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The Possibility of Applying a Combination of Allelic Variants of *IL-1 β* Gene and *WWC1* Gene for Assessing Susceptibility to PTSD (Pilot Investigation)

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Abstract

Memory and fear are two overlapping CNS processes in which mechanism of synaptic plasticity plays a key role. Fear increases likelihood fixation in memory behaviorally important information associated with a traumatic event. For healthy psychological functioning is crucial the ability to update the content and emotional charge of memories (cognitive plasticity) contributing to fading and extinction of fear memories once this event has been passed. Memory performance and its plasticity are associated with ability of synapses to change of number α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (AMPAR) on the post-synaptic membrane surface. AMPAR undergo exocytosis/endocytosis (AMPAR trafficking), thus changing the strength of neural connections (synaptic plasticity) and contributing to formation, maintaining and transformation of memories. Impairment of AMPAR trafficking may become a cause of deficiency of fear extinction, and development of posttraumatic stress disorder (PTSD). AMPAR trafficking is controlled by the nervous and the immune systems jointly. Kidney and brain expressed protein (KIBRA) and interleukin (IL) -1β are important regulators of AMPAR trafficking. Data show that genes encoding of these proteins (KIBRA-*WWC1* gene and *IL-1β* gene) and their alleles mediates of stress impact on synaptic plasticity and are a bridge between memory and diseases. Disease susceptibility in humans is most commonly associated with single nucleotide polymorphisms (SNPs), when corresponding sequences of DNA from different individuals differ at one DNA base. PTSD is polygenic disorder, so can be identified the combination of allelic variations of SNPs, associated with strength and plasticity of memory that distinguish PTSD patients from the control. Our preliminary results showed that the combination of the certain allelic variants of *WWC1*, SNP rs17070145 (T/C), and the *IL-1β* gene, SNP rs16944 (A/G), is characteristic for PTSD compared to depressive and healthy groups. We assume that this combination might be used for pre-clinical diagnosis PTSD and in clinical practice.

Keywords: Synaptic plasticity; AMPAR trafficking; Posttraumatic stress disorder; Kidney/brain protein; Interleukin (IL)-1β; *WWC1* gene; *IL-1β* gene.

Abbreviations: AMPAR: α-Amino-3-Hydroxy-5-Methyl-4-IsoxazolePropionic Acid Glutamate Receptors; LTP: Long-Term Potention; LTD- Long-Term Depression; PTSD: Posttraumatic Stress Disorder; KIBRA: Kidney and Brain Expressed Protein; IL-1β: Pro-Inflammatory Interleukin (IL)-1β; SNP: Single Nucleotide Polymorphism; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders; TP: True Positive Result of Test; TN: True Negative Result of Test; FP: False Positive Result of Test; FN: Negative Result of Test

Introduction

Consolidation as well as recall or reactivation of the memory trace storing fear memories are expressed by increasing synaptic insertion of AMPAR and enhance synaptic transmission (long-term potetention-LTP). Extinction of fear memories is associated with reduction of AMPAR in membrane surface (long-term depression-LTD) [1-7]. Balance between LTP- and LTD- forms of synaptic plasticity is considered as key factor of memory performance and its plasticity [8,9]. Modern approach is involves understanding that memories are changing both with the passage of time, and as a function of new experiences [10]. Individuals who demonstrate an opportunity to recover from traumatic experiences, displays the decrease in the strength of the fear memories and their extinction in new conditions [1,11]. At the same time, some individuals after traumatic stress exposure continue to show vivid and resistant fear memories in response to a safe context [12]. It is means that the mechanism of memory plasticity has broken. This disturbance underlies different disorders, particularly, PTSD [13,14]. PTSD is characterized by exaggerated amygdala responses, sub serving to exaggerated acquisition of fear associations and expression of fear responses as well as reducing hippocampal ability to appreciate of safe contexts and to update of memory by the learning new, non-

