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Descending Auditory System/Cerebellum/Tinnitus

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Abstract: The cerebellum and the descending auditory system (DAS) are considered clinically significant for influencing the development of the clinical course of tinnitus of the severe disabling type.

It is hypothesized that the SPECT of Brain perfusion asymmetries in cerebellum, demonstrated since 1993, reflect clinically the influence of an aberrant auditory stimulus i.e. tinnitus, on the activity and function of the descending auditory system highlighted by the cerebellum and the acousticomotor systems.

SPECT of Brain perfusion asymmetries in the cerebellum have been demonstrated in 60–70% of tinnitus patients of the central type. Electrophysiologic support for this finding includes interference in ocular fixation suppression of the vestibulocular (VOR) with rotation and position testing. Abnormalities in cerebellar function are considered to reflect the psychomotor component of tinnitus. Support for the hypothesis is demonstrated with one patient with a predominantly central type tinnitus of the severe disabling type with cerebellar perfusion asymmetries and associated electrophysiologic evidence of interference in the VOR with rotation testing.

Keywords: descending auditory system, acousticomotor system, SPECT of brain, cerebellum, psychomotor component, vestibulo-ocular reflex (VOR)

The purpose of this manuscript is to discuss for the first time, in 1999, the role of the cerebellum and descending auditory system in the development of the clinical course of tinnitus of the severe disabling type, as demonstrated objectively and reported in 1993 with SPECT of Brain perfusion asymmetries [1–5].

Since 1995 tinnitus has been defined as a sensory disorder of auditory perception reflecting an aberrant auditory signal produced by interference in the excitatory/inhibitory processes involved in neurotransmission [6–8].

The clinical experience with the symptom of tinnitus, which is in a state of evolution, has challenged/altered classical concepts of functioning of the auditory system and brain. A new discipline has evolved which we have called Tinnitology [9]. Tinnitology, a discipline involving professionals dedicated to the science of sound perception unrelated to an external source of sound.

The symptom of tinnitus has forced clinicians attempting to establish protocols for an accuracy of the tinnitus diagnosis and for tinnitus treatment to apply basic principles of sensory physiology and findings evolving from the neuroscience of brain function and its underlying neurochemistry [10–14].

Since 1977, my co-worker Dr. Barbara Goldstein, an audiologist, and I have at the Tinnitus Clinic at the Health Sciences Center Brooklyn, State University of New York (HSCB-SUNY) attempted to increase the accuracy for the tinnitus diagnosis, focusing on subjective tinnitus of the severe disabling type; and to identify its medical significance. We have attempted to provide tinnitus relief for an excess of 6,000 patients. Since 1995, the Martha Entenmann Tinnitus Research Center, Inc. (METRC) at the HSCB-SUNY has supported our clinical research and investigations.

Since 1989, the nuclear medicine technique of Single Photon Emission Computerized Tomography (SPECT)

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has been introduced into our medical audiologic tinnitus patient diagnostic protocol (MATPP) to attempt to improve the accuracy of the tinnitus diagnosis as well as to monitor the efficacy of modalities of therapy recommended for attempting tinnitus control [1–8,15,16]. Since 1999, SPECT Imaging of Brain, baseline and the Diamox Stress Test, a test for cerebrovascular reserve, are being recommended to patients with tinnitus of the severe disabling type who are not responding to recommendations for attempting to relieve tinnitus. Eighty-five studies have been completed since 1981. Sequential studies have been obtained since 1996.

The evolving clinical experience with SPECT Imaging of Brain has influenced our definition of tinnitus, protocols for both diagnosis and treatment, and confirmed the significance of the factor of stress [17–19].

This paper on the descending auditory system and cerebellum will present their proposed role in the clinical course of tinnitus. This will include:

First, a brief review of three highlights of our evolving SPECT of Brain experience which includes a) the identification of a Final Common Pathway for tinnitus in the Medial Temporal Lobe System (MTLS) of Brain, b) Tinnitogenesis—a epileptiform auditory phenomenon, and c) perfusion asymmetries in the cerebellum—and their considered role in the clinical course of a predominantly central type tinnitus of the severe disabling type.

Second, the physiologic significance of the descending auditory system; and acousticomotor systems, on the clinical course of tinnitus.

Third, a demonstration of SPECT Imaging of Brain perfusion asymmetries in the cerebellum in one patient with the clinical diagnosis of cerebrovascular disease.

SINGLE PHOTON EMISSION COMPUTERIZED TOMOGRAPHY (SPECT OF BRAIN)

Single Photon Emission Computerized Tomography (SPECT) of Brain with the radioisotope Technetium 99m Hexamethyl Propylenamine Oxime (TC-99-HMPAO) is a nuclear medicine imaging technique which provides an objective analytical detection method of information of regional cerebral perfusion of brain. Cerebral blood flow has been correlated with function [4].

SPECT Imaging of Brain in patients with tinnitus of the severe disabling type has revealed since 1991 pathophysiologic loci in patients with a central type tinnitus [1].

Since 1991 repeated findings in SPECT Imaging of Brain in patients with tinnitus particularly of the severe disabling type using the radioisotope TC-99-HMPAO has revealed perfusion asymmetries in multiple cortical areas including the cerebellum. For the first time *in vivo* the significance of the organicity of brain for a predominantly central type tinnitus was presented in New York City at the Triological Society (January 30, 1993) and subsequently published in *The International Tinnitus Journal* in 1995 [2].

Two regions of interest consistently continue to demonstrate asymmetries in regional cerebral blood flow with significant side to side asymmetries. These areas are: a) medial temporal system; and b) the cerebellum. Common to all has been an incidence of perfusion asymmetries involving the medial temporal lobe system (MTLS) in more than 90% of the cases with a p of less than 0.05 [1–5,7]. Adjacent perfusion asymmetries involving the frontal, temporal and parietal lobes have suggested an interneuronal network resulting in the transition of the sensory to the affect components of the symptom of tinnitus.

It is hypothesized that a fundamental function of the amygdala hippocampal structures is the establishment of a paradoxical auditory memory for tinnitus. 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. It is a result of alteration in all tinnitus patients of a basic function of the auditory system, namely, auditory masking. A paradoxical memory for an aberrant auditory signal, i.e. tinnitus, is considered to be the initial process in the transition of the sensory to the affect component. Underlying mechanisms are hypothesized to exist and to be highlighted by a diminution of inhibition mediated by amino butyric acid (GABA) due to its disconnection from excitatory (glutamate) inputs. Blockage of GABA mediated inhibition results in Tinnitogenesis, a epileptiform auditory phenomenon [8,9].

