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An electrophysiological approach to tinnitus interpretation

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Abstract

Introduction: Serotonin seems to play a central role in tinnitus. The intensity dependence of auditory evoked potential (IDAP) is considered an index of central serotonergic activity in the auditory cortex. The higher the steepness of the N1/P2 component amplitude-stimulus function slope (N1/P2 ASF slope as calculated by IDAP), the lower the central serotonergic activity. Similarly, the N1 amplitude-stimulus function slope (N1 ASF slope) was investigated. Auditory brainstem responses (ABR) examine the auditory system functionality from the periphery and through the brainstem, where serotonergic projections have been identified. **Objectives:** Assessing whether tinnitus perception neurotransmitters activity inbalance could be investigated by an electrophysiological approach. **Materials and Methods:** Ten normoacousic tinnitus patients and 14 healthy controls were included in the study. Subjects underwent EEG (IDAP) recording, ABR recording and psychometric questionnaires administration. **Results:** N1/P2 ASF slope and N1ASF slope tended to have a greater steepness in patients. N1ASF slope was significantly correlated with ABR wave V and interpeak III-V latencies in patients. ABR wave V and interpeak III-V latencies were significantly longer in patients than in controls. **Conclusion:** N1/P2 ASF slope, N1 ASF slope and ABR components appear to be useful electrophysiologic methods to study possible functional alterations related to the serotonergic activity.

Keywords: auditory, brain stem, electrophysiology, evoked potentials, indicators of quality of life, questionnaires, tinnitus.

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INTRODUCTION

Tinnitus is the most common auditory disorder. It is defined as tone or noise sensation in the absence of a physical sound source, that patients can refer in one or both the ears or into the head. It has been theorized that the cause of the disorder could be a sensorineural hearing loss (SNHL) leading to a plastic reorganization of the auditory cortex, characterized by an altered frequency representation[1,2]. Furthermore, a central role is suggested for limbic and paralimbic structures in a gating process, involved in switching on or off the tinnitus sensation[3]. One of the most limbic-relevant neurotransmitter is serotonin (5-HT) and its depletion has been correlated with symptoms, such as hypersensitivity to noise, reduced REM sleep and depression/anhedonia, co-occurring with tinnitus to varying degrees[4,5].

The intensity dependence of auditory evoked potentials (IDAPs) is a non-invasive electrophysiological assessment suggested to be a specific biological marker of central serotonergic activity by Hegerl & Juckel in 1993[6]. In particular, these authors identified in the slope (N1/P2 ASF slope) of the regression line between auditory stimulus intensities and amplitudes of the N1/P2 evoked responses an indirect index of the central serotonergic activity. This could be connected to the serotonergic preactivation level theoryin the auditory cortex[7-9]. The steeper is the N1/P2 ASF slope, the lower will be the central serotonergic activity[6].

N1/P2 component has been chosen to study tinnitus due to its origin, that is primary and secondary auditory cortex[10]. N1 component has been studied as index of primary auditory cortex activity, and linked to tinnitus because of the tinnitus related activity involves the primary auditory cortex[11].

Previous studies concerning tinnitus using IDAP investigations do not provide unequivocal results[10-12]. In particular, some studies identified a difference in the intensity dependence of IDAP response (both N1 latency and N1-P2 amplitude) between tinnitus patients and healthy controls at 2000 and 4000 Hz (approximately the edge frequency of hearing loss)[11], and with a 1000 Hz stimulation[10]. An analogue study, conducted in idiopathic tinnitus patients showed a significant statistical difference in the intensity dependence of N1-P2 amplitude at the Fz and Cz positions, suggesting that the sample presented reduced responses to increased sound intensity and weaker intensity dependence of the response[12].

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In the present study, in addition to IDAP that involves the cortical level, subjects underwent brainstem auditory evoked potentials (ABRs) exam, to investigate the functionality of the auditory system from the periphery and through the brainstem.

