A Final Common Pathway for Tinnitus -Implications for Treatment

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Abstract: A final common pathway for tinnitus is hypothesized to exist for all patients with tinnitus. Its function is the transition of the sensory to the affect component of the symptom of tinnitus. Single Photon Emission Computerized Tomography (SPECT) with the radio isotope TC99-HMPAO has identified side to side perfusion asymmetries highlighted by that of the amygdala - hippocampal complex.

It is hypothesized that a fundamental function of the amygdala - hippocampal structures is the establishment of a paradoxical auditory memory for tinnitus i.e., an aberrant auditory signal. It is a result of alteration in normal auditory masking; and found in all tinnitus patients. Underlying mechanisms are hypothesized to exist and to be highlighted by a diminution of inhibition mediated by gamma aminobutyric acid (GABA) due to disconnection from excitatory (glutamate) inputs. Blockage of GABA mediated inhibition results in Tinnitogenesis, a epileptiform auditory phenomenon. Significant neurochemistry implications for treatment are suggested by the Final Common Pathway for Tinnitus. The overall hypothesis of a final common pathway for tinnitus; and the clinical implications for treatment are presented.

INTRODUCTION

Final Common Pathway (FCP) for tinnitus is hypothesized to exist for all patients with tinnitus. Its function is the transition of the sensory to the affect component of the symptom of tinnitus.^{1,2}

Single Photon Emission Computerized Tomography (SPECT) with the radioisotope TC 99-HMPAO has identified side to side perfusion asymmetries highlighted by that of the amygdala - hippocampal complex. Adjacent perfusion asymmetries involving frontal, temporal, and parietal lobes suggest an interneuronal network resulting in the transition of the sensory to affect component of the symptom of tinnitus.¹⁻⁸

It is hypothesized that a fundamental function of the amygdala - hippocampal structures is the establishment of a paradoxical auditory memory for tinnitus. It is a result of alteration in normal auditory masking and found in all tinnitus patients. A paradoxical memory for an aberrant

<u>Reprint requests</u>: Abraham Shulman, M.D., F.A.C.S., Martha Entenmann Tinnitus Research Center., Health Science Center at Brooklyn - SUNY, Box 1239, 450 Clarkson Avenue, Brooklyn, New York 11203, USA auditory signal i.e., tinnitus is considered to be the initial process in the transition of the sensory to the affected component. Underlying mechanisms are hypothesized to exist and to be highlighted by a diminution of inhibition mediated by GAMMA amino butyric acid (GABA) due to disconnection from its excitatory (glutamate) inputs. Blockage of GABA mediated inhibition results in Tinnitogenesis, an epileptiform auditory phenomena.¹ The concept for a Final Common Pathway for Tinnitus (FCP) has evolved since 1983 from our clinical experience which has revealed that all patients with tinnitus, particularly of the severe disabling type, have as a common denominator a disorder in affect.^{1,2,3} Specifically, a behavioral disorder in response to and as an accompaniment of an aberrant auditory sensory stimulus i.e, tinnitus. Clinically this suggests components of a Final Common Pathway for Tinnitus. The heterogeneity of response both for sensory and affect has been reported by professionals of all disciplines who are involved in this diagnosis and treatment.

In other words, the heterogeneity of the symptom of tinnitus is reflected in a FCP for tinnitus. Such a pathway includes the integration of multiple neuronal circuits in which multiple reciprocal processes occur resulting in the transition/interaction between the sensory and affect components of tinnitus. The origin and localization of sensory/affect processing is hypothesized to be in a key area of brain i.e., the Medial Temporal Lobe system (MTLS). The FCP is presented as a hypothesis focusing on a process within the MTLS of a paradoxical auditory memory with speculations as to its clinical applications for both diagnosis and treatment.

