Posttraumatic stress disorder: A metabolic disorder in disguise?

Vasiliki Michopoulos, *Emory University*
Aimee Vester, *Emory University*
Gretchen Neigh, *Emory University*

Journal Title: Experimental Neurology
Volume: Volume 284, Number Pt B
Publisher: Elsevier | 2016-10-01, Pages 220-229
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.expneurol.2016.05.038
Permanent URL: https://pid.emory.edu/ark:/25593/s59s7

Final published version: http://dx.doi.org/10.1016/j.expneurol.2016.05.038

HHS Public Access

Author manuscript

Exp Neurol. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Exp Neurol. 2016 October ; 284(Pt B): 220–229. doi:10.1016/j.expneurol.2016.05.038.

Posttraumatic Stress Disorder: A Metabolic Disorder in Disguise?

Vasiliki Michopoulos[1,2], **Aimee Vester**[3], and **Gretchen Neigh**[1,2,4,*]

[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

[2]Yerkes National Primate Research Center, Atlanta, Georgia

[3]Department of Environmental Health Sciences, Rollins School of Public Health, Atlanta, Georgia

[4]Department of Physiology, Emory University School of Medicine, Atlanta, Georgia

Abstract

Posttraumatic stress disorder (PTSD) is a heterogeneous psychiatric disorder that affects individuals exposed to trauma and is highly co-morbid with other adverse health outcomes, including cardiovascular disease and obesity. The unique pathophysiological feature of PTSD is the inability to inhibit fear responses, such that individuals suffering from PTSD re-experience traumatic memories and are unable to control psychophysiological responses to trauma-associated stimuli. However, underlying alterations in sympathetic nervous system activity, neuroendocrine systems, and metabolism associated with PTSD are similar to those present in traditional metabolic disorders, such as obesity and diabetes. The current review highlights existing clinical, translational, and preclinical data that support the notion that underneath the primary indication of impaired fear inhibition, PTSD is itself also a metabolic disorder and proposes altered function of inflammatory responses as a common underlying mechanism. The therapeutic implications of treating PTSD as a whole-body condition are significant, as targeting any underlying biological system whose activity is altered in both PTSD and metabolic disorders, (i.e. HPA axis, sympathetic nervous systems, inflammation) may elicit symptomatic relief in individuals suffering from these whole-body adverse outcomes.

Introduction

Post-traumatic stress disorder (PTSD) is a heterogeneous psychiatric disorder whose etiology stems from the occurrence of a psychological traumatic event (Kessler et al., 1995). Epidemiological studies indicate that while approximately 70% of the general population will experience a traumatic event in their lifetime, only 10-20% of those exposed to significant trauma will go on to develop PTSD symptoms. PTSD often presents symptoms

*Corresponding Author Current Address: Gretchen Neigh, PhD, Department of Anatomy & Neurobiology, Virginia Commonwealth University, gretchen.mccandless@vcuhealth.org.

across an array of different domains, including re-experiencing, avoidance, numbing, and hyperarousal (Kessler et al., 1995). The etiology and maintenance of PTSD is related to psychophysiological hyperarousal, an intermediate phenotype that is characterized by an exaggerated fear response (Glover et al., 2011; Jovanovic and Ressler, 2010) and deficits in fear extinction (Norrholm et al., 2015). Alterations in neuroendocrine, sympathetic, metabolic, inflammatory, neurotransmitter and neurobiological systems have all been described in those with PTSD [for review see (Michopoulos et al., 2015a)]. Importantly, PTSD is associated with an array of other adverse mental (e.g., major depression, substance and alcohol abuse, panic disorder, suicide) and physical health diseases and disorders (e.g., cardiovascular disease) (Boscarino, 2004; Jacobsen et al., 2001).

Obesity and metabolic disorders, including type 2 diabetes mellitus (T2DM), are also highly comorbid with PTSD (Rosenbaum et al., 2015). Guidelines for healthy, normal weight are currently based on body mass index (BMI) cut-offs recommended by the World Health Organization (FerroLuzzi et al., 1995). Metabolic syndrome is characterized by the presence of three of the following phenotypes: increased abdominal fat mass (large waist circumference, being overweight or obese), disrupted glucose regulation that often manifests as hyperglycemia (increased fasting plasma glucose), elevated blood pressure, increased levels of triglycerides and decreased levels of HDL cholesterol (National Cholesterol Education Program Expert Panel on Detection and Treatment of High Blood Cholesterol in, 2002). Obesity and metabolic disorder result in reduced sensitivity to the anorexic peptide leptin (secreted from adipose tissue) that results in hyperleptinemia and leptin resistance (Santoro et al., 2015). Hyperglycemia in metabolic disease, including T2DM, occurs in tandem with insulin resistance (Rosmond, 2005).

The high co-morbidity between obesity, metabolic disorders and PTSD suggest that underlying neuroendocrine and metabolic changes are present in PTSD that either increase the risk for systemic metabolic dysregulation or reflect a primary change in metabolism as a result of the traumatic experience. The current review will examine the convergence of PTSD and metabolic syndrome, and garner cause and effect sequela from model animals. Furthermore, alterations in inflammatory signaling secondary to shifts in glucocorticoid receptor sensitivity will be entertained as a possible driving force behind both behavioral symptoms consistent with PTSD and co-occurring physiological manifestation of metabolic disease. Viewing PTSD as a psychiatric and metabolic condition has important treatment implications for eliciting symptomatic relief in individuals suffering from PTSD and its adverse sequelae.

The HPA Axis and Metabolic Alterations in PTSD

Alterations in both the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) are present in PTSD and have been extensively characterized (Michopoulos et al., 2015a). Glucocorticoids, cortisol in humans, are the main effectors of the stressor-activated HPA axis. Glucocorticoids bind to the glucocorticoid receptor (GR), which is a transcription factor, and ultimately stimulate a cascade of gene transcription changes that primarily control energy utilization; therefore, shifts in function of the HPA axis or the GR ultimately impact metabolism. Although baseline cortisol does not consistently differ among

PTSD patients (Meewisse et al., 2007; Yehuda, 2005), results indicate that PTSD is associated with a decreased cortisol response to an acute stressor (Kolassa et al., 2007). In line with this observation, enhanced glucocorticoid negative feedback on the HPA axis in PTSD is consistently reported when the system is assessed using the dexamethasone suppression test (Yehuda et al., 1995). Additionally, peripheral and central levels of corticotropin-releasing hormone (CRH), an initiating step in activation of the HPA axis, are elevated in individuals with PTSD (Baker et al., 2005; de Kloet et al., 2008). This suggests a more active HPA axis and potentially a more metabolically labile system. Furthermore, individuals with PTSD are reported to exhibit elevated GR levels (Matic et al., 2013) and enhanced glucocorticoid sensitivity (Yehuda et al., 2004) both of which would theoretically lead to enhanced GR-mediated gene transcription.

The GR is regulated by a series of co-chaperones that appear to guard against overactivation of the GR. Evidence indicates that even levels of GR's primary negative regulator are impacted in PTSD. Levels of the co-chaperone of GR, FKBP5, which inhibits GR ligand binding and nuclear translocation of GRs, are decreased in individuals with PTSD. This may contribute to the increased sensitivity of GR (Yehuda et al., 2009a) and thereby may engage transcription of other energy-related genes in PTSD patients. Rodent models of PTSD indeed have shown differential gene expression within the brain in pathways involved with obesity and metabolic syndrome [i.e. Adiponectin receptor 1 (*ADIPOR1*), dopamine 2 receptor (*DRD2*), neuropeptide Y (*NPY*)] (Muhie et al., 2015). While these findings of HPA axis dysregulation are cross-sectional in nature, prospective studies indicate that augmented baseline GR levels (van Zuiden et al., 2012), diminished FKBP5 mRNA levels (van Zuiden et al., 2012), and a blunted cortisol response to an acute stressor are all associated with increased risk for PTSD symptoms following trauma exposure, further suggesting a relationship between HPA axis dysfunction and risk for PTSD.

Many of the HPA axis modifications noted in individuals with PTSD harken back to HPA axis-centric changes documented in metabolic syndrome, including increased abdominal fat mass (being overweight or obese) (Eckel et al., 2010). Importantly, the increase in adiposity characteristic of metabolic disorders is associated with alterations in HPA axis regulation. Glucocorticoid negative feedback inhibition is diminished (Pasquali et al., 2002), cortisol response to an acute stressor is heightened (Epel et al., 2000), and morning cortisol levels are heightened (Duclos et al., 2005; Walker et al., 2000). This increased basal cortisol tone is associated with insulin resistance, glucose intolerance, and hypertriglyceridemia (Anagnostis et al., 2009). Furthermore, peripheral GR expression is increased in individuals with insulin resistance (Reynolds et al., 2002). Overall these data suggest that effects of the HPA axis and stress on metabolism act to exacerbate hyperglycemia and insulin resistance already present in metabolic disorders (Rosmond, 2005). HPA axis and metabolic alterations in both people with PTSD and people with metabolic syndrome appear to confer a state of energy availability that could promote a more efficient response to a stressor, but could also carry the adverse implications of excess energy.

It is important to note that at first glance the dysregulation of the HPA axis reported in PTSD and metabolic syndrome are opposite in nature. As described above, enhanced glucocorticoid negative feedback and diminished cortisol response to stressor exposure have

been documented in PTSD (Kolassa et al., 2007; Yehuda et al., 1995).Conversely, diminished glucocorticoid negative feedback and increased cortisol response to stressor exposure have been documented in metabolic syndrome (Epel et al., 2000; Pasquali et al., 2002). Additionally, while increased basal cortisol levels have been described in obesity and metabolic disorders (Duclos et al., 2005; Walker et al., 2000), the effects of PTSD on morning cortisol have been equivocal in nature (Meewisse et al., 2007; Yehuda, 2005). One factor that may be critical in influencing the dysregulation of the HPA axis in those with PTSD is the chronicity of PTSD and subsequent exposures to psychosocial stressors that are known to be associated with GR resistance (Gragnoli, 2014).

Furthermore, single nucleotide polymorphisms (SNPs) within the *FKBP5* gene have been shown to influence individual risk for increased GR sensitivity or GR resistance (Binder et al., 2008). More specifically, these SNPS in the *FKBP5* gene are associated with higher FKBP5 mRNA induction upon cortisol release and increased PTSD symptom severity in those with high levels of child abuse (Binder et al., 2008). Theat-risk alleles of these *FKBP5* SNPs are associated with enhanced glucocorticoid sensitivity, whereas the other alleles of these SNPs are associated with GR resistance in individuals with PTSD (Binder et al., 2008). Thus, genetic variability in traumatized individuals with PTSD confers differential risk for GR resistance that may lead to HPA dysregulation typically seen in metabolic syndrome and obesity. Indeed, work in translational rodent models indicate that FKBP5 mRNA expression in adipose tissue following dexamethasone administration is increased and associated with glucocorticoid-induced insulin resistance (Pereira et al., 2014). Increases in hypothalamic FKBP5 mRNA expression have also been associated with increased body weight gain in mice (Balsevich et al., 2014).

