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The Significance Of (CA)n Tandem Repeat in GABA(A) Beta-3 Subunit Gene in Tinnitus Manifestation

Význam (CA)n repetitivní sekvence genu pro beta-3 podjednotku GABA(A) receptoru při manifestaci tinnitu

Abstract

Study aim: Study objective was to explore associations between manifestation of tinnitus, auditory evoked potentials and genetic background of gamma-aminobutyric acid type A (GABA(A) receptors) to support the disinhibited feedback hypothesis of tinnitus generation. *Materials and methods:* A population of 131 patients was assessed for severity of hearing loss, quantification of tinnitus, mid-latency responses (MLR) and brainstem auditory evoked potentials (BAEP), and (CA)n tandem repeat polymorphism in GABA(A) Beta-3 subunit gene to establish any correlation with manifestation of tinnitus. *Results:* It was observed that tinnitus score correlates with V/III amplitude ratio in BAEP ($R = 0.22$, $p < 0.001$) and with mean pure tone audiometry (PTA) threshold ($R = 0.22$, $p = 0.017$). Analysis of the MLR results showed a significant correlation between the PA wave amplitude and the tinnitus score ($R = 0.31–0.37$; $p < 0.001$). MLR result analysis showed no statistically significant correlation between the wave amplitudes and the mean auditory threshold. An analysis of a subgroup with shorter clinical history (less than nine months) revealed a statistically significant difference in the tinnitus score in relation to the genotype of (CA)n tandem repeat of the GABRß3 receptor subunit gene ($p = 0.002$). This result was also consistent with the distribution of the PA wave amplitude in the given subpopulation. *Conclusion:* Our findings indicate existence of two main regulatory mechanisms of tinnitus generation: first, the brainstem mechanism is dependent on the severity of the hearing loss; second, the cortical mechanism is likely to be dependent on the genotype of (CA)n tandem repeat in GABA(A) beta-3 subunit gene.

Souhrn

Cíl studie: Cílem studie bylo zjištění vztahů mezi manifestací tinnitu, nálezem na sluchových evokovaných potenciálech a genetickým pozadím u receptoru pro gamaaminomáselnou kyselinu typu A (GABA(A) receptor), podporující desinhibiční hypotézu vzniku tinnitu. *Soubor a metodika:* Bylo vyšetřeno 131 pacientů z hlediska sluchové ztráty, provedena kvantifikace tinnitu, sluchové evokované potenciály střední latence (MLR) a kmenové sluchové evokované potenciály (BAEP) a dále stanovení genotypu (CA)n repetitivní sekvence pro beta-3 podjednotku GABA(A) receptoru. Následně byly hledány vztahy mezi jednotlivými výsledky a manifestací tinnitu. *Výsledky:* Byla nalezena korelace tinnitus skóre s amplitudovým poměrem vln V/III v BAEP ($R = 0,22$, $p < 0,001$) a s průměrným sluchovým prahem ($R = 0,22$, $p = 0,17$). Rovněž byla nalezena korelace tinnitus skóre s amplitudou vlny PA v MLR ($R = 0,31–0,37$; $p < 0,001$). Výsledky MLR neukázaly žádný vztah k průměrnému sluchovému prahu. U skupiny s kratší anamnézou tinnitu (méně než devět měsíců) byl prokázán rozdíl v manifestaci tinnitu na genotypu pro (CA)n repetitivní sekvenci genu pro beta-3 podjednotku GABA(A) receptoru ($p = 0,002$). Tento výsledek byl rovněž konzistentní s rozložením amplitudy vlny PA v dané subpopulaci. *Závěr:* Tyto výsledky svědčí o existenci dvou hlavních regulačních mechanizmů vzniku tinnitu: první, který je závislý na velikosti sluchové ztráty, je na úrovni mozkového kmene, zatímco druhý je na úrovni korové s možnou souvislostí s genotypem (CA)n repetitivní sekvence pro beta-3 podjednotku GABA(A) receptoru.

The study was supported by the Grant NS/10101–4, Ministry of Health, Czech Republic.

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.
Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.
Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Accepted for review: 9. 7. 2013
Accepted for print: 15. 10. 2013

Key words

tinnitus – GABA-A receptor – auditory evoked potentials

Klíčová slova

tinnitus – GABA-A receptor – sluchové evokované potenciály

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Introduction

Tinnitus is a symptom that commonly accompanies sensorineural hearing loss (SNHL). The relationship between chronic tinnitus and serious psychological conditions with subsequent substantial reduction of the quality of life is reported in only 0.5–1% of these cases [1].

