

Electrical Suppression of Tinnitus with High-Rate Pulse Trains

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Hypothesis: Application of high-rate pulse trains (e.g., 4800 pps) to the cochlea may represent an effective treatment of tinnitus.

Background: Tinnitus is a widespread clinical problem with multiple treatments but no cure. A cure for tinnitus would restore the perception of silence. One plausible hypothesis for the origin of tinnitus associated with sensorineural hearing loss is that it is due to loss or alteration of the normal spontaneous activity in the deafferented regions of the cochlea. Electrical stimulation of the cochlea with 5000-pps pulse trains can produce spontaneous-like patterns of spike activity in the auditory nerve.

Methods: Eleven volunteer human subjects with bothersome tinnitus and high-frequency sensorineural hearing loss underwent myringotomy and temporary placement of a round window electrode. High-rate pulse train stimuli were presented at

various stimulus intensities and tinnitus, and stimulus perception were scaled by the subject. Three cochlear implant recipients with tinnitus in the implanted ear underwent similar stimulation.

Results: Five of 11 (45%) of transtympanic subjects showed substantial or complete tinnitus suppression with either no perception or only a transient perception of the stimulus. Three showed tinnitus suppression only in association with the perception of the stimulus. Three showed no effects on tinnitus. A similar pattern of responses was seen in the cochlear implant subjects.

Conclusions: Although the study lacked an ideal placebo control, the results are promising and support further research to develop a clinically useful intervention for this troubling disorder. **Key Words:** Tinnitus—Electrical stimulation—Auditory nerve—Hearing loss.

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Tinnitus affects between 10% and 30% of the population. Of those affected, 20% have tinnitus sufficiently bothersome to seek medical attention (1). For many of these patients, tinnitus is a handicap that interferes significantly with their quality of life. Arguably more than any other otologic disorder, tinnitus remains refractory to current therapy. Masking is an effective management strategy for some patients (2), and unblinded, uncontrolled clinical experience suggests that “tinnitus retraining therapy” may benefit others (3). Antidepressants are effective if depression coexists with the tinnitus (4). Likewise, with comorbid anxiety, anxiolytics may be of benefit. Yet, none of the above therapeutic strategies

actually decreases the loudness of tinnitus in the absence of a masking stimulus.

Substantial literature exists to establish the psychoacoustic properties of tinnitus (5). Recent studies demonstrate, in addition, that a physiologic correlate of tinnitus may be visualized using a variety of functional imaging techniques (6,7). Thus, whereas it is clear that emotional responses to tinnitus vary widely across subjects and are clearly pathologic in some, there is no question that the underlying perception of tinnitus can by itself be a disabling handicap deserving of significant intervention efforts (8).

There is a long history of attempts to suppress tinnitus with electrical stimulation. Beginning in 1801 and continuing throughout the 19th century, several authors described the effects of electrical stimulation on the ear (9). These early attempts concluded that anodal direct current applied to the ipsilateral mastoid or zygoma could suppress or eliminate tinnitus in some patients, whereas cathodal stimulation caused auditory percepts and an increased intensity of tinnitus. These findings were subsequently verified in this century by Hatton (10) and in multiple publications from Bordeaux (11–14). The latter

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group applied electrical stimuli via a transtympanic electrode to the round window and promontory.

Subsequently, it was reported that tinnitus suppression is a common beneficial side effect of cochlear implantation (15–22), although the reported efficacy rate varied from 28% to 79% of patients. These effects may be mediated either peripherally or centrally. Peripheral electrical stimulation may have a direct electrical influence on a peripheral tinnitus, or it may have an indirect influence by creating activity that is passed to a central mechanism where the tinnitus reduction occurs. In addition, it is important to consider whether auditory perception of the electrical stimulation occurs during electrical suppression of tinnitus.

