

Post-traumatic stress disorder risk and brain-derived neurotrophic factor Val66Met

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Abstract

Brain-derived neurotrophic factor (BDNF), which regu-

lates neuronal survival, growth differentiation, and synapse formation, is known to be associated with depression and post-traumatic stress disorder (PTSD). However, the molecular mechanism for those mental disorders remains unknown. Studies have shown that BDNF is associated with PTSD risk and exaggerated startle reaction (a major arousal manifestation of PTSD) in United States military service members who were deployed during the wars in Iraq and Afghanistan. The frequency of the Met/Met in BDNF gene was greater among those with PTSD than those without PTSD. Among individuals who experienced fewer lifetime stressful events, the Met carriers have significantly higher total and startle scores on the PTSD Checklist than the Val/Val carriers. In addition, subjects with PTSD showed higher levels of BDNF in their peripheral blood plasma than the non-probable-PTSD controls. Increased BDNF levels and startle response were observed in both blood plasma and brain hippocampus by inescapable tail shock in rats. In this paper, we reviewed these data to discuss BDNF as a potential biomarker for PTSD risk and its possible roles in the onset of PTSD.

Key words: Post-traumatic stress disorder; Brain-derived neurotrophic factor; Depression; Biomarker; Startle

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Core tip: Brain-derived neurotrophic factor (BDNF), which regulates neuronal survival, growth differentiation, and synapse formation, is known to be associated with depression and post-traumatic stress disorder (PTSD). However, the molecular mechanism for those mental disorders remains unknown. In this paper, we reviewed these data to discuss BDNF as a potential biomarker for PTSD risk and its possible roles in the onset of PTSD.

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INTRODUCTION

Brain-derived neurotrophic factor (BDNF), first discovered in the early 1980s, is considered a member of the nerve growth factor family of neurotrophins^[1], which have important roles in the development, physiology, and pathology of mental disorders^[2,3]. BDNF is expressed in a number of tissues and cell types, including the brain and blood^[4]. In recent years, BDNF has been implicated in a number of psychiatric disorders, such as depression, anxiety, eating disorders, and posttraumatic stress disorder (PTSD) (Table 1). In this review, we will focus on the findings of the association between BDNF and PTSD and expand upon our recent works to provide an argument for the potential role of BDNF in additional psychiatric disorders with their roots in emotional dysregulation, specifically PTSD.

BDNF is a precursor protein (proBDNF) that is proteolytically cleaved to generate mature BDNF^[5] *via* tissue-type plasminogen activator (tPA)/plasminogen^[6]. P11 (S100A10), a component of the Annexin II and PTSD associated gene^[7,8], greatly enhances the activation of plasmin by tPA^[6]. It is suggested that p11 may act through the tPA/plasminogen/BDNF pathway to achieve its antidepressant effect^[6]. BDNF binds to either of two functionally different classes of cell surface receptors, the TrkB receptor tyrosine kinase or the p75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor receptor super family^[9]. ProBDNF and mature BDNF differentially interact with the TrkB receptor tyrosine kinase or the p75NTR, respectively^[9,10]. ProBDNF induces neuronal apoptosis *via* activation of a receptor complex of p75NTR and sortilin^[11]. ProBDNF induced p75NTR signaling gives rise to an increase in c-Jun N-terminal kinase and nuclear factor κ B, regulating apoptosis, axonal retraction, or the pruning of dendritic spines^[12]. BDNF-induced TrkB receptor signaling regulates neurotrophic responses *via* rapid activation of the PI-3 kinase, Ras/MAPK, and Phospholipase C- γ pathways; therefore influencing transcriptional events that affect the cell-cycle, neurite outgrowth, and synaptic plasticity (Figure 1), suggesting that the BDNF plays a key role in stress response and stress-related behaviors^[13].

BDNF AND PTSD

In the animal model, it is found that BDNF protein was over-expressed in the plasma and hippocampus of stressed rats compared with non-stressed controls. These data are in agreement with others showing that stress results in BDNF over-expression in the hippocampus, leading to the hypotheses of a BDNF-related compensatory mechanism^[14] and the blood levels

of BDNF mirror the hippocampus levels induced by traumatic stress^[15]. The rats with up-regulated BDNF in both blood and hippocampus induced by inescapable tail shock demonstrated increases of startle response^[15]. Acoustic challenge is known to trigger a range of physiological responses, including startle. The startle reaction (also known as the startle response, the startle reflex, or the alarm reaction) is the psychological and physiological response to a sudden unexpected stimulus, such as a flash of light, a loud noise (acoustic startle reflex), or a quick movement near the face. Abnormality of the startle response, which results from an elevated activation of the autonomic nervous system, is a core symptom of PTSD-hyperarousal^[16,17]. These data from the studies in animal model suggests that both BDNF and stress play important roles in startle response, although the mechanism needs to be further analyzed.

