EDITORIAL

Tinnitus Neural Substrates: An Addendum

Since its initial publication in 1995, the *International Tinnitus Journal* (*ITJ*) has been dedicated to providing its readers with state-of-the-art information, not only of basic science but of its integration and translation into clinical medicine for achieving a cure for all clinical types of tinnitus. A report that integrates the clinical and basic science identifying neural substrates and biochemical markers that have been implicated in tinnitus is recognized as a basis for developing drugs for all clinical types of tinnitus.

The team at State University of New York (SUNY) Downstate has identified drug development for the tinnitus patient as *tinnitopharmacoproteogenomics*. Integration and discussion of basic science and clinical reports are essential to progress in drug development for all clinical types of tinnitus for the benefit of the tinnitus patient. The target audience of the *ITJ*, both professionals and tinnitus patients, is deserving of state-of-the-art information.

The recent publication of J.J. Eggermont's "The Neuroscience of Tinnitus" [1] is a significant contribution to understanding the basic science of the symptom of tinnitus and its clinical application (i.e., translation) for diagnosis and treatment. Unfortunately, the article was not a state-of-the-art reflection of the efforts of professionals involved in both the basic sciences and clinical tinnitus research that have also identified neural substrates involved with tinnitus. The article is considered to be reflective predominantly of basic science and academic efforts limited to neural substrates identified in animal experimentation. The article has omissions that render it incomplete and not reflective of the current state of the art for clinical investigations.

In general, concepts developed particularly from tinnitus patient research in clinical medicine have been translated into hypotheses that have contributed to the interpretation of findings of neural substrates in tinnitus patients since 1979 at SUNY Downstate. Our team has considered that the interpretation of tinnitus neural substrate data in experimental animals and tinnitus patients embodies certain elements.

DEFINITION

The definition in the aforementioned Eggermont publication [1] is standard but not reflective of nuclear medicine findings that corroborate that tinnitus is a sensory disorder of auditory perception reflecting an aberrant auditory signal produced by interference in excitatory-inhibitory processes involved in neurotransmission [2]. Tinnitus is considered in the Eggermont article to be a phantom sensation; however, since 1993 our team has held that theory to be an "old" concept. Clinical experience with tinnitus patients since 1979, electrodiagnostic correlates of cochleovestibular function since 1981, and objective nuclear medicine imaging experience since 1989 have identified neural substrates involved in an aberrant auditory stimulus: tinnitus.

SENSORY PHYSIOLOGY

Basic sensory physiology differentiates among different components of a sensation (i.e., sensory, affect, and psychomotor). We have recommended that such differentiation be applied for interpreting the significance of locations identified as "tinnitus neural substrates."

CLINICAL TYPES OF TINNITUS

The Eggermont publication implies that tinnitus is a unitary symptom; however, clinical experience has identified different clinical types of tinnitus. Tinnitus of the severe disabling type is a special clinical type of tinnitus. Recognition of the existence of clinical types of tinnitus has implications for both the investigation and identification of underlying mechanisms of tinnitus production, drug development, and treatment. For example, the identification of "epileptic foci" in the brain (i.e., tinnitogenesis) in tinnitus patients with clinically diagnosed predominantly central tinnitus of the severe disabling type has supported the rationale for recommendation of antiseizure drugs [3–5].

Specifically, additional publications [2,6–10], to the best of our knowledge, have reported the identification, in tinnitus patients, of neural substrates that are considered significant for both diagnosis and long-term tinnitus treatment (i.e., relief).

NUCLEAR MEDICINE IMAGING

Since 1989, many clinicians using single-photon emission computed tomography (SPECT) and positron emission tomography have identified perfusion asymmetries in

multiple regions of interest in tinnitus patients. These findings support the clinical concept of an integrated interneuronal neurotransmission pathway reflecting an underlying neurochemistry. Regions of interest include the frontal, temporal, and parietal lobes, thalamus, primary auditory cortex, and cerebellum. The consistent finding of involvement of the medial temporal lobe system and in excess of 60% of the cerebellum is significant. The medial temporal lobe system has been hypothesized to be the location of transformation of a sensory perception to one of affect, the first process of which is the establishment of a paradoxical auditory memory for the aberrant auditory stimulus—tinnitus.