ABR data from previous studies in tinnitus patients reported an elongation of latencies of waves I, III, V, and, although within the normal range, a prolongation of the interpeak I-III, III-V and I-V relative to control subjects[13].

Furthermore, psychometric questionnaires were administered to all subjects. THI test was administered to tinnitus sufferers to investigate the impact of the tinnitus on the quality of life.

The aim of the present study was to investigate by an electrophysiological and, secondly, behavioral approach the possible underlying neurotransmitters mechanisms involved in tinnitus perception.

The choice of including only male patients in the study was due to the hormonal modulation of the auditory function[14], in order to isolate as much as possible the variables investigated. Furthermore, a very recent study suggested that the sex could influence depressive state more in females than in males tinnitus patients[15].

MATERIALS AND METHODS

Subjects

Thirty-eight male subjects were enrolled in the study (tinnitus patients n = 22 and control subjects n = 16). Inclusion criteria were: age interval ranging from 18 to 65 years; male sex; normal hearing (hearing threshold up to 20 dB HL) in the clinical audiometric test ranging from 0.125 to 8 kHz frequency; absence of hyperacusis as indexed by the dynamic range measure; tinnitus patients onset of symptoms from no longer than two years. Exclusion criteria were: psychiatric pathologies on the base of DSM-IV-R; neuropathy; substances of abuse and serotonergic drugs assumptions; other major pathologies. 14 subjects were excluded due to: migraine (n = 3), depression (n = 7), ABR abnormalities (n = 2) and partial refusal of one test or one questionnaire execution (n = 2). All subjects signed an informed consent.

A total of 10 patients were included in the study (mean age 43.9 ± 11.04), 5 presenting unilateral tinnitus, and 5 presenting bilateral tinnitus. The control group (n = 14, mean age: 45.143 ± 11.948), consisted of age-matched male subjects. Audiometric test and stapedius reflex test with the measure for the diagnosis of hyperacusis were performed in all subjects.

Electrophysiological assessment

*Auditory Evoked Potentials (*AEPs*):* the EEG recording was conducted in a quiet and electrically shielded room with the subject sitting in a comfortable

armchair. For the stimulation and the acquisition the Neuroscan Stim Audio System p/n 1105 by Compumedics (USA) was used. The active electrode was placed in Cz, two reference electrodes on the mastoids and the ground electrode on the forehead. The bipolar electro-oculogram (EOG) was recorded from above and below the left eye. AEPs were evoked by four runs of 250 stimuli each with a randomized inter stimulus interval ranging from 500 to 900 ms. Tones of 1000 Hz and 50 ms duration (rise-fall times: 10 ms) were delivered binaurally through earphones at four different intensities (60, 70, 80 and 90 dB HL) in a pseudo-randomized order. Sounds were presented and controlled by a PC running system. The subjects were not informed about the sequence of different tones and were instructed to ignore themselves. For each intensity level, at least 150 trials were collected. The analysis epoch was of 600 ms with a 100 ms pre-stimulus baseline. All recordings were averaged off-line. Ocular artifacts were rejected automatically, while muscular artifacts by visual inspection. AEPs were digitally bandpass filtered at 1-20 Hz. Amplitudes of the N1 (between 50 and 150 ms post-stimulus) and P2 (between 90 and 230 ms post-stimulus) peaks were measured. The N1/P2 ASF slope was calculated as the linear amplitude/stimulus intensity function slope for block averages (μV/dB). An analogue procedure was used in order to calculate the slope of the N1 amplitude values matched with the intensities of stimulation (N1 ASF slope).

