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Antioxidant micronutrient impact on hearing disorders: concept, rationale, and evidence☆,☆☆

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Abstract

Purpose: Although auditory disorders are complex conditions, device-related modalities dominate current treatment. However, dysfunction from the central cortex to the inner ear apparatus is increasingly thought to be related to biochemical pathway abnormalities and to free radical–induced oxidative damage and chronic inflammation. Therefore, considering appropriate biologic therapy as an adjunct to standard care against these damaging factors may provide rational expansion of treatment options for otolaryngologists and audiologists.

Methods: This review outlines the biologic concepts related to some auditory and vestibular conditions and details the current rationale for utilizing antioxidants for a spectrum of hearing disorders. The strategy is based on the authors' collective experience in antioxidant science and supported with published research, pilot animal data and preliminary clinical observations.

Results: A comprehensive micronutrient approach was developed to exploit these pathways, and demonstrated safety and efficacy against oxidative damage and inflammation and clinically relevant neuroprotection. Cooperative research with Department of Defense institutions used prospective, randomized designs to show (1) reduction in oxidative damage measured in plasma and urine over six months, (2) protection against oxidative damage during 12 weeks of intense military training, (3) protection against inflammation after total body blast exposure (rodents), (4) strong neuroprotection against chemically-induced Parkinson's disease (rodents), (5) nerve VIII function improvement after concussive head injury in military personnel, and (6) tinnitus improvement in majority of patients after 90-day evaluation.

Conclusion: This systematic review of biologic strategies against hearing disorders combined with new animal and human observations may provide a rational basis for expanding current practice paradigms.

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1. Introduction

The current management of hearing loss and tinnitus emphasizes technical and device-related modalities that may yield reasonable results for some but less than optimal results for others. There is increasing recognition that at least part of the abnormalities noted from the cortical level through the inner ear apparatus appear to be related to biochemical pathways, free radical–induced oxidative damage and inflammation. Nevertheless, biologic approaches to therapy that may exploit these factors have not been widely incorporated into otolaryngology or audiology practice, and this potential to expand treatment options has not been fully appreciated. This review will (1) examine the concepts of biochemical mechanisms, oxidative stress and inflammation in some auditory and vestibular disorders; (2) review the evidence that suggests that a science-based antioxidant strategy may be considered as an adjunct to standard care; and (3) propose the rationale for and components of a possible micronutrient formulation to impact patients with hearing abnormalities.

2. Etiologic factors

The initiation and progression of the spectrum of hearing disorders are caused by a wide variety of exposures and conditions and represent the most common occupational illness in the United States. Hearing loss and tinnitus affect more than 50 million people, 10 million of whom suffer permanent disability with significant impact on their quality of life [1]. Exposure in industries such as mining and manufacturing, aviation, music, and entertainment and participation in sports including speed racing and recreational shooting are associated with particular risk. Acute acoustical trauma from exposure to high-intensity noise and vibratory wave impact (ie, explosions) may also have long-term effects on military personnel in training and in combat [2]. In addition, a number of medications have been implicated in sensorineural hearing loss [3]. In fact, in 2007, the US Food and Drug Administration published cautionary language about sudden deafness related to erectile dysfunction drugs. Although auditory impairment is also related to aging, noise exposure, and diseases such as Meniere's, recent studies indicate that hearing loss may be a common, under-recognized complication of diabetes [4,5]. Research also indicates that chronic noise exposure may be a contributing factor to the balance disorders that affect up to 10% of the population [6]. These conditions carry a particularly high morbidity and even mortality because of fall-related injuries [7].

