International Tinnitus Journal, Vol. 4, No. 1, 5–9 (1998)

EDITORIAL

Tinnitology: Recent Advances for Both Diagnosis and Treatment

Abraham Shulman, M.D.

Martha Entenmann Tinnitus Research Center, Health Science Center at Brooklyn, State University of New York, Brooklyn, NY

My co-Editors and I are pleased to share with you what we consider to be significant advances in the field of Tinnitology, highlighted by a developing neuropharmacology and advance in instrumentation for both diagnosis and treatment for the symptom of tinnitus.

Tinnitology is an integrated discipline of basic science, neuroscience and clinical medicine for the understanding of aberrant auditory phenomena unrelated to an external source of sound [1].

Increasingly, clinical experiences in otology/neurotology are recommending complete cochleovestibular function. The advances described both in basic science and clinical medicine are considered to support the need for ongoing testing both in the initial and follow-up examinations of the patient with tinnitus. The extent and degree of testing is individual and determined by the clinical course and type of the tinnitus. The introduction of nuclear medicine techniques of PET and SPECT offer significant insight into CNS function and its relationship to the symptom of tinnitus.

In 1997 and 1998 significant advances have taken place both for improving the accuracy for diagnosis of tinnitus and for the introduction of treatment modalities offering the tinnitus patient increased chances for achieving tinnitus relief (i.e., tinnitus control). Presentations of advances for both diagnosis and treatment have been presented in 1998 by me in Germany, Japan, Boston, Italy and Portugal.

BASIC SCIENCE

For the basic sciences highlights are considered to be: a) animal investigation of efferent function within the cochleovestibular system; b) animal experimentation for noise protection using Calpain inhibitors [2]; c) animal and human work using calcium channel blocking agents [3]; d) the objective demonstration in a tinnitus patient of tinnitus relief achieved by anti-seizure drugs for control and elimination of an epileptogenic focus demonstrated with SPECT Imaging of Brain [4]; and e) efferent system and tinnitus [5]. The reports provide a basis for ongoing development of a neuropharmacology for tinnitus of different clinical types.

Reprint requests: Abraham Shulman, M.D., Martha Entenmann Tinnitus Research Center, Health Science Center at Brooklyn, State University of New York, Box 1239, 450 Clarkson Avenue, Brooklyn, NY 11203.

TINNITUS DIAGNOSIS

Significant advances for increasing the accuracy of the tinnitus diagnosis have been reported by Salvi and Lockwood from State University of New York at Buffalo [6]; and by Shulman et al. using SPECT Imaging of Brain from the State University of New York, HSCB-SUNY [7]. Salvi and Lockwood, using PET Imaging of Brain in a patient with tinnitus particularly of the severe disabling type, identified auditory areas in brain associated with the influence of clenching of the teeth on the intensity of tinnitus. This study confirmed previous findings with SPECT of brain first reported by Shulman et al. in 1990 of the significance of brain and auditory areas in patients with tinnitus [8]. In 1996 Shulman et al. in a follow-up report with SPECT of the brain have been able to identify in a tinnitus patient an epileptogenic focus in the brain [3]. Treatment with antiseizure medication followed by sequential SPECT examination demonstrated an elimination of the epileptogenic focus. The elimination of the epileptogenic focus correlated with the clinically reported subjective relief by the patient of tinnitus intensity.

Electrophysiological investigation of auditory evoked responses and event related potentials are providing a basis for attempts to establish electrophysiologic correlates for different clinical types of tinnitus. Brain map-

ping techniques are providing objectivity in patients with tinnitus [9].

The establishment of a tinnitus diagnosis by a medical audiologic team approach is increasingly applied by professionals in an attempt to establish increased accuracy for tinnitus diagnosis. Preliminary investigations of brain mapping and imaging have been reported in patients with the symptoms of tinnitus and vertigo [10]. Imaging techniques, including brain electrical activity mapping (BEAM), single photon emission computer tomography (SPECT), positron emission tomography (PET), magneto-electroencephalography (MEG), and functional MRI, offer the potential of an insight into the medical significance of tinnitus, underlying mechanisms of tinnitus production, and specifically neurologic/neurotologic implications both for tinnitus diagnosis/treatment [8]. Multiple regions of abnormalities in brain have been correlated with electroencephalogram (EEG) asymmetries [9,11].