In the original ten tinnitus patients with a severe disabling, predominantly central type tinnitus, examined in a basal state, and compared with four matched controls, 73 regions of interest were analyzed. Nine of 73 regions of interest analyzed were found to have a significantly increased blood flow in patients compared to controls with a p of less than 0.05. Five of the 9 regions were the cerebellum [1,3].

Persistence of findings of perfusion asymmetries involving the cerebellum in a significant number of patients with severe disabling tinnitus supports consideration of the role of the cerebellum in the clinical course of tinnitus.

One of the implications of the hypothesis of a Final Common Pathway for Tinnitus has been its innovative application for treatment. Selected patients are recommended a neuroprotective drug therapy for treatment based on neurochemistry influencing, predominantly the GABA/glutamate and dopamine/serotonin systems. It is hypothesized that in the Final Common Pathway for Tinnitus the homeostasis between sensory and affect, modulated by stress, is interrupted and displaced toward the affect. A stress diathesis model for tinnitus has been formulated in 1992 [19,20]. Significant are the reports by McEwen of the high concentration of steroid receptors and benzodiazepine receptors in the hippocampus [21–24] and of stress by Sapolsky [25,26]. Therapy directed to influencing the GABA benzodiazepine receptor and circulating corticosteroid accompanying stress, when combined with anxiolytic/antidepressant medication, has resulted clinically in a significant degree of tinnitus control.

It is hypothesized that the model of the Final Common Pathway in the patient with tinnitus relief reflects a reestablishment of the homeostasis between the sensory and affect components of tinnitus.

A principle of sensory physiology is that every sensation has components [10]. The components are sensory, affect, and psychomotor. For the symptom of tinnitus the sensory component is clinically manifest by the quality and intensity of the symptom. For the affect component, it is the behavioral and emotional response of the patient to the presence of the tinnitus sensation. For the psychomotor component, behavioral motor changes reflected in facial and body movements have been reported [27,28].

All sensory systems involve a sensory stimulus input and a behavioral response output. Tinnitus, a sensory disorder of the cochleovestibular system, is compelling professionals, regardless of discipline, to address the issue of how an auditory sensory stimulus results in a particular behavioral response; or conversely—does an antecedent behavioral pattern of response, influence the sensory perception of a normal or an aberrant auditory sensory input, resulting in the auditory perception of tinnitus of the severe disabling type. Tinnitology, a discipline involving professionals dedicated to the science of sound perception unrelated to an external source of sound, reflects this effort. The search for understanding how the transition occurs from sensory to affect in brain is not new [13,29].

The Final Common Pathway is hypothesized to rely on the properties of an interneuronal cortical/subcortical network which transforms one representation that is sensory into one that is affect. The anatomical substrate is the medial temporal lobe system. This can create an error in pattern recognition of the normal auditory signal. The SPECT findings at present suggest a common interneuronal cortical/subcortical network.

One can for tinnitus speculate on six layers of such a network [8]: (1) the periphery, i.e. Organ of Corti; (2) the brain stem; (3) ascending auditory system to the level of the inferior colliculus; (4) inferior colliculus and thalamus; (5) thalamus and auditory cortex; and (6) multiple neuronal circuits within the brain cortex (i.e. frontal, temporal, parietal). Feedback loops exist at brain stem, thalamus, temporal lobe, and the medial temporal lobe system. The feedback loop is considered a clean-up layer. Such layers attempt to reestablish a homeostasis within the sensory system. Significant are the physiologic effects of the ascending, descending auditory systems and the cerebellum on the auditory signal both normal and aberrant. Hinton et al. have described such neuronal networking in investigations simulating brain damage [30].

LeDoux has reported a neuroanatomical subcortical emotional processing circuit (i.e. thalamo-amygdala in which the emotional significance of an auditory stimulus can be learned, stored in memory, and expressed in body physiology via the autonomic nervous system and behavior via the somatosensory system) [31,32]. Sensory processing occurs across the medial region of the auditory thalamus and the intralaminar nucleus to the lateral nucleus of the amygdala, that is, the thalamo-cortical-amygdala and the short thalamo-amygdala emotional pathways.

The emotional pathways identified by LeDoux are considered significant particularly for understanding the anatomical substrates involved in the development of the behavioral/emotional affect component of the symptom of tinnitus, particularly of the severe disabling type; as well as for future therapies. One such therapy, reported in 1996, is medial thalotomy performed on 104 patients with "chronic therapy resistant positive symptoms" by Jeanmonod [33]. Six patients had severe tinnitus, and half of them were reported to have experienced relief. The rationale is the identification of low threshold calcium spike bursts (LTS). The LTS bursts reflect deinactivation of calcium channels which result in a membrane hyper-polarization by either a loss of excitation or an increase of inhibition. The end result is the appearance of a bursting activity at the neural site and reflected clinically in a positive symptom. The positive symptoms treated included tremor, action tremor, pain, or epilepsy, tinnitus, and central nervous system (CNS) disorders.

Steriade considers the neocortex and thalamus to be a unified oscillatory machine [34]. Different types of brain rhythms, which characterize various behavioral states, are combined within complex wave sequences. Short term plasticity processes could be used to consolidate memory traces acquired during wakefulness, but also lead to paroxysmal episodes similar to that observed in epileptic seizures. A relationship has been demonstrated between GABAergic thalamic reticular and local circuit neurons and their effects on thalamocortical neurons.

The highest concentration of GABA-A is considered to be in the cerebellum [35]. The relationship between the cerebellum and the thalamus is considered significant and reflected in the acousticomotor systems. GABAergic reticular neurons project not only to thalamocortical neurons but also to local inhibitory neurons. Contact of these inhibitory cells with other inhibitory cells, e.g. thalamocortical neurons would result in a dysinhibition. Consequent to the inhibition of related local neuronal circuits this could result in an excitation through dysinhibition. The end result could be an epileptic type seizure phenomenon reflected clinically by symptoms of interference in function of the region of brain involved.

Therapy directed to an increase in GABA function has been hypothesized to reduce the excitatory glutamate influence. It was speculated and reported in animal experimentation by Kandel in 1995 that the GABAergic inhibition and resultant glutamate excess produced a disruption in motor behaviors, and complex affective and cognitive behaviors, e.g. feeling and learning [36].

Underlying mechanisms reflected in processes within the Final Common Pathway are considered to be highlighted by the glutamate theory of neuroexcitotoxicity. It is speculated that the GABAergic inhibition and resultant glutamate excess produces a disruption in calcium homeostasis with resultant hyperexcitability and epileptic characteristics, i.e. epileptogenesis. It is speculated that any system or mechanism or drug that blocks GABA mediated inhibition can produce a seizure type activity [37].