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fearful information [13]. Researches have shown that an increasing of responsiveness of the synapses in the amygdala to future stimulus presentations as well as a decrease in the ability of hippocampus to modify of fear memory trace in safe conditions is a result of blocking of the AMPAR removal [15-17]. When recollection occurs temporarily AMPAR there is a reduction in membrane surface and weakening of neural connections (LTD) returning previously consolidated neural network to a labile state. Destabilization is facilitates ability to establish new connections and pathways that can result incorporation of new, non-fearful information into existing knowledge stores [18]. Thus, reduction of AMPAR receptors in membrane surface contributes to plastic changes at the synaptic level that inhibit of fear memory strengthening and underlies of reinterpretation of memory content leading to extinction of fear [19]. After the retrieval is complete reconsolidation of the memory trace in its new form occurs. This enables to strength and to update memory (reconsolidation update) and such plasticity of memory is crucial for healthy psychological functioning [20-23]. Blocking of the AMPAR removal on the stage of reconsolidation and prevalence LTP over LTD can lead to over-consolidation, i.e. to deep engraving of the traumatic memories that manifested as intrusive recollection [17,24,25]. Overly strong fear association reduces memory ability to connection with new context and to updating, and thus they begin to exist, how would, outside of time and space [26]. Subjects with strong fear memories and with deficiency of fear extinction (which are key characteristics of PTSD) demonstrated impairment of removal of AMPAR within amygdala and hippocampus [16,17]. Consequently, it is important to identify biomarkers, which allows distinguish risk versus resilience to AMPAR blocking after trauma exposure. Many factors, including polymorphism of genes encoding proteins participating in AMPAR trafficking, determine in which direction LTP will be changed after stress [12,27]. KIBRA is a protein that plays crucial roles in AMPAR trafficking and synaptic plasticity in several brain regions [28,29]. KIBRA- *WWC1* gene is associated with hippocampal LTP. Researches are reveals an association between allelic variants of *WWC1*, SNP rs17070145 (C/T) and memory performance [30]. This SNP contains two alleles: C and T and as usual have three genotypes: "CC", "CT" and "TT". Data show existence of strong and weak versions of memory associated with *WWC1* polymorphism. Carriers of rs17070145 "CC" genotype demonstrated less efficiency of hippocampal LTP and significantly lower performance of episodic memory than carriers of the "TT" and "CT" genotypes [31,32]. Allelic variants SNP rs17070145 are considered as genetic link between features of the memory mechanisms and anxiety and depressive disorders. Results of researches indicates that variants of more efficiency of hippocampal LTP and higher performance of episodic memory ("CT" and "TT") are associated with increasing the likelihood of PTSD development [33], while "CC" variant rs17070145 is associated with depressive disorder [34]. Role of the immune system in synaptic plasticity is becoming increasingly apparent [35-37]. Researchers are highlighting the fact that physiological level of *IL-1β* is important for potentiation of synaptic efficiency [38]. At same time, stress-induced increasing the level of this pro-inflammatory cytokine can cause aberrations of AMPAR trafficking. Literature data demonstrates that *IL-1β* -related inhibition of regular AMPAR trafficking can manifest both by the blocking of their expression in the synaptic site, impairing the induction of LTP-form of synaptic plasticity [39-44] or inhibition of AMPAR internalization [45-47] that impairs of the induction of LTD. Different impacts of *IL-1β* on the AMPAR trafficking, is thought associated with polymorphism of the *IL-1β* gene. For example, it has been identified the association of the G-allele (genotype "GG") of *IL-1β* gene, SNP rs16944 (G/A) with suppression of AMPAR exocytosis and inhibition of LTP-induction at depressive patients. This aberration of AMPAR trafficking was accompanied by the reducing responsiveness of the amygdala to emotional stimulation [48], and weakening of the consolidation in the hippocampus [49,50]. Relation of the allelic variants SNP rs16944 (G/A) with impairment of AMPAR endocytosis and PTSD still obscure, at same time, there are indirectly data allowing suggest the relationship of PTSD with A-allele ("AA" genotype), SNP rs16944. It has been found that A-allele is associated with increases susceptibility to osteoarthritis [51,52], herewith patients with PTSD were more likely to have osteoarthritis [53]. Available data suggest that PTSD is highly complex and polygenic disorder. In studies of such disorders, a measurement of genetic variants can be used to identify combinations of allelic variations of different SNPs that are found in patients PTSD and which can be separated from those combinations occurring in control persons [54]. Carriers of various combinations of genotypes *WWC1* gene and *IL-1β* gene can differ in performance and plasticity of memory [55,56]. The strong and non-plastic emotional memory, which outcome is deficiency of fear extinction, is considered relatively specific characteristic of PTSD compared to depressive patients (weak memory) and mentally healthy persons (plastic memory) [19]. We believed that by comparing the frequency of genotypes "CC", "CT" and "TT", SNP rs17070145, *WWC1* and genotypes "GG", "GA" and "AA", SNP rs16944, *IL-1β* gene in the PTSD, depressive and healthy groups one can identify a combination of these genotypes, which is specific for PTSD, and which can be used as a diagnostic test.

