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Glutamate Antagonists, Steroids, and Antioxidants as Therapeutic Options for Hearing Loss and Tinnitus and the Use of an Inner Ear Drug Delivery System

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Abstract: A wealth of anecdotal, empirical, and double-blind, placebo-controlled data exists on medicines that may have a beneficial role in the management of patients with tinnitus. Tinnitus is a symptom that affects between 40 and 45 million Americans alone; this represents approximately 14% of the US population. Data exist for Japan (population: 125,732,794), Europe (population: 503 million), and Australia (population: 18,426,900), and estimates suggest that tinnitus affects a similar percentage of those populations (B. Tabachnick, personal communication, 1998). Thus, in those industrialized nations, approximately 90 million may experience tinnitus to some degree. One to two percent of the population experiences debilitating tinnitus, severely limiting the quality of life of affected individuals. All too often, the response from well-trained medical professionals is, "Learn to live with it" or "There is no cure." Although the author does not dispute that currently no cure exists, I contend that help is available. This article discusses the use of glutamate antagonists, steroids, and antioxidants for the management of hearing loss and tinnitus. Additionally, the results of using an inner ear drug delivery system on nine patients with a variety of inner ear disorders are reviewed briefly.

More than 70 medicinal options are used to treat tinnitus, ranging from such alternative therapies as *Gingko biloba*, niacin, and melatonin to more conventional therapies such as lidocaine, carbamazepine, and alprazolam (Xanax; Table 1). Some of these medications have survived stringent double-blind, placebo-controlled studies, whereas others have been used anecdotally. A detailed review by Shulman [1] carefully evaluated neuroprotective therapies for the control of tinnitus.

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GLUTAMATE ANTAGONISM

Glutamate and related excitatory amino acids, such as aspartate, are postulated to be among the most important afferent neurotransmitters in the cochlea and also account for most of the excitatory synaptic activity in the mammalian central nervous system. Excitatory amino acids have been shown to be used by an estimated 40% of all synapses [2].

Glutamatergic transmission is associated with the well-established phenomenon of excitotoxicity (Fig. 1) [3]. Excessive stimulation of glutamate receptors can lead to neuronal injury and death, by either direct or indirect activation of receptors on the postsynaptic neuron, leading to an opening of gated channels that allows for an influx of sodium, potassium, and calcium. This alters ionic and water homeostasis and results in dendritic and cellular edema, activation of arachidonic acid, diacyl glycerol, and many other internal control mechanisms, ultimately leading to the generation of re-

Table 1. Medications That May Be Useful for Tinnitus

Anesthetics	Lidocaine-lignocaine (Xylocaine IV)*
	Procaine (Novocain IV)
	Tocainide (Tonocard): oral lidocaine analog*
	Flecainide acetate (Tambocor)*
	Mexiletine: oral lidocaine analog*
Antidepressants	Trimipramine (Surmontil)*
	Nortriptyline (Pamelor)*
	Paroxetine (Paxil): nontricyclic*
	Fluoxetine (Prozac)
	Sertraline (Zoloft)
	Bupropion (Wellbutrin)
	Anitriptyline (Elavil)
	Protriptyline (Vivactil)*
Anticonvulsants	Carbamezepine (Tegretol)*
	Phenytoin (Dilantin)*
	Primidone (Mysoline)*
	Aminooxyacetic acid (AOAA)*
Antianxiety agents (benzodiazepines, tranquilizers, barbiturates)	Alprazolam (Xanax)*
	Clonazepam (Klonopin)*
	Diazepam (Valium)*
	Oxazepam (Serax)*
	Flurazepam (Dalmane)*
	Amylobarbitone (barbiturate)*
Antihistamines	Terfenadine (Seldane)*
	Chlorpheniramine (Chlor-Trimeton)*
	Dexchlorpheniramine*
	Meclizine*
Diuretics	Furosemide (Lasix)*
	Chlorothiazide*
	Diamox
Calcium channel blockers	Flunarizine (Sibelium)*
	Nifedipine*
	Nimodipine*
Vasoactive medications	Niacin*
	Histamine*
	Betahistine hydrochloride (Serc)*
	Ginkgo biloba (plant extract)*
	Hydergine
	Vinpocetine*
	Vincamine: extract of periwinkle
	Pentoxifylline (Trental)*
Others prostaglandin*	Misoprostol (Cytotec): synthetic
	Glutamic acid diethylester*
	Caroverine*
	Amylobarbitone*
	Aniracetam*
	Nicotinamide: niacin/nicotinic acid*
	Oxypentifylline/pentoxifylline (Trental)*
	Vitamin A*
	Eperisone hydrochloride: muscle relaxant
	Arlidin*
	Clonidine (Catapres-TTS) = antihypertensive
	Stugeron, Stugeron Forte
	Dimethyl sulfoxide
	Zinc
	Scheussler's cell salts
	Manganese
	Magnesium
	Vitamin B_{12}
	Adenosine*
	Adenosine triphosphate*
	Body Language Vitamin Co. Antiage Formula*
	Canabinoids
	Lifurizine
	Calpain inhibitors

