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Symposium

Adaptation to extreme stress: post-traumatic stress disorder, neuropeptide Y and metabolic syndrome

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Abstract

The prevalence rates of obesity and metabolic syndrome are on the rise in the United States. Epidemiological surveys suggest that the rates of these medical conditions are especially high among persons with psychiatric disorders, including post-traumatic stress disorder (PTSD). A variety of factors are thought to contribute to the risk for metabolic syndrome, including excessive caloric intake, decreased activity and energy expenditure, use of certain medications, stress and genetic influences. Recent research demonstrates that stress, acting through the neuropeptide Y (NPY) and glucocorticoid systems, potentiates the development of obesity and other aspects of metabolic syndrome in mice fed a high caloric, fat and sugar diet. Alterations in the NPY and glucocorticoid systems also impact behavioral adaptation to stress, as indicated by studies in animals and persons exposed to severe, life-threatening or traumatic stress. The following review examines the biology of the NPY and neuroactive steroid systems as physiological links between metabolic syndrome and PTSD, a paradigmatic neuropsychiatric stress disorder. Hopefully, understanding the function of these systems from both a translational and systems biology point of view in relation to stress will enable development of more effective methods for preventing and treating the negative physical and mental health consequences of stress.

Keywords: metabolic syndrome, post-traumatic stress disorder, neuropeptide Y, obesity hypertension, neurosteroids, depression, dehydroepiandosterone, testosterone, cortisol, allopregnanolone


Introduction

Neurophysiological adaptation to stress involves a broad reorganization of biological systems within the individual, with implications for the function of the mind and body. Given that stress, by definition, taxes available physiological capacities, it is not surprising that stress adaptation involves basic metabolic changes that influence energy availability – impacting both energy reserves and ease of energy mobilization. It follows that specific variations in neurobiological factors with broad influence on stress adaptation might lead to predictable and coherent patterns of co-morbid stress-related psychiatric, medical and metabolic conditions. Enumerating the multisystem effects of such broad-impact neurobiological factors may therefore allow us to better understand and perhaps dissociate, manipulate and optimize multisystem patterns of stress adaptation. With such goals in mind, we undertake a discussion of the neuropeptide Y (NPY) system and other potential neurobiological mediators of the observed relationships among stress, post-traumatic stress disorder (PTSD) and metabolic syndrome (Figure 1).

Rates of metabolic syndrome in PTSD

Metabolic syndrome is characterized by a group of medical risk factors that signal abnormal underlying pathophysiological processes that increase risk for morbidity (e.g. cardiovascular disease and Type II diabetes) and mortality. Although there is not complete consensus on specific risk factors, they are generally thought to include abdominal
obesity (usually characterized by waist/hip ratio or body mass index [BMI; see Table 1]), hypertension, hyperglycemia and/or insulin resistance, atherogenic dyslipidemia (e.g. high cholesterol or low high-density lipoprotein [HDL] levels), a prothrombic state and elevated proinflammatory factors (e.g. C-reactive protein).

In a recent study specifically focused on PTSD, Heppner et al.1 used validated, rigorous semi-structured interviews to diagnose psychiatric disorders, and ascertained metabolic syndrome by measuring triglycerides, HDL, systolic and diastolic blood pressures, waist/hip ratio and glucose in 253 veterans who entered treatment programs for Gulf War Syndrome and PTSD at the Cincinnati VA Medical Center. Most of the participants (92%) were men and their average age was 51.5 y (standard deviation [SD] = 9 y). The prevalence of metabolic syndrome was 40% in the total sample, 29% in veterans with major depressive disorder (MDD) alone, 34% in veterans with PTSD alone, 46% in veterans with co-morbid PTSD/MDD and 43% among all veterans with PTSD, regardless of MDD status. The rates of metabolic syndrome among the veterans with PTSD were judged to be higher than the 21–30% rates for adults aged just 4–7 y younger included in the National Health and Nutrition Examination Survey. In addition, each one-point increase in the severity of PTSD symptoms, as measured by the Clinician Administered PTSD Scale,2 conferred a one-point increase in the risk for metabolic syndrome – in accordance with the work by Violanti et al.3 which showed that the rate of metabolic syndrome among police officers with the most severe PTSD was three times higher than in officers with the lowest PTSD severity. In this context, it is important to note that co-morbid PTSD/MDD is not thought to represent a confluence of two independent disorders. PTSD and MDD have several symptoms that overlap. In addition, several epidemiological studies show that rates of MDD

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Table 1 Age-adjusted rates of obesity in US adults is increasing according to the periodic National Health and Nutrition Examination Survey (NHANES)1

<table>
<thead>
<tr>
<th>NHANES</th>
<th>Overweight 25 ≤ BMI† &lt; 30</th>
<th>Obese BMI ≥ 30</th>
<th>Extremely obese BMI ≥ 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976–1980</td>
<td>32.1</td>
<td>15.0</td>
<td>1.4</td>
</tr>
<tr>
<td>n = 11,765</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988–1994</td>
<td>32.7</td>
<td>23.2</td>
<td>3.0</td>
</tr>
<tr>
<td>n = 14,468</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999–2000</td>
<td>33.6</td>
<td>30.9</td>
<td>5.0</td>
</tr>
<tr>
<td>n = 3603</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001–2002</td>
<td>34.4</td>
<td>31.3</td>
<td>5.4</td>
</tr>
<tr>
<td>n = 3916</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2003–2004</td>
<td>33.4</td>
<td>32.9</td>
<td>5.1</td>
</tr>
<tr>
<td>n = 3756</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005–2006</td>
<td>32.2</td>
<td>35.1</td>
<td>6.2</td>
</tr>
<tr>
<td>n = 3835</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


