Peripheral Biomarker Candidates of Posttraumatic Stress Disorder

Hee Jin Kang¹, Sujung Yoon¹* and In Kyoon Lyoo¹,²,³

¹Ewha Brain Institute, ²Department of Brain and Cognitive Sciences, ³College of Pharmacy, Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul 03760, Korea

There is high variability in the manifestation of physical and mental health problems following exposure to trauma and disaster. Although most people may show a range of acute symptoms in the aftermath of traumatic events, chronic and persistent mental disorders may not be developed in all individuals who were exposed to traumatic events. The most common long-term pathological consequence after trauma exposure is posttraumatic stress disorder (PTSD). However, comorbid conditions including depression, anxiety disorder, substance use-related problems, and a variety of other symptoms may frequently be observed in individuals with trauma exposure. Post-traumatic syndrome (PTS) is defined collectively as vast psychosocial problems that could be experienced in response to traumatic events. It is important to predict who will continue to suffer from physical and mental health problems and who will recover following trauma exposure. However, given the heterogeneity and variability in symptom manifestations, it is difficult to identify biomarkers which predict the development of PTSD. In this review, we will summarize the results of recent studies with regard to putative biomarkers of PTSD and suggest future research directions for biomarker discovery for PTSD.

Key words: posttraumatic stress disorder (PTSD), posttraumatic syndrome (PTS), biomarkers, neuroendocrine system, inflammation, neurotransmission

INTRODUCTION

Acute stress reactions are considered as a normal response to a major traumatic event and an evolutionarily adaptive function in human. While the majority of people may naturally recover from these acute stress reactions, a variety of persistent mental or emotional distress may also be observed in substantial proportion of trauma-exposed individuals [1]. Posttraumatic stress disorder (PTSD) is one of the most common anxiety disorders that may occur after exposure to traumatic events such as threatening experiences, military combats, natural disasters, terrorist attacks, serious accidents, or physical or sexual assaults. A lifetime prevalence of PTSD is approximately 8% in the general population [2]. It is characterized by re-experiencing, avoidance, alterations in cognition and mood, and hyperarousal [3]. There is high comorbidity with other mental (e.g., depression, substance and alcohol abuse, panic disorder, suicide) or medical (e.g., diabetes, cardiovascular disease, dementia) conditions [4, 5]. Posttraumatic syndrome (PTS) is a broader concept of various problems following exposure to trauma or disasters. It may manifest itself in several ways ranging from the development of PTSD and other several psychiatric disorders to various daily problems in interpersonal relationship, social adaptation, or occupational function. Other behavioral disturbances such as deviant behavior,
suicide, violence, and decreased quality of life may also be frequently observed in trauma-exposed individuals. Given the heterogeneity and variability in symptom manifestations, the application of valid biological markers in combination with clinical interviews would be necessary to accurately diagnose PTSD [6].

Not all people who are exposed to traumatic events develop chronic and persistent psychiatric disorders [1]. Therefore, it is essential to differentiate those with increased risk of developing persistent physical and mental health problems and those with high levels of psychological resilience to recover, following trauma exposure [7]. There has been significant research effort to find social, psychological, and biological factors to predict the risk for PTSD development and resilience against it [8].

A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention” [9] and is applied to predict the vulnerability to a specific disease or diagnose a disease. Molecular, enzymatic, imaging, electrophysiological, and genetic measures are commonly used as biomarkers.

Although a substantial number of studies have reported neurobiological alterations related to PTSD, reliable and specific biomarkers which would accurately predict or diagnose PTSD are not yet currently available [6]. This is partly because PTSD is highly heterogeneous with various symptom presentations and high comorbidities. Furthermore, since several neurobiological mechanisms are known to be involved in the pathophysiology of PTSD, it is unlikely that a single biomarker is able to identify the risk, diagnose PTSD, and measure the level of resilience with high reliability [10].

However, increasing evidence has suggested the potential usefulness of biological markers in the diagnosis of PTSD. Several candidate biomarkers have also been proposed to identify PTSD-related alterations in the neuroendocrine, neurotransmitter and immune systems [10].

