Research Article

Evaluation of Cochlear Synaptopathy in Tinnitus Patients with Normal Hearing Using Auditory Brainstem Response and Electrocochleography Tests

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Highlights

- ABR and ECochG were recorded in normal hearing subjects with and without tinnitus
- Primary auditory nerve fibers' activity was significantly lower in tinnitus patients
- ABR and ECochG show possible occurrence of cochlear synaptopathy in tinnitus patients

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ABSTRACT

Background and Aim: Tinnitus is defined a phantom sound percept. Few studies have examined the occurrence of synaptopathy in tinnitus patients utilizing a battery of tests that indicate synaptopathy. This study aimed to investigate the role of synaptopathy in tinnitus production and compare the various characteristics of the auditory brainstem response (ABR) test and electrocochleography (ECochG) in normal-hearing people with and without tinnitus.

Methods: This cross-sectional study was conducted on 34 normal-hearing individuals, 20 without tinnitus as controls (11 females and 9 males) and 14 with tinnitus (8 females and 6 men). The test components (amplitude, growth and slope of wave I, V/I ratio, action potential (AP) amplitude, and summating potential (SP)/AP) ratio were recorded during the ABR and ECochG tests for each subject.

Results: The control group had higher mean values of amplitude, growth and slope of wave I, and AP amplitude compared to the tinnitus group, and this difference was statistically significant ($p<0.05$). The mean V/I ratio and SP/AP ratio were lower in the control group than in the tinnitus group, and this difference was statistically significant ($p<0.05$).

Conclusion: The significant difference in the parameters of ABR and ECochG tests between normal-hearing people with and without tinnitus indicates that these parameters can be used to evaluate the presence of synaptopathy in tinnitus patients. These findings suggest the need for proper interpretation of the results of ABR and ECochG tests in tinnitus patients with a focus on the parameters indicating synaptopathy.

Keywords: Tinnitus; synaptopathy; auditory brainstem response; electrocochleography; normal hearing

Introduction

Tinnitus is defined as the perception of sound in the absence of external acoustic stimuli [1]. Although hearing loss is the most important cause of tinnitus, it can also occur in some people with normal hearing [2, 3]. The incidence of tinnitus in various studies has been reported to be 5-43%, which is influenced by geographical location, methodology, and tinnitus definition [4, 5]. Tinnitus can occur as a result of cochlear damage without hearing loss and loss of outer hair cells [6, 7]. So far, many studies on animal models have indicated the role of synaptopathy in the occurrence of tinnitus. Synaptopathy is defined as a condition in which the cochlear synapses are damaged with no hair cell loss, leading to reduced spontaneous firing rate in the auditory nerve [2, 8, 9]. Animal studies have shown that a damage > 50% inner hair cell (IHC) ribbons can lead to tinnitus [10]. Damage to the ribbon of IHCs can lead to increased gain in the central auditory system (CAS) in subcortical regions, which occurs due to the brain's prolonged habituation to reduced sensory input [11]. The lack of accurate knowledge of the neurophysiological mechanisms of tinnitus has made it difficult to develop successful treatment methods. There is currently no definitive medical treatment for tinnitus. It is usually managed by rehabilitation techniques [12].

Auditory brainstem response (ABR) test and electrocochleography (ECochG) are commonly used to evaluate synaptopathy in most studies due to their ease of use, cost-effectiveness, and non-invasiveness. These studies have reported a reduction in the amplitude of wave I under the ABR test, and in the amplitude of action potential (AP) under ECochG in the presence of synaptopathy [13-16]. In Kujawa and Liberman' study on 32 IHC healthy mice, 21 mice suffered 60% damage after exposure to a noise intensity of 100 dB SPL for two hours. Their study showed a decrease in the amplitude of wave I under the ABR test in the experimental group compared to the control group [13]. In another study, Mehraei et al. examined 54 mice in three groups including two experimental groups and one control groups. The first experimental group received 94 dB SPL noise, while the second experimental group received 100 dB SPL noise. Due to the presentation of noise in the frequency range of 8-16 kHz for two hours, synaptic damage and hidden hearing loss were reported. Their study showed a decrease in wave I amplitude and wave I amplitude growth in the second experimental group under the ABR test compared to the first experimental group and the control group [14]. Schaette and McAlpine, in a study on 33 women with normal audiograms (15 with tinnitus) reported a decreased ABR wave I amplitude in the tinnitus group compared to the control group [2]. Shim et al. examined 43 unilateral tinnitus patients (24 females and 19 males) with normal and symmetrical hearing threshold and 18 non-tinnitus subjects with normal audiogram. They showed a decrease in wave I amplitude and an increase in wave V amplitude in people with unilateral tinnitus. They attributed the increase in wave V amplitude to the increased gain in the CAS [15]. Mehraei et al., in a study on 9 females and 14 males with hidden hearing loss (assessed by click-evoked otoacoustic emissions and interaural time di-erence), reported a decrease in wave I amplitude growth and an increase in the V/I amplitude ratio [14]. In the above human studies, since tinnitus patients had normal otoacoustic emissions and a normal hearing threshold of up to 16 kHz, they attributed the decrease in ABR wave I amplitude to synaptopathy. Liberman et al. used the wave AP as equivalent to wave I to control the factors affecting the ABR wave I amplitude (e.g. signal to noise ratio, gender and head shape). In their study, a group of tinnitus patients with normal hearing in both groups were studied using the ECochG test. Their results showed an increase in summating potential (SP)/AP amplitude ratio in tinnitus patients [16].

