
Central Nervous System Neurodegeneration and Tinnitus: A Clinical Experience

Part II: Translational Neurovascular Theory of Neurodegenerative CNS Disease and Tinnitus

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Abstract: The translation of a neurovascular hypothesis for Alzheimer's disease to subjective idiopathic tinnitus (SIT) is presented as a challenge to the predominantly sensorineural view of SIT and its clinical application for tinnitus treatment. The concept of neurovascular dysfunction and neurodegeneration (ND) in SIT patients has been proposed and reported as an etiology in a particular subset of tinnitus patients with a diagnosis of medical-audiological tinnitus, through a medical-audiological tinnitus patient protocol, to be a predominantly central-type, severe, disabling SIT (n = 54 of 96). A medical-audiological ND tinnitus profile was the basis for selection of 18 SIT patients (n = 18 of 54) for nuclear medicine brain imaging (i.e., single-photon emission computed tomography or positron emission tomography, or both). Objective findings were reported in 16 of this cohort of 18 SIT patients selected for nuclear medicine imaging (88.9%). Classification of central nervous system (CNS) ND and tinnitus differentiated between (1) ND, nonspecific and of unknown etiology; (2) ND manifested by perfusion asymmetries in brain associated with ischemia (n = 11 of 18); and (3) ND CNS disease consistent with nuclear medicine criteria for senile dementia Alzheimer's-type disease (n = 5 of 18). The diagnosis was associated with cerebrovascular disease (n = 16 of 18). The identification of pathological processes of inflammation and ischemia, linked to ND, in a particular cohort of SIT patients may provide a basis for establishing the medical significance and treatment of SIT and influence the clinical course of the tinnitus.

Key Words: inflammation; ischemia; neurodegeneration; neuroprotection; neurovascular theory

This publication is the second part of a report of our clinical experience since 1979 with subjective idiopathic tinnitus (SIT) wherein the concept of neurovascular dysfunction has evolved as an etiology in a particular cohort of SIT patients, its medical significance being neurodegenerative (ND) central nervous system (CNS) disease [1]. A neurovascular theory of ND CNS disease has been proposed for Alzheimer's disease (AD) [2].

A clinical translation of this neurovascular theory of ND CNS disease for tinnitus—translational neurovascular theory of (CNS disease) neurodegeneration and tinnitus (TNTNT)—is presented as a hypothesis to explain and support the clinical observation that a vascular etiology, initiated by the pathological processes of inflammation and ischemia in a particular cohort of tinnitus patients, reflects ND underlying the clinical manifestations and course of the tinnitus [1].

Classification of central nervous system (CNS) ND and tinnitus differentiated between (1) ND, nonspecific and of unknown etiology; (2) ND manifested by perfusion asymmetries in brain associated with ischemia (NDDI; n = 11 of 18); and (3) ND CNS disease with nuclear medicine criteria for senile dementia Alzheimer's-type

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disease (NDD-SDAT; $n = 5$ of 18). The diagnosis was associated with cerebrovascular disease ($n = 16$ of 18) [1].

Identification of this particular cohort of tinnitus patients was reported to be based on (1) the establishment of an accurate tinnitus diagnosis of a predominantly central-type, severe, disabling SIT ($n = 54$ of 96); (2) the positive identification with a medical-audiological neurodegenerative tinnitus profile (MANTP) of CNS dysfunction in a selected cohort of tinnitus patients with a diagnosis of a predominantly central-type, severe, disabling tinnitus ($n = 16$ of 96; 16.6%); and (3) the clinical application of nuclear medicine brain imaging that provided a metabolic correlate of neural activity reflective of a vascular etiology [1].

The clinical application of the MANTP for patient selection for nuclear medicine brain imaging (i.e., single-photon emission computed tomography [SPECT] or positron emission tomography [PET] or both), resulted in objective evidence of ND in 16 of 18 patients (88.9%). The etiology of the diagnosis of ND was associated in the clinical history with cerebrovascular disease in 16 patients ($n = 16$ of 18; 88.9%). A link was established between neurovascular dysfunction and ND in SIT patients. This link clinically presents a challenge to the predominant sensorineural view of tinnitus, which focuses on the psychophysical and psychoacoustical elements [1].

The pathological process of inflammation and ischemia, when identified in a particular cohort of SIT patients, may provide a basis for treatment and influence the clinical course of the tinnitus. The clinical translation of a neurovascular theory for ND CNS disease for AD to SIT is presented, with its clinical applications for tinnitus diagnosis and treatment.