In this review, we aim to provide an overview of the present knowledge with regard to biomarkers of PTSD and suggest future research directions to identify more reliable biomarkers of PTSD in the general population. Specifically, this review focuses on potential peripheral biomarkers in blood sample (serum or plasma), peripheral blood cells (red blood cells, platelets, or lymphocyte), and urine sample, which can be used as surrogates for central nervous system (CNS) and predict and diagnose PTSD.

We will outline the research findings about molecular biomarkers related to the neuroendocrine hormones, neurotransmitters, and proinflammatory cytokines.

PERIPHERAL BIOMARKER CANDIDATES OF POSTTRAUMATIC STRESS DISORDER

Since PTSD has been regarded as a ‘brain disease’, research using CNS-derived samples such as brain tissue or cerebrospinal fluid (CSF) could provide more pertinent information regarding biomarkers of PTSD. However, the biopsy of the living brain is very rarely performed to diagnose noncancerous pathology including psychiatric disorders. Although the postmortem brains have been used to investigate neurobiological alterations related to PTSD, it is difficult to determine the origins of pathology; for instance, whether observed changes occur prior to the development of PTSD or secondary to disease itself [11]. Furthermore, it is still not easy to obtain a sufficient sample size of the postmortem brains of PTSD patients for optimal assessments.

Emerging evidence has indicated that some biomarkers may be altered identically in both the brain and peripheral tissues of patients with psychiatric diseases, implying the commonality in biological processes among different tissue types [12–14]. A recent expression quantitative trait loci analysis has found that brain tissues and blood shared many cis-acting single nucleotide polymorphisms (SNPs) [13]. Transcript abundance has similarly been influenced in multiple tissues including the brain and blood [12]. Gene expression profiles related to mitochondrial function has been altered similarly in both the amygdala and peripheral blood in a rodent model of stress-related disorders [14]. Interestingly, these alterations in mitochondrial-focused gene expression have also been observed in peripheral blood of patients with PTSD [14]. Peripheral sample cells also have advantages of conducting functional cellular analysis and directly evaluating dynamic cellular responses underlying various cellular events [11]. However, since different tissue types do not always show similar biological changes related to diseases [15], it is important to find biomarkers with the shared mechanisms which are preserved between CNS and peripheral samples in predicting and diagnosing psychiatric diseases, including PTSD. Furthermore, peripheral biomarkers need to be validated for their reliability, sensitivity, and cost efficacy [16].

Taken together, biomarkers in peripheral tissues, which may reflect CNS alterations, can be useful surrogate measurements and could practically be applied in clinical settings [11]. Several candidate biomarkers in peripheral tissues, which can supplement symptomatic information and enhance diagnostic accuracy, have been reported in studies on many psychiatric diseases [11]. Along with increasing interest in applying PTSD biomarkers in multiple clinical fields, including emergency rooms, military settings, or disaster management settings, increasing number of studies have
recently identified the potential biomarkers of PTSD.

**POTENTIAL BIOMARKERS OF PTSD DIAGNOSIS**

It is indeed known that PTSD is currently diagnosed through clinical interviews and history taking by a trained professional. In a large-scale screening process, however, symptoms may not be fully disclosed by patients or clinicians may not always be available to make a diagnosis [6]. Symptoms self-reported by patients may not be sufficient information to make an accurate diagnosis and symptoms can be possibly undetected in this case [6]. Furthermore, it is somewhat challenging to distinguish comorbid conditions based on reported symptoms. For instance, symptoms such as insomnia, numbing, loss of pleasure, and impaired concentration could be related to either PTSD or depression [17]. Distinguishing between newly emergent PTSD symptoms and preexisting traits or determining a threshold for abnormality could also be difficult [7]. In this regard, biomarkers that can objectively confirm the diagnosis of PTSD would be very useful and need to be applied in clinical settings. Furthermore, reliable biomarkers can also be a worthwhile screening tool to detect PTSD in patients who have difficulties in describing their symptoms. In addition to the diagnosis and screening, peripheral biomarkers may be useful tools in differentiating the subtypes of PTSD or providing relevant information regarding response to treatment interventions [18].

