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Alterations in early auditory evoked potentials and brainstem transmission time associated with tinnitus residual inhibition induced by auditory electrical stimulation

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Abstract

Introduction: Residual inhibition (RI) is the temporary inhibition of tinnitus by use of masking stimuli when the device is turned off. **Objective:** The main aim of this study was to evaluate the effects of RI induced by auditory electrical stimulation (AES) in the primary auditory pathways using early auditory-evoked potentials (AEPs) in subjective idiopathic tinnitus (SIT) subjects. **Materials and Methods:** A randomized placebo-controlled study was conducted on forty-four tinnitus subjects. All enrolled subjects based on the responses to AES, were divided into two groups of RI and Non-RI (NRI). The results of the electrocochleography (ECochG), auditory brain stem response (ABR) and brain stem transmission time (BTT) were determined and compared pre- and post-AES in the studied groups. **Results:** The mean differences in the compound action potential (CAP) amplitudes and III/V and I/V amplitude ratios were significantly different between the RI, NRI and PES controls. BTT was significantly decreased associated with RI. **Conclusion:** The observed changes in AEP associated with RI suggested some peripheral and central auditory alterations. Synchronized discharges of the auditory nerve fibers and inhibition of the abnormal activity of the cochlear nerve by AES may play important roles associated with RI. Further comprehensive studies are required to determine the mechanisms of RI more precisely.

Keywords: auditory, auditory, brain stem, evoked potentials, evoked potentials, tinnitus.

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INTRODUCTION

McFadden defined that "tinnitus is the conscious expression of a sound that originates in an involuntary manner in the head of its owner, or may appear to him to do so"[1,2]. This symptom may become a source of significant disability for those who fail to adapt. Feldman reported in his classic studies that many subjects with tinnitus experienced a brief elimination of their tinnitus following the application of a masking stimulus[3]. He also reported that Grapergiesser initially suppressed tinnitus by transcutaneous electrical stimulation using Volta's Platinum-Zinc cell[4]. In fact, one of the outstanding features of this phantom sound is that it can be inhibited by auditory external stimuli such as acoustical, electrical, and magnetic fields[5-8]. It is obvious that following the offset of appropriate masking stimuli, tinnitus may remain suppressed for a short period of time. This phenomenon is known as "residual inhibition" (RI) in the tinnitus literature, although the term of "post-masking effect"[9] is more neutral with regard to its possible underlying mechanisms[10].

Although the RI phenomenon is one of the few methods that may temporally relieve tinnitus, only few studies on RI have been published until now[11]. It would be a critical step to define the factors that create these phantom sensations and develop rational treatments for this chronic and disabling disorder[12]. RI can also be contrasted with tinnitus inhibition produced by auditory electrical stimulation (AES)[7,8,13,14]. In 1981, Vernon & Meikle[15] speculated that the mechanism of RI may be related to mechanisms that suppress pain for a period of time after electrical stimulation. Tonndorf[16], in 1987, proposed a theory for RI based on the neuroscience of pain. He described the similarities between chronic pain and tinnitus RI by a gate control theory. According to Watanabe et al. report[14], RI induced by AES may act at the peripheral site of the auditory system. In 1971, Harald Feldmann[3] proposed a theory that RI occurred in the brain rather than the ear. Specifically, he suggested that this may be due to neural inhibition.

Through the electrophysiological approaches, we may be able to determine the manner for abnormal brain electrical activity in the auditory pathway and provide quantitative information regarding tinnitus and RI phenomenon. It has been shown that there is a relationship between the auditory evoked potentials (AEP) and the tinnitus phenomenon[17]. Previous studies has made it clear that both tinnitus and residual inhibition phenomenon (RI) involved a number of regions of the auditory system[18-21] and numerous electrophysiology and neuroimaging investigations have shown that tinnitus is associated with abnormal activity in the auditory system[22-24]. Most hypotheses postulate that the generation of tinnitus is associated with cochlear or acoustic nerve or central auditory dysfunction and their interactions[25-28]. Previous works has assumed that the perception of tinnitus was associated with abnormally high ("tinnitus-related") neural activity in the central auditory pathways by means of AEPs measures and functional imaging. Such activity may occur in the subcortical and cortical portions of the central auditory system[29-31]. A demonstration of such alterations was investigated in the occurrence of unusual increased or reduced waves in the AEPs. However, emphasis just in measurement of AEPs parameters (amplitude and latency) for assessment of tinnitus can be misleading. Previous studies have reported using other alternatives measurement of time interval between certain waves[32-34].

Since the transmission time-interval is a presentation of the progress of neural excitation from the distal portion of auditory nerve to the inferior colliculus of the brainstem, this interval has been referred to as brainstem transmission time (BTT) (Figure 1). It has been shown that BTT is one of the most stable features in assess of neurotological conditions[34]. These investigators have found that BTT to be significantly more stable and it is independent to intensity and frequency of stimulus. Also, it is invariant for stimulus rates below 20/sec, and is constant even in the presence of a conductive hearing-loss. The present study evaluated the changes occurring in BTT associated with tinnitus residual inhibition induced by auditory electrical stimulation in subjects with problem-tinnitus.

It is possible that the neural mechanisms involved in the RI phenomenon are similar to those that cause tinnitus[10,35]. Aberrant increase in function of neural networks or enhancement of stimulatory synapses function or decreased function of inhibitory synapses may be responsible for impairing pathways. In order to compensate for the tinnitus signal, the processing of auditory stimuli in the presence of tinnitus-related activity may require an increase in firing rate of neurons, the use of more neural substrate, or a combination of both[36]. The experiment reported in this paper was guided by the hypothesis that alterations in activity seen during residual inhibition can return the abnormal neural activity to normal levels. According to this hypothesis, efforts to understand RI phenomenon should be guided by develop in our knowledge of the underlying mechanisms of tinnitus. In the present study, primary parts of auditory pathways were evaluated using early evoked responses provided by electrocochleography (ECochG) and auditory brainstem response (ABR). The purpose of this study was to investigate alterations of BTT and other parameters of early AEPs in tinnitus subjects associated with RI induced by AES.