3. Mechanisms of damage

Although hearing disorders have many etiologies, there are only a few final common pathways of damage. Hair cell injury anywhere within the auditory apparatus releases glutamate, an excitatory neurotransmitter that is highly toxic to neuronal tissue. A recently described biochemical mechanism of cyclo-oxygenase blockade and arachidonate release sensitizes the glutamate receptor, *N*-methyl-D-aspartate (NMDA) to enhance the damaging auditory effects [8]. It is now established that increased oxidative stress and chronic inflammation may play a role in some aspects of hearing disorders. Oxidative stress from production of excessive amounts of free radicals (highly reactive molecules that can cause undesired cellular changes) such as nitric oxide and peroxynitrite is involved in noise-related injury [9-11]. Oxidative damage is also associated with medication-induced hearing impairment [12]. In addition, acute and chronic inflammation that produces proinflammatory cytokines such as tumor necrosis factor–α and interleukin-6 is implicated in causing injury to the auditory apparatus, including cochlear, sensory, and vestibular hair cells [13,14]. Furthermore, the concept of the brain's neuroplasticity and the ability to biologically modify the development of spiral ganglion neurons have potential implications for hearing preservation related to devices such as cochlear implants [15-17].

Tinnitus is complex, multifactorial, and involves many etiologic loci that are vulnerable to oxidative damage and inflammation. Most are thought to be related to central nervous system factors such as imbalance between excitatory and inhibitory neurotransmitters in the midbrain, hyperactivity of the auditory cortex and dorsal cochlear nucleus, oscillatory abnormalities of hair cells, irritation of the vestibular nucleus, and hyper-excitability of ganglion cells [18]. Levels of the potentially toxic glutamate NMDA receptor and multiple free radicals are markedly elevated in patients with tinnitus [19]. Noise-induced nuclear and mitochondrial injury, depletion of glutathione (an important endogenous antioxidant), nerve VIII function, and aging are also exquisitely sensitive to these damaging factors [20,21].

Finally, deficiencies of certain B vitamins have been documented in patients with chronic tinnitus and noise-induced hearing loss [18,22]. In the context of these known mechanisms, a potential biologic strategy as an adjunct to standard treatment should employ safe and effective agents that restore normal vitamin levels, inhibit glutamate release, and reduce oxidative damage and inflammation, thereby facilitating improvement in clinical symptoms. This approach may also have particular relevance to patients with tinnitus and vestibular disorders related to their cochlear implantation [23,24].

4. Biologic strategy rationale

Although technical device approaches for hearing disorders have provided symptomatic relief, the opportunity to further improve long term results for patients have led to the search for additional options. A number of potential drugs as effective biologic adjuncts have been used (Table 1). These

Table 1
Pharmacologic agents used in hearing disorders

Inhaled carbon dioxide
Dextran 40 with betahistine, pentoxifyllin or heparin
Anti-epileptics
Systemic corticosteroids (oral or intravenous)
Allopurinol
Hyperbaric oxygen
Anti-depressants (selective serotonin reuptake inhibitors)
Homeopathic agents
Rebamipide
Glutamate and NMDA receptor antagonists (MK-801, ifenprodyl, memantine)
Phospholipids
Herbals (ginkgo biloba)
Nonsteroidal anti-inflammatory drugs

pharmacologic agents have generally had only modest impact on patient outcomes although several showed promising experimental data. Therefore, to successfully exploit the mechanisms responsible for hearing disorders and enhance device-related treatments, a more comprehensive and targeted biologic approach may be desirable. A meaningful addition to current otolaryngology or audiology practice can be constructed upon a platform based on the beneficial effects from antioxidant micronutrients. Because they neutralize free radicals, reduce inflammation, and decrease the impact of glutamate toxicity, the proper types and combinations of antioxidant supplementation may improve the efficacy of standard therapy for some hearing disorders.

This rationale is supported by extensive scientific experience from animal and human studies. Single agents have demonstrated some preventive benefit against noise-induced damage and medication-related ototoxicity. Vitamin E reduces cochlear damage from these factors [25,26]. α-Lipoic acid has similar effects [27]. *N*-acetyl cysteine (NAC) also can protect the inner ear apparatus [28,29]. Coenzyme Q10 and vitamin C both have shown damage preventive properties [30,31]. In addition, magnesium improves recovery from hearing loss [32,33]. Other free radical scavengers have also shown benefit in vivo [34,35]. Finally, vitamin E blocks glutamate release and, as well as coenzyme Q10, can prevent glutamate-induced neurotoxicity [36,37].