The disinhibited feedback hypothesis of tinnitus generation is based on the presumption that the spontaneous neuronal activity of the central auditory pathways occurs as a negative-feedback response to deafferentation. In general, it does not matter which factor causes deafferentation. Deafferentation leads to hypo-reactivity of the descendent inhibitory connections and, at the same time, hyper-reactivity of the excitatory descendent neuronal connections, which may increase the influx of Ca^{2+} ions to the pre-synaptic neuronal terminal region and, therefore, the activation of synaptic vesicles of glutamate synapses and the spontaneous neuronal activity [2]. The disinhibition may also lead to specific changes in brainstem auditory evoked responses (BAEP) and mid-latency responses (MLR).

Currently, there are two basic models of tinnitus pathophysiology. The psychological model [3] is based on the effect of tinnitus-induced emotional stress that can, via autonomous neuronal system, induce and facilitate the perception of tinnitus. The neurophysiological model [4,5] focuses on the increased gain of the auditory pathways occurring as a reaction to the lack of stimulation due to deafferentation.

Although mechanisms of tinnitus generation have not been fully elucidated, possible effect of γ-aminobutyric acid (GABA) neurotransmission on these mechanisms is widely discussed in the literature and it is generally accepted that GABA is likely to be involved in these processes [6,7].

Involvement of GABA signaling in tinnitus generation also implies that differences in genetic background of the protein structures involved in GABA signaling could play a role in the severity of tinnitus symptomatology.

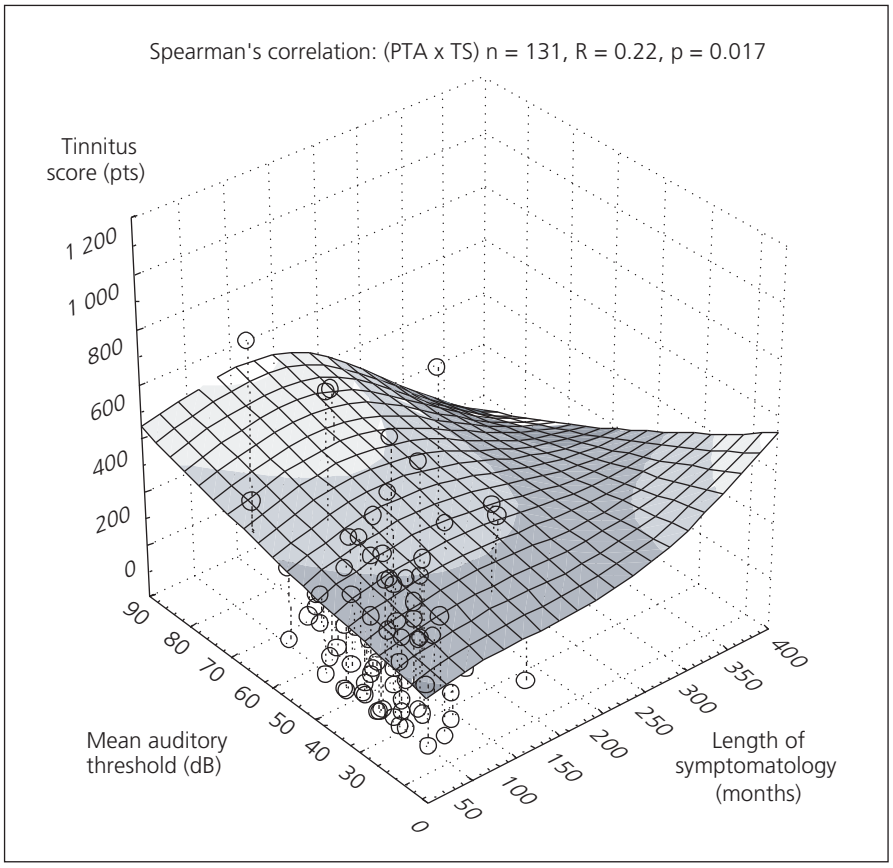

Fig. 1. Correlation between tinnitus score and mean auditory threshold in relation to length of sensorineural hearing loss history.