Material and Methods

The study was approved by Ethics (Helsinki) Committee. Groups were formed from volunteers (males and females aged 18-60) after an explanation of the study (receiving information sheet distributed to volunteers) and signing a consent form. Experimental group includes 21 individuals (males-18; females-3; mean age=41.6) who were diagnosed as suffering from PTSD (in accordance with standard criteria in the Diagnostic and Statistical Manual of Mental Disorders-DSM-IV-TR). First control group includes 30 individuals mental health (males-14; females-16; mean age=41.1). The second control group includes 20 individuals (males-6; females-14; mean age=47.9) who were diagnosed as suffering from major depressive disorder MDD (DSM-IV-TR).

Isolation of genomic DNA and SNPs genotyping

About 30 ml of peripheral blood were taken from all volunteers. Genomic DNA was isolated from blood using QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. Genomic DNA concentration was assessed using a NanoVue plus spectrophotometer (GE Healthcare, US). Genotyping for the Single nucleotide polymorphisms (SNPs) in *IL-1β* gene and *WWC1* gene was performed by means of a TaqMan 5′ allelic discrimination assay (Applied Biosystems, Foster City, CA) for rs16944 and rs17070145 respectively. The PCR reaction was carried out in a total volume of 25 μl, containing 20 ng of genomic DNA, with the following amplification protocol: pre-incubation at 50°C for 2 min and then 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, and annealing/extension at 60°C for 1 min. The genotype of each sample was attributed by Roche software for allelic discrimination (LightCycler 480 II, Roche).

Mathematical processing

The difference of frequencies of investigated allelic variants was assessed by Chi-square test for goodness of fit [57]. To assess the effectiveness of test using genetic parameters, has been analyzed its sensitivity and specificity in the binary classification process [58-60].

Results

The findings show a significant difference ($p<0.05$) in allele distribution within and between analyzed groups. Figure 1 shows differences of the frequency of allelic variants SNP rs16944. In the Healthy group the frequency of variants "GG" and "AG" is higher than "AA" ("AG"-46.7% versus "AA"-13.3%; "GG"-40.0% versus "AA"-13.3%). At same time, in PTSD group the frequency "AA" and "AG" variants is higher than "GG" ("AG"-47.6% versus "GG"-14.3%; "AA"-38.1% versus "GG"-14.3%). In the MDD group the significant differences are absent.

Comparison between groups Figure 2 shows that the frequency "AG" variant in groups is not different. Herewith, the PTSD group is different from Healthy group higher frequency of "AA" allelic variant

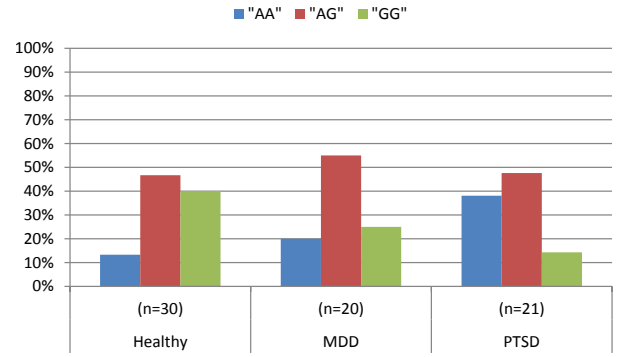

Figure 1: Frequency of allelic variants SNP rs16944 in the analyzed groups.

