise is decreased cochlear blood flow[23] suggested to be caused by vasoactive lipid peroxidation products such as isoprostanes [24]. A feedback loop of ROS-dependent generation of a vasoconstrictor causing ischemia and subsequent reperfusion, which, in turn, would favor ROS, is a postulate consistent with experimental observations.

An excess release of the excitatory neurotransmitter glutamate at the inner hair cell synapses in response to traumatic noise may cause excitotoxicity [25] with a loss of synaptic connections to the auditory nerve (spiral ganglion). Glutamate overload can allow entry of Ca^{2+} which in turn can trigger a cascade of metabolic events eventually leading to type I spiral ganglion cell death [26]. Expression of a glutamate receptor, AMPA receptor, is reversibly decreased in response to acoustic overstimulation, and its reduction is correlated with change in acoustic sensitivity [27]. A moderate acoustic exposure, which is normally not excitotoxic, can be made excitotoxic if the auditory neuron is prevented from regulating surface AMPA receptor removal [28].

Another neurotransmitter, GABA, is associated with the regulation of auditory function and sensitivity to noise exposure [29]. $GABA_{B1}$ receptors are expressed in both type I and type II ganglion cells and in their terminals under inner hair cells and outer hair cells, respectively. The deletion of the $GABA_{B1}$ receptor subunit led to an elevation of hearing thresholds and increased resistance to acoustic trauma.

Aside from direct effects on the auditory system, noise also can cause psychological and physiological stress. A good example is the hypothalamus-pituitary-adrenal (HPA) axis, which can modulate the sensitivity of the auditory system and which can be activated by acoustic stress [30]. Glucocorticoid receptors are widely distributed in the inner ear [31] where they appear to serve a protective function. When animals are exposed to noise, activation of the HPA axis leads to the release of glucocorticoids into the circulation from where they can enter the inner ear [32]. If glucocorticoid synthesis is suppressed or glucocorticoid receptor are blocked, noise-induced hearing loss is exacerbated [32,33].

The corticotropin-releasing factor (CRF) system also modulates hearing sensitivity. Mice lacking CRF receptors in the cochlea exhibited lower hearing thresholds under normal conditions, but an increased susceptibility to noise trauma. Dysregulation of AMPA receptor expression in response to noise was suggested to be one of the underlying mechanisms in the increased susceptibility [34].

As a consequence of any or all of these reactions, cell death ensues. Apoptosis is the primary mode of cell death in the initial phase after noise exposure [35]; subsequently, morphological criteria for both apoptosis and necrosis become evident [36].

1.3 Protection and rescue from noise trauma in animal studies

Although attempts to ameliorate acoustic trauma by pharmacological means have a long history, the recent delineation of potential pathways of cell death has now placed such attempts on a firm theoretical basis. Supporting the notion of multifaceted contributions to cell death in NIHL is the (at least partial) success of a variety of different ameliorative treatments.

Antioxidants, such as glutathione (GSH) [37,38], D-methionine [39], ebselen [40], resveratrol [41], ascorbic acid [42,43], or water-soluble coenzyme Q10 [44], all attenuated NIHL in animal models when applied prior to noise exposure. [A comprehensive list of 28 compounds tested by 2005 can be found in a review by Lynch and Kil [45]]. Treatments up to 3 days *after* exposure also attenuated NIHL to some degree, particularly the combined administration of ROS and RNS scavengers (salicylate and trolox, respectively) [46], or A1 adenosine receptor agonists [47], ferulic acid [48], and D-methionine [39]. Among the antioxidants, N-acetylcysteine (NAC) has probably been the most extensively evaluated in terms of its efficacy on reducing noise trauma under a variety of conditions, animal models, and dosages [49,50]. The diverse experimental conditions preclude direct comparisons of individual studies and make it difficult to establish a single efficacious treatment modus [51,52], but NAC showed protective effects when given prior to noise [53,54] and also rescued from NIHL after exposure [55]. However, some studies failed to see protection by NAC [56,57], an issue that yet needs to be resolved.

Another line of protection has successfully utilized neurotrophins, though the efficacy of neurotrophic factors varies with the individual compounds and the dose administered [58,59,60,61,62]. Direct injection of glial cell line-derived neurotrophic factor (GDNF) into the guinea pig cochlea provided protection in a dose-dependent manner, although high doses of GDNF actually increased susceptibility to noise [58]. The efficacy of GDNF may reside in its ability to reduce free radical generation, as well as modulate intracellular Ca^{2+} through inducing calcium binding protein, and interfere with apoptotic factors [58].