Increasingly, otolaryngologists performing balance testing in patients with tinnitus with or without complaints of vertigo are reporting a significant incidence of occurrence of abnormalities [12–17]. The vestibular abnormality when treated has improved the efficacy of tinnitus control using instrumentation [12–13]. The vestibular evoked response (VbEP) is a technique which records the electrical response from brain cortex in response to rotation. The VbEP in combination with brain mapping provide a topodiagnostic application for clinical identification of the tinnitus site of lesion. Treatment of the symptom of tinnitus based upon the vestibular evoked response has been introduced by Claussen with significant success for tinnitus control [15].

Whiplash injuries have been reported to include a significant incidence of occurrence of tinnitus. A late whiplash syndrome has been identified [18–19]. The clinical identification and treatment of the late whiplash injury syndrome has resulted in increased tinnitus control. At the NES 1998 meeting topognostic testing with brain mapping of auditory responses in whiplash tinnitus patients has identified abnormalities in the central nervous system considered to be associated with the symptom of tinnitus.

Weider [20] has reported a significant incidence of occurrence of perilymphatic fistula in patients with tinnitus. The relationship of cerebrospinal fluid and perilymph has been dramatically demonstrated by a treatment modality directed to both surgical repair of the fistula and normalization of CSF pressure with accompanying tinnitus relief.

TREATMENT

The treatment highlights are: instrumentation, introduction of new medication, and surgery. For the first time ear surgery, specifically for a predominantly cochlear type tinnitus is being recommended for attempting tinnitus control.

INSTRUMENTATION

The results of tinnitus retraining therapy (TRT) continue to report very good to excellent results [21]. Electrical stimulation for tinnitus control continues to report success [22–23]. Tinnitus control continues to be reported by some patients using the cochlear implant [24]. Investigations of electrical stimulation continue. This experience supports the continuation of such efforts [1]. A collaboration has started between David W. House, M.D., William H. House, M.D. of AllHear Inc., Miles M. Goldsmith, M.D., of the International Center for Otologic Training (ICOT), Savannah, GA, and A. Shulman, M.D. of the Martha Entenmann Tinnitus Research Center, Inc., SUNY–Brooklyn to prepare for an Investigation Device Exemption (IDE) to the FDA for the adaptation of the single channel cochlear implant for attempting tinnitus suppression. The program of "The International Tinnitus Forum," San Antonio, TX, September 12, 1998 focused on this effort.

MEDICATION

For medication an increasing neuropharmacology includes neuroprotection, pathology modifying pharmacologies, and treatment of specific etiologies. The introduction and application of the concept of neuroprotection highlighted by Calpain inhibitors are significant [2,4,25]. Calpain is a normal intracellular cytostolic protease activated by excess intracellular calcium. It is considered to be a site of action for neuroprotective agents.

A collaboration of basic science and clinical research efforts was established in 1997 with the support of the Martha Entenmann Tinnitus Research Center, Inc., Health Sciences Center at Brooklyn, State University of New York, (A. Stracher, A. Shulman) and the State University of New York at Buffalo (R.J. Salvi) in an attempt to develop neuroprotective drug therapies for hearing and balance system complaints, particularly tinnitus, hearing loss, and vertigo. One of the neuroprotective agents under investigation in this collaborative research is LX1C, a calpain antagonist [4]. It has been determined that neuroprotection can protect against noise induced hearing loss and hair cell loss. In the animal model, chinchilla, hair cell loss in the leupeptine treated ear was demonstrated to be significantly less than in the control ear following noise exposure. These preliminary results suggest leupeptine may protect against noise induced hearing loss [2].

NEW AND EXISTING TINNITUS PROTOCOL

The recently reported SPECT of Brain and PET of Brain findings with nuclear medicine technology have significantly influenced existing protocols for attempting tinnitus diagnosis and treatment [26]. Its clinical application has been the development and application of a neurochemistry protocol for attempting tinnitus treatment for both its sensory and affect components [4].

The original term of neuropharmacology introduced by Pujol [27] has been significantly increased with the addition of pharmaceuticals based upon a neuroprotective drug therapy, a pathology modification, and etiology based protocols. Selection of pharmaceuticals are considered to reflect and influence the neurochemistry of brain and ear function (i.e. two neurotransmitter systems namely the GABA/glutamate system and the dopamine/serotonin system). One for inhibition/excitation and the other for modulation [4,26].

There is a development of a neuropharmacology for tinnitus and an understanding of the underlying mechanisms of tinnitus production both within the peripheral and central portions of the cochleovestibular system [3] based on a understanding of the neurochemistry of brain and ear function.