2BMI (kg/m²): body mass index calculated as (weight in kilograms)/(height in meters)² or as 703 × ([weight in pounds]/[height in inches])²

In a recent study specifically focused on PTSD, Heppner et al.1 used validated, rigorous semi-structured interviews to diagnose psychiatric disorders, and ascertained metabolic syndrome by measuring triglycerides, HDL, systolic and diastolic blood pressures, waist/hip ratio and glucose in 253 veterans who entered treatment programs for Gulf War Syndrome and PTSD at the Cincinnati VA Medical Center. Most of the participants (92%) were men and their average age was 51.5 y (standard deviation [SD] = 9 y). The prevalence of metabolic syndrome was 40% in the total sample, 29% in veterans with major depressive disorder (MDD) alone, 34% in veterans with PTSD alone, 46% in veterans with co-morbid PTSD/MDD and 43% among all veterans with PTSD, regardless of MDD status. The rates of metabolic syndrome among the veterans with PTSD were judged to be higher than the 21–30% rates for adults aged just 4–7 y younger included in the National Health and Nutrition Examination Survey. In addition, each one-point increase in the severity of PTSD symptoms, as measured by the Clinician Administered PTSD Scale,2 conferred a one-point increase in the risk for metabolic syndrome – in accordance with the work by Violanti et al.3 which showed that the rate of metabolic syndrome among police officers with the most severe PTSD was three times higher than in officers with the lowest PTSD severity. In this context, it is important to note that co-morbid PTSD/MDD is not thought to represent a confluence of two independent disorders. PTSD and MDD have several symptoms that overlap. In addition, several epidemiological studies show that rates of MDD
alone remain the same (~5%) before and after trauma exposure. The steep increase in MDD observed after trauma is almost fully accounted for by MDD co-morbid with PTSD, suggesting that PTSD/MDD may essentially constitute more severe PTSD (e.g. reference 6).

In a study of traumatized mothers of pediatric cancer survivors and non-traumatized mothers of healthy children, Glover et al. reported a similar association between PTSD and allostatic load. Allostatic load is thought to represent the physiological wear-and-tear on the body that accumulates as a result of adaptation to frequent and prolonged stress. Similar to metabolic syndrome, it is defined by multiple medical indicators that predict morbidity and thus offers a plausible model to account for the poor physical health associated with PTSD wherein many of the biological alterations are relatively small and fall within the normal range. In the Glover et al. study, BMI, resting systolic and diastolic blood pressures, total cholesterol, glycosylated hemoglobin (an indicator of average blood glucose levels), and urinary cortisol, norepinephrine (NE) and epinephrine were considered as risk factors, while HDL and serum dehydroepiandrosterone sulfate (DHEAS), an adenally derived peripheral and centrally acting neuroactive steroid, were considered as protective factors. The mothers with PTSD had greater allostatic load than the traumatized and non-traumatized mothers without PTSD.

Several other studies have addressed the relationship between PTSD and individual components of metabolic syndrome or allostatic load. For example, although obesity has increased markedly in the United States over the past 25 y (Table 1), overweight and obesity rates among US veterans appear to have climbed even higher, with the highest rates among veterans with PTSD. For the year 2000, Das et al. reported that among 93,290 female veterans, 68.4% were at least overweight and 37.4% were obese; among 1,710,032 male veterans, 73% were at least overweight and 32.9% were obese. Similarly, Vieweg et al. using national VA administrative data for a sample of over 47,000 veterans, found that 33.5% of male veterans without PTSD were overweight and 30.5% were obese, whereas 33.5% of 1819 veterans with PTSD were overweight and 40.4% were obese. Data from a local VA Medical Center (Richmond, VA) revealed even higher rates of obesity in veterans with PTSD, which did not change with age as observed in the general population. Veterans with PTSD in this cohort were on average, obese, with a mean BMI of 30.0 ± 5.7. Consistent with these studies in veterans, Glover et al. found that BMI was the only component of allostatic load that was significantly increased in subjects with PTSD compared with healthy controls.

Other studies have focused more specifically on the cardiovascular components of metabolic syndrome. Most supporting evidence for an association between PTSD and hypertension comes from studies in which participants self-reported that they had hypertension; only Emdad et al. reported negative findings. Of the remaining studies, Kang et al. found that PTSD was related to greater treatment utilization for hypertension among elderly prisoners of war. Santic et al. found a greater prevalence of physician-diagnosed hypertension among civilians with PTSD, but only if they had lost a loved one in the Croatian civil war. Schnurr et al. failed to find an increased incidence of physician-diagnosed hypertension associated with PTSD in a sample of elderly US combat veterans prospectively followed since the 1960s. However, these men had been selected for good health at study entry, so those who had already developed hypertension had been excluded. Recent large studies lend stronger support to the idea that trauma exposure may increase the risk for hypertension. Granada et al. reported that after adjusting for potential confounding variables, active duty personnel with multiple exposures to combat had a 1.33 increased odds of reporting new hypertension over those not exposed to combat. Andersen et al. using VA administrative data for a sample of veterans of the Iraq or Afghanistan Wars, reported that a chart diagnosis of PTSD was associated with a 38% increase in the odds of hypertensive disorder and a 56% increase in the rate of new onset hypertension.

There is relatively more evidence on resting or tonic levels of blood pressure in laboratory and ambulatory settings than on measures of clinical hypertension in PTSD. A recent meta-analysis by Pole indicates that there are small but statistically reliable elevations in resting systolic and diastolic blood pressure in PTSD patients relative to controls. An earlier meta-analysis reported that differences in resting blood pressure were greater for comparisons between PTSD and non-traumatized control groups than for comparisons between PTSD- and trauma-exposed control groups.

