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Neuroprotective Drug Therapy: A Medical and Pharmacological Treatment for Tinnitus Control

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Abstract: The role of neuroprotective agents for maintaining or improving inner ear function, specifically for the symptom of tinnitus, is presented on the basis of neurootological, neurological, and neurosurgical clinical experiences. These clinical experiences involved the use of calcium channel blockers, free radical scavengers, corticosteroids, antagonists of glutamate at *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors, and various thrombolytic agents for the etiologies of ischemia, trauma, and hemorrhage. A pharmacological basis for such drug efficacy includes a property described as *neuroprotection*. A pathology-based protocol for drug selection is proposed for tinnitus control.

The goal of this article is to introduce to the neurootologist or otologist and other professionals attempting tinnitus control neuroprotective drug therapies that are being applied to such central nervous system pathological processes as ischemia, trauma, hemorrhage, and neurodegeneration. The innovative application of such drug therapies for treating the symptom of tinnitus of the severe disabling type is considered. The use of neuroprotective drugs in intratympanic drug therapy via the round window, for treatment of inner ear complaints of hearing loss, tinnitus, and vertigo, is discussed.

Keywords: affect; cochlea-type tinnitus; final common pathway for tinnitus; neuroprotection; NMDA and non-NMDA receptors; perfusion; sensory

The neuroprotective drugs discussed in this article are considered to be a reflection of a development of a neuropharmacology for tinnitus. Neuroprotective drug therapy reflects new images of tinnitus in terms of its neurochemistry.

Tinnitus is defined as a disorder of auditory perception due to an altered state of excitation and inhibition in neuronal networks that results in a dysynchrony of neuronal signaling. The underlying mechanism is considered to be that of dysynchrony that is, a lack of synchrony or interference in timing of the discharge rate and phase locking of the auditory signal that is located peripherally or centrally or both [13]. The efficacy of recommendations for treatment of subjective idiopathic tinnitus is reflected in the accuracy of the tinnitus diagnosis [4].

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Our efforts for tinnitus diagnosis and treatment have been ongoing since 1977. A Medical Audiological Tinnitus Patient Protocol (MATPP) has been applied to more than 4,500 patients with tinnitus, particularly of the severe disabling type, at the Tinnitus Clinic of the Health Science Center at Brooklyn, State University of New York (HSCB-SUNY).

Various elements of the clinical investigation are considered to be significant for tinnitus diagnosis and for efficacy of its treatment and control:

1. Several clinical types of tinnitus can be identified. Tinnitus is a symptom of neurootological disease, but it is not a unitary symptom.
2. The symptom of tinnitus includes sensory, affective, and psychomotor components.
3. The masking characteristic of each tinnitus patient is individual.
4. Single-photon emission computed tomography (SPECT) imaging of the brain has identified, for the first time, in vivo differences in blood flow in sev-

eral regions of brain in patients with a predominantly central-type tinnitus [5–9].

5. A final common pathway is hypothesized to exist in the medial temporal lobe system for tinnitus, the basic process of which is the establishment of a paradoxical auditory memory for an aberrant dysynchronous auditory signal [10].
6. Stress is a significant factor influencing the clinical course of tinnitus. The establishment of a paradoxical auditory memory of an aberrant dysynchronous auditory signal results in tinnitus of the severe disabling type, with associated complaints of mood (e.g., depression) and emotion (e.g., fear). Abnormal cortisol levels due to dysregulation in the hippocampus provide the neurochemical basis for the stress effect (i.e., stress model for tinnitus) [10].

The goal of therapy for any bodily complaint is to provide relief and a cure. Numerous treatment recommendations for tinnitus have been reported, with varying degrees of success, particularly in the subjective and severe disabling type of tinnitus. The term *tinnitus control* that is, relief reflects the realization that the goal of recommendations for the tinnitus patient does not include a cure at this time.

Increased efficacy of tinnitus control has consistently been achieved by tinnitus patients completing an MATPP that has identified (1) the clinical type of tinnitus; (2) factors known to influence a clinical course of tinnitus, which, when treated, have resulted in an increased incidence of tinnitus control; and (3) recommendations for treatment based on differentiation among the sensory, affective, and psychomotor components of the symptom of tinnitus [1,4,10,11].

Neuroprotective agents have been investigated for various injuries to the central nervous system (CNS). Such injuries traditionally have included ischemic stroke, aneurysmal rupture, and traumatic brain and spinal cord injury [12]. Our clinical experience with such etiologies that affect the cochleovestibular system supports the application of neuroprotective drug therapy in the clinical practice of neurootology, specifically for the symptom of tinnitus.

Intratympanic drug therapy for inner ear complaints, specifically tinnitus, was first reported in 1982 by Sakata et al. [13]. Originally, Meniere's disease patients were treated with this technique for control of vertigo. Associated complaints of hearing loss, ear blockage, and tinnitus were reported with significant improvement. The application of this technique using dexamethasone specifically for tinnitus has been reported [13]. It is hypothesized that the efficacy of dexamethasone for tinnitus control may reflect its neuroprotective action.

In this article, the innovative application of existing and future neuroprotective drug therapies for achieving tinnitus control and patient selection for intratympanic drug therapy for inner ear complaints are discussed. Also, a clinical rationale for drug selection for tinnitus control, based on SPECT imaging of brain findings considered to reflect a final common pathway for tinnitus, is proposed.

NEUROPROTECTIVE AGENTS AND DIAGNOSTIC ENTITIES

General Information

Neuroprotection refers to processes that protect neuronal function from injury or that improve such function after injury. It is hypothesized that common etiological agents that cause injury to the CNS have similar effects on the inner ear. The chief etiologies to be considered include ischemia, trauma, or hemorrhage, and neurodegenerative disease.

Cellular and neuronal death are reflected in interference in function. For the inner ear, such injury is reflected clinically in complaints of hearing loss, tinnitus, vertigo, and other abnormal auditory and vestibular sensations. Among the clinical neurootological syndromes are Meniere's disease, endolymphatic hydrops, fluctuating hearing loss syndrome, sudden hearing loss syndrome, and sudden tinnitus syndrome. With cellular or neuronal death, alterations occur in blood flow, cellular metabolism, free oxygen radical permeation, toxic extracellular accumulations of excitatory neurotransmitters, vasogenic and cytotoxic edema, and influx of calcium and other ions through altered cell membrane channels.

Pharmacological agents that are considered to be *neuroprotective* have been identified and include calcium channel blockers, free radical scavengers, corticosteroids, antagonists of glutamate at *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors, and various thrombolytic agents. An innovative application of such drug therapy is to provide neuroprotection.

Ischemia, Hemorrhage, and Trauma

Ischemia within the peripheral nervous system or CNS results in cellular and neuronal damage [12]. With ischemic cell damage, calcium ion homeostasis between cytosolic and extracellular calcium is disrupted. Normally, glutamate, an excitatory neurotransmitter, is present in the extracellular space. Ischemia is accompanied by a reduction in the intracellular energy and a depolarization of the neurons, which results in an increase in extracellular glutamate and increased flow and accumulation of intracellular calcium. Increasing cytosolic cal-

cium levels are accompanied by cell death. The proposed mechanism is based on the glutamate neuroexcitotoxicity theory. The toxic buildup of extracellular glutamate results in further neuronal excitotoxic injury [14].