For tinnitus one can speculate on a Tinnitogenesis, that is a seizure-type activity resulting in the perception of an aberrant auditory stimulus. In such a manner a tinnitus of a central type may arise due to a seizure type activity [9]. At a cortical level, via the Final Common Pathway, a paradoxical auditory memory is hypothesized to develop with a cascade of neurochemical activity reflecting the theory of calcium neuroexcitotoxicity. Clinically this is manifested in a heterogeneity of behavioral/emotional changes highlighted by anxiety, depression, and interference with sleep and communication, task performance, memory and speech expression associated with severe tinnitus.

The descending auditory system and cerebellum are considered critical in maintaining the homeostasis between excitation/inhibition within the peripheral as well as central cochleovestibular system.

THE CEREBELLUM AND TINNITUS

General/Literature

Classically the cerebellum has been postulated to be involved with motor function. Although it is not considered to initiate voluntary movement, it has been considered to serve as a suprasegmental coordinator for muscle activity, especially motor functions requiring sequential, repetitive or complex movements. Also, the cerebellum has been identified to regulate muscular tone and maintain proper balance for standing, walking, and running [38].

Significant are recent new anatomical labeling methods which identify the distribution of input pathways to the cerebellar cortex; and output of the deep nuclei which have led to the identification and understanding that distinctive cerebellar units are important in almost all nervous functions. Cerebellar activity characterized as "coordination" no longer applies only to motor function and control [39].

Technical advances in disciplines of molecular biology, network modeling, functional neuroanatomy and brain imaging with PET, SPECT, fMRI have led to the development of concepts about the cerebellum, which is different from what was classically taught and understood.

Significant for tinnitus are the reports supporting existence of cerebro-cerebellar "loops" and their involvement in motor and non-motor aspects of behavior [40]; and reports of classical conditioning, which have indicated that the cerebellum is significant for the establishment, retrieval and use of associations between stimuli to generate new context dependent and adaptive responses [41].

Functional images of cerebellar activity in patients with tinnitus of the severe disabling type as demonstrated with SPECT Imaging of Brain correlate with abnormal electrophysiologic recordings of cocheovestibular function, including interferences in cognition, motor function, and maintenance of balance [42].

Long term depression (LTD) from synaptic transmission at parallel-fiber/Purkinje-cell synapses of the cerebellum has been considered to play a role in the adaptive modification of the vestibulocular reflex (VOR). The VOR automatically stabilizes the visual image on the retina during head movements by producing eye movements in the direction opposite to that of the head. Ito considers the cerebellum and LTD to be involved in VOR plasticity; and the flocculus to play a role in learning mechanisms which contribute to the VOR [43]. Our clinical experience with routine vestibular testing in patients with tinnitus particularly of the severe disabling type has revealed significant incidence of occurrence of abnormalities in vestibular testing in tinnitus patients who do and do not report interference in balance function [9,44,45]. Significantly, our tinnitus patients with significant cerebellar abnormalities, have all demonstrated failure of fixation suppression of the VOR with eyes open upon rotation [42].

Middleton and Strick have reported that the cerebellum contributes to non-motor as well as motor function [46]. Cerebellar signal to non-motor areas of cortex are involved in cognitive function. Desmond and Fiez, based on functional imaging studies, report the cerebellum to be involved in working memory, implicit and explicit learning and memory, and language. Motor and non-motor functions are reported to be distributed within different regions of the human cerebellar cortex [47]. Schmahmann suggests that in humans cognitive and emotional changes may be prominent [48]. A specific neurologic condition called "cerebellar cognitive affective syndrome" is proposed in which cerebellar damage leads to a dysmetria of thought. There is a deprivation of cognitive circuits by interference in cerebellar modulation. Cerebellar influence on cognitive processing is considered analgous to its influence on motor processing. Does this neurologic syndrome reflect the tinnitus patient's complaint of interference in performance and concentration?

Auditory Stimuli and Cerebellar Response

In the past it has been reported that, in general, natural peripheral stimuli affect activity of larger numbers of cerebellar neurons. Many cerebellar neurons respond to several types of peripheral stimuli [38].

Vestibular, visual, and auditory stimuli, both peripheral and/or central in origin, activate cerebellar inputs to the cerebellar cortex with cerebellar afferent projections to brainstem and cerebral cortices [49].

Vestibular stimulation results in increased neuronal activity in the nodulus, flocculus, uvula, lingula, lobus simplex, lobules I–X of the vermis (i.e. a large cerebellar cortical region). The flocculonodular lobe has been designated as the classic location of the vestibulocerebellum. The extensive distribution of vestibular stimulation to the cerebellum reflects the input of the vestibular nuclei in the brainstem to the lateral reticular nucleus, which, in turn, has input to multiple locations in the vermis and paravermis of cerebellum. There is a convergence in the cerebellum from the vestibular inputs as well as inputs activated by afferents which control eye and head position. Response to visual stimuli are from neurons in multiple regions of the cerebellar cortex particularly the posterior lobe [49].

Auditory responses by cerebellar stimulation have been reported to be modified since 1966 [50,51]. The cerebellum is known to process auditory information by interactions within the cerebellar cortex and by its influence on neurons and nuclei in ascending central auditory pathways, including the cochlear nuclei, inferior colliculus and the superior olive. The regions of response of the cerebellar cortex to auditory stimuli overlap with those of the visual stimuli [49]. Such regions include primarily the posterior lobe. In the past, cerebellar neurons responding to auditory stimulation have been differentiated with respect to frequency identification; interaural time and intensity between stimuli; and to movement of the auditory stimuli [52].

Responses to auditory stimuli are evoked by a cortical and subcortical pathways of the auditory system [53,54]. Ablation of the auditory cortex has been shown to cause marked changes in responses evoked by auditory stimulation [55]. The responses of the evoked auditory responses have been considered to be due to projections involving the cochlear nuclei and projections from the inferior colliculus to the pontine nuclei from the cerebellum [56].

The responses of the cerebellum to auditory stimuli have been considered to be important in adjusting the position of the body and the head to the location of the sound [49]. Cerebellar neurons have binaural response properties [56]. Some cerebellar neurons which respond to auditory stimulation in lobules VI/VII show little specificity to differences in frequency of stimulation, but demonstrate sensitivity to the interaural time and intensity of the two stimuli. In addition, other cerebellar neurons respond selectively to movement of the auditory stimulus [56]. A cerebello-cochlear nucleus pathway has been identified in the cat [57].