**HPA axis-related parameters**

Previous studies have reported heterogeneous findings of the baseline cortisol levels and a recent meta-analysis has suggested no significant differences in peripheral cortisol levels between trauma-exposed subjects with PTSD and those without it [19]. Given the crucial role of hypothalamus-pituitary-adrenal (HPA) axis dysregulation in the pathophysiology of PTSD [20], a more promising and valid approach to measure cortisol reactivity, for instance cortisol awakening response and diurnal cortisol profiles, rather than the simple measurement of peripheral cortisol levels may be necessary to determine the HPA axis-related dysfunction induced by PTSD.

In this regard, greater cortisol awakening response has recently been suggested as a pre-exposure risk factor for acute stress disorder symptoms and peri-traumatic dissociation during police academy training [21]. Combat veterans with PTSD have also shown an enhanced glucocorticoid negative feedback inhibition of the HPA axis as evidenced by increased suppression of cortisol levels after a dexamethasone suppression test [22]. Along with the enhanced HPA negative feedback in PTSD, increased cortisol and corticotrophin-releasing hormone (CRH) levels were observed in CSF but not in peripheral blood of combat veterans with PTSD [23]. Hormone binding potential of the glucocorticoid receptor (GR) receptor was reduced in peripheral blood mononuclear cells (PBMCs) of trauma-exposed individuals with PTSD relative to those without PTSD [24]. Enhanced sensitivity to glucocorticoids in PBMCs was also observed in PTSD [25].

Analysis of gene expression patterns in whole blood has clearly identified abnormalities in genes generally involved in HPA axis [26]. In this study, the expression of GR-regulatory gene FK506-binding protein 5 (FKBP5) was reduced in patients with PTSD [26]. FKBP5, as a co-chaperone of GR, plays a role in inhibiting ligand binding and nuclear translocation of GRs and then leading to decreased GR signaling capacity [27]. Consistent with this finding, the results from genetic association studies have strongly suggested that the functional variants of FKBP5 polymorphisms may be related to specific type of HPA axis dysfunction and then determine the biologically distinct subtypes of PTSD [28, 29].

**Other neuroendocrine/metabolic system-related parameters**

Oxytocin and arginine vasopressin (AVP), members of a family of neuropeptide hormones, are synthesized in the hypothalamus and have been known to control anxiety, stress-coping, and sociality [30]. Central oxytocin appears to exert anxiolytic effects and alleviate PTSD symptoms, while AVP may increase anxiety and fear responses [30, 31]. Higher levels of oxytocin were associated with improved posttraumatic coping in female survivors of motor vehicle accidents [32]. Another study to assess salivary oxytocin and AVP levels has also found lower oxytocin levels in male police officers with PTSD than in those without PTSD [33]. In contrast, salivary AVP levels showed no group differences [33].

Adiponectin and resistin are protein markers belonging to the adipokines, which are soluble mediators and released by adipose tissue [34]. Their roles in regulating insulin resistance and energy metabolism have widely been investigated [34]. Recently, there is growing evidence that these adipokines may also play a central role in modulating the inflammatory and immune systems [34]. Specifically, adiponectin may exert anti-inflammatory effects [35], while resistin is known as a pro-inflammatory substance [36, 37]. Alterations in the levels of adiponectin and resistin have frequently observed in patients with obesity, metabolic syndromes, or coronary heart disease [35-37]. Based on preliminary findings regarding the relationship between experiences of stressful events during childhood and inflammatory abnormalities, a recent study has investigated the serum adiponectin and resistin levels in individuals who were exposed to childhood maltreatment [38]. The level of adiponectin was found to be lower in those with
childhood maltreatment history than those without, implying the potential effects of increased early life stress on lowering adiponetin, the anti-inflammatory marker [38].

