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Acoustic startle reflex and pre-pulse inhibition in tinnitus patients

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Abstract

Gap induced pre-pulse inhibition (Gap-PPI) of acoustic startle reflex has been used as a measurement of tinnitus in animal models. However, whether this test is sensitive to detect tinnitus in humans is still unclear. Based on the testing procedure used in animal studies, a human subject testing method was formulated and conducted to investigate if a similar result could be found in tinnitus patients. Audiologic and tinnitus assessments and acoustic startle reflex measurements were performed on seven tinnitus subjects and nine age matched subjects without tinnitus. There was no significant difference found between the control and tinnitus group on the Gap-PPI across the frequencies evaluated. The amplitude of the startle response in the tinnitus group with normal hearing thresholds was significantly higher than the control group and those with tinnitus and hearing loss. This preliminary result suggests that hyperexcitability in the central auditory system may be involved in tinnitus. There was no correlation between hearing thresholds and the increased amplitude of startle response.

Keywords: Tinnitus; Startle reflex; Prepulse inhibition; Hearing loss

1. Introduction

Tinnitus is a phantom auditory perception often described as a ringing, buzzing, chirping or whooshing noise in the ear despite the absence of an external sound source (Jastreboff, 1990). This phantom sound can be constant or intermittent and range in severity from being barely noticeable to causing extreme distress, even suicide (Saunders, 2007). The variability in how tinnitus is perceived lends itself to the different thoughts of what the causes of tinnitus are, and where this auditory stimulation originates. The current focus of research is on spontaneous neuron discharges (Norena et al., 2003), although the peripheral auditory system and neuroplasticity in the regions of the brainstem and auditory cortex (Saunders, 2007) or any combination thereof have also been hypothesized as possible etiologies. The exact cause of tinnitus is still not clear.

It is believed that up to 10% of the general population perceives tinnitus. Veterans receive service related compensation for their tinnitus (Saunders and Griest, 2009). However, there are few objective, concrete measurements for the manifestation of tinnitus (Lockwood et al., 1998). The large numbers estimated of those who suffer from tinnitus and the amount of compensation for tinnitus are based solely on subjective measures which can lead to false positives and other unwanted situations. The need for an objective test for tinnitus is obvious.

The acoustic startle reflex (ASR) is a sudden muscular movement in response to a loud unexpected sound (Arnfred et al., 2004) which has been used to detect tinnitus in animal models (Engineer et al., 2011; Turner et al., 2006; Yang et al., 2007). The ASR pathway begins in the peripheral auditory system and moves up the brainstem to the reticular

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formation which then descends back to the spinal motor neurons leading to subsequent muscle movement. This pathway is thought to be the reason for the rapid reaction to the stimulus, as short as 8 ms in animals and ranging in speed from 10 ms to 150 ms in humans. There are a number of factors which may affect the ASR (Faraday and Grunberg, 2000). One such factor that can affect the ASR is a change in stimulus prior to the startling sound which leads to inhibition of the ASR response (Arnfred et al., 2004). This change in stimulus is known as a pre-pulse and the resulting inhibition is called the pre-pulse inhibition (PPI). Aurally this pre-pulse can be presented as a noise burst pre-pulse or in contrast by a silent break in continuous noise known as a gap pre-pulse. Recently research has begun in testing rats with tinnitus and the effects of tinnitus on PPI and the acoustic startle reflex (Chen et al., 2013; Turner et al., 2006; Yang et al., 2007). Research by Yang et al. showed statistically significant results using gap pre-pulse at the frequency in which tinnitus occurs in rats treated with salicylate (Sun et al., 2009; Yang et al., 2007). Turner et al. has shown that rats with tonal tinnitus exhibited less pre-pulse inhibition utilizing a gap pre-pulse than controls when the background noise was composed of the frequency similar to the rats' tinnitus (Turner et al., 2006), further lending to the idea that poor gap detection in tonal background noise is related to tinnitus.

The purpose of this study is to gauge the possibility of an objective means of tinnitus testing utilizing the gap induced pre-pulse inhibition of ASR in narrowband background noise. Using the knowledge gained through previous research on rats, an objective means of tinnitus testing is seen as a possibility.

2. Methods

2.1. Subjects

Two groups of subjects (male and female, 20–55 years old) were used in this project. The control group consisted of individuals without complaints of tinnitus and with hearing within normal limits (hearing thresholds are above 20 dB HL). The test group consisted of individuals suffering from tinnitus. As it is often found that persons suffering from tinnitus have a hearing loss, hearing losses through the moderate range were accommodated for and included in this group, though hearing within normal limits was considered to be optimal.

2.2. Audiology tests

The subjects first received a brief hearing screening. Otoscopy was done first, followed by a screening tympanogram of both ears to check for normal ear canal volume, pressure and compliance. A screening acoustic reflex at 1000 Hz was included. Air conduction threshold checks were conducted utilizing a GSI 61 audiometer and insert ear phones (ER-3A). Pure tone testing was conducted at 0.25, 0.5, 1, 2, 4, and 8 kHz for subjects with no complaints of tinnitus. Subjects with tinnitus were tested at the additional frequencies of 3 and 6 kHz, using a pulsed tone. Tinnitus pitch and loudness matching was performed and a brief questionnaire about their tinnitus was also given.

2.3. Acoustic startle reflex using Gap-PPI

Subjects were instructed to keep their eyes open, to remain awake and were informed about the sounds they would be hearing via the headphones. Lights in the testing booth were turned off to assist ;in reducing unnecessary muscle activity. Electrode site placement occurred at the locations immediately next to the outer corner of the subjects right eye (ground electrode) and below their right eyes, just above the inferior margin of the orbital socket (active electrode) (Hawk and Kowmas, 2003). The signal was amplified by a TDT preamplifier (RA16PA and RA16LI). The noise, both background and startle sound was calibrated (824, Larson Davis) with a ½ inch microphone (2540). The background noise was a narrowband noise with a 100 Hz bandwidth presented at 38–40 dB SPL centered at frequency of patient's tinnitus. The startle noise was a broadband signal at 100 dB SPL.

Startle reflex testing was controlled via the appropriate software. The inter-trial interval was random with a variation of 20–30 s. The gap duration was 100 ms and the duration of startle stimulus was 50 ms (rise/fall time 1 ms). Gap and no gap trials of the various frequencies tested were presented at random with a total of ten trials at each frequency (0.5–8 kHz). For subjects with a hearing loss, the startle schedule was modified to the fullest extent possible to accommodate for the increased threshold.

2.4. Data Analysis

All the data was organized and analyzed through Microsoft Excel and GraphPad Prism software. The gap-PPI was calculated based on the formula: (EBAng-EBAg)/EBAng x 100% (EBAng is the amplitude of the eye-blink measured in the presence of continuous noise and EBAg is the amplitude in the presence of gap).

3. Results

3.1. Audiologic tests

All 16 test subjects received an audiologic assessment prior to the startle reflex testing. Patients with external or middle ear dysfunction were excluded, with the exception of one subject in the tinnitus group who had a long standing tympanic membrane perforation. Comparison of the hearing thresholds between the control and tinnitus groups revealed a significant difference between the thresholds of the two groups (Fig. 1).

A screening acoustic reflex at 1 kHz was performed on all subjects as part of the audiologic assessment. In comparison of the control group to the tinnitus group it was found that the acoustic reflex was often absent in subjects of the tinnitus group, while the reflex was present in the subjects of the control group.