PHYSIOLOGY

Peculiarities of Brain Information Processing in Persons with Different Serotonin Transporter Gene Variants

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Association of brain processes presumably underlying aggression with serotonin transporter gene polymorphism in men was studied. Carriers of more active gene variant are characterized by higher aggression index, increased component of brain potential mismatch negativity responsible for automatic difference detection, and decreased P300 component characterizing involuntary attention and cognitive control.

Key Words: *aggression; perception; evoked potentials; serotonin transporter genotype*

Brain processes presumably underlying aggression were investigated including the following components of averaged brain activity evoked by extrinsic stimulus (evoked potential, EP): mismatch negativity (MMN) and a positive component with a latency about 300 msec (P300). It was found that criminals convicted for delinquency associated with violations appeared to exhibit decreased amplitude of P300 in comparison with criminals, whose crime was not associated with act of violence (*e.g.*, fraud) [3]. Information processing in aggressive criminals was assumed to break off earlier, and these people are going to actions before completing analysis of situation. MMN component was also higher in high impulsive individuals [4]. These and other results drove to an assumption about dual nature of aggression, which can be explained by higher sensitivity to perceptual data and by lower cognitive control. An association of aggression with serotonin system function was also reported [6].

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The objective of this study was to elucidate peculiarities of information processing in the brain of carriers of different serotonin transporter (5-HTT) gene variants and to trace their connection with aggression.

MATERIALS AND METHODS

EEG was recorded using 256-chennel Electrical Geodesics encephalograph (500 Hz sampling rate, reference electrode Cz), filtered within the range 1-30 Hz, and recalculated taking into account averaged reference. We used "optimal paradigm" for obtaining MNN component modified by us [8] and allowing one to obtain MMN responses to changes in stimulus duration, frequency, and intensity and to varying differences between the deviant and standard stimuli. In our modification, the examinee was asked to memorize words presented on the monitor (approximately 1word per 2 seconds). Auditory signals were presented every 500 msec through headphones. Harmonic tones were used as the stimuli. Parameter of the standard stimulus were: main frequency 1000 Hz, intensity 60 dB over subjective threshold, duration 75 msec. Deviant

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stimuli varied by the main frequency (1050, 1200 Hz), intensity (50, 45 dB) and duration (50 and 25 msec). A total of 240 standard stimuli and 40 deviant stimuli of each type were presented. Standard and deviant stimuli alternated: each standard stimulus was followed by the deviant one, two deviant stimuli of one type could not follow each other. For statistical analysis, the mean MNN and P300 amplitudes were calculated for intervals 120-160 msec and 280-320 msec, respectively.

Forty male individuals aging 18-32 years participated in the experiment. Blood samples for 5-HTT genotype were preliminary obtained. Venous blood samples were used for genetic analysis. Changes in 5-HTT gene promoter region were determined using PCR by the differences in the lengths of PCR products for each allele. Protocol details, primers, and program of PCR-amplification were described earlier [1] together with genotyping technique [1]. 5-HTT eliminates serotonin form synaptic cleft and determines the magnitude and duration of the signal on the postsynaptic membrane. Activity of this protein depends on 5-HTT promoter polymorphism, which can be presented by two forms: L-allele consisted of 16 elements and S-allele consisted from 14 repeated elements (each element includes 20-23 b.p.). Polymorphism determines differences in mRNA concentration and protein density on the membrane. S-allele corresponds to lower transcription and, consequently, lower density of the protein in the membrane compared to L-carriers. It results in reduced serotonin reuptake and, hence, determines higher possibility of relevant receptor activation.

The examinees also filled in Buss–Durkee Hostility Inventory (adapted by Osnitskii) [2]. The study was approved by local ethic committee.

RESULTS

The total aggression index was significantly higher in LL-genotype carriers in comparison with SS (65±3 and 55±5, respectively, $p<0.05$), what agrees with the data on association between aggression and the serotonin system [6].

In our records, MMN component had typical topography of brain activity distribution with negativity in frontal leads and positivity in the mastoid region. Results of numerous studies showed that this phase inversion is determined by bilateral localization of MMN generators in the auditory (*supratemporal gyrus*, STG) and frontal cortex [12].

MMN amplitude in response to any modification of the standard sound was maximum in carriers of LL-variant of 5-HTT gene, this parameter significantly decreased in carriers of the LS-genotype and attained minimum in carriers of the SS-genotype (Fig. 1). This regularity was observed in both frontal leads, where the MMN amplitude is calculated by the negative component, and mastoid areas, where this component becomes positive, which is indicative of MMN ($p<0.05$).

Genotype association with EP in response to various stimulus alterations by frequency, duration and intensity was analyzed separately. Thus, although MMN association with 5-HTT genotype was observed for all deviation types, it reached statistical significance only for great changes in the duration and frequency, but not in intensity. This indicates the possibility for different mechanisms of MMN appearance in response to various modification types, what was assumed previously [5]. Moreover, variations in sound intensity can be subjectively perceived as lesser deviation.

MMN is a stable typological parameter. This component appears after emergence of deviant "unexpected" stimulus among repeated tones. Moreover, the amplitude of this component correlates with the measure of discrepancy between the regular and deviant stimuli. In addition, this component does not depend on attention to the stimulus and appears even in cases, when the examinee ignores the presented sounds. Thus, this EP wave reflects automatic involuntary sensory information processing. Experimental studies revealed reduction of this component in patients with dyslexia, schizophrenia, and Parkinson disease [13]. As was already mentioned, the increase in this component in healthy subjects is associated with impulsiveness [4].