INTRODUCTION TO A TRANSLATIONAL NEUROVASCULAR THEORY OF (CNS DISEASE) NEURODEGENERATION AND TINNITUS

A neurovascular theory of ND disease and AD has been proposed. Neurovascular mechanisms of ND CNS disease involve a neurovascular unit. Common pathways have been identified as a target of inflammation and link inflammation and ND CNS disease [2,3]. Long-term ischemia, with resultant axonal transport defects, synapse loss, and neuroinflammation may lead to or accompany future pathological tau-mediated neurodegenerative disease (NDD) called *tauopathies* [4]. Long-term magnetic resonance imaging (MRI), SPECT, and PET-computed tomography (PET/CT) brain studies of these patients is planned to identify the clinical course of SIT patients for development of clinical manifestations of NDD-STAD, AD, and frontotemporal dementia (FTD).

The translational neurovascular theory of ND CNS disease and tinnitus (translational neurovascular theory of neurodegenerative CNS disease and tinnitus [TNTNT]) hypothesizes that tinnitus is a “soft sign” of gradual progressive CNS disease in a particular cohort of SIT patients. It is said to be initiated by a vascular etiology and mediated by pathophysiological processes (primary or secondary) of inflammation and ischemia in neural substrates associated with tinnitus (i.e., a final common pathway [FCP] for tinnitus) [5]. The cascade of changes associated with ischemia and inflammation are controlled by molecular proteogenomic mechanisms involving glutamate, calcium, and calpain activities [6–8].

It is hypothesized that alterations in this neurovascular unit in the brain (i.e., brain capillaries, pial and intracerebral arteries, large cerebral arteries) by ischemia or inflammation (or both), when localized in neural substrates identified to be involved in the FCP for tinnitus, can result in ND and progression to SIT (i.e., NDDI and NDD-SDAT). A primary ND CNS disease clinically manifest as, for example, AD (FTD) can, by secondary extension or involvement of the FCP, include the symptom of SIT. For both, NDDI of the primary auditory cortex or associative cortices is primarily involved. For NDD-SDAT, the posterior cortices are primarily involved, with secondary involvement of the primary and secondary associative auditory cortices. What needs to be observed long-term is what, if any, is the incidence of transformation of the NDDI and NDD-SDAT to ND CNS disease (e.g., AD, FTD, and Parkinson’s disease).

This translational theory integrates the pathological processes involved with ischemia and inflammation to explain tinnitus in the context of cerebrovascular disease, a neurovascular unit, supported by the positive results of nuclear medicine imaging (brain SPECT, fluorodeoxyglucose-PET/CT [FDG-PET/CT], and quantitative electroencephalography [QEEG]). Significantly, a correlation that has been clinically established has diagnostic and treatment implications for a particular cohort of SIT patients in whom the medical significance of the SIT has been identified to be a “soft sign” of CNS disease [9–11].

Significantly, brain SPECT or FDG-PET/CT imaging in SIT patients has revealed the incidence of association of NDDI to be limited, with involvement primarily of the FCP neural substrates highlighted by medial temporal lobe and primary auditory and frontal cortices and not that frequently reported for NDD-SDAT—that is, frontoparietotemporal in AD and frontotemporal in FTD. Alterations in regional cerebral blood flow in multiple neural substrates were consistent with ischemia in 11 patients (NDDI = 11 of 18; NDD-SDAT = 5 of 18) and with the etiology of gradual progressive cerebrovascular disease in 16 patients ($n = 16$ of 18) [1].

A review of the literature for the interaction between the pathophysiological processes of ischemia and inflammation are considered translational for the clinical diagnosis of ND, NDDI, or NDD-SDAT in a particular cohort of SIT patients and as targets for treatment strategies attempting tinnitus relief. Translational highlights for SIT from the literature include what follows.

COMORBIDITY OF SIT, ISCHEMIA, AND CEREBROVASCULAR DISEASE

Cerebrovascular disease has been identified and reported with brain MRI, SPECT, and FDG-PET/CT in a cohort of SIT patients ($n = 16$ of 18) [1]. In one patient, auditory hallucinations were reported to be localized to the same side as that of the tinnitus. All patients reported interferences in speech expression and memory, which preceded the tinnitus onset.