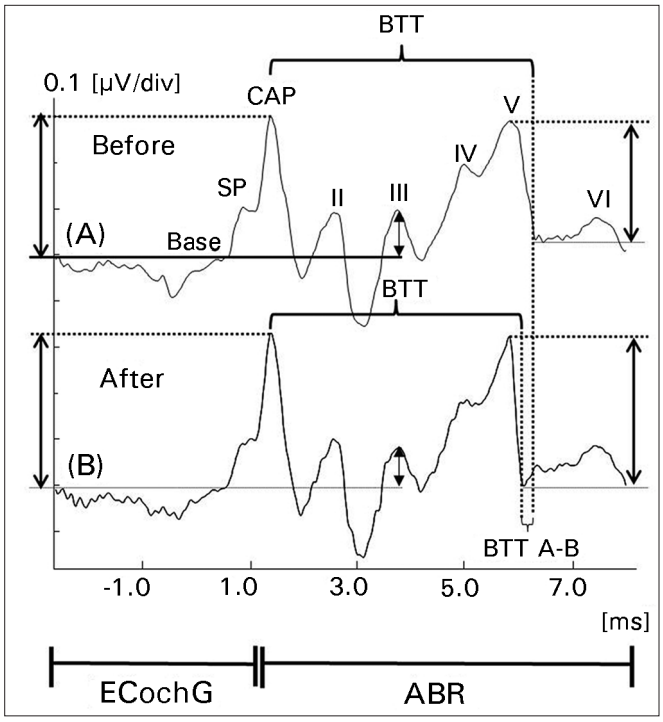

Figure 1. Typical alterations in the AEP waveform associated with RI induced by auditory electrical stimulation. The CAP amplitude increased from before (A) to after (B) AES, whereas the amplitude ratio of waves III/V, I/V and auditory brainstem transmission time (BTT) decreased from pre- to post-AES at 20 dB over the AEP threshold level. BTT is defined as the time interval between the initial earlobe-negative wave (the response of the auditory nerve - the 'input' to the brain stem) and earlobe-positive wave from the inferior colliculus region (the 'output' of the brain stem). CN: Cochlear nucleus; SOC: Superior olivary complex; LL: Lateral lemniscus; IC: Inferior colliculus; MGB: Medial geniculate body.

MATERIALS AND METHODS

Subjects

This cross-sectional and randomized, placebo-controlled trial was conducted on 44 adults (32 males, 12 females) suffering from severe subjective idiopathic tinnitus (SIT) referred to the ENT and Head & Neck Research Center of Hazrate Rasoul Hospital for an evaluation and management of their tinnitus during 2010 and 2011. The tinnitus subjects included in the research received AES in the tinnitus ear. Following the offset of the appropriate AES, tinnitus may remain inhibited for a period. Thus, the responses among the subjects were divided into two groups, including those subjects who had tinnitus residual inhibition (RI) and those who had tinnitus non-residual inhibition (NRI). The first studied group consisted of 24 tinnitus subjects with RI (17 males, 7 females; mean age, 44.71 years; age range, 18-65 years), and the second group included 20 subjects with NRI (15 males, 5 females; mean age, 42.19 years; age range, 19-57 years).

The location of the tinnitus was the left ear in 13 subjects (29.6%), the right ear in 6 subjects (13.6%) and was bilateral in 25 subjects (56.8%). The tinnitus subjects included in the research received electrical stimulation in the tinnitus ear. In the subjects with bilateral tinnitus, AES was administered in the ear with predominant or louder tinnitus. Each subject provided informed consent in accordance with the Declaration of Helsinki, Committee on Ethics at the ENT and Head & Neck Research Center of Iran University of Medical Sciences (IUMS) prior to participating in the study. All subjects had intractable permanent chronic moderate to severe SIT, which had been present for 4 to more than 180 months (Table 1). The subjects reported subjective tinnitus, and there was no evidence of evoked tinnitus. The perceived sense of tinnitus varied among the subjects and included a single high-pitch tone or noise, cricket sound, hissing, whistling or ringing. The subjects were included in the study if they fulfilled the following criteria:

1. Normal external and middle ear function and appearance as revealed by an otoscopy and tympanometry;
2. behavioural pure tone audiometry threshold levels of ≤ 30 dB HL at octave frequencies of 500 to 2000 Hz and no more than 60 dB HL at frequencies of 4000 and 8000 Hz;
3. each participant was healthy, not taking specific medications and/or undergoing audiological management at least 3 months prior to the study;
4. none of the subjects were left-handed or had invasive therapeutic interventions on the brain or ears before or after the onset of the tinnitus;
5. a primary complaint of chronic tinnitus (i.e., a duration greater than six months);
6. severe tinnitus as indexed with loudness matching of tinnitus more than 5-decibel sensation level (dB SL), tinnitus questionnaire (T.Q) score of 44 or more and visual analogue scale (VAS) rated greater than 6 out of 10 point;
7. the tinnitus had been assessed by both an otolaryngologist and audiologist;
8. the willingness to participate in a research-oriented study.

Additionally, the subjects were considered homogenous because of the constant and steady-state feature of their tinnitus. The subjects with the following characteristics were not included: pregnancy, psychiatric disorders (according to psychiatrist verification), any treatment for tinnitus during the previous three months, dementia, seizures or alcohol/drug abuse in the previous six months, head and neck diseases or space occupying lesions, and/or any organic disease that cause tinnitus.

Table 1. The duration of tinnitus between two groups of RI and NRI (n = 44).

