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Review

Metabolic dysfunctions in people with post-traumatic stress disorder

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SUMMARY

Objectives

The association between post-traumatic stress disorder (PTSD) and metabolic dysfunctions has attracted growing attention in recent years. Understanding and identifying common inflammatory and neuroendocrine mechanisms can help clinicians to improve the treatment and prognosis of these co-occurring conditions.

Methods

We conducted an overview, summarizing biological mechanisms and related biomarkers underlying the relationship between PTSD and metabolic dysfunctions

Results

Evidence suggests that PTSD may be associated with metabolic abnormalities. Metabolic syndrome in PTSD may impact both cardiovascular health and central nervous system functions. The role of traumatic events in influencing inflammatory and immuno-metabolic systems seems supported by available studies. Exposure to trauma may determine neuroendocrine responses and long-lasting changes in the regulation of the hypothalamic-pituitary-adrenal axis, affecting its physiological activity

Conclusions

Dysfunctional adaptation to stress may increase the vulnerability to metabolic abnormalities which, in turn, may favor the occurrence of psychopathological features after traumatic experiences. Approaching PTSD as a systemic condition by assessing, monitoring, and treating metabolic variations may lead to a significant improvement in its management and prognosis. Further research is needed to test novel treatments for PTSD, targeting neuroendocrine and immune-metabolic systems.

Key words: PTSD, metabolic, trauma, neuroendocrinology, inflammation, biomarkers

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Introduction

Posttraumatic stress disorder (PTSD) is a mental health condition related to the exposure to traumatic events and characterized by different post-traumatic symptom clusters, including intrusion symptoms, avoidance of trauma-related stimuli, negative changes in cognitions and mood, alterations in arousal and reactivity [1]. These symptoms are associated with significant distress and functional impairment. Data from 36,309 adults in the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions-III, showed past-year and lifetime prevalence rates of 4.7 and 6.1%, respectively, with higher rates among females and younger subjects [2]. A comprehensive epidemiological study based on participants from the Environmental Risk Longitudinal Twin Study, a population-representative cohort of 2232 children born in England and Wales in 1994-95, found that about one third of participants reported trauma exposure and 7.8% experienced PTSD by the age of 18 years [3]. Recently, there has been consid-

erable attention on the relationship between metabolic dysfunctions and mental disorders [4], including PTSD that may represent a risk condition in terms of metabolic and cardiovascular health [5 6]. Subjects with a history of trauma have higher risk of heart failure, angina pectoris, and stroke [7]. Meta-analytic data pointed that PTSD was independently associated with increased risk for incident coronary heart diseases, recurrent cardiac events, and mortality [8,9]. An increasing body of literature actually suggests that the effects of traumatic stress equally impact on both physical and psychological health and should be considered a major clinical challenge given this dual perspective [10]. Metabolic changes observed in PTSD, such as hypertension, dyslipidemia, and obesity, may be the expression of an individual pattern of increasing sensitivity to environmental load [10], with this complex phenotype emerging from interactions among genetic, environmental, and biological factors [11]. Along with healthy risk behaviors, underlying biological mechanisms linking traumatic experiences and PTSD to metabolic abnormalities have been proposed, possibly including an increased autonomic nervous system activity, dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis system, and a systemic low-grade inflammatory state [11-13]. In this overview, we summarize epidemiological data on the association between metabolic disorders and PTSD, analyzing the potential biological vulnerability underlying this relationship.