We hypothesized that GABA receptors for neuromediators involved in the descending part of the auditory pathways could play a significant role in tinnitus pathogenesis. Identification of (i) the role of their genetic variability together with (ii) electrophysiological changes accompanying tinnitus could contribute to our understanding of the origin and structures involved in tinnitus. Therefore, the objective of the study was to map possible associations between auditory evoked potentials (AEP) characteristics, genetic variability in GABA(A) receptor gene, and manifestation of tinnitus.

We selected the polymorphic site of the GABRß3 subunit gene located on chromosome 15q11–13 as a candidate genetic polymorphism site. This site plays an important role in clinical manifestation of alcoholism [8] and post-traumatic stress disorder [9].

Materials and methods

Study population

131 patients (61 males, 70 females, mean age ± SD was 52 ± 13.8 years) with unilateral idiopathic SHNL (ISNHL) were selected for the study. Patients were included in the study if they had unilateral hearing loss and the mean calculated decrease of at least 25 dB from the auditory thresholds observed during pure-tone threshold audiometry (PTA) at 250, 500, 1 k, 2 k, 3 k, 4 k, 6 k and 8 kHz. Patients with pulsatile tinnitus possibly caused by vascular anomaly, retrocochlear hearing loss and those who had not signed the informed consent form, were excluded from the study.

Tinnitus assessment

Severity of tinnitus symptoms was assessed with a simplified psychometric tinnitus questionnaire that provided a quantitative tinnitus score (TS) as a measure of patients' tinnitus sensation. To calculate the TS, a correction parameter based on three qualities obtained from the questionnaire (knowledge of relief conditions/mechanisms (–10%), increase of tinnitus after noise exposure (+10 pts), tinnitus is stable and not changing in time (+10 pts) was added to/deduced from self-assessment of tinnitus intensity on a visual analog scale (from 0 = no tinnitus to 10 = most intensive tinnitus) and the result was than multiplied by the pro-

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portion of time the tinnitus was sensed by patients over the two weeks prior to assessment (0–100%). Therefore, TS values in patients with tinnitus range from 9 to 1.020 points. Patients with ISNHL not experiencing tinnitus were assigned a score of 0 points.

Genotyping

Genomic DNA was extracted from peripheral leukocytes. The DNA of the selected gene locus gene was amplified by polymerase chain reaction (PCR), separated in 2% agarose gel and the length of tandem CA-repeat was determined by fragmentation analysis on the capillary sequencer ABI 3600 (Applied Biosystems, USA). According to the length of the CA repetition, 12 alleles were detected: A1 (181 bp), A2 (183 bp), A3 (185 bp), A4 (187 bp), A5 (189 bp), A6 (191 bp), A7 (193 bp), A8 (195 bp), A9 (197 bp), A10 (199 bp) and A11 (201 bp). According to the Feusner's findings, alleles were divided into 2 groups – the major allele of 181 bp comprised the A1 group whereas the other minor alleles comprised the An group. Genotypes then fell into three groups – A1A1, A1An and AnAn. The following primers were used for PCR amplification – forward: 5'-CTCTTGTTCCTGTTGCTTTCAATACAC-3' and reverse: 5'-FAM-CACTGTGCTAGTAGATTCAGCTC-3'.

AEP measurement

The additional measurement of BAEP and MLR using stimulation by a broadband alternate click at the intensity levels of 80, 90, 100 and 110 dB SPL was performed under standard conditions. The sweep frequencies were 22/s for BAEP and 11/s for MLR. AEPs were recorded from both sides. For the analysis, measurement obtained for the tinnitus-affected side was used. Examination was done using the AMPLAID MK 12 machine (Amplifon, Milano, Italy). Latencies and amplitudes of the wave I, III, V in BAEP were recorded as well as latencies and amplitudes of P(A), P(B) and P(C) elements in MLR. Amplitudes were measured peak-to-peak between maximum and subsequent minimum of the response waveform. Inability to record the MLR response due to interference with myogenic potentials was not a reason to exclude a patient from the study.