Tinnitus treatment/control has been reported based on recommendations which differentiate between the components of tinnitus i.e., sensory/affect/psychomotor; and identification and treatment, when appropriate, of factors known to be influence the clinical course of tinnitus. Such an approach has resulted in tinnitus control in our series with medical means of approximately 25%-30%; instrumentation 65%-70%; and persistent problems 10%-15%. The problem cases are highlighted by a significant association of refractive behavioral responses, highlighted by anxiety/depression. The availability of SPECT of brain provides a means to improve the accuracy of the tinnitus diagnosis and to monitor the efficacy of treatment/control methods advised.²

Neuroscience reports which have identified the MTLS for memory, emotion, behavior - are speculated to be related to the SPECT findings in our tinnitus patients of significant perfusion asymmetries in an anatomical substrate i.e., MTLS. It is hypothesized that transition from perception to memory i.e., sensory to affect/memory as reported by Squire et al. in 1991 has a direct application to tinnitus particularly for the severe disabling type. The Medial Temporal Lobe System (MTLS) has been identified for the function of memory and stress.^{9,10,11} Both are clinically significant for tinnitus (SIT). Significant implications for treatment are suggested by the Final Common Pathway for Tinnitus.

The symptom of tinnitus is compelling otology/ neurotology, and other disciplines who are involved in its understanding and attempts for medical audiologic diagnosis and treatment to become knowledgeable for what is and is not known of brain action; and what is the mind.¹ Tinnitology, a discipline involving professionals dedicated to the science of sound perception unrelated to an external source of sound, reflects this effort.^{12,13} The clinical application of the FCP hypothesis has improved the accuracy of the tinnitus diagnosis and provides a basis for integration of past protocols of therapy both for medication and instrumentation with new protocols based on the identification of a pathophysiological concept of the significant role of glutamate and excitatory amino acid neurotransmission and GABA; and the modulatory role of dopamine/serotonin neurotransmitters for tinnitus.

The highlights of new protocols for tinnitus treatment/ control are presented in the context of a neurochemistry conceptualization of tinnitus, using the FCP as a model, and differentiating recommendations for treatment between the components of the tinnitus symptom i.e., sensory, affect, and psychomotor.

PROTOCOLS TINNITUS TREATMENT/ CONTROL

A. Existing

It is recommended that all patients with tinnitus particularly of the severe disabling type complete a Medical Audiologic Tinnitus Patient Protocol (MATPP).¹² The goal is to attempt to identify the clinical type(s) of tinnitus; identification and treatment when appropriate for factors known to influence the clinical course of tinnitus; and to apply this information for the selection of modalities of therapy now available for both tinnitus treatment and/or control.¹³

The highlights of our present approach include the following. $^{10\text{-}14}$

- a. Sensory Component:
 - 1. Diagnosis to establish accurate tinnitus diagnosis based upon exclusion of disease of the head and neck and the identification of clinical type(s) of tinnitus.
 - 2. Identification and treatment, when appropriate, of factors known to influence the clinical course of tinnitus i.e., aeration of the middle ears; metabolic factors of sugar, thyroid, cholesterol, triglyceride level determinations.
 - 3. Noise control.
 - 4. Instrumentation.
 - 5. Medication.
- b. Affect:
 - 1. Psychiatric consultation evaluation/treatment anxiety/depression.
 - 2. Stress management control.
 - 3. Cognitive behavior training.
 - 4. Instrumentation
 - 5. Medication.

B. New

1. Neurochemistry Concept - Final Common Pathway for Tinnitus:

The concept for a Final Common Pathway for Tinnitus (FCP) has evolved from clinical experience which has revealed that all patients with tinnitus, particularly of the severe disabling type have as a common denominator, a disorder in affect. Specifically, a behavioral disorder in response to and as an accompaniment of an aberrant auditory sensory stimulus i.e., tinnitus. Clinically this suggests components of a Final Common Pathway.

