Tinnitology, Tinnitogenesis, Nuclear Medicine, and Tinnitus Patients

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Abstract: Since the 1970s, clinical interest in otolaryngology and audiology for both diagnosis and treatment of the symptom of tinnitus has witnessed the evolution of a new discipline: tinnitology. Tinnitology is an integrated discipline of basic sciences, neuroscience, and clinical medicine for the understanding of aberrant auditory phenomena unrelated to an external source of sound. To patients with subjective idiopathic tinnitus, nuclear medicine techniques of positron emission tomography and single-photon emission computed tomography provide correlation of structure and function, which improves the accuracy of the tinnitus diagnosis. Additionally, they provide a monitoring system to establish the efficacy of modalities of therapy attempting to provide tinnitus relief. Further, they provide information of neuroreceptors and neurochemistry in brain underlying or accompanying basic mechanisms for production of specific clinical types and subtypes of tinnitus. This study reports the application of nuclear medicine techniques for a new clinical neuropharmacology protocol for tinnitus treatment highlighted by intratympanic drug therapy in predominantly cochlear-type tinnitus. We further report a neuroprotective drug therapy to control tinnitogenesis, an auditory epileptiform phenomenon. Additionally, we report the hypothesis of a benzodiazepine deficiency syndrome.

Keywords: benzodiazepine-deficiency syndrome, epileptogenesis, final common pathway (FCP), neuroprotection, positron emission tomography, single-photon emission computed tomography, tinnitogenesis, tinnitology

Since the 1970s, clinical interests in subjective idiopathic tinnitus for both diagnosis and treatment have led to the development and emergence of a new discipline: tinnitology [1]. *Tinnitology* is an integrated discipline of basic science, neuroscience, and clinical medicine for the understanding of aberrant auditory phenomena unrelated to an external source of sound. Specialties involved at this time are highlighted by otolaryngology, otology, neurootology, audiology, psychology, neuropsychiatry, and auditory science.

Since 1992, tinnitus has been defined on the basis of our experiences in single-photon emission computed tomography (SPECT) of brain as a disorder of auditory perception due to an altered state of excitation and inhibition in neuronal networks and resulting in a dyssynchrony of neuronal signaling [2]. Since 1979, the underlying mechanism has been considered to be that of dyssynchrony, a lack of synchrony or interference of timing of the discharge rate and phase locking of the auditory signal that is located peripherally or centrally (or in both areas) [3].

Classic teaching places emphasis on the psychoacoustic and psychophysical aspects of tinnitus. Neurootological teaching places emphasis on ear and brain; mind and brain; and a multifactorial medical audiological approach to both tinnitus diagnosis and treatment.

Our efforts to diagnose and treat tinnitus have been ongoing since 1977 [1–3]. A Medical Audiologic Tinnitus Patient Protocol has been applied to more than 5,000 patients with tinnitus, particularly of the severe

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disabling type, at the Tinnitus Clinic of the Health Sciences Center at Brooklyn, State University of New York. Our clinical investigations have identified the following highlights to be significant for tinnitus diagnosis and treatment and control efficacy:

Tinnitus is not a unitary symptom; some clinical types of tinnitus are a symptom of neurootological disease.

Components of the symptom of tinnitus are sensory, affect, and psychomotor.

The masking characteristic of each tinnitus patient is individual.

Since 1990, SPECT imaging of brain identified for the first time in vivo differences in blood flow in several regions of brain of patients with a predominantly central-type tinnitus

Fear and stress in tinnitus patients, particularly of the severe disabling type, are a result of development of a paradoxical auditory memory for an aberrant, dyssynchronous auditory signal.

Since 1983, our recommendations for tinnitus treatment and control have been based on recommendations differentiating between components of tinnitus originally described in 1983 (i.e., sensory, affect, and psychomotor) and identification and treatment (when appropriate) of factors known to influence the clinical course of tinnitus [4,5]. In our series, such an approach has resulted in overall tinnitus control of 65–70%. Of this number, 35–40% with medication, 45-55% with instrumentation, and 10–15% with persistent problems.

Our clinical experience with tinnitus of the severe disabling type continues to emphasize the need for establishing an accurate tinnitus diagnosis and for the development of protocols for increasing efficacy of tinnitus treatment. For increasing the accuracy of identifying the anatomical structures involved, radiological techniques of ear and brain include computed tomography scans and magnetic resonance imaging. For determination of function, nuclear medicine techniques are useful: SPECT provide perfusion information, and positron emission tomography (PET) provides metabolic information. In addition, PET and SPECT provide information of neurotransmitter receptors. For tinnitus, receptor information is a means by which the neurochemistry underlying or accompanying basic mechanisms of tinnitus production can be identified. Coregistration (i.e., the fusing of data of structure, function, and neurochemistry) offers both to professionals involved with tinnitus diagnosis and treatment and to patients an increased understanding of the medical significance of the tinnitus symptom and an ability to provide enhanced

efficacy of therapeutic modalities recommended for tinnitus relief [2,6–14].