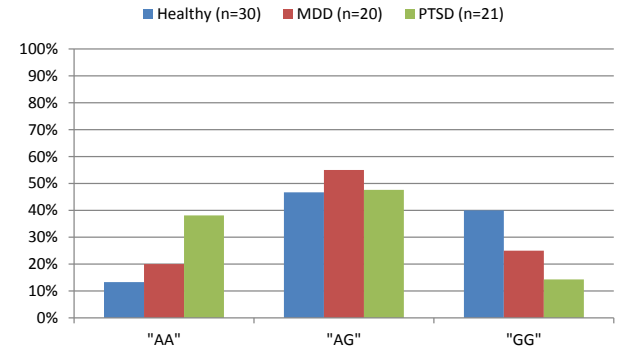

Figure 2: Comparison the frequency of allelic variants SNP rs16944 between the analyzed groups.

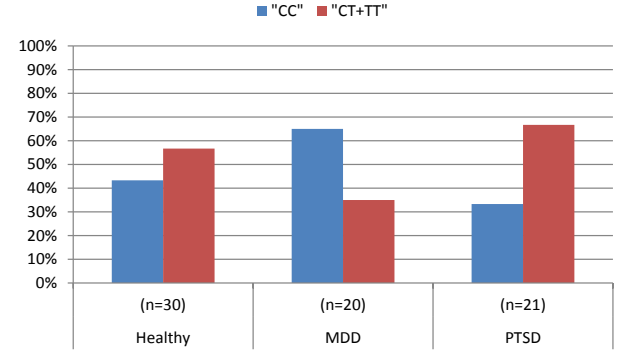

Figure 3: Frequency of allelic variants SNP rs17070145 in the analyzed groups.

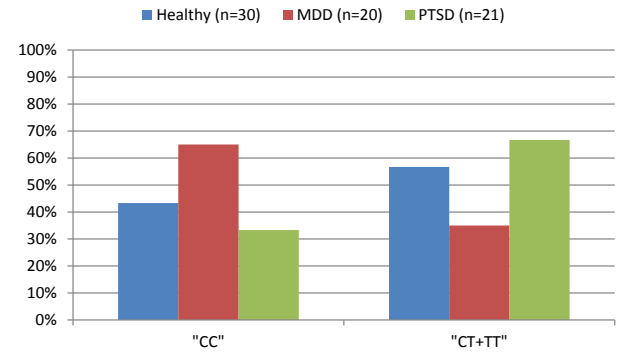

Figure 4: Comparison the frequency of allelic variants SNP rs17070145 between the analyzed groups.

(PTSD group-38.1% versus Healthy group-13.3%) and lower frequency of "GG" variant (PTSD group-14.3% versus Healthy group-40.0%).

Thus, it can be suggested that there is link between allelic variant "AA" rs16944 and PTSD, and that carriers of this variant perhaps have an increased likelihood of PTSD after the traumatic event, while carriers of variant "GG" possibly have lower probability of PTSD development.

Figure 3 showed differences in frequency of allelic variants SNP rs17070145. The results showed that in the Healthy group percentage carriers of genes associated with strong (*WWC1*-KIBRA SNP rs17070145 "CT" or "TT" allelic variants) and weak ("CC" variant) memory performance, splits about equally ("CT"-46.7%; "CC"-43.3%. Because of the small numbers of carriers of the TT variant, we combined of carriers "CT" and "TT" variants in the same group of strong memory-56.7%), whereas in the MDD group is predominated carriers of variant a weak memory ("CC" -65% versus "CT" and "TT"-35%) and in the PTSD group dominated carriers of genotype a strong memory ("CT" and "TT"-66.7% versus "CC"-33.3).

