International Tinnitus Journal, Vol. 7, No. 2, 122–127 (2001)

Long-Term Inhibition of Tinnitus by UltraQuiet Therapy: Preliminary Report

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Abstract: Masking of tinnitus by noise can produce residual inhibition, a persistence in the reduction in tinnitus after the noise is removed. Typically, this relief is very short-lived, on the order of minutes. This report highlights long-term inhibition of tinnitus by UltraQuiet therapy, a new technique that employs patterned sound in the 10- to 20-kHz range, presented through bone conduction. Nine subjects participated in a study of the efficacy of this tinnitus suppression technique. Eight reported improvement in tinnitus symptoms; one did not complete the study. The duration of the improvement ranged from days to weeks. This long-term inhibition may involve a truly plastic change in the brain at the central level.

Key Words: cortical plasticity; masking; residual inhibition; tinnitus; UltraQuiet

The ultimate goal in tinnitus therapy is the long-term inhibition or elimination of the tinnitus. Masking of tinnitus by noise delivered through a tinnitus masker either alone or in conjunction with a hearing aid has been one of the most effective therapies but, in most cases, the relief is short-term, primarily occurring while the masking noise is present [1]. In a phenomenon called *residual inhibition* [RI], however, the reduced intensity of the tinnitus persists for some time after the masking noise is removed. This report presents the preliminary results of tinnitus treatment with a new technique intended to induce RI: UltraQuiet therapy. The report also provides a basis for continued studies and discusses central mechanisms that may lead to long-term inhibition of tinnitus.

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UltraQuiet is a proprietary tinnitus treatment developed by Sound Technique Systems, LLC, with patents pending. Martin Lenhardt holds an equity position in Sound Technique Systems and serves as vice president of research and technology. He was not directly involved with data collection or analysis.

MASKING AND RESIDUAL INHIBITION

Masking

For masking of an externally applied tone, only energy in a critical band around the tone frequency, corresponding to the filtering capability of the basilar membrane, should be effective in masking (i.e., a conventional psychophysical tuning curve) [2]. However, Feldmann [3], Shailer et al. [4], Tyler et al. [5], Penner [6], Smith et al. [7], and others, using maskers of varying bandwidths, have shown that tinnitus is not masked like a tone in many subjects. Instead, a wide range of frequencies typically provides roughly equivalent masking. These wide tuning curves suggest that tinnitus is not processed as if it were a pure tone. Penner [6] suggested that this is evidence that the tinnitus and masking noise interact retrocochlearly (i.e., masking may have a central origin). This conclusion is reinforced by the phenomenon of contralateral masking; in some patients, masking noise presented to the contralateral ear is as effective as noise presented to the ipsilateral ear, so the interaction of tinnitus and masking noise must be at some point in the auditory pathway where binaural interaction takes place [3].

Not only is the frequency of the noise not important in tinnitus masking in many cases, but tinnitus can be

masked by noise not containing the subjective tinnitus frequency at all. Kitajima et al. [8] found that masking with wide-band noise—in which a narrow band of noise around the tinnitus frequency had been *removed*—was as effective as a band of noise covering the tinnitus frequency. This finding opens up the possibility that tinnitus could be masked by sound outside the speech range entirely, which would offer the advantage of not interfering with speech reception. For example, Meikle et al. [9] reported success in masking tinnitus with ultrasound delivered through bone conduction. (Lenhardt et al. [10] showed that hearing through bone conduction can extend up to 100 kHz.)

Two other studies using much higher-frequency ultrasound (500 kHz) demonstrated conflicting results. The study by Carrick et al. [11] significantly abated tinnitus, whereas the study by Rendell et al. [12] was unable to confirm that result. (Note that 500 kHz is well beyond the upper limit for detection of bone-conducted ultrasound found by Lenhardt et al. [10].)

Residual Inhibition

Forward masking of tones is a well-known psychophysical effect in which a masking tone can prevent detection of a tone after the masker is cut off. This is a very short-duration phenomenon, however, normally lasting less than 100 msec, and may correspond to the time required for the receptors to regain their sensitivity [2]. RI, a postmasking effect with much longer duration, was first reported by Feldmann [3]. The term *residual inhibition* refers to a decrease in the perceived intensity of the tinnitus for a time after the masking noise stops.