**Neurotrophic factors-related parameters**

Brain-derived neurotrophic factor (BDNF), as one member of the neurotrophin family, plays an important role in promoting the proliferation, survival, and differentiation of nerve cells [39]. Previous clinical and preclinical studies have provided a substantial amount of evidence suggesting the relationship between prolonged stress exposure and reduced expression of BDNF [40-44]. Patients with PTSD, as compared with healthy control subjects, showed lower plasma BDNF levels [41]. A recent longitudinal study of survivors of motor vehicle accidents has suggested a potential role of serum BDNF levels in predicting the development of PTSD [43]. Interestingly, changes in serum BDNF levels were associated with changes in PTSD symptom severity over 6 months [43]. Increased levels of BDNF and pro-BDNF have been observed in traumatized people with 12 weeks of docosahexaenoic acid treatment [45], implying serum pro-BDNF/BDNF levels as a putative biomarkers of treatment in patients with PTSD.

The BDNF Val66Met polymorphism has also been associated with the modulation of fear extinction in both human and animal models [46]. In addition, recovery from PTSD was related to effects of BDNF polymorphism via thickening the dorsolateral prefrontal cortex, which may contribute to enhance cognitive control over negative emotion [47].

**Neurotransmitters-related parameters**

The sympathetic nervous system and HPA axis of the neuroendocrine system, as two major stress hormone systems, have long been proposed to be involved in the pathophysiology of PTSD [8, 48]. Dopamine- and norepinephrine-mediated neurotransmission may be altered in patients with PTSD [48-50]. Specifically, increased noradrenergic activity has frequently been observed in traumatized individuals in response to stressors [48, 51]. For instance, individuals who were exposed to childhood trauma have demonstrated increased 3-methoxy-4-hydroxyphenylglycol (MHPG, the major metabolite of norepinephrine) responses to aversive visual stimuli [52]. Higher urinary epinephrine levels immediately after exposure to trauma may also predict the development of PTSD at 6 weeks after trauma exposure [53]. A recent genetic study of 580 participants has reported the associations between the SNP in the promoter region of the norepinephrine transporter gene SLCA6A2 (rs2242446) and anxious arousal symptoms [54]. Since dopamine β-hydroxylase (DBH) is a critical enzyme that converts dopamine to norepinephrine, it has been suggested that the activity of DBH may also be involved in the pathophysiology of PTSD [55]. Reduced plasma DBH activity, which was associated with carrying the CC genotype of the -1021C/T DBH polymorphism, was observed in combat veterans with PTSD [55]. However, this finding was not replicated by a subsequent study of combat veterans using the genotype-controlled analysis [56]. Platelet monoamine oxidase B activity, which may modulate dopamine metabolism, has been found to be higher in veterans with psychotic PTSD as compared to those in healthy individuals or the veterans without it [57].

The findings of platelet 5-HT concentration have been controversial and heterogeneous, depending on diverse settings. For instance, veterans with PTSD than in those without PTSD showed higher platelet 5-HT concentrations [58]. However, another study has reported lower platelet 5-HT concentrations in suicidal patients with PTSD relative to healthy individuals [59]. The findings of the effects of serotonin transporter promoter gene polymorphism (5-HTTLPR) on PTSD appear to be consistent across studies. The presence of short allele (S) of the 5-HTTLPR polymorphism, which is related to low transcriptional efficiency, was associated with increased risk for post-deployment adjustment problems in veterans [60]. Furthermore, PTSD symptoms may be more severe in the S allele carriers relative to those with homozygous for the high functioning long (L) allele [61]. Gene-environment interactions also exist at the serotonin transporter gene locus. In adolescent survivors of the earthquake, the interaction effects of 5-HTTLPR and earthquake exposure as well as those of 5-HTTVNTR polymorphisms and earthquake exposure on the diagnosis of PTSD were statistically significant [62].

Neuropeptide Y (NPY) may exert control over anxiety and stress and may be related to resilience against stress [63]. Veterans with PTSD, as compared with healthy individuals, showed lower levels of NPY in CSF [63]. However, a recent study to assess serum NPY levels did not find its relationship with PTSD in survivors of motor vehicle accidents [64].