The promising early results with direct current anodic stimuli, the knowledge that direct current cannot be applied continuously without causing tissue injury, and the success with cochlear implants has led to numerous studies of alternating current stimulation for suppression of tinnitus (23–28). These studies have used external and middle ear electrodes and a variety of stimulus waveforms. Again, they suggest that in some patients, tinnitus can be suppressed and occasionally eliminated. None of these studies was placebo controlled, however, and this is of significant concern. A tinnitus suppression device, the Theraband, initially produced considerable enthusiasm (29) but was relegated to historic interest after a carefully designed, double-blind placebo-controlled trial (30). This device did, however, produce a verifiable, repeatable, and clinically relevant tinnitus suppression in one subject. Such a rigorous study is feasible only if tinnitus can be suppressed without producing an auditory or somatosensory percept.

In our efforts to better understand the physiology of cochlear implants and to improve signal processing strategies for them, we have uncovered certain properties of auditory nerve responses to electrical stimulation that may be of benefit to some tinnitus patients (31). Ideally, electrical stimulation would suppress tinnitus without producing any new auditory percepts. Patients with tinnitus who successfully make therapeutic use of acoustic masking still find the sound of the masker intrusive, although less so than the tinnitus. Preliminary work indicates that electrical stimulation of the cochlea can decrease tinnitus in some patients, but this is best documented in people with cochlear implants. In this setting, tinnitus is suppressed along with the production of an auditory percept, and it is unclear whether the tinnitus suppression is due to a nonspecific increase in neural activity (masking) or specifically affects tinnitus-related activity. If tinnitus originates from abnormal firing patterns of the auditory periphery, restoration of normal patterns should alleviate it. Current cochlear implants provide high levels of speech perception in some patients but do not restore “normal” activity to the auditory nerve.

Normally, the peripheral auditory nerve fibers are spontaneously active in quiet (32). This spontaneous firing of the auditory nerve is due to continuous, undriven

release of neurotransmitter by the inner hair cell synapse (33). This release process and the resulting firing patterns of the spiral ganglion have been extensively observed, modeled, and analyzed in multiple species. For durations on the order of seconds, transmitter release reflects a Poisson process (34). Refractory properties of the auditory neurons modify the transmitter release process, resulting in spike times reflecting a renewal process; i.e., a Poisson process with dead time. Early theories about the peripheral origin of tinnitus suggest that loss of this normal pattern of spontaneous activity can lead to abnormal central auditory activity perceived as sound (35,36). In this light, spontaneous activity may be viewed as the “code for silence.” This theory is consistent with the fact that most tinnitus is associated with hearing loss and most hearing loss is associated with loss or alteration of spontaneous activity (37). It also explains why cochlear nerve section is usually ineffective and not uncommonly makes tinnitus worse (15). The efficacy of acoustic masking with white noise can then be explained through the effect of such noise on the periphery, evoking spike intervals similar to spontaneous activity. The primary difference between spontaneous activity and noise-evoked responses is the across-fiber correlation that acoustic noise produces in the neurons that innervate adjacent locations on the basilar membrane.

We have demonstrated with a computational model that an appropriate electrical stimulus may produce a spontaneous-like renewal process in the auditory nerve, which is uncorrelated across fibers (31). Much of the underlying theory has been confirmed in animal studies (38,39). The purpose of this study was to test the hypothesis that such a high-rate pulsatile electrical stimulus can suppress tinnitus in humans without producing an audible percept.

MATERIALS AND METHODS

Our methods for subject recruitment, informed consent, psychoacoustic and electrophysiologic testing, surgical placement of a transtympanic electrode, electrical stimulation, and data analysis were reviewed and approved by our institutional review board.

Subjects and Procedures

Two groups of human subjects with severe tinnitus were recruited to take part in our studies. One group (cochlear implant [CI] group) consisted of 3 adults with severe to profound sensorineural hearing loss who had already received a cochlear implant in an ear that perceived stable tinnitus. This group was studied by reprogramming their cochlear implant.