Typically, RI lasts for only a few seconds or minutes but occasionally can persist substantially longer. Hazell and Wood [13] reported a few cases in which 15 minutes of masking noise resulted in RI of tinnitus for the entire day. Clearly, a therapeutic technique for tinnitus that did not require continuous masking noise would be of great benefit. However, the factors resulting in persistence of inhibition and the mechanism are not well understood.

Tyler et al. [5] noted that factors influencing RI include the duration of the masker over a period of 60 seconds and possibly longer. They contrasted this with forward masking of two acoustic tones, whereby increasing masker duration beyond approximately 400 msec generally produces no increase in the amount of forward masking.

Terry et al. [14] conducted a parametric study of RI to determine the dependence of RI on masker characteristics, such as center frequency, bandwidth, intensity, and duration. These authors wanted to know whether maskers could be designed to be maximally efficient in producing RI and whether the incidence and extent of RI could be predicted from the type of tinnitus. They found that RI increased with masker intensity, but the relationship to duration was not clear. Duration increased RI only when a relatively intense masker was used; not known is whether this holds for masker durations of more than 10 minutes. The relationship of RI to tinnitus frequency and to masker center frequency and bandwidth was complex and varied among individuals. No attempt was made to assess the effect of masking noise outside the tinnitus frequency. In contrast to Feldmann [3], Terry et al. [14] did not find evidence of contralateral masking and were unable to identify any obvious predictor of whether a particular subject would exhibit RI.

ULTRAQUIET THERAPY

UltraQuiet therapy provides patterned auditory stimulation in the high audio and ultrasonic ranges (10–20 kHz) using a bone conduction transducer (Figure 1). It is based on the work of Lenhardt et al. [10], demonstrating ultrasonic perception by humans through bone conduction up to 100 kHz. UltraQuiet therapy differs from the conventional masker in that none of the sound overlaps the range of reported tinnitus. Nevertheless, ultrasound was even more effective than was speech-range masking noise for tinnitus masking and producing RI in a study by Meikle et al. [9]. In UltraQuiet therapy, the auditory stimulation, rather than the band of noise commonly used for masking, is music that has been processed and shifted in pitch. Davis and Wilde [15] demonstrated music to be a more effective tinnitus masker than noise. They attributed the greater effectiveness of music in part to the involvement of more central and cognitive processes. In UltraQuiet therapy, the processed music is presented through a bone con-

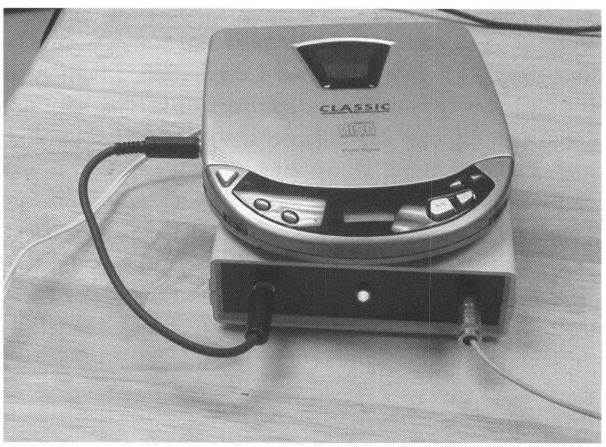

Figure 1. Setup for UltraQuiet tinnitus therapy.

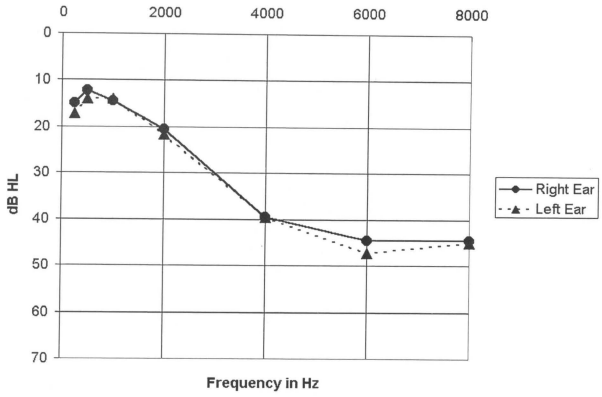

Figure 2. Average of audiograms for the original nine subjects. (*dB HL* = decibels of hearing loss.)

