

Review

Adverse Human Health Outcomes Associated with Psychological Trauma: A review

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Abstract:

Until 30 years ago it was believed that psychological stress increases cortisol secretion, but later studies gave contradictory results. Decrease in cortisol levels in post-traumatic stress disorder (PTSD) reflects a nonnormative and inadequate response to severe stressors, with its pathophysiology involving maladaptation or dysfunction in stress-regulatory systems. To have more insights in response of human body to physiological stress, inflammatory signals, oxidative stress parameters and other health parameters were measured. As for the cortisol level results, also inflammatory signals, including proinflammatory and anti-inflammatory cytokines and C-reactive protein (CRP), have been reported to increase and decrease in PTSD. Levels of interleukin (IL)-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, tumour necrosis factor (TNF)- α , interferon gamma (IFN- γ) and CRP were reported higher and lower in blood samples of individuals with PTSD. Some studies report that dysregulation of the stress axis could have direct effects on brain regions responsible for the regulation of fear and anxiety (such as the prefrontal cortex, insula, amygdala, and hippocampus). Early-life stress, such as childhood adversity (abuse, neglect, or family disfunction), is a potent risk factor for developing PTSD in response to later trauma, and elevated peripheral markers of inflammation are one of the best-replicated findings in children and adults with early-life stress. Those who develop PTSD may have an inability or failure to activate an innate immune response. PTSD can also result in other adverse outcomes, such as heightened oxidative stress (OXS), eating disorders, metabolic disorder, and cardiovascular disease (CVD). Since the results are very contradictory for PTSD and inflammation response of the human body, further research is important. Small cellular particles that can be isolated from body fluids present potential biomarkers of the clinical status and will be considered in planning the future research. This contribution presents perspectives in assessment of psychological stress by objective parameters.

Keywords: Cortisol; Post-traumatic stress disorder; Inflammatory response; Oxidative stress; Cytokines; Eating disorders; Metabolic disorder; Cardiovascular disease; Small cellular particles as stress markers, Extracellular vesicles as stress markers

1. How can Psychological Trauma affect human body

Post-traumatic stress disorder (PTSD) is a chronic disorder with dysregulated stress axis function (Michopoulos et al., 2015). It is associated with psychological, genomic and biological risk factors (Michopoulos et al., 2015) as well as other morbidities including major depression, substance and alcohol abuse, panic disorder, suicide, reduced life expectancy. It can also result in increased health care utilization and disability in daily activities (Coughlin, 2011). Studies also confirmed connection between PTSD and obesity, diabetes as well as cardio-vascular disease (Boscarino, 2004; Heppner et al., 2009). PTSD has also been linked to accelerated aging, reduced cortical thickness, and neurodegeneration (Miller and Sadeh, 2014; Yang et al., 2021). Developing PTSD is associated with psychological trauma in childhood (Edwards et al., 2003). Maltreated children with significant emotional problems showed higher average daily cortisol levels across 1 week (Cicchetti and Rogosch, 2001). Similarly, maltreated children with PTSD showed higher 24-h urinary free cortisol and daily salivary cortisol levels compared to a healthy comparison group with no maltreatment history (Carrion et al., 2002; De Bellis et al., 1999). Focus in the scientific literature has been on disturbance in the hypothalamic–pituitary–adrenal (HPA) axis in connection with PTSD. HPA axis is activated in acute stress conditions and the hypothalamus starts to secrete corticotropin-releasing hormone (CRH) under the influence of serotonin from the amygdala. Afterwards, the pituitary is stimulated by the CRH to release adrenocorticotrophic hormone (ACTH). This activation results in the production of glucocorticoids (cortisol) in the adrenal cortex. Cortisol serves to stop many metabolic, neuronal defensive and immune reactions (Meewisse et al., 2007). Described process with inflammation and oxidative stress (OXS) pathway can be seen in **Figure 1**. Over time and with continuous exposure to stressors, both HPA and immune function become dysregulated. Studies using psychological stress to stimulate the HPA axis have shown an exaggerated cortisol response in PTSD (de Kloet et al., 2006). However, studies from more than 30 years ago suggested that PTSD has been associated with lower levels of cortisol (Yehuda et al., 1990). This paradigm involved the acknowledgment that stress is not necessarily equal to high cortisol secretion, but indeed reflects a nonnormative and inadequate response to severe stressors, with its pathophysiology involving maladaptation or dysfunction in stress-regulatory systems (Yehuda and McFarlane, 1995). Contradictory results forced the researchers to rethink prevailing models of stress and disease and expand research.