ABR: the test was conducted in a quiet and electrically shielded room with the subject lying on a couch. For the stimulation and the acquisition the Epic Plus apparatus by Labat (Mestre, Italy) was used. The active electrode was attached to the patient's scalp, placed in Cz, and one electrode was attached to each mastoid (reference and ground electrode, depending on the stimulated side). Series of 90 and 80 dB HL stimuli (click +/-) were delivered through ear phones placed over the patient's ears to each ear separately. At least 1500 free of artifacts electrical responses were averaged for each stimulation, and every stimulation was repeated at least three times to obtain replicable waves. Band pass filter 150-1500 Hz was used in an on-line filtering. Stimulus duration was 100 μs. The rate was 11 stimuli/s. Epoch duration 10 ms. Variables investigated for the ABR test were: peak I, III, V latency and interpeak I-III, III-V and I-V latency.

Behavioral assessment

The Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI) were administered to all the subjects. Tinnitus Handicap Inventory (THI) by Newmann was administered only to patients suffering from tinnitus.

Statistical analysis

Mann-Whitney U test was used in the comparisons among groups; Pearson's index of correlation was used both for questionnaires scores and electrophysiological data.

Concerning ABR, data from the affected ear or, in the case of bilateral tinnitus, the mean of the evoked responses from the two ears were included in the analysis. The decision to not perform the analysis dividing the tinnitus group in unilateral and bilateral patients was due to the fact that when comparing the ABR parameters among groups, no significant difference was observed. Only the interpeak III-V 80 dB elicited showed a tendency of a significant difference, in particular the bilateral tinnitus group reported a longer mean latency of that variable compared to the unilateral group ($P = 0.054$).

RESULTS

Concerning questionnaires, the analysis didn't reveal any statistical difference between the tinnitus and the control group (PSQI $P = 0.39$; STAI1 $P = 0.93$; STAI2 $P = 0.86$; BDI $P = 0.57$). The tinnitus group, on the basis of the THI score, consisted of: no subject with catastrophic grade, 1 subject with severe tinnitus grade, 2 subjects with moderate tinnitus grade, 1 subject with mild tinnitus grade and 6 subjects with slight tinnitus grade.

Concerning the N1/P2 ASF slope and the N1 ASF slope values, there wasn't a statistical significance in the difference between the two experimental groups, although a steeper slope was evident for the tinnitus group for both the variables (N1/P2 ASF slope: tinnitus group 0.826 ± 1.48 and control group 0.037 ± 2.152; N1 ASF slope: tinnitus group -0.356 ± 1.115 and control group 0.016 ± 0.794) Figure.1. The tinnitus group only, showed a significant correlation between N1 ASF slope and interpeak III-V latency evoked by both 80 and 90 dB intensity stimulation (Pearson's correlation: $r = -0.632$, $P = 0.05$ and $r = -0.693$ $P = 0.026$ respectively); while the control group only, showed a significant correlation between N1/P2 ASF slope values and questionnaires scores (Pearson's correlation: STAI-1 $r = -0.664$ $P = 0.01$; STAI-2 $r = -0.621$ $P = 0.018$; BDI $r = -0.63$ $P = 0.016$) and between N1 ASF slope values and questionnaire scores (Pearson's correlation: BDI $r = 0.543$ $P = 0.045$).

Concerning ABR components, there was a statistical significant difference in the peak V latency and in the interpeak III-V latency with an intensity of stimulation of 80 dB between the tinnitus and the control group (Mann-Whitney U test $P = 0.035$ and $P = 0.04$ respectively). The tinnitus group in fact reported longer latencies in these components compared to the control group (peak V latency: tinnitus group 5.932 ± 0.191, control group 5.746 ± 0.213; interpeak III-V latency: tinnitus group 1.979 ± 0.109, control group 1.837 ±