This study is organized into four sections that highlight the significance of our evolving nuclear medicine experience with tinnitus patients:

A brief presentation of a final common pathway (FCP) hypothesis for tinnitus, such pathway having its anatomical substrate in the medial temporal lobe system (MTLS; based on SPECT of brain findings in tinnitus patients first presented at the Fourth International Tinnitus Seminar, Bordeaux, France, in 1991 and formally presented in Prague in 1995).

Presentation of a particular clinical central type of tinnitus reflecting the mechanism of tinnitogenesis and, for the first time, sequential objective evidence via SPECT imaging of brain of tinnitus control in a patient with tinnitogenesis treated with antiseizure medication.

Presentation of the concept of a neuroreceptor deficiency syndrome—in brain or ear (or both)that may be an etiology for a subgroup of central-type tinnitus patients.

Presentation of tinnitus treatment protocols that prescribe neuroprotective drug therapy based on the FCP for tinnitus and its application for tinnitus control with intratympanic drug therapy.

FINAL COMMON PATHWAY FOR TINNITUS

An FCP is hypothesized to exist for all tinnitus patients, particularly those with the severe disabling type (subjective idiopathic tinnitus) [2,10,15,16]. The pathway's function is the transition from the sensory to the affect component of the tinnitus symptom and the interaction between the two [1,2]. Historically, the search for understanding the transition from the sensory to the affect component and how it occurs in brain is not new. Descartes regarded the mind as something immaterial, separate from brain but interacting with it in some manner. In other words, the heterogeneity of the tinnitus symptom is considered to be reflected in an FCP for tinnitus.

The hypothesis is based on clinical examination of 62 tinnitus patients since 1989 using SPECT of brain with the radioisotope technetium 99–HMPAO. Side-to-side perfusion asymmetries have been highlighted by the amygdala-hippocampal complex in the MTLS. Adjacent perfusion asymmetries involving frontal, temporal, and parietal lobes and the auditory cortex suggest an interneuronal network resulting in the transition of

the sensory to the affect component of the tinnitus symptom. For the first time, the 1990 demonstration of increased activity in important auditory regions in brain provided a starting point from which to investigate pathophysiological mechanisms of a predominantly central-type tinnitus [1,7,9].

The concept for an FCP for tinnitus evolved since 1983 from our clinical experience revealing that all patients with tinnitus (particularly of the severe disabling type) have as a common denominator a disorder in affect. Specifically, that disorder is a behavioral response to and an accompaniment of an aberrant auditory sensory stimulus (i.e., tinnitus). Clinically, this suggests components of an FCP for tinnitus. The heterogeneity of the tinnitus symptom both for sensory and affect has been reported by professionals of all disciplines who are involved in the diagnosis and treatment of this disorder.

The origin and localization of sensory-affect processing is hypothesized to be in a key area of brain (i.e., the MTLS). Clinical evidence suggests that mechanisms involved in the transition of sensory to affect processing involve the anatomical structures of the MTLS and the limbic lobe. The clinical significance of the limbic system for emotion was described by Papez in 1937 [17] and was emphasized in our tinnitus text [11]. The MTLS and the limbic lobe are hypothesized to represent the primary cortical anatomical sites of brain action in an FCP for tinnitus wherein the sensory-affect transition for tinnitus is initiated by the establishment of a paradoxical auditory memory, with resultant alteration in mood [10].

A paradoxical memory for an aberrant auditory signal (i.e., tinnitus) is considered to be the initial process of transition of the sensory to the affect component of tinnitus. It is considered to result from an alteration in normal auditory masking for all tinnitus patients. Underlying biochemical and physiological mechanisms are hypothesized to exist and to be highlighted by a diminution of inhibition mediated by gamma-aminobutyric acid (GABA) due to a disconnection from its excitatory glutamate inputs. The FCP provides a model on which to base speculations as to its clinical application for both diagnosis and treatment [10].