A blockade of Ca^{2+} overload-induced cell death pathways proved to be another successful approach for prevention of NIHL [21,63,64,65]. A blockade of L-type voltage-gated Ca^{2+} channels protected against NIHL in mice [63] and in guinea pigs [64], while a blockade of T-type voltage-gated Ca^{2+} channels had protective effects in mice [65]. Also consistent with a contribution of calcium-mediated events in hair cell damage, application of the calcineurin inhibitor FK506 attenuated NIHL in guinea pigs [65].

Regulation of glutamate excitotoxicity is another candidate for the prevention of NIHL. Application of a glutamate antagonist reduced the dendritic damage and subsequently noise trauma [25]. An NMDA receptor antagonist, MK-801, showed some protection against NIHL [53,66].

Consistent with vasoconstriction as a consequence of noise trauma, the reduction of cochlear blood flow was prevented by administration of an 8-iso-PGF2alpha antagonist, SQ29548 [67]. Likewise, protective effects exerted by Mg^{2+} supplementation might arise from targeting blood flow. Mg^{2+} may reduce calcium influx into the cell block apoptosis in hair cells; it can also limit ischemia by inducing vasodilation of cochlear arterioles [68]. Consequently, long term administration of Mg^{2+} after exposure to gunshot impulse noise improved hearing thresholds in guinea pigs [68]. Conversely, Mg^{2+} deficiency may lead to

an increased release of glutamate via exocytosis and overstimulation of NMDA receptors on the auditory nerve [69].

Engaging hormonal modulation of auditory performance and sensitivity to noise as protective strategies has focused on steroid hormones. Direct administration of dexamethasone into inner ear and intravenously administered dehydroepiandrosterone lessened NIHL [70,71]. However, the therapeutic time window was very short [72] and another study did not find a protective effect of dexamethasone [73]. The hormone estradiol may also be involved in a protective circuit, acting through estrogen receptor (ER) β as well as by interaction with BDNF [74]. The ERβ-selective agonist 2,3-bis(4-hydroxyphenyl)-proprionitrile protected mice from noise trauma while, conversely, ERβ knock-out mice had an enhanced sensitivity to noise overexposure.

Finally, anti-apoptotic agents are another potential therapy, and several animal studies show protection against or enhanced recovery from NIHL by blocking apoptotic cascades, such as the MAP kinase (MAPK) – c-Jun-N-terminal kinase (JNK) pathway [75,76,77,78]. Local administration of a JNK-inhibitor into the inner ear had a protective effect against NIHL [75], and a round window administration of the JNK-inhibitor restored hearing as much as 12 hours after noise exposure [76]. 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 [77,78].

1.4 Limitations of animal studies

The discrepancies in the evaluation of potential protectants in different studies (e.g. for NAC or dexamethasone) bring up one important caveat in the interpretation of such experiments. Studies on NIHL generally employ a variety of experimental conditions and a given compound may be a suitable protectant for one noise exposure paradigm and not for another; systematic evaluations are largely missing. The tests frequently also lack rigorous dose-response curves that might clearly establish a compound's efficacy (or lack thereof) and the extent to which noise trauma can be suppressed or rescued.

In this context, it is also important to note that a physiologically significant impact on auditory performance in humans requires a shift of about 15 dB. A lesser deterioration in the case of noise damage or amelioration in the case of hearing loss will have little impact on everyday 'hearing' and speech perception. Compounds providing a statistically significant small protection of 5 or 10 dB in animals might prove a principle but it remains to be established in clinical trials whether such compounds (or any others emerging from animal experiments) can meet stringent criteria of a physiologically relevant protection.

2. Medical Need and Existing Treatments

Considering the prevalence of NIHL in today's society, proper prevention of and treatment for NIHL is critical. Since there is no established clinical treatment for NIHL yet, prevention of exposure to loud noise, for example by using ear protectors, is currently the primary strategy against NIHL. However, the effectiveness of such devices depends on their proper use and compliance with hearing prevention programs, and the promotion of use of hearing protection is conspicuously needed [79]. An epidemiological study demonstrated the benefit of earplugs in military personnel [80], but also found that NIHL could not be completely prevented. Furthermore, shielding the ear from noise might conflict with the need for environmental awareness and communication both in industrial settings and the military. In recreational activities, noise might even be accepted as a part of the recreational environment and, therefore, difficult to eliminate. At the FIFA 2010 world cup, spectators experienced the unique sound of the African vuvuzela which has an energy output as high as

131 dBA at horn opening [81] and significant changes in post-match hearing thresholds were observed in football spectators [82].

