Review Article

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Experimental Neurobiology

Peripheral Biomarker Candidates of Posttraumatic Stress Disorder

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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 find 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 to 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, neurotrophins, neurotransmitters, and proinflmmatory 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 trail 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 feat 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-hydroxy-phenylglycol (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 SLC6A2 (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 promotor 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].

ACKNOWLEDGEMENTS

REFERENCES

1. Foa EB, Stein DJ, McFarlane AC (2006) Symptomatology and psychopathology of mental health problems after disaster. J Clin Psychiatry 67 Suppl 2:15-25.

2. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048-1060.

3. Friedman MJ, Resick PA, Bryant RA, Brewin CR (2011) Considering PTSD for DSM-5. Depress Anxiety 28:750-769.

4. Boscarino JA (2004) Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci 1032:141-153.

5. Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, Kluse M, Marmar C (2010) Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry 67:608-613.

6. Lehrner A, Yehuda R (2014) Biomarkers of PTSD: military applications and considerations. Eur J Psychotraumatol 5. doi: 10.3402/ejpt.v5.23797.

7. Yehuda R, Neylan TC, Flory JD, McFarlane AC (2013) The use of biomarkers in the military: from theory to practice.

Psychoneuroendocrinology 38:1912-1922.

8. Schmidt U, Willmund GD, Holsboer F, Wotjak CT, Gallinat J, Kowalski JT, Zimmermann P (2015) Searching for non-genetic molecular and imaging PTSD risk and resilience markers: Systematic review of literature and design of the German Armed Forces PTSD biomarker study. Psychoneuroendocrinology 51:444-458.

9. Biomarkers Definitions Working Group (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 69:89-95.

10. Zoladz PR, Diamond DM (2013) Current status on behavioral and biological markers of PTSD: a search for clarity in a conflicting literature. Neurosci Biobehav Rev 37: 860-895.

11. Hayashi-Takagi A, Vawter MP, Iwamoto K (2014) Peripheral biomarkers revisited: integrative profiling of peripheral samples for psychiatric research. Biol Psychiatry 75:920-928.

12. Emilsson V, Thorleifsson G, Zhang B, Leonardson AS, Zink F, Zhu J, Carlson S, Helgason A, Walters GB, Gunnarsdottir S, Mouy M, Steinthorsdottir V, Eiriksdottir GH, Bjornsdottir G, Reynisdottir I, Gudbjartsson D, Helgadottir A, Jonasdottir A, Jonasdottir A, Styrkarsdottir U, Gretarsdottir S, Magnusson KP, Stefansson H, Fossdal R, Kristjansson K, Gislason HG, Stefansson T, Leifsson BG, Thorsteinsdottir U, Lamb JR, Gulcher JR, Reitman ML, Kong A, Schadt EE, Stefansson K (2008) Genetics of gene expression and its effect on disease. Nature 452:423-428.

13. Hernandez DG, Nalls MA, Moore M, Chong S, Dillman A, Trabzuni D, Gibbs JR, Ryten M, Arepalli S, Weale ME, Zonderman AB, Troncoso J, O'Brien R, Walker R, Smith C, Bandinelli S, Traynor BJ, Hardy J, Singleton AB, Cookson MR (2012) Integration of GWAS SNPs and tissue specific expression profiling reveal discrete eQTLs for human traits in blood and brain. Neurobiol Dis 47:20-28.

14. Zhang L, Li H, Hu X, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, Li X, Wu H, Benevides KN, Le T, Smerin S, Russell DW, Ursano RJ (2015) Mitochondria-focused gene expression profile reveals common pathways and CPT1B dysregulation in both rodent stress model and human subjects with PTSD. Transl Psychiatry 5:e580.

15. Glatt SJ, Everall IP, Kremen WS, Corbeil J, Sásik R, Khanlou N, Han M, Liew CC, Tsuang MT (2005) Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. Proc Natl Acad Sci U S A 102:15533-15538.

16. Schmidt U, Herrmann L, Hagl K, Novak B, Huber C, Holsboer F, Wotjak CT, Buell DR (2013) Therapeutic action of fluoxetine is associated with a reduction in prefrontal cortical miR-1971 expression levels in a mouse model of posttraumatic stress disorder. Front Psychiatry 4:66.

17. Gros DF, Price M, Magruder KM, Frueh BC (2012) Symptom overlap in posttraumatic stress disorder and major depression. Psychiatry Res 196:267-270.