Neuroscience reports that have identified the MTLS for memory, emotion, and behavior are considered to support our FCP hypothesis and include LeDoux [18], who has identified neuroanatomical subcortical and cortical emotional processing circuits (i.e., thalamo-amygdala and thalamocorticoamygdala pathways) in which the emotional significance of an auditory stimulus can be learned, stored in memory, and expressed in body physiology by the autonomic nervous system or in behavior by the somatomotor system. Other support-

ers include Murray and Gaffan [19], Gallagher and Chiba [20], Brown et al. [21], Tiitien [22], and others who are involved in stress research and have focused on the role of the hippocampus in steroid control of cortisol since the 1980s [23–25].

TINNITOGENESIS

Tinnitogenesis is a seizure-type activity, cortical-subcortical in location, with a resultant aberrant auditory perception. It is an epileptiform auditory phenomenon [1,13].

For tinnitus, one can speculate that a seizure-type activity resulting in the perception of an aberrant auditory stimulus (i.e., tinnitogenesis) is a mechanism for tinnitus production in a subgroup of patients with tinnitus of the severe disabling type. The seizure-type activity (e.g., at a cortical level) may interfere with or reduce central masking capability or efferent function (or both), with alterations in calcium homeostasis and the activity of the neurotransmitters glutamate and GABA.

The calcium neuroexcitotoxicity theory has application for understanding the underlying mechanism of one type of tinnitus production (i.e., tinnitogenesis). The excitatory action of the amino acid glutamate is conceived possibly to result in more than one physiological function [26,27]. Different attributes of tinnitus may be the clinical reflection of multiple functions of a particular protein (e.g., glutamate) in different areas of brain. Such a protein may demonstrate a degree of adaptability of different functions. An imbalance in protein activity may contribute to neuronal damage. The result is probable stimulation of the MTLS and activation of the FCP for tinnitus, with the development of a paradoxical auditory memory. The ensuing cascade of biochemical and physiological events is reflected clinically in a heterogeneity of behavioral and emotional changes highlighted by anxiety or depression, fear, and interference with sleep and communication.

Therefore, tinnitus is not considered to be a phantom phenomenon. Rather, it is an auditory image and a clinical symptom of auditory dysfunction having an identifiable neuronal substrate at a cortical and subcortical level. Any system or mechanism or drug that blocks GABA-mediated inhibition or increases glutamate concentration is speculated to produce a seizure-type activity (i.e., epileptogenesis) [26,27].

A new neuroprotective tinnitus drug therapy protocol was applied clinically to a patient identified as having a predominantly central-type tinnitus [12,28]. SPECT imaging of brain in October 1996 in this patient had revealed an area of hyperexcitability in the posterior one-third of the MTLS, consistent with an epilepto-

genic focus. Treatment with antiseizure medication (phenytoin [Dilantin], GABA-pentin, and clonazepam [Klonopin]) resulted in significant tinnitus control to date (16 months' duration).

Objective evidence, as demonstrated by SPECT imaging of brain in sequential studies conducted at 9-month intervals, demonstrated significant improvement in overall brain perfusion and elimination of the epileptogenic focus, which correlated with the subjective report by the patient of significant tinnitus relief. Also, for the first time in 1997, hyperactivity, as demonstrated by increased perfusion in the amygdala, was correlated with the subjective report by the tinnitus patient of increased intensity of tinnitus at the start of the SPECT examination in October 1997 (i.e., a stressful situation).

BENZODIAZEPINE DEFICIENCY SYNDROME AND TINNITUS

The high concentration of steroid and benzodiazepine (BZ) receptors in the MTLS of brain has been reported since the early 1970s by McEwen et al. [29]. The stress diathesis model of tinnitus presented in 1992 considers stress to be a modulator of the FCP for tinnitus [6,8]. Cortisol regulation is considered to occur in the hippocampus [23,24].

Clinical experience has established a significant positive degree of tinnitus control by treatment of the affect component of tinnitus with anxiolytic-antidepressant medications and stress management. The BZ receptor has been reported to exert its effect by attachment to the $GABA_A$ receptor. Steroid receptors are known to modulate $GABA_A$ activity. Stress activity is known to be involved intimately in cortisol steroid BZ activity.

A deficiency syndrome is hypothesized to exist in the MTLS that influences sensory-affect transformation. Specifically, when a BZ is received by tinnitus patients, the reported tinnitus relief is considered to reflect a replacement therapy for a BZ deficiency. Its positive effect for tinnitus control is hypothesized to be the reestablishment of a BZ level sufficient to allow normal processing of affect, expressed clinically by the tinnitus patient as a reduction in anxiety or depression (or both) and return to a normal mood with elimination or control of fear.