MMN is also related to the serotonin system, although there is no agreement concerning this issue yet. MMN amplitude was shown to decrease with decreasing serotonin content in the brain; however, MMN amplitude was not affected by psilocybine, 5-HT_{2a}-receptor agonist [14].

MMN component emerging about 100-200 msec after stimulus presentation is usually followed by P300 component associated with attention to the stimulus, working memory, and cognitive effort [10]. In the applied paradigm, attention to sounds was not necessary, so this positive component reflects the measure of involuntary attention to deviant stimulus. In other studies, the decrease in the amplitude of this wave was proposed to weakening of the inhibitory processes [15].

P300 component in the frontal, central, and central-parietal regions was increased in SS-genotype carriers in comparison with LL-5-HHT gene variant ($p<0.05$; Fig. 1). It probably suggests that the major part of external information processing in SS-genotype carriers is transferred from earlier automatic stage to late one, associated with cognitive control. It should be noted, that only amplitude was affected. In our study, the latency of P300 component did not differ signifi-

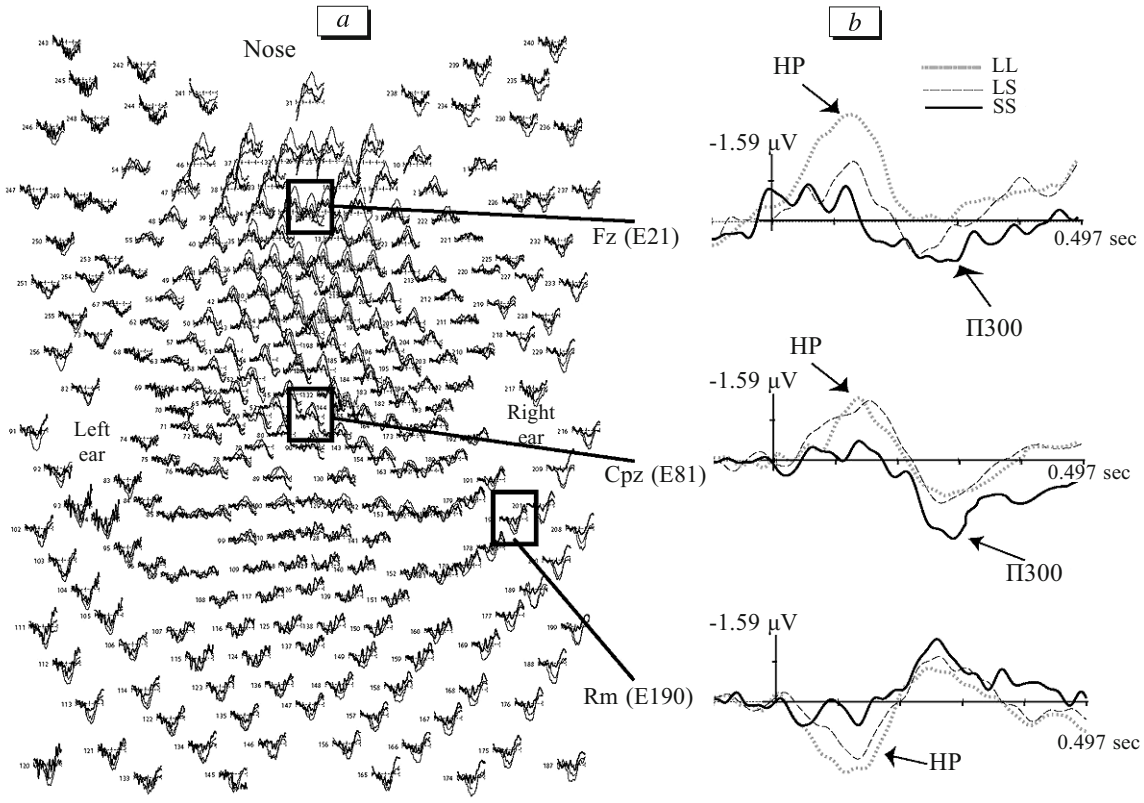

Fig. 1. Distribution of sound-induced brain potentials in carriers of different 5-HTT gene variants (differential brain potentials obtained by subtraction of EP in response to standard stimulus from that in response to deviant stimulus). *a*) potentials recorded in 256 channels, *b*) enhanced responses for channels Fz, Cpz and Rm. SS: differential brain potentials for carriers of SS-5-HTT-genotype; LS: differential brain potentials for carriers of LS-5-HTT-genotype; LL: differential brain potentials for carriers of LL-5-HTT-genotype. Arrows: significant differences in the studied MMN and P300 components.

cantly in carriers of different 5-HTT gene variants.

Thus, carriers of the LL-genotype with more active gene variant and, consequently, with more intensive serotonin reuptake from the synaptic cleft, exhibit higher sensitivity to external stimulation and more precise involuntary detection of differences even without conscious brain control. Moreover, P300 component in LL-genotype carriers is lower than in SS-genotype carriers. It can indicate that SS-genotype carriers involve more extensive cognitive resource into information processing. There are two possible explanations for this phenomenon: 1) stimulus by itself could appear to be more complex, which results in engagement of additional frontal cortex resources; 2) in-depth analysis of incoming information is more characteristic for SS-genotype carriers. This serious analysis of external information probably underlies rejection from impulsive aggressive actions.

Differences in processing of external non-relevant information did not affect task performance (word memorizing): number of words remembered in LL- and SS-genotype carriers was similar (14 and 11 words were reproduced, 31 and 29 words were recognized after a prompt, subsequently). These findings probably suggest that the studied components do not depend on voluntary switch of attention from auditory stimuli to visually presented words, otherwise word memorizing task should result in less number of words memorized.

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