* Studies have been done. Those compounds without an asterisk have anecdotal support.
Note: This list is not all-inclusive.

active oxygen metabolites (ROMs), lipid peroxidation and, finally, cell death [4, 5].

The toxic effects of glutamate and other agonists are well documented [6–9]; however, only one study has demonstrated a release of glutamate into the extracellular fluid in response to loud noise [10]. The excitotoxic effects of glutamate in response to noise could, in part, be the result of increased release or inadequate removal of glutamate, primarily due to breakdown of recycling mechanisms. Eventually, this condition may result in toxic cellular events leading to neuronal degeneration and cochlear damage, perhaps resulting in tinnitus. The challenge of testing glutamate excitotoxicity contributions to noise-induced hearing loss and tinnitus is complicated by evidence that several types of glutamate receptors exist [11]. The ionotropic receptors mediating the depolarizing action of glutamate have been named after their most potent agonists and can be distinguished by their pharmacological and electrophysiological properties [12, 13]. Generally, at least three receptor types are accepted: those selectively activated by *N*-methyl-D-aspartate (NMDA), quisqualate, and kainate, respectively. The latter two are termed *non-NMDA receptors.* Excitotoxicity appears to depend mainly on NMDA and kainate receptor activation. No toxic effect of quisqualate has been observed [12]. Furthermore, electrophysiological data suggest the presence of ionotropic receptors of both NMDA and non-NMDA subtypes in the cochlea [7, 13–16].

Experimental work has demonstrated that monosodium L-glutamate administered to neonatal rats is toxic to the auditory system, producing a high-frequency hearing loss [6]. The primary peripheral target appears to be the spiral ganglion. Cochlear hair cells, which are presynaptic to afferent fibers of the spiral ganglion, are spared [12, 17]. The selectivity of this toxicity is similar to glutamate excitotoxicity, which specifically affects neurons postsynaptic to glutamatergic terminals. This effect is influenced further by the fact that the mechanism for removing or recycling glutamate is not efficient enough when the neurotransmitter is released in excess, particularly after neuronal damage, such as that caused by ischemia, anoxia, or acoustic trauma.