18. Keers R, Uher R (2012) Gene-environment interaction in major depression and antidepressant treatment response. Curr Psychiatry Rep 14:129-137.

19. Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M (2007) Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. Br J Psychiatry 191:387-392.

20. Schmidt U, Kaltwasser SF, Wotjak CT (2013) Biomarkers in posttraumatic stress disorder: overview and implications for future research. Dis Markers 35:43-54.

21. Inslicht SS, Otte C, McCaslin SE, Apfel BA, Henn-Haase C, Metzler T, Yehuda R, Neylan TC, Marmar CR (2011) Cortisol awakening response prospectively predicts peritraumatic and acute stress reactions in police officers. Biol Psychiatry 70: 1055-1062.

22. Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr (1995) Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Arch Gen Psychiatry 52:583-593.

23. Baker DG, Ekhator NN, Kasckow JW, Dashevsky B, Horn PS, Bednarik L, Geracioti TD Jr (2005) Higher levels of basal serial CSF cortisol in combat veterans with posttraumatic stress disorder. Am J Psychiatry 162:992-994.

24. Matić G, Milutinović DV, Nestorov J, Elaković I, Jovanović SM, Perišić T, Đunđerski J, Damjanović S, Knežević G, Špirić Ž, Vermetten E, Savić D (2013) Lymphocyte glucocorticoid receptor expression level and hormone-binding properties differ between war trauma-exposed men with and without PTSD. Prog Neuropsychopharmacol Biol Psychiatry 43:238-245.

25. Yehuda R, Golier JA, Yang RK, Tischler L (2004) Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. Biol Psychiatry 55:1110-1116.

26. Yehuda R, Cai G, Golier JA, Sarapas C, Galea S, Ising M, Rein T, Schmeidler J, Müller-Myhsok B, Holsboer F, Buxbaum JD (2009) Gene expression patterns associated with posttraumatic stress disorder following exposure to the World Trade Center attacks. Biol Psychiatry 66:708-711.

27. Michopoulos V, Norrholm SD, Jovanovic T (2015) Diagnostic biomarkers for posttraumatic stress disorder: promising horizons from translational neuroscience research. Biol Psychiatry 78:344-353.

28. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ (2008) Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA 299: 1291-1305.

29. Mehta D, Gonik M, Klengel T, Rex-Haffner M, Menke A, Rubel J, Mercer KB, Pütz B, Bradley B, Holsboer F, Ressler KJ, Müller-Myhsok B, Binder EB (2011) Using polymorphisms in FKBP5 to define biologically distinct subtypes of posttraumatic stress disorder: evidence from endocrine and gene expression studies. Arch Gen Psychiatry 68:901-910.

30. Neumann ID, Landgraf R (2012) Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci 35:649-659.

31. Olff M (2012) Bonding after trauma: on the role of social support and the oxytocin system in traumatic stress. Eur J Psychotraumatol 3. doi: 10.3402/ejpt.v3i0.18597.

32. Nishi D, Hashimoto K, Noguchi H, Kim Y, Matsuoka Y (2015) Serum oxytocin, posttraumatic coping and C-reactive protein in motor vehicle accident survivors by gender. Neuropsychobiology 71:196-201.

33. Frijling JL, van Zuiden M, Nawijn L, Koch SB, Neumann ID, Veltman DJ, Olff M (2015) Salivary oxytocin and vasopressin levels in police officers with and without post-traumatic stress disorder. J Neuroendocrinol (in press).

34. Tilg H, Moschen AR (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 6:772-783.

35. Han SH, Quon MJ, Kim JA, Koh KK (2007) Adiponectin and cardiovascular disease: response to therapeutic interventions. J Am Coll Cardiol 49:531-538.

36. Kougias P, Chai H, Lin PH, Yao Q, Lumsden AB, Chen C (2005) Effects of adipocyte-derived cytokines on endothelial functions: implication of vascular disease. J Surg Res 126:121-129.

37. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA (2001) The hormone resistin links obesity to diabetes. Nature 409:307-312.

38. Lehto SM, Elomaa AP, Niskanen L, Herzig KH, Tolmunen T, Viinamäki H, Koivumaa-Honkanen H, Huotari A, Honkalampi K, Valkonen-Korhonen M, Sinikallio S, Ruotsalainen H, Hintikka J (2012) Serum adipokine levels in adults with a history of childhood maltreatment. Prog Neuropsychopharmacol Biol Psychiatry 37:217-221.