Excitatory amino acids include glutamate, aspartate and their analogs and glutamate have been reported to be neurotoxic in the cochlea in vivo. Excitotoxicity has been implicated in cochlear diseases such as sudden deafness, noise-induced hearing loss, neuropresbycusis, and some forms of peripheral tinnitus [15,16]. Significantly, sufferers of sudden deafness and noise trauma frequently demonstrate a recovery of hearing after a temporary loss. The actions are mediated by the NMDA receptor, a ligand-gated ion channel that increases postsynaptic membrane sodium and calcium conductance. Excess glutamate release from depolarized presynaptic neurons, together with reduced uptake mechanisms of glia and neurons, results in increases in synaptic glutamate concentrations and pathological stimulation of the NMDA receptors.

NMDA receptor antagonists consistently reduced the volume of cerebral infarction in models of focal ischemia [17]. Among such drugs currently being developed is CNS 1102 (Cerestat) from Cambridge Neuroscience Inc., Cambridge, MA. Cerestat is a selective ligand for the NMDA ion channel modulatory site, to which dizocilpine (MK801) and ketamine bind [18]. The cardiovascular and cerebrovascular effects are similar to those of ketamine. CNS 1102 has been found to be neuroprotective in preclinical models of stroke when given 60 minutes after ischemia.

Brain temperature has been found to influence directly the extent of histopathological injury in brain areas secondary to ischemia [19]. The neuroprotective effects of agents such as MKA1 and nicardipine depend on hypothermic brain conditions. Hypothermia increases glutamate-induced hyperexcitability in oxygen free radicalinduced lipoperoxidation, with resultant neurotoxicity. Complex interaction exists between excitatory amino acid (EAA) release and toxicity and cerebral function (e.g., temperature regulation). NMDA antagonists are now being developed for their neuroprotective effects, particularly for postischemic global and focal ischemia attacks. A muscarine cholinergic partial agonist, U80816E, has been shown to reduce brain temperature in gerbils, with accompanying improvement in survival of hippocampal neurons after 10 minutes of global ischemia. Increasing evidence is accumulating that hypothermia may be a therapeutic modality to limit potential neuronal damage, particularly that which occurs secondary to an ischemic process [20]. Hypothermic agents may have a neuroprotective effect.

Drugs that have been used and are recommended in an attempt to provide neuroprotection after acute spontaneous ischemic stroke include NMDA and alpha-amino-3-hydroxy 5 methyl-4-isoxazole proprionate (AMPA) receptor antagonists, antioxidants and corticosteroids, calcitonin gene-related peptide, antiseizure drugs, EAAs, growth factors, adenosine, magnesium, lifarizine, cannabinoids, and lidocaine.

NMDA and AMPA Receptor Antagonists

NMDA and non-NMDA receptors are situated in various types of neurons including cholinergic, adrenergic, and somatostatinergic neurons. All can be damaged by EAA toxicity. Such receptors lose their efficacy for removal of extracellular glutamate and other EAAs in the aging brain. It is speculated that such neurons are susceptible to increased excitotoxic damage and eventual death [21], which reflect two postulated mechanisms of neuronal degeneration. Antagonists of the NMDA subtype of glutamate receptors afford neuroprotection.

NMDA and AMPA receptor antagonists have also been shown to provide neuroprotection in ischemia and neurodegenerative disease [16,22]. Both central and peripheral damage secondary to EAAs have been identified [15,23], though NMDA and AMPA receptor antagonists have been reported in animals to provide a reduction in ischemic damage secondary to EAAs. NMDA antagonists now are in early clinical trials [17,18,24].

Nimodipine, a lipophilic calcium channel blocker, has been shown to have a statistically significant positive effect when patients were treated following ischemic stroke within 18 hours of the onset of symptoms [25]. The significance of these studies, regardless of the differences of opinion and results reported, is that a therapeutic window of time needs to be established in order for the nimodipine to have any efficacy for neuroprotection. It has been identified that for central ischemia, a 48-hour time delay is too long and a 3- to 4-hour maximum window is considered to be advantageous to increase the potential for treatment [26,27].

Nimodipine has an increased microcirculation. This drug has been shown to restore to a more normal pattern the electroencephalogram of geriatric patients [28]. Dosage usually is 30 mg orally three times daily for 36 months. Improvement is reported in orientation, language, attention, information, memory, calculation, registration, and recall. Hypotension with nimodipine appears to be synergistic with the effects of standard hypotensive drugs [29].

The combination of a glutamate antagonist (MK801) and a gamma-aminobutyric acid (GABA) agonist (Muscimol) was found to be more effective than either agent alone in protecting visuospatial learning after unilateral embolic lesioning in rats. GABA blocks voltage-gated intracellular calcium influx associated with glutamate. The combination of an NMDA antagonist and a GABA

agonist, which blocks the entrance of calcium ions into the neuron [30], may be an approach for the future for neuroprotection not only within the CNS but also in the peripheral cochlea.

Thrombolytic agents have been demonstrated to provide some neuroprotection in acute ischemic stroke. A new preparation is ANCROD, a purified fraction of Malayan pit viper venom that dissolves fibrinogen and allows increased local blood flow after infarction. Again, the need for a narrow therapeutic window of 34 hours after onset of ischemic stroke is considered significant [31].

Nimodipine and nicardipine have been reported to incite some reduction in vasospasm in patients with cerebral hemorrhage [32,33]. Nimodipine also has been reported to reduce the number of cerebral infarcts and, possibly, the incidence of rebleeding [34]. Intravenous nicardipine was reported to reduce significantly the incidence of vasospasm and symptomatic vasospasm. However, the overall outcome was not influenced [35]. Both nimodipine and nicardipine are used to improve cerebral perfusion by reducing vasospasm and the toxic influx of calcium into ischemic neurons. In general, this effect is the function of the calcium channel blocking quality of these agents. It is speculated that beneficial cellular effects will be found in those cells that have been subjected to relatively short periods of ischemia within a therapeutic window of 34 hours after onset of CNS ischemia [36]. Nimodipine, 60 mg orally every 4 hours for 21 days, is the dosage presently approved by the US Food and Drug Administration for the indication of subarachnoid hemorrhage.

Nimodipine is believed to influence the levels of circulating corticosteroids under most conditions except extreme stress [37]. It alters the balance between mineralocorticoid and glucocorticoid receptor occupancy that would occur in the absence of the drug. The membrane actions of the adrenal hormones too are altered, with consequent changes in mood and behavior. Nimodipine also alters the reward value of morphine [38] and facilitates the effects of antidepressants. Interactions have been demonstrated between nimodipine and adrenal hormones. Nimodipine can potentiate the hypothermia produced by diazepam but not the motor incoordination produced by benzodiazepines.