SURGERY

The surgical technique of Intratympanic Drug Therapy (ITDT) reintroduced in the 1970's by Sakata et al. finds application for attempting relief for a predominantly cochlear type tinnitus [28]. Pharmaceuticals which are being used provide neuroprotection (i.e. protection of neuronal function from injury or improvement of function after injury or following injury). Such pharmaceutical therapy, now newly recommended for the ear complaints highlighted by tinnitus, hearing loss, vertigo and other abnormal auditory sensations, has been developed over the past 15-20 years for injury to the central nervous system for the etiologies of ischemia, trauma, hemorrhage, and neurodegeneration [4]. The pharmaceutical agents of calcium channel blockers, free radical scavengers/antioxidants, and corticosteroids offer neuroprotection. These pharmaceuticals, approved by the FDA for other applications, are already being used to treat Menière's Disease. Steroids have been recommended and used specifically for the control of a predominantly cochlear type tinnitus [28].

A new delivery system of microcatheters, inserted into the middle ear and positioned in the round window niche and connected to a minipump system, assures the delivery of a pharmaceutical (e.g. steroid) to the round window, at regulated predetermined doses and rates, to the inner ear for attempting tinnitus control of a predominately cochlear type tinnitus [29].

The use of neuroprotective drugs in intratympanic drug therapy via the round window is considered significant for treatment of inner ear complaints of hearing loss, tinnitus, and vertigo [4].

The key issue for success of this technique is the establishment of an accuracy for clinical diagnosis of a predominantly cochlear-type tinnitus [4]. Diagnostic protocols (e.g. the Medical Audiologic Tinnitus Patient Protocol [MATPP]) have been in place since 1979 [1]. Since 1979 cochleovestibular testing has been considered critical for the establishment of an accurate diagnosis of a cochlear-type tinnitus and/or other types of tinnitus.

Future issues of "The International Tinnitus Journal" (ITJ) will report on the progress of Intratympanic Drug Therapy with or without microcatheters for tinnitus control.

EDUCATION

The education efforts of The Martha Entenmann Tinnitus Research Center, Inc., the 4GF/Neuroequilibriometric Society (NES) and its collaborators have shared the advances for diagnosis and treatment of tinnitus with colleagues world-wide. The International Tinnitus Journal, now in its 4th year of publication, is the official journal of the Neuroequilibriometric Society, which presents up-to-date information to patients and professionals on the state-of-the-art of basic science, clinical diagnostic and treatment approaches for the symptom of tinnitus.

Tinnitus conferences in 1997 and 1998 have presented the above mentioned advances. The major meetings were: the Annual International Tinnitus Forum, formerly the International Tinnitus Study Group, September 9, 1997 San Francisco, and September 12, 1998, San Antonio; NES, April 19, 1997, Haifa, Israel; NES, March 19–22, 1998, Bad Kissingen; University of Tokyo, April 1998; Harvard School of Public Health, May 1998; Ototoxicity Conference, June 18–21, 1998, Bari, Italy; Tinnitus courses at the University of Brasilia, August 1997; Porto, Portugal June 1998; a Tinnitus Course of Tinnitus Treatment Strategies at the American Academy of Otolaryngology—Head and Neck Surgery, September 16, 1998; and future tinnitus presentations at the scientific program of the 34th Brazilian Congress of Otorhinolaryngology, November 18–22, 1998.

The above mentioned educational efforts have clearly established an international network of professionals, who are dedicated to the advancement of Tinnitology for the benefit of the tinnitus patient.

Another goal of the Martha Entenman Tinnitus Research Center (METRC) is to develop an anti-noise/anti-tinnitus pharmaceuticals. The application of calpain antagonists is considered significant.

To further the development of a neuropharmacology for tinnitus the 1st International Think Tank was held October 5–6, 1997 in New York City. The 13 collaborators of the METRC attended. The theme of the meeting was "Neurochemistry of Tinnitus." The 2nd International Think Tank will take place in New York City, November 5–6, 1998. The goal is to advance the development of a neuropharmacology for all clinical types of tinnitus. The upcoming meeting will be honored by the attendance of Professor K. Ehrenberger of Vienna, who will present his experiences with the calcium channel blocking agent Caraverine.

We welcome visitors to the METRC where Education programs are offered at no cost. Arrangements are tailored to the goals and needs of each visitor. The Martha Entenmann Tinnitus Research Center Visiting Scholar is a new program for professionals which is directed to physicians to provide an intimate exchange of clinical experiences for diagnosis and treatment of tinnitus. One outgrowth of this has been the re-establishment of investigation for electrophysiologic correlates of tinnitus based on cochleovestibular testing as well as attempting tinnitus control using electrical stimulation. Our first Visiting Scholar was J. Matsushima, M.D., Associate Professor of the Department of Otolaryngology of Hokkaida, University of Japan.