The wave I amplitude and AP amplitude have been used in few studies to investigate the incidence of synaptopathy in tinnitus patients. Recent studies in the field of synaptopathy in human models have indicated the importance of using a battery of tests [16, 17]. The current study aimed to investigate the occurrence of synaptopathy in tinnitus patients using ABR test and its simultaneous use with ECochG. Our goal was to investigate alterations in wave I amplitude, wave I amplitude growth, and AP wave amplitude, and V/I and SP/AP ratios in people with tinnitus compared to non-tinnitus individuals. In the present study, the slope of wave I was used as a novel variable, which probably can show a decrease in tinnitus patients.

Methods

Participants

This study was carried out during 2019-2020 in the audiology clinic of Iran University of Medical Sciences and was funded with this university. Participants were 34 eligible people with normal audiograms aged 18-38 years divided randomly into two groups of control with no tinnitus (11 females and 9 males; mean age=23.10±2.10 years) and patients with tinnitus (8 women and 6 men; mean age=28.50±5.71 years). The inclusion criteria

were normal hearing thresholds in the frequency range of 250 Hz to 16 kHz (<15 dB), normal tympanogram, and age < 40 years. The exclusion criteria were a history of otologic, neurological, psychological, or traumatic diseases and use of ototoxic and psychotropic drugs.

Procedure

Case history and otoscopic examinations were first performed to check the condition of the external ear canal and tympanic membrane. The tympanometry test was carried out with a 226 Hz probe tone. Conventional audiometric tests in the frequency range of 250-8000 Hz were carried out in the acoustic test room using a supra-aural headphone and B71 bone vibrator, while high-frequency (HF) audiometry tests were performed in the frequency range of 8-16 kHz using a circumaural headphone. In conventional audiometry, a hearing threshold ≤15 dB is considered as a norm, to control the effect of hearing thresholds in the frequency range of 8-16 kHz on the results of electrophysiological tests, high frequency audiometry was performed on all participants. The similarity of high frequency thresholds in the participants of the present study was investigated using independent t-test. The results of independent t-test showed no statistically significant difference between the high frequency thresholds into two groups of control with no tinnitus and patients with tinnitus. The recording system for the ABR and ECochG tests (2-channel Interacoustic Eclipse 25, Denmark) had two inverting electrodes placed on the mastoid for the ABR test and in the external ear canal for the ECochG test, as well as a ground electrode placed on the Fpz region and a non-inverting electrode on the Fz region. For the ABR test, click stimulus, alternate polarity, 30-3000 Hz band-pass filter, 10 ms time window, a transducer rate of 11/1 Hz, and 2000 sweeps were used. The stimulus was provided at three intensity levels of 70, 80, and 90 dB nHL, with two separate recordings averaged for reducing variability at each intensity level. For the ECochG test, click stimulus at 90 dB nHL, alternate polarity, 30-3000 Hz band-pass filter, a transducer rate of 11/1 Hz, 5 ms time window, and 2000 sweeps were employed. In this test, the baseline was set to 0 ms. The SP/AP ratio was averaged into two separate recordings for less variability. Since the selection of right or left ear do not affect the statistical results, ABR and ECochG tests in control group were carried out only on one ear (12 right ears and 8 left ears). In the tinnitus group, these tests were conducted on the affected ear (9 right ears and 5 left ears). To analyze the growth of wave I amplitude at all three intensity levels, the growth curve of wave amplitude at each intensity level was plotted in the two groups [14]. After selecting a point at the top of graph (wave peak) and a point at the bottom, the time interval between the two points was calculated. Then, using the determined amplitude divided by the time interval, the slope of wave I was computed [18].