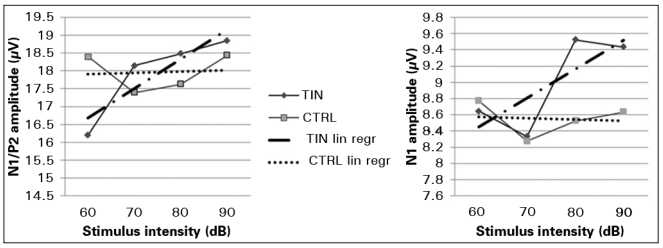

Figure 1. N1/P2 ASF slope and N1 ASF slope. On the left: N1/P2 amplitude values and stimulus intensity in the tinnitus and the control group; the linear regression of these values shows the amplitude-stimulus function whose slope is the N1/P2 ASF slope. On the right: N1 amplitude values and stimulus intensity in the tinnitus and the control group; the linear regression of these values shows the amplitude-stimulus function whose slope is the N1 ASF slope.

0.198) . Furthermore, only the tinnitus group showed a correlation between ABR parameters and questionnaires (PSQI - 90 dB I r = -0.784 *P* = 0.007; PSQI - 90 dB I-III r = 0.667 *P* = 0.035; STAI-2 - 90 dB I-III r = 0.665 *P* = 0.036; STAI-2 - 90 dB I-V r = 0.693 *P* = 0.026).

DISCUSSION

IDAP

Concerning IDAP, previous articles didn't provide univocal results. Some studies identified a difference in the EEG responses (both N1 latency and N1/P2 amplitude) between tinnitus patients and healthy controls at 2000 and 4000 Hz[11], and with a 1000 Hz stimulation[10]. Another study, showed a significant statistical difference in the intensity dependence of N1/P2 amplitude, suggesting reduced responses to increased sound intensity and weaker intensity dependence of the response in the sample[12].

In the present study, even without reaching the statistical significance, both the N1/P2 ASF slope and the N1 ASF slope appeared steeper in the tinnitus group compared to the control group. Kadner et al.[11] hypothesized that the persistent activation of the auditory cortex by tinnitus could compete with the processing of auditory stimuli for neural substrate. A compensatory mechanism therefore could be established in order to face this phenomenon, with the possible consequence of an increased intensity dependence and a steeper function in the responsiveness.

ABR

The latencies enlargement in the peak V and in the interpeak III-V latencies reported by the tinnitus group falls within the normal range, ensuring that the data obtained are not depending on peripheral or central causes. These findings agree with previous studies[13], and could be related to abnormal activity previously observed in tinnitus patients at the level of the inferior colliculus e.g.[16]. Very recent studies suggest that an auditory deficit acoustic trauma-induced is capable of producing modest but significant decreases in the density of serotonergic fibers innervating the inferior colliculus[17]. Rauscheker et al.[3] hypothesized a noise cancellation mechanism able to block the conscious perception of tinnitus. In particular they theorized the presence of a gating process on repetitive unwanted noises exerted by limbic and paralimbic structures, in particular the Nucleus Accumbens with its projections from the Raphe Nuclei, through projections to the thalamus. In case subcallosal areas activity is compromised, cancellation of the auditory signal at the thalamic level is no longer possible, tinnitus perception results and long-term reorganization of auditory cortex sets in to render the tinnitus chronic. Furthermore, electrophysiological evidence, using polysomnography, suggest an alteration in the serotonergic activity at the Raphe Nuclei level in tinnitus patients, as revealed by variations in the sleep architecture[18]. Auditory deficit in tinnitus patients, even if not always identified due to the limited number of frequencies evaluated in the clinical audiometry, are very often present, so we can't exclude the presence of an ultra high frequencies auditory deficit in our sample.

In this scenario, the increase in the peak V and in the interpeak III-V latencies showed by our tinnitus patients is consistent with the noise-cancellation mechanism and suggests that not only serotonergic projections from Raphe Nuclei could be able to modulate tinnitus perception, but also serotonergic projections in the inferior colliculus, both meeting at the thalamic level. ABR latencies seem to be influenced by serotonin in an excitatory manner mainly. Published data provide evidence in which reserpine-induced serotonin depletion prolonged ABR latency in migraine patients[19], and latency tended to negatively correlate with plasma serotonin in healthy subjects[20]. In addition, the inferior colliculus, the principal generator of wave V, receives serotonergic input from the dorsal Raphe nucleus[21], that as seen above represents one of the principal actor of the noise-cancellation mechanism theory by Rauschecker [3]. In the inferior colliculus serotonin often coexists with GABA, both acting in the suppression of fearful and aversive behavior[22]. This joint action, once altered, could be the cause of intolerance and annoying responses displayed by patients toward tinnitus.