Duration (months)	Number of subjects with RI (%)	Number of subjects with NRI (%)
4-6	2 (8.3)	0 (0)
6-12	3 (12.5)	1 (5)
12-24	7 (29.2)	3 (15)
24-120	10 (41.7)	10 (50)
> 120	2 (8.3)	6 (30)
Total	24 (100)	20 (100)
Mean ± SD	40.72 ± 48.38	86.19 ± 88.81

The subjects were examined by an ENT specialist for head and neck disorders, a neurologist for neurologic disorders, an internist for other medical diseases and a psychiatrist for psychological disorders.

Procedure

The screening tests included history taking, medical examinations, temporal bone imaging, an audiological evaluation (pure tone audiometry and tympanometry) and tinnitus psychoacoustic measurement (pitch and loudness matching) were performed for all tinnitus subjects. In the current study, all included tinnitus subjects were randomly allocated into two groups: those subjects who received AES and those who received placebo electrical stimulation (PES). We considered the additional session of PES as a control. The identical procedure as AES was repeated, except that the electric current produced by the device was turned off. Since the studied subjects has not been any experienced for electrical stimulation, prior to each study session were mentioned that they might or might not feel any sensations of AES. Because the different subjects with tinnitus indicated various durations of RI following AES, a time interval was considered between the sessions. The washout period for the crossover study was considered one week after the initial recording session. Then the studied subjects were "switched" in the "crossover study". The electrophysiological procedures consisting of ECochG and ABR were recorded before and immediately a few minutes after the applying of AES and PES. The visual analogue scale (VAS) for tinnitus loudness was measured pre-and post-AES and PES to monitor tinnitus loudness changes during the procedure (Figure 2). The VAS was administered prior to ECochG and ABR recordings. All the subjects who showed RI followed-up as an outpatient for one week.

All studied subjects was initially received AES for three different durations of 60, 120 and 180 seconds delivered to the tinnitus ear. This action was solely performed to ensure increased competence and effectiveness of the stimulation process to generate RI prior to electrophysiological procedures. Although no difference was observed between the duration of AES and occurrence and/or depth of RI, the 60-second stimulus duration criteria was elected for considering RI in the three groups of subjects in this study.

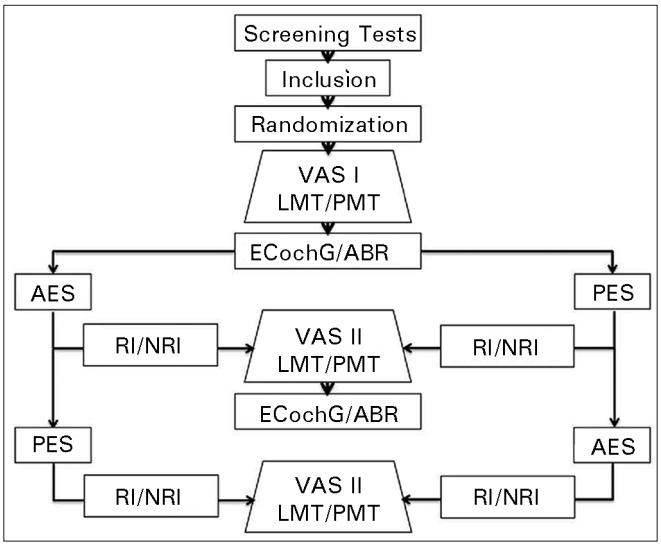

Figure 2. The model and design of the study. All subjects with tinnitus were randomly allocated into two groups: AES and PES. An additional session of PES was considered as a control. The washout period for the crossover study was considered at least one week after the initial recording session. VAS, LMT and PMT were administered pre-and post-AES during each session to assess tinnitus loudness changes. VAS: Visual Analogue Scale; AES: Auditory Electrical Stimulation; PES: Placebo Electrical Stimulation; RI: Residual Inhibition; NRI: Non Residual Inhibition; ECochG: Electrocochleography; ABR: Auditory Brain Stem Response; LMT: Loudness Match of Tinnitus; PMT: Pitch Match of Tinnitus.

With respect to the responses to AES, the subjects were enrolled into one of two pre-defined groups, including subjects with RI and those with non-residual inhibition (NRI). The results of the ECochG and ABR recordings were determined and compared before and after the applying AES and PES.

Behavioral assessment

A few minutes following AES, the inhibitory effects on perceived tinnitus loudness (residual inhibition) were estimated using a visual analogue scale (VAS) and pitch-match and loudness balance tests. Changes in tinnitus loudness were classified into three groups: (I) tinnitus became inaudible or reduced (complete or partial residual inhibition); (II) tinnitus was not changed (non-residual inhibition) and (III) tinnitus became worse than before AES (rebound effect). In the current study, the subjects' RI group was (I) and another group was entitled NRI, which included (II) and (III).

The subjective criteria for evaluating tinnitus after AES using a psychoacoustic tinnitus assessment included diminishing or worsening of tinnitus loudness by

at least 2 dB SL and reduction or increment in the pitch of tinnitus at least by 1000 Hz. Increased, unchanged or reduced less than 2 scores of VAS test were considered as NRI, 3 scales and more decrement were considered as RI.

Tinnitus assessment

We used a tinnitus evaluation device (TinnED®, designed in Research Center of Otolaryngology; Head and Neck of IUMS), which has 6 channels to reconstruct the most troublesome tinnitus (MTT) with a similar frequency and intensity. TinnED® measured four important parameters of tinnitus, including pitch-matching and loudness-matching of tinnitus (PMT and LMT), minimal masking level (MML) measured by narrow band noise to the affected ear until the tinnitus was fully covered and RI using a narrow band noise for 60 seconds when the intensity was 10 dB over MML. The accuracy of the calibrating equipment was sufficient to determine that the TinnED® was within the tolerances permitted by the American Standard Specification for Audiometers, S3.6-2004.