Data analysis

Collected data were statistically analyzed in SPSS v.24 software. Mean and standard deviation were used for describing the results of ABR and ECochG tests. The normality of data distribution was assessed by Kolmogorov-Smirnov test whose results showed abnormal distribution for the wave I slope variables at 80 dB nHL, V/I amplitude ratio at 70 and 80 dB nHL, AP wave amplitude, and SP/AP amplitude ratio. Hence, nonparametric tests including Mann-Whitney test were used for them. Parametric tests including t-test were used for other variables with normal distribution.

Results

The ABR test parameters (wave I amplitude, wave I amplitude growth, wave I slope and V/I ratio) were examined and compared between the two study groups. The results are shown in Table 1 and Figure 1. The mean of wave I amplitude, wave I amplitude growth, and wave I slope in the control group were higher than in the tinnitus group, while the mean V/I ratio in the control group was lower compared to the tinnitus group. These differences between the two groups were statistically significant ($p<0.05$).

Table 2 shows the results of the ECochG test parameters at the intensity level of 90 dB nHL (AP wave amplitude and SP/AP ratio) in two groups. The control group reported higher mean AP amplitude and lower mean SP/AP ratio compared to the tinnitus group, which were statistically significant ($p<0.05$). Mean AP amplitude was significantly larger than wave I amplitude in the control group ($p=0.001$). Their correlation was statistically significant ($n=20$, $p=0.001$, $r=0.672$). In the tinnitus group, although mean AP amplitude was lower than that of wave I at 90 dBnHL, their difference was not significant ($p>0.05$). In addition, their correlation was not statistically significant ($n=14$, $p=0.641$, $r=-0.137$) (Figure 2).

Discussion

In the present study, the ABR and ECochG tests were used to evaluate the occurrence of synaptopathy in tinnitus patients. The results of this study showed a significant difference in the components of ABR test (wave I amplitude, wave I amplitude growth, wave I slope and

Table 1. Statistical indices related to auditory brainstem response test characteristics (wave I amplitude, wave I amplitude growth, wave I slope and V/I ratio) in control and tinnitus groups (n=34)

Parameters	Intensity level dB nHL	Mean (SD)		Mean difference	p
		Control	Tinnitus		
Wave I amplitiude (µv)	90	0.251 (0.063)	0.199 (0.028)	0.052	0.007
	80	0.210 (0.051)	0.151 (0.019	0.059	<0.001
	70	0.104 (0.024)	0.076 (0.016)	0.027	0.001
Wave I amplitiude growth (µv/dB)	90	0.0027 (0.0007)	0.0021 (0.0003)	0.0005	0.008
	80	0.0025 (0.0006)	0.0018 (0.0002)	0.0007	<0.001
	70	0.0014 (0.0003)	0.0010 (0.0002)	0.0004	<0.001
Wave I Slope (µv/ms)	90	0.486 (0.099)	0.346 (0.044)	0.140	<0.001
	80	0.395 (0.093)	0.272 (0.025)	0.122	<0.001
	70	0.213 (0.032)	0.164 (0.021)	0.049	<0.001
V/I ratio (%)	90	2.109 (0.418)	3.116 (0.427)	-1.007	<0.001
	80	2.432 (0.567)	4.416 (1.062)	-1.984	<0.001
	70	3.200 (0.590)	6.126 (1.007)	-2.926	<0.001

V/I ratio) and ECochG test (AP amplitude and SP/AP ratio) between tinnitus and non-tinnitus groups, indicating the possible role of synaptopathy in occurrence of tinnitus in patients with normal hearing. The mean wave I amplitude at all three intensity levels in the control group was significantly higher than in the tinnitus group. The wave I amplitude shows the amount of function in the primary auditory neurons originated from IHC ribbons. Since the participants in the present study had normal hearing thresholds in the range of 250 Hz to 16 kHz, reduced wave I amplitude in tinnitus patients can be attributed to the reduction in the function of primary auditory fibers due to the occurrence of cochlear synaptopathy [8, 19]. Schaette and MacAlpine reported that the mean decrease in the amplitude of ABR wave I was significantly higher in those with tinnitus than in non-tinnitus ones [2]. Shim et al also showed a decrease in the amplitude of wave I in people with unilateral tinnitus [15]. Some animal studies also reported a reduction in wave I amplitude after inducing noise-induced synaptic damage [13, 20, 21]. The decrease in the wave I amplitude in the present study probably indicates the decrease in the function of afferent fibers due to the occurrence of synaptopathy.