Significantly, brain SPECT or FDG-PET/CT revealed the incidence of ND to be limited, with involvement primarily of the neural substrates of the FCP for tinnitus (i.e., medial temporal lobe, primary auditory and frontal cortices) and not that frequently reported with NDD-SDAT (i.e., frontoparietotemporal in AD, and frontotemporal in FTD). In this reported cohort of SIT patients ($n = 18$), the alterations in regional cerebral blood flow in neural substrates were consistent with ischemia in 11 patients (NDDI = 11 of 18) and with SDAT in 5 (NDD-SDAT = 5 of 18). The diagnosis was thereby established of gradual progressive cerebrovascular disease in 16 patients ($n = 16$ of 18) [1].

Recent neurology and neuroscience reports have emphasized the link between AD and cerebrovascular disease [12,13]. The diagnosis of cerebrovascular disease in our clinical experience suggests possible significance for SIT patients.

The reports of ischemia and inflammation are clinically considered support for and the basis of the proposed neurovascular hypothesis of ND for AD. Interference in cognition and memory in the clinical history is considered to be a consequence of neurovascular dysfunction. A neurovascular unit is conceptualized by which regulation of local cerebral blood flow molecular transport across the blood-brain barrier maintains tight control of the chemical composition of the neuronal internal environment. Dysfunction of local cerebral blood flow in the neurovascular unit (i.e., at the level of brain capillaries, pial and intracerebral arteries, large cerebral arteries) can result in a reduction in blood supply to the brain, with resultant interferences at the blood-brain barrier, cerebrovascular hypoperfusion, and neuronal injury. Ultimately, multiple neurovascular pathogenic cascades of activities associated with ischemia and inflammation are controlled by molecular proteogenomic mechanisms

that involve glutamate, calcium, and calpain activities [6–8], with resultant aberrant angiogenesis, senescence in neuronal cells, and dysfunction at the level of the neurovascular unit and hypoperfusion with resultant AD [2].

Stroke, which occurs with sudden occlusion of blood flow to a part of the brain, results in interference in function of the involved regions in the brain. Ischemic stroke is reported to be responsible for approximately 90% of strokes. Pathophysiologically, the reduced oxygen supply to affected neurons in brain cells results in an ischemic core surrounded by moderate ischemic brain tissue called *penumbra*. The penumbra is exposed to secondary damaging processes of excitotoxicity, spreading depolarization and inflammation. Neuroprotective therapies attempt to treat the penumbra [3].

For SIT, similar sequences of activity as hypothesized in the neurovascular hypothesis are proposed; they initiate or are additive on the existing circuitries in neural substrates involved in SIT [14,15]. Where ischemia is the primary pathophysiological process, it is hypothesized that the input of a dyssynchronous auditory signal (i.e., tinnitus) originating in the peripheral or ascending and descending cochleovestibular system interacts at the thalamus and influences the existing ongoing thalamocortical oscillations. Specifically, the ischemia interferes with the resultant synchrony of electrical activity at the cortex involving the primary auditory cortex and its interaction with multiple neural substrates—frontal, temporal, MTL, parietal, and cerebellum [16]. The initial process is the establishment of a paradoxical memory for the aberrant auditory signal—tinnitus—by interaction between the medial temporal lobe and orbitofrontal cortex, its activity modulated by the insula, and its perception as a conscious awareness of the tinnitus (i.e., the FCP for tinnitus) [5,17]. GABA_A receptor deficiency, particularly in the medial temporal lobe, may predispose to SIT. This interaction at multiple neural substrates has been objectively demonstrated with SPECT or PET and correlated with a pattern of electrical activity in the brain of $\delta > \beta > \theta > \alpha$, considered to reflect the interaction and severity of the interaction of the sensory-affect components of the SIT [7,9–11].

Significant for translation to treatment in SIT patients of the identification of ND, NDDI, and NDD-SDAT is the report of the contribution of hemichannel openings, or half-gap junctions, in neurons in stroke and ischemic insults. Hemichannels are open, unapposed half-gap junctions that form large conductance channels and allow flux of ions and molecules. They are putative conduits for adenosine triphosphate release from astrocytes and in the cochlea. Ischemia-like conditions (i.e., oxygen and glucose deprivation) activate hemichannels with resultant neuronal excitability, increase in plasma membrane permeability and swelling, calcium dysregulation, and

neuronal necrosis [18]. A treatment strategy targeting hemichannel openings with blockers against glutamate receptors and voltage-dependent potassium, sodium, and calcium channels may prevent neuronal death and influence SIT.