Blood pressure reactivity has also been measured in PTSD patients compared with controls — usually in laboratory studies exposing individuals to standardized trauma cues (e.g. the same combat scene) or individualized trauma cues. According to the meta-analysis by Pole, there are no effects of PTSD on systolic blood pressure responses to either type of cue, but there is a moderate increase in diastolic blood pressure responses to individualized cues among individuals with PTSD.

Several groups of investigators have used ambulatory monitoring to obtain more naturalistic information about baseline blood pressure and blood pressure reactivity than can be obtained from a single measurement session. These investigators found no differences between resting levels, but greater reactivity or variability in blood pressure among individuals with PTSD compared with those without PTSD. Further, PTSD appeared to moderate effects of hostility on heart rate and diastolic blood pressure; hostility, in turn, has been associated with cardiovascular risk. These studies suggest that resting blood pressure measures in the laboratory or a doctor’s office fail to fully capture blood pressure dynamics among individuals with PTSD and may underestimate cardiovascular risk in this population.

In summary, among persons exposed to psychological trauma, those who develop PTSD, and particularly those with more severe PTSD or co-morbid PTSD/MDD, appear to be at increased risk for metabolic syndrome. The following discussion focuses on the role of NPY and stress steroid systems that interact with NPY as potential physiological mediators linking stress exposure, PTSD and metabolic syndrome.
Links between stress, PTSD and metabolic syndrome: NPY and stress steroids

To be diagnosed with PTSD, an individual must have experienced a traumatic event that posed a perceived threat to life or physical wellbeing, followed by the development of sustained re-experiencing, hyperarousal and avoidance symptoms of sufficient frequency and intensity.27 The precise composition and severity of PTSD symptoms vary among individuals with PTSD and are associated with variations in underlying neurobiological perturbations (e.g. references28–31). Similarly, components of metabolic syndrome and allostatic load vary among patients with PTSD, suggesting that individually variable neurobiological processes might also underlie variations in this non-psychiatric condition. Understanding how particular individually variable neurobiological characteristics might translate into such co-morbid neuropsychiatric and medical disease – or multisystem disease – will hopefully enable the development of new and more effective multisystem therapeutics. The NPY system is an important candidate to consider in this context. Relevant neuroactive steroids that interact with the NPY system, as well as exert independent effects on stress adaptation, are considered in kind (Figure 1).

Beneficial effects of NPY during stress

NPY is a stress-activated sympathetic cardiovascular and metabolic regulator that could influence co-morbidity patterns of stress-related disorders such as metabolic syndrome and PTSD. The following discussion outlines animal as well as human studies from which emerges a picture of NPY-mediated, short-term, stress-moderating neurophysiological processes that might also underlie variations in this non-psychiatric condition. Understanding how particular individually variable neurobiological characteristics might translate into such co-morbid neuropsychiatric and medical disease – or multisystem disease – will hopefully enable the development of new and more effective multisystem therapeutics. The NPY system is an important candidate to consider in this context. Relevant neuroactive steroids that interact with the NPY system, as well as exert independent effects on stress adaptation, are considered in kind (Figure 1).

Evidence of beneficial effects of NPY on psychological and behavioral responses to stress is ample. NPY activation of amygdalar NPY-Y1 receptors (Y1Rs) has been shown to have clear anxiolytic and anticonflict effects in multiple animal models.32–37 In addition, activation of the central NPY system has been shown to stimulate neurogenesis in the hippocampus and subventricular zone, and in this way may support recovery from stress.38,39

In humans, NPY gene variants associated with increased NPY expression are associated with reduced trait anxiety and reduced activation of the amygdala in response to emotionally provocative stimuli.40 Higher plasma NPY levels achieved during intensely stressful military training procedures are associated with psychological resilience and superior performance.41,42 Increased baseline plasma NPY levels and NPY release in response to intravenous administration of the noradrenergic alpha2 receptor antagonist yohimbine43 have been associated with reduced PTSD symptoms in combat veterans,28 and higher baseline plasma NPY levels were prospectively associated with greater improvement in PTSD symptoms over time.44 In addition, intravenous NPY administration has been shown to decrease sleep latency, increase stage 2 sleep and modulate hypothalamic-pituitary-adrenal (HPA) axis reactivity.45,46

NPY also supports adaptive cardiovascular responses to stress. At rest, NPY exerts a Y2 receptor-mediated bradycardiac effect in the nucleus tractus solitarius.47,48 When released during stress, NPY inhibits vagal action at the heart via presynaptic Y2 Rs to facilitate heart rate increases,49–51 and acts at NPY-Y1 Rs in the vasculature to amplify the effects of NE and increase overall blood pressure. In the meantime, dipeptidyl peptidase 4 (DPP4), which is abundantly present in endothelial cells of the microvasculature as well as released from the adrenal gland during stress, removes two amino acids from NPY to produce NPY3–36, a Y2/Y5-selective agonist which then acts presynaptically at NPY-Y2 Rs to return the firing rate of sympathetic neurons to baseline.52

Over the long run, NPY increases the capacity to sustain high blood pressure during sympathetic challenge by mitogenic induction of vascular smooth muscle hypertrophy – mediated by NPY-Y1 Rs and β-adrenergically inducible Y5Rs53,54 – and via β-adrenergic receptor-mediated priming of vascular smooth muscle cell responses to NPY during high noradrenergic states.55