BRAIN MAPPING, TOPOGNOSTIC TESTING, AND QUANTITATIVE ELECTROENCEPHALOGRAPHY

Neural substrates in tinnitus patients have been reported with brain mapping, source localization, and quantitative electroencephalography [11–15]. Clinical application of the reported findings has contributed to the increased efficacy of drug treatment modalities for tinnitus.

SOMATOSENSORY SYSTEM

Eggermont states, "The second largest cause of tinnitus is abnormal activity in the somatosensory system." Since 1991, SPECT of brain in tinnitus patients has identified (as mentioned) a perfusion asymmetry in approximately 60% of the cerebellum. The role of the cerebellum for auditory processing and cognitive function has been documented [16]. The cerebellum, descending auditory system, and acousticomotor systems have established in the animal model connections between the external nucleus of the inferior colliculus with acousticomotor and somatosensory systems.

BIOCHEMICAL MARKERS

The Eggermont article makes no mention of the identification of a biochemical marker—the $GABA_A$ receptor—for the first time in a predominantly central-type tinnitus of the severe disabling type. Published studies [9,10] support the reported involvement of the frontal and temporal lobes and the cerebellum in the tinnitus disorder.

TREATMENT

Eggermont states that "Drug treatment of long-standing tinnitus in humans so far has not been proven." This statement is based on limited references and is not state of the art for drug treatment for tinnitus.

Since 1996, long-standing significant tinnitus relief has been reported with a receptor-targeted therapy directed to the $GABA_A$ receptor (RTT-GABA) for a predominantly central-type severe disabling tinnitus. This protocol is a clinical application for treatment of a predominantly central-type disabling tinnitus, based on the identification of a biochemical marker, the $GABA_A$ receptor. RTT-GABA recognizes the clinical significance and need to differentiate among various clinical types of tinnitus.

The efficacy of treatment depends on the accuracy of diagnosis. The $GABA_A$ receptor is considered to be only one of other biochemical markers that are expected to be identified and will provide a basis for future drug development for a specific type of tinnitus. Sequential SPECT of brain and quantitative electroencephalography have provided objective evidence to support treatment improvement reported for the subjective tinnitus complaint. These two protocols also provide objective methods for monitoring efficacy and long-term dosage in therapy [17].

Significant for readers is that the clinical experience of professionals and patients with drug therapy for tinnitus is similar to that used with depression. Specifically, different clinical types of depression are now recognized to require different drugs, used alone or in combination. This finding is being experienced also by professionals involved in attempting tinnitus relief.

Tinnitology is a new discipline of basic sciences, neuroscience, and clinical medicine. It attempts to understand an aberrant auditory phenomenon unrelated to an external sound and to advance its diagnosis and treatment. The *ITJ*, the first peer-reviewed journal dedicated to the symptom of tinnitus, celebrated its tenth anniversary in 2004. My co-chief editors and I and the editorial board are pleased that the *ITJ* continues to contribute to advances in tinnitology. Since our first publication of the *ITJ*, professionals involved in tinnitology have been invited to submit manuscripts to the journal. Citations of *ITJ* publications in other journals will accelerate advances in the understanding of tinnitus and the clinical application of such information for tinnitus diagnosis and treatment. A synergism between basic science and clinical medicine and a translation of information between the two is a primary goal of the *ITJ*. Open discussion and interchange of information is the essence of science. Eggermont's article points out the need to strengthen the link that must exist between basic scientists and clinicians involved in the new discipline of tinnitology for the ultimate benefit of the tinnitus patient.

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Abraham Shulman, MD, FACS