INFLAMMATION AND ND AND SIT

Classic inflammatory disease of the brain demonstrates ND. Common pathways link inflammatory and ND diseases. In primary ND, progressive CNS damage is controlled and promoted by immune mechanisms. T cells and microglia play significant roles in classic neuroinflammatory diseases [19].

Inflammation in the CNS can contribute to the progression of, as well as protection against, ND. Both are linked in human pathology (e.g., Parkinson's disease, AD, motor neuron disease) and are influenced by multiple factors that influence the immune system. The interactions between inflammation and ND are complex. The immune response is significant and includes elements of neuroprotection and cytotoxicity. Microglia activation is a key component of the inflammatory CNS responses [19]. Inflammatory responses in ischemic brain injury result in activation, proliferation, and hypertrophy of microglia and astrocytes [20]. This is similar to that reported in AD at this time.

The identification of the processes involved with inflammation and ND is a work in progress. The site and extent of the ND is variable [21]. The inflammatory response in the CNS for autoimmune disease and ND differs from that accompanying stroke (i.e., necrosis), probably through upregulation of heat shock protein production [22].

It has been postulated that classic inflammatory and ND disease or injury pathologies of the CNS share common molecular mechanisms. Common immunological pathways result in neurotoxicity and resultant ND. Targets for therapy may be identified to result in specific therapies for specific CNS diseases [3].

Neuroinflammation is a host defense mechanism associated with neutralization of an insult and restoration of normal structure and function of the brain. Neuroinflammation after focal ischemia induces secondary injury in the region of the surrounding insult in both white and gray matter [23].

“Secondary” inflammation in primarily noninflammatory ND diseases of the CNS or stroke refers to attraction of leukocytes to denervated areas [24]. Postischemic inflammation may be significant in brain damage [25].

Differentiation is made between acute and chronic neuroinflammatory disease and primary and secondary inflammation. ND can follow in both. Meningitis is an example of an acute primary neuroinflammatory disease.

Multiple sclerosis is the most common chronic inflammatory disease. Immune cells, T cells, and microglia, when activated, are attracted to the primary neural substrate (e.g., myelin sheath in multiple sclerosis or bacteria in meningitis). In classic neuroinflammatory diseases, collateral damage, referring to damage in neuronal substrates other than the primary target, can result from interaction of the primary targeted neurons and surrounding neurons (e.g., diverse neurological symptoms after meningitis control). Collateral and neuronal damage accompany primary neuroinflammatory diseases. Neuroinflammation is considered a probable result of primary ND [3]. Examples of such symptoms can include hearing loss, tinnitus, seizures, motor deficits, and cognitive impairment.

Brain ischemia is recognized to contribute to the pathogenesis of AD. Individuals with interference in cognition are at increased risk for the consequences of ND and possible underlying AD. Neuroinflammation is a characteristic feature that links AD and brain ischemia. Proinflammatory pathways are triggered also in stroke and ischemic brain insults. Typical neuroinflammatory processes and the molecular mechanisms involved are marked by activation of glial cells and upregulation of inflammatory mediators, complement, cytokines in microglia, and astrocytes and result in significant increasing neuronal death in AD models. The initial mechanisms of inflammation are different for stroke and AD (i.e., not primarily vascular but neuronal-axonal in origin, targeting microglia). Microglial reactions have implications for ND. Inflammation is thought to contribute to the progression of AD and to aggravate the outcome after ischemic insult [26].

IMMUNOLOGY, ND, AND SIT

Alterations in the immune system have been cited to result in ND [19]. When clinically identified specifically for ND, clinical treatment applications of what is known of neuroimmunological mechanisms and the processes involved in the interface between the immune response and neuronal homeostasis may influence the clinical course of the ND in SIT patients, with resultant tinnitus relief.

To be considered is that SIT is an early expression of an altered immune system affecting T cells and microglia, which—irrespective of antigenicity—attacks neurons and initiates processes of inflammation and ischemia in specific CNS regions of interest in the brain and resultant ND as identified in this report of SIT patients. A particular subset of SIT patients may reflect a common immunological pathway precipitated by neurovascular mechanisms that target multiple neural substrates in the CNS and predominantly the central cochleoves-

tibular system. The reports of primary and secondary ND and the concept of “secondary” neuroinflammation in primarily noninflammatory ND diseases of the CNS are considered to have clinical translation to SIT patients for diagnosis and treatment. Specifically, neuroimmunological mechanisms and the processes involved may explain the transformation of a sensory stimulus to one of affect, with associative complaints highlighted by interference in attention, cognition, and memory. Cerebrovascular disease, a primary noninflammatory CNS disease, may be the “trigger” resulting in ischemia and followed by secondary inflammation.