In this study, the mean ABR wave I amplitude growth and ABR wave I slope at all three intensity levels were significantly higher in the control group than in the tinnitus group. These results are consistent with the results of Mehraei et al., who reported a decrease in the growth of wave I amplitude in tinnitus patients [14]. The reason for the decrease in the wave I amplitude growth is that the amplitude of this wave in synaptopathy patients is generally low. The ABR wave I slope variable has less been used in previous studies; only in one study by Gopal et al. as a case report of a 27-year-old female with hyperacusis without hearing loss and tinnitus, the wave III and wave V slopes showed a significant decrease, but no decrease was observed in the wave I slope [18]. We used

Table 2. Statistical indices related to electrocochleography test characteristics at 90 dB nHL intensity level (AP wave amplitude and summating potential/action potential ratio) in control and tinnitus groups (n=34)

Parameters	Mean (SD)		Mean difference	p
	Control	Tinnitus		
Wave AP amplitude (µv)	0.278 (0.061)	0.167 (0.021)	0.111	<0.001
SP/ AP ratio (%)	0.113 (0.022)	0.211 (0.024)	-0.097	<0.001

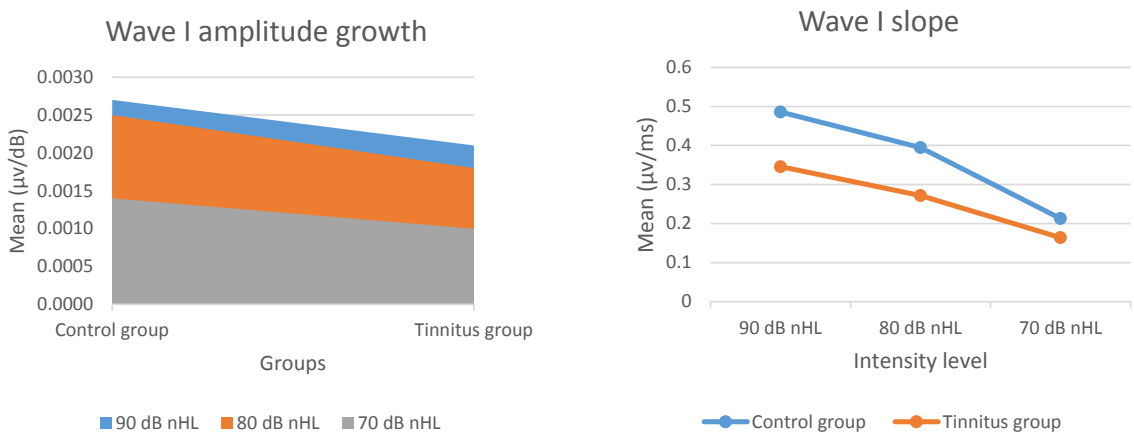

Figure 1. The average wave I amplitude growth, wave I slope, in the control and tinnitus groups

the wave I slope variable in tinnitus patients as a novel parameter for diagnosing synaptopathy. The decrease in the wave I slope may be due to an increase in the time interval between the peak and the bottom of wave I in tinnitus patients. Since the participants in our study had normal hearing, the increased time interval indicates the possibility of synaptopathy involvement in the occurrence of tinnitus.

In comparing the difference in mean V/I amplitude ratio at all three levels of intensity, the control group showed a significantly lower ratio compared to the tinnitus group. Gu et al. in a study on 15 men with tinnitus (Mean age=42 years), 21 men without tinnitus (Mean age=43 years), and 11 men without tinnitus but younger (Mean age=23 years), reported that the mean V/I ratio in the group with tinnitus was significantly larger than in the two groups without tinnitus [22]. Mehraei et al. also reported an increase in the V/I amplitude ratio in tinnitus patients [14]. Some studies have reported an increase in the amplitude of V wave in people with tinnitus, due to a gain in the subcortical areas of the CAS to compensate for the decrease in sensory inputs to the peripheral auditory system. This reason, in addition to reduced wave I amplitude, justifies the increase in the V/I amplitude ratio in tinnitus patients [11, 15].