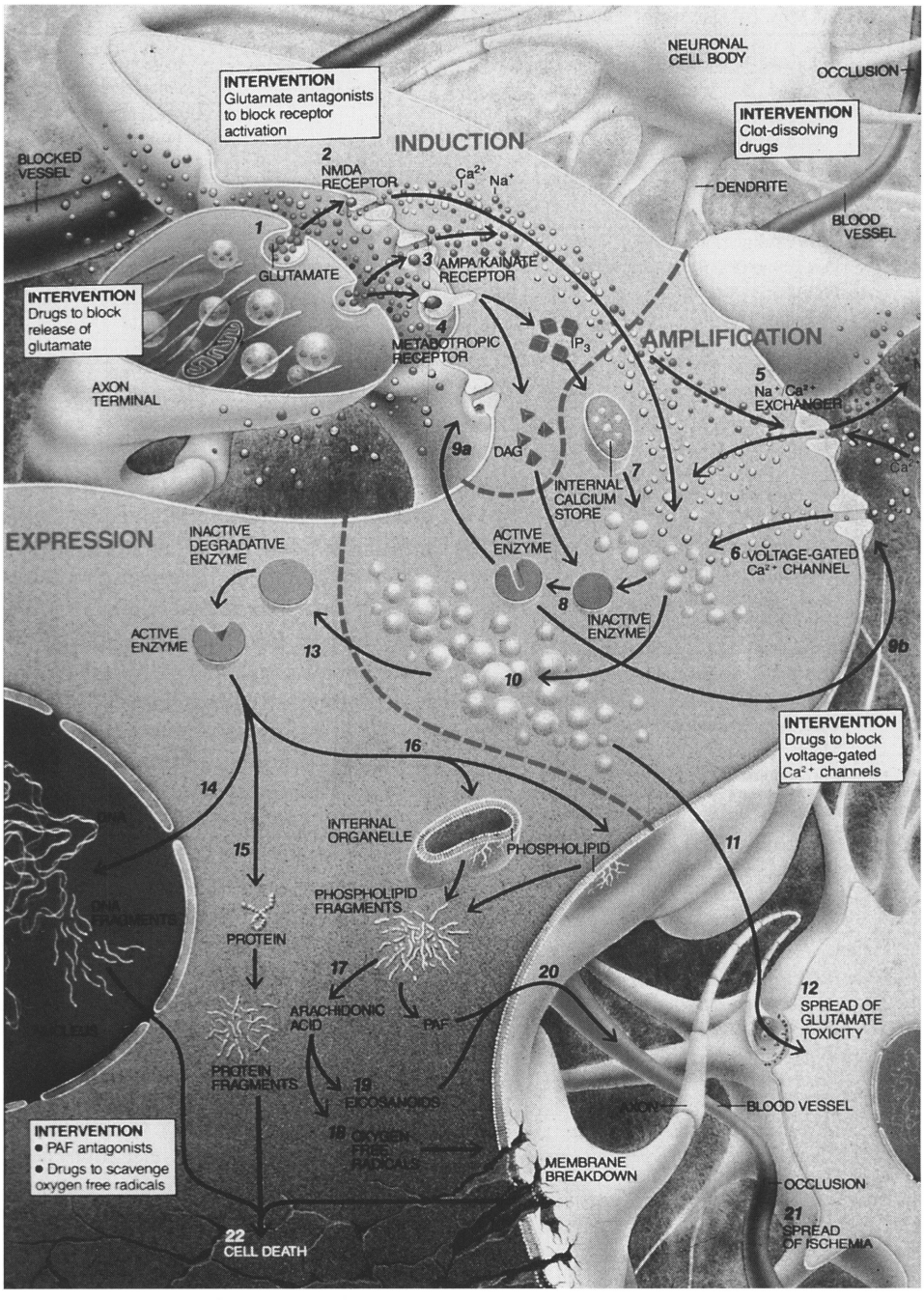

Figure 1. This figure represents a glutamatergic synapse and demonstrates the biochemical activity in response to excitotoxicity.

Earlier work in our laboratory studied the effects of glutamate and noise trauma using a broad-spectrum glutamate receptor antagonist, kynurenic acid (KYNA). KYNA is a tryptophan metabolite and has selective activity against NMDA, kainate, and quisqualate receptors, respectively, in the central nervous system [13, 18, 19]. Guinea pigs were assigned randomly to three separate groups. Baseline compound action potentials (CAP) and cochlear microphonic thresholds were recorded. Group 1 received a vehicle control (1.5 M NaCl) applied to the round-window membrane, followed by 110 dB SPL wide-band noise for 90 minutes. Group 2 received 5 mM KYNA followed by the same noise exposure, and group 3 received 5 mM KYNA alone, without noise. Postdrug and postnoise CAP and cochlear microphonic thresholds then were obtained. Results demonstrated that noise ex-

posure caused a moderate temporary threshold shift (TTS) of 30–40 dB across the frequencies tested (3, 6, 9, 12, and 18 kHz), with a maximum TTS of 40 dB at 9 kHz. Animals that received 5 mM KYNA prior to noise exposure showed significant protection against noise-induced damage, demonstrating minimal TTS ranging between 5.4 and 8.4 dB at 3, 6, 9, 12, and 18 kHz ($p <$ .001). Animals that received KYNA without receiving noise did not experience changes in thresholds. Additionally, cochlear microphonics showed no considerable difference in threshold shifts if controls were compared to KYNA-treated animals. These results suggest that antagonizing non-NMDA glutamate receptors attenuates noise-induced TTS. The data further support that glutamate excitotoxicity may play a direct role in the generation of acoustic trauma and an indirect role in the production of tinnitus (in press, Eur. Arch. of Otology).

Contrary results from another study in our laboratory demonstrated that 2,3-aminophosphonavaleric acid, a specific NMDA antagonist, potentiated noise-induced hearing loss. One possible explanation for these divergent results is that by blocking a specific NMDA channel, glutamate may have overstimulated other NMDA and non-NMDA channels, leading to additional acoustic trauma (unpublished data). Clinicians in Austria have treated patients with Caroverine, a specific glutamate antagonist, and have observed significant improvement in the patients' tinnitus [20]. Caroverine is not approved for use in the United States; however, magnesium sulfate (which is available in the United States) is approved for human use, is a potent glutamate antagonist, and is the medication used in one patient with severe tinnitus, reported briefly at the end of this study. Further studies are warranted.

