Review

Biological Psychiatry

Diagnostic Biomarkers for Posttraumatic Stress Disorder: Promising Horizons from Translational Neuroscience Research

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a heterogeneous disorder that affects individuals exposed to trauma (e.g., combat, interpersonal violence, and natural disasters). Although its diagnostic features have been recently reclassified with the emergence of the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition, the disorder remains characterized by hyperarousal, intrusive reminders of the trauma, avoidance of trauma-related cues, and negative cognition and mood. This heterogeneity indicates the presence of multiple neurobiological mechanisms underlying the etiology and maintenance of PTSD. Translational research spanning the past few decades has revealed several potential avenues for the identification of diagnostic biomarkers for PTSD. These include, but are not limited to, monoaminergic transmitter systems, the hypothalamic-pituitary-adrenal axis, metabolic hormonal pathways, inflammatory mechanisms, psychophysiological reactivity, and neural circuits. The current review provides an update to the literature with regard to the most promising putative PTSD biomarkers, with specific emphasis on the interaction between neurobiological influences on disease risk and symptom progression. Such biomarkers will most likely be identified by multi-dimensional models derived from comprehensive descriptions of molecular, neurobiological, behavioral, and clinical phenotypes.

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Posttraumatic stress disorder (PTSD) is a severe psychiatric disorder that occurs after a psychological traumatic life event and increases individual vulnerability to adverse health outcomes (1). PTSD is heterogeneous, often presenting across different symptom domains, including re-experiencing, avoidance/numbing, and hyperarousal symptoms (2). While extensive work has successfully identified psychological, genomic, and biological risk factors that are associated with PTSD in trauma survivors (3–5), the identification of discrete diagnostic biomarkers for PTSD remains elusive. The lack of diagnostic biomarkers for PTSD is not due to a lack of intensive study but rather likely due to the complexity of PTSD and the complex set of rules by which we classify individuals according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as illustrated by the recent description of 636,120 different ways in which an individual can be diagnosed with PTSD (6). Furthermore, PTSD is associated with significant mental health (e.g., major depression, substance and alcohol abuse, panic disorder, suicide) and general medical (e.g., diabetes, cardiovascular disease) comorbidities (7,8), which can obscure the search for diagnostic biomarkers for PTSD. Given that DSM-5 criteria are not based on the underlying biology, PTSD research could benefit significantly from the new approach to mental health diagnoses using the Research Domain Criteria (RDoC) (9). One of the tenets of this approach is dimensional analyses of neurobiological metrics and symptoms, rather than diagnostic classification. The putative biomarkers listed in this review are reflective of the extant literature but can also serve RDoC objectives in future studies by linking PTSD symptoms to relevant biological underpinnings.

The vast heterogeneity inherent in PTSD symptom presentation makes it highly unlikely that a valid, singular biomarker will be identified for PTSD (10,11). However, comprehensive biological phenotyping of the factors associated with PTSD may yield a parsimonious diagnostic model with which to diagnose PTSD in the future. The current review will highlight several biomarkers associated with PTSD symptomatology and vulnerability, in addition to underscoring how individual factors, such as one's comorbid diagnoses and gender, must be considered, as they can profoundly influence biology and thus influence our search for true biomarkers of PTSD. Specifically, we will emphasize monoamine, neuroendocrine, inflammatory, genetic, epigenetic, psychophysiological, neuroanatomical, and neuroactivational phenotypes associated with PTSD to illustrate the potential efficacy of using multidimensional phenotypic data to characterize unique profiles of PTSD.

MONOAMINE SYSTEMS IN PTSD

PTSD is characterized by increased sympathetic nervous system tone that is coincident with augmented levels of catecholamine secretion (12). Urinary and central levels of norepinephrine (NE) are heightened in individuals with PTSD (13) and in child trauma victims (14), and peripheral and central

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levels of NE in response to threatening stimuli are also elevated in PTSD (15,16). Recent evidence suggests that this increase in NE in PTSD is due to attenuated levels of the NE transporter within the brainstem locus coeruleus (17). PTSD has also been associated with decreased expression of peripheral α2-adrenergic receptors, receptors that underlie an autoreceptor-driven mechanism that serves to inhibit synaptic transmitter release (18). Further, facilitation of NE release via blockade of presynaptic α2-adrenergic receptors with the antagonist yohimbine can produce panic attacks and an increase in anxiety- and trauma-related symptoms in individuals with PTSD (19,20). A prospective study of motor vehicle accident survivors indicated that urinary levels of NE were associated with increased development of PTSD 1 month following trauma but only in men (21), indicating that gender may be important for characterizing catecholaminergic biomarkers of PTSD. Increased catecholamines, however, are also coincident with panic attacks and other fear-related psychopathology (22), indicating that increased sympathetic activation is not a specific biomarker of PTSD but rather of a common neurobiological feature of fear- and anxiety-related disorders.