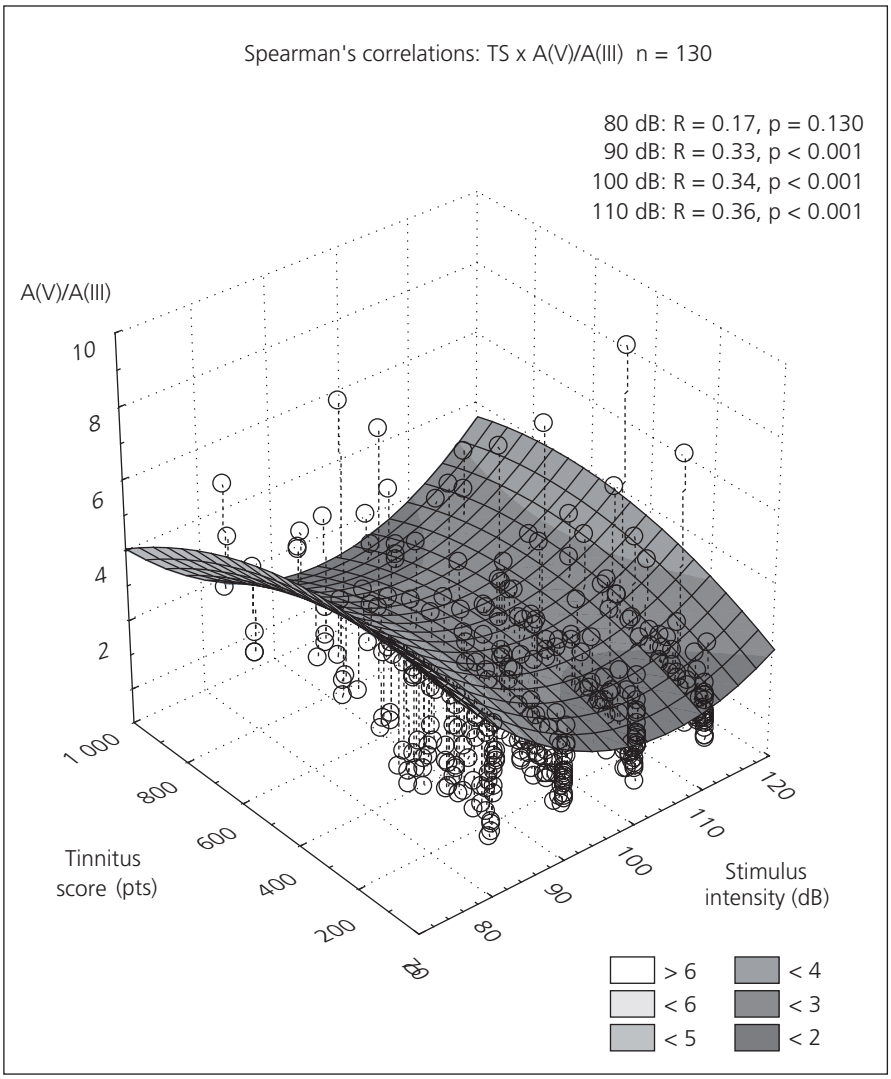

Fig. 2. Correlation between TS and V/III wave amplitude ratio.

Data analysis

Statistical analysis was performed using the STATISTICA software package (StatSoft, Inc. (2005), version 7. www.statsoft.com). Due to prevailing non-normal distribution of the data non-parametric tests were preferred for all subsequent analyses. Spearman correlation coefficients between the tinnitus score and mean auditory thresholds and electrophysiologic parameters were calculated. Kruskal-Wallis ANOVA was used to test the differences between tinnitus score and electrophysiological parameters in genotype groups. Multidimensional principal component analysis (PCA) was used for explorative data analysis. Value of $p < 0.05$ was considered statistically significant.

The study was approved by the Ethics Committee of the St. Anne's University Hospital, Brno. All patients included in the study were fully informed and consented to their participation in the study. The authors do not have any concealed financial interests with the organization that sponsored the study or any conflict of interests associated with this study.

Results

An association between characteristics of tinnitus and the level of hearing impairment

Severity of tinnitus showed statistically significant correlation with the degree of hearing loss (n = 131; R = 0.22; p = 0.017) (Fig. 1). This association was obvious particularly in patients with a shorter history. This connection was not so pronounced in patients with long-lasting hearing impairment; in contrary there was a ten-