Calcium channel antagonists (e.g., nimodipine, nicardipine, and nifedipine) have been reported to have variable results for blood flow in animal studies of spinal cord injury. However, spinal cord blood flow is increased in uninjured animals [39].

Barbiturates and diazepam block glutamate, NMDA, and non-NMDA receptors and may reduce cellular damage in ischemia [40]. There have been no published clinical trials with respect to NMDA antagonists in subarachnoid hemorrhage (SAH) and coronary artery bypass surgery. In the acute spontaneous ischemic stroke state, rapid application of neuroprotective drug therapy is reported to be necessary if neuroprotection is to be achieved. Barbiturates, scopolamine, and diazepam block some of the psychomimetic symptoms associated with some NMDA antagonists. Morphological changes in the CNS may be blocked by the NMDA antagonists if they exert GABA-mimetic activities that are stronger than the NMDA antagonist activity. This is the basis for consideration of combined therapy consisting of an NMDA antagonist and a GABA-mimetic agent for neuroprotection from injury, without drug-induced side effects and neuronal damage [40].

Remacemide, a weak NMDA antagonist, has been used in patients with acute ischemic stroke, to reduce vasospasm significantly due to its action on the NMDA receptors in cerebral microvessels and to exert an anti-Parkinsonian action. Its activity is attributed to a reduction in activity at the EAA receptors of the NMDA type [41,43]. Remacemide hydrochloride has also been shown to exhibit neuroprotective properties relative to the noncompetitive NMDA receptor, as it is an antagonist of this receptor. Originally, this agent was developed as an antiepileptic (Fisons Pharmaceutical, Rochester, N.Y.).

Remacemide and other NMDA antagonists may not only reduce the clinical symptoms in Parkinson's disease but might actually reduce the progression of the disease by reducing cell destruction by glutamate excitotoxicity [44]. Excitatory glutamate projections from the subthalamus to the globus pallidus and substantia nigra may become overactive and result in the clinical picture of such neurodegenerative disease as Parkinson's and Huntington's diseases. This suggests that the glutamate receptor antagonist may reduce the consequence of such overactivity.

The action of levodopa (L-dopa) is potentiated by the NMDA receptor antagonists [45]. L-Dopa is a weak excitotoxin. The combination of a dopa-derived excitotoxin in the extracellular space and an endogenous glutamate can produce degeneration of striatal neurons, as seen in the pattern of Huntingtons disease [43]. The NMDA protective action may be a method for controlling such diseases as Parkinsons and Huntingtons. Use of an NMDA antagonist should therefore be considered in Parkinsons disease patients who suffer from accompanying tinnitus.

Common problems after acute administration of NMDA antagonists include inhibition of learning and memory, induction of phencyclidine-like behavior, motor hyperactivity, increased sensitivity to an auditory stimulus, and ataxia [44,46]. Such effects were not found, however, in patients given large doses of rema-

cemide hydrochloride [42,47,48]. Remacemide is a safe, effective compound for epilepsy control. As a neuroprotective agent, it exhibits efficacy in animals models of global and focal ischemia, subarachnoid hemorrhage, and Parkinsons disease. This efficacy probably is due to the ability to limit activity at EAA receptors, principally of the NMDA type.

The treatment experiences now being reported of NMDA antagonists used in patients after transient global and focal ischemia attacks may have important implications for the neurootologist who is called on to treat ischemia of the inner ear.

Antioxidants and Corticosteroids

Antioxidants and corticosteroids have been reported to result in some neuroprotection in CNS ischemia [12]. Glucocorticoids are a class of neuroprotective agents that have been used for reduction of brain damage due to cerebral ischemia. It is noteworthy, however, that in some cases, a chronic increase in the level of glucocorticoids can actually cause damage, particularly in the hippocampus [49,50].

Dexamethasone was shown to have a neuroprotective effect of prevention of neonatal hypoxic ischemic brain damage [51,52]. Dexamethasone relieves the effects of ischemia by reducing local cerebral blood flow and by producing either a reduction in cerebrovascular resistance or an elevation in perfusion pressure.

Dexamethasone, 0.1 mg/kg, is reported to be neuroprotective in neonatal rats when given 6 hours before global hypoxia [53]. Hall [54] has proposed a hypothesis that high-dose methylprednisolone inhibits oxygen free radicalinduced lipoperoxidation. The Hall hypothesis states that, after ischemia, pathophysiological increase of oxygen free radical formation and cell membrane lipoperoxidation occur early in the injured nervous system [36].

The adrenocortical hormone receptors of the hippocampus have great affinity for corticosterone [37,55].

Antioxidative agents, including U74006F (Upjohn), is considered to reduce vasospasm by reducing lipoperoxidation in primates [56]. Lipoperoxidation has been implicated in the process of vasospasm in SAH and so, antioxidative agents probably are beneficial only in cells subjected to relatively short periods of ischemia.

Methylprednisolone (MPS), 30 mg/kg in a single dose, was recommended to reduce free radical reactions, reduce lipoperoxidation, and increase the activity of Na/K-ATPase, with beneficial effects, in spinal cord contusion [57]. Higher doses of MPS are discouraged because cell membrane concentration at a higher dose causes cellular membrane instability. Allopurinol is an oxygen free radical scavenger and a xanthine oxidase inhibitor and reduces hypoxic ischemic damage [58].

Vitamin E (alpha-tocopherol) has been demonstrated to attenuate the effects of spinal cord ischemia [59].

New antioxidants include the nonglucocorticoid steroid analogs of MPS and the 21amino steroids, lazeroids. These are more effective inhibitors of lipoperoxidation than previous steroid compounds. Significant results have been reported in spinal cord injury [59].

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide is a powerful vasodilator that has been demonstrated to improve cerebral blood flow in focal ischemia [60] and in patients with cerebral vasoconstriction after SAH [61]. Early clinical results in vasospasm after SAH are reported to be encouraging. The instillation of calcitonin gene-related peptide into the subarachnoid space at the time of surgery for cerebral aneurysm has been shown to have a marked protective effect against cerebral ischemia [62,63].

Antiseizure Drugs

Seizures are associated with excessive neuronal discharge and an increased accumulation of extracellular glutamate. EAA concentrations are markedly elevated in conjunction with excessive neuronal discharge associated with seizures. Secondary transient and permanent excitotoxic damage has been reported in status epilepticus [12]. NMDA, non-NMDA, and glutamate antagonists are effective antiepileptic drugs (AEDs).

Most effective AEDs are weak ion channel blockers (i.e., glutamate antagonists), which allow normal brain receptor interaction to take place. Other NMDA receptor associated antagonists include magnesium, ketamine, and kynurnate, all of which improve neurological function.

Three classes of antiepileptogenic agents are identified: (1) drugs that enhance sodium channel inactivation (i.e., phenytoin, carbamazepine, and, possibly, valproic acid); (2) GABA-ergic inhibition (i.e., barbiturates, gabapentin and, possibly, valproic acid); and (3) drugs that block calcium current conductance (i.e., calcium channel blockers). Frequently used antiseizure NMDA antagonists are phenytoin, carbamazepine, valproic acid, and barbiturates.