Within the last several years, the biological basis of PTSD has been an important focus of research in psychiatry due to the Iraq and Afghanistan wars. There are data showing that the blood BDNF is a potential biomarker for PTSD, the traumatic stress-related disorders, and debilitating psychiatric disorders^[4,15,18-21]. A common single nucleotide polymorphism (SNP) in the BDNF gene leading a valine to methionine substitution at position 66 (Val66Met) influences human hippocampal volume^[22], memory^[23] and susceptibility to PTSD^[23]. The BDNF Val66Met polymorphism is associated with sense of coherence, a presumed stress-related protective cognition in a non-clinical community sample^[24]. Individuals carrying the Met had decreased activity-dependent BDNF secretion from neurons, leading to impairment of learning^[22]. Recently, a study demonstrated that the frequency distribution of Val66Met polymorphism was different between subjects with and without PTSD^[15]. The frequencies of Met/Met genotype and Met carriers are significantly higher in individuals with PTSD than those without PTSD. The allelic frequency of Met was two-fold higher (33.3% vs 17.5%) in individuals with PTSD than in non-PTSD controls, supporting the notion that Met carriers have a smaller hippocampal volume relative to Val/Val homozygous^[25-27] and decreased volumes in the temporal and occipital lobe grey matter^[28].

These data suggest a role of BDNF in the plasticity of the brain, which might be associated with PTSD. It was found that Met carriers performed more poorly than control subjects (Val/Val carrier) on the memory tasks^[29]. The interaction of Met-allele and stress can result in depression, anxiety and arousal^[30]. There is a significant three-way interaction between Val66Met, serotonin transporter linked promoter region (5-HTTLPR), and maltreatment history in predicting depression^[31]. Children with the Met allele and two short alleles of 5-HTTLPR demonstrated the highest depression scores. However, the vulnerability associated with these two genotypes was only evident in the maltreated children^[31]. There is a report showing that veterans with psychotic PTSD carried more Met alleles of the BDNF

Table 1 Brain derived neurotrophic factor and common psychiatric disorders

Mental disorders	Results and references
Schizophrenia	Polymorphisms and BDNF ^[39] The Val66Met allele association ^[40] The TrkB receptor decreased in the hippocampus ^[41]
Major depressive disorder	Up- ^[41] and down ^[42] regulated BDNF in the frontal cortices Antidepressant increases BDNF levels ^[43] BDNF protein increased in the NAc ^[44] The decreased prefrontal cortex is correlated with decreased BDNF and TrkB levels ^[45,46] BDNF dose-dependently decreases 5HT uptake ^[47] Unclear whether BDNF polymorphisms contribute to expression of MDD symptoms or antidepressant efficacy ^[48,49]
Bipolar	Both lithium and valproic acid increase BDNF expression in corticolimbic brain ^[40] BDNF protein levels decreased in post mortem hippocampal tissue ^[40] Serum BDNF levels decreased ^[49] The V66M BDNF allele strongly correlated to BD ^[35,50]
PTSD	PTSD risk associated with BDNF Val66Met and BDNF overexpression ^[15] Blood BDNF levels and PTSD ^[4,15,18-21]

NAc: Nucleus accumbens; BDNF: Brain derived neurotrophic factor; MDD: Microgram per square decimeter per day; PTSD: Post-traumatic stress disorder.

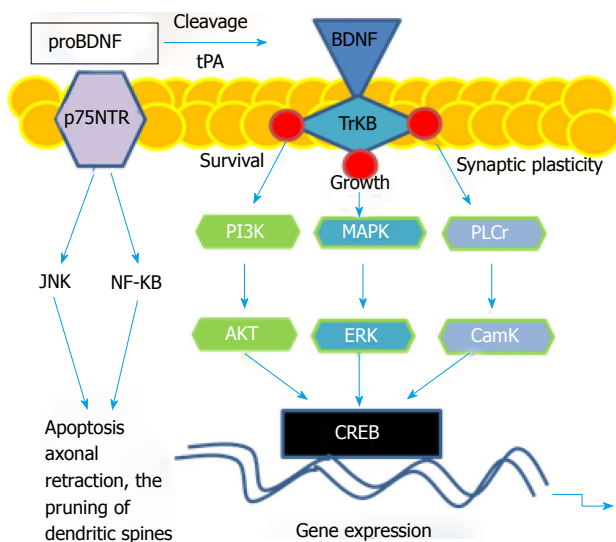


Figure 1 Brain-derived neurotrophic factor signaling pathway. The binding of proBDNF to the p75NTR up-regulates c-Jun N-terminal kinase and nuclear factor κ B, triggering apoptosis, axonal retraction, or the pruning of dendritic spines. The proBDNF is cleaved to generate mature BDNF via tPA/plasminogen. When BDNF binding to its receptors, the receptor tyrosine kinase TrkB becomes phosphorylated, leading to phosphorylation at various sites or activation of downstream pathways. Such activation shows at PI3K sites, which activates AKT, regulating cell survival. The activation of MAPK/ERK leads to cell growth and differentiation. The activation of PLC- γ pathway regulates IP3 receptor to release intracellular calcium stores, in turn to enhance CamK activity, regulating synaptic plasticity. All three pathways converge on transcription factor CREB, playing a key role in BDNF-induced gene expression. BDNF: Brain derived neurotrophic factor; PTSD: Post-traumatic stress disorder; tPA: Tissue-type plasminogen activator; CamK: Calmodulin kinase; CAMP: Cyclic adenosine monophosphate; CREB: CAMP response elements; CRE: CAMP response elements; AKT: Protein kinase B; IP3: Inositol trisphosphate.

