The Use of Antioxidants in the Prevention and Treatment of Noise-Induced Hearing Loss

Haley Hullfish, BS[a,*], Luis P. Roldan, MD[a], Michael E. Hoffer, MD[a,b]

KEYWORDS

• Noise-induced hearing loss • Antioxidants • Reactive oxygen species
• N-acetylcysteine • Acetyl-L-carnitine • D-methionine • Resveratrol

KEY POINTS

- Continuous or excessively loud noise exposure leads to an accumulation of intracellular free radicals, particularly reactive oxygen species (ROS) and reactive nitrogen species (RNS), for at least 7 to 10 days after injury.
- Experimental animal studies with systemic or local antioxidant use have been shown to protect hair cells and reduce hearing loss from acoustic trauma.
- Combination antioxidant therapy may better attenuate NIHL than single-agent therapy by targeting multiple pathways in ROS and RNS formation.

INTRODUCTION TO NOISE-INDUCED HEARING LOSS

Noise-induced hearing loss (NIHL), which occurs due to excessive noise exposure, is a preventable cause of sensorineural hearing loss. The CDC approximates that at least 40 million adults aged between 20 and 69 years in the United States have audiological evidence of NIHL in one or both ears,[1] affecting as much as 17% of the adolescent population.[2] The severity of hearing loss relies on several factors, including individual characteristics, sound intensity, and duration of sound exposure. Although sensitivities vary among individuals, sound intensity at or above 85 decibels (dB) can precipitate hearing loss, a sound level equivalent to that of a food blender or city traffic. Those exposed to sound exceeding 85 dB for only 5 hours per week can suffer permanent hearing loss.[3] There are several proposed theories to explain the pathogenesis of NIHL. Evidence demonstrates that inflammation, increased oxidative stress,

[a] Department of Otolaryngology, University of Miami Miller School of Medicine, 1120 Northwest 14th Street, Miami, FL 33136, USA; [b] Department of Neurological Surgery, University of Miami Miller School of Medicine, 1120 Northwest 14th Street, Miami, FL 33136, USA
* Corresponding author.
E-mail address: hmhullfish@med.miami.edu

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Abbreviations	
ABR	Auditory brainstem response
ALCAR	acetyl-l-carnitine
BBB	Blood-brain barrier
CDC	Centers for Disease Control and Prevention
COX-2	Cyclooxygenase-2
dB	Decibels
D-met	D-methionine
DPOAE	Distortion product otoacoustic emission
FDA	Food and Drug Administration
GSH	Glutathione
HC	Hair cell
NAC	N-acetyl cysteine
NIHL	Noise-induced hearing loss
OBN	Octave band noise
PTS	Permanent threshold shift
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
TTS	Temporary threshold shift

elevated calcium, and reduced blood flow are all mechanisms underlying NIHL.[4] Importantly, no treatment has proven effective in reversing the damage inflicted by excessive noise exposure. Primary prevention by noise avoidance and regular use of personal protective hearing equipment is the standard of care at this time.

Impulse noise is defined as a quick burst of acoustic energy. Common examples are gunfire, explosions, fireworks, and heavy machinery. These acoustic bursts can elicit acute effects, including transient tinnitus, hyperacusis, and tympanic membrane perforations. High-intensity exposure can cause loss of cochlear sensory hair cells (HCs), leading to permanent threshold shift (PTS). In contrast, hearing loss associated with more mild acoustic exposure is typically reversible and recovers in days to weeks, referred to as temporary threshold shift (TTS). This is thought to be due to reversible swelling and damage to the stereocilia of HCs.[5] However, the impact of TTS may misrepresent the damage of noise-induced cochlear toxicity. Recent studies have demonstrated that even mild acoustic trauma associated with TTS can lead to the loss of more than 50% of the synapses between cochlear nerve fibers and inner HCs, without HC loss and without alteration of hearing thresholds.[6] The resulting synaptopathy is sometimes referred to as "hidden hearing loss." Although seemingly plausible, there is no current data to support this synaptopathy in humans; thus, the concept of hidden hearing loss remains controversial.