In the current study, the LMT and PMT of all subjects were estimated pre- and post-AES. We objectively estimated the tinnitus identification parameters. For the tinnitus pitch-match test, we used a two-alternative forced-choice method. We generated different pairs of pitch sounds at 11 frequencies (from 125 Hz to 12 kHz); we then decreased or increased the pitch (which was not similar to tinnitus), after which the subjects were asked to identify which pitch best matched the pitch of their tinnitus. The pitch-match test was typically in multiples of 1 KHz. Finally, we administered an octave confusion test to more accurately determined tinnitus frequency. The tone pairs were adjusted to a loudness level equivalent to that of the tinnitus before each pair was presented. LMT was obtained at each of the test tones used in the pitch-matching procedure[14]. Subsequently, the auditory threshold level at that specific frequency (A) was increased in 1-dB steps until the subject reported that the external tone equaled the loudness of the tinnitus (B). The sound level was then slightly raised by 1-dB increments to obtain a threshold, which was slightly louder than that of the tinnitus (C). We used the mean level of loudness between points (B) and (C) as the representative loudness of the tinnitus. The formula for the loudness (expressed as decibels of sensation level) was as follows:

$$\text{Loudness of tinnitus} = [(B+C)/2-A] \text{ (dB SL)}$$

Electrophysiological procedures

Stimuli for ECochG/ABR were generated using Bio-logic Navigator Pro electrophysiological system (Bio-logic Systems Corp., a Natus Company, Mundelein, IL). The subjects lay on a bed in an acoustically and electrically shielded room. The responses were recorded with a vertical montage of four-disk Ag-AgCl electrodes (non-inverting on the vertex (Cz), grounded on the forehead, and inverting the electrodes on each mastoid). Contact impedance indicators for the disk electrodes were less than 2 Kohms except for the inserted ECochG electrode, which was maintained at less than 5 Kohms. We performed the ECochG procedure to obtain the obvious compound action potentials (CAP) using the active surfacetympanic membraneelectrode (Tymptrode), which was inserted into the lower posterior-inferior region of the external auditory canal at the point closest to the tympanic membrane. Initially, we used conductive gel on the tip of the Tymptrode before inserting it into the ear canal. The Tymptrode was fed into the ear canal until it reached the eardrum. When placed properly, the electrode rested gently on the eardrum, and the gel assisted in making contact with the eardrum. The acoustic stimuli were delivered monaurally by an insert phone (ER-3; Etymotic Research, Elk Grove Village, IL) to the tinnitus ear. The stimuli were alternate 0.1-ms clicks presented at a rate of 11.1 per second and recording band pass filtration of 30-3000 Hz. The responses were accumulated 2000 times. We estimated the amplitudes, latencies and inter-peak intervals of the ECochG and ABR. The AEPs amplitudes and latencies were administered to estimate the input-output functions. The threshold level of the auditory evoked potentials (AEP) was determined as the minimum sound pressure level in which the detectable and reproducible waveforms of the compound action potential (CAP) for ECochG and wave V for ABR. In this research, the changes in amplitude and latency of the CAP and ABR values (waves I, III, and V) were estimated at 20 dB over the AEP threshold level.

The arrangement of the electrodes was not changed during the ABR recording. Simultaneous ABR/ECochG recordings were performed pre-and post-AES in all subjects. The CAP amplitudes were calculated from baseline to N1, and the ABR I, III and V amplitude waves were calculated from baseline to their respective peaks. The time-interval between the peaks wave I (auditory-nerve response) and the vertex negative wave following wave v (endpoint of wave V descending part) was measured as an auditory brainstem transmission time (BTT) (Figure 1). We re-measured the ECochG and ABR parameters within a few minutes after performing AES in the RI, NRI and PES control subjects.

Auditory electrical stimulation (AES)

AES was applied by inserting an active surface tympanic membrane electrode through the external auditory canal into the posterior inferior of the tympanic membrane and placing silver surface electrode on the forehead and

delivered by a stimulation system (promontory stimulator; cochlear company, Australia) used for evaluating cochlear implant (CI) candidates. We then placed a saline solution in the ear canal and measured five current levels: (1) the lowest current level for inducing vibration sensation in the subjects' ears was the Threshold level; (2) the current level that induced sound sensation was termed the auditory sensation level (ASL); (3) tinnitus inhibition level (TSL); (4) the most comfortable level (MCL) and (5) the uncomfortable current level (UCL), at which the subjects experienced pain. Bipolar burst of alternating current (square pulses) were applied in the tinnitus ear for 500 ms (a pulse rate of 1 Hz) and a frequency modulation of 50 Hz. The AES intensity varied among the subjects with tinnitus according to their tolerance and satisfaction level. Because of the differences in the intensity levels of electrical stimulation for generating RI among the subjects with tinnitus, we performed AES slightly above TSL at the MCL. The AES included current levels ranging from 60 to 500 microamperes (μA). The stimulus duration of the AES to generate RI was implemented in a 60-second period. Afterwards the saline was removed from the external auditory canal prior reassessing ECochG and ABR.

Statistical analysis

An analysis of variance was used to analyses the differences between the RI, NRI and PES controls for auditory pure tone averages (PTA). A comparison of the means of the ECochG and ABR parameters between-subjects group (RI/NRI/PES) pre-and post-AES was conducted using a repeated measures ANOVA, and a post-hoc Bonferroni analysis was performed to determine the between-groups relationships for amplitude (μV), latency (ms) and threshold (dB SPL). Carry-over effects were estimated using the interaction between period, main and sequence effects. The calculated P-value exceeded 0.05 in all interaction analyses. A probability value of less than 0.05 was considered to be significant. The summary data are presented as the means ± SD. All analyses were performed using the Statistical Package for Social Science (SPSS V.16; Chicago, United States).

RESULTS

Residual inhibition and electrical stimulus duration

Overall, 24 of 44 subjects (54.6%) indicated RI after applying AES (Table 1). Five subjects reported a complete inhibition (complete RI) of their tinnitus, and 19 subjects reported a significant attenuation of their tinnitus (partial RI). Tinnitus did not become worse in any of our subjects. The duration of RI and the length of post-stimulus inhibition are shown in Table 2.

