EDITORIAL

International Tinnitus Forum, Twenty-Second Annual Meeting: Tinnitology of the Twenty-First Century

The twenty-second annual meeting of the International Tinnitus Forum introduced to its attendees a perspective for considering the new discipline of tinnitology and the symptom of tinnitus as the neurootologic symptom of the twenty-first century. In addition, it offered a reflection of the new discipline of tinnitology and projected a future for treatment that will benefit the tinnitus patient.

The program focused on tinnitus treatment and on new molecular genetic approaches for tinnitus drug development—tinnito-proteo-pharmacogenomics—specifically for all tinnitus types and subtypes based on the identification of specific proteins and their function and of the kinetics of gene regulation. In general, the presentations provided state-of-the-art information regarding both basic science and clinical medicine, focusing on neuroprotection and tinnitus treatment. The question-and-answer periods and the discussions that followed reflected the attendees' increased sophistication in advances in neuroscience and their translation for tinnitus diagnosis and treatment.

Attendees were informed of the latest methods for establishing accuracy in tinnitus diagnosis and treatment. These up-to-date techniques included a receptor-targeted therapy, ultra-high-frequency acoustic stimulation, and intratympanic steroid therapy.

Histochemical and biochemical considerations adapted for complaints of the cochleovestibular system (highlighted by tinnitus, hearing loss, and vertigo) provided attendees with a basic science approach for understanding the neurochemistry of the auditory system and its application for tinnito-proteo-pharmacogenomics. The future of tinnitus drug development is conceived to be individual and directed toward a specific clinical type of tinnitus. Identification of a particular protein and its function and mutations (if present and individualized for each tinnitus patient), when integrated with an understanding of the kinetics of the genome for such patients, will provide a basis for drug development and application to a particular target (i.e., ear or brain or both). Systems for drug delivery to the ear and brain will influence results in tinnitus relief for tinnitus patients.

In this context, the basic science section of the meeting opened with R. Penha's presentation of the anatomical basis for understanding drug delivery into the inner ear. The ensuing discussion projected anatomical considerations of the round window for intratympanic drug therapy.

A. Stracher discussed the protease calpain, its projected role in apoptosis in the cochleovestibular system, and the action of the protease inhibitor leupeptin. The concentration of calpain in the cell membrane, "upstream" in the process of apoptosis, was differentiated from the location and action of the proteases called *caspases* in the nucleus, "downstream" in the process of apoptosis. Leupeptin, a calpain inhibitor, has demonstrated neuroprotective action for control of gentamicin ototoxicity and of muscle disorders highlighted by muscular dystrophy and epilepsy. The potential application of leupeptin for neurodegenerative disorders is under investigation at the Health Science Center at Brooklyn–State University of New York.

R.D. Kopke explained in detail the role of reactive oxygen species, the process of apoptosis, and possible application for developing drugs for noise control and tinnitus therapy. Drug delivery systems include oral as well as intratympanic approaches into the inner ear.

M.E. Hoffer presented updated results in the rat model of concentrations of leupeptin after intratympanic drug delivery for noise protection. This presentation stressed the positive effects of noise protection with leupeptin. An ototoxic effect was reported in one animal, although its significance remains to be established. A discussion focused on the processes involved in apoptosis in providing an apparently common pathway influenced by multiple drugs, which have reported noise protection, conservation of hearing, and tinnitus control.

In general, therapies using various drugs and recommended for control of complaints of the cochleovestibular system (both in animals and in humans) have demonstrated varying durations of time between the introduction of an agent and its reported efficacy for tinnitus relief or noise protection (or both). In short, a

latency period definitely is present in some treatments. M.E. Hoffer discussed the introduction and establishment of pharmacokinetic curves for a particular drug and their clinical application in determining effective use for controlling vertigo and associated cochlear vestibular complaints (hearing loss and tinnitus).

C-F. Claussen presented a neurootological perspective covering whiplash injury and innovative methods for diagnosing complaints of the cochleovestibular system and the symptom of tinnitus. He explained in detail the new objective test, craniocorpography, focusing on its application for the objective identification of the psychomotor component of tinnitus and its application as a monitoring tool to establish the efficacy of therapies attempting tinnitus relief.

M.L. Lenhardt presented the theory of ultrasonic, ultra-high-frequency acoustic stimulation and its application for tinnitus control. He discussed a method for identifying patients who qualify for this therapy and the future role of ultrasonic ultra-high-frequency stimulation for tinnitus relief.