The concept of a Final Common Pathway for Tinnitus derived from SPECT imaging of brain in patients with

tinnitus particularly of the severe disabling type, reflects new images of tinnitus i.e., tinnitus in terms of its neurochemistry i.e., a neurochemistry of tinnitus. SPECT and/or PET of brain provides the potential to establish a relationship between the clinical manifestations of tinnitus and specific identified chemical changes in the regions of interest examined. The identification of chemical abnormalities in the anatomic regions of interest reflect the clinical course of tinnitus and its state of manifestation i.e., subclinical and/or clinical. In-situ radioactive tracers can serve as biochemical markers in tinnitus studies and are hypothesized to have the potential to become drugs used to alter the symptom/disease process i.e., tinnitus. The FCP explains in part the positive clinical treatment/control experience achieved and reported with recommendations based on speculations of mechanisms of tinnitus production, specifically neurotransmitter systems.¹³

Nuclear Medicine offers the ability of identification of new images of pathophysiologic processes and the neurochemistry involved.^{15,16} For the symptom of tinnitus it offers the possibility of establishing a relationship between a clinical manifestation and biochemical change(s) i.e., a neurochemistry of chemical abnormalities which can be identified before or during their clinical manifestation(s).

Techniques of nuclear medicine of PET and SPECT introduce the possibilities to identify the neurochemistry involved in specific regions of interest in brain to explain the heterogeneity for both subclinical and clinical tinnitus. In summary a new neurochemistry protocol is recommended for tinnitus treatment/control, which until now has been limited to verbal and written descriptions of neuropsychology, for both the sensory and affect component of tinnitus.

The FCP finds application to SIT treatment/control by:

- a. Identification of anatomical regions of interest of brain involved in the sensory/affect interaction/ association i.e., MTLS and adjacent paracortices; and interneuronal circuits.
- b. Pharmaceutical clinical trials to focus on drugs known to have specific neurotransmitter action in the anatomical areas identified in the FCP e.g., Dopamine (DOPA)/Serotonin; Gama Aminobutyric Acid (GABA) and Glutamatinergic N-methyl d-aspartate (NMDA) receptors.
- c. Differentiation for tinnitus therapy between its components i.e., sensory/affect/psychomotor.
- d. Identification of tinnitus to be a aberrant sensory stimulus of the cochleovestibular system with a resultant behavioral disorder.

SENSORY COMPONENT - PROTOCOL TINNITUS TREATMENT/CONTROL

Medical recommendations are highlighted by the need to identify clinical types of tinnitus and its differentiation from factors known to influence the clinical course of tinnitus. I refer you to our publications and text describing the MATPP, and the tinnitus treatment/control protocols and medical results highlighted by control of aeration of middle ear, Secondary Endolymphatic Hydrops and Noise.¹³

Instrumentation in general continues to result in a significant incidence of treatment/control when the clinical type of tinnitus is primarily of the cochlear type; and factors known to influence the clinical course of tinnitus are identified and controlled. Specifically, negative results with instrumentation accompanies persistence by the patient of noise exposure; use of hallucinogenic/ mind altering drugs; fluctuation in aeration of the middle ears; persistence of uncontrolled and unidentified disease of the head and neck e.g., tumor, allergy, infection and Secondary Endolymphatic Hydrops. Secondary Endolymphatic Hydrops in our series is approximately 25%-35%, of which 60% of tinnitus patients are not vertiginous. Recruitment and/or hyperacusis significantly interferes with tinnitus treatment/control with instrumentation or may even be increased.

The recent introduction of a device called the "tinnitus habituator" to produce "habituation" is reported to significantly provide tinnitus treatment/control. The device distracts the patient from the tinnitus by habituation. Habituation is a retraining therapy wherein the patient is conditioned to a sound stimulus other than that of their tinnitus, and, over time, results in a significant reduction in awareness of the perception of tinnitus. Counselling plays a significant role in this therapy both before and during therapy with the habituator. The habituator device is of a particular interest in relation to the FCP. Recent neuroscience reports have identified the role of the MTLS in conditioning of fear, sleep, behavior and emotion.