CONCLUSIONS

Significant advances for Tinnitology have been reported in 1997 and 1998. Objectivity and an increased accuracy for the tinnitus diagnosis are highlighted by nuclear medicine techniques (PET and SPECT) and functional MRI.

Clinical observations are supporting the need for total cochleovestibular evaluation in patients with tinnitus, particularly of the severe disabling type. Its practical application is to select appropriate modalities of therapy for attempting tinnitus control. Imaging studies and electrophysiologic determinations, in response to auditory and vestibular stimulations, offer an increased accuracy for the tinnitus diagnosis.

The increase in accuracy of the tinnitus diagnosis with MATPP is being supported internationally by reports of the need for total cochleovestibular evaluation and for recommendations for tinnitus relief to differentiate between the sensory and affect components of the symptom of tinnitus.

The neuropharmacology for tinnitus has been expanded from one based on treatment for underlying factors influencing the clinical course of tinnitus to that of innovative protocols for specific etiologies considered to underly or accompany the symptom of tinnitus and for modification of the ensuing pathology.

Neuroprotective drug therapy either alone or in combination with instrumentation increases the efficacy of recommendations for attempting tinnitus control.

Since 1997 existing and new protocols for attempting tinnitus control have integrated objective evidence from our SPECT of brain experiences and the PET reports of others of the increased diagnostic accuracy of the MATPP. They have provided information of the neurochemistry of the brain, which has enlarged the existing neuropharmacology for tinnitus.

The diagnostic accuracy of protocols like the Medical Audiologic Tinnitus Patient Protocol, which includes cochleovestibular (CV) testing, provides a basis for patient selection for intratympanic drug therapy (ITDT) for attempting tinnitus relief by the identification of a predominantly cochlear type tinnitus.

The introduction of neuroprotective agents for maintaining or improving inner ear function, specifically for the symptom of tinnitus, is considered significant for attempting tinnitus control. Neuroprotective drug therapies have been investigated and recommended for the central nervous system (CNS) over the past 15–20 years for pathological processes (inflammation, oxidative stress, etc., and etiologies of ischemia, trauma, hemorrhage and neurodegeneration). The innovative application of such drug strategies for treating the symptom of tinnitus of the severe disabling type is now recommended.

The pioneering work of Sakata et al. in Japan with Intratympanic Drug Therapy, now followed by the availability of a round window microcatheter, improves the ability for a otologist/neurotologist to provide a patient with tinnitus relief for a predominantly cochlear-type tinnitus. Microcatheters attached to a minipump provide a known quantity of pharmaceutical at a given rate of delivery over a selected period of time.

For the first time the otologist is in a position of applying the increased diagnostic accuracy of the MATPP and cochleovestibular testing in tinnitus patients to select a modality of therapy (e.g. ITDT) which offers a significantly increased chance of success for tinnitus control for a predominantly cochlear type tinnitus.

My co-Editors and I share with you our enthusiasm for our role, along with others working internationally, in the progress reported in 1997 and 1998 for tinnitus diagnosis and treatment, which increases chances of success for relief for the tinnitus patient. These advances are considered a significant step forward in attempting to establish a cure for different clinical types of tinnitus.

In conclusion, although no cure exists for the symptom of tinnitus, major advances offer significant hope to the clinician and the tinnitus patient for increased tinnitus relief in the future.