Inflammation can promote ND. Nitric oxide production by macrophages in addition to increases in cytokines, free radicals, CD 8+ T cells, and glutamate are considered to be an important mechanism in selective damage to small axons [5,27,28]. Excess release of excitatory amino acids (i.e., glutamate) is another mechanism for neuronal injury in inflammatory CNS disease [29,30].

AUTOPHAGY AND ND AND SIT

ND, particularly in the aging brain, requires an understanding of cell death pathways and apoptosis. Autophagy is a regulated lysosomal pathway for degrading organelles and long-lived proteins. It is a key adaptive response that can preclude death in stressed or diseased cells. The pathway includes the ubiquitin-dependent proteasome system. Autophagy provides a basis for understanding the crosstalk between cell death pathways, and experimental designs may increase or eliminate a given death pathway [31].

For the future, information of autophagy mechanisms will provide additional targets for neuroprotective drug development and have clinical application for treatment of ND processes underlying and contributing to the clinical course and chronicity of SIT.

STRESS, AGING, ND, AND SIT

Attention to recent reports in neuroscience of molecular mechanisms involved in age and stress and resultant ND are anticipated to have clinical application for attempts at relief of SIT. The incidence of occurrence of NDDI and NDD-SDAT and their age distribution in the cases reported suggest that both are not restricted to the geriatric age group [1]. Age-related findings have been identified unexpectedly in younger patients.

The incidence of occurrence of NDDI and NDD-SDAT and their age distribution in the patients in this report suggests that both are not restricted to the geriatric age group. In the brains of AD patients, activation of the insulin-activating pathway suppresses the toxicity

of aggregates of amyloid B42. The study suggests new therapeutic strategies targeting exiting cellular mechanisms that prevent protein misfolding (i.e., protein homeostasis) [32]. Though the identification of the molecular basis of aging is a work in progress, the identification of the biological pathways involved may provide targets for treatment of ND and, specifically, a basis for differentiation between pathological and normal aging processes.

Stress and aging are toxic diseases and influence the quality of life. Both are risk factors for ND. Persistence can lead to ND CNS disease. A fundamental process has been identified (i.e., protein folding). Proteins are essential for gene expression. Misfolding of proteins is followed by proteotoxic states with resultant damaging molecular events and cellular dysfunction. Processes influencing both age and stress and the molecular basis of the toxicity involved are critical to the underlying mechanisms of these diseases. Successful aging depends on the ability of a cell to resist the effects of stress by the avoidance of protein misfolding and resultant interference in protein function. Experiments in mice that influenced heat shock factor 1 (required by the insulin-signaling pathway) and associated polyglutamine-mediated toxicity influenced the animals' life span [33].

Stress and noise exposure are two sources of increasing tinnitus severity in our experience [34]. A stress model for tinnitus has been described, and the translation of the basic science of stress for tinnitus control has been clinically applied for attempting tinnitus relief [5,7,35,36].

COGNITION, AGING, MILD COGNITIVE IMPAIRMENT, AND ND

Cognitive functions include language, attention, reasoning, judgment, reading, writing, and memory. It is hypothesized that SIT patients identified as having NDDI and NDD-SDAT may reflect minimal cognitive impairment, not AD [1]. Long-term follow-up is planned to distinguish for SIT between minimal cognitive impairment from NDDI and NDD-SDAT.

Minimal cognitive impairment has been clinically considered to be a transition between cognitive changes of normal aging and AD. Though minimal cognitive impairment is associated with an increased risk of dementia, many individuals do not progress to dementia. Approximately 12% of patients older than age 65 have minimal cognitive impairment [37].

The most common ND disease in the aging population associated with interference in cognitive functions (e.g., in memory) is AD. It is estimated that approximately 5 million individuals in the United States have

AD and that in 40 years, with the increasing aging population, 16 million will have the disease [38].

Minimal cognitive impairment refers to a stage of cognitive impairment, specifically a subtype with memory loss (i.e., amnesic minimal cognitive impairment, as differentiated from nonamnesic minimal cognitive impairment) prior to attaining clinical criteria of AD. Controversy exists for the concept of minimal cognitive impairment and its clinical application and treatment. Its pathophysiology is unknown. Treatment is nonspecific and has included cholinesterase inhibitors [39].