The second group (transtympanic group) consists of 11 adults with varying degrees of mild to moderate high-frequency sensorineural hearing loss and normal speech discrimination in an ear with disturbing tinnitus. This group was chosen on the assumption that any deafferented auditory neurons are located in the basal cochlea near the round window and are accessible to electrical stimulation from the middle ear. Common causes would include presbycusis, noise-induced hearing loss, and aminoglycoside ototoxicity. The latter two causes have been demonstrated to produce decreased and otherwise abnormal

spontaneous activity in the cat (35–37). High-frequency presbycusis with normal speech discrimination is typically due to hair-cell loss (40), which would also be expected to produce loss of spontaneous activity if inner hair cells are affected (33). With any of these mechanisms, decreased peripheral spontaneous activity could lead to central hyperactivity perceived as tinnitus (41,42). If loss or alteration of normal spontaneous activity is a common cause of tinnitus, these clinical populations would be expected to include a significant percentage of such cases. Some preliminary work suggests that tinnitus that is not maskable acoustically is not suppressed with electrical stimulation (24). Psychoacoustic measures may permit identification of patients with “peripheral” tinnitus, although no subjects were excluded on the basis of these tests. Rather, we hoped to correlate tinnitus suppression results with preoperative psychoacoustic measures—a process that could be critical to subsequent patient selection. The possibility existed that some of the subjects had only pathologic changes in the outer hair cells, without loss of spontaneous activity, and would not have been expected to experience suppression of tinnitus using our stimuli. We performed otoacoustic emission testing on all subjects to address this issue, but no correlations with outcome were obtained in this small sample. Audiograms from 10 of our subjects are shown in Figure 1. Other clinical details are provided in Table 1.

In addition to the audiometric criteria, transtympanic subjects were selected for adequate vocabulary and education to reliably describe the unusual sensory percepts provided by electrical stimulation. Potential subjects were excluded if they had obvious evidence of psychiatric or personality disorder, medicolegal issues involving tinnitus, or abnormalities of the middle ear or tympanic membrane. The relatively low Tinnitus Handicap Questionnaire scores seen in Table 1 may reflect these selection criteria. Myringotomy was performed with the subject under topical phenol anesthesia, and a custom-built platinum ball electrode was placed in the round window niche. Testing sessions typically lasted 2 to 3 hours. After completion

of testing, the subject was clinically treated exactly as if he or she had undergone a routine clinical myringotomy. Any residual inhibition of tinnitus was documented by the subject until the tinnitus returned to its pretest level.

Electrical Stimulation

Transtympanic Subjects

A Sprint speech processor and CI-24 cochlear implant (Cochlear Corporation, Englewood, CO, U.S.A.) were used to produce 4800-pps charge-balanced biphasic pulses of various pulse widths. This signal was partially shunted using a multiple turn potentiometer as a current divider, allowing constant current of various levels to be applied without transient effects of turning the processor on or off. The current applied was monitored in two ways:

1. A battery-powered oscilloscope constantly monitored the current flowing through a resistor in series with the transtympanic electrode.
2. The Spring processor was calibrated with both in vitro resistive and realistic in vivo loads so that an approximate mapping from the clinical units used by the programming software to the current applied was generated. This mapping was obtained under the same high-rate conditions that were used with round window stimulation.

Thus, the maximum current to be applied was set by the speech processor. The current divider further limited the current to less than the speech processor setting. All stimuli were gradually increased to the maximum to avoid pain, typically produced above 300 to 400 μ A when the stimulus was suddenly switched on. Stimulus pulse durations were 25, 50, or 80 μ s/phase.

Cochlear Implant Subjects

The subject’s Cochlear Corporation CI-24 Sprint processor was reprogrammed to provide 4800 pulses per second on an electrode that was pitch matched to the tinnitus. Stimuli were