Although these single agents may provide some benefit, use of this approach may be less than optimal because an individual antioxidant, when oxidized, acts as a free radical [38,39]. Therefore, combinations of antioxidants may be expected to be more effective [40,41]. Vitamin E and vitamin C combined improve recovery from idiopathic sudden sensorineural hearing loss [42]. Antioxidants and magnesium may also prevent permanent noise-induced hearing loss when given before and for a few days after exposure [43]. High dose NAC has been combined with acetyl-L-carnitine before and after noise exposure to attenuate hearing loss [44,45]. Of interest, NAC as a single agent has not been as protective in a clinical setting [46]. To avoid the potential problems of single agents and in light of the promising benefits from limited antioxidant combinations, it can be anticipated that a more comprehensive micronutrient strategy may provide broader symptomatic benefits.

5. Proposed micronutrient solution

It appears reasonable that among other considerations, a formulation proposed for hearing disorders must (1) be based on the tenets of antioxidant science; (2) have neuroprotective application to hearing disorders; (3) impact oxidative damage, inflammation, and immune function; and (4) demonstrate benefit in controlled animal or human studies. Therefore, a rationale biologic approach as an adjunct to standard therapy may include a multiple constituent blend containing dietary and endogenous antioxidants as well as glutathione-elevating agents, appropriate B-vitamins, minerals and other micronutrients.

A broad spectrum of antioxidants and their derivatives is necessary because different types of free radicals are produced and each antioxidant has a different affinity for each of these. In addition, the organ and cellular distributions of micronutrients differ, and they exhibit varying mechanisms of action. Dose ranges are critical not only for toxicity issues but also because at certain doses, antioxidants may reduce free radicals but may not decrease chronic inflammation [47]. Dose schedules are equally important because of the great fluctuations in antioxidant levels associated with only once a day or every other day dosing. The pharmacokinetic half-life of water-soluble and fat-soluble antioxidants is brief enough that twice a day dosing maintains more constant levels to increase biologic effectiveness, protect the genetic machinery of the cell, and decrease cellular stress [48].

The many differing antioxidant effects suggest that a comprehensive, multiple micronutrient strategy to hearing disorders rather than the limited combination approach should be used. For example, beta-carotene is most effective in quenching oxygen radicals and performs certain biologic functions that cannot be produced by its metabolite, vitamin A, and vice versa [49,50]. Vitamin E more effectively neutralizes free radicals in reduced oxygen environments whereas beta-carotene and vitamin A are more effective in higher atmospheric pressures [51]. Vitamin C is critical to maintain vitamin E levels by recycling the vitamin E radical (oxidized) to the reduced (antioxidant) form [52]. The natural form of vitamin E is more selectively absorbed and alpha-tocopheryl succinate has been shown to be the most effective type in vitro and in vivo [53,54]. Glutathione, a vital endogenous antioxidant, provides potent intracellular protection against oxidative damage [55]. However, because it is hydrolyzed in the gastrointestinal system, it cannot be directly taken as a supplement and other glutathione-elevating agents must be used [56].

Besides considering beneficial components, it is equally important to recognize which constituents commonly included in commercial preparations should be avoided. A micronutrient combination containing iron, copper, or

manganese may be problematic because these components interact with vitamin C and generate excessive amounts of free radicals. The inclusion of heavy metals such as molybdenum, zirconium, and vanadium is also not ideal because accumulation of these metals after long-term consumption may be toxic to nervous tissue including the brain. Herbs, stimulants and other unproven constituents are generally not desirable because they may be difficult to standardize, have unknown long-term safety profiles, may contain unwanted contaminants and many are known to interact with prescription and nonprescription drugs in adverse manner [57]. Finally, homeopathic preparations or herbal antioxidants are not necessary because they do not produce any unique beneficial effect that cannot be produced by standard antioxidants.