The Sympathetic Nervous System and Metabolic Alterations in PTSD

The dysregulation of the HPA axis in PTSD is coincident with increased activity of the faster acting portion of the stress response as evidenced by increased sympathetic tone. Increased heart rate and skin conductance following an acute stressor are characteristic of individuals with PTSD (Blanchard et al., 1982; Keane et al., 1998; Orr et al., 2003; Shalev et al., 2000) and can be predictive of PTSD development in the aftermath of trauma (Shalev et al., 2000). Heart rate variability (HRV), a measure of beat-to-beat fluctuations in heart rate, is also dampened in individuals with PTSD (Shah et al., 2013), suggesting impaired autonomic regulation. Coincident with these physiological alterations in autonomic function is augmented catecholamine secretion (Southwick et al., 1999), as greater levels of circulating norepinephrine (NE) peripherally and centrally are found in individuals with PTSD (Geracioti et al., 2001). Levels of NE in response to stressor/threat exposure are also increased in individuals with PTSD (Blanchard et al., 1991; Geracioti et al., 2008). This increase in NE has recently been shown to be due to decreased levels of NE transporter in the locus coeruleus (Pietrzak et al., 2013). Additionally, peripheral α2- adrenergic receptors are attenuated in PTSD (Perry et al., 1987). Taken together, these data suggest that autonomic function is impaired in PTSD.

Metabolic syndrome and obesity are also associated with increased sympathetic activity (Canale et al., 2013; Thorp and Schlaich, 2015), including augmented muscle sympathetic

nerve activity, increased heart rate, and decreased HRV (Chintala et al., 2015; Grassi, 2007; Hsiung et al., 2015; Stuckey et al., 2015). Furthermore, urinary levels of NE and whole-body plasma levels of NE are increased in metabolic syndrome (Lee et al., 2001; Vaz et al., 1997). The effect of adiposity on sympathetic tone is driven by visceral adipose tissue, as sagittal adiposity but not subcutaneous fat is concomitant with increased heart rate and increased NE (Grassi, 2004).

The mechanisms by which adiposity is linked to augmented sympathetic tone are multifaceted. For instance, hyperinsulinemia in metabolic disorders can facilitate sympathetic tone by increasing sympathetic activity to skeletal muscle (Anderson et al., 1991; Lembo et al., 1992). Additionally, increased levels of leptin secretion due to greater adiposity in metabolic disorders indirectly affect sympathetic tone by inducing hyperinsulinemia (Thorp and Schlaich, 2015) and results in leptin resistance (Santoro et al., 2015). Hyperleptinemia also can facilitate sympathetic activity of the renal system leading to hypertension (Correia and Rahmouni, 2006). Importantly, catecholamine activity is central to the regulation of energy expenditure and body weight, primarily through the stimulatory effects of β-adrenergic receptors and inhibitory effects of α2- adrenergic receptors (Masuo, 2010). Polymorphisms in these β-adrenergic receptors are associated with metabolic syndrome and obesity in humans, corroborating the notion that increased adrenergic drive is pathophysiological (Masuo, 2010). Although not completely overlapping, both PTSD and metabolic syndrome are associated with disruptions of the autonomic nervous system. The interactions of these disruptions with metabolic hormones may mediate the convergence between PTSD and metabolic syndrome.

Metabolic Hormones and Metabolic Alterations in PTSD

Concurrent with changes in the HPA axis and sympathetic nervous system in individuals with PTSD are alterations in the expression and regulation of metabolic hormones. Increased leptin levels have also been described in trauma survivors with PTSD (Liao et al., 2004). Furthermore, NPY is an orexigenic peptide (Keen-Rhinehart et al., 2013) that also elicits anxiolytic responses by blocking CRH and noradrenergic activity (Britton et al., 2000; Rasmusson et al., 2000). Peripheral levels of NPY are decreased in individuals exposed to trauma (Morgan et al., 2003) and with PTSD (Rasmusson et al., 2000), while augmented levels of NPY have been associated with resilience to trauma (Morgan et al., 2002). The heightened adrenergic activity present in individuals with metabolic syndrome results in similarly increased release of NPY, as NPY is also released from catecholaminergic neurons both centrally and in the periphery and has been shown to directly control both stress- and diet-induced adipose accumulation in rodents (Zhang et al., 2014). In humans, levels of NPY are increased in obese patients (Baltazi et al., 2011; Baranowska et al., 1997), and genetic polymorphisms in the *NPY* gene are associated with increased NPY levels and influence individual risk for obesity (Yeung et al., 2011).

By definition, metabolic syndrome includes disruption to glucose metabolism and homeostasis. Similarly, insulin resistance is also present in individuals with PTSD, as PTSD is associated with a mild increase in insulin levels and increased insulin response to an oral glucose tolerance test (OGTT; (Rao et al., 2014)). Insulin and glucose responses following

acute stress exposure are also increased in men with PTSD (Nowotny et al., 2010). Furthermore, individuals with PTSD are more likely to show abdominal obesity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol and hypertension (Rosenbaum et al., 2015). While the above data indicate that metabolism is disrupted in PTSD peripherally, fluorodeoxyglucose positron emission tomography (FDG-PET) studies show that central glucose metabolism is also disrupted in individuals with PTSD. Decreased activation of prefrontal regions, including cingulate gyri and the hippocampus, is present in men with chronic PTSD (Molina et al., 2010). Similarly, women with PTSD following sexual assault have lower glucose metabolic activity in the hippocampus (Kim et al., 2012), an area of the brain whose volume is decreased in PTSD (Admon et al.; Bremner et al., 2008) and has been implicated in the etiology of PTSD (Gilbertson et al., 2002). Resting glucose metabolic rate has also been shown to be increased in the amygdala of veterans with PTSD (Yehuda et al., 2009b), an area of the brain whose hyperactivity is characteristic of PTSD (Hughes and Shin, 2011).

Corresponding functional MRI studies in obese patients show increased activation of striatal regions in response to food cues (Burger and Berner, 2014). However, these studies do not examine brain areas that are implicated in the etiology of PTSD, such as the amygdala and hippocampus, as these regions are not typically of interest to studying obesity and metabolic disease. Thus, there are brain regions relevant to PTSD that have not yet been studied in the context of obesity and metabolic syndrome. In addition, there is a paucity of neuroimaging studies that characterize brain glucose metabolism in metabolic syndrome and obesity. One study suggests that decreases in brain derived neurotropic factor (BDNF) are associated with altered brain glucose metabolism in diabetic individuals (Li et al., 2015). Moreover, alterations in brain metabolism have also been reported in metabolic syndrome, including increased myoinositol/creatine and glutamate/creatine rations in occipitoparietal gray matter (Haley et al., 2010). This metabolic profile is a phenotype that has been linked to neuroinflammation in diabetes (Ajilore et al., 2007). Blunted neural activation in the frontal gyrus and parietal lobule during a cognitive challenge has also been described in individuals with metabolic syndrome (Hoth et al., 2011). More research is clearly necessary to understand how obesity and metabolic syndrome influence limbic and prefrontal regions typically altered in PTSD. One potential impediment to undertaking these studies is the body size limit that typically exists in utilizing MRI machines for neuroimaging data.

Overall, alterations in some of the hallmark characteristics of metabolic syndrome observed in people with PTSD further emphasize the overlap between these two disorders. However, there are some discrepancies and important caveats to consider. First, peripheral levels of NPY are decreased in individuals with PTSD (Rasmusson et al., 2000) and increased in those with obesity (Baltazi et al., 2011; Baranowska et al., 1997). This difference is likely due to sample composition, as the PTSD study was conducted only on average weight males exposed to combat-related trauma (Rasmusson et al., 2000). Studies in obesity typically compare average weight individuals to obese and overweight individuals using BMI thresholds. The study found that in males with PTSD, NPY levels were positively associated with body weight (Rasmusson et al., 2000). The finding suggests that even in a generally healthy and physically fit population increased NPY is associated with greater body weight. Other factors that contribute to the NPY level discrepancy include the chronicity of PTSD

symptoms, presence of co-morbid psychopathologies such as depression, and behavioral sources of GR resistance such as intake of high fat and high sugar diets (Scott et al., 2008), and smoking (Fu et al., 2007; Morissette et al., 2007).

Delineating the Relationships: Insight from Animal Models

As with other complex comorbid conditions, animal models play an essential role in delineating the relationship between PTSD and metabolic disorders and elucidating underlying mechanisms. Translational animal models of PTSD help assess the directionality of relationships between metabolic factors and behaviors related to PTSD. Most commonly, fear conditioning is used to assess the neurobiological and physiological systems that contribute to the manifestation of aberrant fear responses.

Fear conditioning paradigms based on Pavlovian learning have been leveraged in rodent models to study the etiology of PTSD-like phenotypes. In these paradigms, a neutral conditioned stimulus is paired with an aversive unconditioned stimulus, and after repeated exposure an association is formed so that the conditioned stimulus alone elicits the conditioned fear response (Jovanovic and Ressler, 2010). Fear conditioning in rodents results in alterations of serotonin and norepinephrine in the hippocampus and prefrontal cortex (Wilson et al., 2014a) and altered metabolism of dopamine and acetylcholine (Okada et al., 2015), both characteristics of PTSD pathophysiology in humans. Animal models have also implicated alterations in the transcriptome of the amygdala in underlying neuronal plasticity (Ponomarev et al., 2010) and changes in hippocampal plasticity via proteomic alterations (Rao-Ruiz et al., 2015). Similar to the HPA axis dysregulation in PTSD, fear conditioning in rodents has been linked to prefrontal GR activity (Reis et al., 2015) and FKBP5 expression (Chakraborty et al., 2015). This same experimental paradigm has been used to assess the effects of corticosterone on contextual fear memory formation (reviewed in (Pecoraro et al., 2006)), and the findings have been equivocal. Studies show that corticosterone administration immediately preceding fear learning both protects against (Cohen et al., 2008; Jia et al., 2015) and facilitates the formation of increased fear responses to a conditioned stimulus (Kaouane et al., 2012; Thompson et al., 2004). However, administration of hydrocortisone to humans during and immediately after trauma exposure may protect against later PTSD development by increasing serum cortisol levels, and interfering with aspects of traumatic memory function (de Quervain et al., 2000; Schelling et al., 2006).