Therefore, the development of pharmacological interventions to reduce or prevent NIHL is crucial. While treatment to protect against potential PTS seems most urgent, protection from TTS must also be seriously considered in view of its late-life effects.

3. Clinical and military trials in humans

Several clinical and military trials for attenuation of NIHL have already been concluded or are in progress, but no recommended therapy has yet emerged. Because of the ethically problematic nature of exposing volunteers to potentially permanently damaging noise levels, most trials have used TTS as a model to evaluate protective drugs. As noted before, it remains to be established whether extrapolations from TTS to PTS are valid.

3.1 Protection against TTS

The efficacy of Mg^{2+} was tested in a double-blind manner in 20 human subjects on temporary (TTS) threshold shift [83]. The subjects were assigned to take 122 mg Mg^{2+} in drinking juice for 10 days, or placebo, and subsequently exposed monaurally to 90 dB SL white noise for 10 minutes. When TTS was defined as a change of >5 dB, a lower incidence of TTS in the magnesium group was borderline significant, compared to the placebo group. Moreover, only 12% of the ears in the magnesium group had TTS of greater than 20 dB compared with 28% in the placebo group. The recovery rate of TTS, measured by distortion-product otoacoustic emissions (DPOAE) 15 and 30 minutes after noise exposure, was also accelerated in the magnesium group. Further analysis showed that, following Mg^{2+} intake, higher Mg^{2+} blood levels were associated with some protection from TTS. However, the correlation was relatively small ($r = 0.36$) and large variations existed in the serum level of Mg^{2+}. Serum Mg^{2+} levels in placebo subjects were not reported.

Vitamin B_{12} is another nutrient that might influence auditory performance and sensitivity to noise. Army personnel with vitamin B_{12} deficiency showed a greater incidence of noise-induced tinnitus and hearing loss than subjects with normal levels [84]. Conversely, the administration of high doses of vitamin B_{12}, reduced noise-induced TTS in a double-blind clinical study [85]. Cyanocobalamin (vitamin B_{12}) or placebo was administered intramuscularly to ten normal-hearing volunteers daily for a total of seven doses of 1 mg and one dose of 5 mg. Approximately 1 hour after the final injection, baseline thresholds were measured, and then a continuous narrowband noise masker centered at 3 kHz was delivered to the right ear at an overall level of 112 dB SPL for 10 minutes. Two minutes after the noise ended, thresholds were measured again. In comparison to placebo administration, vitamin B_{12} provided significant protection at 3 kHz and a suggestive reduction at 4 kHz. The mean blood vitamin B_{12} concentrations were >2350 pg/ml after treatment, above the highest detectable value and considerably out of the normal range of 226–966 pg/ml. The exact mechanisms are not clear but vitamin B_{12} is generally involved in stabilizing neural activity, possibly reducing the excitatory effects of excess noise stimulation.

Based on the results from animal experimentation, the antioxidant NAC might be expected to afford protection. It was, however, ineffective in one evaluation of its ability to reduce TTS from exposure to loud music [86]. Thirty-two participants with normal hearing, aged from 19 to 29 years (mean 22 years), were enrolled in a randomized, double-blind study. Half of the participants took a 900 mg oral dose of NAC and the other half of the participants took a placebo 30 minutes before they entered a nightclub where levels of noise exposure ranged from 93 to 103 dBA. After two hours, their hearing function was evaluated

and TTS (approximately 10 dB at 3, 4, and 6 kHz) was similar in both groups as determined by audiograms, as well as by DPOAE, which reflect the function of the outer hair cells.