The results for tinnitus control with anticonvulsants reported by Melding et al. [64] influenced us to use AEDs for similar conditions, with similar results. Our findings led us to consider that a mechanism for a central-type tinnitus was *tinnitogenesis*, an epileptiform auditory seizure phenomenon caused by disinhibition of GABA activity with an increase in the excitotoxic effect of glutamate at NMDA receptors [10]. Nimodipine has been used for attempting tinnitus control since the late 1980s [65]. NMDA antagonists can be considered to be anticonvulsants. GABA-ergic activity also exerts an anticonvulsant effect.

Gabapentin (Neurontin) is related structurally to the neurotransmitter GABA but does not interfere with GABA receptors. The mechanism of its anticonvulsant action is unknown, though it is speculated that it acts as do other marketed anticonvulsants. The drug is available in 100-mg, 300-mg, and 400-mg tablets. Significantly, in vitro studies with radiolabeled gabapentin reveal a gabapentin binding site in areas of rat brain, including neocortex and hippocampus [66]. Neurontin is indicated as adjunctive or sole therapy in the treatment of partial seizures with or without secondary generalization in adults with epilepsy.

Clinical trials do not indicate that routine monitoring of clinical laboratory parameters is necessary to ensure safe use of this agent. Gabapentin is not appreciably metabolized and it does not interfere with the metabolism of commonly coadministered AEDs (i.e., phenytoin carbamazepine, valproic acid, cimetidine). Because gabapentin is eliminated primarily by renal excretion, the dose should be adjusted consistent with blood creatinine and blood urea nitrogen levels.

Effective doses range from 900 to 1,800 mg/day given in divided doses three times daily, using 300- or 400-mg capsules. Doses up to 2400 mg/day have been well tolerated. Doses of 3600 mg/day have been given for short durations and have also been well tolerated. Discontinuation of the drug or administration of alternative anticonvulsants in the regimen should be accomplished gradually over a minimum of 1 week [66].

High concentrations of NMDA receptors are found in limbic structures, particularly the hippocampus [55]. Increase in activation of metabotropic glutamate receptors by extrinsic glutamate agonists leads to limbic seizures [67]. Increase of endogenous extracellular concentrations of glutamate and aspartate result in an increase in limbic discharges, which may extend to similar areas on the opposite side as well as throughout the neocortex. Kindling of seizures is considered to be related to glutamate and aspartate toxic effects. As stated earlier, NMDA antagonists have now been introduced in an innovative application as anticonvulsants. Remacemide is a weak NMDA antagonist that limits activity at EAA receptors and is associated with a low incidence of side effects [41,42].

Glutamate antagonists, a new category of neuroprotective compounds, are now undergoing clinical trials. The majority of effective AEDs are weak ion channel blockers and allow normal brain receptor interaction to take place. To produce neuroprotective efficacy, higher receptor affinity is considered to be necessary to prevent the accumulation of an excess glutamate concentration.

The problem with all these drugs is that of psychomotor and behavioral effects. Side effects include hypotension and sedation. Many of the compounds produce disturbances of higher mental function, reflecting their effect on the limbic system and hippocampus in particular, where the density of NMDA receptors is high [17,67].

Excitatory Amino Acids

The excitotoxic hypothesis states that excessive release of EAAs is an important cause of brain damage, especially in ischemia and chronic neurodegeneration [14]. Animals models have shown that EAA-induced events may be responsible for posttraumatic sequelae and that these effects can be blocked by EAA antagonists. Such substances include dextrorphan, magnesium, ketamine, phencyclidine (PCP), Kynurenate, and indol-2-carboxylic acid.

EAA neurotransmitters (e.g., glutamate and aspartate) function as neurotoxins and are involved in cell injury in ischemic brain by triggering a complex cascade of chemical events. Glutamate antagonists particularly of the NMDA receptor sites attenuate glutamate-induced neuronal damage in vitro and in vivo.

NMDA receptor antagonists are potent anticonvulsants [40] and demonstrate neuroprotection from degeneration secondary to ischemia [25,40], hypoxia [68,69], and hypoglycemia [70].

Dextrorphan hydrochloride has a long history as an antitussive agent. Dextrorphan and dextromethorphan are synthetic, non-opioid, dextrorotary morphinans that act as noncompetitive antagonists (of the NMDA subtype) of the glutamate receptor complex in the CNS. Dextrorphan is a more potent glutamate antagonist of neuronal injury or damage than is dextromethorphan both in vivo and in vitro. The total cumulative doses used in reported series were 4751,280 mg for 12-hour administration and 9452,140 mg for 24-hour administration [71–76].

Dextrorphan hydrochloride is neuroprotective in animal models of ischemic stroke. The neuroprotective effects in vivo are dose-dependent and increase with higher serum concentrations. In vivo experience demonstrates a consistent pharmacological effect and adverse experience profile. The safe loading dose is less than 200 mg/hour, and the maintenance dose is 5090 mg/hour for 24 hours [76].

Indications of NMDA receptor blockade include nystagmus, nausea, agitation, hallucinations, confusion, and somnolence. All patients experienced pharmacological effects that were mild to moderate, short-lived, and reasonably well tolerated. Attention must be paid to the possible development of hypotension, which is related to the rate of loading dose administration, not to plasma concentration. Altered levels of consciousness and respiratory depression have been reported. The highest safe

and tolerable loading dose and maintenance infusion doses were less than 180 mg/hour and 50–90 mg/hour, respectively.

NMDA receptor associated antagonists have been demonstrated to have a role in the treatment of traumatic brain injury. Among these drugs are magnesium and ketamine, which improve cognitive function, and dextromethorphan, magnesium, and Kynurenate, which improve neurological function [77].

A new category of NMDA antagonists that block glutamate release from synaptic vesicles are now being tested in animals [77]. Among these agents are ketamine and PCP. Alterations in such cortical areas as cingulate and retrosplenial areas in rats have been identified.

Glutamate and aspartate antagonists are under investigation [77]. Glutamate antagonists currently in clinical trials for neuroprotection include (1) CGS 19755-Selfotel (CIBA-GEIGY), a competitive glutamate-site NMDA glutamate antagonist; (2) CNS 1102-Cerestat (Cambridge Neuroscience), a noncompetitive NMDA gated ion channel blocker; (3) SL82-Eliprodil (Synthelabo), a polyamine-site NMDA glutamate antagonist; (4) Ro-01-6794/706 (Hoffmann-LaRoche), a dextromethorphan derivative and a noncompetitive NMDA channel blocker; (5) Remacemide (Fisons), a noncompetitive NMDA channel blocker; and (6) CI977-Enadoline (Parke-Davis), a kappa opiate agonist that inhibits glutamate release. Unwanted effects of glutamate antagonists include such psychomotor and behavioral disturbances as agitation, confusion, depression, nystagmus, somnolence, hallucination, vomiting, and seizures. Hemodynamic effects are highlighted by hypotension [12,67].