Fear responses are, in and of themselves, normal and adaptive; therefore, contrived sensitivities must be manufactured in the laboratory in order to address the mechanisms that push the responses into the aberrant range. Frequently, environmental stressors, such as predatory stress, are used to invoke susceptibility and to further study the mechanisms of the aberrant response to fearful stimuli. One type of predatory stress model places a rodent in close proximity with a cat (Wilson et al., 2014a) or places a mouse in proximity to a rat (Burgado et al., 2014). Other predatory stress models pair the experimental animal with an aggressive conspecific (Gautam et al., 2015; Muhie et al., 2015). This exposure elicits increased anxiety-like behaviors, impaired memory recognition, and deficits in both contextual and cued fear conditioned memory (Zoladz et al., 2015). The exposure has also

been shown to increase plasma corticosterone, elevate gut-derived metabolites, and lead to hyperlipidemia as long as four weeks after the stressor exposure (Gautam et al., 2015). Exposure to predatory stress elicits an array of PTSD-like phenotypes, including increases in prefrontal and hippocampal levels of NE (Wilson et al., 2014a), increased interleukin (IL)-1β and NALP3, and oxidative stress as measured by total reactive oxygen species (ROS) within the same regions (Wilson et al., 2013). A mouse model of aggressor exposure also elicits deficits in fear conditioning and is associated with genome-wide transcriptome alterations, including changes in expression of signals important for the regulation of the HPA axis, neurogenesis, and fear memory consolidation and extinction (Muhie et al., 2015).

Regulators of metabolism conversely modulate fear circuitry and the expression of fear. For example, fasting prior to fear conditioning impairs fear acquisition, but fasting prior to extinction improves extinction learning (Verma et al., 2015). NPY may play a critical role as it modulates both NE and CRH activity, resulting in the attenuation of anxiety-like behavior and HPA axis activity (Hastings et al., 2004; Rasmusson et al., 2000; Sah and Geracioti, 2013). In a fear-conditioning paradigm, NPY reduces or inhibits the acquisition of contextual fear memories (Karlsson et al., 2005; Lach and de Lima, 2013) and also increases the extinction of conditioned fear in rats (Gutman et al., 2008). In addition, leptin acts to facilitate fear extinction (Wang et al., 2015), suggesting that the beneficial effect of leptin on fear expression in individuals with PTSD and metabolic disorders is diminished due to leptin resistance (Santoro et al., 2015). Contrariwise, ghrelin secretion from the stomach increases following stressor exposure via adrenergic activation of the sympathetic nervous system (Zhao et al., 2010) and enhances the formation of fear memories (Meyer et al., 2014; Spencer et al., 2015). Similar to ghrelin, insulin like growth factor II (IGF-II) enhances fear memory retention (Chen et al., 2011) and enhancement of memory formation (Stern et al., 2014). Glucocorticoid secretion serves a dual role in the face of stressor exposure. It not only influences fear memory learning, but also interferes with insulin action (Amatruda et al., 1985), leading to insulin resistance via interference of glucose transporter (GLUT 4) translocation (Garvey et al., 1989a; Garvey et al., 1989b). Although not a focus of this review, sex differences in metabolism and, in particular, sex differences in expression of glucose transporters following stress (Harrell et al., 2014; Kelly et al., 2014), may contribute to sex differences in the prevalence and incidence of PTSD (Kessler et al., 1995; Tolin and Foa, 2006).

There are limitations of validity that must be considered when translating findings from animal models of PTSD (Daskalakis et al., 2013). To have PTSD, an individual must experience or be exposed to a life-threating event (APA, 2014). Thus, to have construct validity, an animal model must in the least utilize a life-threatening stressor. Some rodent models of PTSD, such as predator exposure and resident-intruder (social defeat) paradigms, may ascertain construct validity due to the naturalistic stressors (Burgado et al., 2014; Gautam et al., 2015; Hammels et al., 2015; Muhie et al., 2015; Wilson et al., 2014a; Zoladz et al., 2012; Zoladz et al., 2015). However, other models such as prolonged immobilization may fall short due to the artificial nature and duration of the stressor. The predictive validity of translational animal models of PTSD is further limited because only two pharmacological agents are approved for the treatment of PTSD in humans (sertraline and paroxetine), and results have been equivocal in a predator stress model (Wilson et al., 2014b) as well as in

clinical populations (Friedman et al., 2007). While all of these rodent models result in some PTSD-like phenotypes such as increased sympathetic activity and fear responses and deficits in fear extinction, it is sometimes difficult to induce phenotypes that are unique to PTSD such as dysregulated HPA function.

Furthermore, it is critical that the stressors employed in these models result in phenotype variability so that we can understand factors that explain individual vulnerability to PTSD-like phenotypes in the aftermath of stressor exposure (Daskalakis et al., 2013). One largely understudied factor that influences behavioral and physiological responses to stressor exposure in translational animal models is sex. While some models, like social defeat, inconsistently produce adverse phenotypes in females, others can be employed to study the etiology of the robust sex difference in PTSD that affect females more than males (Kessler et al., 1995; Tolin and Foa, 2006).

Inflammation as a Common Underlying Mechanism

Up to this point, we have highlighted similarities between PTSD and traditional metabolic disorders. The question then becomes, what drives these points of convergence? PTSD and metabolic disorders bear phenotypic similarities, but they are also mechanistically related. To start, one pervasive physiologic response that is capable of driving somatic and cerebral shifts in function is the inflammatory response. Heightened inflammation is highly coincident with increased sympathetic tone in obesity and metabolic syndrome. This is due to the fact that the noradrenergic system also acts to stimulate the innate immune response (Sanders, 2006), including IL-6 production (Pal et al., 2014). Additionally, levels of pro-inflammatory markers, including C-reactive protein (CRP), IL-6 and TNFα, are increased in both obesity and metabolic syndrome (Bastard et al., 2000a; Bastard et al., 2000b; Fontana et al., 2007; Gregor and Hotamisligil, 2011; Pannacciulli et al., 2001). This increase in systemic inflammation in obesity has been linked to macrophage infiltration of adipose tissue as well [reviewed in (Karalis et al., 2009)].

Exacerbated levels of IL-6 and TNFα are associated with insulin resistance and hyperglycemia in T2DM (Daniele et al., 2014). Data from *in vivo* and *in vitro* models indicate that IL-6 plays a direct role in the development of hyperinsulinemia and insulin resistance (reviewed in (Pal et al., 2014)). Recent clinical data show that increased systemic inflammation in the form of increased peripheral levels of IL-6 differentiates obese women with T2DM from obese women with normal glucose tolerance (van Beek et al., 2014).

Indeed, the neuroendocrine and autonomic phenotypes associated with PTSD described above are also coincident with increased levels of inflammation. Levels of pro-inflammatory cytokines, such as IL-6 (Maes et al., 1999), IL-1β (Spivak et al., 1997), and IL-2 (Smith et al., 2011), are augmented in individuals with PTSD. Importantly, levels of pro-inflammatory markers are positively correlated with PTSD symptoms in traumatized individuals (von Kanel et al., 2007). Elevated levels of CRP in individuals with PTSD are associated with greater PTSD symptoms and increased odds for a PTSD diagnosis (Michopoulos et al., 2015b; Miller et al., 2001; Plantinga et al., 2013). High CRP levels are also associated with diminished inhibition of fear-potentiated startle (FPS) (Michopoulos et al., 2015b), which is

a psychophysiological biomarker of PTSD (Glover et al., 2011; Jovanovic and Ressler, 2010). Peripheral levels of nuclear factor-kB (NF-kB) are also increased in women with PTSD and associated with decreased sensitivity to glucocorticoid negative feedback (Pace et al., 2012). A recent systematic meta-analysis confirmed that increased inflammation is coincident with PTSD in traumatized individuals (Passos et al., 2015).

Neuroinflammation has also been studied in translational animal models and studies indicate that inflammatory processes disrupt hippocampal function via central receptors (Loddick et al., 1998; Williamson and Bilbo, 2013). Most rodent models have used lipopolysaccharide (LPS) administration to assess the effects of central and systemic inflammation on behavior and cognition. LPS administration impairs contextual fear learning in rodents, suggesting that inflammation interferes with memory consolidation (Pugh et al., 1998). More recently, studies have elucidated the mechanism by which inflammation interferes with the acquisition and extinction of fear. Specifically, LPS administration disrupts cellular processes in the hippocampus critical for memory formation (Czerniawski et al., 2015), and increases in IL-6 (Burton and Johnson, 2012) and IL-1β (Gonzalez et al., 2013) interfere in this LPS-induced deficit in memory. Additionally, site-specific injections of both IL-6 (Hao et al., 2014) and TNFα (Jing et al., 2015) into the amygdala impair the acquisition and extinction of fear conditioning. Taken together, these data suggest that increased inflammation may serve as the biological mechanism by which metabolic alterations occur in individuals with PTSD (Figure 1). If inflammation is a driving force in the etiology and maintenance of PTSD (Felger et al., 2016), then pharmacological treatments that target inflammatory mechanisms may be effective treatment strategies for PTSD and metabolic disease intervention (Michopoulos and Jovanovic, 2015).

The use of angiotensin-converting enzyme inhibitors (ACE-I) and blockers (ARBs) for the treatment of PTSD and cardiometabolic disease may support the involvement of inflammatory mechanisms. ACE-I/ARBs are typically prescribed for the treatment of hypertension and increased sympathetic activity. These pharmacological agents not only attenuate blood pressure (Savoia and Schiffrin, 2007), but also reduce neuroinflammation (Benicky et al., 2011; Welty et al., 2015), as angiotensin-II acts as a pro-inflammatory signal to induce the release of CRP (Peng et al., 2007; Zhao et al., 2013) and IL-6 (Sano et al., 2001). Furthermore, recent findings from traumatized individuals indicate that ACE-1/ARB medication usage is associated with decreased odds for having a diagnosis of PTSD and lower levels of PTSD symptom (Khoury et al., 2012). Data from translational rodent models indicate ACE-I/ARB could act to attenuate the development and/or maintenance of PTSD by enhancing the extinction of fear memories (Marvar et al., 2014). These data suggest that use of interventions that target multiple phenotypes and underlying neurobiology may be the most efficacious in reducing the health burden of PTSD.