39. Hartmann M, Heumann R, Lessmann V (2001) Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. EMBO J 20:5887-5897.

40. Czéh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? Eur Arch Psychiatry Clin Neurosci 257:250-260.

41. Dell'Osso L, Carmassi C, Del Debbio A, Catena Dell'Osso M, Bianchi C, da Pozzo E, Origlia N, Domenici L, Massimetti G, Marazziti D, Piccinni A (2009) Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 33:899-902.

42. Duman RS (2002) Synaptic plasticity and mood disorders. Mol Psychiatry 7 Suppl 1:S29-S34.

43. Matsuoka Y, Nishi D, Noguchi H, Kim Y, Hashimoto K (2013) Longitudinal changes in serum brain-derived neurotrophic factor in accident survivors with posttraumatic stress disorder. Neuropsychobiology 68:44-50.

44. Rasmusson AM, Shi L, Duman R (2002) Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock. Neuropsychopharmacology 27:133-142.

45. Matsuoka Y, Nishi D, Tanima Y, Itakura M, Kojima M, Hamazaki K, Noguchi H, Hamazaki T (2015) Serum pro-BDNF/BDNF as a treatment biomarker for response to docosahexaenoic acid in traumatized people vulnerable to developing psychological distress: a randomized controlled trial. Transl Psychiatry 5:e596.

46. Andero R, Ressler KJ (2012) Fear extinction and BDNF: translating animal models of PTSD to the clinic. Genes Brain Behav 11:503-512.

47. Lyoo IK, Kim JE, Yoon SJ, Hwang J, Bae S, Kim DJ (2011) The neurobiological role of the dorsolateral prefrontal cortex in recovery from trauma. Longitudinal brain imaging study among survivors of the South Korean subway disaster. Arch Gen Psychiatry 68:701-713.

48. Southwick SM, Bremner JD, Rasmusson A, Morgan CA 3rd, Arnsten A, Charney DS (1999) Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol Psychiatry 46:1192-1204.

49. Glover DA, Powers MB, Bergman L, Smits JA, Telch MJ, Stuber M (2003) Urinary dopamine and turn bias in traumatized women with and without PTSD symptoms. Behav Brain Res 144:137-141.

50. Hamner MB, Diamond BI (1993) Elevated plasma dopamine in posttraumatic stress disorder: a preliminary report. Biol Psychiatry 33:304-306.

51. Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS (1993) Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry 50:266-274.

52. Otte C, Neylan TC, Pole N, Metzler T, Best S, Henn-Haase C, Yehuda R, Marmar CR (2005) Association between childhood trauma and catecholamine response to psychological stress in police academy recruits. Biol Psychiatry 57:27-32.

53. Delahanty DL, Nugent NR, Christopher NC, Walsh M (2005) Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. Psychoneuroendocrinology 30:121-128.

54. Pietrzak RH, Sumner JA, Aiello AE, Uddin M, Neumeister A, Guffanti G, Koenen KC (2015) Association of the rs2242446 polymorphism in the norepinephrine transporter gene SLC6A2 and anxious arousal symptoms of posttraumatic stress disorder. J Clin Psychiatry 76:e537-e538.

55. Mustapić M, Pivac N, Kozarić-Kovacić D, Dezeljin M, Cubells JF, Mück-Seler D (2007) Dopamine beta-hydroxylase (DBH) activity and -1021C/T polymorphism of DBH gene in combat-related post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet 144B:1087-1089.

56. Tang YL, Li W, Mercer K, Bradley B, Gillespie CF, Bonsall R, Ressler KJ, Cubells JF (2010) Genotype-controlled analysis of serum dopamine beta-hydroxylase activity in civilian post-traumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 34:1396-1401.

57. Pivac N, Knezevic J, Kozaric-Kovacic D, Dezeljin M, Mustapic M, Rak D, Matijevic T, Pavelic J, Muck-Seler D (2007) Monoamine oxidase (MAO) intron 13 polymorphism and platelet MAO-B activity in combat-related posttraumatic stress disorder. J Affect Disord 103:131-138.

58. Pivac N, Kozaric-Kovacic D, Mustapic M, Dezeljin M, Borovecki A, Grubisic-Ilic M, Muck-Seler D (2006) Platelet serotonin in combat related posttraumatic stress disorder with psychotic symptoms. J Affect Disord 93:223-227.