Val66Met than non-psychotic veterans with PTSD or veterans without PTSD^[32]. This further supports the linkage between BDNF and PTSD, especially in a military population at war^[15]. However, not all studies show the same results. There is a case-control genetic association study showing no relationship between BDNF Val66Met

and PTSD diagnosis^[23]. It is possible the difference in frequency of trauma exposure, age, and other study conditions among the participants in the studies can explain these divergent results^[33]; however, this remains to be determined.

In an association study between BDNF Val66Met and the startle score of PTSD Checklist (PCL), a core symptom of hyperarousal in PTSD is observed to be associated with the polymorphism. The distribution of the Met/Met frequency was significantly different between those with and without exaggerated startle^[15]. The frequency of the Met/Met genotype was almost four-fold (12.2% vs 3.3%) higher in subjects with exaggerated startle than in those without exaggerated startle. In addition, the frequency of the Met allele was higher in subjects with exaggerated startle than in those without exaggerated startle (24.4% vs 15.3%), indicating that Met/Met is associated with hyperarousal vulnerability^[15]. Since the frequency of Val/Val genotype is higher in the non-startle group than in those endorsing startle reactions, it suggests that Val/Val is related to protection from exaggerated startle reactions and perhaps PTSD. Subjects with fewer stressful life events and carrying the Met/Met homozygote have significantly higher startle scores than those Val carriers, indicating that less exposure to stressful life events is associated with higher risk of hyperarousal in Met/Met carriers, but lower risk of hyperarousal in Val carriers^[15].

It is found that the BDNF Val66Met does not significantly effect on the PCL total score in the subjects who experienced higher (four or more) stressful life events. However, among those subjects who reported fewer exposures of stressful life events, the Met carriers show higher PCL total scores (*i.e.*, reported greater PTSD symptoms) than Val carriers. Therefore, at a lower exposure of stressful life events, Met carriers had a higher risk of PTSD symptoms, and the presence of Val led to a lower risk of PTSD symptoms^[15]. This indicates that there are protective effects at higher levels of

stress exposure. A similar phenomenon is observed in a catechol-O-methyltransferase gene association study, which showed that those homozygous for the Met allele demonstrated a high risk for PTSD, independent of the severity of traumatic load^[34]. Alternatively, different neuronal mechanisms^[35] may be active in minimally exposed and highly exposed individuals who develop PTSD, supporting different underlying trajectories of this disorder and perhaps different treatments^[15].

It is also found that at protein levels, subjects with PTSD had significantly higher serum levels of BDNF than the non-PTSD controls^[20]. In addition, the BDNF levels in Met carriers are higher than in Val/Val homozygotes^[36]. The findings are consistent with other results showing that serum BDNF levels in individuals with PTSD are higher than in age and sex matched controls right after traumatic events^[19,37]. However, some studies have shown either significantly lower levels of BDNF among those with PTSD^[4] or significant difference of BDNF levels in serum between PTSD and non-PTSD controls^[21]. These contradictory results may be due to the different methods used in the various studies. The samples may have been collected from dissimilar population^[18,20,21,37], at different time points during the course of the disease^[18,20,21,37], or from different animal models^[38]. These assumptions need to be further analyzed. Nevertheless, these data suggest that BDNF is associated with PTSD risk at both translational and genomic levels^[15]. Therefore, blood levels of BDNF may be of benefit in developing non-invasive diagnostics for PTSD^[15].

CONCLUSION

The association between BDNF and PTSD has been suggested. The frequency of the Met/Met was greater among those with PTSD than non-PTSD controls. In addition, this SNP is associated with exaggerated startle, but not with other items on the PCL. Among individuals who experienced fewer lifetime stressful events, Met carriers have significantly higher total and startle scores on the PCL than Val/Val carries. At protein levels, subjects with PTSD had higher levels of BDNF in their peripheral blood plasma than the non-PTSD controls. In a rodent model, complementing the data from the human subjects, increased BDNF protein levels accompanied by an obvious elevation of the startle response were obtained in both blood plasma and brain hippocampus by inescapable tail shock. Therefore, protein BDNF in the blood and startle test, aside from genotype, and neuroimaging could also serve as biomarkers to direct more personalized PTSD treatment. Future studies on patient cohorts will elucidate whether these biomarkers, particular BDNF for PTSD prove to be useful in a clinical setting.

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