Previous attempts to identify cognitive decline associated with aging included benign senescent forgetfulness, age-associated memory impairment, and age-associated cognitive decline [40,41]. Imaging studies with brain CT and MRI have reported that hippocampal atrophy may correlate with minimal cognitive impairment [42].

Brain ischemia and neuroinflammation has been recognized to contribute to the pathogenesis of AD and to patients with cognitive decline. Such patients are at increased risk for ischemic insults in the brain [43]. It is hypothesized that interactions between the pathophysiological processes of inflammation and ischemia involving neural substrates of the FCP underlie SIT in a particular cohort of SIT patients [1].

In general, the incidence of occurrence of tinnitus with age is a work in progress [44]. In our clinical experience, the age distribution of the population seeking our neurootological consultation since 1979 has remained essentially unchanged. However, it is projected that the incidence of tinnitus occurrence will probably increase, reflecting the increased prevalence of noise exposure and the increasing aging population. The need to differentiate in general between the incidence of the symptom of tinnitus and that of a predominantly central-type, severe, disabling tinnitus (SIT) must be stressed. Furthermore, there is a need to identify in the SIT population the incidence of ND, NDDI, and NDD-SDAT and, long-term, that of occurrence or transition, if any, of NDDI and NDD-SDAT to AD and of NDDI to stroke.

Significantly, the clinical history of SIT cases reported ($n = 18$ of 18) reflected an associated anxiety and depression and interference in memory and speech expression prior to the initial onset of (or increase in intensity and annoyance of) the SIT. SIT onset was an exacerbation or recurrence of a preexisting tinnitus. In cases of SIT patients referred for SPECT and PET, all reported activation of a preexistent tinnitus and an increase in annoyance within 6 months to 2 years before neurootological consultation [1].

The early diagnosis of ND, NDDI, and NDD-SDAT in the SIT population may provide a basis for treatment of early ND and result in tinnitus relief based on neuro-

protection [45]. Consequences include (1) diagnostic identification of subsets of SIT that differentiate between ND, NDD-SDAT, and NDDI; (2) SIT patient selection for different neuroprotective treatment protocols that influence the clinical course of the tinnitus by providing a modality of tinnitus relief; and (3) long-term reduction in the statistics projected at this time for AD.

STRATEGIES FOR CLINICAL APPLICATIONS, TREATMENTS, AND TINNITUS RELIEF

Neuroprotection refers to processes that protect neuronal function from injury or that improve such function after injury [45]. In general, neuroprotection is the goal of therapies targeting processes identified as insults to the CNS with resulting ND. Such insults include blocking hyperexcitability, overexpression of glucose and glutamate, accumulation of reactive oxygen species, heat shock protein response, apoptosis, inflammation, and neurotoxicity [46].

The calpain theory of ND suggests a common pathway for ND involving calpain, a calcium-activated protease that may have future clinical application for ND, NDDI, and NDD-SDAT. In the animal model, the application of the calpain antagonist leupeptin has resulted in positive results for noise protection, muscular dystrophy, and neuromuscular recovery after median-nerve repair in primates [8,47].

The early identification of ND, NDDI, and NDD-SDAT in a selected cohort of patients having a predominantly central-type, severe, disabling SIT has resulted in long-term tinnitus relief based on neuroprotection (i.e., antiepileptics and a receptor-targeted therapy directed at the GABA_A receptors, such as gabapentin). The mechanisms underlying neuroprotection are hypothesized to reflect reestablishment of a normal homeostasis of neuronal activity for normal brain function [7,16,45,48].

It is proposed that innovative modalities of therapy be considered for SIT relief. In an attempt to influence the clinical course of the ND and attempt tinnitus relief, such treatment must target the identification of CNS neurological insults highlighted by the pathophysiological processes of inflammation and ischemia with resultant neurotoxicity, neuronal loss, and ND.

For SIT patients with identified ND, NDDI, and NDDI-SDAT, inflammatory processes are hypothesized to underlie the alterations in CNS function as reported with nuclear medicine imaging [1]. Brain MRI techniques are planned to identify any possible inflammatory change in SIT patients with an early sign of ND. To be considered is that the early identification of SIT as a "soft sign" of neurodegeneration, and targeting of treatment to inflammatory changes in brain, may influ-

ence not only the clinical course of the SIT but also the clinical course of ND, NDDI, and NDD-SDAT.