PTSD and metabolic disorders

Although a large body of literature is available on the increased vulnerability to metabolic abnormalities in various mental disorders [4 14-17], there are fewer studies exploring this issue in PTSD. Metabolic syndrome is characterized by a cluster of metabolic abnormalities and cardiovascular risk factors. It is defined by the occurrence of at least three out of five conditions, including waist circumference ≥ 102 cm in men and ≥ 88 cm in women (with cut-offs varying according to geographical area and population), fasting serum glucose ≥ 100 mg/dl, serum triglycerides ≥ 150 mg/dl, high density lipoprotein (HDL) cholesterol level < 40 mg/dl in men and < 50 mg/dl in women, and blood pressure ≥130/85 mmHg [18]. A body mass index > 28.8 can be used as a substitutive criterion when information on abdominal circumference is not available [19,20]. Metabolic syndrome has attracted increasing attention in PTSD, even if most of studies have been conducted on war veterans [21-23], with less data available from community samples. Findings from meta-analytic studies, estimated significant associations of PTSD with both metabolic syndrome and obesity [24,25]. The prevalence of metabolic syndrome is estimated between 32.1 and 45.6%, with high rates also considering relevant subcomponents, i.e., abdominal obesity (29.7 to 69.0%), hyperglycemia (18.8 to 55.6%), hypertriglyceridemia (12.2 to 81.9%), low high density-lipoprotein-cholesterol (26.4 to 67.0%), and hypertension (67.9 to 84.8%) [26]. Prospective data analyzing the longitudinal association between PTSD symptoms and metabolic syndrome are also available. In 1,355 male and female U.S. Army or Marine Corps veterans, military deployed to the wars in Iraq and/or Afghanistan, cross-lagged panel models estimated that PTSD severity predicted subsequent increases in metabolic syndrome severity, whilst metabolic syndrome did not predict subsequent PTSD symptoms [27]. Metabolic syndrome in PTSD may impact also central nervous system (CNS). A neuroimaging study, based on 274 US military veterans, estimated that PTSD predicted metabolic syndrome which, in turn, was associated with reduced cortical thickness [28]. In particular, the authors found an association between metabolic syndrome and cortical thickness in: (a) bilateral temporal lobe, including temporal pole, fusiform gyrus, and insula, and extending into occipital cortex (left hemisphere) and orbitofrontal cortex (right hemisphere); (b) bilateral precuneus, posterior cingulate, calcarine, and occipital-parietal cortex; and (c) right rostral anterior cingulate cortex and central sulcus/postcentral gyrus. In addition, data from 204 male veterans aged 55-89 showed that veterans with metabolic syndrome may have poorer performance on tasks of executive function and immediate verbal memory regardless of PTSD status [29].

High rates of metabolic dysfunctions in PTSD increased the interest on possible mechanisms underlying this relationship that seems determined by three possible interconnections. First, lifestyle and health risk behaviors or specific treatments for PTSD may explain metabolic dysfunctions observed in PTSD. Several health risk behaviors, including poor diet, sedentary lifestyle, and smoking, may contribute to the increased risk of cardiovascular and metabolic disorders [30]. On the other hand, physical exercise seems to improve, along with individual metabolic health, also PTSD symptoms [31]. In addition, possible metabolic effects of treatments should be taken into account. Antidepressants are effective in PTSD [32], but they may be associated with weight gain [33]. Moreover, the off-label use of antipsychotics in PTSD does not seem rare [34,35] and antipsychotic-induced metabolic side effects [36,37] may at least partly explain the greater likelihood of weight gain, hyperglycemia, and dyslipidemia in PTSD. Nevertheless, Weiss et al. [38] highlighted that the association between current PTSD and metabolic syndrome seems independent to the use of antipsychotic drugs. It should be noted that stressful life events themselves may represent indicators of poor metabolic health, being associated with insulin resistance, obesity, and dyslipidemia [39]. It seems plausible to

hypothesizing a role of biological vulnerability to stress that may determine both the likelihood of developing PTSD and metabolic dysfunctions after the exposure to traumatic experiences. Metabolic syndrome might thus represents the consequence of individual neuroendocrinal adaptations to chronic stress [40].

Biological and neuroendocrine mechanisms underlying metabolic dysfunctions in PTSD