Strick, using retrovirus techniques for identification of internal networks, involved in activation of the primary motor cortex control, has reported that 20–30 percent of the cerebellum can only be identified as directly related to motor function involving the primary motor cortex. Additional cerebellar functions have been identified with the prefrontal area for cognition as well as the visual cortex. Investigation is ongoing for cerebellar areas of auditory function [46].

Many physiologic studies have demonstrated auditory processing in the cerebellum, e.g. Vermis [58–60]. The inferior colliculus (IC), and particularly the external nucleus of the inferior colliculus (ICX), a multisensory nucleus, has connections with the superior colliculus (SC), cerebellum (C) and medial nucleus of the medial geniculate body (mMGB). Electrical stimulation of the IC evokes potentials in the vermis [56].

The literature has identified acousticomotor systems in the descending auditory system [61]. The acoustico-motor systems include the acoustico-motor centers of the cerebellum, medial division of the medial geniculate body (mMGB) and the superior colliculus (SC). The ICX projects to these centers (i.e. medial division of MGB, SC, and cerebellum) which themselves subserve multisensory integrative functions.

Ongoing studies are attempting to answer questions presented by the descending auditory system as it applies to the symptom of tinnitus; and in particular the multisensory integrative functions of the ICX with the cerebellum and other acousticomotor systems.

SPECT of Brain

The perfusion asymmetries identified in cerebellum with SPECT of Brain in patients with tinnitus of the severe disabling type are considered to be objective evidence for what may be a reflection clinically of the psychomotor component of tinnitus; and explain some different central types of tinnitus. It may reflect the activity of the descending auditory system; and the multisensory integrative activity of acoustico-motor systems including the cerebellum, external nucleus of the inferior colliculus (ICX), and Superior Colliculus (SC), and the medial division of the medial geniculate body (mMGB).

At this time, a positive correlation can be reported in patients with tinnitus of the severe disabling type between the cerebellar perfusion asymmetries and positive abnormal electrophysiologic test results of interference in cerebellar function e.g. abnormal ocular fixation suppression of the VOR, abnormal position postural testing with electronystagmography (ENG) recording, and abnormal results of craniocorpography (CCG) [27].

SPECT of brain images in one patient with tinnitus of the severe disabling type and the clinical diagnosis of cerebrovascular disease has been selected to demonstrate the multiple perfusion asymmetries in brain, highlighted by the primary auditory cortex, medial temporal lobe system and cerebellum (Figure 1). The multicolor display accentuates asymmetry of cerebellum as demonstrated in the upper transaxial reconstructed image. The arrow points to area of abnormal diminished activity in medial right cerebellum. Coronal Image of same below (Figure 2).

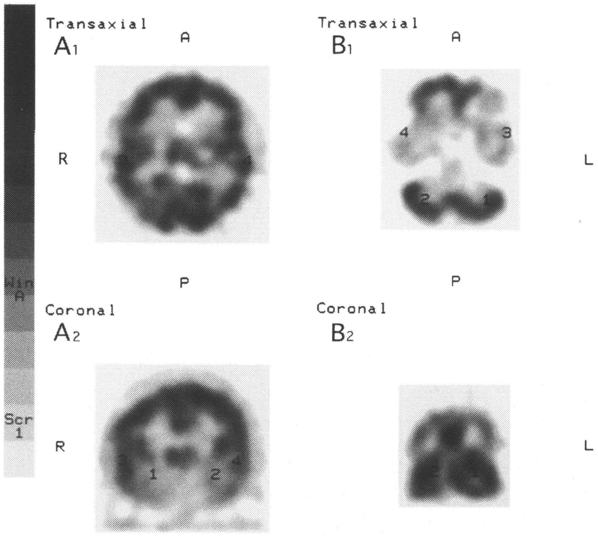

Figure 1. Abnormal SPECT Brain–Cerebrovascular Disease Right (R) Left (L)
A_1 A_2 Medial Temporal Lobe – Reduced perfusion Rt. and Lt.
Primary Auditory cortex – Increased perfusion Rt., Reduced Lt.
B_1 B_2 Cerebellum – Reduced uptake Left greater than Right.
– Temporal Lobes – reduced bilateral
A_1 – Transaxial (Upper Left) 3 – Primary Auditory Cortex (R) Increased Perfusion
4 – Primary Auditory Cortex (L) Decreased Perfusion
A_2 – Coronal (Lower Left): 1 – Medial Temporal Lobe System (R) Reduced Perfusion
2 – Medial Temporal Lobe System (L) Reduced Perfusion
B_1 Transaxial (Upper Right) 1 – Cerebellum (L)
2 – Cerebellum (R)
3 – Temporal Lobe (L)
4 – Temporal Lobe (R)
B_2 Coronal (Lower Right) 1 – Cerebellum (L)
2 – Cerebellum (R)

DESCENDING AUDITORY SYSTEM/ ACOUSTICOMOTOR SYSTEMS

The anatomico-physiologic information of the descending auditory system and its multiple functions are considered significant for understanding not only auditory function in general but specifically the clinical course of the tinnitus particularly of the severe disabling type.

History/Literature

An excellent review of the descending auditory pathway and acousticomotor systems can be found in Huffman and Henson Jr. (1990) [61].

From the start (1979) the symptom of tinnitus was conceptualized as an aberrant sensory phenomenon which clinically could arise in any part of the cochleovestibular system—peripheral and/or central [62]. This was the basis for the formulation of a Medical Audiologic Tinnitus Patient Protocol reflecting a neurotologic/audiologic team approach for both diagnosis and treatment [9,62,63]. It is a dynamic protocol reflecting advances in the basic science and clinical research efforts for tinnitus diagnosis and treatment [64]. A similar approach was applied for tinnitus applying basic neurotologic teaching for complaints of hearing loss and vertigo. Subtypes of a cochlear and central type tinnitus were theorized in 1981 [65–67].