One biological process that has been increasingly interrogated over the last decade is the inflammatory system, as it has a clear role in the pathophysiology of chronic mental and physical illness. Also, oxidative stress in human body as well as other health parameters such as eating disorder, metabolic disorder, and cardiovascular disease (CVD) are of interest.

Increased inflammation in PTSD is probably caused by the activation of the stress response in central and peripheral immune cells that then release cytokines (Michopoulos et al., 2020). Peripheral monocytes can infiltrate the brain and produce macrophages that secrete cytokines and promote neuroinflammation under stressful conditions. Peripherally produced inflammatory mediators as well as glucocorticoids can stimulate microglia which after activation produce cytokines and other substances that are important for adaptive regulation (Dantzer et al., 2008; Nair and Bonneau, 2006). Many blood-based immune mediators, including proinflammatory and anti-inflammatory cytokines as well as chemokines were measured within 3 hours after a traumatic exposure and after up to 12 months after a traumatic exposure (Michopoulos et al., 2020). Monitored individuals were classified in three groups: 1) those who were resilient and did not develop PTSD, 2) those who developed symptoms but recovered, and 3) those who developed chronic PTSD symptoms. The authors found that blood-based levels of all proinflammatory cytokines, in particular tumour necrosis factor (TNF)- α and interferon (IFN)- γ , immediately after the traumatic exposure are not the same for those individuals who went on to develop chronic PTSD symptoms from those who were resilient or had recovered from their symptoms at the time of follow-up.