The NPY system likewise helps to maintain energy balance and promote recovery from stress-induced energy depletion. NPY neurons projecting from the arcuate nucleus to the paraventricular nucleus and lateral hypothalamus facilitate feeding and weight gain, while NPY neurons projecting from the dorsomedial hypothalamus to the nucleus tractus solitarius and dorsal motor nucleus of the vagus influence circadian feeding and modulate intrameal satiety signals.56 Intracereally, NPY decreases the expression of mitochondrial uncoupling protein, thereby suppressing thermogenesis and promoting ATP formation,57 a process of apparently greater relevance to non-neuronal cells than neurons.58

Recent groundbreaking work in mice by Kuo et al.59 has also shown powerful peripheral effects of the NPY system on energy balance – effects that may be beneficial or detrimental, depending on the constancy of a plentiful food supply. Stress can lead to weight loss via effects of NE on lipolysis. In contrast, when stress is extreme and combined with a high fat/sugar diet, the endogenous release of NPY into visceral fat increases the formation of new adipocytes and accelerates abdominal obesity and the development of metabolic syndrome. These processes were shown to be:

- (a) mediated by upregulation of adipogenic NPY system constituents in fat (NPY, Y2 Rs and DPP4, which converts NPY to NPY3–36, the NPY-Y2-R preferring agonist); (b) facilitated by glucocorticoids; and (c) strikingly reversed by the local or systemic injection of an NPY-Y2-R antagonist, or the administration of the antiglucocorticoid, RU-486.

Paradoxical link between PTSD and metabolic syndrome

Numerous basic research studies have shown that NPY inhibits NE release and activation of the locus coeruleus via stimulation of presynaptic NPY-Y2 Rs.60 Research also shows that intense chronic stress reduces plasma NPY levels. Rodents exposed to intense, variable stressors over 12 d showed decreased baseline plasma NPY levels and increased NE responses to subsequent acute footshock.61 In male
veterans and active duty military personnel, respectively, baseline plasma NPY levels correlated negatively with combat exposure and previous exposure to life threat, \( P = 0.001 \) (Rasmusson et al., preliminary observations). In general, then, NPY behaves like a high-pressure valve – inhibiting the release of NE during low sympathetic system activity and potentiating its impact during high activity. NPY thus conserves bioenerg for periods of high demand, at which point it helps to maintain organism function as energy and neurotransmitters are depleted.

Lower NPY levels in persons with PTSD could therefore be expected to lower the stress threshold and increase the frequency of NPY release. A compelling hypothesis thus emerges. The frequency with which NPY and other stress reactants are released into the fat, as well as the amplitude of release may critically contribute to the risk for metabolic syndrome. This may help explain why PTSD severity influences the risk for metabolic syndrome, and why individuals without PTSD who carry neuroprotective gain-in-function NPY polymorphisms that increase the amplitude of NPY release are also at risk. The risk for metabolic syndrome in the psychologically resilient would be expected to increase with exposure to repeated unconditioned stressors in objectively threatening environments such as war zones. In PTSD, lower amplitude NPY stress responses may occur at high frequency in reaction to overgeneralized, condition threat cues in environments that are objectively safe, thus multiplying risk over time. Simply dichotomizing the risk for metabolic syndrome based on PTSD diagnosis, trauma exposure, genetic predisposition or plasma NPY levels measured at any single point in time thus may be misleading.

Perturbations in NE and NPY function may also be relevant to increases in blood pressure reactivity seen in PTSD. Male combat veterans with PTSD who had reduced resting, as well as stress-activated plasma NPY levels, had enhanced and sustained increases in heart rate, blood pressure and NE release in response to sympathetic stimulation. In addition, blood pressure regulation appeared to be shifted from noradrenergic modulation to control by NPY – similar to the shift seen in mice that developed stress-induced obesity and metabolic syndrome. Systolic blood pressure increases were positively correlated with yohimbine-stimulated increases in plasma NPY, but not NE, in the veterans with PTSD, while in healthy controls, they were correlated with increases in NE, but not NPY. This is consistent with vasconstrictor hyper-responsivity to NPY resulting from adrenergic receptor-mediated priming of vascular smooth muscle cell responses to NPY as well as vascular smooth muscle hypertrophy. Since NPY has a substantially longer half-life than NE, an over-ride of blood pressure modulation by NPY may increase the risk of sustained ischemia and serious cardiovascular complications such as stroke and myocardial infarction, the prevalence of which appears to be increased in PTSD. The extent to which such phenomena may contribute to the recently documented increased risk for mortality after surgery in PTSD patients is yet to be examined.