59. Kovacic Z, Henigsberg N, Pivac N, Nedic G, Borovecki A (2008) Platelet serotonin concentration and suicidal behavior in combat related posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 32:544-551.

60. Kimbrel NA, Morissette SB, Meyer EC, Chrestman R, Jamroz R, Silvia PJ, Beckham JC, Young KA (2015) Effect of the 5-HTTLPR polymorphism on posttraumatic stress disorder, depression, anxiety, and quality of life among Iraq and Afghanistan veterans. Anxiety Stress Coping 28:456-466.

61. Telch MJ, Beevers CG, Rosenfield D, Lee HJ, Reijntjes A, Ferrell RE, Hariri AR (2015) 5-HTTLPR genotype potentiates the effects of war zone stressors on the emergence of PTSD, depressive and anxiety symptoms in soldiers deployed to Iraq. World Psychiatry 14:198-206.

62. Tian Y, Liu H, Guse L, Wong TK, Li J, Bai Y, Jiang X (2015) Association of genetic factors and gene-environment interactions with risk of developing posttraumatic stress disorder in a case-control study. Biol Res Nurs 17:364-372.

63. Sah R, Ekhator NN, Strawn JR, Sallee FR, Baker DG, Horn PS, Geracioti TD Jr (2009) Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder. Biol Psychiatry 66:705-707.

64. Nishi D, Hashimoto K, Noguchi H, Matsuoka Y (2014) Serum neuropeptide Y in accident survivors with depression or posttraumatic stress disorder. Neurosci Res 83:8-12.

65. Baker DG, Nievergelt CM, O'Connor DT (2012) Biomarkers of PTSD: neuropeptides and immune signaling. Neuropharmacology 62:663-673.

66. Yehuda R (2002) Post-traumatic stress disorder. N Engl J Med 346:108-114.

67. Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, O'Connor DT, Baker DG; Marine Resiliency Study Team (2014) Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA Psychiatry 71:423-431.

68. Raison CL, Capuron L, Miller AH (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27:24-31.

69. Weiss T, Skelton K, Phifer J, Jovanovic T, Gillespie CF, Smith A, Umpierrez G, Bradley B, Ressler KJ (2011) Posttraumatic stress disorder is a risk factor for metabolic syndrome in an impoverished urban population. Gen Hosp Psychiatry 33: 135-142.

70. Plantinga L, Bremner JD, Miller AH, Jones DP, Veledar E, Goldberg J, Vaccarino V (2013) Association between posttraumatic stress disorder and inflammation: a twin study. Brain Behav Immun 30:125-132.

71. von Känel R, Abbas CC, Begré S, Saner H, Gander ML, Schmid JP (2010) Posttraumatic stress disorder and soluble cellular adhesion molecules at rest and in response to a trauma-specific interview in patients after myocardial infarction. Psychiatry Res 179:312-317.

72. Bücker J, Fries GR, Kapczinski F, Post RM, Yatham LN, Vianna P, Bogo Chies JA, Gama CS, Magalhães PV, Aguiar BW, Pfaffenseller B, Kauer-Sant'Anna M (2015) Brain-

derived neurotrophic factor and inflammatory markers in school-aged children with early trauma. Acta Psychiatr Scand 131:360-368.

73. Zhang L, Su TP, Choi K, Maree W, Li CT, Chung MY, Chen YS, Bai YM, Chou YH, Barker JL, Barrett JE, Li XX, Li H, Benedek DM, Ursano R (2011) P11 (S100A10) as a potential biomarker of psychiatric patients at risk of suicide. J Psychiatr Res 45:435-441.

74. Su TP, Zhang L, Chung MY, Chen YS, Bi YM, Chou YH, Barker JL, Barrett JE, Maric D, Li XX, Li H, Webster MJ, Benedek D, Carlton JR, Ursano R (2009) Levels of the potential biomarker p11 in peripheral blood cells distinguish patients with PTSD from those with other major psychiatric disorders. J Psychiatr Res 43:1078-1085.

75. McFarlane AC, Barton CA, Yehuda R, Wittert G (2011) Cortisol response to acute trauma and risk of posttraumatic stress disorder. Psychoneuroendocrinology 36:720-727.

76. van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Heijnen CJ, Kavelaars A (2011) Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. Am J Psychiatry 168:89-96.

77. van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Amarouchi K, Kavelaars A, Heijnen CJ (2012) Glucocorticoid receptor pathway components predict posttraumatic stress disorder symptom development: a prospective study. Biol Psychiatry 71:309-316.