Of course, pharmacological interventions are not the only options available, as cognitive and behavioral therapies may also be efficacious in dampening the adverse effects of PTSD on metabolic outcomes. Community-based educational intervention in African American women, a group typically at increased risk for trauma exposure and PTSD (Gillespie et al., 2009) as well as cardiovascular disease and metabolic syndrome, was effective in reducing inflammation (CRP and TNFα) (Villablanca et al., 2015). However, it still remains to be

determined whether effective behavioral therapies for PTSD (Butler et al., 2006), including prolonged exposure (Powers et al., 2010), are also capable of reducing inflammation in traumatized individuals. Any interventions that decrease inflammation and oxidative stress could also benefit individuals with PTSD, including meditation and yoga (Black and Slavich, 2016; Pascoe and Bauer, 2015). Weight loss, decreasing adiposity via exercise, or eating diets high in omega-3 fatty acids could also mitigate PTSD symptoms. This is suggested by a study showing weight loss occurs in parallel with a decrease in BMI and PTSD symptoms in traumatized individuals (Johannessen and Berntsen, 2013).

Summary and Conclusions

In summary, the underlying alterations in sympathetic nervous system activity, neuroendocrine pathways, and metabolism described in individuals with PTSD are similar to those present in metabolic syndrome and associated phenotypes, such as obesity and diabetes (Table 1). These mutual changes in biology are concomitant with increased inflammation and suggest a common mechanism by which exposure to trauma and coincident PTSD increases risk for the development of physical diseases, including obesity and T2DM (Rosenbaum et al., 2015). Indeed, low-grade inflammation in metabolic disorders is coincident with adverse changes in behavioral and cognitive symptoms, namely mood and cognitive disruptions (Lasselin and Capuron, 2014). While the specific mechanism by which inflammation increases severity of PTSD and mood disruptions in metabolic syndrome remains uncertain, recent evidence from individuals with depression suggests that inflammation drives central alterations in corticostriatal functional connectivity that are associated with anhedonia (Felger et al., 2015).

Importantly, behavioral sources of inflammation may also contribute the increased inflammation, as those with PTSD have disrupted sleep patterns, and are more likely to engage in unhealthy behaviors such as consuming alcohol, smoking, eating poorly and a sedentary lifestyle. All of these behavioral phenotypes are associated with a pro-inflammatory state (Bryant et al., 2004; Frohlich et al., 2003; Fu et al., 2007; Jamal et al., 2014; Scott et al., 2008). Increases in adiposity due to excess energy intake and decreased energy expenditure in individuals with PTSD could also contribute to the emergence of metabolic disorders in those with PSTD via heightened secretion of pro-inflammatory cytokines and GR resistance (Karalis et al., 2009). Indeed, the epidemiologic data suggest that PTSD increases one’s risk for developing metabolic disorder and cardiovascular disease (Boscarino, 2004; Rosenbaum et al., 2015). While this indicates that obesity and metabolic disorder are a consequence of behavioral phenotypes associated with PTSD in traumatized individuals, it is critical to note that PTSD in the absence of obesity is associated with increased inflammation, augmented SNS activity, and dysregulation of the HPA axis as noted in this review. However, it is not yet known whether preexisting metabolic disorder increases individual risk for developing PTSD in the aftermath of trauma. A recent study suggests that preexisting inflammation, which is a characteristic of cardio-metabolic disease, increases risk of PTSD development, as greater CRP levels pre-deployment were associated with increased risk for PTSD following deployment (Eraly et al., 2014). In active duty military personnel, increased inflammation can arise from behavioral sources (i.e. alcohol consumption) and the chronic stress associated with living with PTSD and depression (Groer

et al., 2015; Reyes-Guzman et al., 2015). This increased inflammation may be due to the rising rates of obesity in active duty military personnel (Reyes-Guzman et al., 2015), suggesting a mechanism by which inflammation may result in increased risk for PTSD development in a sample otherwise thought to be in good health.

Clearly future studies are not only necessary to elucidate the underlying etiology of metabolic changes in traumatized individuals with PTSD, but also to determine the effectiveness of therapeutic interventions aimed at attenuating the adverse mental and physical consequences of PTSD. The implications of treating PTSD as a whole-body condition are significant for treatment as doing so may elicit symptom relief in individuals suffering from these whole-body adverse outcomes. It has already been suggested that alleviating inflammation may provide benefit to individuals suffering from PTSD and metabolic disorders, and even help prevent the onset of metabolic syndrome in individuals with PTSD (Michopoulos and Jovanovic, 2015). However, empirical evidence must be generated to support the efficacy of such interventions and others designed to target other biological systems whose activity is altered in both PTSD and metabolic disorders (i.e. HPA axis, SNS). To begin to accomplish this goal, the field must recognize that chronic PTSD is both a psychiatric and metabolic disorder.

Acknowledgments

Funding Sources:

V.M. was supported by K12HD085850.

G.N.N. was partially supported by R01MH110364 and K18MH105098.

References

Admon R, Lubin G, Rosenblatt JD, Stern O, Kahn I, Assaf M, Hendler T. Imbalanced neural responsivity to risk and reward indicates stress vulnerability in humans. Cereb Cortex. 2013; 23:28–35. [PubMed: 22291028]

Ajilore O, Haroon E, Kumaran S, Darwin C, Binesh N, Mintz J, Miller J, Thomas MA, Kumar A. Measurement of brain metabolites in patients with type 2 diabetes and major depression using proton magnetic resonance spectroscopy. Neuropsychopharmacology. 2007; 32:1224–1231. [PubMed: 17180124]

Amatruda JM, Livingston JN, Lockwood DH. Cellular mechanisms in selected states of insulin resistance: human obesity, glucocorticoid excess, and chronic renal failure. Diabetes Metab Rev. 1985; 1:293–317. [PubMed: 3915256]

Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. The Journal of clinical endocrinology and metabolism. 2009; 94:2692–2701. [PubMed: 19470627]

Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. The Journal of clinical investigation. 1991; 87:2246–2252. [PubMed: 2040704]

APA, A.P.A. Diagnostic and Statistical Manual of Mental Disorders. 2014

Baker DG, Ekhator NN, Kasckow JW, Dashevsky B, Horn PS, Bednarik L, Geracioti TD Jr. Higher levels of basal serial CSF cortisol in combat veterans with posttraumatic stress disorder. The American journal of psychiatry. 2005; 162:992–994. [PubMed: 15863803]

Balsevich G, Uribe A, Wagner KV, Hartmann J, Santarelli S, Labermaier C, Schmidt MV. Interplay between diet-induced obesity and chronic stress in mice: potential role of FKBP51. The Journal of endocrinology. 2014; 222:15–26. [PubMed: 24781256]

Baltazi M, Katsiki N, Savopoulos C, Iliadis F, Koliakos G, Hatzitolios AI. Plasma neuropeptide Y (NPY) and alpha-melanocyte stimulating hormone (a-MSH) levels in patients with or without hypertension and/or obesity: a pilot study. Am J Cardiovasc Dis. 2011; 1:48–59. [PubMed: 22254185]

Baranowska B, Wasilewska-Dziubinska E, Radzikowska M, Plonowski A, Roguski K. Neuropeptide Y, galanin, and leptin release in obese women and in women with anorexia nervosa. Metabolism. 1997; 46:1384–1389. [PubMed: 9439531]

Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H, Hainque B. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. The Journal of clinical endocrinology and metabolism. 2000a; 85:3338–3342. [PubMed: 10999830]

Bastard JP, Jardel C, Bruckert E, Vidal H, Hainque B. Variations in plasma soluble tumour necrosis factor receptors after diet-induced weight loss in obesity. Diabetes Obes Metab. 2000b; 2:323–325. [PubMed: 11225749]

Benicky J, Sanchez-Lemus E, Honda M, Pang T, Orecna M, Wang J, Leng Y, Chuang DM, Saavedra JM. Angiotensin II AT1 receptor blockade ameliorates brain inflammation. Neuropsychopharmacology. 2011; 36:857–870. [PubMed: 21150913]

Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen B, Kirschbaum C, Nawroth PP. A mechanism converting psychosocial stress into mononuclear cell activation. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100:1920–1925. [PubMed: 12578963]

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. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. Jama. 2008; 299:1291–1305. [PubMed: 18349090]

Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. Annals of the New York Academy of Sciences. 2016

Blanchard EB, Kolb LC, Pallmeyer TP, Gerardi RJ. A psychophysiological study of post traumatic stress disorder in Vietnam veterans. Psychiatr Q. 1982; 54:220–229. [PubMed: 7187510]

Blanchard EB, Kolb LC, Prins A, Gates S, McCoy GC. Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with posttraumatic stress disorder. J Nerv Ment Dis. 1991; 179:371–373. [PubMed: 2051153]

Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Annals of the New York Academy of Sciences. 2004; 1032:141–153. [PubMed: 15677401]

Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. Progress in brain research. 2008; 167:171–186. [PubMed: 18037014]

Britton KT, Akwa Y, Spina MG, Koob GF. Neuropeptide Y blocks anxiogenic-like behavioral action of corticotropin-releasing factor in an operant conflict test and elevated plus maze. Peptides. 2000; 21:37–44. [PubMed: 10704717]

Bryant PA, Trinder J, Curtis N. Sick and tired: Does sleep have a vital role in the immune system? Nat Rev Immunol. 2004; 4:457–467. [PubMed: 15173834]

Burgado J, Harrell CS, Eacret D, Reddy R, Barnum CJ, Tansey MG, Miller AH, Wang H, Neigh GN. Two weeks of predatory stress induces anxiety-like behavior with co-morbid depressive-like behavior in adult male mice. Behavioural brain research. 2014; 275:120–125. [PubMed: 25200517]

Burger KS, Berner LA. A functional neuroimaging review of obesity, appetitive hormones and ingestive behavior. Physiology & behavior. 2014; 136:121–127. [PubMed: 24769220]

Burton MD, Johnson RW. Interleukin-6 trans-signaling in the senescent mouse brain is involved in infection-related deficits in contextual fear conditioning. Brain Behav Immun. 2012; 26:732–738. [PubMed: 22062497]

Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev. 2006; 26:17–31. [PubMed: 16199119]

Canale MP, Manca di Villahermosa S, Martino G, Rovella V, Noce A, De Lorenzo A, Di Daniele N. Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity. Int J Endocrinol. 20132013:865965. [PubMed: 24288531]

Chakraborty N, Meyerhoff J, Gautam A, Muhie S, Jibitu M, De Lima TC, Hammamieh R, Jett M. Gene and stress history interplay in emergence of PTSD-like features. Behavioural brain research. 2015; 292:266–277. [PubMed: 26025510]

