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Tinnitus and Role Of Antioxidants - PART - 1

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TINNITUS AND ROLE OF ANTIOXIDANTS
PART - 1

Risk Factors and Markers of Hearing Loss

In order to develop an effective antioxidant strategy, it is essential to know about agents that can induce hearing disorders and the mechanisms by which they cause damage to hearing-related structures. Dispensing professionals are well aware that there are many agents and conditions that cause hearing disorders, and a comprehensive list of hearing loss risk factors is beyond the scope of this article. Some occupations with high risks for hearing loss include musicians, industrial workers, and military personnel in training and in combat who are exposed to high intensity noise and vibration.

High noise intensities and vibrations, cancer chemotherapeutic agents (eg, cisplatin), and antibiotics (eg, gentamicin) can damage hearing-related structures like cochlear hair cells, sensory hair cells, and vestibular hair cells. Injury to these hair cells can cause hearing loss, tinnitus, and balance problems.

When hair cells become damaged, gluta-mate an excitatory neurotransmitter responsible for converting vibrational sound into electrical signal is produced in excessive amounts. Excessive amounts of gluta-mate are very toxic to neurons. Damage to peripheral auditory and somatosensory systems causes imbalance between excitatory and inhibitory neurotransmitters in the mid-brain auditory cortex and brainstem. This imbalance causes hyperactivity in the auditory cortex leading to the perception of phantom sounds (tinnitus).

Age-related hearing loss (presbycusis) is also an attributed cause of hearing loss in humans, although it is debated whether presbycusis is more closely related to long-term noise exposure or the degeneration of hearing structures due to aging. Meniere's disease (MD) also causes the death of cochlear hair cells and damage to vestibular (motion sensing) hair cells.

Involvement of oxidative stress and chronic inflammation in hearing disorders. Several scientific papers show that increased oxidative stress due to production of excessive amounts of free radicals derived from oxygen and nitrogen, and acute and/or chronic inflammation produced by diverse groups of agents such as high intensity noise, vibration, cisplatin, gentamicin, aging, and Meniere's disease are major factors in the initiation and progression of hearing disorders.

Free radicals are atoms or molecules that have an unpaired electron and are therefore very likely to take part in chemical reactions. While free radicals are a natural product of cellular activity, they can also participate in unwanted side reactions that have been implicated in a vast number of diseases, including cancers, liver damage, Parkinson's disease, Alzheimer's disease, and even the process of aging itself. Our bodies have several strategies for minimizing the effects of free radicals, including the production of enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase.

The data for the involvement of increased oxidative stress in hearing disorders comes from two sources: 1) directly by measuring oxidative stress, and 2) indirectly by use of antioxidants. Exposure to high intensity noise causes a decrease in serum total antioxidant capacity and an increase in nitric oxide in guinea pigs.[1] Increased nitric oxide causes formation of peroxynitrite, which is very damaging to hair cells. Formation of free radicals following exposure to impulse noise has been reported in some animal studies.[2-8]

Exposure to vibration also produces hearing disorders. In animal models (guinea pig), older animals were twofold more sensitive to vibration-induced hearing loss than younger animals.[9]

In studies, certain chemotherapeutic agents, such as cisplatin, and antibiotics, such as aminoglycosides, induced hearing loss by increasing oxidative stress, and this effect was reduced by antioxidants. Reactive oxygen species are involved in cisplatin-induced hearing loss.[10] Carboplatin depresses significantly the levels of antioxidant enzymes, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione transferase, and catalase—all antioxidants that protect cells from toxins such as free radicals. Similarly, carboplatin elevates the levels of products of lipid peroxidation,[11] a process in which free radicals degrade the cell membrane. It also depletes the level of glutathione,[4] another important antioxidant.

The levels of nitric oxide, peroxynitrite, oxidative stress, nuclear factor kappa-beta (NF-kappa), glutamate receptor (N-methyl-D-aspartate), and calcium are elevated in patients with tinnitus.[12,13] About 21% to 42% of tinnitus cases are induced by exposure to noise.[14] About 34% of tinnitus patients have post traumatic stress disorder (PTSD), suggesting there may be some linkage of neuronal mechanisms that cause both tinnitus and PTSD.[15] Evidence for increased oxidative stress and chronic inflammation has also been found in patients with PTSD.

The role of oxidative stress in Meniere's disease is supported by the fact that free radical scavengers (ie, rebamipide, vitamin C, and glutathione), when administered orally for 8 weeks to 25 patients with poorly controlled MD, improved tinnitus, hearing loss, and disability.[16]

Age-related cochlear structural alterations and degeneration of sensory and neural cells also occur.[17] Increased oxidative stress and chronic inflammation are likewise associated with aging.