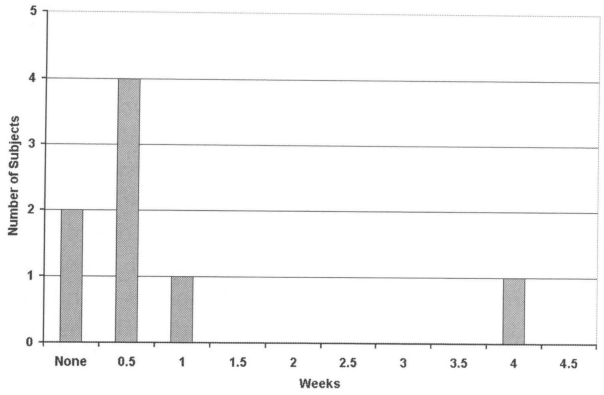

Figure 3. Duration of residual inhibition in eight subjects who underwent UltraQuiet therapy.

duction transducer at a low level—approximately 6 dB above threshold—for periods of 30 minutes to 1 hour twice weekly. The goal is to effect changes in the central nervous system mechanisms of tinnitus, resulting in long-term inhibition.

Subjects and Methods

Subjects

The subjects were nine adults with severe disabling tinnitus (seven male, two female; age range, 35–72 years). All subjects underwent evaluation for tinnitus, including audiograms and pitch matches. All subjects had mild to moderate high-frequency hearing loss. Figure 2 shows the average of the audiograms for the nine subjects. The pitch match to the tinnitus for all subjects was high-pitched, matching to either a pure tone or narrow band noise with frequencies between 5 and 16 kHz (mean, 7.3 kHz).

Stimulus

The tinnitus treatment stimulus was produced using Kyma Version 5 software with a Capybara 320 Sound Computation Engine (Symbolic Sound Corporation, Champaign, IL) and was recorded on a compact disk. The stimulus consisted of music digitally processed and used to modulate a signal in the 10- to 20-kHz range. The compact disk was played through a custom-made amplifier into a piezoelectric bone conduction transducer. The transducer was held in place on the mastoid bone of the subject by a headband. Although the stimulus is presented on only one side of the head, it is heard binaurally through bone conduction.

Procedure

The subjects listened to the tinnitus treatment stimulus for eight sessions (twice weekly for 4 weeks), beginning with 30-minute sessions and increasing to 60-minute sessions. The stimulus was presented at 6 dB above the threshold of each individual.

Results

All eight subjects who completed the study reported abatement of their tinnitus symptoms during the course of treatment. (One subject dropped out for reasons unrelated to the tinnitus study.) The duration of the improvement varied. For two patients, the improvement lasted for 2 or more weeks. For the others, it lasted for 1–2 hours for up to 3 days (Figure 3). A long-term follow-up questionnaire was administered 2–8 months after the end of the treatment; results are as follows. On the question, "How do you feel that your overall tinnitus symptoms have changed since before you began the tinnitus treatment?" one person answered "moderately improved," five people answered "slightly improved," and two people answered "about the same." One person reported benefit lasting 4 weeks after the last treatment, one person reported benefit for 1 week, four people reported benefit for 3–5 days, and two people reported no lasting benefit. No one reported any adverse effects or worsening of symptoms (Figure 4). The mean change between the pretreatment and posttreatment audiograms was less than 5 dB (Figure 5), which was not statistically significant. No individual audiogram showed any notable change.

Subjects occasionally reported an "afterimage" of the stimulus after the sessions, but this was not perceived as aversive and, in some cases, seemed to enhance the suppression of tinnitus. Some subjects also reported a subjective improvement in hearing, but this was not supported by the posttreatment audiometric results. However, discrimination was not assessed.

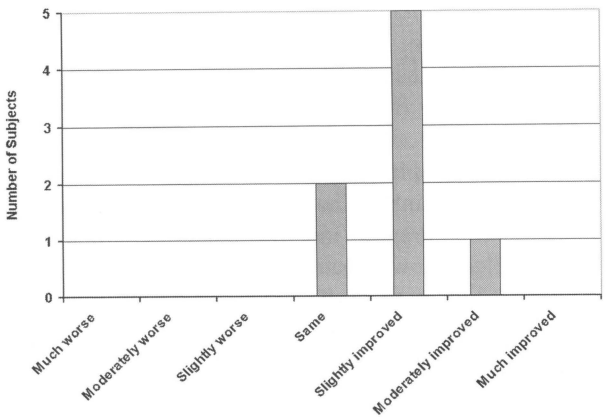

Figure 4. Long-term rating of tinnitus severity in eight subjects who underwent UltraQuiet therapy.