Available clinical and translational data seem to support the notion that PTSD itself is a metabolic disorder and suggest that dysfunctions of the inflammatory responses may be the common underlying mechanism [41]. Abnormalities involving neuroendocrine and inflammatory systems in PTSD seem similar to those occurring in metabolic disorders, such as metabolic syndrome, obesity, and diabetes [41]. In particular, increasing evidence has supported the hypothesis that traumatic events may be associated with a pattern of immune activation and inflammatory markers that may explain immunometabolic abnormalities in subjects with PTSD [11-13]. A relatively recent systematic review and meta-analysis [42] highlighted that several inflammatory cytokines are increased in subjects with PTSD. In particular, data showed that interleukin (IL) 6 (standardized mean difference [SMD]: 0.88), IL-1β (SMD: 1.42), and interferon γ (SMD: 0.49) levels in individuals with PTSD were higher than in healthy controls. In addition, subgroup analyses based on subjects who were not receiving any treatment, estimated higher tumor necrosis factor α (TNF-α) levels (SMD: 0.69) in PTSD subjects. Cytokines levels in PTSD were increased also after excluding individuals with co-occurring major depressive disorder. This is worth of mention considering that subjects with co-occurring PTSD and major depressive disorders, are generally considered at higher risk of metabolic disorders [43]. Consistently, the possible role of chronic low-grade inflammation as a potential target of PTSD treatment or biomarker of stress-related disorders, has been analyzed. In a large prospective study on war zone-deployed US Marines [44], the authors found that baseline plasma C-Reactive Protein (CRP) levels were significant predictors of post-deployment PTSD-related symptoms scores, after adjusting for relevant covariates. In particular, each 10-fold increment in CRP concentration was associated with an OR of 1.51 of any PTSD symptoms. Interestingly, the relationship between traumatic experiences and inflammatory biomarkers seems transdiagnostic. A previous meta-analysis [45], including 36 independent samples and based on 14,991 participants, showed that trauma exposure was positively associated with CRP, IL-1β, IL-6, and TNF-α, whereas no association was found for fibrinogen, IL-2, IL-4, IL-8, or IL-10. Meta-regression analyses estimated that psychiatric symptoms were significant predictors of increased effect sizes for IL-1β and IL-6, and positive correlations between inflammation and trauma exposure across different mental disorders were found. These results confirmed the hypothesis that chronic inflammation might represent one of possible mechanisms underlying the risk of health problems [46] also in trauma survivors. Exposure to trauma seems to determine neuroendocrine responses and long-lasting changes in the regulation of the HPA axis compromising its physiological activity [47]. In particular, abnormal functions in the sympathetic-adrenergic nervous system influencing the release of hormones via the endocrine HPA axis, may play a role in metabolic dysfunctions in subjects with PTSD [48]. Cortisol stimulation may contribute to changes in inflammatory biomarkers such as CRP and may facilitate the development of central obesity and metabolic syndrome [48]. However, mixed support of this hypothesis has been provided by previous research, showing a decrease or no variations of cortisol levels in individuals with PTSD. Pooled data from 37 studies including 828 individuals with PTSD and 800 relevant controls did not show any differences in plasma/serum cortisol levels in PTSD, whereas decreased levels were found in samples including females, as well as in studies testing traumatic experiences related to physical or sexual abuse [49]. In addition, a subsequent systematic review and meta-analysis [50] estimated salivary cortisol levels in PTSD lower than in healthy controls (SMD = -0.28). It has been suggested that these might be a vulnerability marker for PTSD development after trauma exposure [51]. In particular, a hypoactive HPA axis prior to trauma may predispose to PTSD, possibly leading to failure in mobilizing adequate energy resources to cope with stressors induced by traumatic experiences, and in restoring homeostasis after the challenge has subsided [52]. Lower levels of cortisol may lead to an adaptation of the HPA axis to increase sensitivity of glucocorticoid receptors in the pituitary gland [53]. Along with cortisol, despite generally less studied than cortisol, the dehydroepiandrosterone (DHEA) and its sulfate form DHEA-S, secreted by the adrenal cortex, are important factors for clarifying the role of HPA axis dysfunctions in PTSD [54]. While low concentrations of DHEA and DHEA-S can be neuroprotective, high concentrations of DHEA can be ineffective or neurotoxic [55]. A relatively recent systematic review and meta-analysis [56] did not show any significant differences in DHEA or DHEA-S levels between PTSD and control groups, despite DHEA levels in trauma-exposed controls were higher than in controls not exposed to trauma, suggesting that trauma exposure, irrespective of PTSD development, might increase steroid hormones.