The early identification and treatment of ND, NDDI, and NDD-SDAT will influence the progression and control of the underlying pathophysiological alterations associated with ND and possible progression to AD. The early identification of ND, neurovascular etiologies, and their treatment introduces for consideration in selected SIT patients innovative clinical strategies and drug therapies recommended for ischemia, stroke prophylaxis and treatment, and antiinflammatory drugs. Future targets for drug development in SIT should be directed at the physiological processes associated with the neurovascular unit (i.e., neurovascular repair and cellular protection) and, in NDD-SDAT, to amyloid beta peptide.

Antiinflammatory drugs, such as aspirin and its analogs (including 5-lipoxygenase [5-LOX]) are considered to be future treatment strategies to counter the effects of the inflammatory process. In vivo benefits have been marked by prevention and treatment of AD-like neuropathology and ischemic insults [43]. Beneficial effects are reported in animal models of ischemic injury [49].

An increase of 5-LOX, a proinflammatory molecule and rate-limiting enzyme in the metabolism of arachidonic acid that produces leukotrienes, has been demonstrated after cerebral ischemia, and its inhibitors exert neuroprotective effects [50,51]. Minocycline, a second-generation tetracycline compound, exerted anti-inflammatory effects after ischemia and perfusion injury in rats by inhibition of 5-LOX expression and its activation in an ischemic brain after focal cerebral ischemic injury [52]. Significant are reports of antiinflammation-directed strategies attempted for ND control and of the development of autoimmune disease responses, multifocal leukoencephalopathy, and encephalitis [19].

The report of the contribution of hemichannel openings, or half-gap junctions, in neurons in stroke and ischemic insults for translation to treatment of ND, NDDI, and NDD-SDAT is significant. Hemichannels are open, unapposed half-gap junctions that form large conductance channels and allow flux of ions and molecules. They are putative conduits for adenosine triphosphate release from astrocytes and in the cochlea. Ischemia-like conditions (i.e., oxygen and glucose deprivation) activate hemichannels with resultant neuronal excitability, swelling, and calcium dysregulation, processes proposed to be central components of the resultant neuronal necrosis, which in turn is suspected to be an increase in permeability of the plasma membrane. Treatment targeting hemichannel openings with blockage against glutamate receptors and voltage-dependent potassium, sodium, and calcium channels may prevent neuronal death [18].

An antagonist strategy of treatment (i.e., the CB2 receptor) directed at cannabinoid-mediated inflammation

and hypoxic ischemia may influence resultant ND alterations in the brain by protecting against excitotoxic damage during the acute insult stage. Endocannabinoids are released after brain injury [53]. In hypoxic ischemia, microglia-derived macrophages are the key cells involved in the initial stages of brain inflammation after the acute stage of injury by CB1 receptors [54]. The cannabinoid CB2 receptor has been identified in CB2-positive macrophages in the brain after stroke and hypoxic ischemia [55].

Treatment directed at controlling tau production may interfere with the progression to AD and provide relief for an associated SIT. It has been reported that the timing of treatment directed at early tau reduction in mice may reduce clinical manifestations of AD (i.e., early treatment before ND onset). SIT and NDD-SDAT, when identified, may be the soft ND sign of AD and may indicate the early timing of a tau-directed therapy for treatment of both AD and associated SIT [56].

For the future, neuroprotective gene therapy against neurological insults, with resultant neurotoxicity and ND, may, by attenuation of the immune process, increase the efficacy of treatment both for SIT patients with ND (e.g., AD and FTD), NDDI, and NDD-SDAT [46].

CONCLUSIONS

Translation of the neurovascular hypothesis of ND for AD to SIT is a challenge to the sensorineural view of SIT, which focuses on psychophysical and psychoacoustical elements and underlying mechanisms. The neurovascular hypothesis of ND for a particular cohort of SIT patients provides them with the diagnosis of its etiology and medical significance and a basis for a therapy targeting pathophysiological processes of inflammation and ischemia linked to and underlying ND. CNS neurovascular dysfunction may, in a particular cohort of SIT patients, “trigger” (influence) the clinical course of SIT.

The occurrence and localization of inflammation and ischemia is random in the CNS. In SIT patients, it involves primarily the neural substrates of the FCP of tinnitus (frontal, temporal, and medial temporal lobes).

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