78. Bryant RA, Felmingham KL, Silove D, Creamer M, O'Donnell M, McFarlane AC (2011) The association between menstrual cycle and traumatic memories. J Affect Disord 131:398-401.

79. Glover EM, Mercer KB, Norrholm SD, Davis M, Duncan E, Bradley B, Ressler KJ, Jovanovic T (2013) Inhibition of fear is differentially associated with cycling estrogen levels in women. J Psychiatry Neurosci 38:341-348.

80. Michopoulos V, Rothbaum AO, Corwin E, Bradley B, Ressler KJ, Jovanovic T (2015) Psychophysiology and posttraumatic stress disorder symptom profile in pregnant African-American women with trauma exposure. Arch Women Ment Health 18:639-648.

81. Glover EM, Jovanovic T, Mercer KB, Kerley K, Bradley B, Ressler KJ, Norrholm SD (2012) Estrogen levels are associated with extinction deficits in women with posttraumatic stress disorder. Biol Psychiatry 72:19-24.

82. Reijnen A, Geuze E, Vermetten E (2015) The effect of deployment to a combat zone on testosterone levels and the association with the development of posttraumatic stress symptoms: a longitudinal prospective Dutch military cohort study. Psychoneuroendocrinology 51:525-533.

83. Amstadter AB, Nugent NR, Yang BZ, Miller A, Siburian R, Moorjani P, Haddad S, Basu A, Fagerness J, Saxe G, Smoller JW, Koenen KC (2011) Corticotrophin-releasing hormone type 1 receptor gene (CRHR1) variants predict posttraumatic stress disorder onset and course in pediatric injury patients. Dis Markers 30:89-99.

84. Wolf EJ, Mitchell KS, Logue MW, Baldwin CT, Reardon AF, Humphries DE, Miller MW (2013) Corticotropin releasing hormone receptor 2 (CRHR-2) gene is associated with decreased risk and severity of posttraumatic stress disorder in women. Depress Anxiety 30:1161-1169.

85. Kilpatrick DG, Koenen KC, Ruggiero KJ, Acierno R, Galea S, Resnick HS, Roitzsch J, Boyle J, Gelernter J (2007) The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. Am J Psychiatry 164:1693-1699.

86. Clark R, DeYoung CG, Sponheim SR, Bender TL, Polusny MA, Erbes CR, Arbisi PA (2013) Predicting post-traumatic stress disorder in veterans: interaction of traumatic load with COMT gene variation. J Psychiatr Res 47:1849-1856.

87. Wu G, Feder A, Cohen H, Kim JJ, Calderon S, Charney DS, Mathé AA (2013) Understanding resilience. Front Behav Neurosci 7:10.

88. Zhang L, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, Li XX, Hu XZ, Li H, Jia M, Xing GQ, Benevides KN, Ursano RJ (2014) PTSD risk is associated with BDNF Val66Met and BDNF overexpression. Mol Psychiatry 19:8-10.

89. Feder A, Nestler EJ, Charney DS (2009) Psychobiology and molecular genetics of resilience. Nat Rev Neurosci 10:446-457.

90. Yehuda R, Flory JD (2007) Differentiating biological correlates of risk, PTSD, and resilience following trauma exposure. J Trauma Stress 20:435-447.

91. Berger W, Mehra A, Lenoci M, Metzler TJ, Otte C, Tarasovsky G, Mellon SH, Wolkowitz OM, Marmar CR, Neylan TC (2010) Serum brain-derived neurotrophic factor predicts responses to escitalopram in chronic posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 34:1279-1284.

92. Morgan CA 3rd, Rasmusson AM, Wang S, Hoyt G, Hauger RL, Hazlett G (2002) Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. Biol Psychiatry 52:136-142.

93. Morgan CA 3rd, Wang S, Southwick SM, Rasmusson A, Hazlett G, Hauger RL, Charney DS (2000) Plasma neuropeptide-Y concentrations in humans exposed to military survival training. Biol Psychiatry 47:902-909.

94. Yehuda R, Brand S, Yang RK (2006) Plasma neuropeptide Y concentrations in combat exposed veterans: relationship to trauma exposure, recovery from PTSD, and coping. Biol Psychiatry 59:660-663.

95. Miller MW, Sadeh N (2014) Traumatic stress, oxidative stress and post-traumatic stress disorder: neurodegeneration and the accelerated-aging hypothesis. Mol Psychiatry 19:1156-1162.