Discussion

The response of the patients suggests that the UltraQuiet therapy is able to induce RI of tinnitus for a duration substantially longer than that of conventional masking noise. Potentially, the improvement reported by the patients is truly a plastic change at the central level that may, over time, reflect the establishment of a "new" interneuronal network for auditory perception and the elimination of the aberrant auditory phenomenon (i.e., tinnitus). Central nervous system involvement in tinnitus has been found at both subcortical and cortical levels. Both levels could play a role in long-term inhibition.

Subcortical Habituation

Jastreboff et al. [16, 17] have developed a neurophysiological approach to tinnitus—called *tinnitus retraining therapy* (TRT)—based on subcortical habituation. The concept is that the annoyance of tinnitus depends on a subcortical conditioned response that creates distress through a link to the limbic system. The goal of the therapy is to habituate this response so that the tinnitus is no longer perceived. In TRT, the role of the sound is not to mask the tinnitus but to accomplish changes in the auditory system, including (1) decreasing the contrast between the neuronal activity that represents tinnitus and the background neuronal activity, (2) interfering with the brain's ability to detect the tinnitus signal, and (3) reducing the abnormal gain in the auditory system and thus reducing hypersensitivity.

The Jastreboff approach uses broadband noise but at levels that are adjusted low enough to *avoid* masking the tinnitus. The intent is to facilitate habituation with enriched sound stimulation. The idea is to enhance background neural activity within the auditory pathways and to habituate the tinnitus signal at a subcortical level. Jastreboff et al. [17] use noise with stable temporal characteristics; the spectrum is not as important as the stability of the signal because, in their model, fluctuation of the sound level might attract the attention of the patient and create problems with adapting to the sound. This contrasts with the form of cortical reprogramming discussed later, in which attention may be *necessary* for the changes to take place, relevant to the effect of the UltraQuiet.

Habituation of tinnitus by TRT requires long-term treatment. Sheldrake et al. [18] reported that tinnitus awareness is reduced by 61% and is virtually abolished in 16% of cases but that this can take up to 2 years of wearing the device for 8–10 hours per day. The much more rapid reduction of tinnitus by UltraQuiet therapy suggests that subcortical habituation is not a sufficient explanation.

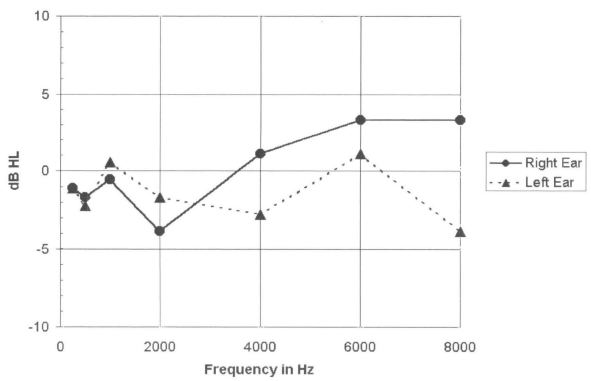

Figure 5. Average change in audiograms for the subjects from pretreatment to posttreatment. (*dB HL* = decibels of hearing loss.)

Cortical and Limbic System Mechanisms

There is evidence for considerable cortical plasticity after hearing loss. For example, Schwaber et al. [19] mapped the tonotopic organization of the cortex in monkeys before and 3 months after cochlear deafening for high frequencies. The deprived area of the cortex reorganized and became responsive chiefly to the frequencies intact at the cochlea. The low-frequency region did not change.

Several studies have demonstrated cerebral cortex changes specifically associated with tinnitus. These include changes in both the auditory cortex and the limbic system. Recent studies that are especially significant include those of Shulman [20], Llinas and Pare [21], Jeanmonod et al. [22], Muhlnickel et al. [23], and Lockwood et al. [24].