Hearing loss may also result from continuous moderate noise exposure. In contrast to impulse noise, continuous noise has been shown to be more damaging because there is less recovery time between acoustic insults.[7] Initial hearing loss patterns for both acute and chronic noise exposure seem similar. Nerve fiber degeneration and HC damage occur bilaterally at the cochlear region corresponding to a 4-kHz notch on audiograms.[8] As noise exposure persists, the damage extends in the basilar direction toward the high-frequency portion of the cochlea, eventually resulting in mid-frequency to high-frequency hearing loss. There is a limit to the severity of hearing loss because NIHL rarely exceeds 70 to 90 dB threshold even after many years of continuous noise exposure.[8] Because both chronic and acute noise exposure can induce NIHL, it is important to obtain an adequate patient history of environmental risk factors, including occupational and recreational noise exposures.

INTRODUCTION TO ANTIOXIDANTS

Continuous or excessively loud noise exposure leads to an accumulation of intracellular free radicals, particularly reactive oxygen species (ROS) and reactive nitrogen species (RNS), for at least 7 to 10 days after injury.[9] At high levels, these agents overwhelm the cells' antioxidant systems, which maintain redox homeostasis. Glutathione (GSH), GSH peroxidase, GSH reductase, methionine sulfoxide reductase, superoxide dismutase, catalase, and coenzyme Q_{10} are all redox enzymes found in the inner ear.[5] Once these natural defenses are depleted, toxic reactive species induce inflammation, permanent damage, and cell death of cochlear neurons and HCs. The cochlear distribution of these defensive proteins may correspond to the pattern of hearing loss observed in noise exposure. The antioxidant GSH is distributed in a high-to-low gradient from the apex to the base in the organ of Corti, suggesting a lower tolerance of basal HCs to acoustic insult.[10]

The pathophysiological mechanism underlying NIHL has translational potential for pharmacological intervention to prevent or rescue HC injury from free radical damage. Multiple antioxidants have been investigated for both the prophylaxis and treatment of NIHL. The various antioxidants work via different mechanisms involving scavenging free radical species, quenching singlet oxygen molecules, reducing concentrations of intracellular oxygen, chelating metals, interrupting free radical reactions, and preventing the oxidation of protein or DNA.[11] Given the variety of pathways by which ROS and RNS are generated, the use of multiple antioxidants that target different pathways of noise-induced ototoxicity may be most effective in preventing cochlear damage.

ANTIOXIDANT STUDIES

Experimental animal studies with systemic or local antioxidant use have been shown to protect HCs and reduce hearing loss from acoustic trauma. Among the most extensively studied are N-acetyl cysteine (NAC), methionine, acetyl-L-carnitine (ALCAR), and resveratrol.

N-Acetyl Cysteine

NAC is one of the few antioxidants that have been studied in both animal and human trials for the treatment of NIHL. It is an over-the-counter anti-inflammatory medication commonly used to treat acetaminophen-induced oxidative hepatic injury. NAC replenishes cysteine, the limiting substrate in GSH synthesis. GSH reduces and conjugates ROS and RNS formed during intracellular oxidative stress and is a major antioxidant enzyme in HCs.[12] Similar to GSH, NAC also acts as a scavenger of reactive oxygen species through the reduction of disulfide bonds.