**Impact of stress-induced NPY responses on the risk for metabolic syndrome**

Under baseline conditions, NPY acts presynaptically at NPY-Y1Rs to inhibit sympathetic neuron activation. As stress increases, NE release increases, followed by increases in NPY release, but only with intense stimulation, including high-intensity exercise. Once released, NPY acts postsynaptically at NPY-Y1Rs to potentiate the postsynaptic effects of NE (or other neurotransmitters with which it was co-localized). The release of NPY under conditions of intense stress has been demonstrated in humans undergoing exercise at \( \sim 75\% \) of VO\(_2\) max, \( \sim 69\) electroconvulsive therapy, injection of the \( \alpha_2\)-noradrenergic receptor antagonist yohimbine and mock interrogation exercises during military survival school training. Data from maximum load exercise tests suggest that the release of NPY during intense sympathetic system activation occurs at the lactate threshold when oxidative metabolism no longer supports energy demands and anaerobic systems are engaged. The thresholds for plasma NPY and lactate increases, expressed as %VO\(_2\) max during maximum load exercise testing in seven healthy subjects, were highly correlated: \( r = 0.95, P < 0.001 \) (Rasmusson et al., preliminary observations). In general, then, NPY behaves like a high-pressure valve – inhibiting the release of NE during low sympathetic system activity and potentiating its impact during high activity. NPY thus conserves bioenerg for periods of high demand, at which point it helps to maintain organism function as energy and neurotransmitters are depleted.
Allopregnanolone/pregnanolone
Cerebrospinal fluid levels of the neuroactive steroids, allopregnanolone and its equipotent enantiomer, pregnanolone (collectively termed ALLO), have been found to be low in PTSD and depression and to correlate negatively with PTSD re-experiencing and depression symptoms. Allopregnanolone and pregnanolone, 3α-hydroxy-5α-pregnan-20-one and 3α-hydroxy-5β-pregnan-20-one, respectively, are 3α-reduced biosynthetic derivatives of progesterone. Their production is driven by oxidative stress and the accumulation of NADPH, a co-factor for the bidirectional p450 enzyme 3α-hydroxysteroid dehydrogenase (3α-HSD) that converts 5α- or 5β-dihydroprogesterone (5α- or 5β-DHP) to the respective 3α-reduced steroid. These steroids are the most potent and selective positive endogenous modulators of the action of γ-aminobutyric acid (GABA) at brain GABA<sub>A</sub> receptors, enhancing Cl<sup>-</sup> flux into neurons seven- to 10-fold. Their effects at extrasynaptic GABA<sub>A</sub> receptors maintain a tonic inhibitory conductance that moderates gain in neuronal output during periods of increased excitation, as during stress. Multiple studies in animals have demonstrated their potent anxiolytic, sedative and anesthetic effects at nanomolar concentrations, as well as their capacity to provide negative feedback inhibition of the HPA axis. In addition, allopregnanolone exerts neuroprotective actions, supporting neurogenesis, enhancing myelination and reducing apoptosis and inflammation. Experimental reduction of brain ALLO in rodents has been shown to increase anxious, aggressive and depressive behaviors, and to enhance contextual fear conditioning, a process thought to facilitate development of PTSD in humans. Low central nervous system levels of ALLO in persons with PTSD would therefore be expected, like low baseline NPY levels, to enhance HPA axis and sympathetic system reactivity and the release of cortisol and NPY into visceral fat during extreme stress.

Testosterone
Research in rodents has shown that testosterone and/or its metabolites increase NPY synthesis and release. It is therefore notable that the most potent testosterone metabolite, 5α-dihydrotestosterone (5α-DHT), is deactivated by 3α-HSD, the same enzyme that converts 5α/β-DHP to ALLO. In women with PTSD, the ratio of cerebrospinal fluid 5α-DHP to ALLO is increased, suggesting that low ALLO in this population is due to deficient function of 3α-HSD. Deficient function of 3α-HSD thus may increase tissue 5α-DHT levels, and in this way could enhance NPY synthesis and increase the risk for metabolic syndrome – particularly in PTSD patients with co-morbid major depression, in whom ALLO levels appear to be lowest (see Figure 2). It is also notable that 3α-HSD gene expression decreases as a result of reductions in testosterone due to gonadectomy in male rodents, that plasma testosterone levels fall dramatically in male military personnel exposed to extreme stress, and that low testosterone levels in males and females have been associated with depression. Stress-related reductions in testosterone levels and depression could thus paradoxically be associated with an increase in tissue 5α-DHT and NPY levels, and increase the risk for metabolic syndrome. These hypotheses are currently under investigation.
Cortisol

Alterations in cortisol regulation have been reported in PTSD. Low cortisol levels are found in some populations, while high cortisol levels and increased cortisol reactivity have been seen in others, such as women with co-morbid PTSD/MDD (e.g. references97–99). As discussed, cortisol reactivity is potentiated by low allopregnanolone levels.88 Persons with 3α-HSD deficits resulting in low allopregnanolone levels, possible high tissue 5α-DHT levels and increases in cortisol reactivity may be particularly prone to development of metabolic syndrome.

It is also important to consider effects of intrinsic deficiencies in cortisol production. Greater than 65 functional mutations of the 21-hydroxylase gene diminish cortisol production and shunt cortisol precursors into the androgen pathways. Increases in androgens would be expected to facilitate NPY synthesis and release. Furthermore, expression of the 3α-HSD gene is upregulated by cortisol.100 Individuals with deficiencies in cortisol production and release during stress thus may not appropriately upregulate allopregnanolone levels or deactivate 5α-DHT when exposed to stress. Inadequate cortisol levels may also fail to contain inflammatory reactions.101 It is thus notable that 21-hydroxylase deficiency is associated with an increased risk for obesity, hypertension and glucose intolerance.102