A family of N,N1-disubstituted guanidines, including CNS 1237, block voltage-activated calcium and sodium channels that govern glutamate release [78]. They block glutamate release with greater efficacy under conditions of persistent or repetitive depolarization, as is found in pathological circumstances. These blockers of sodium and calcium channels that control presynaptic release of glutamate exhibit use dependence in their actions: That is, they sustain depolarization of the postsynaptic membrane, as occurs during ischemia or trauma in brain, which results in a relief of the block of the NMDA receptors ion channel by extracellular magnesium and allows these drugs to block the channel. This action is considered to complement the function of neuroprotection. Blocking of glutamate release in an earlier stage of the process prevents excessive activation of both NMDA and non-NMDA receptor subclasses and, in theory, combines the advantages of blockers of ion channel activity mediated by both NMDA and non-NMDA receptors.

Very high receptor affinity is considered to be necessary if the binding to receptors of supraphysiological concentrations of glutamate is to be prevented. Hence, successful neuroprotection can be possible only with compounds that offer sufficient receptor affinity and sufficient brain concentration to influence such pathological processes.

Growth Factors

Two pathways have been shown to be involved in delayed cell death: selective neuronal loss, which is considered apoptotic and closely coupled with microglia reaction, and delayed necrosis, which occurs independently of such processes. Insulinlike growth factor (IGF-1) is a potent trophic factor for most types of neurons. Tumor growth factor($_1$ (TGF-($_1$) is a regulator of injury response and modulates macrophage and microglial reactions and the expression of other growth factors. Studies have shown that this factor has reduced the extent of neuronal loss. Endogenous IGF-1 and TGF-($_1$ are believed to be involved during recovery from injury and so such growth factors might be considered in the future for neuroprotective therapies [79].

Adenosine

Adenosine is a nucleoside consisting of adenine and the pentose sugar d-ribose. It has been confirmed to have neuroprotective properties in cerebral ischemia. The neuroprotective action of adenosine is presented for consideration of its future application not only for perfusion of the inner ear but also for general attempts at controlling disorders of the cochleovestibular system, particularly the symptom of tinnitus [80–82].

Adenosine has been confirmed to have neuroprotective properties in cerebral ischemia [81,82], seizures [83], and in vitro hypoglycemia [84]. Reduction of brain blood supply results in a rapid depolarization of neuronal membranes. Increased release of EAAs and excitation of postsynaptic glutamate, NMDA, and non-NMDA receptors is followed by an increased influx of calcium and its release from intracellular stores [85]. The resultant increase in intracellular calcium results in events that lead to cell death [14].

Adenosine analogs have been investigated for interruption of several ischemia-associated events, including hypoxic depolarization at membrane, neurotransmitter release, hyperexcitation of NMDA receptors, and calcium influx. Experimental studies of the neuroprotective effects of adenosine and its analogs and agents have been positive [86–90]. Significant neuroprotection has been reported in virtually all studies of focal, global, and forebrain ischemia. Such agents include A1 receptor agonists. The use of antagonists has resulted in increased mortality [88] and increased neuronal destruction [87].

Endogenous adenosine acts at three principle G-pro-

tein-associated receptor subtypes: A1, A2, and A3. The principle function of adenosine in brain is as an inhibitory neuromodulator [91,92]. The inhibitory effects of adenosine are mediated mainly via presynaptic and postsynaptic A1 receptors. Activation of presynaptic A1 sites inhibits neuronal calcium uptake, which results in a reduced release of neurotransmitters (e.g., acetylcholine, norepinephrine, dopamine, serotonin, and glutamate) [93,96].

Adenosine A2 receptors regulate cerebral blood flow [23] and the accumulation of cyclic adenosine monophosphate (cAMP) in brain [87]. Evidence exists that the excitatory A2 receptors are present in the hippocampus [97] and may be involved in the potentiation of calcium-dependent neurotransmitter release and modulation of electrically evoked release of GABA in the globus pallidus [98–100]. This evidence is considered to support the clinical basis for the stress model for tinnitus [10].

The A1 receptor has been identified to be involved in neurodegeneration. The focus for neuroprotection has been these A1 adenosine receptors [86,87]. The activity of A2 receptor agonists is not clear at this time.

Acute neuroprotective treatment with adenosine A1 agonists has two major side effectshypothermia and hypotension [100]. The use of adenosine for neuroprotection is limited by the facts that its therapeutic efficacy is not yet established, endogenous adenosine degradation contributes to the generation of highly destruction free radicals [101], and no information is available regarding the interaction of individual adenosine receptor subtypes [102].

Magnesium

Intracellular calcium overload due to unregulated entry via voltage-gated channels or an NMDA receptor ion channel initiates metabolic events and cell death. Magnesium is a physiological antagonist of calcium that regulates vascular tone and cell membrane function [103]. It acts as a voltage-dependent blocker of the NMDA receptor ion channel and behaves pharmacologically as a noncompetitive NMDA antagonist.

Lifarizine

Lifarizine is a lipophilic basic compound having sodium and calcium channel modulation properties [104]. It exerts neuroprotective and global effects in focal ischemia but exhibits minimal systemic effects. Lifarizine binds to dopamine DA2 receptors.

Cannabinoid

A synthetic cannabinoid Hu-211 is now under investigation for its neuroprotective activity [105]. It has minimal affinity to cannabinoid receptors and no psychotropic effects in animals. This agent has reduced neuroclinical signs, brain edema, and calcium influx in closed head injury. It is considered a promising a neuroprotective agent with a dual mechanism of action NMDA blockage and free radical scavenging that does not involve cannabinoid activity.

Lidocaine

The inhibition of tinnitus by lidocaine is called the *lidocaine effect*. Lidocaine is a short-term anticonvulsant as well as a local anesthetic. Intravenous local anesthetic agents for the treatment of tinnitus have a long and well-documented history. Tinnitus may be increased, decreased, or suppressed after lidocaine administration [64,65,106]. This agents anticonvulsant and analgesic action is the basis for considering that it might have a beneficial effect for tinnitus control.

It is hypothesized that the neural pathways for tinnitus and pain are similar, thereby explaining the similarity of response, among patients with pain and tinnitus, to local anesthetic drugs given intravenously. Lidocaine blocks sodium channels from the inside of the axon (i.e., axoplasma side). It is speculated that the sodium-blocking action of lidocaine reduces the neural hyperactivity that is causing tinnitus. The sodium channel blocking action of lidocaine is the basis for a trial of other anticonvulsants, including carbamazepine, primidone, and phenytoin.

The protocol recommended by Shea and Emmett [106] and now followed by our offices is an initial 100 mg lidocaine given rapidly intravenously as a test dose. Patients who respond favorably to intravenous lidocaine then are started on 200 mg carbamazepine twice daily with an increase in dose as weekly increments of 200 mg to a maximum of 800 mg/day. Lidocaine amide or tocainide is an oral-active amine analog of lidocaine. The dose recommended is 400 mg at bedtime or two, three, or four times daily. Side effects include nausea, skin rash, and gastrointestinal upset [65].