As shown in Figure 4, the frequency of allelic variants associated with weak ("CC") and strong ("CT"+"TT") memory in the healthy group significantly not different from the MDD and PTSD groups. At same time, percentage of carriers allelic variants, associated with weak memory was higher in the MDD group compared PTSD group (MDD-65% versus PTSD -33.3%), while percentage of carriers allelic variants, associated with strong memory was significantly higher in the PTSD group compared to the MDD group (PTSD-66.7% versus MDD -35%).

These results are confirmed the literature data, which associates a weak memory with MDD, and a strong memory with PTSD (23-26). Thus, it can be assumed that the carriers of variant "CT" (or "TT"), rs17070145 have an increased likelihood of PTSD development after traumatic stress exposure, while carriers of variant "CC" have lower probability of PTSD, but higher risk of MDD.

Discussion

Our results suggest that selected allelic variants can be used for screening individuals with predisposition to development of PTSD. For this, we estimated an efficiency of allelic variants "AA" and "GG" SNP rs16944 for separation of PTSD patients and healthy persons, as well as allelic variants "CT" ("TT") and "CC" SNP rs17070145 for separation of PTSD patients and MDD patients during binary classification process. Binary classification is the classification of the elements of a given set into two groups on the basis of a certain classification rule. Classification of two datasets was carried out. The first set consisted in

SNPs genotyping	Test outcome	Surveyed with PTSD (as confirmed by DSM-IV-TR) and Healthy participants	
		Condition positive (PTSD)	Condition negative (Healthy)
IL-1b gene SNP rs16944	Positive: "AA" allelic variant	True Positive (TP) 72.72%	False Positive (FP) 25%
	Negative: "GG" allelic variant	False Negative (FN) 27.27%	True Negative (TN) 75%
--		Sensitivity=72.72%	Specificity=75.0%

Table 1: Sensitivity and specificity of allelic variants "AA" and "GG" SNP rs16944 for binary classification of PTSD patients and healthy participants.

SNPs Genotyping	Test outcome	Surveyed with PTSD and MDD (as confirmed by DSM-IV-TR)	
		Condition positive (PTSD)	Condition negative (MDD)
KIBRA-WWC1	Positive: "CT"("TT") allelic variants	True Positive (TP) 66.7%	False Positive (FP) 35%
SNP rs17070145	Negative: "CC" allelic variant	False Negative (FN) 33.3%	True Negative (TN) 65%
--		Sensitivity=66.7%	Specificity=65.0%

Table 2: Sensitivity and specificity of allelic variants "CT ("TT") and "CC"SNP rs16944 for binary classification of PTSD and MDD patients.

carriers SNP rs16944, allelic variants "AA" and "GG", healthy persons and PTSD patients (n=27: PTSD=11; Healthy=16). In accordance with our classification rule, carriers of variant "AA" belongs to class PTSD (positive variant for PTSD) and carriers of "GG" variant belongs to class healthy persons (negative variant for PTSD). Thus, the carrier of "AA" allelic variant with diagnose PTSD is considered as true positive (TP) result, while the carrier of the "GG" variant, who was not diagnosed with this disorder, was considered as a true negative (TN) result. An important point is that for binary classification the relative proportion of different types of errors is of interest. For example, "AA" allelic variant at person without PTSD was evaluated as false positive (FP) result and "GG" allelic variant at person with PTSD was evaluated as false negative (FN) result. Percentage of TP results of the total number of people diagnosed with PTSD (TP/(TP+FN)) considered as sensitivity of "AA" allelic variant as diagnostic test, i.e. its performance for detection persons with PTSD. Percentage of TN results of the total number of healthy people (TN/(FP+TN)) considered as specificity, i.e. ability of "GG" allelic variant correctly identify individuals as not having the PTSD. The test quality is determined by its sensitivity and specificity. Table 1 shows the sensitivity and specificity of diagnostic test using allelic variants "AA" and "GG".