Alterations in the serotonergic system have also been implicated in the pathophysiology of PTSD. Individuals with PTSD show decreased levels of paroxetine binding, suggesting that levels of the serotonin transporter are attenuated in PTSD (23) and involved in the manifestation of arousal and avoidance symptoms (24). Empirical evidence has shown that serotonin transporter expression within the amygdala is attenuated in PTSD and is significantly associated with higher anxiety and depressive symptoms (25). Brainstem and forebrain levels of the serotonin 1A receptor are higher in individuals with PTSD (26), similar to what has been described in depression (27). Likewise, reductions in central serotonin 1B receptors in trauma-exposed individuals are associated with increased PTSD and depression symptoms (25). Taken together, these data indicate that alterations within the serotonergic system could reveal putative biomarkers for depressive symptoms common to both PTSD and major depression (26). The effectiveness of selective serotonin reuptake inhibitors (e.g., sertraline) for reducing the symptoms of PTSD (28–30), major depression, and other psychiatric conditions with which PTSD is highly comorbid (2,22) further suggests that more careful examination of serotonergic phenotypes is warranted to better disentangle the specificity of biomarkers for PTSD- and depression-specific phenotypes.

One way in which to elucidate the specificity of monoaminergic biomarkers on PTSD symptomology is to concurrently characterize sympathetic and serotonergic function within the same individuals. Using a repeated-measures design, Southwick *et al.* (20) found that both yohimbine and meta-chlorophenylpiperazine treatment increased panic attacks, anxiety, and trauma-related symptoms in veterans diagnosed with PTSD in a manner that suggested at least two different biological subtypes of PTSD, thus underscoring the need for more robust phenotyping of biological factors including the monoaminergic transmitter systems.

NEUROENDOCRINE BIOMARKERS OF PTSD

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is present in PTSD and has been extensively characterized (Figure 1) [for review see (31)]. Evidence suggests that individuals with PTSD have attenuated levels of basal cortisol (31) and that a low level of cortisol in trauma survivors is associated with increased risk for subsequent development of PTSD (32,33). However, findings on baseline cortisol levels have been mixed, and a recent meta-analysis concluded that there are no consistent differences between PTSD and control subjects (34). Similarly, equivocal results exist surrounding the cortisol response to acute cognitive stressors, as reports show heightened or no differences in cortisol response to a stressor (35,36). In part, these discordant HPA results appear to be due to different sampling methods, the diurnal rhythm of cortisol release, and confounding analyses that have disregarded the influence of sex on HPA activity (37).

Rather than focus on baseline cortisol, a more promising approach is to measure cortisol reactivity to a challenge. Blunted cortisol reactivity to acute stress exposure is associated with increased prospective risk for PTSD (38). Low cortisol levels in PTSD have been coupled to enhanced glucocorticoid negative feedback inhibition of the HPA axis as evidenced by increased suppression of cortisol levels following a dexamethasone suppression test (39). This enhanced HPA negative feedback in PTSD is coincident with 1) augmented levels of peripheral and central corticotropin-releasing hormone (40,41); 2) elevated glucocorticoid receptor (GR) levels (42); 3) increased glucocorticoid sensitivity (43); and 4) decreased levels of FKBP5 (44), a co-chaperone of GR that inhibits ligand binding and nuclear translocation of GRs. A recent prospective study indicates that augmented baseline GR levels and diminished FKBP5 messenger RNA levels are associated with increased risk for PTSD symptoms following trauma (45).

While extensive work has alluded to HPA-based biomarkers of PTSD, it is clear that additional neuroendocrine factors influence PTSD vulnerability and symptomology (Figure 1; Table 1). For example, menstrual cycle phase (46,47) and pregnancy (48) influence PTSD symptom expression profile and psychophysiology in women, suggesting that ovarian steroid hormones are important modulators of PTSD susceptibility and symptom presentation. Indeed, low levels of estradiol are associated with impaired fear extinction in PTSD (49), and high levels of pituitary adenylate cyclase-activating polypeptide, a peptide implicated in stress-related behavior and physiology (50–52), are associated with PTSD only in women (53). Furthermore, central levels of the anxiolytic neuroactive steroid allopregnanolone, a potent modulator of gamma-aminobutyric acidergic inhibition, are decreased in women with PTSD (54). Low levels of testosterone in men, on the other hand, have prospectively been associated with increased rates of PTSD (55) and increased risk for PTSD (56). These data, along with epidemiologic studies strongly suggesting that female sex is a risk factor for psychopathology (including PTSD) (57) and reinforce the need to better understand the influence of gonadal steroid hormones in men and women with PTSD.

An additional avenue of exploration with regard to PTSD and putative biomarkers is the expression and regulation of metabolic hormones in individuals with PTSD. Neuropeptide Y (NPY) is an orexigenic peptide neurotransmitter (58) that also shows anxiolytic properties via antagonism of corticotropin-releasing hormone and noradrenergic systems (59). Trauma