Neurodegenerative Disorders

Drug therapies for neurodegenerative disorders are based on a rationale that a common thread calcium hyperexcitotoxicity exists in the pathogenesis of all types of such degeneration [12]. Extracellular glutamate levels are increased in such pathological conditions as hypoxia, hypoglycemia, seizure, trauma, hemorrhage, neurotoxicity, and Alzheimer's disease. Increased extracellular glutamate has been implicated in cellular damage.

Neurodegenerative illnesses are accompanied by selective loss of certain defined groups of neurons. Among such diseases are Alzheimer's, Parkinson's, Huntington's diseases, amyotrophic lateral sclerosis, and cerebellar degenerations [107]. Possibly, some common underlying mechanisms in such disorders sim-

ilarly may occur within the cochleovestibular system. One of the soft signs may be the symptom of tinnitus.

Excitotoxicity, mitochondrial dysfunction, and free radical induced oxidative damage have been implicated in the pathogenesis of different neurodegenerative diseases. It has been postulated that excitotoxic lesions are produced by specific inhibitors of the mitochondrial transport chain. If this is so, agents that bypass or ameliorate the energy defect should attenuate a lesion [107].

Interference in calcium homeostasis is reported, in the aging brain, to be a key factor related to neuronal damage and subsequent dendritic atrophy and cell death [108]. Intracellular calcium increase in injured or aging neurons is accompanied by deficits in learning and memory [28,109]. Causes of interference in calcium homeostasis include anoxia, ischemia, hypoglycemia, epilepsy, trauma, neurotoxicity, and Alzheimers disease [108,109]. The characteristic plaques and dendritic tangles in Alzheimers disease are hypothesized to be a secondary response to the primary EAA-induced neurodegenerative process. Normal loss of neurons, considered to begin in middle age, is speculated to be a reflection of an age-linked alteration of balance between excitotoxic agonist and antagonist forces exerting their effects on the NMDA and non-NMDA receptors. Similar interference of calcium homeostasis in the cochlea has been reported by Pujol et al. [15,16].

A number of drugs are applied in an attempt to provide neuroprotection in neurodegenerative diseases. Among them are nimodipine, cholinesterase inhibitors, calpain inhibitors, glutamine, nicotinamide, and coenzyme Q10.

Nimodipine

Nimodipine is a calcium channel blocker of the L-type calcium channels on the neuromembrane. It restores intracellular calcium to normal levels. No effect is reported on normal, healthy cells. Also, nimodipine produces an increased microcirculation (see the section, NMDA and AMPA Receptor Antagonists) [28].

Cholinesterase Inhibitors

Colinesterase inhibitors function as neuroprotective agents and increase the available amount of brain acetylcholine. These agents include tacrine, selegiline, and such selective serotoninergic reuptake inhibitors (SSRIs) as fluoxetine hydrochloride (Prozac) and paroxetine hydrochloride (Paxil). The effect of serotonin levels on the efferent auditory system and on the symptom of tinnitus is of clinical interest for tinnitus control [110].

Calpain Inhibitors

Calpain is a normal intracellular cytosolic protease activated by excess intracellular calcium. It is considered to be a future site of action for neuroprotective agents. Ischemic injury damages calcium homeostasis. Excessive calcium enters the cell by NMDA and AMPA receptors, voltage-gated ion channels, or activated intracellular calcium pools. Calpain initiates intracellular proteolysis and destroys intracellular and membrane proteins. A final common pathway for cell destruction and cell death (i.e., apoptosis) is the *calpain hypothesis* [12]. Activation of calpain results in an influx of an excess amount of intracellular calcium and resultant glutamate receptor toxicity.

Calpain inhibitors (AK275, AK295) have been shown to reduce the size of an infarct after focal ischemia in brain [111,112]. Proteolytic inhibition by calpain antagonists is now being investigated for neurodegenerative diseases in which glutamate receptor toxicity is a common factor. Whether the site of action of neuroprotective agents is at this level has not yet been identified. Calpain inhibitors as well as antagonists are being developed and should be investigated in perfusion techniques, particularly into the inner ear, and for their effect(s) on peripheral and central portions of the cochleovestibular system [113].

A collaboration of basic science and clinical research efforts was established in 1997 with the support of the Martha Entenmann Tinnitus Research Center, Inc., Health Science Center at Brooklyn, and the State University of New York at Buffalo, in an attempt to develop neuroprotective drug therapies for hearing and balance system complaints, particularly hearing loss, tinnitus, and vertigo. One of the neuroprotective agents under investigation in this collaborative research is LXIC, a calpain antagonist [113].

Glutamine

Glutamine, an amide of glutamic acid, has been shown to cause an increased release of glutamate from various brain preparations, particularly striatal slices. Extracellular CNS glutamate levels increase with neurotoxic exposures, hepatic failure, renal failure, head trauma, or stroke. Investigations are now in progress to establish whether glutamate within glia may be an important factor in glutamine-mediated elevation of extracellular glutamate levels. The glia may be the primary source of increased glutamate release from brain slices, produced by exogenous glutamine. Specific drugs are being developed to modulate this glutamine-enhanced glutamate release [113].

Nicotinamide

Nicotinamide is a cofactor of the electron transport chain and has been reported to be effective in the treatment of patients with mitochondrial encephalopathies [114]. Combinations of nicotinamide with coenzyme

Q10 now are being investigated and have shown an additive effect for neuroprotection.

Coenzyme Q10

Coenzyme Q10 (CoQ10), an antioxidant, is a vitamin Klike molecule, essential in energy-releasing respiratory reactions, a component in the electron transfer system, and an essential component of the mitochondrial membrane [115]. It acts by blocking adenosine triphosphate (ATP) depletion, which suggests that it might improve the efficiency of the electron transport chain in vivo. Administration of CoQ10 in vivo and in vitro has been demonstrated to protect against ischemia in the heart [115].

Glutamate release inhibitors, NMDA and non-NMDA antagonists, free radical scavengers, neurotrophic factors, and calcium chelators may be beneficial either alone or in combination to improve mitochondrial function. A combination of therapies is suggested in neurodegenerative diseases [107].

PRINCIPLES OF TINNITUS DIAGNOSIS AND DRUG TREATMENT

The MATPP provides a method by which to establish an accurate tinnitus diagnosis [1–4]. Treatment efficacy reflects the degree of accuracy of the tinnitus diagnosis.

Important concerns are the need initially to identify clinical types of tinnitus, to identify factors known to influence the clinical course of tinnitus (and to apply appropriate treatment as necessary), and to attempt to identify the medical significance of tinnitus [1–4,11]. The MATPP emphasizes the clinical history, definition and classification of tinnitus, identification of the clinical types of tinnitus, and definition of the Feldmann masking characteristics and parameters of tinnitus identification. Details of the MATPP can be found in the text Tinnitus Diagnosis/Treatment [4].

Tinnitus, a chronic complaint, is characterized by its relapsing and episodic drug response. For any drug therapeutic regimen, regardless of its classification, the effects of each drug for each of the components of the symptom of tinnitus (i.e., sensory, affective, and psychomotor) should be identified [1–4].