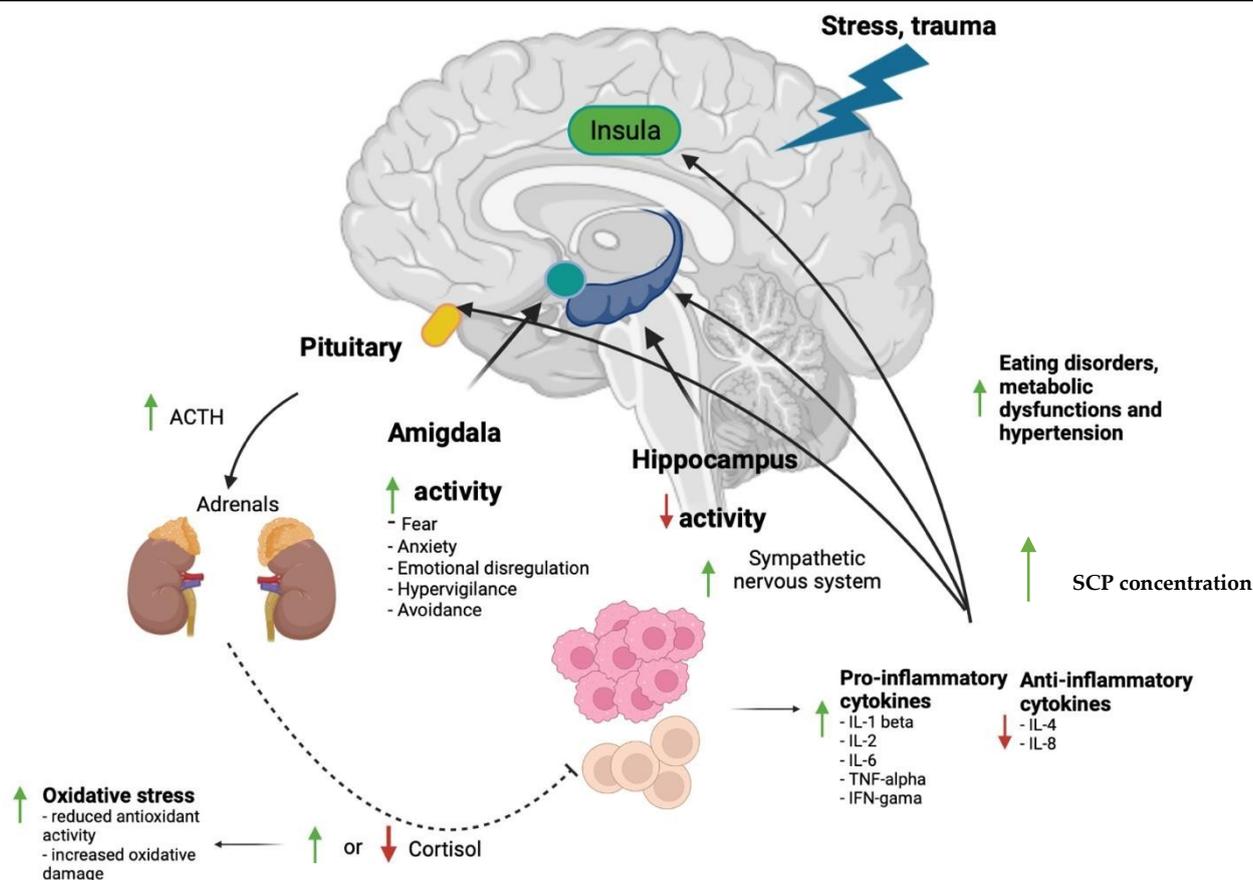


Figure 1. Inflammation process in post-traumatic stress disorder (PTSD). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is present in PTSD. Gonadal steroid hormones and the HPA axis modulate neurotransmitter and neuropeptide systems, influence amygdala activity, influencing inflammatory and oxidative stress responses. Also, eating disorders (ED), metabolic disorder and cardiovascular diseases (CVD) increase. Some studies report that cortisol levels decrease in case of PTSD, on contrary, other studies report increasing of cortisol levels. Although results are also contradictory for PTSD association with inflammatory response, cross-sectional data linking PTSD to a pro-inflammatory state and associates PTSD with chronic inflammation. Increase in immune activity in both the periphery and the central nervous system via stress and trauma effects neuroendocrine systems and the sympathetic nervous system (SNS). The overactivity of the SNS and decreased activity of the parasympathetic nervous system increases the release of pro-inflammatory cytokines (Interleukin (IL)-1 β , IL-2, IL-6, tumour necrosis factor (TNF)- α and interferon (INF)- γ) and decrease anti-inflammatory cytokines (IL-4 and IL-8) that can influence neurotransmitter systems, neurocircuitry, and finally, affective behaviour. Cytokines may contribute to the maintenance of fear- and anxiety-based symptoms by affecting the activity and connections of regions of the brain implicated in the etiology of these disorders, including the amygdala, hippocampus, insula, medial prefrontal cortex, and the anterior cingulate (adapted from (Michopoulos, Norrholm, and Jovanovic 2015), (Meewisse et al. 2007) and (Michopoulos et al. 2017)).

2. Psychological Trauma and inflammation

Exposure to psychological trauma is associated with inflammatory activity. Inflammation is present during high PTSD symptom state, but it is not yet clear if inflammation plays a role in PTSD risk. A prospective study (Marine Resiliency Study) of PTSD development in service members deployed to combat zones reported that high levels of plasma CRP collected before deployment were associated with increased risk for developing PTSD after combat (Eraly et al., 2014). Similarly, those that developed PTSD after combat exhibited altered gene expression patterns in peripheral immune cells collected before combat compared to those that did not go on to develop PTSD after combat (Breen et al., 2015) and also, higher glucocorticoid-dependent cytokine production and T-cell proliferation before deployment is associated with increased PTSD symptoms after combat. These findings suggest that immune factors might not only be markers for symptom state, but also contribute to pre-existing risk for PTSD upon trauma exposure. It can be suggested that immune factors might be markers for symptom state of PTSD and can also contribute to pre-existing risk for PTSD upon trauma exposure (Deslauriers et al., 2017).

Some studies report increase in circulating concentrations of pro-inflammatory signals - interleukin (IL)-1 β (Hoge et al., 2009), IL-2 (Guo et al., 2012), IL-6 (Bersani et al., 2016), TNF- α (Bersani et al., 2016), INF- γ (Hoge et al., 2009) and the acute phase reactant C-reactive protein (CRP) (Tursich et al., 2014). IL-1 β was suggested as biomarker of illness duration, and IL-6 as a biomarker of PTSD severity (Passos et al., 2015). It is also reported that childhood maltreatment can result in increased inflammation in adulthood. Anti-inflammatory signals were reported to decrease - IL-4 (Smith et al., 2011) and IL-8 (Song et al., 2007). Authors reported increased levels of CRP in adulthood (Bertone-Johnson et al., 2012; Lin et al., 2016; Matthews et al., 2014; Tietjen et al., 2012), also concentrations of IL-6, IL-1 β , and TNF- α are increased (Tietjen et al., 2012; Gouin et al., 2012; Kiecolt-Glaser et al., 2011; Smith et al., 2011). Increase in TNF- α concentration in PTSD also positively correlate with total PTSD symptomatology, as well as all three Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – text revision symptom sub-clusters (avoidance, re-experiencing, and hyperarousal) (von Känel et al., 2007). Elevated CRP is associated with impaired inhibition of fear-potentiated startle in the presence of a safety signal, a well-characterized biomarker of PTSD (Jovanovic et al., 2012). Perhaps it might be speculated that a certain degree of inflammation is necessary for adaptive plasticity.