It was hypothesized in 1991 that tinnitus may arise in multiple areas of brain and/or periphery of the cochleovestibular system due to the development of an epileptogenic focus (foci) [9]. The process was called Tinnitogenesis. It was suggested in 1993 to be explainable by the glutamate neuroexcitotoxicity theory [68]. In 1997 it

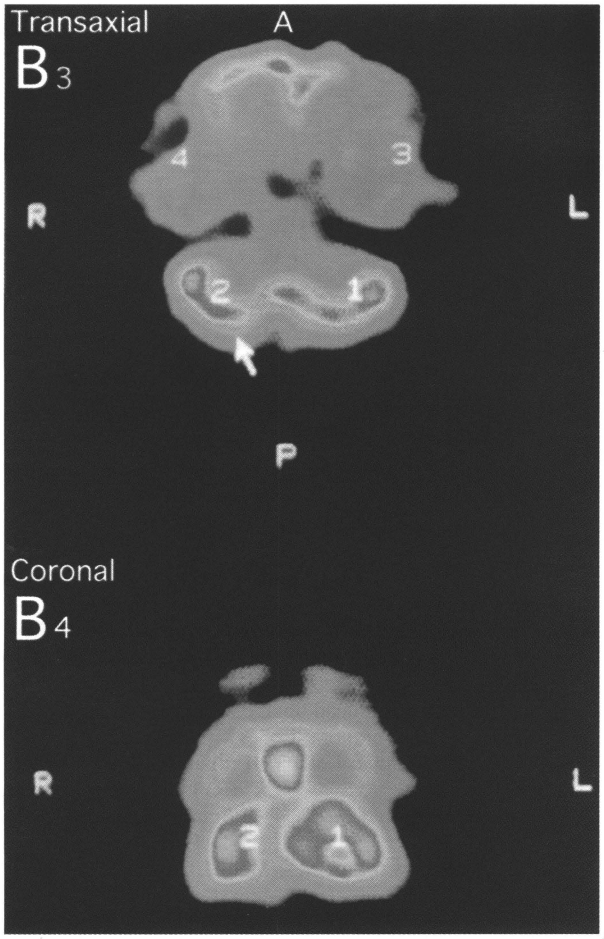

Figure 2. Abnormal SPECT Brain – Cerebrovascular Disease Right (R), Left (L)
B_3 B_4 – Cerebellum – reduced uptake Left greater than Right
– Temporal Lobes – Reduced Bilateral
B_3 – Transaxial (Upper Right)
1 – Cerebellum (L)
2 – Cerebellum (R)
3 – Temporal Lobe (L)
4 – Temporal Lobe (R)
B_4 – Coronal (Lower Right)
1 – Cerebellum (L)
2 – Cerebellum (R)
Arrow – Medial Cerebellum (R)

was suggested that the resulting calcium cascade involved proteases highlighted by calpain [69]. Recent reports from the neurosciences find support for our clinical neurotologic/audiologic reports and clinical approaches to tinnitus for clinical types/subtypes of both cochlear and central types of tinnitus [26,31,32,69–71].

Descending Auditory System [61]

The descending auditory system is considered significant not only for the origin and site of lesion for an aberrant auditory phenomenon, called tinnitus, but also for its role in the clinical course of tinnitus, particularly of the severe disabling type and its modulation.

Significant for our discussion of the descending auditory system for tinnitus is to consider the following:

a. The ascending system consists of essentially eight levels: 1) cochlea (CO); 2) cochlear nucleus (CN); 3) superior olivary complex (SOC) and trapezoid (T); 4) lateral lemnisus (LL); 5) inferior colliculus (IC); 6) medial geniculate body (MGB); 7)thalamus (THAL); and 8) auditory cortex (AC).

b. Three major projections comprise the descending auditory pathway:
   1) Auditory cortex to MGB and IC;
   2) IC to the CN and SOC; and
   3) SOC to CO

   In general, for each projection in the ascending pathway from the CN to AC there is a parallel descending projection with one exception—no geniculocolliculus fibers.

c. The inferior colliculus—an obligatory synaptic station in the descending auditory pathways.

d. The descending inputs to the inferior colliculus from the auditory cortex which include:
   1) Corticocollicular projections;
   2) Corticogeniculate projections;
   3) Colliculocochleonuclei projections;
   4) Colliculolivary projections;
   5) Colliculo-cerebellar projections;
   6) Acousticomotor systems; and
   7) Cerebello-cochlear nucleus projection.

Auditory Cortex to MGB and IC

It has been proposed that regions of the auditory cortex (AC) are homologous across many species. In the rat three AC areas are Broca 41, 22, and 36. Three parallel descending pathways provide a major projection to a nucleus in each of three auditory centers i.e. IC, MGB, an AC (Figure 3) [61]. The three sets of connections are mutually exclusive and provide a system of multiple parallel feedback loops between the AC and the IC. From the AC to the IC the descending auditory pathway is a segregated projection. The majority of the corticocollicular fibers terminate in the dorsal and external nucleus of the IC. There is an absence of projections to the central nucleus. Although this is the case for the cat, rat, and tree shrew, monkeys may be an exception [72,73].

The AC can modulate the response of the IC neurons to sound [74].

The AC projects to both the IC and MGB by the corticogeniculate projections which like the corticocollicu-

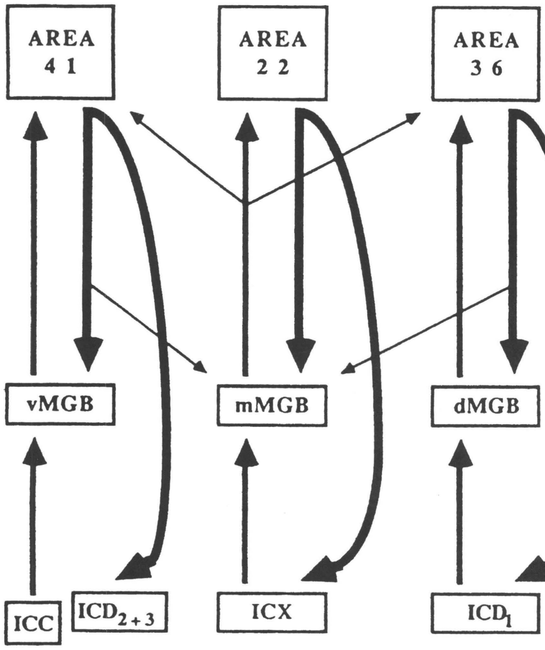

Figure 3. Multiple feedback loops in the descending auditory system of the rat. Each of three parallel descending pathways provides a major projection to a nucleus of 3 auditory centers: inferior colliculus, medial geniculate body and auditory cortex. v MGB, ventral division medial geniculate body; mMGB, medial division medial geniculate body, dMGB, dorsal division medial geniculate body; ICC, central nucleus inferior colliculus; ICD, dorsal nucleus inferior colliculus; ICX, external nucleus inferior colliculus. From: Huffman, R.F., Henson, O.W. Jr. The descending auditory pathway and acousticomotor systems, connections with the inferior colliculus. *Brain Research Reviews* 15 (1990) 295–323. Elsevier, with permission from Elsevier Science.

lar fibers originate from pyramidal cells in the AC [61]. There are three distinct corticocolliculo-geniculocortical pathways in the rat. A system of three parallel descending pathways in the cat and rat exists in other animals suggesting a common mammalian scheme. The anatomical and physiological characteristics of these projections are similar to those that reach the IC. There are two parallel cortical projections in the descending auditory pathway. One to the IC, the other to the MGB. The projections from the AC to both the IC and the MGB originate from the pyramidal cells in AC.