Chen DY, Stern SA, Garcia-Osta A, Saunier-Rebori B, Pollonini G, Bambah-Mukku D, Blitzer RD, Alberini CM. A critical role for IGF-II in memory consolidation and enhancement. Nature. 2011; 469:491–497. [PubMed: 21270887]

Chintala KK, Krishna BH. Heart rate variability in overweight health care students: correlation with visceral fat. J Clin Diagn Res. 2015; 9:CC06–08. N, M.R. [PubMed: 25737980]

Cohen H, Matar MA, Buskila D, Kaplan Z, Zohar J. Early post-stressor intervention with high-dose corticosterone attenuates posttraumatic stress response in an animal model of posttraumatic stress disorder. Biological psychiatry. 2008; 64:708–717. [PubMed: 18635156]

Correia ML, Rahmouni K. Role of leptin in the cardiovascular and endocrine complications of metabolic syndrome. Diabetes Obes Metab. 2006; 8:603–610. [PubMed: 17026484]

Czerniawski J, Miyashita T, Lewandowski G, Guzowski JF. Systemic lipopolysaccharide administration impairs retrieval of context-object discrimination, but not spatial, memory: Evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation. Brain Behav Immun. 2015; 44:159–166. [PubMed: 25451612]

Daniele G, Guardado Mendoza R, Winnier D, Fiorentino TV, Pengou Z, Cornell J, Andreozzi F, Jenkinson C, Cersosimo E, Federici M, Tripathy D, Folli F. The inflammatory status score including IL-6, TNF-alpha, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. Acta Diabetol. 2014; 51:123–131. [PubMed: 24370923]

Daskalakis NP, Yehuda R, Diamond DM. Animal models in translational studies of PTSD. Psychoneuroendocrinology. 2013; 38:1895–1911. [PubMed: 23845512]

de Kloet CS, Vermetten E, Geuze E, Lentjes EG, Heijnen CJ, Stalla GK, Westenberg HG. Elevated plasma corticotrophin-releasing hormone levels in veterans with posttraumatic stress disorder. Progress in brain research. 2008; 167:287–291. [PubMed: 18037027]

de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nature neuroscience. 2000; 3:313–314. [PubMed: 10725918]

Duclos M, Marquez Pereira P, Barat P, Gatta B, Roger P. Increased cortisol bioavailability, abdominal obesity, and the metabolic syndrome in obese women. Obesity research. 2005; 13:1157–1166. [PubMed: 16076984]

Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2010; 375:181–183. [PubMed: 20109902]

Epel ES, McEwen B, Seeman T, Matthews K, Castellazzo G, Brownell KD, Bell J, Ickovics JR. Stress and body shape: stress-induced cortisol secretion is consistently greater among women with central fat. Psychosom Med. 2000; 62:623–632. [PubMed: 11020091]

Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, O'Connor DT, Baker DG. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA Psychiatry. 2014; 71:423–431. [PubMed: 24576974]

Felger, JC.; Haroon, E.; Miller, AH. Inflammation and Immune Function in Post-Traumatic Stress Disorder: Mechanisms, Consequences and Translational Implications. In: Ressler, KJ.; Liberzon, I., editors. Neurobiology of PTSD. Oxford Press; 2016.

Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, Miller AH. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Molecular psychiatry. 2015

FerroLuzzi A, Garza C, Haas J, Habicht DP, Himes J, Pradilla A, Raman L, RansomeKuti O, Seidell JC, Victora C, Wahlqvist ML, Yip R. Physical status: The use and interpretation of anthropometry - Introduction. Who Tech Rep Ser. 1995; 854:1–3.

Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes. 2007; 56:1010–1013. [PubMed: 17287468]

Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. The Journal of clinical psychiatry. 2007; 68:711–720. [PubMed: 17503980]

Frohlich M, Sund M, Lowel H, Imhof A, Hoffmeister A, Koenig W. Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). Eur Heart J. 2003; 24:1365–1372. [PubMed: 12871694]

Fu SS, McFall M, Saxon AJ, Beckham JC, Carmody TP, Baker DG, Joseph AM. Post-traumatic stress disorder and smoking: a systematic review. Nicotine Tob Res. 2007; 9:1071–1084. [PubMed: 17978982]

Garvey WT, Huecksteadt TP, Birnbaum MJ. Pretranslational suppression of an insulin-responsive glucose transporter in rats with diabetes mellitus. Science (New York, N.Y. 1989a; 245:60–63.

Garvey WT, Huecksteadt TP, Monzon R, Marshall S. Dexamethasone regulates the glucose transport system in primary cultured adipocytes: different mechanisms of insulin resistance after acute and chronic exposure. Endocrinology. 1989b; 124:2063–2073. [PubMed: 2651092]

Gautam A, D'Arpa P, Donohue DE, Muhie S, Chakraborty N, Luke BT, Grapov D, Carroll EE, Meyerhoff JL, Hammamieh R, Jett M. Acute and chronic plasma metabolomic and liver transcriptomic stress effects in a mouse model with features of post-traumatic stress disorder. PloS one. 2015; 10:e0117092. [PubMed: 25629821]

Geracioti TD Jr. Baker DG, Ekhator NN, West SA, Hill KK, Bruce AB, Schmidt D, Rounds-Kugler B, Yehuda R, Keck PE Jr. Kasckow JW. CSF norepinephrine concentrations in posttraumatic stress disorder. The American journal of psychiatry. 2001; 158:1227–1230. [PubMed: 11481155]

Geracioti TD Jr. Baker DG, Kasckow JW, Strawn JR, Jeffrey Mulchahey J, Dashevsky BA, Horn PS, Ekhator NN. Effects of trauma-related audiovisual stimulation on cerebrospinal fluid norepinephrine and corticotropin-releasing hormone concentrations in post-traumatic stress disorder. Psychoneuroendocrinology. 2008; 33:416–424. [PubMed: 18295412]

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nature neuroscience. 2002; 5:1242–1247. [PubMed: 12379862]

Gillespie CF, Bradley B, Mercer K, Smith AK, Conneely K, Gapen M, Weiss T, Schwartz AC, Cubells JF, Ressler KJ. Trauma exposure and stress-related disorders in inner city primary care patients. Gen Hosp Psychiatry. 2009; 31:505–514. [PubMed: 19892208]

Glover EM, Phifer JE, Crain DF, Norrholm SD, Davis M, Bradley B, Ressler KJ, Jovanovic T. Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. Depress Anxiety. 2011; 28:1058–1066. [PubMed: 21898707]

Gonzalez P, Machado I, Vilcaes A, Caruso C, Roth GA, Schioth H, Lasaga M, Scimonelli T. Molecular mechanisms involved in interleukin 1-beta (IL-1beta)-induced memory impairment. Modulation by alpha-melanocyte-stimulating hormone (alpha-MSH). Brain Behav Immun. 2013; 34:141–150. [PubMed: 23968970]

Gragnoli C. Hypothesis of the neuroendocrine cortisol pathway gene role in the comorbidity of depression, type 2 diabetes, and metabolic syndrome. Appl Clin Genet. 2014; 7:43–53. [PubMed: 24817815]

Grassi G. Leptin, sympathetic nervous system, and baroreflex function. Curr Hypertens Rep. 2004; 6:236–240. [PubMed: 15128478]

Grassi G. Qualitative assessment of sympathetic neural drive in cardiometabolic disease: a new challenge. Hypertension. 2007; 50:835–836. [PubMed: 17909119]

Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011; 29:415–445. [PubMed: 21219177]

Groer MW, Kane B, Williams SN, Duffy A. Relationship of PTSD Symptoms With Combat Exposure, Stress, and Inflammation in American Soldiers. Biol Res Nurs. 2015; 17:303–310. [PubMed: 25202037]

Gutman AR, Yang Y, Ressler KJ, Davis M. The role of neuropeptide Y in the expression and extinction of fear-potentiated startle. J Neurosci. 2008; 28:12682–12690. [PubMed: 19036961]

Haley AP, Gonzales MM, Tarumi T, Miles SC, Goudarzi K, Tanaka H. Elevated cerebral glutamate and myo-inositol levels in cognitively normal middle-aged adults with metabolic syndrome. Metab Brain Dis. 2010; 25:397–405. [PubMed: 21063759]

Hammels C, Pishva E, De Vry J, van den Hove DL, Prickaerts J, van Winkel R, Selten JP, Lesch KP, Daskalakis NP, Steinbusch HW, van Os J, Kenis G, Rutten BP. Defeat stress in rodents: From behavior to molecules. Neuroscience and biobehavioral reviews. 2015; 59:111–140. [PubMed: 26475995]

Hao Y, Jing H, Bi Q, Zhang J, Qin L, Yang P. Intra-amygdala microinfusion of IL-6 impairs the auditory fear conditioning of rats via JAK/STAT activation. Behavioural brain research. 2014; 275:88–95. [PubMed: 25193320]

Harrell CS, Burgado J, Kelly SD, Neigh GN. Ovarian steroids influence cerebral glucose transporter expression in a region- and isoform-specific pattern. Journal of neuroendocrinology. 2014; 26:217–225. [PubMed: 24612045]

Hastings JA, Morris MJ, Lambert G, Lambert E, Esler M. NPY and NPY Y1 receptor effects on noradrenaline overflow from the rat brain in vitro. Regulatory peptides. 2004; 120:107–112. [PubMed: 15177927]

Horowitz MA, Zunszain PA. Neuroimmune and neuroendocrine abnormalities in depression: two sides of the same coin. Annals of the New York Academy of Sciences. 2015; 1351:68–79. [PubMed: 25943397]

Hoth KF, Gonzales MM, Tarumi T, Miles SC, Tanaka H, Haley AP. Functional MR imaging evidence of altered functional activation in metabolic syndrome. AJNR Am J Neuroradiol. 2011; 32:541–547. [PubMed: 21183618]

Hsiung DY, Liu CW, Cheng PC, Ma WF. Using non-invasive assessment methods to predict the risk of metabolic syndrome. Appl Nurs Res. 2015; 28:72–77. [PubMed: 25908541]

Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. Expert review of neurotherapeutics. 2011; 11:275–285. [PubMed: 21306214]

Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. The American journal of psychiatry. 2001; 158:1184–1190. [PubMed: 11481147]

Jamal O, Aneni EC, Shaharyar S, Ali SS, Parris D, McEvoy JW, Veledar E, Blaha MJ, Blumenthal RS, Agatston AS, Conceicao RD, Feldman T, Carvalho JA, Santos RD, Nasir K. Cigarette smoking worsens systemic inflammation in persons with metabolic syndrome. Diabetol Metab Syndr 6, 79. 2014

Jia M, Smerin SE, Zhang L, Xing G, Li X, Benedek D, Ursano R, Li H. Corticosterone mitigates the stress response in an animal model of PTSD. Journal of psychiatric research. 2015; 60:29–39. [PubMed: 25307716]

Jing H, Hao Y, Bi Q, Zhang J, Yang P. Intra-amygdala microinjection of TNF-alpha impairs the auditory fear conditioning of rats via glutamate toxicity. Neurosci Res. 2015; 91:34–40. [PubMed: 25448547]

Johannessen KB, Berntsen D. Losing the symptoms: weight loss and decrease in posttraumatic stress disorder symptoms. J Clin Psychol. 2013; 69:655–660. [PubMed: 23382106]

Jovanovic T, Ressler KJ. How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. The American journal of psychiatry. 2010; 167:648–662. [PubMed: 20231322]

Kaouane N, Porte Y, Vallee M, Brayda-Bruno L, Mons N, Calandreau L, Marighetto A, Piazza PV, Desmedt A. Glucocorticoids can induce PTSD-like memory impairments in mice. Science (New York, N.Y. 2012; 335:1510–1513.