Electrical stimulation continues to be applied externally for patients who have significant recruitment and/or hyperacusis.^{13,14} Of interest are recent neuroscience reports identifying a thalamo-amygdala circuit which upon electrical stimulation has resulted in a reported increase in the amplitude of the auditory potential.²⁵

New, is the increasing frequency of recommendations for utilization of drug therapy considered to influence neurotransmitter systems highlighted by e.g., glutamate/ GABA; oxygen saturation of blood (Trental); oxygen free radicals (Cytotec); and calcium metabolism (Nimodopine) either alone and/or in combination with

instrumentation.¹³

Neurochemistry protocols, specifically for tinnitus treatment have in the past been both clinical and in the basic sciences. Pioneering efforts are found in the protocols of Claussen¹⁷ for medication for balance control influencing the DOPA and Noradernergic systems; Ehrenberger with calcium channel blockers for the glutamate excitatory amino acid neurotransmission (Caravorine);¹⁸ Goody for the anti-epileptic effect of Tegretol;¹⁹ and Lechtenberg/Shulman²⁰ (1984) with clonazapam and Johnson et al for Xanax,²¹ both, for the GABA mediated benzodiazepine effect.

GABA mediated benzodiazepine effect. Basic science highlights include Pujol,²² who identified the glutamate receptor in the afferent cochlea neurons; and Zenner²³ et al., for information concerning calcium channels and mechanisms for tinnitus action at a cellular level.

New for tinnitus treatment is the application of the tinnitus clinical experience for the identification of components of the tinnitus symptom; association of basic neurotransmitter mechanisms of action to attempt to explain and provide a rationale for drug protocols of the past, present, and future.

It is speculated that for patients with tinnitus, particularly of the severe disabling type, two neurotransmitter systems are significant both from the standpoint of a pathophysiologic correlate; and application for tinnitus treatment/tinnitus control:

a. Serotonin/Dopamine neurotransmitter systems.²⁴

b. GABA/Glutamatinergic NMDA excitatory amino acid transmitter systems.¹³

The significance of these two systems is suggested based upon perfusion asymmetries identified in multiple areas of cortex as revealed by SPECT imaging of brain in patients with tinnitus particularly of the severe disabling type.¹⁻⁸ For example, the four major dopaminergic pathways i.e., mesocortical tract, mesolimbic tract, nigrostriatal pathway, tuberoinfudibular tract - all - with the exception of the tuberoinfudibular tract have revealed regions of interest in brain with SPECT imaging of brain in tinnitus patients i.e., MTLS accompanying perfusion asymmetries.

The GABA inhibitory/glutamatinergic excitatory amino acid transmitter systems are considered to reflect a primary underlying mechanism of signal transmission. A disturbance in homeostasis results in an epileptiform auditory phenomenon. Specifically a diminution of inhibition, mediated by a GABA disconnection from excitatory glutamate inputs. Significant innovative drug therapy to attempt tinnitus control include calcium channel blocking agents; benzodiazepines, pentoxyfylline; and carbamazepine.

AFFECT COMPONENT - PROTOCOL TINNITUS TREATMENT/CONTROL

The identification of an anatomic substrate for the FCP in the area of the MTLS and adjacent paracortical areas suggest multiple neurotransmitter systems and the need for a combined treatment reflecting influence on the various portions of neurotransmitter system(s) involved highlighted by that of the Serotonin/Dopamine system; GABA/glutamatenergic NMDA system.

The relationship of Dopamine/Serotonin/Noradrenergic activity is considered significant for the limbic system. Dysfunction in the mesocortical tract/pathway alters descending modulating influences on the limbic system function by Dopamine. Dysfunction in this pathway alters modulating influences of the limbic system function with appropriate change in affect i.e., behavior/emotion.²³

It is speculated that dysfunction of both these neurotransmitter systems in the MTLS and associated paracortices reflect either a primary pathology or secondary interference from other primary agents i.e., noise exposure resulting in tinnitus particularly of the severe disabling type.

A primary etiologic degradation in the Dopaminergic function especially in neurons projecting to the frontal cortex have clinically manifested themselves with negative symptoms in Schizophrenia. Positive symptoms reflect compensatory changes which lead to maladaptive changes in FH2 activity and an increase in Dopaminergic and Noradrenergic activity in the limbic system. The FCP reflects an interrelationship between multiple neuro-transmitter systems which we believe are highlighted by the two mentioned above.²³

Significant drug therapy to consider for the future may very well be that of neuroleptics i.e., antipsychotics. All neuroleptics have in common an ability to bind to Dopamine D2 receptors. D2 antagonists block Dopaminergic neurotransmission in the meso limbic pathway e.g., Halperidol. However, Halperidol has the disadvantage of having increased extrapyramidal symptoms due to a reduction further in the Dopamine at the basal ganglion level.