In animal studies, NAC has shown promising otoprotectant results. Kopke and colleagues exposed chinchillas to 6 hours of 105 dB octave band noise (OBN) centered at 4 kHz. Animals received salicylate and NAC 1 hour before or 1 hour after the noise exposure. PTSs were significantly reduced to approximately 10 dB in the pretreatment groups compared with the 20 to 40 dB threshold shift in controls at 3 weeks postexposure. Those treated after noise exposure had no protection from HC loss.[13] Additionally, Kopke's laboratory investigated combining NAC with 2,4-disulfophenyl-*N*-tert-butylnitrone (HPN-07), a nitrone-based free radical trap. HPN-07 has been shown to be effective in treating acute acoustic trauma in chinchillas.[14] Rats exposed to 115 dB OBN (10–20 kHz) for 1 hour were treated with combined NAC and HPN-07 starting 1 hour after noise exposure for 2 consecutive days. Results demonstrated reduced auditory brainstem response (ABR) threshold shifts, decreased distortion

product otoacoustic emission (DPOAE) shifts, and HC loss reduction by 85% to 64% in the outer and inner HC regions, respectively.[15]

In contrast, NAC administration in humans with extreme noise exposure has shown varying results. Kramer and colleagues[16] administered 900 mg of NAC or placebo to 31 participants 30 minutes before exposure to live music at a nightclub and no significant difference between treatment groups was found in distortion product otoacoustic emissions (DPOE) measurements before and 2 hours after exposure. However, the inconsistency of sound exposure and the wide variance of subject sensitivity could be confounders. Lin and colleagues performed a prospective, double-blind crossover study on 53 male industrial workers exposed to approximately 88 to 89 dB of noise daily. The intervention was 1,200 mg/day of NAC for 2 weeks followed by placebo for 2 weeks or vice versa. The data indicate reduced high-frequency TTS by NAC with such effects more prominent among men carrying GSH S-transferase M1 and T1 null genotypes. The TTS at low frequency was not significantly different between the postplacebo and post-NAC phases of the study.[11] In 2003, the US Department of the Navy conducted a large trial with 566 Marine Corps. The subjects received 900 mg of NAC or placebo with each meal for a total dose of 2700 mg during the first 16 days of weapon training. There was no statistical evidence that NAC reduced the rate of threshold shifts; however, post hoc analysis showed significant decreases in threshold shift rates when handedness was considered.[17] Due to the lack of significant differences in overall hearing loss between treatment and placebo, further studies are warranted to clarify dose–response and other factors, including differences in risks between ears. Trials in human subjects have been limited in scale and current evidence demonstrates varied support for NAC alone as a reliable otoprotectant in NIHL.

Methionine

Methionine is one of the most easily oxidized amino acids and can react readily with various reactive oxygen species to form methionine sulfoxide.[18] Its functional role as an otoprotectant has been elicited by studies that demonstrate HC apoptosis and deafness in subjects with mutations that reduce cochlear concentrations of methionine.[19,20] Methionine can also increase intracellular stores of GSH, and similar to NAC, can serve as a cysteine supplier for GSH synthesis.[21,22] The enantiomer D-methionine (D-met) is often used clinically because it has a more stable shelf life and better bioavailability than L-methionine.

D-met has been widely shown to protect against cisplatin-induced and carboplatin-induced ototoxicity in animals.[23–25] Kopke and colleagues[26] demonstrated that D-met delivered 48 hours before and 48 hours after noise exposure protected against permanent NIHL and HC loss in chinchillas. Campbell further demonstrated that D-met could rescue permanent NIHL when given 1 hour after noise exposure.[27] Claussen and colleagues[28] also illustrated that D-met preloading 2 to 3 days before noise exposure reduced ABR threshold shifts and outer HC loss in chinchillas. Clifford and colleagues investigated the effects of low-dose intraperitoneal D-met and NAC administered to chinchillas before and after continuous noise exposure. D-met and NAC together demonstrated significant improvement of ABR thresholds. D-met seemed to be the primary compound responsible for hearing restoration as D-met alone showed gradual improvement with statistically significant recovery in middle frequencies.[29] Furthermore, dose-dependent otoprotective effects of D-met have been reported in guinea pigs with NIHL. Animals were treated 1 hour after noise exposure with 200, 400, or 600 mg/kg of D-met by intraperitoneal injection. The level of rescue from noise-induced PTS was dose-dependent. Administration of D-met 200 mg/kg did not reduce the mean PTS but 600 mg/kg dosage achieved a complete rescue response.[30] In addition, dose-

dependent decreases in ATPase activity, mean lipid peroxidation, and nitric oxide levels were also observed.[30] Clinical trials are necessary to evaluate the efficacy of D-met for preventing and treating NIHL in humans.