The results show that the "AA" variant correctly classifies subjects as PTSD patients (true positive results) in 72.7% of the cases. 27.3% of patients with a diagnosis of PTSD were carriers of allelic variants of "GG" thus, the used test denies at them the presence of disorder and classifies as healthy (false negative result). "GG" variant correctly classifies of the subjects as the healthy (true negative results) in 75% of cases. 25% of healthy subjects were carriers of allelic variants of "AA", thus the test erroneously classifies them as a patient with PTSD (false positive results). Sensitivity of this test is 72.7%, specificity- 75.0% that allow to estimate accuracy of diagnostic method using allelic variants "AA" and "GG", with the evaluation "fair" (sensitivity and specificity=70%-80%, gim.unmc.edu/dxtests/roc3.htm).

The second set consisted in patients diagnosed with PTSD and MDD, which were carriers of allelic variants "CC","CT" and "TT" SNP rs17070145 (n=41; PTSD=21; MDD=20). Our classification rule proposed that carriers of allelic variants associated with strong memory ("CT" or "TT" variants) belongs to class PTSD (positive variant for PTSD) and carriers of allelic variant associated with poor memory (" CC " variant) belongs to MDD class (negative variant for PTSD). In accordance with classification rule, the carrier of "CT ("TT") allelic variants with diagnose PTSD is considered as true positive (TP) result, while the carrier of the "CC" variant diagnosed as MDD patients was considered as a true negative (TN) result. "CT" or "TT" allelic variants at person with diagnose MDD evaluated as false positive (FP) result and "CC" allelic variant at person with diagnose PTSD was evaluated as false negative (FN) result. Table 2 shows the sensitivity and specificity of diagnostic test using allelic variants "CT ("TT") and "CC".

The results showed that the allelic variants associated with a strong memory [variants "CT" ("TT")] correctly classified the subjects as PTSD patients (true positive results) in 66.7% of cases. 33.3% of patients with a diagnosis of PTSD were carriers of allelic variant associated with poor episodic memory ("CC" variant), i.e. test denies at them the presence of PTSD and erroneously classifies them as a MDD (false negative result). "CC" variant, rs17070145 correctly classifies subjects as MDD patients (true negative results) in 65% of cases. 35% of MDD patients were carriers of allelic variants of the "CT" and "TT" thus test erroneously classifies them as patients with PTSD (false positive results). The findings characterize the classification capability of rs17070145 (C/T) as middling but reliable (sensitivity and specificity=60%-70%).

Thus, one can believe that classification capability of allelic variant "AA", SNP rs16944 and allelic variants "CT" ("TT"), SNP rs17070145 allows correctly identify individuals with predisposition to PTSD. At same time, allelic variant "GG", SNP rs16944 and allelic variant "CC", SNP rs17070145 can correctly identify individuals without of this predisposition.

In addition to the obtained results, which show that the frequency of allelic variant "AA" rs16944 in the PTSD group was higher than in the healthy group, and allelic variants "CT" ("TT") rs17070145 was higher than in the MDD group, it has been found that 28.6% in PTSD group were carriers of combinations the allelic variants "AA" rs16944 and "CT" or "TT" rs17070145 (in healthy group-6.7%; in MDD group -10.0%). Herewith, the carriers of combination "GG" rs16944 and "CC" rs17070145 in the PTSD group are absent (0%), while 16.7% healthy subjects and 15.0% depressive patients were carriers of such combination.

Conclusion

Recent researches have shown that stress facilitates consolidation of stressful experiences into long-term memory by enhancing LTP. One of ways is to protect the LTP from interference of new information, which is incorporated during LTD. For this, subsequent LTD may be suppressed (60) by the blocking of AMPAR removal. Obtained results were allows make speculative suggesting that genotype "AA", SNP rs16944 within *IL-1β* gene is associated with blocking AMPAR removal

from membrane surface, i.e. involved in the suppression inducing of LTD and inhibition of memory plasticity. In combination with genotypes of strong memory it can be cause of over-consolidation fear memories and reducing of their ability to be updated. The results of binary classification allow believe that identified combination can be used as diagnostic test for screening individuals with predisposition to PTSD. Identification of new genetic factors associated with PTSD may improve screening individuals with elevated susceptibility to disorders of fear and thus will improve the impact of preclinical diagnostic on prevention and treatment of PTSD. The small number of subjects in this work does not allow make any ultimate conclusions, however it seems promising for further studies in this direction.

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