6. Status of pilot data

A possible biologic approach was tested in Cooperative Research and Development Agreements with Department of Defense institutions and approved by their institutional review board. Because potential toxicity is always a concern, the therapeutic index and a careful safety assessment of the proposed formulation was undertaken. All constituents were well-characterized nutritional supplements with a long history of safe public consumption at the doses utilized. They belonged to a group of components considered by the US government to be designated as "GRAS" (Generally Recognized As Safe) substances. Vitamin A, vitamin D and the mineral selenium have reported toxicity at high doses, but the doses used in these protocols were far below the levels associated with any adverse effects. The remaining vitamins, minerals, and other antioxidants are non-toxic as no known overdoses have been reported. Drug interactions with these substances are also very rare. At much higher doses than used, vitamin E may show anti-platelet activity and could augment the effect of blood thinners. Theoretically, some endogenous antioxidants may enhance glucose uptake so blood sugar should be monitored in patients taking anti-diabetic medications. These issues have not proven to be of practical concern. Nevertheless, it is known that all ingested substances have the potential for adverse reactions in people with hypersensitivity to them; nutritional supplements are no exception.

Taking all of these factors into consideration, appropriate informed consent was obtained from the subjects after the nature of the experimental procedure was explained. The antioxidant micronutrients were assessed for preventive effects (supplementation before insult), protective effects (supplementation proximate with insult) and reversal effects (supplementation after insult). The protocols used animal models for evaluation of hazardous exposures and included pilot human experiences in civilian and military personnel (active, injured and in training). These preliminary observations suggest that the formulation is safe and effective against oxidative damage and inflammation as well as clinically neuroprotective. Because these factors are implicated in many hearing disorders, the results provide some rational basis for anticipating beneficial effects. Therefore, the following "preventive" and "protective" studies may be considered indirectly relevant with specific regard to auditory and vestibular abnormalities, while the "reversal" studies may be considered more directly relevant.

7. Preventive studies

1. Rodents were administered oral doses of the antioxidants seven days before exposure to a lethal dose (150 kP) of total body blast wave pressure. The micronutrients blocked the expected dramatic elevation of inducible nitric oxide synthase, a marker of inflammation, without affecting enzymatic markers of oxidative damage such as heme-oxygenase-1 and superoxide dismutase [58].
2. Rodents were administered oral doses of the formulation before intra-peritoneal injection with 1-methyl, 4-phenyl-1,2,3,6-tetrahydro-pyridine, a chemical agent that is a contaminant in certain recreational drugs and induces the neurologic symptoms of Parkinson's disease. The micronutrients significantly decreased the incidence of Parkinsonian symptoms by 86% compared to controls thereby demonstrating strong neuroprotection. These findings are potentially relevant because 1-methyl, 4-phenyl-1,2,3,6-tetrahydro-pyridine also induces similar neuronal damage in humans [59].

8. Protective effects

1. Oral supplementation was administered twice daily to 24 human volunteers throughout a six-month prospective, randomized trial [60]. There was a gradual but steady decrease in an index of oxidative damage as measured by levels of the lipid peroxidation product, malondialdehyde in plasma (Fig. 1) and urine. There was a concomitant increase in immune competency as measured by the lymphocyte transformation assay in

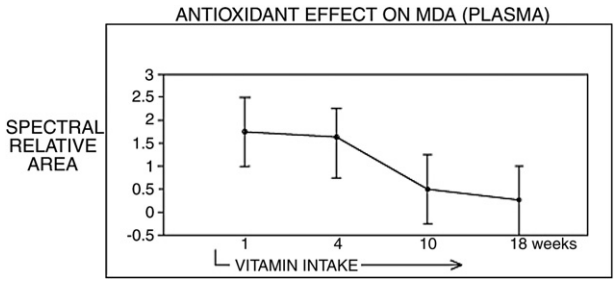

Fig. 1. Plasma level of malondialdehyde, a measure of oxidative damage, in human subjects while consuming antioxidant micronutrient formulation.