Contradictory to results of increase pro-inflammatory signals, other authors report decreases or no relation between PTSD and circulating concentrations of IL-1 β (Tucker et al., 2004; Song et al., 2007), IL-2 (Smith et al. 2011; Hoge et al. 2009), IL-6 (von Känel et al., 2007) and CRP (McCanlies et al., 2011). In relation to that, also pro-inflammatory signals were reported to increase: IL-4 and IL-10 (Guo et al., 2012; Hoge et al., 2009; von Känel et al., 2007) as well as IL-8 (Guo et al., 2012; Hoge et al., 2009). IL-4 concentrations have been correlated negatively with total hyperarousal symptoms (von Känel et al., 2007) and in a small clinical trial in soldiers with PTSD, symptom improvement during psychotherapy was accompanied by increases in peripheral TNF- α (Himmerich et al., 2016).

3. Psychological Trauma and Oxidative stress

OXS is a biological process which triggers pro-inflammatory signalling pathways and can be activated by inflammation (Miller and Sadeh, 2014). It can cause cellular damage due to an imbalance between levels of antioxidants and free radicals. Variety of biomarkers can be measured for detecting OXS with the aim to quantify either antioxidant capacity or the degree of oxidative damage present in a bio-sample. It is connected with neurodegeneration, aging, accelerate cellular aging and pathogenesis of several chronic conditions (including diabetes, cardiovascular illnesses and neurodegenerative conditions) (Miller et al., 2018). OXS markers were suggested to be associated with PTSD. In most studies on patients with PTSD levels of specific OXS markers increased and activity of antioxidant enzymes reduced (Borovac Štefanović, et al. 2015; Zieker et al., 2007; Tylee et al., 2015; Atli et al., 2016). Possibly, the traumatic experience itself responds by increasing OXS. Potentially relevant process that links between PTSD and OXS is sleep disturbance – a common symptom of PTSD that manifests as recurrent nightmares, restless sleep and difficulty falling and staying asleep - sleep disturbance promotes OXS in the brain by interrupting elimination of free radicals, which, in turn, contributes to cognitive decline and neurodegeneration (Calhoun et al., 2007). In earthquake-exposed individuals with PTSD authors report significantly decreased paraoxonase-1 activity and elevated malondialdehyde concentration in comparison with healthy controls; in the same study, such differences were not significant between healthy controls and earthquake survivors who did not develop PTSD (Atli et al., 2016). Also, other authors reported that OXS parameters were associated with risk for PTSD development (Glatt et al., 2013; Tylee et al., 2015). Similarly, Stefanovic et al. (Borovac Štefanović et al., 2015) found decrease in blood levels of superoxide dismutase and glutathione transferase in Croatian war veterans with PTSD compared to controls. Studies have shown that clinically depressed patients show elevated levels of oxidative DNA damage and suppressed antioxidant activity (Forlenza and Miller, 2006). Patients with generalized anxiety disorders have shown evidence of elevated lipid peroxidation (Bulut et al., 2013) and suppressed antioxidant activity was found in bio-samples from patients with panic disorder (Ozdemir et al., 2012). There are reports for altered reactive oxygen species (ROS) and glutathione S-transferase (GST) in chronic PTSD (Neylan et al., 2011). Future studies with larger samples are needed to investigate the levels of OXS markers and the role of this biological process in PTSD (Peruzzolo et al., 2022).