AES was presented to subjects with tinnitus with an average intensity of 295.95 μA (SD = 108.05) (range 77.5 - 495) in the RI group and 283.89 μA (SD = 107.75) (range 92.5 - 500 μA) in the NRI group. The mean stimulus intensity difference in both groups was not significant, $p = 0.61$.

Table 2. The duration of residual inhibition among the tinnitus subjects.

Recurrence time	Number of subjects (%)
Less than 30 minutes	11 (45.8)
30 minutes to 1 hour	7 (29.2)
1 hour to 1 day	4 (16.7)
1 day to 1 week	2 (8.3)

Auditory pure tone averages and visual analogue scale

The mean duration of tinnitus was 40.72 months (SD = 48.38) in the RI group (ranging from 4 months to 15 years) and 86.19 months (SD = 88.81) in subjects with NRI (ranging from 8 months to 18 years). The mean differences between the two groups in the onset of tinnitus indicated a significant increase among the NRI group, $p < 0.05$ (Table 1). Most subjects with tinnitus (93.4%) had experienced tinnitus for at least 2 years.

An ANOVA assessed the statistical significance between the RI, NRI and PES controls for the auditory pure tone averages (PTA). Overall, there were no significant differences between the studied groups. The mean PTA for the five octave frequencies (0.05, 1, 2, 4 and 8 kHz) was 41.08 dB HL, SD = 17.10, n = 24, range 15-65 dB HL in the RI group, M = 42.20, SD = 16.79, n = 20, range 15-65 dB HL in the NRI group and M = 41.59, SD = 16.93, n = 44, range 15-65 dB HL in the PES controls. The mean difference in the PTA was not significant among the groups, $p > 0.05$.

When rating the average pre-stimulation tinnitus loudness, the subjects rated their tinnitus as greater than 6 on a 10-point visual analogue scale. A repeated measures ANOVA was used to test for the loudness rating differences using VAS between the groups pre-and post-AES. The results revealed that the loudness rating differed significantly between RI, NRI and PES control groups; $F_{2,85} = 18.41$; $p < 0.001$. Post-hoc comparisons using a Bonferroni test indicated that the mean loudness score for the RI group (from M = 6.83, SD = 1.37 to M = 3.13, SD = 1.65) was significantly different than the NRI group (from M = 6.90, SD = 1.17 to M = 6.65, SD = 1.04) and PES controls (from M = 6.86, SD = 1.27 to M = 6.68, SD = 1.25), $p < 0.05$). There were no significant differences between the NRI and control groups, $p > 0.05$ (Figure 3).

The pitch and loudness of tinnitus

A repeated measures ANOVA was used to test for differences of PMT and LMT pre-and post-AES among the

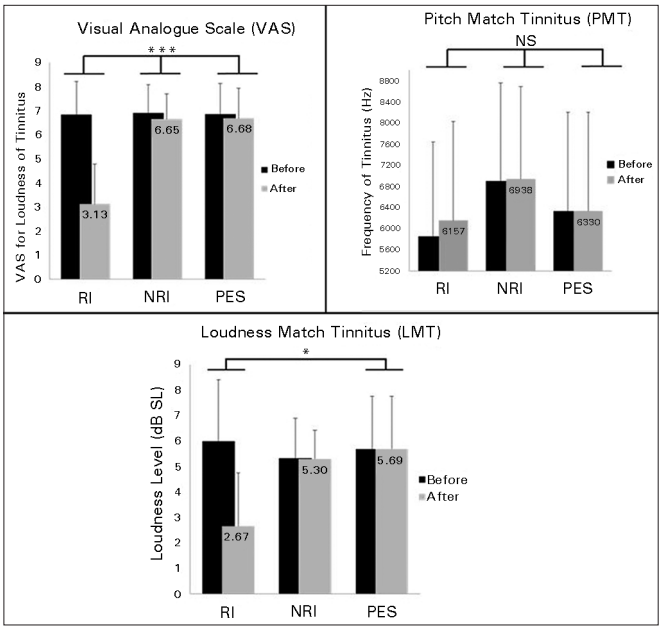

Figure 3. Observed changes in the visual analogue scale (VAS) scores for tinnitus loudness, the perceived frequency of tinnitus (pitch match of tinnitus) and perceived loudness of tinnitus (loudness match of tinnitus) pre-and post-AES among the three groups of subjects using repeated measures ANOVA. The asterisks indicate a significant difference of $p < 0.05$; * $p < 0.01$; ** $p \leq 0.001$; *** $p \leq 0.0001$; NS: Non-Significant, $p > 0.05$.

RI, NRI and PES control groups. The mean differences of PMT for the RI group (from 5856 Hz, SD = 1783 to 6157 Hz SD = 1874), NRI (from 6900 Hz, SD = 1861 to 6938 Hz, SD = 1751) and PES controls (from 6330 Hz, SD = 1873 to 6330 Hz, SD = 1873) did not indicate a significant difference before or after AES, $F_{(2,85)} = 1.39$; $p < 0.05$ (Figure 3).

The comparison of LMT means differed significantly across the three groups, $F_{(2,85)} = 3.81$; $p < 0.02$. Bonferroni post-hoc comparisons of the three groups indicated that the RI group (from 6.00 dB SL, SD = 2.40 to 2.67 dB SL, SD = 2.08) was significantly different than the PES control group (from 5.69 dB SL, SD = 2.07 to 5.69 dB SL, SD = 2.07), $p < .05$. Comparisons between the RI (from 6.00 dB SL, SD = 2.40 to 2.67 dB SL, SD = 2.08) and NRI groups (from 5.33 dB SL, SD = 1.57 to 5.30 dB SL, SD = 1.13) were not statistically significant at $p < .05$ (Figure 3). The duration of RI among the subjects with tinnitus using AES are indicated in Table 2.