Another trial testing NAC against noise-induced TTS studied workers employed at a steel manufacturing company [87]. NAC or placebo was orally administered at 1200 mg a day, for 14 days, in a 2 × 2 crossover design with 14-day wash-out periods between treatments. The average daily noise exposure ranged from 88.4 dB to 89.4 dB, assessed by personal noise monitoring. The overall difference of TTS at 3, 4, and 6 kHz was not significant. However, when the subjects were subdivided based on the genetic polymorphisms of glutathione S-transferase (GST) T1 and M1, a subgroup with null genotypes in both GSTT1 and GSTM1 (20 of the 53 subjects) had experienced significant protection by NAC (3.1 ± 3.1 dB after placebo, and 1.2 ± 3.6 dB after NAC, at 3, 4, and 6 kHz). The result not only underlines the importance of endogenous antioxidant defenses but also points to genetics as an important modulator of noise trauma.

3.2 Protection from permanent NIHL (PTS)

Magnesium had been explored as an interventive agent against permanent NIHL even before its evaluation for TTS, based on early demonstrations of magnesium-mediated modulation of NIHL in experimental animals and humans [88,89]. In a placebo-controlled, double-blind study [90], subjects were 300 normal-hearing army recruits who underwent 2 months of basic military training. They were exposed to shooting range noises with an average peak level of each shot of 164 dBA and less than a 1-milli-second duration; ear plugs were worn, reducing the peak noise level by approximately 25 dBA. The subjects received daily either 6.7 mmol magnesium-aspartate or a placebo and the Mg^{2+} content of the diet was averaged to 387 ± 23 mg per person per day. When PTS was defined as a threshold greater than 25 dB hearing loss for at least one frequency (2 to 8 kHz), the incidence of PTS in the magnesium group (11.2%, left ear; and 11.2%, right ear) was significantly smaller than in the placebo group (21.5%, left ear; and 28.5%, right ear). Moreover, the incidence of bilateral PTS was remarkably higher in the placebo group (11.5%) than in the magnesium group (1.2%). An important observation needs consideration: regardless of the treatment, the degree of PTS was low in subjects with high serum Mg^{2+} levels and higher in subjects with low serum Mg^{2+} levels. The result underscores the influences of individual genetics and physiology (here the tendency of hypomagnesemia) on susceptibility to trauma.

3.3 Post-traumatic rescue

An anti-apoptotic cell-permeable JNK ligand, AM-111, was employed as post-trauma treatment in a clinical study using intratympanic injections in a double-blind, randomized parallel-dose phase I/II trial [91]. Subjects suffering from NIHL due to firecracker exposure were treated within 24 hours or less with two different doses (0.4 mg/ml, 7 subjects; or 2.0 mg/ml, 4 subjects) of AM-111 in a single injection of 250 μl administered intratympanically. The average pure-tone hearing loss at 4 and 6 kHz was 36 ± 16 dB before treatment. The mean was 11 ± 12 dB after 3 days and 11 ± 14 dB after 30 days with no difference between the two treatment groups. Placebo-controls were absent in this study because ethical considerations make such controls problematic if a promising therapy is being withheld. However, 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. This conclusion was based on the authors estimate, based on clinical experience, that recovery of hearing threshold levels in these cases significantly exceeded the spontaneous recovery observed in patients following acute noise trauma.

Combined treatment with a steroid (prednisolone) and the nootropic drug piracetam also appeared to rescue subjects from noise damage by gunshots [92]. As in the trial with

AM-111, there were no untreated controls but subjects were divided into three groups based on the onset of treatment following acoustic trauma. A larger number of patients recovered (69%) when treatment was begun within the first hour after the acute trauma, rather than after a delay of > 1 to 16 h (24% recovery) or more than 24 h (13% recovery). Furthermore, final threshold shifts were significantly lower in the group treated immediately.

3.4 The influence of genetics on susceptibility to noise

The two studies described above testing Mg^{++} against PTS in the military and NAC against TTS in a steel factory [87] point to genetics as an important modulator of noise trauma. In fact, the workers with GST null genotypes had previously been shown to be more sensitive to noise-induced TTS during a daily shift [93]. Polymorphisms in superoxide dismutase (SOD)2 likewise appeared to influence responses to noise in a Taiwanese population [94], and single nucleotide polymorphisms in SODs were associated with NIHL in Chinese workers [95]. Additionally, polymorphisms of HSP 70 enhanced susceptibility to NIHL [96]. Finally, a candidate gene association study for NIHL in Swedish and Polish factory workers suggested that two genes (*PCDH15* and *MYH14;* out of 644 single nucleotide polymorphisms) might represent noise-susceptibility genes [97]. Thus, sensitizing or protecting genetic influences might be confounding factors in human studies and important consideration in the design of therapy.