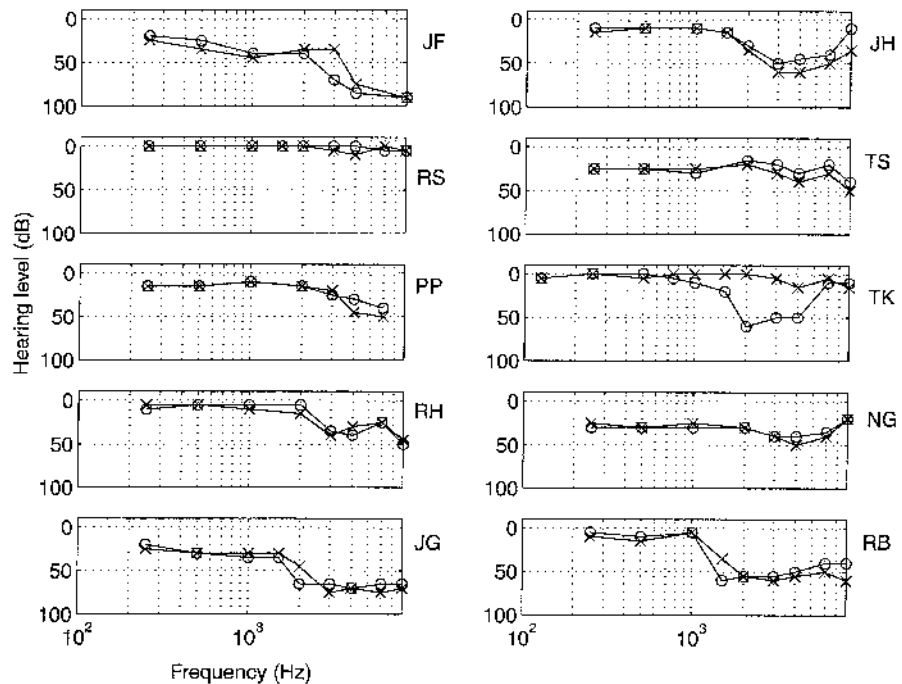


FIG. 1. Audiograms from 10 of the 11 transtympanic subjects. Subject HA (not shown) had borderline normal hearing thresholds, as did subject RS.

TABLE 1. Clinical features of the 11 transtympanic subjects

Subject	Cause	THQ	Annoyance	Loudness (dB)	Pitch (kHz)	Response
NG	NIHL	21	30–90	29	5	Suppress
JH	NIHL	13	20	6	5.3	Mask
TK	NIHL	33	35	4	11.5	Mask
TS	Presbycusis	19	80	4	7.3	Suppress
RS	NIHL	18	30–40	16	5.1	Mask
JF	Presbycusis	48	100	6	2.5	Suppress
JG	NIHL	28	60	2.5	10	Suppress
PP	NIHL	24	10–15	17	0.11	Pain
RH	NIHL	42	80	34	4.28	Suppress
RB	NIHL	NA	40	4.5	7.2	None
HA	normal hearing	56	80	17	8	None/pain

THQ, score on tinnitus handicap questionnaire (Kuk et al., 1990). Annoyance, subjective scaling from 0 to 100, 100 being the “worst tinnitus imaginable.” Loudness match is in dB SL (corrected for hearing threshold).

presented at increasing levels and pulse widths until either tinnitus suppression occurred or the onset of the stimulus was at the maximal comfortable loudness. Stimulus levels were recorded in clinical units for the Cochlear Corporation device.

Perceptual Assessment

All transtympanic subjects initially underwent medical evaluation, standard audiometry, and measures of spontaneous and click-evoked otoacoustic emissions. All subjects then completed the Tinnitus Handicap Questionnaire. This instrument is reliable, and its psychometric properties have been evaluated in 275 subjects with tinnitus (43,44). These measures allowed comparison of tinnitus severity across all subjects independently of subsequent loudness measures. All subjects then reported the loudness of their tinnitus using a scaling technique on a 100-point scale: 0 corresponding to “no tinnitus” and 100 corresponding to the subject’s usual tinnitus level (21). During electrical stimulation, loudness scaling for tinnitus as well as any electrically induced percepts was repeated for all subjects at all current levels, typically at 30-second intervals.

In addition to the questionnaire and the loudness scaling measures, the subjects underwent prestimulation psychophysical testing. Loudness (45) and dominant pitch (46) of tinnitus was assessed by comparison with tones presented to the contralateral ear. Any corrections necessary for recruitment were performed (47). The amount of broadband noise required to mask the tinnitus in each ear was determined (48). In unilateral tinnitus, similar broadband noise levels required for masking across ears is suggestive of a central cause. In bilateral tinnitus, the ability of a unilateral masker to suppress tinnitus bilaterally also suggests a central process. Psychophysical tuning curves for masking with tones and narrow-band noise are performed both for the tinnitus and for tones of matching loudness and pitch (49). These latter two measures help to determine whether a subject’s tinnitus behaves consistently with a peripheral source. Correlations of such localization tests with acoustic masking measures and electrical suppression seem likely but were not performed because of the small number of subjects. This issue will be analyzed in the future as data from more subjects become available. After round window stimulation, poststimulus suppression and recovery effects (24) have been measured and classified in a manner similar to postacoustic masking recovery (50,51).