PROTOCOLS OF TINNITUS TREATMENT AND CONTROL

Application of nuclear medicine reports of neurochemistry of brain forms the basis of new protocols for tinni-

tus treatment and control. The FCP model provides a neurochemistry approach for tinnitus. It is a direct application of clinical neuroscience for attempting tinnitus control. Both existing and new protocols for tinnitus diagnosis recommend that all patients with tinnitus, particularly of the severe disabling type, complete a Medical Audiologic Tinnitus Patient Protocol [4,5]. The highlights of our existing approach include various areas of inquiry [4,5,23,24].

Existing Protocol

Tinnitus control has been achieved predominantly by combining drug strategies with instrumentation and not by a single drug or device.

Sensory Component
We have sought to establish accurate tinnitus diagnosis on the basis of exclusion of disease of the head and neck and of the identification of clinical types of tinnitus. It has included identification and treatment (when appropriate) of factors known to influence the clinical course of tinnitus (e.g., aeration of the middle ears and metabolic factors of sugar, thyroid, cholesterol, and triglyceride level determinations). Management has included noise control, instrumentation, and medication.

Affect
In the region of the affect, we have pursued psychiatric consultation for the evaluation and treatment of anxiety and depression. To that end, we have included stress management control and cognitive behavior training as well as instrumentation and medication.

New Neurochemistry Protocols

Nuclear medicine affords identification of new images of pathophysiological processes and neurochemistry involved in brain [12,14]. For the tinnitus symptom, it offers the possibility of establishing a relationship between a clinical manifestation and biochemical changes (i.e., a neurochemistry of abnormalities that can be identified before or during their clinical manifestation) [30].

Neurochemistry protocols of the past, specifically for tinnitus treatment, include neurootological experiences both clinical and pertaining to the basic sciences. Pioneering efforts are found in the clinical protocols of Claussen [31] in the 1970s, with medications for balance control, which influence the dopaminergic and noradrenergic systems, now adapted for tinnitus; in the 1980's work of Ehrenberger and Brix [32], who used calcium channel blockers and Caroverine for glutamate excitatory amino acid neurotransmission; in the work

of Goodey [33] in the 1970s focusing on the antiepileptic effect of carbamazepine (Tegretol); and in Lechtenberg and Shulman's research in 1984 [34] exploring clonazepam and that of Johnson et al. in 1990 [35] exploring alprazolam (Xanax) for the GABA-mediated benzodiazepine effect. Basic science highlights include efforts by Pujol [36], who identified the glutamate receptor in the afferent cochlear neurons, and Zenner [37], who provided information concerning calcium channels and mechanisms for tinnitus action at a cellular level.

Drug selection in the neurochemistry protocols for tinnitus control are based on attempts to provide neuroprotection for treatment of a specific etiology and underlying pathological mechanism. The focus is on drugs known to have specific neurotransmitter action in the anatomical areas identified in the FCP (e.g., dopamine-serotonin; GABA, and glutamatergic *N*-methyl-D-aspartate (NMDA) receptors [1,28]. The specific etiologies are ischemia, hemorrhage, trauma, and neurodegeneration.

Drugs are prescribed for pathology, including modification of inflammation, oxidative stress, modification of protein processing, neurotrophic (neuronutritional) factors, and memory enhancement. These pathological processes are hypothesized to underlie or to contribute to mechanisms of tinnitus production (or to do both).

Neuroprotection refers to processes that protect neuronal function from injury or that improve such function after injury. Clinically, the common etiological agents of ischemia, trauma, hemorrhage, and neurodegeneration that cause injury to the central nervous system (CNS) are hypothesized to have a similar occurrence in the inner ear. This approach has been ongoing for etiologies of the CNS for the last 15–20 years [38,39].

Pharmacological agents considered to be neuroprotective have been identified for the CNS and include benzodiazepines, calcium channel blockers, free radical scavengers, corticosteroids, antagonists of glutamate at NMDA and non-NMDA receptors, various thrombolytic agents, antioxidants and glucocorticoids, and antiseizure medication. An innovative application of such drug therapy for tinnitus control is the attempt to provide neuroprotection. Specific information for each neuroprotective drug and dosages can be found in Neuroprotective Drug Therapy [28].

Neuroprotective drug development and its clinical application to tinnitus patients are based on the glutamate neuroexcitotoxicity theory [40]. The excitatory amino acids glutamate and aspartate contribute to synaptic plasticity and calcium permeability. Briefly, the excitotoxic hypothesis states that excessive release of excitatory amino acids (i.e., glutamate) results in interference in extracellular and intracellular calcium homeostasis. The end result is gradual reduced cellular function and eventual cell death (i.e., apoptosis). This result is an important cause of neuronal brain damage. The establishment of glutamate neuroexcitotoxicity occurs in three stages. In the *induction stage*, cell death induction is initiated by intracellular glutamate action on calcium receptors, resulting in intracellular calcium overload and intracellular derangements. In the *amplification stage*, increased intracellular calcium concentration results in modulatory events that recruit additional neurons into the injury process. The *expression stage* is characterized by increased interference in cellular function and eventual apoptosis.