In contrast, a recent, relatively small study by Livadas et al.103 suggests that heterozygosity for 21-hydroxylase deficiency may protect against the development of metabolic syndrome. While 21-hydroxylase deficiency heterozygotes typically have a mild diminution in the capacity to synthesize cortisol, some show a paradoxical increase in cortisol responses to maximum adrenal stimulation,104 such as may occur during intense stress. This is thought to be due to a lack of glucocorticoid negative feedback, resulting in increased adrenocorticotropin hormone (ACTH) release and hypertrophy of the adrenal glands—effects likely to be amplified by stress over time. It therefore will be important to investigate whether exposure to extreme or chronic stress interacts with 21-hydroxylase heterozygosity (or other gene polymorphisms that affect cortisol synthesis) to impact risk for metabolic syndrome and PTSD. Interestingly, Yehuda et al.105 showed an association between lower cortisol levels in the healthy offspring of Holocaust survivors and PTSD diagnoses among their parents, a group expected to have high rates of functional 21-hydroxylase gene polymorphisms.96 While this finding has been interpreted as evidence for a possible epigenetic effect of parental PTSD on HPA axis function in the offspring, transmitted via the intrauterine or postnatal environment, it is possible that direct transmission of a genetic trait may influence cortisol output and risk for PTSD.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA), the immediate precursor for androgen synthesis, is secreted from the adrenal gland episodically and synchronously with cortisol in response to fluctuating ACTH levels.106 While DHEA and its sulfated metabolite DHEAS, collectively termed DHEA(S), are detectable in the brain, peripherally derived DHEA is thought to be the only source of brain DHEA(S) in humans.107 As reviewed previously,97 DHEA(S) antagonizes GABA_A receptors and facilitates N-methyl-D-aspartate receptor function. It also protects against excitatory amino-acid- and oxidative-stress-induced neuronal damage, restores cortisol-induced decrements in long-term potentiation (LTP), regulates programmed cell death and promotes neurogenesis in the hippocampus—effects that may be conferred, in part, by its antiglucocorticoid properties. For instance, 7-hydroxylated metabolites of DHEA interfere with the nuclear uptake of activated glucocorticoid receptors in neurons of the hippocampus108 and DHEA enhances the activity of 11β-HSD-2 (11β-HSD-2),109 which converts cortisol to the inactive glucocorticoid, cortisone.

Many studies suggest that DHEA(S) is beneficial to humans; an increasing DHEA(S) level in the face of stress appears to confer psychological and neurocognitive resilience and may protect against negative health outcomes. For example, although DHEA responses to ACTH were increased in premenopausal women with PTSD compared with healthy non-traumatized and trauma-exposed comparison subjects, increased responses were associated with lower PTSD symptoms in the PTSD group.20 In addition, the ratio of DHEA to cortisol at peak adrenal activation was inversely related to negative mood among all subjects. Similarly, Gill et al.29 found lower morning cortisol, higher DHEA, higher DHEA/cortisol ratios and higher stimulated interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α levels in women with PTSD compared with trauma-exposed and -unexposed healthy controls. However, lower DHEA and higher IL-6 and TNF-α levels were present in patients with co-morbid PTSD/MDD compared with those with PTSD alone. (Note discrepancies in Gill et al.110 between the abstract and text with regard to comparing DHEA and immune markers between subjects with PTSD/MDD and subjects with PTSD alone). This is consistent with other studies finding higher IL-6 and IL-6 receptor levels in subjects with PTSD/MDD compared with those with PTSD alone,111,112 and with the observation that DHEA, as well as cortisol, restrains cell-mediated immunity.113

There are similar findings in men. In a study of refugees from Kosovo, increasing DHEA(S) levels over time were associated with the development of PTSD without MDD, while lower DHEA(S) levels were associated with PTSD/MDD.110 Increased morning plasma DHEAS levels were seen in male combat veterans with PTSD compared with those without PTSD,114 and in male combat veterans with lifetime PTSD compared with those without.115 In the group with lifetime PTSD, higher plasma DHEA(S) levels were associated with greater improvements in PTSD symptoms over time. In healthy male military personnel, higher DHEA(S) to cortisol ratios at the peak of intense survival training predicted fewer dissociative symptoms and better military performance.116 Higher DHEA(S) levels before and immediately after intense training stress in Navy divers predicted better navigation skills that depend upon optimum hippocampus and frontal lobe function.117

DHEA administration studies also suggest that DHEA contributes to mental and physical health. Subchronic DHEA administration enhances peak ACTH and cortisol responses
to psychological stress and exercise without lengthening the time it takes for these stress reactants to return to baseline.\textsuperscript{118,119} Similarly, administration of RU486, another anti-glucocorticoid with antidepressant potential, enhances pituitary-adrenal reactivity, while increasing the peak and reducing the nadir of the cortisol diurnal curve.\textsuperscript{120,121} Chronic low-dose DHEA reduces baseline cortisol levels, increases baseline allopregnanolone levels\textsuperscript{122,123} and reduces negative mood and depression in humans, including those refractory to standard antidepressants.\textsuperscript{124,125}

DHEA(S) may also play a role in the prevention and treatment of metabolic syndrome. Low DHEA(S) levels have been associated with metabolic syndrome in several studies\textsuperscript{126} and its administration to elderly men and women in a double-blind, placebo-controlled study reduced visceral and subcutaneous fat and enhanced insulin sensitivity.\textsuperscript{127} The mechanisms for these positive effects include: enhancement of lipolysis,\textsuperscript{128} blockade of NPY-mediated overeating,\textsuperscript{129} upregulation of adiponectin gene expression in human visceral fat\textsuperscript{130} and activation of peroxisome proliferator-activated receptor, which facilitates fatty acid entry into cells and enzymes involved in lipolysis (reviewed in reference\textsuperscript{130}).

Whether DHEA(S) might protect against neuropsychiatric symptoms and metabolic syndrome in younger individuals generally or only in those with measurable deficits in DHEA(S), or in those undergoing chronic or intense stress is yet to be seen. In some individuals, stress may decrease DHEA(S) levels. The pregnane X receptor (PXR), a nuclear hormone receptor found in the brain, liver and other tissues, increases the transcription of genes for CYP450 enzymes involved in DHEA metabolism, such as CYP3A4.\textsuperscript{131} PXR is activated by stress levels of glucocorticoids, DHEA, DHEA(S), pregnanalone and progesterone. In this context though, it may be important to note that DHEA administration can sometimes result in symptoms of androgen excess (e.g. hirsutism), presumably mediated at the tissue level by 5α-DHT – raising the possibility that it might also increase tissue NPY levels and the risk for aspects of metabolic syndrome in some individuals (e.g. reference\textsuperscript{132}). Clearly, learning to target appropriately such a promising treatment will be important.