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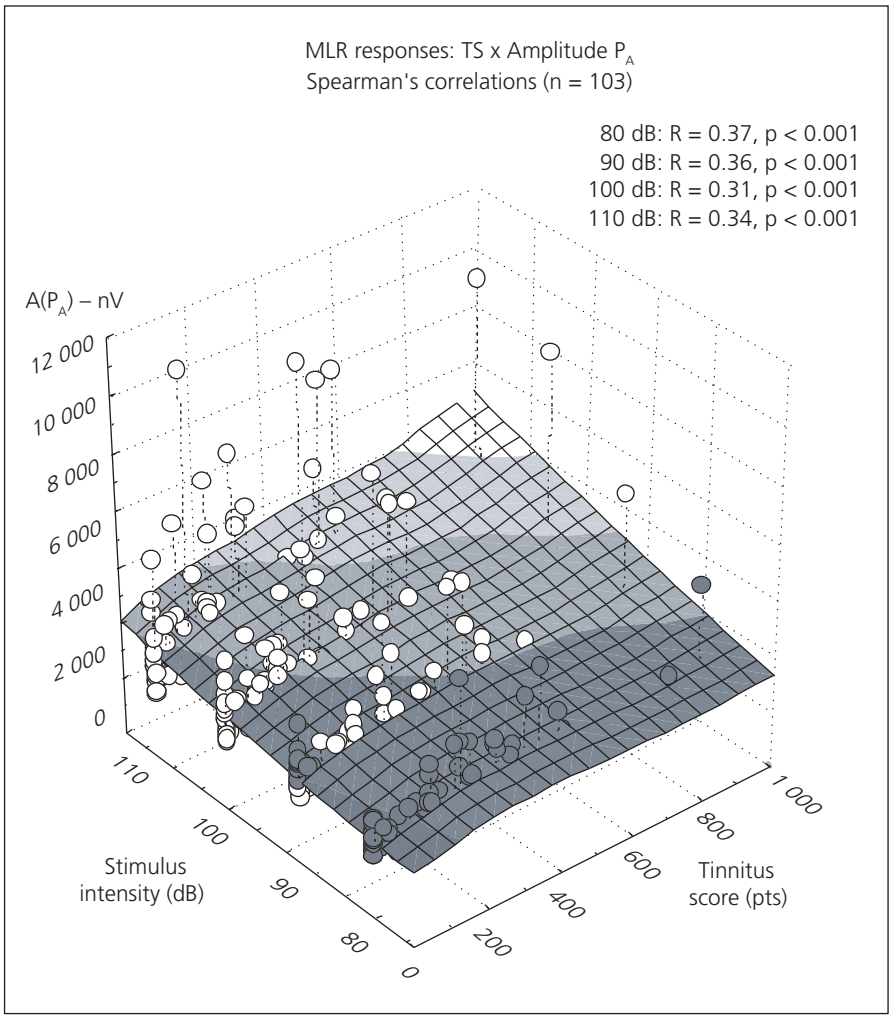

Fig. 3. Correlation between TS and amplitude of PA in MLR response.

dency towards higher scores of tinnitus manifestation in patients with lower degree of hearing impairment. This relationship was not proved as statistically significant in patients with chronic stage of hearing loss, possibly due to a small number of such subjects within the study group.

Electrophysiological tests

Statistically significant correlation between the tinnitus score and the ratio of V/III wave amplitudes was found in the BAEP record of the following intensities: 90–110 dB (n = 130; R = 0.33 (90 dB), 0.34 (100 dB), 0.36 (110 dB); p < 0.001) (Fig. 2). The same correlation was not observed at the intensity level of 80 dB. No statistically significant correlations were observed between latencies and absolute amplitudes in the response waveform of the BAEP and clinical scores of tinnitus.

Analysis of the MLR results showed a significant correlation between the PA wave amplitude and the tinnitus score (n = 106; R = 0.31–0.37; p < 0.001) (Fig. 3). Further analysis showed a statistically significant correlation between the mean auditory threshold and the ratio of the V/III wave amplitudes (with the exception of 80 dB stimulation level again) (n = 130; R = 0.21–0.27; p < 0.021). MLR results analysis showed no statistically significant correlation between the wave amplitudes and the mean auditory threshold.

Genetic analysis

Genotyping showed no significant difference in sex and age in either of the three genotype groups. The most frequent allele was A1 (181 bp) with a frequency of 0.41. This is in accordance with the results described in literature (Noble et al. [8], Feusner et al. [9]). No statistically significant differences in tinnitus manifestation or the electrophysiological data were found in the entire study population with respect to genotype groups. The study population was then divided into two subgroups – a subgroup with short clinical history and a subgroup of patients with chronic tinnitus.