A *final common pathway* for tinnitus is hypothesized to exist for all patients with this symptom. Its function is the transition from the sensory to the affective component of the symptom of tinnitus. It is postulated that a fundamental function in brain is the establishment of paradoxical auditory memory for tinnitus within the amygdala and hippocampal structures (i.e., the medial temporal lobe system). The paradoxical auditory memory is considered to reflect an abnormal alteration in auditory masking found in all tinnitus patients. Underlying mechanisms have been hypothesized to exist and to be highlighted by a diminution of inhibition mediated by GABA due to a disconnection from excitatory glutamate inputs. Blockage of GABA-mediated inhibition results in tinnitogenesis, an epileptic auditory phenomenon [10].

The significance of the final common pathway for tinnitus treatment and control is hypothesized to reflect an alteration in the neurochemical homeostasis of neurotransmitter systems, especially GABA-glutamate and dopamine-serotonin. Identifying which neurotransmitter system is involved provides a basis for introducing existing drugs known to influence such neurotransmitters and a basis for developing future neuropharmacological agents for tinnitus control [110,116].

Affective drug therapy, particularly, should respect the chronicity of the complaint for which it is being prescribed. Because insomnia is a chronic complaint, the clinical drug experiences of a chronic complaint as insomnia find application for drugs selected for the affect component of tinnitus [117].

The neuroprotective drugs suggested for tinnitus control are considered innovative as their predominant site of action is in the medial temporal lobe system. Significantly, for those neuroprotective drugs currently available, the site of action is particularly the hippocampus, where the drugs achieve high concentrations [12]. This finding is considered supportive of the theory of the final common pathway for tinnitus and can explain the overlapping of positive drug effects for both the sensory and the affective components of the symptom of tinnitus. Such overlapping effects are seen especially with nimodipine and the benzodiazepines, particularly alprazolam, clonazepam, and the antidepressant amitriptyline.

The neuroprotective drugs cited in this article offer the possibility of establishing and identifying a relationship between clinical manifestations and biochemical changes i.e., a neurochemistry. The neuroactive drugs mentioned focus on specific neurotransmitter actions in anatomical areas identified in the final common pathway for tinnitus (e.g., dopamine-serotonin; GABA and glutaminergic NMDA receptors). Drug selection among these agents for tinnitus therapy is based on differentiation between the components of tinnitus (i.e., sensory, affective, and psychomotor) [1–4,110].

PHARMACOTHERAPEUTIC MANAGEMENT: A PROTOCOL FOR TINNITUS CONTROL

Theory

Neuroprotective agents are proposed for pharmacotherapeutic management of the symptom of tinnitus, partic-

ularly the severe disabling type. Such drugs for the CNS have been developed on the basis of what is known of the neuroexcitotoxic theory of tissue damage [12]. Specifically, neuroprotective drug development reflects what is known of the influence at NMDA and non-NMDA receptor sites; antagonists to voltage-gated ion channels for calcium intracellular influx; treatment of ion channels (e.g., magnesium); drug action on an intracellular and nuclear level (e.g., protease antagonists); adenosine; calcium channel antagonists (i.e., calcium channel blocking agents); removal of extracellular glutamate; balance of excitotoxic agonists and antagonists and the NMDA and non-NMDA receptors; and oxygen free radicals and scavengers.

Excitotoxic neuronal death provides an example of death mediated by lethal cellular calcium overload. Although not all cell deaths involve calcium overload, elevated intracellular calcium does accompany glucocorticoid-mediated apoptotic death of thymocytes (*apoptosis* being a term for processes that result in cellular death [14]). It is possible that interventions aimed at reducing cellular calcium overload can help to protect against excitotoxic death. Whether excitotoxic death is a necrosis remains to be established. Excitotoxic injury mediated by glutamate or related compounds contributes to peripheral and central neuronal death in hypoxia-ischemia, trauma, or prolonged seizures. The role of excitotoxicity and its contribution to neuronal loss and such neurodegenerative disorders as Alzheimer's disease is not known but is being investigated currently.

Calcium overload and its role in excitotoxic death is of particular interest from the standpoint of the aging process as it affects all sensory systems. Considerable evidence exists that calcium is intermittently involved in cell deterioration and death in a variety of disease processes. One example is glutamate neurotoxicity that accompanies ischemia [14]. Since 1990, glutamate neurotoxicity has been hypothesized to be one of a number of underlying mechanisms for tinnitus development, particularly within the medial temporal lobe system [5–10,110,116].

Glutamate neurotoxicity is hypothetically modeled as a three-stage process analogous to long-term potentiation [14]. In the *induction* stage, extracellular glutamate initiates cell death by activating neuronal membrane receptors and triggering a set of defined intracellular derangements, particularly intracellular calcium overload. In the *amplification* stage, modulatory events amplify the derangements, increase their intensity, and recruit additional neurons into the injury process. In the *expression* stage, death is expressed when these derangements set in motion the final cascade that is directly responsible for neuronal disintegration, described as *calcium cascade neurotoxicity.*

Calcium is required for the function of all cells in the body. It also is involved in a variety of plastic changes in brain (e.g., such adaptive processes as learning and development, changes in neuronal excitability, and structural connectivity). Therefore, calcium is likely to incite both extracellular and intracellular processes that underlie age-related changes in brain, including normal age-associated memory impairments and severe dementia such as occurs in Alzheimer's disease.

Precise calcium homeostasis at intracellular levels is critical for many neuronal processes. The calcium hypothesis postulates that in the aging brain, transient or sustained increases in the average concentration of intracellular free calcium contribute to impaired function and eventually lead to cell death. The hypothesis suggests that a final common pathway involves increased free calcium within neurons, which may contribute to cognitive deterioration in aging vertebrates. The functional impairment becomes manifest in the patient at the time of an age-related disease process and can be relieved by reducing excessive calcium influx. The use of calcium antagonists can pharmacologically reduce the additional loss of neurons that results from altered calcium influx. This therapy may be significant for tinnitus control.

In its most controversial form, the calcium hypothesis asserts that a breakdown in calcium homeostasis is a primary cause of age-associated pathological processes, including Alzheimer's disease [28]. A study suggests that some critical neuronal calcium-regulating systems are altered in aging neurons and that these alterations underlie, to some degree, an enhanced vulnerability of an aging brain to various types of insults. Such insults include excessive glutamate activation or oxidative stress [78]. Free radical induced cell damage is a major mechanism in the aging process.

Principles

Five basic principles of pharmacotherapeutic management of tinnitus, particularly of the severe disabling type, are recommended [117]:

1. Use the lowest effective dose.
2. Follow intermittent dosage schedules.
3. Employ short-term drug therapy.
4. Gradually wean a patient from the medication after a 4- to 6-week trial.
5. Ensure that both patient and physician are aware of the possibility of and are alert for rebound and side effects after drug use is discontinued.

Drug Selection Strategies

The neuroprotective drugs have been integrated into a protocol that attempts to provide tinnitus control (i.e., re-

lief). Drug strategies for attempting tinnitus control are directed at pathological entities of inflammation, oxidative stress, modification of protein processing, neurotrophic (neuronutritional) factors, and memory enhancement, which are hypothesized to underlie or contribute to mechanisms of tinnitus production [118–121].