Genetic and epigenetic contributions to medical conditions co-morbid with PTSD

Gene variants in the NPY and noradrenergic signaling pathways have been found to impact physiological processes of relevance to risk for PTSD and metabolic syndrome. The Leu7Pro gain-in-function NPY polymorphism increases NPY release and contributes to components of metabolic syndrome,\textsuperscript{73–75,133,134} while loss-of-function NPY gene polymorphisms have been associated with increased anxiety and emotional reactivity.\textsuperscript{38} A loss-of-function NPY-Y1R polymorphism, found thus far in a Swedish population, contributes to slim body habitus and hard bones.\textsuperscript{135} This gene variant would also be expected to facilitate NPY release and psychological/behavioral resilience during stress, while protecting against poststress complications such as hypertension and obesity. NPY-Y1R variants were shown to decrease NPY-Y1R expression in vitro, diminish baroreceptor responses and increase blood pressure reactivity to the cold pressor test\textsuperscript{136} – findings in accordance with work by Michalkiewicz et al.\textsuperscript{137} demonstrating the dominant effect of central NPY-Y1Rs activation in restraining blood pressure reactivity over peripheral NPY-Y1R mediation of vasconstriction. Possession of a noradrenergic α2c receptor gene polymorphism (\textsuperscript{2c}-Del322–325) is associated with increases in heart rate, blood pressure, NE release and negative emotional reactions in response to low-dose yohimbine in healthy individuals, sympathetic system stress reactions typical of PTSD.\textsuperscript{138,139}

Numerous genes have polymorphisms that affect either ACTH or cortisol responses to stress.\textsuperscript{140–147} These include polymorphisms of genes for the μ-opioid receptor, catechol-O-methyl-transferase (COMT) and angiotensin 1-converting enzyme, the glucocorticoid receptor, the ACTH receptor and corticotropin-releasing factor (CRF) and the CRF receptor. In addition, heterozygosity for 21-hydroxylase deficiency is extremely common, affecting one in three persons of Ashenazi Jewish descent, one in four Hispanics, one in five Yugoslavians, one in eight Yupik Eskimos, one in 10 Italians and one in 16 persons from a mixed US population.\textsuperscript{104}

Clearly, the above list of genetic polymorphisms with the potential to influence risk for metabolic syndrome and PTSD is incomplete. Nor is it likely that possession of any one of these possible ‘fixed’ risk factors is a determinant. It may take a combination of such factors in the absence of countering protective factors, and in the context of facilitating environmental influences, to induce development of these disorders. This point is illustrated by work finding an interactive influence on the risk for PTSD in adulthood between childhood trauma and polymorphisms or decreased expression of the FKBP5 gene, which regulates glucocorticoid receptor signaling.\textsuperscript{148,149}

In addition, epigenetically mediated suppression of gene transcription can mimic loss-of-function polymorphisms and result in similar disease phenotypes. As an interesting example, maternal under-nutrition increases the risk for obesity, insulin resistance, Type II diabetes and cardiovascular illness, as well as defensive behavioral reactivity in adulthood, in part through epigenetic changes in genes for the glucocorticoid receptor and 11β-HSD-2 that promote glucocorticoid hyper-reactivity.\textsuperscript{150} Of note, the NPY gene has promoter-based CpG dinucleotide repeats that also may confer susceptibility to transcriptional inactivation by stress (Zukowska et al., preliminary observations in a model of prenatal stress exposure).

Therapeutic implications

Reducing episodic psychological stress via effective trauma-focused cognitive treatments and other psychosocial interventions may broadly benefit patients with PTSD and co-morbid metabolic syndrome, as some early studies suggest.\textsuperscript{151,152} However, some PTSD patients, such as those with co-morbid MDD, appear to be more resistant to the psychological benefits of such treatments in addition
to being at greater risk for metabolic syndrome.\textsuperscript{153} Perhaps correcting or compensating for underlying biological disturbances with broad impact in such relatively refractory patients (e.g. reference\textsuperscript{159}) will have both psychiatric and medical benefits.\textsuperscript{154–156} Ascertaining the specific neurobiological source(s) of risk for co-morbid metabolic syndrome and PTSD within individual patients thus will be important. To accomplish this, we must take into account the combined effects of individual neurobiological risk and resilience factors. As one simple example, the increased risk for metabolic syndrome conferred by a gain-in-function NPY gene polymorphism may be reduced or even nullified by a loss-of-function NPY-Y\textsubscript{2}R gene polymorphism. In contrast, a loss-of-function polymorphism in the 3α-HSD gene resulting in low allopregnanolone levels could synergize with the noradrenergic autoreceptor\textsubscript{2C}Del322–325 gene polymorphism and a loss-of-function NPY gene polymorphism or an epigenetically suppressed normal NPY gene (e.g. reference\textsuperscript{157}) to increase markedly the risk for severe co-morbid PTSD and metabolic syndrome and necessitate the use of multitarget pharmaceuticals.\textsuperscript{158–160} Such combinations of risk and resilience factors could be defined \textit{a priori}, based on our growing knowledge of relevant biological systems, and tested as intermediate biophenotypes in risk models for multisystem disease. The data reduction resulting from combining such factors meaningfully may also enhance the power of biomarker studies in populations of limited size.