CORTICOSTEROIDS

Commonly, corticosteroids are used in the management of a variety of inner ear disorders. The activity of steroids varies widely but primarily affects carbohydrate, lipid, and protein metabolism by interacting with specific protein receptors in target tissues to regulate the expression of regulatory genes.

Some reports have suggested that steroids may be harmful to the inner ear [21, 22]; consequently, our laboratory initiated a study to investigate the effects of transtympanic steroids on cochlear blood flow, auditory sensitivity, and histology. Results demonstrated a significant increase in cochlear blood flow within 30 seconds of steroid application to a mean of 29%. This increase in blood flow persisted and did not return to baseline for at least 1 hour after drug delivery. No histological changes were observed between the control side and the treated side [23].

Typically, steroids for inner ear disorders have been administered via the systemic route. However, the blood-labyrinthine barrier [24, 25] raises a valid concern of achieving adequate inner ear drug levels. Recent studies have demonstrated significant variation of inner ear levels of several steroid preparations using oral, intravenous, and transtympanic routes. The results demonstrated significantly higher perilymphatic drug levels using the transtympanic route as compared to other methodology [26]. Steroids represent a scientifically proven therapeutic option for many inner ear disorders and their use, although controversial, is not likely to cause additional harm.

ANTIOXIDANTS

Antioxidants are a class of medications whose primary action is to reduce the deleterious effects of oxygen on biomolecules. Many antioxidant mechanisms exist but primarily include the scavenging or blocking of ROMs. ROMs are species that contain an unpaired number of electrons, rendering them chemically reactive and extremely toxic to subcellular and cellular structures. ROMs have been speculated to be involved in more than 100 clinical conditions [27]. They are produced in vivo during mitochondrial respiration and via autooxidation of chemical and biological molecules. ROMs also are environmental contaminants and can be formed from ionizing and ultraviolet radiation. Typically, the effects of these molecules and their activation is deleterious to the cell and tissue involved. Some of these molecules have the ability to upregulate adhesion receptors, to increase vascular permeability, to damage DNA and tissues, to impair endothelial function [28, 29], and possibly to contribute to hearing loss and, ultimately, tinnitus.

Many intrinsic enzyme systems protect cells from oxidative damage. They include superoxide dismutase (SOD) [30], glutathione peroxidase [31], glutathione transferases [32], and catalase. Additionally, a variety of small molecules in the human diet are required for antioxidant mechanisms. Vitamin E (tocopherol), an excellent example, functions to trap radicals in lipid membranes and has been used clinically in a variety of oxidative stress–induced diseases [33]. Vitamin C is another important water-soluble antioxidant vitamin.

Experimentally and clinically, ROM generation occurs through ischemia-reperfusion or prolonged hypoperfusion, such as is seen in myocardial infarction, cerebrovascular accidents, and possibly sudden sensorineural hearing loss. An increasing body of evidence implicates ROMs in the damage associated with cochlear ischemia, noise trauma, and ototoxicity. Specifically, localized inner ear ischemia and hypoxia induced via

selectively clamping the anteroinferior cerebellar artery normally abolishes the CAP within seconds, and the effect becomes permanent after 8 minutes of ischemia. When subjects were pretreated with allopurinol or SOD–polyethylene glycol followed by ischemia, CAP thresholds were maintained [34]. Additionally, these experiments were extended to study noise-induced hearing loss, which has been shown to cause vascular perturbations. In the groups pretreated with scavengers and blockers of ROMs, less of a threshold shift occurred as compared to controls ($p < .05$) [35]. Recent investigations have supported the view, for example, that aminoglycosides damage the cochlea by ROM formation when they combine with iron as an aminoglycoside-iron complex. Thus, iron-chelating agents have been useful in attenuating this damage [36]. This group has also demonstrated the possible relationship of dietary factors and ototoxicity. Specifically, a ROM scavenger (glutathione) was shown to attenuate gentamicin-induced hearing loss in guinea pigs after maintenance on a low-protein diet as opposed to a regular diet [37]. The same researchers have reported evidence of gentamicin conversion to a cytotoxin, with implications for the participation of sulfhydryl-sensitive groups or ROMs in this conversion [38].

Other investigators have found similar mechanisms underlying ototoxicity secondary to other compounds. For example, Gabaizadeh et al. [39] have shown ROM scavengers affording protection from cisplatin. Direct ROM-induced cochlear injury after cisplatin administration has been demonstrated in guinea pigs [40]. This group also has demonstrated protection from trimethyltinchloride-induced ototoxicity with SOD [41].