Karalis KP, Giannogonas P, Kodela E, Koutmani Y, Zoumakis M, Teli T. Mechanisms of obesity and related pathology: linking immune responses to metabolic stress. FEBS J. 2009; 276:5747–5754. [PubMed: 19754872]

Karlsson RM, Holmes A, Heilig M, Crawley JN. Anxiolytic-like actions of centrally-administered neuropeptide Y, but not galanin, in C57BL/6J mice. Pharmacology, biochemistry, and behavior. 2005; 80:427–436.

Keane TM, Kolb LC, Kaloupek DG, Orr SP, Blanchard EB, Thomas RG, Hsieh FY, Lavori PW. Utility of psychophysiological measurement in the diagnosis of posttraumatic stress disorder: results from a Department of Veterans Affairs Cooperative Study. J Consult Clin Psychol. 1998; 66:914–923. [PubMed: 9874904]

Keen-Rhinehart E, Ondek K, Schneider JE. Neuroendocrine regulation of appetitive ingestive behavior. Front Neurosci. 2013; 7:213. [PubMed: 24298235]

Kelly SD, Harrell CS, Neigh GN. Chronic stress modulates regional cerebral glucose transporter expression in an age-specific and sexually-dimorphic manner. Physiology & behavior. 2014; 126:39–49. [PubMed: 24382486]

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Archives of general psychiatry. 1995; 52:1048–1060. [PubMed: 7492257]

Khoury NM, Marvar PJ, Gillespie CF, Wingo A, Schwartz A, Bradley B, Kramer M, Ressler KJ. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. The Journal of clinical psychiatry. 2012; 73:849–855. [PubMed: 22687631]

Kim SY, Chung YK, Kim BS, Lee SJ, Yoon JK, An YS. Resting cerebral glucose metabolism and perfusion patterns in women with posttraumatic stress disorder related to sexual assault. Psychiatry research. 2012; 201:214–217. [PubMed: 22464826]

Kolassa IT, Eckart C, Ruf M, Neuner F, de Quervain DJ, Elbert T. Lack of cortisol response in patients with posttraumatic stress disorder (PTSD) undergoing a diagnostic interview. BMC Psychiatry. 2007; 7:54. [PubMed: 17916253]

Lach G, de Lima TC. Role of NPY Y1 receptor on acquisition, consolidation and extinction on contextual fear conditioning: dissociation between anxiety, locomotion and non-emotional memory behavior. Neurobiology of learning and memory. 2013; 103:26–33. [PubMed: 23603424]

Lasselin J, Capuron L. Chronic low-grade inflammation in metabolic disorders: relevance for behavioral symptoms. Neuroimmunomodulation. 2014; 21:95–101. [PubMed: 24557041]

Lee ZS, Critchley JA, Tomlinson B, Young RP, Thomas GN, Cockram CS, Chan TY, Chan JC. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. Metabolism. 2001; 50:135–143. [PubMed: 11229419]

Lembo G, Napoli R, Capaldo B, Rendina V, Iaccarino G, Volpe M, Trimarco B, Sacca L. Abnormal sympathetic overactivity evoked by insulin in the skeletal muscle of patients with essential hypertension. The Journal of clinical investigation. 1992; 90:24–29. [PubMed: 1634611]

Li B, Lang N, Cheng ZF. Serum Levels of Brain-Derived Neurotrophic Factor Are Associated with Diabetes Risk, Complications, and Obesity: a Cohort Study from Chinese Patients with Type 2 Diabetes. Molecular neurobiology. 2015

Liao SC, Lee MB, Lee YJ, Huang TS. Hyperleptinemia in subjects with persistent partial posttraumatic stress disorder after a major earthquake. Psychosom Med. 2004; 66:23–28. [PubMed: 14747634]

Loddick SA, Liu C, Takao T, Hashimoto K, De Souza EB. Interleukin-1 receptors: cloning studies and role in central nervous system disorders. Brain research. 1998; 26:306–319. [PubMed: 9651547]

Maes M, Lin AH, Delmeire L, Van Gastel A, Kenis G, De Jongh R, Bosmans E. Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. Biological psychiatry. 1999; 45:833–839. [PubMed: 10202570]

Marvar PJ, Goodman J, Fuchs S, Choi DC, Banerjee S, Ressler KJ. Angiotensin type 1 receptor inhibition enhances the extinction of fear memory. Biological psychiatry. 2014; 75:864–872. [PubMed: 24094510]

Masuo K. Roles of beta2- and beta3-adrenoceptor polymorphisms in hypertension and metabolic syndrome. Int J Hypertens. 20102010:832821. [PubMed: 20981286]

Matic G, Milutinovic DV, Nestorov J, Elakovic I, Jovanovic SM, Perisic T, Dunderski J, Damjanovic S, Knezevic G, Spiric Z, Vermetten E, Savic D. Lymphocyte glucocorticoid receptor expression level and hormone-binding properties differ between war trauma-exposed men with and without PTSD. Prog Neuropsychopharmacol Biol Psychiatry. 2013; 43:238–245. [PubMed: 23333536]

Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. Br J Psychiatry. 2007; 191:387–392. [PubMed: 17978317]

Meyer RM, Burgos-Robles A, Liu E, Correia SS, Goosens KA. A ghrelin-growth hormone axis drives stress-induced vulnerability to enhanced fear. Molecular psychiatry. 2014; 19:1284–1294. [PubMed: 24126924]

Michopoulos V. Stress-induced alterations in estradiol sensitivity increase risk for obesity in women. Physiology & behavior. 2016

Michopoulos V, Jovanovic T. Chronic inflammation: a new therapeutic target for post-traumatic stress disorder? Lancet Psychiatry. 2015; 2:954–955. [PubMed: 26544737]

Michopoulos V, Norrholm SD, Jovanovic T. Diagnostic Biomarkers for Posttraumatic Stress Disorder: Promising Horizons from Translational Neuroscience Research. Biological psychiatry. 2015a; 78:344–353. [PubMed: 25727177]

Michopoulos V, Rothbaum AO, Jovanovic T, Almli LM, Bradley B, Rothbaum BO, Gillespie CF, Ressler KJ. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. The American journal of psychiatry. 2015b; 172:353–362. [PubMed: 25827033]

Miller RJ, Sutherland AG, Hutchison JD, Alexander DA. C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. Cytokine. 2001; 13:253–255. [PubMed: 11237435]

Molina ME, Isoardi R, Prado MN, Bentolila S. Basal cerebral glucose distribution in long-term post-traumatic stress disorder. World J Biol Psychiatry. 2010; 11:493–501. [PubMed: 20218804]

Morgan CA 3rd, Rasmusson AM, Wang S, Hoyt G, Hauger RL, Hazlett G. Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. Biological psychiatry. 2002; 52:136–142. [PubMed: 12114005]

Morgan CA 3rd, Rasmusson AM, Winters B, Hauger RL, Morgan J, Hazlett G, Southwick S. Trauma exposure rather than posttraumatic stress disorder is associated with reduced baseline plasma neuropeptide-Y levels. Biological psychiatry. 2003; 54:1087–1091. [PubMed: 14625151]

Morissette SB, Tull MT, Gulliver SB, Kamholz BW, Zimering RT. Anxiety, anxiety disorders, tobacco use, and nicotine: a critical review of interrelationships. Psychol Bull. 2007; 133:245–272. [PubMed: 17338599]

Muhie S, Gautam A, Meyerhoff J, Chakraborty N, Hammamieh R, Jett M. Brain transcriptome profiles in mouse model simulating features of post-traumatic stress disorder. Mol Brain. 2015; 8:14. [PubMed: 25888136]

National Cholesterol Education Program Expert Panel on Detection, E.; Treatment of High Blood Cholesterol in, A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]

Norrholm SD, Glover EM, Stevens JS, Fani N, Galatzer-Levy IR, Bradley B, Ressler KJ, Jovanovic T. Fear load: The psychophysiological over-expression of fear as an intermediate phenotype associated with trauma reactions. Int J Psychophysiol. 2015; 98:270–275. [PubMed: 25451788]

Nowotny B, Cavka M, Herder C, Loffler H, Poschen U, Joksimovic L, Kempf K, Krug AW, Koenig W, Martin S, Kruse J. Effects of acute psychological stress on glucose metabolism and subclinical inflammation in patients with post-traumatic stress disorder. Hormone and metabolic research. Hormon- und Stoffwechselforschung. 2010; 42:746–753. [PubMed: 20665427]

Okada R, Fujiwara H, Mizuki D, Araki R, Yabe T, Matsumoto K. Involvement of dopaminergic and cholinergic systems in social isolation-induced deficits in social affiliation and conditional fear memory in mice. Neuroscience. 2015; 299:134–145. [PubMed: 25943484]

Orr SP, Metzger LJ, Lasko NB, Macklin ML, Hu FB, Shalev AY, Pitman RK, Harvard/Veterans Affairs Post-traumatic Stress Disorder Twin Study, I. Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: association with posttraumatic stress disorder. Archives of general psychiatry. 2003; 60:283–288. [PubMed: 12622661]

Pace TW, Wingenfeld K, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim CM. Increased peripheral NF-kappaB pathway activity in women with childhood abuse-related posttraumatic stress disorder. Brain Behav Immun. 2012; 26:13–17. [PubMed: 21801830]

Pal M, Febbraio MA, Whitham M. From cytokine to myokine: the emerging role of interleukin-6 in metabolic regulation. Immunol Cell Biol. 2014; 92:331–339. [PubMed: 24751614]