\section*{Conclusion}

Rates of obesity and metabolic syndrome are increasing in the US and are associated with a number of mental health disorders in addition to PTSD (e.g. references\textsuperscript{64,161}). Future studies will be needed to ascertain the extent to which diet, decreased activity, medications, psychological or physical stress and neurobiological risk factors, such as those discussed, differentially contribute to risk across these disorders. In the meantime, a number of interrelated neurobiological factors, including alterations in the NPY and neuroactive steroid stress steroid systems, appear to be good candidates for a role in the pathophysiology of co-morbid PTSD and metabolic syndrome. Targeting these neurobiological systems directly, as well as reducing stress generally through psychosocial interventions, may present promising novel means for enhancing the current multidisciplinary approaches to the prevention and treatment of metabolic syndrome in this population.

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\section*{REFERENCES}


7 Schnurr PP, Green BL. Trauma and Health: Physical Health Consequences of Exposure to Extreme Stress. Washington, DC: American Psychological Association, 2004


Downloaded from http://ebm.rsmjournals.com/ at Florida State University on November 10, 2011
29 Rasmusson AM, Vasek J, Lipschitz D, Mustone ME, Vojvoda D, Shi Q, Gudmundsen G, Wolfe J, Morgan CA III, Charney DS. An increased capacity for adrenal DHEA release is associated negatively with avoidance symptoms and negative mood in women with PTSD. *Neuropsychopharmacology* 2004;29:1546–57
31 Gill J, Vythilingam M, Page GC. Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. *J Trauma Stress* 2008;21:530–9
46 Held K, Antonijevic I, Murck H, Kuenzel H, Steiger A. Neuropeptide Y (NPY) shortens sleep latency but does not suppress ACTH and cortisol in depressed patients and normal controls. *Psychoneuroendocrinology* 2006;31:100–7
49 Potter EK, Ulman LG. Neuropeptides in sympathetic nerves affect vagal regulation of the heart. *NIPS* 1994;17:147–77
60 Morgan CA, Rasmusson AM, Winters B, Hauger RL, Hazlett G. Trauma exposure rather than PTSD is associated with reduced baseline plasma neuropeptide-Y levels. *Biol Psychiatry* 2003;54:1087–91
71 Kallio J, Pesonen U, Kaipio K, Heimonen OJ, Uusitupa MI, Koulu M. Altered intracellular processing and release of neuropeptide Y due to leucine7 to proline7 polymorphism in the signal peptide of pre-proneuropeptide Y in humans. FASEB J 2001;15:124–4
73 Uusitupa MI, Karvonen MK, Valkonen VP, Lakka TA, Salonen R, Koivula M, Pesonen U, Valkonen VP. Leucine7 to proline7 polymorphism in the preproneuropeptide Y is associated with the progression of carotid atherosclerosis, blood pressure and serum lipids in Finnish men. Atherosclerosis 2001;159:145–51
75 Kallio J, Pesonen U, Kaipio K, Heimonen OJ, Uusitupa MI, Koulu M. Altered intracellular processing and release of neuropeptide Y due to leucine7 to proline7 polymorphism in the signal peptide of pre-proneuropeptide Y in humans. FASEB J 2001;15:124–4
75 Kallio J, Pesonen U, Kaipio K, Heimonen OJ, Uusitupa MI, Koulu M. Altered intracellular processing and release of neuropeptide Y due to leucine7 to proline7 polymorphism in the signal peptide of pre-proneuropeptide Y in humans. FASEB J 2001;15:124–4
75 Kallio J, Pesonen U, Kaipio K, Heimonen OJ, Uusitupa MI, Koulu M. Altered intracellular processing and release of neuropeptide Y due to leucine7 to proline7 polymorphism in the signal peptide of pre-proneuropeptide Y in humans. FASEB J 2001;15:124–4
75 Kallio J, Pesonen U, Kaipio K, Heimonen OJ, Uusitupa MI, Koulu M. Altered intracellular processing and release of neuropeptide Y due to leucine7 to proline7 polymorphism in the signal peptide of pre-proneuropeptide Y in humans. FASEB J 2001;15:124–4
Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. *Front Neuronuclon 2000; 21:1–56*


Schmidt P, Daly RC, Bloch M, Smith MJ, Danazea MA, Simpson St, Clair L, Murphy JH, Haq N, Rubinow DR. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry 2005;62:154–62*


Villareal DT, Holloszy JO. Effect of DHEA on adiponectin action in elderly women and men: a randomized controlled trial. *JAMA 2004;292:2243–8*


Navar D, Saulis D, Coril C, Svec F, Porter JR. Dehydroepiandrosterone (DHEA) blocks the increase in food intake caused by neuropeptide Y (NPY) in the Zucker rat. *Nutr Neurosci 2006;9:225–32*


Michalkiewicz M, Zhao QQ, Jia Z, Michalkiewicz T, Racadio MJ, Central neurosteride Y peptide signaling ameliorates N(omega)-nitro-l-arginine methyl ester hypertension in the rat through a Y1 receptor mechanism. *Hypertension 2005;45:780–5*


Wust S, Van Rossum EF, Federenko IS, Koper JW, Kunstra R, Hellhammer DH. Common polymorphisms in the glucocortiroid
144 Slawik M, Reisch N, Zvermann O, Maser- Gluth C, Stahl M, Klink A, Reincke M, Beuschlein F. Characterization of an adrenocorticotropin (ACTH) receptor promoter polymorphism leading to decreased adrenal responsiveness to ACTH. J Clin Endocrinol Metab 2004;89:565–73
151 Rauch SA, Grunfeld TE, Yadim E, Cahill SP, Hembree E, Foa EB. Changes in reported physical health symptoms and social function with prolonged exposure therapy for chronic posttraumatic stress disorder. Depress Anxiety 2009;26:732–8