While genetics appears to influence the extent of noise trauma, nutrition and the physiological state of subjects might also contribute. This is suggested by animal studies [38] and the possibility that deficiencies of Mg^{2+} or vitamin B_{12} which increase sensitivity to noise trauma [90,84] could also be influenced by diet.

4. Market Review

The potential for NIHL exists in all societies. The World Health Organization's estimate of 10% of the world population being exposed to potentially harmful noise includes developing as well as industrialized countries. The National Institute of Occupational Safety and Health in the U.S. estimates that approximately 30 million workers in the US are exposed to potentially hazardous noise and that 12.2% of work-related accidents in 2008 were cases of NIHL with an economic impact of an estimated $242.4 million dollars annually [2]. In the US military, 30% of soldiers in combat had mild to severe hearing loss in 1975 [98]. In 2004 and 2005, a 21% prevalence of NIHL was assessed in post-deployment military personnel [99], making dysfunction of the auditory system the 3rd most common disability among veterans in the U.S and requiring compensation payments of $660 million annually [2]. In 2010, NIHL has become the most prevalent disability in war veterans [100].

Data for developing countries are difficult to assess, but given the high incidence of NIHL despite strict guidelines for worker protection and improving technology in industrialized countries, we might safely assume that the prevalence of hearing loss is even higher in developing countries.

5. Current Research Goals and Scientific Rationale

Several different kinds of protective treatments have already been shown to work effectively in animal models and support our current understanding of the mechanisms behind NIHL. Because of such successful animal experimentation, much effort is geared toward translation of laboratory results to the clinic. Nevertheless, several basic issues still require attention because protection, even in animals, is often incomplete and clinical application is not a certainty.

1. Protection from noise with different spectral and intensity characteristics. Many animal models use continuous noise as the stimulus, but most severe trauma is caused by impulse noise, the prevalent form in industrial and military settings, as well as in recreational activities like target shooting or hunting. Agents that are efficacious against one form of noise may also protect against the other, but dose and timing for best efficacy might vary [50,101]. Detailed studies of therapeutic efficacy under different noise exposure conditions would help in the design of future trials.
2. Enhanced protection using combination treatment. Comparison of studies from different laboratories is difficult because of variations in animal models and exposure conditions. However, it appears that protection might be more effective when a combination of agents is used rather than a single compound. In particular, combinations that target potentially separate mechanisms of noise action might be promising, for example complementary therapies to modulate oxidative stress, excitotoxicity, blood flow, calcium overload, apoptotic pathways and neurotrophic or hormonal control mechanisms.
3. Routes of delivery. A potential issue in field applications of protective therapy is the daily availability of the drug and compliance with taking such a pill. The efficacy and success of treatment would be considerably increased if a long-term release formulation could be devised, akin to skin patches or subdermal depots currently in use in other contexts.
4. Window of opportunity. Animal experiments have demonstrated that protection after sustaining acoustic trauma is possible although less effective than when treatment is begun before exposure. The existence of a post-exposure time window for rescue in humans can be surmised [91] and is supported by some preliminary data. We need more information on this window of rescue and its dependence on duration and type of exposure and possible interspecies variations.
5. In parallel to the exploration of pharmacological protection, the development of “rescue agents” should be fostered. Different means of intervention might be indicated for pre- or post-exposure treatment: a calcium channel blocker might be effective in an early period of trauma while an apoptosis inhibitor might be more effective later. Such drugs would be administered on the battle field, field hospital, or emergency room to reduce post-exposure damage to the ear. Post-traumatic rescue might be an area where commitment of increased resources could pay off earlier than in pre-treatment protection.

6. Competitive Environment

Several trails are underway (table 1) to test pharmacological intervention in permanent noise-induced hearing loss. Current approaches are based on the premise that antioxidants (or antioxidant combinations) or anti-apoptotic agents effective in animal experiments will attenuate noise trauma in industrial and military settings. Results have not yet been published as of this writing (November 2010).

7. Potential Development Issues

Trials on human subjects to prevent NIHL are limited to field conditions in military and industrial settings where noise exposure and potential noise trauma is inevitable. The use of volunteers was acceptable until recently for the investigation of temporary threshold shifts, since they were considered to be without lasting consequences. This notion has now been challenged by results on mice that completely reversible temporary threshold shifts can give rise to slow nerve degeneration and accelerated age-related hearing loss [102]. It remains

unknown to what extent TTS of any magnitude will affect human hearing in later life but ethical questions might eliminate the voluntary TTS model from the development of protective therapies.