In the current study, the mean AP wave amplitude was significantly greater in the control group, while the mean SP/AP amplitude ratio was significantly higher than in tinnitus patients. Liberman et al. conducted a study on a group of tinnitus patients with normal hearing using the ECochG test. Subjects were divided into two groups of low-risk (less exposed to noise by using hearing protection devices) including 7 females and 15 males, and high-risk including 8 females and 4 males. Their results showed a decrease in AP amplitude and an increase in SP/AP amplitude ratio in the high risk group. The decrease in AP amplitude, however, was not statistically significant, while the increase in the SP/AP ratio

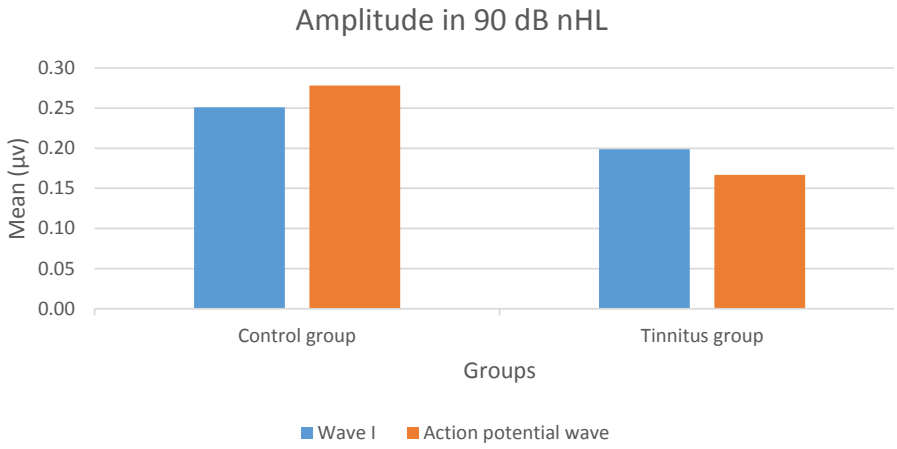

Figure 2. Comparison of wave I amplitude with action potential wave amplitude at the intensity level of 90 dB nHL in the control and tinnitus groups

was significant [16]. The AP amplitude, like the wave I amplitude, shows the activity of the primary auditory nerves. Since the participants in our study had normal hearing, the decreased AP amplitude in those with tinnitus suggests that synaptopathy may have a role in reducing the synchrony and activity of primary auditory neurons in them. In the present study, 0 ms was selected as a baseline for both groups and also the SP/AP ratio was averaged after two separate ECochG recordings for having less variability in recording response for the SP amplitude. Since the SP potential is not dependent on the cochlear synapse function, its amplitude is not affected by the synaptopathy in people with tinnitus. In contrast, the AP amplitude in our study was decreased in patients with tinnitus, suggesting the possibility of synaptopathy involvement. Lack of the effect of synaptopathy on SP amplitude along with reduced AP amplitude in patients with tinnitus led to an increase in SP/AP ratio [16, 23]. An increase in the amplitude of wave AP compared to wave I was expected in the current study due to the simultaneous use of ABR and ECochG tests, electrode placement in the ECochG test, and putting the recording electrode closer to the source. dB nHL the lower amplitude of wave AP compared to wave I amplitude at 90 dB nHL in tinnitus patients with normal hearing may suggest that the wave AP is more influenced by synaptopathy than wave I.

It is recommended that future studies use larger sample size to investigate synaptopathy in tinnitus patients. Due to time constraints and prolonged time for testing, other variables that could be effective in the study of synaptopathy (e.g. wave V latency shift in the presence of noise) were not used. Therefore, these variables as well as suprathreshold testing such as gap in noise test can be used in future studies for better and more evaluation of synaptopathy in tinnitus patients. Since synaptopathy studies on human models have many limitations due to the lack of histological evidence, detailed interpretation of the findings of this study based on synaptopathy was difficult and limited like previous studies.

Conclusion

In both ABR and ECochG testing, a reduction in the amplitude of waves connected to the peripheral axons of the auditory nerve fibers suggests the synaptopathy involvement in the occurrence of tinnitus. There is a need to interpret the ABR test results with an emphasis on the parameters indicating synaptopathy as well as related parameters, such as wave I amplitude growth and wave I slope amplitude in tinnitus patients with normal hearing. The further decline in the amplitude of AP wave compared to that of wave I in these patients suggest the need for a test to better monitor the mechanism of synaptopathy in this tinnitus patients.

Ethical Considerations

Compliance with ethical guidelines

Ethical Consideration: this research approved by Ethical committee of IUMS with Code number IR.IUMS.REC. 1398.041

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Authors' contributions

TA: Study design, acquisition of data, interpretation of the results, statistical analysis, and drafting the manuscript; RT: Study design, interpretation of the results, and drafting the manuscript; AP: Interpretation of the results and drafting the manuscript; MK: Statistical analysis.

Conflict of interest

No conflicts of interest were disclosed by the authors.

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