ECochG Results

The intensity-latency/amplitude functions were analyzed before and after AES in all subjects. A repeated measures ANOVA comparing the CAP amplitude means indicated a significant between-group difference, $F_{(2,85)} = 4.73$; $p < 0.01$ (Figure 4). The Bonferroni correction indicated a significant increase in CAP amplitude in the RI group (from 0.20 μV, SD = 0.15 to 0.37 μV, SD = 0.16) but not the NRI group (from 0.18 μV, SD = 0.10 to 0.19 μV, SD = 0.10), $p < 0.05$. The Bonferroni analysis also showed a significant increase in the CAP amplitude in the RI group (from 0.20 μV, SD = 0.15 to 0.37 μV, SD = 0.16) but not the PES controls (from 0.19 μV, SD = 0.13 to 0.21 μV, SD = 0.19), $p < 0.05$ (Figure 4 and Table 3).

In all groups, the CAP thresholds were the same

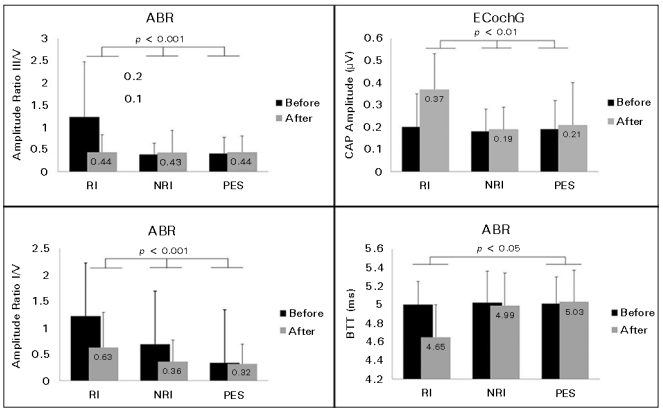

Figure 4. Changes in CAP amplitude, amplitude ratios of III/V and I/V and BTT parameter, pre-and post-AES between the three groups using repeated measures ANOVA.

level before and after AES. No significant effects were observed in the CAP threshold means between the RI (from 99.8 dB SPL, SD = 11.5 to 95.0 dB SPL, SD = 11.9) and NRI groups (from 93.5 dB SPL, SD = 12.8 to 93.8 dB SPL, SD = 12.9) and PES controls (from 96.9 dB SPL, SD = 12.4 to 93.8 dB SPL SD = 9.9), ($F_{(2,85)} = 0.91$; $p = 0.407$), Figure 4 and Table 3.

A repeated measures ANOVA for CAP latency revealed no significant differences between the RI (from 1.90 ms, SD = 0.53 to 1.85 ms, SD = 0.43), NRI (from 2.04 ms, SD = 0.55 to 2.08 ms, SD = 0.52) or (from 1.96 ms, SD = 0.54 to 1.95 ms, SD = 0.42) PES control groups ($F_{(2,85)} = 0.82$; $p > 0.05$), Table 3.

ABR Results

The results of the repeated measures ANOVA revealed that the wave III/V amplitude ratio differed significantly across groups, $F_{(2,85)} = 7.49$; $p < 0.001$. According to the Bonferroni post-hoc comparisons, in the RI group, a decrease in the wave III/V amplitude ratio mean (from 1.23, SD = 1.24 to 0.44, SD = 0.39) was more significant than the NRI group (from 0.39, SD = 0.25 to 0.43, SD = 0.50), $p < 0.05$. This result also showed a more significant decrease in the wave III/V amplitude ratio in the RI group (from 1.23, SD = 1.24 to 0.44, SD = 0.39) than in PES controls (from 0.41, SD = 0.36 to 0.44, SD = 0.36), $p < 0.05$ (Figure 4 and Table 4).

Table 3. A comparison of means using repeated measures ANOVA for amplitude (μV), latency (ms) and threshold (dB nHL) of CAP in three groups of RI (n = 24), NRI (n = 20) and PES (n = 44), pre-and post-AES.

	RI Group		NRI Group		Control Group		*p* value	$F_{(2,85)}$
	Pre-AES	Post-AES	Pre-AES	Post-AES	Pre-PES	Post-PES		
	(means ± SD)	(means ± SD)	(means ± SD)	(means ± SD)	(means ± SD)	(means ± SD)		
CAP amplitude	0.20 ± 0.15	0.37 ± 0.16	0.18 ± 0.10	0.19 ± 0.10	0.19 ± 0.13	0.21 ± 0.19	0.01*	0.47
CAP latency	1.90 ± 0.53	1.85 ± 0.43	2.04 ± 0.55	2.08 ± 0.52	1.96 ± 0.54	1.95 ± 0.42	0.44	0.82
CAP threshold	99.8 ± 11.5	95.0± 11.9	93.5 ± 12.8	93.8 ± 12.9	96.9 ± 12.4	98.3 ± 9.9	0.40	0.91

AES: Auditory electrical stimulation; RI:Residual inhibition; NRI: Non residual inhibition; PES: Placebo electrical stimulation; CAP: Compound action potential; * The asterisk indicates a significant level in the RI group than the NRI and PES Controls.

Table 4. A comparison of means using a repeated measures ANOVA for amplitude (μV), latency (ms) and threshold (dB nHL) of ABR's parameters in three groups of RI, NRI and PES pre-and post-AES.