Furthermore, descending serotonergic projections from Raphe nucleus may also modulate superior olive neurons[23] and the cochlear nucleus[24], the generators of ABR wave III and II respectively[25].

It is interesting to note that the ABR portion affected by the latency elongation in our sample was correlated with the N1 ASF slope. According to Kadner et al.[11] this led to confirm the reliability of the N1 ASF slope as a useful and detailed index of tinnitus evaluation by IDAP.

Taken together this evidence suggests a focus on N1 ASF slope and ABR parameters in order to investigate abnormalities in the auditory pathway of tinnitus patients.

All evidence reported in the present study prompt the serotonin dysfunction hypothesis relative to tinnitus perception[26]. In this context, pharmacological and imaging data indicate the role of 5-HT receptor subtypes as extremely worthy. Results reported in the present article suggest the presence of some alterations in the primary auditory cortex and in the inferior colliculus in tinnitus patients. At the primary auditory cortex level high 5-HT_2 and 5-HT_{1A} receptors binding has been demonstrated[27], whilst at the inferior colliculus level, 5-HT_{1A} and 5-HT_{1B} receptors have been identified[28,29]. In particular, in the inferior colliculus, 5-HT_{1A} is located at the somatodendritic level exerting a suppressive effect, whilst 5-HT_{1B} is present at the presynaptic level exerting a facilitatory effect (through a decrease in GABA-A mediated inhibition) on evoked responses of neurons. Unfortunately, the mechanism of the interaction between 5-HT_{1A} and 5-HT_{1B} receptors in the inferior colliculus is still unknown. PET studies showed that 5-HT_{1A} receptors are also particularly concentrated in the limbic system[30], a region considered fundamental for tinnitus suppression[3]. The sum of these evidences led to confirm the hypothesis of an alteration in the serotonin pattern, where a particular role could be displayed by 5-HT_{1A} receptor, ubiquitous of the regions involved in tinnitus perception. It is interesting to note that among pharmacological treatments of tinnitus the efficacy of Gabapentin is still controversial[31,32]. In addition, application of 5-HT_{1A} and 5-HT_{1B} receptor agonists influenced spike rate and frequency bandwidth additively, each of them moderating the effect of the other[33]. Furthermore, the 5-HT_{1A} agonist influence dominated latencies and interspike intervals during co-application. An alteration in 5-HT_{1A} receptor activity could be one of the mechanisms responsible for both: 1) the increased activity found in the inferior colliculus of tinnitus patients[34] presumably by an imbalance between 5-HT_{1A} and 5-HT_{1B} receptors activity, and ABR wave V and interpeak III-V latencies enlargement found in our tinnitus sample; 2) the higher intensity dependence of auditory evoked potentials in tinnitus patients, and the failing of cortical tinnitus suppression.

In normoacousic patients suffering from tinnitus, the electrophysiological approach by N1/P2 ASF slope, N1 ASF slope and ABR components investigation, appears to be useful in the investigation of functional alterations at the mesencephalic and cortical levels, possibly related to the serotonergic activity in the same regions.

The clear trend of an increased steepness displayed by N1/P2 ASF slope and N1 ASF slope in tinnitus patients in comparison to control patients, suggests an altered serotonin activity in the primary auditory cortex in these patients, and encourages us to conduct further studies in order to confirm the data in a wider sample. In addition, the investigation of the phenomena in females is fundamental, in order to evaluate sex influences on serotonin activity.

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