Significant for the AC projections to the MGB are the reciprocal connections between both structures for origin and termination. Although all AC areas in the rat i.e. Broca 41, 22, 36 have connections with the MGB, each of these three areas in the rat has a strong individual and separate connection, e.g. Area 41 with the ventral medial geniculate body (vMGB); Area 36 with the deep dorsal medial geniculate body (dMGB); and Area 22 with the medial division of the medial geniculate body (mMGB).

Inhibition is a common feature in descending neural systems [61]. This is performed by inhibitory mechanisms which reduce baseline activity in the absence of sound; and by excitatory mechanisms which prolong the duration of auditory signal processing. In both cases the signal to noise ratio of the system is increased by cortical input. However, input from the AC can facilitate lemniscal synaptic transmission [75]. The overall result can be an increased excitatory synaptic transmission in response to an acoustic signal even though inhibition is a common feature in the descending neural systems.

Cortical influences on the descending auditory pathway include models of inhibition, and increased sensitivity as well as cognitive influences.

Inferior Colliculus to CN and SOC

Briefly, the inferior colliculus (IC) can be divided/classified into central, dorsal, and external nuclei. The IC is a caudal ventrolateral central nucleus that is encapsulated by the dorsal nucleus dorsally and caudally, and by the external nucleus ventrally, laterally and rostrally (Figure 4) [61]. Each nucleus of the IC has been identified to have distinct structural and functional features.

The central nucleus participates directly in ascending and descending primary auditory pathways and receives the principal relay afferent fibers of the ascending auditory system. Fibers synapse rostrally with the principal auditory thalamic relay nucleus which is the ventral divi-

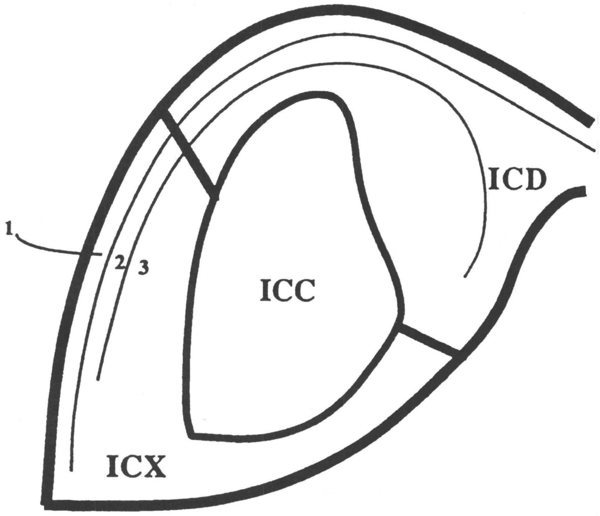

Figure 4. Schematic of a coronal section through the inferior colliculus showing the central (ICC), dorsal (ICD) and external (ICX) nuclei. Lines near the dorsal and lateral surfaces indicate a cytoarchitecture (layers 1–3). *Brain Research Reviews* 15 (1990) 295–323. Elsevier, with permission from Elsevier Science.

sion of the MGB, and caudally with the dorsal and ventral cochlear nuclei, superior olivary complex and nuclei of the LL [76–78].

The dorsal nucleus receives major auditory cortical projections and projects exclusively to the dorsal division of the MGB. It includes the dorsal cortex and areas adjacent to the periaqueductal gray which are dorsal and medial to the central nucleus [79].

The external nucleus receives both auditory and somatosensory input. This suggests a role in multisensory integration. It projects to the medial division of the MGB and descending acousticomotor systems [60]. The cerebellum may also have some influence directly on the ascending core auditory system via the acousticomotor systems. There are multiple feedback loops between the inferior colliculus, MGB and the auditory cortex [80–83].

In summary, the most frequently reported connection intrinsically within the IC is from the central to the external division of the IC. The external nucleus is a multisensory nucleus which functionally separates it from the other auditory IC nuclei. It has connections with SC, cerebellum and mMGB which themselves are multisensory, mutually interconnected, and share descending cortical projections from the AC.

IC/SOC/Cochlea

The IC projects caudally to two auditory brain stem areas, the CN [78,84–87], and the SOC [77,78,84,87, 88]. The projections from the IC allow direct effects not only on the auditory brain stem but also contribute to the descending auditory pathway originating from the SOC. The colliculolivary projections appear to terminate in parts of the SOC where olivocochlear neurons have been identified [61].

Significant for tinnitus is the role of the inferior colliculus and the olivocochlear efferent system. Recent reports of Sahley, Musiek, and Nodar of a model for opiate receptor identification within the auditory system and speculation of its action both central and its effect peripherally within the Organ of Corti is considered significant for understanding the clinical course of tinnitus and for future tinnitus treatment [89]. Tinnitus as Tonndorf has hypothesized may be the "pain" of the auditory system [90].

A trisynaptic pathway has been suggested by anatomical and physiological reports between the auditory cortex and cochlea [61] (Figure 5). The IC provides a possible link between descending information from the AC; and the olivocochlea (OC) efferent system to the outer hair cells (OHC) in the cochlea [91]. The reciprocal ascending and descending connections between any pair of nuclei within the IC/SOC and CN result in a system of multiple feedback loops for auditory information. For auditory information processing caudal to the IC, bilateral projections have not been described.