**Immune system-related parameters**

Increased levels of peripheral markers of inflammation have frequently been observed in patients with PTSD [65, 66] partly because stress hormone dysregulation related to PTSD may lead to alterations in the immune system and inflammatory signaling [67]. Since enhanced inflammation has also been suggested as a hallmark of comorbid diseases with PTSD, including depression and other medical conditions [4, 68, 69], it is not so simple to use
immune factors as a specific diagnostic biomarkers of PTSD [27].

Plasma levels of high sensitivity C-reactive protein (hsCRP) have widely been investigated as a potential biomarker predicting increased risk for PTSD. A recent large-scale study of approximately 2,600 war zone-deployed marines has indicated that plasma hsCRP levels may predict the emergence of PTSD symptoms, implying a strong association between enhanced inflammation and the development of PTSD [67]. Along with elevated plasma hsCRP levels, concentrations of intercellular adhesion molecule-1 and vascular cellular adhesion molecule-1 were higher in patients with PTSD than in those without PTSD [70, 71]. Other pro-inflammatory cytokines including tumor necrosis factor-α were also altered in children with trauma exposure [72]. Likewise, high-mobility group box 1 (HMGB1), which mainly mediates systemic inflammation, could be a potentially useful biomarker of PTSD. After the blunt chest trauma, higher levels of plasma HMGB1 were found in patients with PTSD compared to those without [73].

Miscellaneous
Comparisons of PBMC P11 mRNA levels among individuals with PTSD, major depressive disorder (MDD), bipolar disorder, schizophrenia and controls showed that PBMC P11 mRNA could be a potential biomarker to distinguish PTSD from other psychiatric disorders: MDD, bipolar disorder, and schizophrenia. As compared to healthy controls, those with PTSD had higher levels of PBMC p11 mRNA levels, while those with MDD, bipolar disorder, and schizophrenia had lower levels [74].

POTENTIAL BIOMARKERS OF RISK OR VULNERABILITY TO PTSD

In addition to the identification of reliable biomarkers of PTSD diagnosis, it is also important to find vulnerability or risk biomarkers that can predict the development of PTSD [7]. Since the extent and threshold of trauma exposure, as prerequisites for the emergence of PTSD symptoms, vary across individuals, the development of PTSD tends to be less reliably predicted [6]. Therefore, in addition to pre-trauma risk biomarkers which identify PTSD risks before trauma exposure, immediate peri- or post-trauma risk biomarkers, which can be established with relevant clinical information such as trauma severity, may also be useful in more complicated practical settings. In order to find promising putative pre-trauma or post-trauma biomarkers for identifying traumatized individuals who will be more likely to develop PTSD, the studies using the prospective longitudinal design would be necessary.

The HPA axis plays a key role in not only acute stress responses but also the development of a more chronic condition, PTSD [27]. A study which prospectively observed individuals with traumatic accident has reported that low level of baseline cortisol on the second day after hospitalization was associated with increased risk of PTSD at 6 months afterwards [75]. Moreover, blunted cortisol reactivity in response to acute stress exposure was related to higher risk of PTSD prospectively [27].

In a large prospective cohort study of military personnel, higher GR number in PBMCs at pre-deployment was associated with increased risk for PTSD symptoms at post-deployment [76]. In other words, pre-existing high GR number in PBMCs could be regarded as vulnerability factors for PTSD development later [76]. Likewise, a study which assessed soldiers before and 6 months after the military deployment has demonstrated that low level of FKBP5 mRNA expression and high level of glucocorticoid-induced leucine zipper (GLIZ) mRNA expression may independently predict increased risk of PTSD development after deployment [77]. Taken together, activity of GR pathway before exposure to trauma may be reliable pre-trauma risk biomarker candidates for predicting subsequent development of PTSD.

Given the effects of menstrual cycle and pregnancy on PTSD symptom profiles [78-80], gonadal steroid hormones may also play a role in PTSD susceptibility and symptom presentation. Consistent with this, recent studies have reported that reduced estradiol [81] and testosterone [82] before exposure to trauma were related to increased risk for PTSD development.