The complexity of neurotransmitter systems provides an insight to the complexity of tinnitus drug therapy e.g., positive effects of Halperidol for epilepsy and significant extrapyramidal symptoms, etc.

Significant therapeutic results for tinnitus treatment/ control can be achieved by recommendations for control of stress, anxiety/depression and cognitive behavior:

a. Stress: The stress factor is common to a significant proportion of patients with tinnitus of the severe disabling type. A stress diathesis model for tinnitus was presented

initially in 1992 and published in 1995.^{26,1} The model is based upon the application of pioneer work in neuropsychiatry, psychology and the neurosciences for depression and stress.^{10,11}

A stressor can be defined in the narrow physiological sense as any perturbation in the outside world that disrupts homeostasis. The stress response is a set of neural and endocrine adaptations that help to re-establish homeostasis. ¹⁰ The stress diathesis model for depression, modified for tinnitus, reflects recent reports suggesting that the site of lesion of hypercortisolemia with resultant increase in anxiety and depression is in the hippocampus and not the hypothalamus. ¹¹ The hippocampus is part of the MTLS. Does this factor of stress accentuate and/or modulate primary disease of the ear and/or CNS; which results in the transformation of a physical stimulus to a central sensory aberrant auditory perception which we identify and call tinnitus?

b. Anxiety/Depression: Significant influence on the overall problem of tinnitus particularly of the severe disabling type has been consistently reported by the use of benzodiazepines i.e., Klonopin,²⁰ Xanax,²¹ and Nortriptyline.²⁷

The use of anxyiolytic/antidepressant medication requires a duration of treatment of at least two to six weeks. Such patients are referred for psychiatric consultation and treatment.¹²

c. Cognitive behavioral therapy is an attempt to assist the tinnitus patients to "think differently and alter their attitudes about their problem".²⁸ Its an attempt to reconceptualize the problems presented by a disorder into a form that does not contribute to its severity. The other component, behavior modification, identifies factors that contribute to the problem and the subsequent reaction; and to find ways to modify them through behavior. One speaks of a combined cognitive behavioral approach to assist patients to identify and correct maladaptive behaviors, distorted conceptions, and irrational beliefs.

SUMMARY/CONCLUSIONS

1. The significance of the Final Common Pathway for Tinnitus treatment/tinnitus control is hypothesized to be a reflection of an alteration in the neurochemistry of neurotransmitter systems; the identification of which will provide a basis for use of existing drugs known to influence such neurotransmitter systems, and a basis for the development of a neuropharmacology for tinnitus.

2. The concept of a Final Common Pathway for Tinnitus derived from SPECT imaging of brain in patients with tinnitus particularly of the severe disabling type, reflects new images of tinnitus in terms of its neurochemistry.

3. The Serotonin/Dopamine and GABA/Glutamatinergic NMDA neurotransmitter systems are considered significant in drug selection to attempt tinnitus control.

4. The hypothesis of the Final Common Pathway for Tinnitus is supported by neuroscience reports of sensory/ affect interaction in the area of the MTLS.

5. Neuroscience supports clinical observation/reports of interaction/ association of the sensory/affect components of tinnitus in the MTLS and associated paracortices of brain.

6. Neurotransmitter mediated mechanisms of tinnitus production are reflected in the reported drug efficacy for tinnitus treatment/control e.g., Klonopin, Nortriptyline, and Xanax.

7. SPECT of brain is a technology which offers to the tinnitus patient an increased accuracy of tinnitus diagnosis and a method to monitor the efficacy of therapy prescribed.

8. Tinnitus treatment/control is recommended to be based upon differentiation of recommendations between that for sensory, affect and psychomotor components for the symptom of tinnitus.

9. Instrumentation continues to offer the highest incidence of reported tinnitus treatment/tinnitus control to date with minimum side effects.

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