Post-hoc interventions necessarily suffer from confounding factors such as the type of noise trauma experienced, delay to intervention, a relatively low incidence (unless on the battle field) and the lack of a balanced control group. Nevertheless, coordinated trials under a central guidance could accumulate valuable insights.

8. Conclusion

Despite the current lack of an established therapy, the question of whether results from animal experimentation can be translated to the clinic can probably be positively answered. Preliminary data are tantalizing and, in addition, translation from the laboratory for the clinic has been successfully demonstrated for drug-related auditory toxicity which also involves oxidative stress. The incidence of gentamicin-induced hearing loss was reduced by 75% in a clinical trial [103] that was developed on the basis of laboratory findings [104]. Once the results from ongoing clinical trials on protection from NIHL are known, it will be possible to design improved strategies for both laboratory studies and translational efforts.

9. Expert Opinion

- The current state of development of pharmacological prevention of NIHL is encouraging. The mechanisms of noise-induced damage to the auditory system are well explored and have provided a good basis for effective interventions in animal models. The general feasibility of translating from animal models to clinical protection from acquired hearing has been demonstrated for aminoglycoside ortotoxicity, and preliminary results suggest that noise trauma can also, in principle, be attenuated. With the current pace of development, oral drug treatment(s) to protect against noise-induced hearing loss should be available within the next 5 to 10 years
- Over the same time period, suggestions for improved treatments will come from animal experiments, for example by a more thorough exploration of combination treatments that target some of the multiple pathways of noise-induced cellular changes. Feed-back from currently ongoing trials, combined with such laboratory developments, will increase the efficacy of treatments and accelerate the time from the laboratory bench to clinical treatment.
- As new pharmacological interventions are being tested, a rigorous standard of protection should be established. A reduction of hearing loss of a few dB can be *statistically* significant but would only prove a principle. In reality, an attenuation of 5 or even 10 dB might not be *functionally* significant for the affected individual. Agents are needed that reliably can attenuate hearing loss in excess of 15 or 20 dB.
- We will also find more concern about TTS which hitherto has frequently been treated as a model for PTS. This assumption is now called into question as is the use of volunteers for TTS studies. Basic research will show over the next decade whether any magnitude of TTS will have late-life consequences or whether a threshold for late-life damage exists. Recall of volunteers from earlier TTS studies might be necessary to resolve the question at the clinical level.
- Genetics of susceptibility to NIHL might become an issue in the next 5 to 10 years. Genetic subsets of the population can be more sensitive to noise exposure and the question of preventive screening might be raised so as to exclude sensitive

individuals from hazardous environments. Likewise, pharmacogenetics will play a role as certain nutritional supplementations will be effective in only a subset of the population and protection can be tailored to genetic variants.

- Even after a successful demonstration of a protection, major hurdles of safety and logistics/education remain to be resolved. A “hearing pill” will have to be taken daily by noise-exposed workers for their 30–40 year careers. Safety is assumed but there is currently no information available of the long-term effects even of common nutritional supplements, let alone specific formulations for auditory protection. Furthermore, questions arise as to how individuals can be motivated to take a daily pill and how compliance can be monitored. The development of alternative delivery routes merits early exploration.

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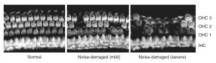

Figure 1. Missing hair cells of the organ of Corti after noise exposure

Outer hair cells (OHC) comprise three rows, inner hair cells (IHC) a single row in the normal cochlea (left). Outer hair cells are a primary pathological target in acute NIHL, and start to disappear following noise exposure (middle). In the severely damaged cochlea, most of the outer hair cells are missing (right). Inner hair cells are usually preserved until all outer hair cells are destroyed.

Table 1

Competitive environment.

Compound	Company	Structure	Stage of development	Mechanism of action
Ebselen	Sound Pharmaceuticals	Benzisoselenazol	Phase II–III	SOD mimic, antioxidant
SPI-1005				
XG-102	Xigen/Auris Medical	Peptide	Phase I–II	Anti-apoptotic
AM-111				
AuraQuell	OtoMedicine	Mg, vitamins A, C, E	Phase II–III	Vasodilator, antioxidant

SOD: Superoxide dismutase.