	RI Group		NRI Group		Control Group		*p* value	$F_{(2,85)}$
	Pre-AES	Post-AES	Pre-AES	Post-AES	Pre-AES	Post-AES		
	(means ± SD)	(means ± SD)	(means ± SD)	(means ± SD)	(means ± SD)	(means ± SD)		
Amplitude III wave	0.20 ± 0.09	0.12 ± 0.08	0.10 ± 0.07	0.11 ± 0.09	0.12 ± 0.13	0.13 ± 0.11	0.14	1.96
Amplitude V wave	0.23 ± 0.14	0.35 ± 0.10	0.28 ± 0.10	0.31 ± 0.12	0.33 ± 0.19	0.30 ± 0.15	0.77	0.26
Amplitude ratio III/V	1.23 ± 1.24	0.44 ± 0.39	0.39 ± 0.25	0.43 ± 0.50	0.41 ± 0.36	0.44 ± 0.36	0.00*	7.49
Absolute latency I wave	1.84 ± 0.33	1.84 ± 0.20	2.02 ± 0.45	2.09 ± 0.44	1.92 ± 0.39	1.87 ± 0.25	0.08	2.55
Amplitude ratio I/V	1.22 ± 1.12	0.63 ± 0.66	0.69 ± 0.59	0.36 ± 0.41	0.34 ± 0.45	0.32 ± 0.37	0.00*	9.95
Absolute latency III wave	3.87 ± 0.26	3.86 ± 0.20	4.08 ± 0.45	4.11 ± 0.47	3.96 ± 0.37	4.02 ± 0.28	0.05	2.92
Absolute latency V wave	5.92 ± 0.33	5.91 ± 0.26	6.09 ± 0.44	6.16 ± 0.43	5.99 ± 0.39	5.95 ± 0.33	0.14	1.99
BTT	5.00 ± 0.25	4.65 ± 0.35	5.02 ± 0.34	4.99 ± 0.35	5.01 ± 0.29	5.03 ± 0.34	0.02**	3.87
IPL I-III	2.05 ± 0.17	2.03 ± 0.17	2.07 ± 0.14	2.03 ± 0.15	2.06 ± 0.16	2.04 ± 0.14	0.95	0.046
IPL III-V	2.05 ± 0.16	2.05 ± 0.20	2.01 ± 0.18	2.04 ± 0.13	2.03 ± 0.17	2.04 ± 0.13	0.81	0.202
IPL I-V	4.08 ± 0.18	3.97 ± 0.44	4.06 ± 0.19	4.06 ± 0.14	4.07 ± 0.18	4.09 ± 0.13	0.47	0.760

AES: Auditory electrical stimulation; RI: Residual inhibition; NRI: Non residual inhibition; PES: Placebo electrical stimulation; IPL: Inter peak latency; BTT: Brain stem transmission time; * The asterisk indicates a significant level in the RI group than in the NRI and PES Control groups; ** The asterisks indicate a significant level between the RI and PES Control groups.

A repeated measures ANOVA was used to test for I/V amplitude ratio differences between the RI, NRI and PES control groups. The results revealed that I/V amplitude ratio differed significantly across groups, $F_{(2,85)} = 9.95$; $p < 0.001$. The mean I/V amplitude ratio differences (from 1.22, SD = 1.12 to 0.63, SD = 0.66) in the RI group indicated significant changes compared to NRI subjects (from 0.69, SD = 0.59 to 0.36, SD = 0.41). The Bonferroni analysis showed a more significant decrease of the I/V amplitude ratio in the RI group (from 1.22, SD = 1.12 to 0.63, SD = 0.66) than the PES control group (from 0.34, SD = 0.45 to 0.32, SD = 0.37), $p < 0.05$ (Figure 4 and Table 4).

A comparison of BTT means using a repeated measures ANOVA indicated significant differences between groups, $F_{(2,85)} = 3.87$; $p < 0.05$. The mean BTT values were significantly lower in the RI (from 5.00 ms, SD = 0.25 to 4.65 ms, SD = 0.35) than PES control group (from 5.01 ms, SD = 0.29 to 5.03 ms, SD = 0.34), $p < 0.05$). Whereas the identical values were not statistically significant between the RI (from 5.00 ms, SD = 0.25 to 4.65 ms, SD = 0.35) and NRI groups (from 5.02 ms, SD = 0.34 to 4.99 ms, SD = 0.35), Figure 4 and Table 4.

We observed a decreasing trend for the absolute latency of wave III in the RI group (from 3.87 ms, SD = 0.26 to 3.86 ms, SD = 0.20) compared to PES controls (from 3.96 ms, SD = 0.37 to 4.02 ms, SD = 0.28); however, this trend was not statistically significant, $F_{(2,85)} = 2.92$; $p = 0.059$. The mean difference in the inter-peak latency intervals of I-III, III-V and I-V pre- and post-AES were not significant in either group (Table 4).

DISCUSSION

The present study evaluated the alterations occurring in early auditory evoked potentials and brainstem transmission time associated with RI induced by AES in tinnitus subjects. This study was performed in the first ten ms after stimulation to identify the effects of tinnitus and RI in neurogenic responses arising from the distal portion of acoustic nerve to the inferior colliculus of the brainstem. The main goal of this study was to evaluate the RI induced by AES through the primary auditory pathways to better understand the neural mechanisms involved in RI.

It appears that the neurophysiological mechanisms involved in RI could be related to both pre- and post-synaptic effects of AES followed by an increase of synchronized neural discharges and inhibition of the abnormal activity of the cochlear nerve. AES can evoke a variety of possible responses through the auditory pathway. Therefore, the RI induced by AES might be explained by interference with tinnitus generating circuits consisting of auditory nerve fibers, cochlear nucleus, inferior colliculus and whereby modification of cortical activity.

Tonndorf outlines the situation for most cochlear damage associated with tinnitus: the stronger inner hair cells (with large diameter nerve fibers) remain relatively undamaged, while the delicate outer hair cells (with small diameter nerve fibers) are destroyed. This auditory deafferentation can cause an increase in spontaneous activity of auditory nerve fibers. This extra activity is the supposed source of the ongoing tinnitus[16]. Making an analogy with a neural theory regarding chronic intractable pain, Tonndorf then suggests that, acoustic masking with its relatively short RI might mechanically re-activate the large diameter, inner-hair-cell fibers in largely the same manner as the large-diameter pain fibers are temporarily re-activated by scratching or by vibratory stimulation. According to gate control theory, the activity of the large diameter, inner-hair-cell fibers act to shut-off (for a time) the aberrant signaling from the small diameter, outer-hair-cell fibers. Thus perception of the tinnitus is stopped for a period of time[16]. Similarly, but more briefly, Vernon & Meikle[15] in 1981 speculated that the mechanism of residual inhibition may be related to mechanisms that suppress pain for a period of time after electrical stimulation.