Controls

Because of the subjective nature of tinnitus, significant placebo effects might be expected in any treatment trial. Strict double-blind placebo control was not possible for this study,

but other techniques were attempted to reduce the likelihood of significant placebo effects in the results. These techniques included the following:

1. The time course of tinnitus suppression and recovery was monitored closely.
2. The pulse frequency was modified to eliminate desynchronized auditory neuron responses (31). We expected tinnitus suppression to cease and stimulus perception to increase under these conditions.
3. The relationship between stimulus intensity and tinnitus loudness was carefully analyzed. In some cases, a “best intensity” was identified, arguing against placebo effects (24).
4. Single-blinded false trials (no stimulus presented) were implemented without feedback to the subject.

It is unclear to what degree earlier trials of electrical stimulation for tinnitus have been affected by placebo responses. Some investigators have reported minimal placebo effects (23), whereas in other studies, placebo was more frequently effective than the treatment (30). It should be noted that in the latter study, placebo effects were so rare that 75% of subjects experienced no tinnitus improvement under either condition. Because of substantial placebo effects in drug trials for tinnitus (52), we are sensitive to the significance of this potential problem. Strict placebo control was not possible with the transtympanic subject group but was accomplished single-blinded in the CI subjects.

RESULTS

No Response or Limited by Pain (3 Transtympanic Subjects, 1 Cochlear Implant Subject)

In 1 transtympanic subject, no perception of the stimulus, pain, or effect on tinnitus could be elicited up to the maximal current output of the stimulator (>1.1 mA at 80 μ s/phase). In 2 other subjects, stimulation above approximately 400 μ A evoked pain. No significant sound percept or tinnitus effect was noted below this pain threshold. Jacobson’s nerve was observed to be abnormally posteriorly displaced in 1 of these subjects, resting on the anterior lip of the round window niche and likely responsible for the atypical pain percept in this subject. Multiple electrode placements were attempted to avoid pain perception without success. The CI subject noted no

change in her tinnitus with current levels up to most comfortable loudness on multiple electrodes.

Electrical Tinnitus "Masking" (3 Transtympanic Subjects, 1 Cochlear Implant Subject)

Three transtympanic subjects showed tinnitus suppression only in the presence of a stimulus percept. All noted the stimulus percept sound to be similar to their underlying tinnitus. Figure 2 illustrates the tinnitus and stimulus percepts over time along with the stimulus current presented for 1 of the subjects. The response pattern was similar for all 3 subjects and did not demonstrate any significant residual inhibition. No particular subject preference for the stimulus percept over the underlying tinnitus was noted in response to questioning. Figure 3 shows a similar "masking" pattern in a CI subject. Tinnitus was suppressed only during perception of the stimulus and virtually mirrored this perception. There was no residual inhibition. Although this phenomenon was clearly different from acoustic masking, we called it a "masking" pattern to differentiate it from tinnitus suppression in the absence of a percept.

Electrical Tinnitus Suppression (5 Transtympanic Subjects, 1 Cochlear Implant Subject)

Five subjects showed suppression of tinnitus in the absence of a stimulus percept, or after complete or nearly complete adaptation to the stimulus percept. In the de-