Analysis of the subgroup with shorter clinical history (less than nine months) revealed a statistically significant difference in the tinnitus score and the PA amplitude in relation to the genotype of (CA)n tandem repeat of the GABRß3 sub-unit gene. Significantly higher tinnitus score (n = 41, p = 0.002) was detected in subjects with AnAn genotype. This result was also consistent with the distribution of the PA wave amplitude in the given subpopulation that was significantly lower in individuals with the A1 allele (n = 41; p < 0.02) (Fig. 4). Therefore, the genotype determining characteristics of the GABA(A) receptor influences tinnitus manifestation predominantly at the early stage of hearing impairment and at the level of the primary auditory cortex.

Discussion

According to the different associations between the BAEP, MLR and tinnitus manifestation there are at least two main levels of tinnitus generation and control in the auditory pathway: a subcortical level that depends on the severity of hearing loss, and a cortical level, not directly related to hearing impairment. This presumption supports the previously published Jastreboff's suggestion there are two regulatory loops of tinnitus generation [5]. According to the latest data published in literature, it is the dorsal cochlear nucleus where the genesis of the tinnitus-related neuronal activity is assumed to occur [10–12]. An increase of the PA wave amplitude was widely studied in animal models of cochlear damage [13,14]; Gerken et al. recently observed increased PA wave amplitude in association to chronic tinnitus [15].

There also was a weaker association with hearing loss in patients with extended periods of symptom persistence; in the studied group, tinnitus tended to disappear in patients with high values of hearing threshold, whereas it tended to persist in patients whose hearing loss was lower (this tendency could not be proven

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statistically but we see this effect quite often in clinical practice – especially in patients with one-sided practical or total deafness). This effect, if it were proved, could have its logic explanation as well: the evidence on animal models shows that the missing afferentation from the periphery causes, after some time, reorganization of neuronal connections in order to optimize utilization of neuronal structures for the remaining capacities of the auditory organ [16]. This can cause substantial mitigation of spontaneous neuronal activity related to tinnitus, as well as weakening of symptom manifestation. This interpretation is also backed up by Ochi et al. [17] who found different potential to mask tinnitus in patients with acute and chronic tone tinnitus.

Our study showed clearly that patients with at least one copy of major A1 allele containing the least number of CA repeats (181 bp) experienced less intensive tinnitus symptoms that were also associated with lower amplitudes of MLR responses in primary auditory cortex. The effect of the CA repeat on tinnitus manifestation might be due to the different degree of the GABRß3 sub-unit transcription when in longer An alleles the speed of transcription might be altered by lower affinity of regulatory nuclear proteins. This is supported by another study of Gebhardt et al. [18] who showed that transcriptional activity diminishes proportionally to the length of CA repeat polymorphism in the EGFR intron. Smaller transcriptional activity of GABRß3 sub-unit, in that case, would result in lower concentration of the GABA(A) receptors on the post-synaptic membranes. Therefore, their function (hyper-polarization and inhibition of neuronal transmission) is weaker. Our analysis showed that the GABA(A) receptor can play an important role in the process of disinhibition. This result is in agreement with SPECT studies reported by Shulman et al. [6,7].

It is still unclear how the size of repetitive sequence influences molecular mechanisms of transcription, translation, and synthesis of a receptor from other sub-units. Literature referring to significance of the different allelic varieties is sometimes contradictory. Feusner et al. [9], for instance, showed higher risk of clinically more severe consequences of post-traumatic stress disorders in heterozygotes