Shulman [20] hypothesized that a final common pathway for tinnitus exists for all patients with tinnitus, based on the identification by single-photon emission computed tomography (SPECT) of brain of side-to-side

perfusion asymmetries, highlighted by the medial temporal lobe system, which includes the amygdala-hippocampus complex. The initial process is the development of a paradoxical memory for an aberrant auditory stimulus. Adjacent perfusion asymmetries involving the frontal, temporal, and parietal lobes suggest an interneuronal network in the medial temporal system, resulting in the transition of the sensory to the affective component of the symptom of tinnitus. Underlying mechanisms are hypothesized to exist and to be highlighted by a diminution of inhibition mediated by γ-aminobutyric acid (GABA) due to a disconnection from excitatory (glutamate) inputs. Blockage of GABA-mediated inhibition with antagonists results in tinnitogenesis, an epileptiform auditory phenomenon [20], and in broadening of cortical neural tuning curves [25]. Treatment with the anticonvulsive GABA agonist drug gabapentin reversed high-frequency-specific tinnitus and reduced hearing loss in animals [26]. Although their reports are only anecdotal, some of our subjects cited the perception of better hearing after the UltraQuiet trial, a finding that will be the subject of further investigation.

Shulman et al. [27, 28] reported identification of a biochemical marker for tinnitus, the $GABA_A$/benzodiazepine/chloride receptor, and long-term tinnitus control with a receptor-targeted therapy binding to $GABA_A$ receptors in patients identified to have predominantly central tinnitus. Llinas and Pare [21] hypothesized that low-threshold calcium spike bursts were at the origin of parkinsonian tremor, action tremor, neurogenic pain, or absence epilepsy and tinnitus. Jeanmonod et al. [22] reported low-threshold calcium spikes in the human thalamus which, after medial thalamotomy, resulted in 50–100% relief in three of six patients with tinnitus and complete relief in only one.

Muhlnickel et al. [23] explored the reorganization of the auditory cortex in tinnitus, using magnetoencephalography. These authors found a marked shift of the cortical representation of the tinnitus frequency into an area adjacent to the expected tonotopic location. They also found a strong positive correlation between the strength of the tinnitus and the amount of cortical reorganization. They pointed out the similarities between tinnitus and phantom limb pain: Both cases exhibit a loss of input from peripheral nerves accompanied by a similar reorganization of the cortex. Muhlnickel et al. [23] suggested a possible therapeutic approach in which patients attend to and discriminate some features of acoustic stimuli that are close to the tinnitus frequency, to drive cortical reorganization of the nontinnitus frequencies into the tinnitus representation, thereby reducing it. Note that this is considerably different from conventional masking, wherein the acoustic stimuli encompass the tinnitus frequency; it is also different from the TRT paradigm, in which the point is to learn *not* to attend to the sounds. It does, however, resemble the UltraQuiet system, which uses patterned stimuli well removed from the tinnitus frequency.

Lockwood et al. [24] provided additional evidence both for cortical plasticity in tinnitus and for evidence of limbic system links. These researchers used positron emission tomographic imaging techniques to look at cerebral blood flow in patients with tinnitus and mapped neural responses to probe tones. They confirmed the SPECT findings of Shulman [20] of limbic and auditory system links. They also noted more widespread activation in patients with tinnitus, as compared with controls, and aberrant links between the limbic and auditory systems. As did Muhlnickel et al. [23], Lockwood et al. [24] made an analogy with phantom limb pain. Although they made no treatment recommendations, they noted (as already demonstrated by Shulman) that pre- and posttreatment functional imaging studies may provide objective measures of tinnitus and thus be useful in evaluating treatments.

Llinas et al. [29] recorded spontaneous magnetoencephalographic activity in awake, healthy human controls and in patients suffering from neurogenic pain, tinnitus, Parkinson's disease, or depression. They reported a thalamocortical dysrhythmia marked by an increased low-frequency rhythmicity in the frequency band of 4–8 Hz. Two other recent studies made a good case for treatment-induced cortical reorganization as therapy for neurological conditions. Liepert et al. [30] investigated rehabilitation of muscles after stroke in humans. Those authors noted that injury-induced cortical reorganization is a widely recognized phenomenon but that there is almost no information on treatment-induced plastic changes in the human brain. In that study, hand-muscle training led to significant enlargement of the muscle output area in the affected hemisphere. Menning et al. [31] documented plastic changes in the auditory cortex induced by intensive frequency discrimination training.

Tinnitus is different from simple cortical reorganization in which adjacent areas expand to fill the region no longer receiving input from the cochlea. In tinnitus, a region of the cortex is spuriously responding in a manner analogous to epileptiform activity, but we contend that it can be remapped to patterned auditory stimuli above the frequency of the tinnitus, presented through bone conduction, with a consequent reduction in tinnitus.

ACKNOWLEDGMENTS

We gratefully acknowledge the support of Sound Technique Systems, LLC, and the Martha Entenmann Tinnitus Research Center.

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