REFERENCES

1. Shulman A, Aran JM, Feldmann H, Tonndorf J, Vernon JA: Tinnitus—Diagnosis/Treatment. Lea & Febiger, Phila., PA, 1991, pp1–571; Singular Publishing Group, San Diego/London, 1997.
2. Salvi RJ, Shulman A, Stracher A: Leupeptine Protects Against Acoustic Overstimulation. Presentation 25th Congress Neuroequilibriometic Society, Bad Kissingen, March 19, 1998. In Press.
3. Ehrenberger K: Caraverine and Tinnitus Control. Update—Personal Communication, March 18, 1998.
4. Shulman A: Neuroprotective Drug Therapy: A Medical and Pharmacological Treatment for Tinnitus Control. *International Tinnitus Journal*, 3:77–96, 1997.
5. Sahley TL, Nodar HR, Musiek FE: Efferent Auditory System—Structure and Function. Singular Publishing Group, Inc., San Diego, London, pp1–228, 1997.
6. Lockwood AH, Salvi RJ: The Functional Neuroanatomy of Tinnitus. *Neurology 50,* Volume 1, No. 6, pp114–120, January 1998.
7. Shulman A: Tinnitology, Tinnitogenesis, Nuclear Medicine and the Tinnitus Patient. Presentation 25th Congress of the Neuroequilibriometric Society, Bad Kissingen, Germany. March 19, 1998. In Press.
8. Shulman A: SPECT of Brain and Tinnitus. Neurotologic/Neurologic Implications. *International Tinnitus Journal*, 1:13–29, 1995.
9. Claussen CF, Schneider D, Constantinescu L: Brain Mapping in the Tinnitus Patient. Presentation 25th Annual Meeting of the Neuroequilibriometric Society (NES), Bad Kissingen, March 18,1998. In Press.
10. Claussen CF, Schneider D et al.: Brain Mapping Tinnitus & Whiplash Syndrome. Presentation, Bad Kissingen, June 1997.
11. Hassan N, Shulman A: Auditory Evoked Responses and Tinnitus—Preliminary Report. Presentation 25th NES Congress, Bad Kissingen, Germany March 1998. In Press.
12. Shulman A: Clinical Types of Tinnitus in "Tinnitus—Diagnosis/Treatment". Lea & Febiger, pp 323–342, 1991. Singular Publishing Group, San Diego/London, 1997.
13. Seabra JC: Vestibular Testing in the Tinnitus Patient. Presentation 25th Congress of the Neuroequilibriometric Society, Bad Kissingen, Germany, March 19, 1998.
14. Seabra JCR, Diamantino H, Almeida F: Neurotologic Evaluation of Tinnitus. *International Tinnitus Journal*, 1:93–98, 1995.
15. Claussen CF, Schneider D: Vestibular Evoked Response, Brain Mapping and Tinnitus—Diagnosis/Treatment. Presentation 25th Annual Meeting of the Neuroequilibriometic Society, March 19, 1998, Bad Kissingen, Germany, In Press.
16. Seabra JCR: The significance of the vestibular evaluation in patients with tinnitus. Presentation First Course in Tinnitus, Porto, Portugal, June 22, 1998.
17. Nagy E, Pongracz E: Complex Therapy of Neck Related Tinnitus, Hypercusia, and Vertigo. *International Tinnitus Journal*,3:141–145, 1997.
18. Claussen CF, Constantinescu L: Tinnitus and Whiplash Injury. *International Tinnitus Journal*, 1:105–115, 1995.
19. Claussen CF, Constaninescu L, Schneider D: Tinnitus in Whiplash Injury. The Late Whiplash Injury Syndrome. Presentation 25th Congress Neuroequilibriometric Society, Bad Kissingen, Germany, March 19, 1998. In Press.
20. Weider DJ: Tinnitus—Report of 10 Cases of Perilymphatic Fistula and/or Endolymphatic Hydrops Improved by Surgery. *International Tinnitus Journal*, 3:11–21, 1997.
21. Mattox DE, Jastreboff P, Gray W: Tinnitus Habituation Therapy. The University of Maryland Tinnitus and Hyperacusis Experience. *International Tinnitus Journal*, 3:31–32, 1997.
22. Shulman A: Electrical Stimulation. In: Tinnitus—Diagnosis/Treatment, Chapter 26, pp514–531, Lea & Febiger, Phila., PA 1991; Singular Publishing Group, San Diego/London, 1997.
23. Matsushima JI: Evaluation of Implanted Tinnitus Suppressor Based on Tinnitus Stress Test. *International Tinnitus Journal*, 3:123–132, 1997.
24. Miyamoto RT, Wynne MK, McKnight C, Bichey B: Electrical Suppression via Cochlear Implants. *International Tinnitus Journal*, 3:2, 1997.
25. Stracher A: Calpain Inhibitors as Neuroprotective Agents in Neurodegenerative Disorders. *International Tinnitus Journal*, 3:2, 1997.
26. Shulman A, Goldstein B: A Final Common Pathway for Tinnitus -Implications for Treatment. *International Tinnitus Journal*, 2: 1996.
27. Pujol R: Neuropharmacology of the Cochlear and Tinnitus. Tinnitus 91: 103–107, 1992, Kugler Publications, Amsterdam.
28. Sakata E, Ito Y, Ito A: Clinical Experience of Steroid Targeting Therapy to Inner Ear for Control of Tinnitus. The International Tinnitus Journal, pp117–122, 3:2, 1997.
29. IntraEar Inc.—Round Window Catheter. Presentation I.K. Arenberg, M.D., Bari, Italy, June 20, 1998.