Pannacciulli N, Cantatore FP, Minenna A, Bellacicco M, Giorgino R, De Pergola G. C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. Int J Obes Relat Metab Disord. 2001; 25:1416–1420. [PubMed: 11673760]

Pascoe MC, Bauer IE. A systematic review of randomised control trials on the effects of yoga on stress measures and mood. Journal of psychiatric research. 2015; 68:270–282. [PubMed: 26228429]

Pasquali R, Ambrosi B, Armanini D, Cavagnini F, Uberti ED, Del Rio G, de Pergola G, Maccario M, Mantero F, Marugo M, Rotella CM, Vettor R. Cortisol and ACTH response to oral dexamethasone in obesity and effects of sex, body fat distribution, and dexamethasone concentrations: a dose-response study. The Journal of clinical endocrinology and metabolism. 2002; 87:166–175. [PubMed: 11788642]

Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, Salum G, Magalhaes PV, Kapczinski F, Kauer-Sant'Anna M. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015; 2:1002–1012. [PubMed: 26544749]

Pecoraro N, Dallman MF, Warne JP, Ginsberg AB, Laugero KD, la Fleur SE, Houshyar H, Gomez F, Bhargava A, Akana SF. From Malthus to motive: how the HPA axis engineers the phenotype, yoking needs to wants. Progress in neurobiology. 2006; 79:247–340. [PubMed: 16982128]

Peng N, Liu JT, Gao DF, Lin R, Li R. Angiotensin II-induced C-reactive protein generation: inflammatory role of vascular smooth muscle cells in atherosclerosis. Atherosclerosis. 2007; 193:292–298. [PubMed: 17055513]

Pereira MJ, Palming J, Svensson MK, Rizell M, Dalenback J, Hammar M, Fall T, Sidibeh CO, Svensson PA, Eriksson JW. FKBP5 expression in human adipose tissue increases following dexamethasone exposure and is associated with insulin resistance. Metabolism. 2014; 63:1198–1208. [PubMed: 24997500]

Perry BD, Giller EL Jr. Southwick SM. Altered platelet alpha 2-adrenergic binding sites in posttraumatic stress disorder. The American journal of psychiatry. 1987; 144:1511–1512.

Pietrzak RH, Gallezot JD, Ding YS, Henry S, Potenza MN, Southwick SM, Krystal JH, Carson RE, Neumeister A. Association of posttraumatic stress disorder with reduced in vivo norepinephrine transporter availability in the locus coeruleus. JAMA Psychiatry. 2013; 70:1199–1205. [PubMed: 24048210]

Plantinga L, Bremner JD, Miller AH, Jones DP, Veledar E, Goldberg J, Vaccarino V. Association between posttraumatic stress disorder and inflammation: a twin study. Brain Behav Immun. 2013; 30:125–132. [PubMed: 23379997]

Ponomarev I, Rau V, Eger EI, Harris RA, Fanselow MS. Amygdala transcriptome and cellular mechanisms underlying stress-enhanced fear learning in a rat model of posttraumatic stress disorder. Neuropsychopharmacology. 2010; 35:1402–1411. [PubMed: 20147889]

Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin Psychol Rev. 2010; 30:635–641. [PubMed: 20546985]

Pugh CR, Kumagawa K, Fleshner M, Watkins LR, Maier SF, Rudy JW. Selective effects of peripheral lipopolysaccharide administration on contextual and auditory-cue fear conditioning. Brain Behav Immun. 1998; 12:212–229. [PubMed: 9769157]

Rao MN, Chau A, Madden E, Inslicht S, Talbot L, Richards A, O'Donovan A, Ruoff L, Grunfeld C, Neylan TC. Hyperinsulinemic response to oral glucose challenge in individuals with posttraumatic stress disorder. Psychoneuroendocrinology. 2014; 49:171–181. [PubMed: 25108160]

Rao-Ruiz P, Carney KE, Pandya N, van der Loo RJ, Verheijen MH, van Nierop P, Smit AB, Spijker S. Time-dependent changes in the mouse hippocampal synaptic membrane proteome after contextual fear conditioning. Hippocampus. 2015

Rasmusson AM, Hauger RL, Morgan CA, Bremner JD, Charney DS, Southwick SM. Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. Biological psychiatry. 2000; 47:526–539. [PubMed: 10715359]

Reis FM, Almada RC, Fogaca MV, Brandao ML. Rapid Activation of Glucocorticoid Receptors in the Prefrontal Cortex Mediates the Expression of Contextual Conditioned Fear in Rats. Cereb Cortex. 2015

Reyes-Guzman CM, Bray RM, Forman-Hoffman VL, Williams J. Overweight and obesity trends among active duty military personnel: a 13-year perspective. Am J Prev Med. 2015; 48:145–153. [PubMed: 25442226]

Reynolds RM, Chapman KE, Seckl JR, Walker BR, McKeigue PM, Lithell HO. Skeletal muscle glucocorticoid receptor density and insulin resistance. JAMA. 2002; 287:2505–2506. [PubMed: 12020330]

Rosenbaum S, Stubbs B, Ward PB, Steel Z, Lederman O, Vancampfort D. The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: a systematic review and meta-analysis. Metabolism. 2015; 64:926–933. [PubMed: 25982700]

Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology. 2005; 30:1–10. [PubMed: 15358437]

Sah R, Geracioti TD. Neuropeptide Y and posttraumatic stress disorder. Molecular psychiatry. 2013; 18:646–655. [PubMed: 22801411]

Sanders VM. Interdisciplinary research: noradrenergic regulation of adaptive immunity. Brain Behav Immun. 2006; 20:1–8. [PubMed: 16140497]

Sano M, Fukuda K, Sato T, Kawaguchi H, Suematsu M, Matsuda S, Koyasu S, Matsui H, Yamauchi-Takihara K, Harada M, Saito Y, Ogawa S. ERK and p38 MAPK, but not NF-kappaB, are critically involved in reactive oxygen species-mediated induction of IL-6 by angiotensin II in cardiac fibroblasts. Circ Res. 2001; 89:661–669. [PubMed: 11597988]

Santoro A, Mattace Raso G, Meli R. Drug targeting of leptin resistance. Life sciences. 2015

Savoia C, Schiffrin EL. Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions. Clin Sci (Lond). 2007; 112:375–384. [PubMed: 17324119]

Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, Briegel J. Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Annals of the New York Academy of Sciences. 2006; 1071:46–53. D, D.E.Q. [PubMed: 16891561]

Scott KM, McGee MA, Wells JE, Oakley Browne MA. Obesity and mental disorders in the adult general population. Journal of psychosomatic research. 2008; 64:97–105. [PubMed: 18158005]

Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic stress disorder and impaired autonomic modulation in male twins. Biological psychiatry. 2013; 73:1103–1110. [PubMed: 23434412]

Shalev AY, Peri T, Brandes D, Freedman S, Orr SP, Pitman RK. Auditory startle response in trauma survivors with posttraumatic stress disorder: a prospective study. The American journal of psychiatry. 2000; 157:255–261. [PubMed: 10671396]

Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley B, Tang Y, Gillespie CF, Cubells JF, Ressler KJ. Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. 2011; 156B:700–708. [PubMed: 21714072]

Southwick SM, Bremner JD, Rasmusson A, Morgan CA 3rd, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biological psychiatry. 1999; 46:1192–1204. [PubMed: 10560025]

Spencer SJ, Emmerzaal TL, Kozicz T, Andrews ZB. Ghrelin's Role in the Hypothalamic-Pituitary-Adrenal Axis Stress Response: Implications for Mood Disorders. Biological psychiatry. 2015; 78:19–27. [PubMed: 25534754]

Spivak B, Shohat B, Mester R, Avraham S, Gil-Ad I, Bleich A, Valevski A, Weizman A. Elevated levels of serum interleukin-1 beta in combat-related posttraumatic stress disorder. Biological psychiatry. 1997; 42:345–348. [PubMed: 9276074]

Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007; 21:901–912. [PubMed: 17475444]

Stern SA, Kohtz AS, Pollonini G, Alberini CM. Enhancement of memories by systemic administration of insulin-like growth factor II. Neuropsychopharmacology. 2014; 39:2179–2190. [PubMed: 24642597]

Stuckey MI, Kiviniemi A, Gill DP, Shoemaker JK, Petrella RJ. Associations between heart rate variability, metabolic syndrome risk factors, and insulin resistance. Appl Physiol Nutr Metab. 2015; 40:734–740. [PubMed: 26140416]

Thompson BL, Erickson K, Schulkin J, Rosen JB. Corticosterone facilitates retention of contextually conditioned fear and increases CRH mRNA expression in the amygdala. Behavioural brain research. 2004; 149:209–215. [PubMed: 15129783]

Thorp AA, Schlaich MP. Relevance of Sympathetic Nervous System Activation in Obesity and Metabolic Syndrome. J Diabetes Res. 2015; 2015:341583. [PubMed: 26064978]

Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychol Bull. 2006; 132:959–992. [PubMed: 17073529]

van Beek L, Lips MA, Visser A, Pijl H, Ioan-Facsinay A, Toes R, Berends FJ, Willems van Dijk K, Koning F, van Harmelen V. Increased systemic and adipose tissue inflammation differentiates obese women with T2DM from obese women with normal glucose tolerance. Metabolism. 2014; 63:492–501. [PubMed: 24467914]

van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Amarouchi K, Kavelaars A, Heijnen CJ. Glucocorticoid receptor pathway components predict posttraumatic stress disorder symptom development: a prospective study. Biological psychiatry. 2012; 71:309–316. [PubMed: 22137507]

Vaz M, Jennings G, Turner A, Cox H, Lambert G, Esler M. Regional sympathetic nervous activity and oxygen consumption in obese normotensive human subjects. Circulation. 1997; 96:3423–3429. [PubMed: 9396437]

Verma D, Wood J, Lach G, Herzog H, Sperk G, Tasan R. Hunger Promotes Fear Extinction by Activation of an Amygdala Microcircuit. Neuropsychopharmacology. 2015

Villablanca AC, Warford C, Wheeler K. Inflammation and Cardiometabolic Risk in African American Women Is Reduced by a Pilot Community-Based Educational Intervention. J Womens Health (Larchmt). 2015

von Kanel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, Schnyder U. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. Journal of psychiatric research. 2007; 41:744–752. [PubMed: 16901505]

Walker BR, Soderberg S, Lindahl B, Olsson T. Independent effects of obesity and cortisol in predicting cardiovascular risk factors in men and women. J Intern Med. 2000; 247:198–204. [PubMed: 10692082]