Many alternative therapeutic options are available, including grape seed extract from red wine and pine bark extract, both of which are excellent antioxidants. Additionally a group of nutritional supplements known as *mitochondrial metabolites* enhances mitochondrial function and energy output. One such compound is a supplement (patent pending) containing acetyl-L-carnitine, α-lipoic acid, glutathione, and coenzyme Q10. The purpose of a recent study was to describe the effects of two mitochondrial metabolites—α-lipoic acid and acetyl-L-carnitine—on the preservation of age-related hearing loss.

Twenty-one 2-year-old Fisher rats were divided into three groups: control, acetyl-L-carnitine, and α-lipoic acid. All subjects were supplemented with a placebo or one of the two nutritional compounds for 6 weeks. Auditory brainstem response testing was used to obtain baseline during and after treatment auditory thresholds. Cochlear, brain, and skeletal muscle tissue was harvested to assess for MtDNA changes. Results showed an age-associated threshold deterioration of 3–7 dB in the control group over the 6-week study. Both subjects treated with acetyl-L-carnitine and those treated with α-lipoic acid experienced a statistically significant overall improvement in auditory thresholds during the same period. These findings support the notion that a decrease in mitochondrial function with age can be slowed by treatment with mitochondrial metabolites [42]. Potentially, this outcome may offer some help to patients with sensorineural hearing loss and, possibly, tinnitus; however, additional studies clearly are required.

CLINICAL APPLICATION

Use of the information from basic scientific studies permits the application to clinical medicine. Over the last 11 months, we have treated nine patients using a round-window microcatheter device (IntraEAR, Denver, CO) to deliver medications to the inner ear. As the primary problem, the patients had classic Menière's disease (n = 5), cochlear variant Menière's disease (n = 1), labyrinthitis (n = 1), sudden sensorineural hearing loss (n = 1), or tinnitus (n = 1). The medications used were gentamicin (10 mg/ml infused at a rate of 2–4 μl/hr for vertigo control in the Menière's patients); methylprednisolone (6.25–62.5 mg/ml at rates of 10–40 μl/hr for sudden sensorineural hearing loss and the cochlear variant Menière's disease); papaverine (3 mg/ml, combined with the methylprednisolone in the patient with mild labyrinthitis); or magnesium sulfate (50–100 mg/ml, used as a glutamate antagonist in the patient in whom tinnitus is the primary complaint). The patients' symptoms and results are listed in Table 2.

Many treatments are available for the management of tinnitus. Many of these management alternatives are directed at improving the symptomatology and helping

Table 2. Symptoms and Results in 9 Patients Treated by Inner Ear Drug Delivery via a Round-Window Microcatheter Device

Symptoms	Results
Vertigo (6/9)	Vertigo improved[a] (6/6)
Fullness (8/9)	Aural fullness improved (6/8)
Hearing loss (9/9)	Hearing loss improved[b] (5/9)
Tinnitus (5/9)	Tinnitus improved[c] (5/9)

[a]Data at this time are preliminary and do not meet the American Academy of Otolaryngology and Head and Neck Surgery reporting criteria of 2 years' follow-up. However, the vertigo is gone or significantly improved in all six patients. Each patient had preoperative vertiginous attacks lasting 1–6 hours. One patient has spells lasting less than 30 seconds, whereas the remainder are free of vertigo but have experienced mild, occasional imbalance (<30–60 sec). All would recommend this treatment to their friends and family.

[b]Hearing improvement was 20 dB at one or more frequencies in 3 of 5 patients or 10 dB at two or more frequencies in 2 patients. Discrimination score improved by 7–40% in all 5 patients.

[c]Tinnitus was graded on a scale of 1–10, with 10 being incapacitating. Patients' symptoms were considered improved if their tinnitus was perceived to be better by 3 or more points.

patients to cope with their problem. It is imperative that we, as physicians, maintain our patients' interest and health as our primary focus and adhere to our Hippocratic Oath to "do no harm." Having said this, our offering hope, education, care, and treatment is vitally important. Without the willingness to breach new frontiers, we never will advance. Also important is to realize that in the management and care of patients with chronic disorders having more than one etiology, one treatment is not likely to work for everyone. Thus, we physicians must have the willingness to keep an open mind, to be dedicated to scientific study, to keep our patients interest as our primary focus, and to offer realistic help. Additionally, further studies, including those that are double-blinded, placebo-controlled, institutional review board–approved, must be performed, but this requires time, perseverance, and funding.

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