Evidence for Beneficial Effects of Antioxidants in Hearing Disorders

Antioxidants are known to reduce oxidative stress and inflammation; therefore, supplementation with antioxidants appears to be one of the most rational approaches to prevent and improve hearing disorders in combination with standard therapy. Several animal and some human studies show that supplementation with antioxidants produces beneficial effects and improves hearing disorders, including:

- In a prospective, double-blind study, supplementation of vitamin E alone provided better recovery than the standard therapy in patients with idiopathic sudden hearing loss.[18]
- In a prospective double-blind study, vitamin E alone administered orally improved the efficacy of standard therapy[19]
- In a prospective randomized study, intravenous administration of magnesium sulfate improved hearing recovery in patients with idiopathic sudden sensorineural hearing loss.[20]
- Coenzyme Q10 (ubiquinol) delayed the progression of hearing loss in patients with a genetic defect (7445A→G mitochondrial mutation).[21]
- The use of glutamate antagonists, steroids, and antioxidants may also be useful in the management of hearing loss and tinnitus.[22]

Several studies have also looked at the use of antioxidants in the prevention of noise-induced hearing loss, including:

- Vitamin E, when administered intraperitoneally 3 days before and 3 days after noise exposure, reduced noise-induced cochlear damage and hearing loss in guinea pigs.[18,19] It also protected against noise-induced damage to the inner ear in cyrinid fish.[23]
- Alpha-lipoic acid protects against noise-induced hearing loss in guinea pigs.[1]
- An intraperitoneal injection of n-acetylcysteine (NAC) significantly reduced hair cell loss in cochlear cells of rats.[24] NAC attenuated noise-induced hearing disorders in guinea pigs.[25] Acetyl-L-carnitine and NAC administered twice a day for 2 days and 1 hour before and 1 hour after noise exposure for an additional 2 days provided protection against hearing loss.[26]
- Coenzyme Q10 helped in recovery from hypoxia-induced sudden deafness by protecting damage to auditory hair cells as well as preventing respiratory metabolic impairment of hair cells.[27] Idebenone, a synthetic analog of coenzyme Q10 with antioxidant properties, protected guinea pigs against noise-induced hearing loss.[28]
- Vitamin C protected against noise-induced hearing loss in albino guinea pigs.[29]

A number of studies have examined the role of these same antioxidants in reducing the effects of ototoxins related to chemotherapy and antibiotics, including:

- Vitamin E protected against cisplatin-induced damage to cochlear hair cells in rats.[30] Trolox, a water soluble analog of vitamin E, when applied locally reduced cisplatin-induced ototoxicity in guinea pigs.[31] Vitamin E reduced gentamicin-induced hearing loss and vestibular dysfunction.[32]Cisplatin-induced cochlear damage is reduced by vitamin E.[33]
- An in vitro study suggested that NAC protected against cisplatin-induced damage to inner ear auditory sensory cells.[34] NAC protected against amino-glycoside-induced ototoxicity in hemodialysis patients.[35]
- Antioxidants attenuate aminoglycoside-induced hearing loss and vestibular dysfunction in an animal model (chinchilla).[36]
- Alpha-lipoic acid protected against carboplatin-induced toxicity in hair cells.[37] Finally, several studies have looked at increased oxidative stress due to aging, MD, and tinnitus, including:

  o In mice and dogs, a diet rich in antioxidants reduced age-related cochlear degeneration.[17]

  o An antioxidant mixture containing reduced glutathione, alpha-lipoic acid, cysteine, and other antioxidants improved the symptoms of MD.[38]

  o An oral supplementation with antioxidants (vitamin E, vitamin C beta-carotene, and phospholipids) reduced the subjective discomfort and tinnitus intensity in patients with idiopathic tinnitus.[39]

In addition to increased oxidative stress, inflammation also appears to be a contributing factor in hearing loss. This was demonstrated in a randomized double-blind placebo control study in which aspirin reduced the risk of gentamicin-induced hearing loss.[40]

Noise can damage cochlear function through inflammation in animal models. This is supported by the fact that the levels of intracellular adhesion molecules and migration of leukocytes increased after exposure to noise.[41]Anti-inflammatory drugs reduced inflammation and improved hearing loss.[42]It has been proposed that repeated inflammatory reactions can produce sac dysfunction and eventual production of MD.[43]

Although physical ear protection can reduce the impact of noise and vibration somewhat, the energy generated from high levels of noise intensity and vibration can penetrate the inner ear in spite of earplugs and earmuffs, causing damage to hair cells. Further, physical protection of the ear plays no role in chemical-induced hearing loss or hearing loss that is truly related to the aging auditory system. Therefore, the authors suggest that physical protection should be supplemented with biological protection using appropriate doses and type of antioxidants and their derivatives via a dose-schedule.

(Continued in next issue)

Dr. Sanjay Agrawal,
Leading Pharmaceutical Consultant
and Editor-in Chief of IJM Today
Post Graduation Diploma in
Naturopathy and Yoga,
6/146, Malviya Nagar,
Jaipur -302017 ,
Rajasthan