Wang W, Liu SL, Li K, Chen Y, Jiang B, Li YK, Xiao JL, Yang S, Chen T, Chen JG, Li JG, Wang F. Leptin: a potential anxiolytic by facilitation of fear extinction. CNS Neurosci Ther. 2015; 21:425–434. [PubMed: 25645604]

Welty FK, Alfaddagh A, Elajami TK. Targeting inflammation in metabolic syndrome. Transl Res. 2015

Williamson LL, Bilbo SD. Chemokines and the hippocampus: a new perspective on hippocampal plasticity and vulnerability. Brain Behav Immun. 2013; 30:186–194. [PubMed: 23376170]

Wilson CB, Ebenezer PJ, McLaughlin LD, Francis J. Predator exposure/psychosocial stress animal model of post-traumatic stress disorder modulates neurotransmitters in the rat hippocampus and prefrontal cortex. PloS one. 2014a; 9:e89104. [PubMed: 24551226]

Wilson CB, McLaughlin LD, Ebenezer PJ, Nair AR, Dange R, Harre JG, Shaak TL, Diamond DM, Francis J. Differential effects of sertraline in a predator exposure animal model of post-traumatic stress disorder. Front Behav Neurosci. 2014b; 8:256. [PubMed: 25126063]

Wilson CB, McLaughlin LD, Nair A, Ebenezer PJ, Dange R, Francis J. Inflammation and oxidative stress are elevated in the brain, blood, and adrenal glands during the progression of post-traumatic stress disorder in a predator exposure animal model. PloS one. 2013; 8:e76146. [PubMed: 24130763]

Yehuda R. Neuroendocrine aspects of PTSD. Handbook of experimental pharmacology. 2005:371–403. [PubMed: 16594265]

Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr. Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Archives of general psychiatry. 1995; 52:583–593. [PubMed: 7598635]

Yehuda R, Cai G, Golier JA, Sarapas C, Galea S, Ising M, Rein T, Schmeidler J, Muller-Myhsok B, Holsboer F, Buxbaum JD. Gene expression patterns associated with posttraumatic stress disorder following exposure to the World Trade Center attacks. Biological psychiatry. 2009a; 66:708–711. [PubMed: 19393990]

Yehuda R, Golier JA, Yang RK, Tischler L. Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. Biological psychiatry. 2004; 55:1110–1116. [PubMed: 15158431]

Yehuda R, Harvey PD, Golier JA, Newmark RE, Bowie CR, Wohltmann JJ, Grossman RA, Schmeidler J, Hazlett EA, Buchsbaum MS. Changes in relative glucose metabolic rate following cortisol administration in aging veterans with posttraumatic stress disorder: an FDG-PET neuroimaging study. J Neuropsychiatry Clin Neurosci. 2009b; 21:132–143. [PubMed: 19622684]

Yeung EH, Zhang C, Chen J, Bowers K, Hu FB, Kang G, Qi L. Polymorphisms in the neuropeptide Y gene and the risk of obesity: findings from two prospective cohorts. The Journal of clinical endocrinology and metabolism. 2011; 96:E2055–2062. [PubMed: 21937627]

Zhang L, Lee IC, Enriquez RF, Lau J, Vahatalo LH, Baldock PA, Savontaus E, Herzog H. Stress- and diet-induced fat gain is controlled by NPY in catecholaminergic neurons. Mol Metab. 2014; 3:581–591. [PubMed: 25061562]

Zhao J, Liu J, Pang X, Wang S, Wu D, Zhang X, Feng L. Angiotensin II induces C-reactive protein expression via AT1-ROS-MAPK-NF-kappaB signal pathway in hepatocytes. Cell Physiol Biochem. 2013; 32:569–580. [PubMed: 24021937]

Zhao TJ, Sakata I, Li RL, Liang G, Richardson JA, Brown MS, Goldstein JL, Zigman JM. Ghrelin secretion stimulated by {beta}1-adrenergic receptors in cultured ghrelinoma cells and in fasted mice. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:15868–15873. [PubMed: 20713709]

Zoladz PR, Fleshner M, Diamond DM. Psychosocial animal model of PTSD produces a long-lasting traumatic memory, an increase in general anxiety and PTSD-like glucocorticoid abnormalities. Psychoneuroendocrinology. 2012; 37:1531–1545. [PubMed: 22421563]

Zoladz PR, Park CR, Fleshner M, Diamond DM. Psychosocial predator-based animal model of PTSD produces physiological and behavioral sequelae and a traumatic memory four months following stress onset. Physiology & behavior. 2015; 147:183–192. [PubMed: 25911267]

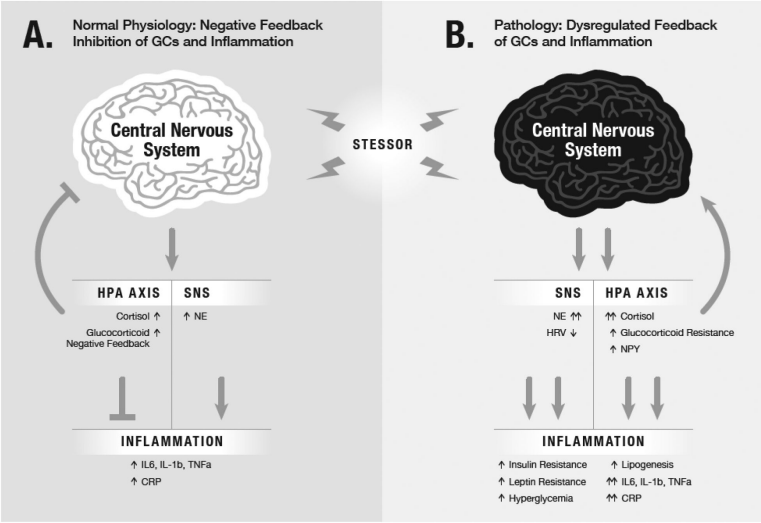

Figure 1.

(A) Normal physiology: the established negative feedback inhibition of the stress axis is mediated by glucocorticoids (GCs). Exposure to a stressor activates the HPA axis and sympathetic pathways, leading to increases in GCs and pro-inflammatory cytokines (Bierhaus et al., 2003; Steptoe et al., 2007). While the sympathetic system increases cytokine release (Bierhaus et al., 2003), GCs act to inhibit subsequent GC and cytokine release in a negative feedback manner that is regulated via GC receptors (Horowitz and Zunszain, 2015; Sanders, 2006). (B) Pathology: heightened sympathetic drive (increased norepinephrine and decreased HRV) and dysregulation of the stress axis can lead to impaired GC-immune feedback such that inflammation is increased in the presence of GC resistance (Horowitz and Zunszain, 2015). The increase in GCs in this pathological state increases NPY levels, facilitates food intake and promotes lipogenesis (Michopoulos, 2016), thus further increasing inflammation that can no longer be inhibited by GC negative feedback. These downstream consequences of augmented inflammation also lead to hyperglycemia, and leptin and insulin resistance.

Table 1

Summary of biological phenotypes associated with both PTSD and Metabolic Syndrome (MetS). Arrow denotes directionality of changes associated with PTSD and MetS.

Phenotype	PTSD	MetS
HPA Axis		
Glucocorticoid receptors (GR)	↑ Peripheral GR levels (Matic et al., 2013; van Zuiden et al., 2012)	↑ Peripheral GR levels (Reynolds et al., 2002)
GR negative feedback	↑ GR negative feedback(Yehuda et al., 2004)	↓ GR negative feedback (Pasquali et al., 2002)
Cortisol levels	↓ Morning cortisol levels (Meewisse et al., 2007; Yehuda, 2005) ↓ Cortisol response to stressor(Kolassa et al., 2007)	↓ Morning cortisol levels (Duclos et al., 2005; Walker et al., 2000) ↑ Cortisol response to stressor(Epel et al., 2000)
Sympathetic Nervous System		
Sympathetic tone	↑ Heart rate and skin conductance(Blanchard et al., 1982; Keane et al., 1998; Orr et al., 2003; Shalev et al., 2000)	↑ Heart rate and sympathetic activity (Canale et al., 2013; Thorp and Schlaich, 2015)
Heart rate variability (HRV)	↓ HRV (Shah et al., 2013)	↓ HRV (Chintala et al., 2015; Stuckey et al., 2015)
Norepinephrine (NE) signaling	↑ Circulating NE peripherally and centrally(Geracioti et al., 2001)	↑ Urinary and whole-body plasma NE(Lee et al 2001; Vaz et al., 1997)
Metabolic Characteristics		
Obesity	↑ Prevalence of abdominal obesity(Rosenbaum et al., 2015)	↑ Abdominal obesity is characteristic(Thorp and Schlaich, 2015)
Type 2 diabetes mellitus (T2DM)	↑ Risk of T2DM (Rao et al., 2014)	↑ Risk of T2DM (Thorp and Schlaich, 2015)
Insulin resistance	↑ Circulating insulin(Rao et al 2014) ↓ Insulin response to oral glucose tolerance test(Rao et al 2014)	↑ Circulating insulin (Thorp and Schlaich, 2015) ↓ Insulin response is characteristic(Thorp and Schlaich, 2015)
Glucose metabolism	↑ Prevalence of hyperglycemia(Rosenbaum et al 2015) Disrupted brain glucose metabolism(Molina et al., 2010)	↑ Prevalence of hyperglycemia (Thorp and Schlaich, 2015) Disrupted brain glucose metabolism via BDNF(Li et al., 2015)
Neuropeptide Y (NPY)	↓ NPY levels (Morgan et al., 2002; Rasmusson et al., 2000)	↑ NPY release in obese patients(Baltazi et al., 2011) *NPY* polymorphisms assoc. with ↑ NPY, obesity(Yeung et al., 2011)
Leptin resistance	↑ Leptin (Liao et al., 2004) Leptin facilitates fear extinction in animal models(Wang et al., 2015)	↑ Leptin (Correia and Rahmouni, 2006)
Inflammation		
CRP	↑ CRP associated with ↑ symptoms(Michopoulos et al., 2015b; Miller et al., 2001; Plantinga et al., 2013) ↑ CRP associated with ↑ fear-potentiated startle(Michopoulos et al., 2015b)	↑ CRP levels (Bastard et al., 2000a; Bastard et al., 2000b)
TNFα	↑ TNFα levels (Pace et al 2012)	↑ TNFα levels (Bastard et al., 2000b)
IL-6	↑ IL-6 levels (Maes et al., 1999) IL-6 amygdala injection ↓ acquisition, extinction of fear conditioning in animal model(Hao et al., 2014)	↑ IL-6 levels (Bastard et al., 2000a; Bastard et al., 2000b) ↑ IL-6 assoc. with insulin resistance, hyperglycemia in T2DM (Daniele et al., 2014)