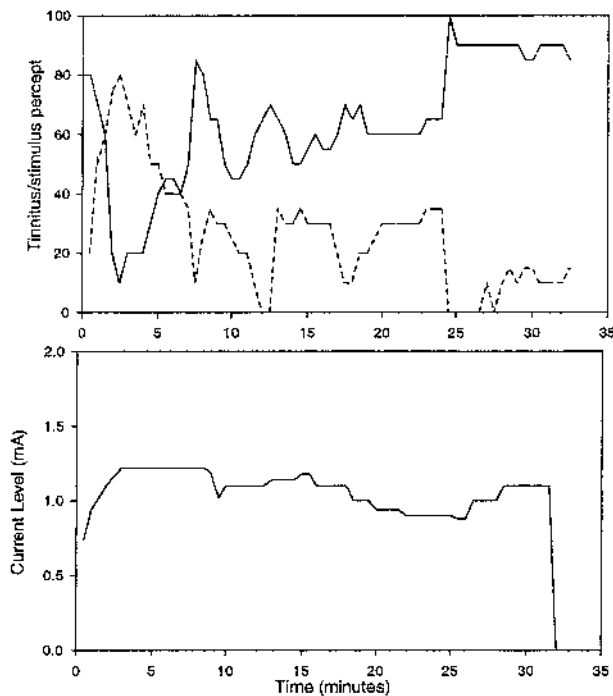


FIG. 2. Tinnitus and stimulus perceptions of subject TK with transtympanic electrical stimulation of the round window. Stimulus frequency 4,800 Hz, 80 μ s/phase. Dashed line, stimulus percept; solid line, tinnitus percept. The perception of the stimulus appeared to produce a masking effect on the perception of tinnitus in this subject.

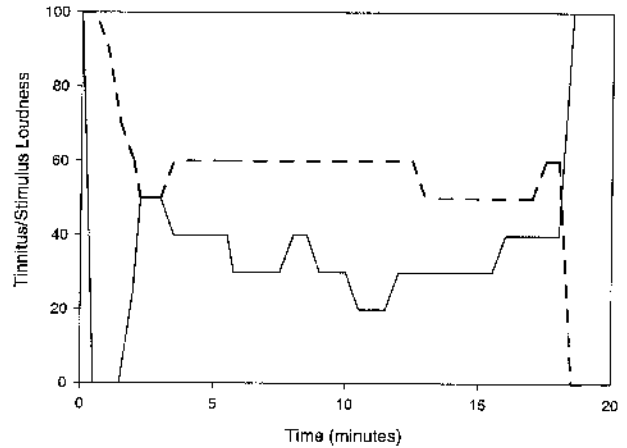


FIG. 3. Tinnitus and stimulus perceptions of subject DU with activation of his CI-24M cochlear implant. Stimulus frequency 4800 Hz, 25 μ s/phase, electrode 14 in monopolar mode. Stimulus onset at time 0, offset at 18 minutes. Dashed line, stimulus percept; solid line, tinnitus percept. The perception of the stimulus appeared to produce a masking effect on the perception of tinnitus in this subject.

velopment of speech processing strategies for cochlear implants, we have noted that there is a dramatic degree of adaptation to the unmodulated high-rate pulse trains used in this study (RS Hong, JT Rubinstein, D Wehner, D Horn, unpublished data, July 2002.). Round window stimulation demonstrated this phenomenon in 3 of the subjects who initially perceived loud tinnitus-like sounds when the stimulus was ramped up. After several minutes (a time course comparable to that observed in our cochlear implant subjects), the stimulus perception adapted to zero or near zero, followed shortly after by a decrement in the perceived tinnitus. There was a residual inhibition lasting from 45 minutes to 72 hours in 4 of the subjects. Four of the 5 who experienced suppression in this manner obtained clinically significant relief from the annoyance of the tinnitus and were very pleased with the result. Figures 4, 5, and 6 show the tinnitus and stimulus percepts from 3 of these subjects. In these 3 subjects, stimulation at lower pulse rates and/or at lower current levels did not evoke tinnitus suppression.

Figure 7 shows tinnitus suppression in 1 of the 3 CI subjects. It verifies that tinnitus suppression in this subject was repeatable. There appeared to be a level-dependent effect, with higher currents evoking more rapid and complete tinnitus suppression. The perceptions produced by the two stimuli were identical, and the tinnitus suppression was therefore effectively single-blinded because no feedback was given to the subject. Residual inhibition lasted approximately 45 minutes.