4. Small cellular particles and extracellular vesicles as stress biomarkers

Already more than 20 years ago it was revealed that small cellular particles (SCPs) detected in isolates of human blood are connected with inflammation processes in human body (Beyer and Pitsetsky, 2010). Research in this field has been developing since and various mechanisms have been considered. Chiaradia et al. (2021) considered SCPs' involvement in the pathophysiology of oxidative stress-related diseases, as mediators of cell-to-cell communication. Direct effects and indirect effects on the regulation of oxidative stress through SCPs were distinguished; SCPs can deliver antioxidant substances or oxides to recipient cells, directly relieving or aggravating oxidative stress, or - they can deliver regulate factors of oxidative stress-related signaling pathways to recipient cells (Qi et al. 2021). In a recent study, it was reported that the quantity of oxidative stress markers correlated with concentration of SCPs isolated from blood (Jan et al., 2021). With all the different roles SCP can play in human body and with all the connection to oxidative stress and inflammation related processes, investigating SCP role in psychological stress is of interest.

5. Eating disorders, metabolic disorder and cardiovascular disease in psychological trauma

PTSD, especially the one caused by childhood maltreatment, especially sexual abuse, is commonly connected to eating disorders (EDs). Yet, EDs can also be triggered by many other forms of victimization, trauma, and neglect, including but not limited to sexual assault (rape and molestation) during adulthood, sexual harassment, physical abuse and assault, emotional abuse, emotional and physical neglect (including food deprivation), teasing, and bullying (Johnson et al., 2002). PTSD is more common in bulimia nervosa and binge-eating disorder and less common in anorexia nervosa (Mitchell et al., 2012).

Connection between PTSD and adverse health disorders and diseases, e.g., CVD (Boscarino 2004) metabolic disorder (including type 2 diabetes mellitus (T2DM)) and obesity (Michopoulos et al., 2016) has been reported. Obesity and metabolic disorder result in reduced sensitivity to the anorectic peptide leptin (secreted from adipose tissue) that results in hyperleptinemia and leptin resistance (Santoro et al., 2015). Effects of the HPA axis and stress on metabolism can provoke hyperglycaemia and insulin resistance already present in metabolic disorders (Rosmond, 2005). When inflammation alters HPA activity, it has adverse effects on cardiovascular function (Nijm and Jonasson, 2009). A longitudinal study of traumatic stress resulting from prolonged war in Beirut found that individuals with more war-related traumatic experiences were at greater risk for CVD-related mortality. Mortality was more evident in women who suffered personal traumas, such as injuries or family deaths, while it was more prominent in men who had suffered property loss, work-related problems, or displacement from home (Sibai et al., 2001). In a study of cardiovascular morbidity in World War II prisoners of war, increased risk of CVD was present in those who developed PTSD (Kang et al., 2006). 30 year follow-up study with Vietnam-era veterans noted that those veterans at PTSD were at increased risk of CVD-related mortality (Boscarino, 2006). In a study of Australian veterans, PTSD associated with increased risk of hypertension (O'Toole and Catts, 2008). Studies report that PTSD is connected with elevated baseline systolic and diastolic blood pressure (Kellner et al., 2003). PTSD was also associated with elevated high density lipoprotein (HDL) cholesterol, low density lipoproteins (LDL), and triglycerides, as well as decreased high density lipoproteins (Solter et al., 2002). Alleviating inflammation might be beneficial to individuals suffering from PTSD and metabolic disorders and could even help prevent the occurrence of metabolic syndrome in individuals with PTSD (Michopoulos et al., 2015).

6. Conclusions

Overall, the cross-sectional data linking PTSD to a pro-inflammatory state and associates PTSD with chronic inflammation, suggesting the inflammation may serve as a possible therapeutic target for alleviating PTSD symptoms et al., 2015). The inconsistencies between published reports on PTSD associated with cortisol level and with inflammation may be related to small sample sizes, distinct study and ethnic populations, the presence of uncontrolled confounders (medication usage, presence of infection, co-morbidity with depression, and other chronic illnesses), and the use of different control groups for comparison. Although this meta-analysis and coincident subgroup analysis move the field forward, future studies and analyses are necessary to determine how other factors (ie, smoking



status, alcohol use, obesity, infection, and pulmonary and CVD) influence the association between PTSD and inflammation (Michopoulos et al., 2017).

Several behaviours may contribute to the increased risk for poorer health in individuals with PTSD. Individuals with PTSD have tendency to engage in increased alcohol use, have higher BMI, and greater rates of smoking. Studies of both men and women report poorer health habits including less physical exercise, less self-care, and greater caloric intake (Dedert et al., 2010).

It would be interesting to investigate impact of Marital and Family Therapy on the health parameters that were listed and presented in this review paper.

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