Another important issue involves possible variations of appetite regulating hormones in PTSD. Adipokines, such as adiponectin and leptin, have been shown to be important factors in different mental disorders, including psychotic and depressive disorders [57-59]. Adiponectin, also called gelatin-binding protein-28 (GBP28), AdipoQ, adipocyte complement-related protein (ACRP30) or apM1 [60], is one of most abundant plasma adipokine [61] synthesized by adipose tissue. It plays a key role in the homeostasis of glucose and lipid metabolism [62], influencing insulin sensitivity [63] (with anti-inflammatory properties [64]. Consistently, meta-analytic data have shown that higher levels of adiponectin are associated with a lower risk of type 2 diabetes with a dose-response relationship [65] and that adiponectin may be an useful biomarker for metabolic syndrome [66]. In addition, entering the brain through the peripheral circulation and interacting with AdipoR1 and AdipoR2 receptors, adiponectin may influence important CNS functions, including energy homeostasis and synaptic plasticity [67]. Recently, variations of appetite regulation have been found in subjects with PTSD. A study sampling in Korea [68] estimated that, among 507 male firefighters, those with PTSD symptoms had adiponectin plasma levels lower than those without PTSD. In addition, severity of PTSD was inversely correlated with adiponectin levels. Consistently, adiponectin effects on extinction of contextual fear and intrinsic excitability of dentate gyrus granule neurons were found in animal models, suggesting that drugs targeting adiponectin may be used to strength extinction-based exposure therapies for PTSD [69]

Similarly, leptin resistance has been involved in the pathogenesis of metabolic disorders in PTSD. Although in physiological conditions leptin reduces appetite as a circulating signal, inhibiting hypothalamic neuropeptide Y (NPY) and activating the release of α-MSH from proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus [70], resistance to leptin induces increasing levels of leptin, with failure in hunger control and weight modulation [71]. In addition, resistance to leptin may contribute to abnormal hypothalamic and CNS functions, leading to dysfunctional reward signaling and uncontrolled appetite [48]. A previous study [72], analyzing the relationship between post-disaster psychiatric symptoms and serum leptin levels, showed a direct relationship between stress-related symptoms and serum leptin levels. In particular, hyperarousal predicted higher leptin levels, suggesting a role for leptin as a neuroendocrinological marker for the hypervigilant state of PTSD. Moreover, paranoid, anxiety, and depressive symptoms have been all positively associated with leptin levels. Consistently, NPY, a hypothalamic hormone regulating feeding behaviors, has also been linked with PTSD [73]. NPY is abundantly expressed in forebrain limbic and brainstem areas that regulate stress and emotional behaviors [74], lowering the stress-signaling hormones norepinephrine and corticotropin-releasing hormone [75]. Multiple lines of evidence supported the relevance of NPY as a potential 'resilience-to-stress' factor involved in the pathophysiology of PTSD [76]. Levels of NPY in cerebrospinal fluid has been negatively correlated with PTSD symptoms, especially intrusive ones [77]. In particular, it has been hypothesized that suboptimal NPY levels in different brain regions, including amygdala, hippocampus, prefrontal cortex, hypothalamus, and brain stem, may represent the biological substrate of the PTSD clinical features [76]. Individuals with lower levels of NPY expression, or who are less capable of activating the NPY system in response to trauma, would be more vulnerable to PTSD and other trauma-related disorders [76].

Main variations of immune-metabolic profile in subjects with PTSD are summarized in Table I.

Conclusions

PTSD and metabolic disorders are both associated with increased cardiovascular risk, and may have similar underlying biological mechanisms. It is likely that changes of inflammatory and neuroendocrine systems may be involved in PTSD, although the direction of this relationship remains unknown. It seems plausible hypothesize that a dysfunctional individual adaptation to stress may increase the vulnerability to metabolic dysfunctions that, in turn, may favor the occurrence of psychopathological features after traumatic experiences. Approaching PTSD as a systemic condition, involving low-grade inflammation, HPA axis dysfunctions, and metabolic abnormalities, along with important psychological burden, has important implications in terms of treatment, man-

TABLE I. *Main variations of immuno-metabolic profile in PTSD.*

Inflammatory markers	
CRP	↑
IL-1β	↑
IL-6	↑
INF-γ	↑
TNF-α	↑
HPA axis	
Cortisol	↓
NPY	↓
Adipokines	
Adiponectin	↓
Leptin	↑

CRP: C-reactive protein; IL: Interleukin; INF-γ: Interferon-γ; HPA axis: hypothalamic-pituitary-adrenal axis; NPY: Neuropeptide Y; TNF-α: Tumor Necrosis Factor-α.

agement, and prognosis. Clinicians should regularly assess, monitor, and treat metabolic abnormalities in subjects with PTSD. Further research is needed to test novel treatments for PTSD, targeting neuroendocrine and immune-metabolic systems.

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