DISCUSSION

At this time, the only clinically effective treatment that decreases the loudness of tinnitus is acoustic masking. Although this is helpful for some patients, for others it simply replaces one undesirable sound with another. An

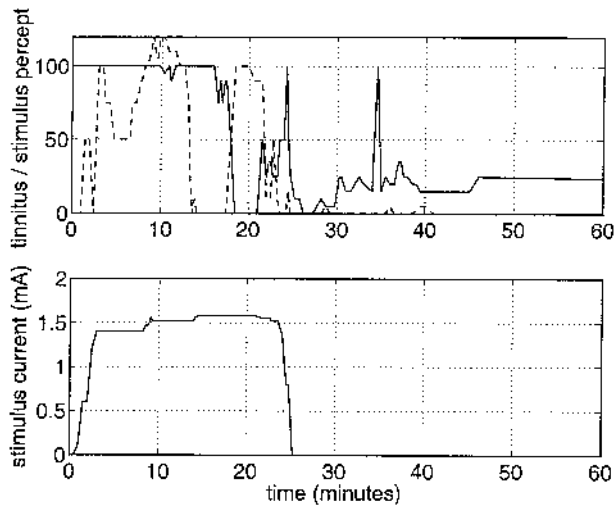


FIG. 4. Tinnitus and stimulus perceptions of subject TS with transtympanic electrical stimulation of the round window. Stimulus frequency 4800 Hz, 80 μ s/phase. Dashed line, stimulus percept; solid line, tinnitus percept. The perception of the stimulus was followed by rapid adaptation and subsequent suppression of tinnitus.

ideal therapy for tinnitus would create the perception of silence or at least decrease the loudness of tinnitus without introducing any new sounds. We have demonstrated in 5 of 11 subjects that this is possible, at least temporarily. Although the placebo control in the current experimental paradigm was not ideal, we doubt that these 5 subjects were demonstrating significant placebo effects, given the similarity of their responses to those of the CI subjects, for whom single-blinded placebo control was possible. In addition, multiple stimulus frequencies and intensities (not shown) did not suppress tinnitus earlier in the process of data acquisition. Because of the prolonged

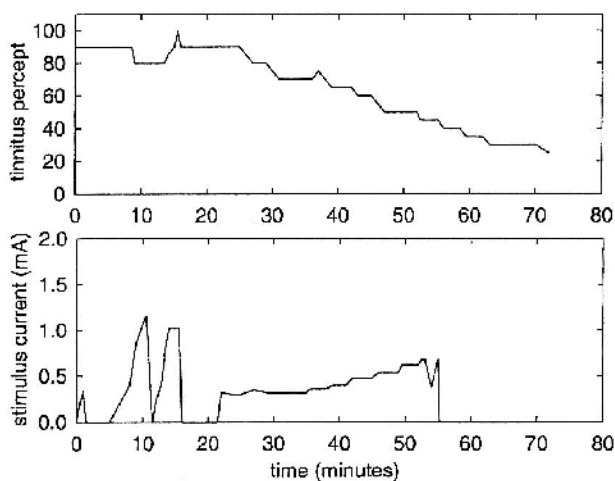


FIG. 5. Tinnitus perceptions of subject JF with transtympanic electrical stimulation of the round window. Stimulus frequency 4800 Hz, 50 μ s/phase. No perception of the stimulus was apparent, and 80% suppression of tinnitus was obtained.