Genetic association studies may also provide important clues regarding pre-trauma risk biomarkers of PTSD. A recent large-scale study has suggested significant interaction effects between four genotype variants of the FKBP5 gene and the severity of child abuse on the prediction of adult PTSD symptoms [28]. Corticotropin-releasing hormone type 1 receptor (CRHR1) gene variant (rs12944712) was related to acute symptom levels in pediatric injury patients and further predicted the trajectory of PTSD symptoms over time [83]. The CRHR2 gene variants were also found to influence the risk of PTSD potentially by modulating the stress response [84]. The 5-HTTLPR polymorphism has been known to be related to the development of PTSD. Participants having low-function S-allele were more likely to develop post-hurricane PTSD [85]. A gene encoding catechol-O-methyltransferase gene (COMT), which metabolizes and inactivates the catecholamine neurotransmitters including dopamine, norepinephrine, and epinephrine, has been implicated as a possible risk factor gene in developing PTSD [86]. This action appears to be mediated by changing the dopaminergic transmission in the prefrontal cortex and its connection to the limbic system [86]. Combat veterans
having heterozygous genotype for the COMT polymorphism rs4680, valine/methionine genotype, were less likely to develop chronic PTSD symptoms than those with homozygous genotype [86]. Genetic polymorphisms in the dopamine transporter (DAT1) and the dopamine receptor genes (DRD2, DRD4) were also associated with vulnerability to PTSD [87]. A common single-nucleotide polymorphism in the BDNF gene (Val66Met), which has been suggested to influence to the hippocampal volume, and thus memory and cognitive function, could be related to susceptibility of neuropsychiatric disorders, including PTSD [88].

**POTENTIAL BIOMARKERS OF RESILIENCE, OR THERAPY RESPONSE**

Biomarkers of resilience, which predict the degree of stress resistance and/or recovery from PTSD, may overlap with vulnerability biomarkers [7, 20]. However, emerging evidence has suggested that a set of biological markers may independently reflect resilience following trauma exposure, which may be distinct from those predicting risk [89, 90]. In addition, biomarkers for PTSD treatment may enable monitoring of the therapeutic response to PTSD treatment options [7, 20].

Trauma-exposed individuals with a valine/valine BDNF gene polymorphism showed greater thickness of the DLPFC and better recovery from the PTSD than those with a methionine allele and controls [47]. Lower levels of serum BDNF may be associated with a better treatment response to escitalopram, a selective serotonin reuptake inhibitor in patients with PTSD [91]. This finding may imply that PTSD patients with low serum BDNF levels, as compared to those with high levels, may be more responsive to putative neurotrophic effects of escitalopram [91].

Elevated serum NPY levels were observed in individuals who experienced uncontrollable stress and harsh military training [92, 93]. Interestingly, individuals with higher serum NPY levels showed less psychological distress and better behavioral performance than those with the lower levels [92, 93]. The finding that combat-exposed veterans without PTSD showed higher plasma NPY levels than those with PTSD may also suggest high plasma NPY levels as a biological marker of resilience [94].

**CONCLUSION**

To date, extensive research efforts have been devoted to identifying reliable biomarkers of PTSD diagnosis, risk for PTSD development, or resilience against it across distinct biological domains, including HPA-axis, sympathetic nervous system, other neuroendocrine/metabolic systems, neurotransmission, neurotrophin, and immune system. The current review provides a summary and an update of recent literature regarding a set of putative biomarkers of PTSD. Despite increasing knowledge over decades, the heterogeneity in PTSD symptom presentations and common comorbidity of PTSD may be considered as a potential obstacle in finding valid and specific biomarkers of PTSD. Furthermore, since putative PTS biomarkers with practical applicability have not been reported so far, further research will be needed for practical application.

The prospective study of large sample sizes will be essential to distinguish biomarkers of risk, diagnosis, and recovery related to PTSD development. Studies on novel molecular targets such as oxidative stress or epigenetic studies focusing on telomere shortening and DNA methylation could be also an important direction [95]. Furthermore, translational research approaches could be of benefit to elucidate the molecular underpinnings of PTSD by combining clinical and animal studies [20].

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