Glutamate neurotransmitter functions are rapid neuronal excitation, neuronal plasticity, and neurotoxicity. By way of review, glutamate receptors are inotrapic and NMDA and non-NMDA receptors and are metabotrophic, associated with G proteins. Increasing levels of intracellular calcium secondary to increasing extracellular glutamate activate calpain. Calpain is a normal intracellular protease. Increased calpain activity results in proteolysis of cell membrane and intracellular proteins, with eventual apoptosis.

The calpain hypothesis is considered to be an FCP for interference in neuronal function and apoptosis. It is the logical basis for development of a neuroprotective drug category called *calpain antagonists and inhibitors* [38,39].

Calpain, a normal intracellular cytosolic protease activated by excess intracellular calcium, is considered clinically to be influenced significantly by neuroprotective agents. Calpain antagonists and inhibitors have been shown to reduce the size of an infarct after focal ischemia in brain [38,39]. Proteolytic inhibition by calpain antagonists is being investigated for use in neurodegenerative disease in which glutamate receptor toxicity is a common factor. Calpain inhibitors and antagonists are being developed and will be investigated in humans via perfusion techniques of the inner ear, for their effects on peripheral and central portions of the cochleovestibular system [40].

Since 1989, we have considered that the glutamate neuronal excitotoxicity theory supports our clinical observations (reported since 1983) of central types and subtypes of tinnitus, our definition of tinnitus, and the 1990 identification (using brain SPECT) of the FCP for tinnitus in patients identified clinically to have a primarily central-type disorder. Also, that theory provides the basis for the innovative application of the drug nimodipine (since 1990) and neuroprotective drug therapy regimens for attempting tinnitus control (since 1997) [4].

Intratympanic drug therapy for inner ear disease and attempts at tinnitus control are recommended for a predominantly cochlear-type tinnitus. Tinnitus control

may be achieved by intratympanic perfusion of neuro-protective drugs in the inner ear. This therapeutic method is hypothesized to produce secondary plastic changes within the central auditory system [28].

FUTURE TINNITUS CONTROL

The efficacy of future recommendations for treatment of subjective idiopathic tinnitus will be reflected in the accuracy of the tinnitus diagnosis [4]. By providing perfusion and metabolic and neurotransmitter receptor information, nuclear medicine techniques of both SPECT and PET will provide a basis for an expanding neuropharmacology aimed at controlling different clinical types and subtypes of tinnitus and for improved accuracy of tinnitus diagnosis and treatment.

Electrophysiological techniques of brain mapping of evoked potentials and event-related potentials, particularly in three dimensions, will provide a basis for accurate localization and identification of cortical elicited auditory evoked potentials in tinnitus patients. Coregistration of electrophysiological and functional information of perfusion, metabolism, and neurotransmitter receptors will provide identification of an objective electrophysiological and metabolic correlate for different clinical types and subtypes of tinnitus.

The expanded application of neurochemistry drug protocols to specific etiologies and modification of pathological processes in tinnitus is expected to increase the efficacy of drug therapy for tinnitus control. It is anticipated that the expansion of drug therapies for neuroprotection will be highlighted by the development of calpain antagonists and inhibitors [28,41].

A collaboration of basic scientific and clinical research efforts between the Martha Entenmann Tinnitus Research Center, Inc., Health Sciences Center at Brooklyn, and the State University of New York at Buffalo was initiated and supported by the Martha Entenmann Tinnitus Research Center, Inc., in 1997. This collaboration was undertaken to develop neuroprotective drug therapies for the hearing and balance systems and for related complaints, particularly of hearing loss, tinnitus, and vertigo. This endeavor reflects the ongoing interest of the Martha Entenmann Tinnitus Research Center in developing a neuropharmacology for tinnitus control. A series of basic scientific investigations are in progress to support the clinical view of the applicability of calpain antagonists for tinnitus control. One of the neuroprotective agents under investigation in this collaborative research is LXIC, a calpain antagonist [28,41,42, and unpublished data]. Additional studies are ongoing for noise-induced hearing loss protection and tinnitus control.

One can speculate that a particular clinical type of tinnitus, which currently is considered a symptom, may be identified in the future, as a specific disease process due to a specific etiology and responsive to a specific therapy.

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