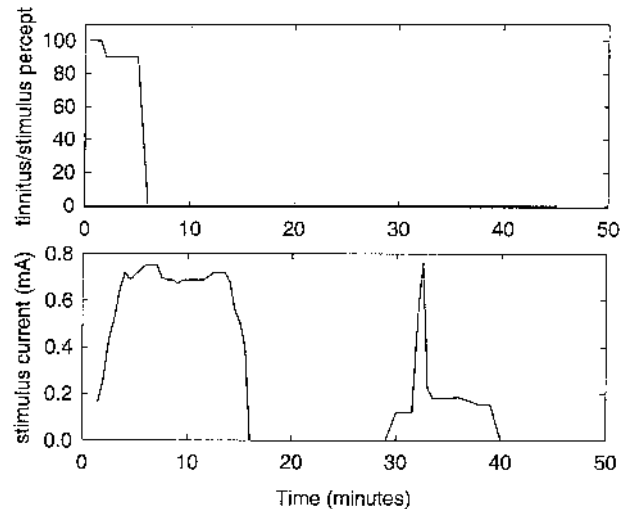


FIG. 6. Tinnitus perceptions of subject JG with transtympanic electrical stimulation of the round window. Stimulus frequency 4800 Hz, 50 μ s/phase. No perception of the stimulus was apparent, and complete suppression of tinnitus was obtained. A second application of current was started at 28 minutes in an unsuccessful attempt to affect the tinnitus in the contralateral ear.

residual inhibition of tinnitus produced by the stimulus, test-retest variability could not be assessed in the transtympanic subjects because this would have required a second myringotomy at a later testing session.

Whereas the theory underlying the hypothesis tested would suggest rapid (<20 ms) onset and offset of spontaneous-like activity in the auditory nerve, tinnitus suppression as induced in the 6 subjects appeared to be a slow process. The onset of tinnitus suppression typically required 5 to 15 minutes of stimulation, and residual

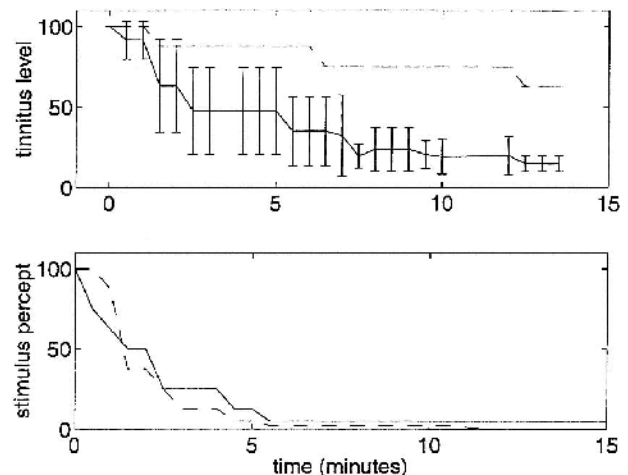


FIG. 7. Tinnitus and stimulus perceptions of cochlear implant subject AG with activation of her cochlear implant. Stimulus frequency 4800 Hz, 25 μ s/phase. Electrode 7 in monopolar mode. Dashed line, stimulus intensity of 134 clinical units; solid line, 142 clinical units. Error bars represent the range of three repetitions on three separate days.

inhibition lasted from minutes to days. This suggested involvement of an unknown central process and was in contrast to the immediate "masking" effects in four subjects. The prolonged residual inhibition is puzzling but must also represent some central effect and does not support or refute the underlying theory. Gibson has reported that 8% of 27 cochlear implant patients with tinnitus note residual inhibition lasting 30 to 60 minutes (18). One of our cochlear implant patients, who was not part of this study, has reported that his tinnitus returns only when his implant is turned off for more than 24 hours. Whereas the residual inhibition reported here was unusually long relative to residual inhibition seen with acoustic masking, it may in fact make the clinical application of a tinnitus suppression device easier.

Our findings support the hypothesis that high-rate electrical pulse trains applied to the round window can result in tinnitus suppression without an ongoing stimulus percept. Two problems must be addressed before a clinical device becomes feasible. First, with the notable exception of one CI subject, it is still not clear whether the effects we describe are repeatable within a subject. Repeatability is critical for the long-term use of a tinnitus suppression device and also for placebo control during a clinical trial. Second, it is not clear whether the stimulation has an effect on acoustic thresholds. On questioning, none of our subjects noted decreased hearing during stimulation. In fact, subject JF spontaneously noted improved clarity of speech perception during the stimulation. Nevertheless, increased hearing thresholds and/or decreased speech recognition are possible, resulting from either a mechanical effect of the round window electrode or an interaction between electrical stimulation and acoustically evoked hair cell activity (54). Answering these questions will require surgical implantation of a device that can be tested repeatedly and used over the long term by humans.

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