Acetyl-L-Carnitine

ALCAR is a naturally occurring amino acid stored in high quantities in muscle and heart tissue. It is a readily available over-the-counter supplement that has been administered in doses ranging from 20 to 50 mg/kg daily in both animal and human studies.[31] ALCAR stabilizes mitochondrial membranes during respiration and aids in cellular energy production by regulating acetyl-CoA, a key substrate in the citric acid cycle. Through several parallel reactions, ALCAR reduces oxidative stress by scavenging ROS and increases cellular stores of other antioxidants, including GSH and coenzyme Q_{10}.[31] Its effect on hearing restoration following acoustic trauma has been studied in animal models suggesting a positive effect.

In one such animal model, Coleman and colleagues investigated the combined efficacy of ALCAR and NAC administered 1, 4, and 12 hours after sustained noise exposure (105 dB for 6 hours). Both ALCAR and NAC demonstrated time-dependent effects on outer and inner HC counts and undamaged mitochondrial density. The most significant reduction in hearing loss for both ALCAR and NAC treated animals occurred in the 1-hour postexposure groups. Treatment groups with delayed administration of more than 4 hours failed to improve hearing suggesting a short window of therapeutic efficacy after noise exposure.[32] In addition to NIHL, Seidman's laboratory demonstrated that ALCAR could protect against age-related hearing loss in rats by preventing and repairing age-induced cochlear mitochondrial DNA damage.[33] The effects of ALCAR to reduce NIHL warrants further study before routine recommendation.

Resveratrol

Resveratrol (trans 3,5,4'-trihydroxystilbene) is a phytoalexin and nutritional supplement found in the skin and seed of red grapes. It is studied in cancer and heart disease due to its antioxidant and anti-inflammatory properties.[34,35] In a study published in 2003, resveratrol supplementation for 7 weeks was noted to reduce threshold shifts in rats exposed to significant acoustic trauma compared with controls.[36] Seidman and colleagues further elicited the protective mechanism of resveratrol by measuring its effect on cyclooxygenase-2 (COX-2) and ROS formation following noise exposure in rats. The data demonstrated that at a dose of 5 mg/kg for 3 days before 24 hour noise exposure, resveratrol reduced noise-induced COX-2 expression and ROS formation in the blood.[37] No trials exist that study the effects of resveratrol on NIHL in humans.

CHALLENGES IN ANTIOXIDANT USE

The animal studies previously mentioned advocate for the translation of these promising antioxidant studies to human trials. However, the route of administration, high experimental dosages, and ability to control noise exposure in animal studies are often not feasible in human subjects. In addition, the bioavailability of antioxidants is varied and needs to be fully elucidated before application in humans. To date, no antioxidant agent for NIHL is approved by the U.S. Food and Drug Administration (FDA).

The selection of an appropriate medication for NIHL should consider bioavailability at the cochlear target organ and its ability to permeate the blood–brain barrier (BBB). Various antioxidants possess potential therapeutic benefits for central nervous system diseases but have limited availability across the BBB. GSH, for instance, penetrates the BBB by <1% when given exogenously thereby diminishing its effect in reducing

oxidative stress in the CNS.[38] Other antioxidants including derivatives of Vitamins A, D, and E have demonstrated similar shortcomings in crossing the BBB, even when given at high doses.[38] However, when the BBB is damaged, for example, in traumatic brain injury, increased brain permeability may facilitate selective drug delivery to affected sites.[39]