Inflammation

Inflammation is accompanied by free radical production. Inflammatory pathways also are believed to contribute to neurodegenerative processes independently of free radical mechanisms. The senile plaques in Alzheimer's disease are associated with inflammatory elements (e.g., microglial cells, complement proteins, cytokines, and acute-phase proteins). Antiinflammatory agents, which have antioxidant properties, may diminish the risk of developing Alzheimers disease and may slow the diseases progression. Potentially beneficial drugs include such glucocorticoids as prednisone [118].

Of interest to tinnitus patients are reports that certain nonsteroidal antiinflammatory drugs elicit tinnitus. Among the agents reported are indomethacin, naproxen, colchicine, and hydroxychloroquine. Both of the latter drugs are characterized by high penetration of the CNS. Tinnitus patients are cautioned regarding such reports [65].

Oxidative Stress

Free radicals are highly reactive molecules of unpaired electrons that are formed as by-products of metabolic processes, especially oxygen. Its combination with proteins and lipids causes damage to tissues, cell membranes, and DNA.

Data suggest that increased oxidative stress may be an important mechanism of brain aging and associated brain dysfunction. Caloric restriction significantly retarded age-associated increases in protein carbonyl content. This finding is significant for the effects of stress particularly in the area of the medial portion of the temporal lobe [10,110,122]. The natural protection that the body has for free radical scavengers is reduced with age. Antioxidants are free radical scavengers that also diminish the toxicity of beta-amyloid. With respect to Alzheimers disease, progression of the disease has been reduced by the introduction of vitamin E, vitamin C, CoQ10, monoamine oxidase inhibitor type B inhibition (selegiline), Debenone, and lazeroids. A new generation of antioxidants having increased penetration of the CNS are being developed and include, among other agents, salen-manganese complexes [118–121].

Modification of Protein Processing

Abnormal modification of normal proteins results in neurodegeneration. Pathologically, this is manifested as identification of amyloid precursor protein and tau protein, both of which result in beta-amyloid and neurofibrillary tangles.

Cholinergic agents (e.g., tacrine [Cognex] and donepezil [Aricept]), in conjunction with neurotrophic factors, influence amyloid production. Antioxidants are hypothesized to reduce the neurotoxicity of beta-amyloid. Antiinflammatory agents and heavy metals may prevent production and aggregation of beta-amyloid [119].

Neurotrophic (Neuronutritional) Factors

The absence of neurotrophic factors results in cell death [118,119]. One such factor is nerve growth factor (NGF), the use of which is limited as it does not cross the blood-brain barrier in conditions such as Alzheimers disease. Alternative methods for supplying neurotrophic factors include genetically modified brain cells that produce NGF or oral agents (e.g., ATT082, which crosses the blood-brain barrier and stimulates NGF). Estrogens are believed to stimulate the growth and development of cholinergic neurons and thus to limit the progression of Alzheimers disease.

Memory Enhancement [119,121]

A significant number of patients with tinnitus, particularly the central type, have an associated complaint of interference in memory and speech production. Particularly in the aged patient with tinnitus and associated memory loss, four drug strategies have been introduced.

One approach is to increase acetylcholine levels. Among the cholinergic drugs that increase levels of acetylcholine are tacrine, donepezil, metrifonate, and ENA713. These drugs inhibit the enzyme that normally breaks down acetylcholine. In other words, acetylcholine is increased by the agents interference with acetylcholinesterase. The most significant complication of tacrine or donepezil use is liver toxicity.

A second approach is to stimulate acetylcholine receptor sites [120]. Two types of receptors exist: muscarinic and nicotinic. Stimulation of the muscarinic receptors is less effective than that of the nicotinic receptors and results in significant side effects. Stimulation of nicotinic receptors with nicotinic agonists (e.g., ABT418, ABT089) is now undergoing clinical trials. A low incidence of side effects is reported [121].

A third approach is to increase the presynaptic release of acetylcholine. Drugs that are GABA-ergic inhibit the release of acetylcholine. In contrast, benzodiazepine receptor antagonists (e.g., Suritazole, Carboline) can diminish this GABA inhibition.

A fourth approach is to use drugs that increase norepinephrine, dopamine, and serotonin and reduce neurodegeneration, particularly that of Alzheimers disease.

A monoamine oxidase inhibitor type B (selegiline), 10 mg/day, increases norepinephrine and dopamine while also exerting antioxidant effects. Selegiline can also be used in combination with tacrine. Side effects are nausea and orthostatic hypertension. An additional consideration is that the drug is expensive. Drugs that increase serotonin levels (e.g., SSRIs) may improve mood but not necessarily memory: The addition of an SSRI has not significantly influenced the tinnitus sensory component, though it has significantly improved the affective component (i.e., mood). Other serotoninergic drugs include ondansetron, which acts on 5-HT_3 receptors; such agents are now in clinical trials [121,122]. Calcium channel blockers (e.g., nimodipine), 30 mg three times daily, crosses the blood-brain barrier; its use has been reported since 1989 [65].

Glutamate is a major excitoneurotransmitter in brain which, if excessive, leads to calcium influx and cell death. Beta-amyloid may facilitate this process. D-Cycloserine, an antituberculous drug, may restore receptor function.

An HSCB-SUNY cocktail, to which has been added both nimodipine and gabapentin, now is being used for Alzheimers disease. The cocktail consists of donepezil, 510 mg/day; vitamin C, 500 mg/day; vitamin E, 400800 IU/day; aspirin (ASA, enteric-coated), 325 mg/day; and conjugated estrogens (Premarin), 0.625 mg/day (in women, after gynecological consultation) [121].

For patients who have received a clinical diagnosis of tinnitus that is primarily of a central type and is determined to be a soft sign of gradual progressive cerebrovascular disease, a cocktail used at the Tinnitus Center at HSCB-SUNY includes nimodipine, gabapentin, vitamin C, vitamin E, enteric-coated aspirins, and clonazepam, alone or in combination with carbamazepine. For a predominantly cochlear type of tinnitus, steroids, misoprostol, and pentoxifylline are selected for use alone or in combination [110].

CONCLUSIONS

Neuroprotective drug therapies for CNS etiologies of ischemia, hemorrhage, and trauma are hypothesized to have innovative applications for control of the symptom of tinnitus, particularly of the severe disabling type. Such neuroprotective drug therapies should be considered for attempts at tinnitus control, for prevention and prophylaxis and for short- and long-term treatment. Neuroprotective drug therapy directed at the calpain protease final common pathway for cell destruction may be of value for tinnitus relief. Innovative application of neuroprotective drug therapy suggests that there are underlying mechanisms of tinnitus production, the most marked being tinnitogenesis at either a cortical or subcortical level.

Intratympanic drug therapy for inner ear disease and attempts at tinnitus control is recommended for a predominantly cochlear type of tinnitus. Tinnitus control may be achieved by intratympanic application of drugs for perfusion of the inner ear. This therapeutic method is hypothesized to produce secondary plastic changes within the central auditory system.

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