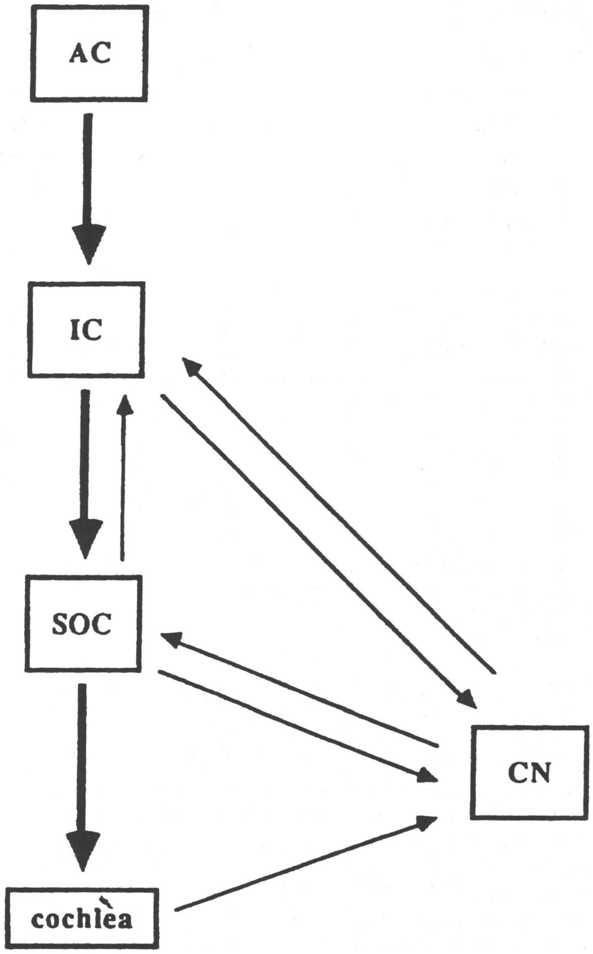

Figure 5. Trisynaptic pathway between auditory cortex and the cochlea (thick arrows). AC, auditory cortex; IC, inferior colliculus; SOC, superior olivary complex; CN, Cochlea nucleus. From: Huffman, R.F., Henson, O.W. Jr. The descending auditory pathway and acousticomotor systems, connections with the inferior colliculus. *Brain Research Reviews* 15 (1990) 295–323. Elsevier; with permission from Elsevier Science.

There are at least five obligatory synapses in the ascending pathway from the cochlea to the AC. Descending impulses from the AC reach the cochlea in a travel time shorter than that of ascending information. This is an advantage since the descending feedback does not interfere in the continuous cycle of reception and modification of incoming sensory information [61].

Many physiologic studies have demonstrated auditory processing in the cerebellum e.g. vermis [59,60,92, 93,94]. The IC, and particularly the external nucleus of the IC, a multisensory nucleus has connections with SC, cerebellum and medial nucleus of the medial geniculate body i.e. the acousticomotor systems.

Acousticomotor Systems

The literature has identified acousticomotor systems. The acousticomotor systems include the medial division of the MGB, the superior colliculus, and cerebellum. Each of the divisions of the acousticomotor systems subserve multisensory integrative functions and participate in coordination of head, ear, and eye movements for sound localization.

Ongoing studies are attempting to answer questions presented by the descending auditory system as it applies to the symptom of tinnitus and, in particular, the multisensory integrative function of the external nucleus of the IC with the cerebellum and acousticomotor systems [96].

The SC is considered a higher center for coordination of directional orientation of head, eyes, and ears [97]. The projection of the IC to the SC has been observed in many species i.e. cat [98], guinea pig [79], kangaroo rat [99], monkey [77], rabbits [100], rat [101] and bats [102].

The findings with SPECT Imaging of Brain and perfusion asymmetries in cerebellum of tinnitus patients are considered to be a reflection of the activity of the descending auditory system and, in particular, the acousticomotor systems in brain and its response to an aberrant auditory stimulus. Clinically this may reflect a psychomotor component of tinnitus and explain some different central types of tinnitus.

Connections of the descending auditory pathway complement those of the ascending pathway. In both systems the IC is a obligatory station for the termination of fibers [61].

The IC has significant roles in both ascending and descending auditory pathways and in acousticomotor systems. The external nucleus of the IC projects to these systems i.e. medial division of MGB, SC, and cerebellum which themselves subserve multisensory integrative functions [61].

The acousticomotor systems/pathways/projections may explain clinical manifestations of both acoustic somatosensory and limbic system dysfunction frequently reported by tinnitus patients of the severe disabling type.

Inferior Colliculus—Additional Roles

It is suggested that the significance of the IC extends beyond that of the ascending, descending, and acousticomotor pathways [61]. Additional roles proposed reflect connections of the IC with the hypothalamus and its role in learning and memory. Significant for tinnitus are studies of acoustic conditioning which indicate that neural activity in the IC changes with conditioning [103,104]. A frequency selective increase in metabolic response has been demonstrated in the IC with associative classical conditioning of an acoustic stimulus to a unconditioned stimulus [105]. In the rat discharge rates of the IC and the CN to an acoustic stimulus (condition stimulus) increase when paired with an unconditioned stimulus. This may explain classical tinnitus relief methods described by patients who report that they are better able to deal with the complaint over time and/or become less disturbed by the stimulus i.e. natural habituation [106]; and tinnitus retraining therapy called "habituation" [107].

It is known that the mMGB projects to the limbic system and subcortical areas involved in processing of emotional behavior i.e. amygdala, caudate, putamen, and ventral medial hypothalamic area. The mMGB may serve as a primary link for attaching emotional significance to acoustic stimuli [31,32,108].

It is questioned whether the IC provides auditory input to the mMGB which has encoded information about acoustic condition to learning. Whether or not the IC has influence on the activity of limbic structures remains to be established. There is discussion of not only auditory but possibly non-auditory processes in the IC [61].

The IC significantly contributes to the descending auditory system as well as descending control of the acousticomotor systems.

The IC is a source of auditory input to integrate auditory, visual and tactile localization cues. Orientation behavior and localization. It also may play a role in acoustic reflex such as the acoustic startle response [110], and middle ear reflex [61].

The external nucleus of the IC projects to the SC and the cerebellum. Both are neural sites of multisensory integration and participate in coordination of head, ear, and eye movements toward a sound source. Connections of the IC with SC, cerebellum and somatosensory system suggest that the external nucleus is a crucial relay in the acousticomotor pathways. It is a role separate from that of the core auditory system (Figure 6) [61]. The connection of the IC with the SC is thought to have a role in acoustic orientation. The SC is generally considered a higher motor center for coordinating directional orientation of head, eyes, and ears. Additional connections of the SC with the auditory system contribute to acousticomotor pathways and also create feedback loops (Figure 6) [61].