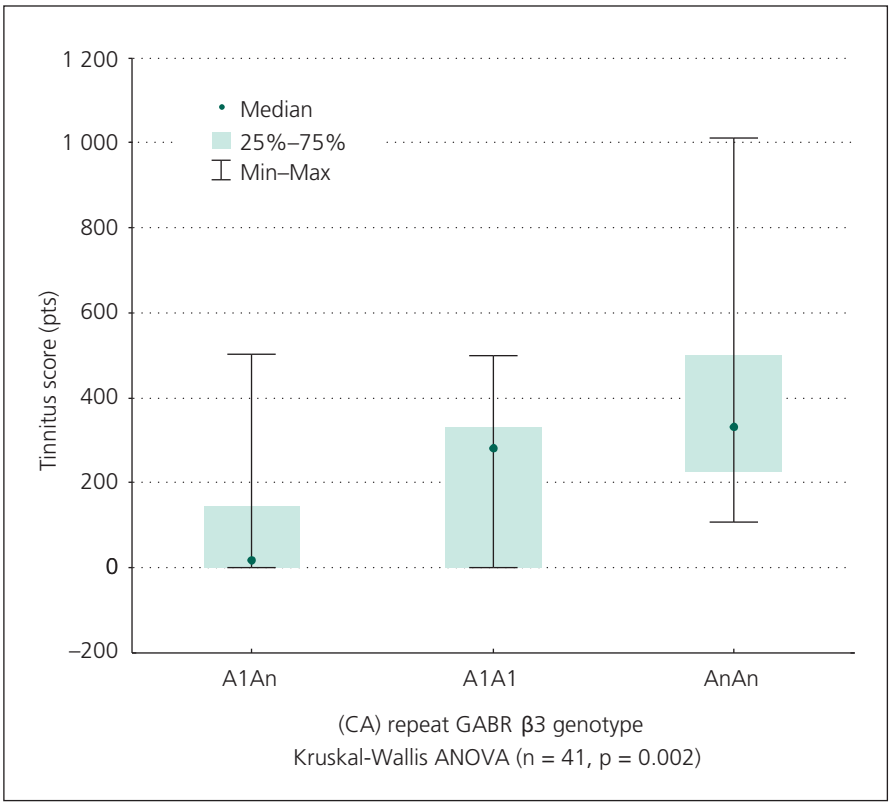

Fig. 4. Distribution of TS in relation to GABRß3 genotype (subpopulation with history < nine months).

than in homozygotes, a result that is inconsistent with our results. Also contrary to our assumptions we found that signs of disinhibition over the primary auditory cortex related to GABRß3 sub-unit genotype were present in the population with relatively short history of hearing loss only, whereas in patients with chronic tinnitus, the association between symptoms of tinnitus and the length of the highly polymorphic site in the GABRß3 subunit gene was not observed. We can only speculate on how to explain this observation. Some recent studies of GABA(A) activity regulation show the long-term impact of GABA synaptic activity on neuronal metabolism and plasticity (as reviewed in Luscher et al. [19]) and, on the other hand, the important role slow changes in metabolic neuronal activity play in GABA signaling. Tinnitus-related spontaneous neuronal activity could influence GABA activity in the brain cortex, and thus trigger long-term metabolic changes in the primary auditory cortex with subsequent changes in neuronal plasticity in which the polymorphism studied in the present study is unlikely to play an important role. A recent study by Huang et al. [20] showed dual action of the brain-derived neurotrophic factor (BDNF) on GABA neurotransmission, whereas genetic background of BDNF was also observed to influence the clinical picture of chronic tinnitus (Sand et al. [13]). Zhen-Zhen et al. [21] studied changes of metabotropic GABA(B) activity followed by noise-induced hearing loss; this finding also supports our concept of tinnitus generation.

GABA neurotransmission had also been studied in an animal model by Brozoski et al. [10] who supported the theory of overcompensation homeostatic mechanism followed by auditory deafferentation located in the brain stem and primary auditory cortex. This study shows a bidirectional and region-specific alterations of GABA and glutamate activity in rats unilaterally exposed to tinnitus. GABA activity was significantly decreased in contralateral medial geniculate body. Possible implications of altered GABA activity in auditory pathways observed in tinnitus for pharmacological interventions were summarized by Richardson et al. [22].

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Conceptually, a substantial part of publications aims to determine a structure in the auditory pathways responsible for tinnitus generation. However, other complex models of tinnitus generation have been proposed based on a different philosophy. De Ridder et al. [23] suggested a model in which the increased activity of sensory/auditory cortex due to neuroplastic changes caused by deafferentation is followed by a complex response of perceptual network, including subgenual and dorsal anterior cingulate cortex and posterior cingulate cortex, precuneus, parietal cortex, and frontal cortex. This triggers a constant learning process in which tinnitus is associated with distress and then recorded in memory areas. Tinnitus then becomes persistent as a result of activity of memory areas in the hippocampus, parahippocampal area and amygdala that makes it independent of peripheral hearing function.

Conclusion

Our findings indicate two main regulatory mechanisms of tinnitus generation: first, the brainstem mechanism, that depends on severity of hearing loss, and second, the cortical mechanism, that is likely to be dependent on the genotype of (CA)n tandem repeat in GABA(A) beta-3 subunit gene. However, regulation of GABA signaling as well as the role of genetic background of GABA-A receptor in patients with chronic tinnitus remains unclear.

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