Electrophysiological recordings associated with tinnitus RI

Using an ECochG test, the CAP amplitude indicated a significant increase associated with RI induced by AES. The CAP reflects the number of the auditory nerve fibers that discharge synchronously[37]. In the present study, the CAP amplitudes and latencies were measured at the identical intensity levels (CAP threshold + 20 dB SPL) before and after AES (Figure 1). Therefore, there was minimal chance that the increased CAP amplitude and thresholds reflected the recruitment phenomenon. These results are compatible with study reported by Watanabe et al.[14]

Since previous studies suggested neural alterations related to the AEPs properties in tinnitus subjects[17,38], the current study used the measurement of BTT as a considerably more stable and invariant parameter in evaluate tinnitus RI phenomenon[34]. In this study BTT significantly decreased associated with RI induced by AES (Figure 4). AES reduced the level of tinnitus-related activity as it reduced the loudness of the tinnitus percept. It can be due to more neural synchronization process of the auditory pathway associated with RI induced by AES. Meanwhile the BTT is a demonstration of progress of excitation from the acoustic nerve to the inferior colliculus of the brainstem. The alterations seen in the peak V, amplitude ratios of III/V and BTT is consistent with the noise-cancellation mechanism[39] and stated that not only serotonergic projections from the Raphe Nuclei could be able to change tinnitus perception, but also serotonergic projections in the inferior colliculus, both meeting at the thalamic level[38]. It seems that early AEPs to be influenced by serotonin in an excitatory manner mainly. In addition, the inferior colliculus, the main generator of wave V, receives serotonergic input from the dorsal Raphe nucleus[40]. Also serotonin often coexists with GABA in the inferior colliculus and both acting in the suppression of fearful and aversive behavior[41]. Furthermore, descending serotonergic projections from Raphe nucleus may also modulate superior olive neurons[42], the generators of ABR wave III[43]. These results are consistent with the results of Shulman & Kisiel[44]. This author used electrical stimuli for tinnitus inhibition and concluded that the morphology and other specifications of ABR waves in tinnitus ears changed to the normal state. According to changes in the AEP recordings associated with RI, it can be also speculated that the RI phenomenon might be caused by increasing synchronization of neural discharges in auditory fibers and distal portion of cranial nerve VIII following the applying of AES and modulating GABAergic activity in the inferior colliculus[45].

Many studies also stated that the majority of tinnitus forms result from a loss of inhibition in central auditory structures[35]. When inhibitory deficits occur, synchronous neural activity, which is normally limited by feed-forward inhibition to acoustic features in the stimulus (normal auditory perception), may develop spontaneously among neuronal networks in the affected auditory cortical regions and generate the sensation of tinnitus[25,46]. AES reduces the spontaneous firing of

the ipsilateral and contralateral cochlear nerves, probably owing to the reactivation of the efferent system. RI induced by AES can cause an increase in GABAergic shaping of the nerve activity when it reaches the inferior colliculus. GABA and the enzyme responsible for GABA synthesis, glutamic acid decarboxylase (GAD), and the genetic information necessary for the synthesis of GAD have been observed in the inferior colliculus of the central auditory pathway. RI could be produced by prolonged activity of the masking-induced released GABA because of masking stimuli. Aminoxyacetic acid (AOAA), an inhibitor of GABA transaminase, has been shown in a controlled study to decrease tinnitus. Because GABA transaminase is responsible for GABA degradation, the effect would be prolongation of the inhibitory activity of released GABA[37].

Also, a comparison of auditory nerve fiber discharges by AES in animal studies indicates that electrical stimulation causes discharge synchronizations in wide groups of nerves. An electrical stimulus delivered to the round window sensory transduction[47] and directly drives both outer hair cells (OHCs) somatic and hair-bundle motility[48,49]. Electrical impulses directly stimulate the cochlear nerve with no effect bypasses on hair cells[50].

There was no significant difference in the pitch match of tinnitus before or after AES. Therefore, we could not conclude whether the RI produced by AES was induced by action on the entire nerve or on some restricted fibers related to tinnitus pitch.

Despite above mentioned facts, the possible mechanisms involved in causing tinnitus RI using electrical trigger have not been precisely recognized, and the origin of this phenomenon in the brain has not yet been obviously recognized. Therefore, more comprehensive neuroscientific studies are required to better understand the mechanisms behind this phenomenon.

CONCLUSION

The current study conducted to examine the neural mechanisms of RI induced by AES in the first ten ms after stimulation include neurogenic responses arising from the auditory nerve to the inferior colliculus of the brainstem. The observed significant alterations in early AEPs consisting of CAP amplitude, brain stem transmission time (BTT) and I/V and III/V amplitude ratios associated with RI, suggested some alterations in peripheral and central auditory functions, including auditory nerve fibers, the cochlear nucleus and inferior colliculus and finally modification of cortical activity. It appears that many factors could be responsible for RI and are involved in suppressing tinnitus. The effects on the cochlear nerve, the synchronization of auditory nerve fiber discharges, inhibition of the abnormal activity of the auditory nerve caused by modulated GABAergic shaping of the nerve activity in the inferior colliculus, serotonergic projections from the Raphe Nuclei and in the inferior colliculus, reactivation of the efferent system over time, revival of the neural coding pattern of auditory information in neural pathways can play important roles in generating RI. It seems that early AEPs to be influenced by serotonin activity in an excitatory manner mainly. Further comprehensive neuroscientific studies may provide absent information regarding RI. These studies should contain a systematic database to evaluate procedures for optimizing RI to contrast it with AES and other intervention methods using specific measures.

Conflict of interest

None. The authors have no relevant financial interest in this article.

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