Auditory information processing has been demonstrated in the cerebellum. Multiple descending auditory projections to the cerebellum via the dorsolateral pontine nucleus (DLPN) parallel those from the IC. The IC connects with the cerebellum by way of tectopontine projections. Electrical stimulation of the IC evokes potentials in the vermis [111]. The DLPN is the principal brain stem relay nucleus projecting to those areas in

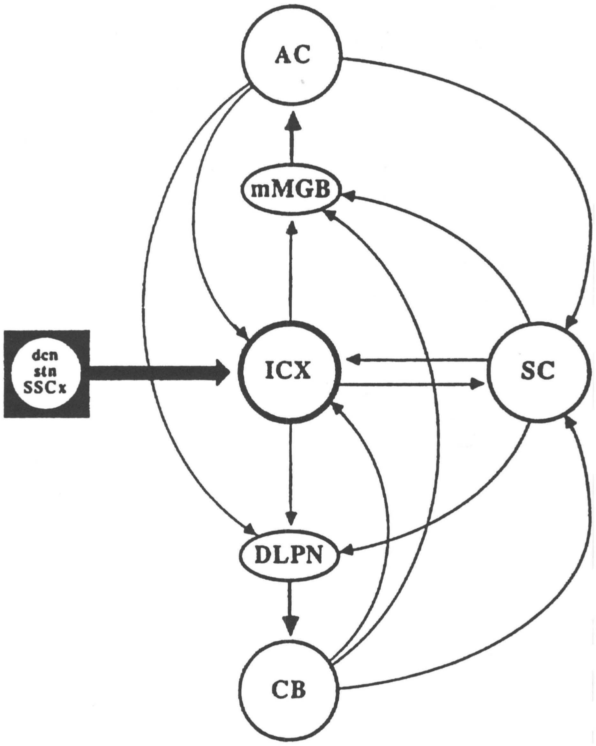

Figure 6. Connections of the external nucleus of the inferior colliculus with acousticomotor and somatosensory systems. CB, cerebellum; dcn, dorsal column nuclei; stn, spinal trigeminal nuclei; SSCx, somatosensory cortex. From: Huffman, R.F., Henson, O.W. Jr. The descending auditory pathway and acousticomotor systems, connections with the inferior colliculus. *Brain Research Reviews* 15 (1990) 295–323. Elsevier, with permission from Elsevier Science.

the cerebellum responsive to acoustic stimuli [112–115]. In the cat it is predominantly the external nucleus which projects heavily to the DLPN. The most concentrated projection is to lobule VII of the vermis; as well as lobules VI, VIII, VX, CRUS I, II and the paraflocculus and the paramedian lobule [115].

DISCUSSION

The classical concept of cerebellar control involving primarily coordination of motor function has within the past 30 years undergone distinct change. Most significant has been the identification that most types of natural peripheral stimuli affect the activity of larger number of cerebellar neurons. This is highlighted by cerebellar responses to vestibular, visual, and auditory stimuli [49].

The control function of the cerebellum originally considered to be that of a "braking" action, has recently been demonstrated to include both gabaergic (braking) and glutaminergic (accelerating) activity [34].

In tinnitus the multiple areas of perfusion asymmetries demonstrated by nuclear medicine SPECT studies is represented by hypo- and hyperactivity and suggest an interneuronal network controlled by neurochemical interaction of multiple neuro-transmitter systems which are hypothesized to influence the clinical course of severe disabling tinnitus [1–5].

To be considered in the understanding of the clinical significance of the perfusion asymmetries in cerebellar cortex are:

a) Interference/increase in gabaergic inhibition to auditory nuclei in the ascending auditory pathway and primary auditory cortex;
b) Interference in thalamic control of speech as well as influence expressed clinically as fear. That is, interference in the emotional response of the patient in the presence of an aberrant auditory signal in the thamalo-amygdala and/or thalamocorticoamygdala pathway;
c) Interference in proprioceptive function manifested in alteration in psychomotor response reflecting the psychomotor component of tinnitus and identified by interference in head and body position;
d) Influence of visual orientation to auditory localization and overall motor response to spatial orientation in the presence of an aberrant auditory signal;
e) Interference in plastic changes within the CNS highlighted by location in the primary auditory cortex, thalamus, and inferior colliculus;
f) The influence of the cerebellum is proposed for the establishment of a paradoxical auditory memory for tinnitus. The establishment of a paradoxical auditory memory has been hypothesized to be the initial process in the transition of the sensory to the affect component of tinnitus which influences the development of the clinical course of tinnitus of the severe and disabling type;
g) Diaschisis, a neuronal cut-off of blood supply manifesting itself in the connected contralateral cerebellum and reflecting an attempt to reestablish homeostasis within the intra-cranial circulation needs to be differentiated from neuronal damage. The diamox stress test may in tinnitus patients differentiate between cerebrovascular insufficiency and/or neuronal change. Autoregulation of intra-cranial blood flow may in the absence of an adequate cerebrovascular reserve result in interference in cerebellar function, and be reflected not only in the primary motor cortex but also in prefrontal areas for cognition, the visual cortex for vision, the vestibular parietal cortex for spatial orientation, the primary auditory

cortices for perception of sound, and the somatosensory cortex.

h) The acousticomotor systems are part of multisensory integrative pathways. The cerebellum plays a role in each acousticomoter system.

Special attention in the cerebellum is recommended for associated symptoms reported by tinnitus patients such as interference in speech expression, psychomotor complaints, gait difficulty, and abnormal orientation of the head and proprioceptive input system in response to auditory stimulation.

CONCLUSION

1) Perfusion asymmetries in the cerebellum, identified with SPECT Imaging in Brain may influence by its overall increase and/or decrease in gabaergic activity the development of the chronic clinical course of severe disabling tinnitus;
2) Cerebellar hypo-perfusion asymmetries may specifically in patients with tinnitus be reflected clinically in various forms of dysacusis; emotion i.e. fear; and manifestations of the psychomotor component of tinnitus e.g. interference in somatosensory and proprioceptive function;
3) Auditory inputs both normal and aberrant have inputs to the cerebellum and interact with other sensory systems;
4) Interneuronal pathway regulation of multiple neuro-transmitter systems may be modulated by cerebellar activity;
5) Close attention is advised for the interaction between areas of abnormality in perfusion between cerebellum; thalamus; medial geniculate body; auditory cortex, Broca and Wernicke areas;
6) One needs to consider whether the cerebellar perfusion asymmetries reflect the phenomenon of diaschisis, or alteration in neuronal function, or a combination of both. The significance of the cerebellar perfusion asymmetries for the clinical course of tinnitus remains to be established;
7) It is postulated/hypothesized that tinnitus may arise in multiple areas of brain and/or periphery due to the development of an epileptogenic focus (foci) reflecting activity of glutamate neuroexcitotoxicity theory and calcium cascade involving the proteases highlighted by that of calpain;
8) The Final Common Pathway for tinnitus between the sensory and affect is modulated by stress and involves the GABA-A receptor modulated by steroids;
9) Finally, cerebellar manifestations of perfusion abnormality have been demonstrated not only with SPECT Imaging of Brain but also have been clinically correlated with manifestations of the psychomotor component as demonstrated by interference in the visual vestibular interaction and prolongation/interference of the VOR, abnormal position posture testing, and craniocorpography (CCG). The clinical significance of these abnormal cerebellar findings in tinnitus patients of the severe disabling type needs to be considered in attempts to establish an accuracy of diagnosis and treatment.

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