Numerous animal studies have validated the use of antioxidants for NIHL in preexposure and postexposure settings. However, experimental study in human populations is far more limited, with many studies relying on cross-sectional data to infer differences between populations and exposures. Both ethical and epidemiological factors restrict further development and research in the clinical setting. Although feasible, obvious ethical considerations exist that prohibit the deliberate exposure of damaging sound in human subjects. Enrollment of subjects with environmental exposure to extreme noise also poses a unique challenge because the therapeutic window for antioxidant therapy is limited and the wait period to obtain appropriate medical attention may be exceedingly long. Additional factors including poor public awareness of NIHL, subclinical symptoms, individual variations in noise susceptibility, and limitations in access to health care make it increasingly difficult to recruit participants in a timely manner immediately following acoustic trauma and before noise-induced cochlear damage becomes permanent.

Early-onset of antioxidant therapy confers the greatest protective benefit against NIHL. Similarly, there is a time-dependent response to therapy, with reduced responses to therapy with greater delay to initial administration. There is strong data that supports the protective effects of antioxidants when given before and immediately after extreme noise exposure. Coleman and colleagues[32] revealed a significant reduction in hearing loss when ALCAR and NAC therapy was given within 4 hours of noise exposure but not when given after 12 hours. D-met has been demonstrated to provide significant PTS rescue up to 7 hours after noise exposure.[40] Prophylactic administration of antioxidants also provides otoprotection from noise-induced trauma. NAC, D-met, and magnesium are among the antioxidants that have reduced HC loss and hearing loss in animal models when given days to hours before exposure.[13,28,41] However, prophylactic treatment in humans is not always feasible because patients usually present once permanent hearing loss has already occurred. Prophylactic administration could be considered especially in settings when occupational noise exposure is anticipated, for example, in military or construction settings. However, this raises further questions about the duration of treatment and long-term drug effects.

Less data exist regarding the efficacy of delayed treatment in NIHL. Yamashita and colleagues[9] found that ROS and RNS persist in HCs for up to 7 to 10 days after acoustic trauma. Consequently, they reported that the greatest window of opportunity was within 3 days of exposure achievable by using a combination of antioxidants with different mechanisms of action and prolonging the duration of treatment.[42] Altogether, there is a need for more conclusive evidence demonstrating the protective effects of antioxidant drug administration if given at least 1 week following exposure. Unfortunately, initial diagnosis and subsequent treatment may often be delayed, minimizing the therapeutic efficacy of antioxidants.

SUMMARY

Antioxidant compounds seem very promising in the prevention and treatment of noise-induced cochlear trauma. However, no single protective agent has proved fruitful at the bedside. It is likely that a combination antioxidant therapy may better attenuate NIHL than a single-agent therapy. The enhanced efficacy of combination therapy

can be explained by the targeting of multiple pathways in ROS and RNS formation. Of course, the benefits of combination therapy should be weighed against the potential for cross-drug reactions and the variable side effects of polypharmacy. The success of these therapies depends on factors such as type of antioxidant, dosage, route of administration, bioavailability, the timing of therapy in relation to noise exposure, and duration of therapy.

In 2011, experts estimated that oral drug therapy to protect against NIHL would be available in the next decade.[43] Although this was not achieved, we can continue to move forward by developing a better understanding of the complex biochemical and molecular mechanisms of cell death in the cochlea and the biochemistry of antioxidants relevant to the cochlea in order to design more effective treatment strategies in hearing loss.[44] Large, randomized, double-blind, placebo-controlled clinical trials demonstrating the efficacy of antioxidant therapy are essential to attest to their value in treating NIHL. In addition, a statistically significant reduction in hearing loss is different than functionally significant. Therapies that can reliably reduce hearing loss by at least 15 dB are needed. Although we have made significant strides in combating acoustic injury, it is apparent we still have a long way to go until an oral drug therapy is available for NIHL. However, antioxidants are a promising option that require further exploration.

DISCLOSURES

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