The presentations of C-F. Claussen and M.L. Lenhardt set forth new approaches for understanding the intricacy of the cochleovestibular system and the need to focus not on ear *or* brain but rather on ear *and* brain. Furthermore, they reinforced (through ongoing clinical experiences reported by others) a need to apply basic physiological principles of sensory physiology for managing the symptom of tinnitus. That approach would include identifying the components of tinnitus (i.e., sensory, affect, and psychomotor) and differentiating between each when making recommendations for tinnitus relief.

L.P. Ryback, the guest of honor, presented the neurochemistry of the peripheral and central auditory system after ototoxic drug exposure and its implications for treating tinnitus. He reviewed the role of reactive oxygen species, drugs being investigated for attempting ear protection for noise trauma, and their potential application for tinnitus treatment. He also discussed his clinical experience with the ototoxic drug cisplatinum and the neuroprotective action of lipoic acid and vitamin E . Multiple agents identified to provide neuroprotection from noise included the neurotrophic agent BDNF and glutathione, leupeptin, and others. Significantly, each of these various drugs has been reported to result in some noise protection and, hopefully, may have an application for tinnitus relief. The possibility of the presence of a common pathway here remains to be established. The significance of the identification of the hyperactivity in the dorsal cochlear nucleus was presented. One question asked was whether this hyperactivity was synchronous or dyssynchronous neuronal activity? Specifically, recent advances in neuroscience have identified that neural ensembles, when synchronous, result in satisfactory neural processing. Whether the hyperactivity in the dorsal cochlear nucleus associated with tinnitus is one of synchrony or dyssynchrony needs further investigation.

The clinical section of the meeting included the following presentations: L. Lavinsky pointed out the need for complete metabolic evaluation focusing on the identification and treatment of hyperinsulinemia. Significant improvement in tinnitus relief was reported by such an approach.

C.A. Oliveira reported a balanced study of intratympanic steroid drug therapy and tinnitus relief. No significant difference between placebo and treatment methods was reported in this study.

D. D'Souza presented a study on intratympanic steroid therapy, reporting positive results for such tinnitus relief. The experience with aquaporins—transmembrane water transporters affected by steroids—was included in the report. S. Desa Souza reported the positive influence of the cochlear implant for tinnitus relief.

J. Matsushima presented a report on electrical stimulation and tinnitus relief related to sleep. The use of sodium enoxaparin for treatment of tinnitus was the subject of a report by R. Mora. That presentation included a discussion of that agent's application in identifying autoimmune inner-ear disease and sensorineural hearing loss.

A. Shulman reported for the first time a study of positron emission tomography (PET) of brain that highlighted results of ultra-high-frequency acoustic stimulation in attempting tinnitus relief. He identified categories of metabolic activity with PET in six patients. The results identified a significant correlation between the ultra-high-frequency audiogram and the PET metabolic category of activity in brain. The study reestablished the need for attention not only to the auditory cortex but to multiple areas of brain. The study also reconfirmed a recommendation for ultra-high-frequency audiometry for all tinnitus patients.

In summary, multiple systems of treatment, including both instrumentation and medication, were presented. Attendees were able to take home and introduce into their practices the latest methods for attempting tinnitus relief and an understanding of the direction of drug development for all clinical types of tinnitus.

The adaptation of basic scientific research of reactive oxygen species and the processes involved in apoptosis to the cochleovestibular system provides a basis for identifying specific proteins, their function, and their regulation through the kinetics of the gene associated with their function. This approach is considered to be the direction in which the basic sciences and neurosciences are focusing their attention for conditions of complaints of ear or brain. It is hoped that the end result

will be the development in the twenty-first century of multiple drugs for treating specific types and subtypes of tinnitus. The ultimate goal remains an increased duration of tinnitus relief and achievement of the final cure for all clinical types of tinnitus.

The meeting adjourned with an invitation to all to attend and participate in the Webcast of the Downstate Medical Center Department of Otolaryngology and the Martha Entenmann Tinnitus Research Center on November 13, 2004.

We look forward to meeting September 24, 2005, in Los Angeles for the twenty-third annual meeting of the International Tinnitus Forum. All are invited to attend for the ultimate benefit of tinnitus patients.

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