Table 2
Antioxidant effect on oxidative damage (Urinary 8-hydroxyguanosine)

Study cohort	Placebo		Antioxidants	
Supplementation status	Before	After	Before	After
Subject number	n = 12	n = 12	n = 17	n = 14
		(% of total subjects)		
Low baseline value	42	25	30	71
High baseline value	58	75*	70	29**

the same population. There were no adverse side effects from the micronutrients.

2. Increased oxidative damage as determined by selected urinary markers of oxidative damage occurred during a 12-week Marine training period [61]. A prospective, randomized, double-blind, placebo-controlled trial demonstrated that the micronutrients consumed twice daily reduced the oxidative damage in some subjects or did not allow it to increase in others (Table 2). While the number of subjects with high baseline levels of oxidative damage increased (58% to 75%; see Table 2)* in the placebo group after intense training, the number of subjects with high baseline levels of oxidative damage significantly decreased (70% to 29%, $P < .05$; see Table 2)** after micronutrient supplementation. Also, plasma levels of antioxidants were significantly increased by supplementation, even under conditions of intense exertion. Again, no adverse side effects were noted.

9. Reversal effects

1. A prospective, randomized, double-blind clinical trial demonstrated significantly improved recovery from nerve VIII dysfunction after concussive blast exposure in Marines supplemented for 12 weeks with adjunctive micronutrients compared to those who received standard treatment alone [62]. Thirty-four patients returning from Iraq with concussive head injury were randomized 3-20 weeks after the insult to either standard care (physical therapy, steroids, vestibular rehabilitation, supportive care) or identical therapy combined with twice daily antioxidant supplementation. At the onset, both groups were similar in the following parameters: Sensory Organization Test by computerized dynamic posturography, Dynamic Gait Index, Activities Balance Confidence Scale, Dizziness Handicap Index, Vestibular Disorders Activities of Daily Life score, and Balance Scoring System test. By 4 weeks, the Sensory Organization Test was 78 for the antioxidant group versus 63 for the control group, a statistically significant difference ($P < .05$). By eight weeks, the improvement noted in the antioxidant group showed a superior trend in all the other tests. By 12 weeks, the therapists who graded these outcomes but were blinded as to which group was receiving the micronutrients, subjectively noted that one group (the antioxidant group) was clearly functioning better. There were no adverse effects from consuming the antioxidants.
2. An initial prospective pilot patient experience was undertaken in thirteen patients with tinnitus [63]. In addition to diagnostic audiology to rule out medical conditions, the 25-item β version of the Tinnitus Handicap Inventory (THI) was administered by an audiologist [64]. This standardized, validated instrument with its objective scoring system provides a self-reported yet accurate global representation of the impact of tinnitus on the subject's quality of life [65]. To be included, patients had to experience at least Grade 2 tinnitus. The study formulation was consumed twice daily per clinical protocol for a period of up to 90 days. The THI was re-administered at the end of the evaluation period. Seven of eleven (64%) evaluable patients experienced a clinically significant reduction in their tinnitus grade. Of the seven responders, four improved their grade by two or more levels. Two patients did not receive a pre-therapy THI. However, they reported a substantial subjective improvement in their tinnitus which was confirmed in a post-therapy THI. There were no adverse effects from the study formulation. Two patients have not yet completed the full course of therapy and are too early to evaluate.

10. Conclusion

The micronutrient preparation utilized in these investigations contains a comprehensive blend of components, and provided a reasonable safety profile while demonstrating preliminary evidence of efficacy. The formulation includes (at the proper dose, type and dose-schedule) a spectrum of dietary and endogenous antioxidants and their derivatives plus additional necessary micronutrients and minerals while eliminating the undesirable constituents commonly present in sub-optimal preparations. Because oxidative damage, inflammation, and neuroprotection are critical factors in hearing health, incorporating a scientifically evidence-based biologic therapy may be a rational way to expand practice beyond the current use of device-driven treatments. This novel strategy as an adjunct to the usual technical modalities may be considered by otolaryngologists and audiologists and offers some potential to benefit patients by improving clinical symptoms and possibly enhancing the efficacy of standard therapy.

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