

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

Ann M Rasmusson^{1,2,3}, Paula P Schnurr^{4,5}, Zofia Zukowska⁶, Erica Sciolli^{1,2,3} and Daniel E Forman^{1,7}

¹VA Boston Healthcare System; ²National Center for PTSD, Women's Health Science Division, Boston, MA 02130; ³Boston University School of Medicine, Boston, MA, 02118; ⁴National Center for PTSD, Executive Division, White River Junction, VT 05009; ⁵Dartmouth Medical School, Hanover, NH 03755; ⁶Department of Physiology and Biophysics & Stress Physiology and Research Center, Georgetown University Medical Center, Washington, DC 20057; ⁷Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

Corresponding author: Ann M Rasmusson, VA Boston Healthcare System/116B-3, 150 South Huntington Avenue, Boston, MA 02130, USA. Email: ann.rasmusson@gmail.com

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, dehydroepiandrosterone, testosterone, cortisol, allopregnanolone

Experimental Biology and Medicine 2010; **235**: 1150–1162. DOI: 10.1258/ebm.2010.009334

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

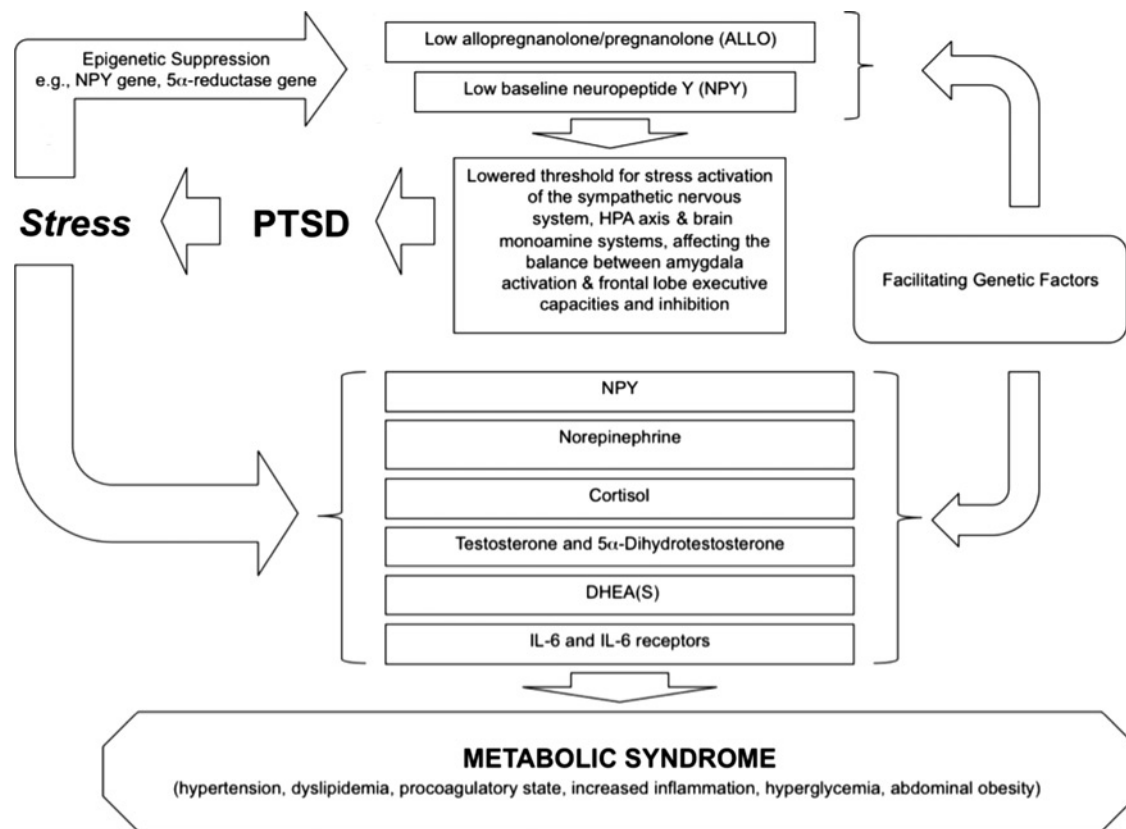


Figure 1 A diagram of stress-related modulators that impact risk for metabolic syndrome. DHEA, dehydroepiandrosterone; GR, glucocorticoid receptor; HSD, hydroxysteroid reductase; IL-6, interleukin-6; MDD, major depressive disorder; NE, norepinephrine; PTSD, post-traumatic stress disorder

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).

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

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

*Prevalence of overweight, obesity and extreme obesity among adults: United States, trends 1960–1962 through 2005–2006[†], Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, December 2008. Available at: www.cdc.gov/nchs/data/hestat/overweight/overweight_adult.htm#table1

[†]BMI (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. reference⁴).

In a study of traumatized mothers of pediatric cancer survivors and non-traumatized mothers of healthy children, Glover *et al.*⁵ 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.⁶ 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.^{7,8} 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 adrenally 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.*⁹ 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.*¹⁰ 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.¹⁰ 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.*⁵ found that BMI was the only *individual 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,^{11–15} only Emdad *et al.*¹⁶ reported negative findings. Of the remaining studies, Kang *et al.*¹⁷ found that PTSD was related to greater treatment utilization for hypertension among elderly prisoners of war. Santic *et al.*¹⁸ 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.*¹⁹ 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.*²⁰ 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.*²¹ 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 Pole²² 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-analysis²³ 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,²² 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.²⁴ Further, PTSD appeared to moderate effects of hostility on heart rate and diastolic blood pressure;²⁵ hostility, in turn, has been associated with cardiovascular risk.²⁶ 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. references^{28–31}). 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 benefits, as well as potential NPY-mediated, long-term medical liabilities.

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 α_2 receptor antagonist yohimbine⁴³ have been associated with reduced PTSD symptoms in combat veterans,²⁸ and higher baseline plasma NPY levels were retrospectively 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 Y₂Rs to facilitate heart rate increases,^{49–51} and acts at NPY-Y₁Rs 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 NPY_{3–36}, a Y₂/Y₅-selective agonist which then acts presynaptically at NPY-Y₂Rs 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-Y₁Rs and β -adrenergically inducible Y₅Rs^{53,54} – 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 Intracellularly, 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, Y₂Rs and DPP4, which converts NPY to NPY_{3–36}, the NPY-Y₂R-preferring agonist); (b) facilitated by glucocorticoids; and (c) strikingly reversed by the local or systemic injection of an NPY-Y₂R 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-Y₂Rs.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,^{28,62} as well as with NE reactivity.^{28,63} Since increased NE activity at β -adrenergic receptors normally induces lipolysis,⁵⁹ reductions in plasma NPY and related increases in noradrenergic system reactivity would be expected to result in reduced bodyweight. And indeed, bodyweight and plasma NPY levels were positively correlated in the veterans with PTSD studied by Rasmusson *et al.*²⁸ and chronically stressed mice loose weight when fed a normal diet.⁵⁹

Then why are rates of metabolic syndrome increased among patients with PTSD? It is possible that patients with PTSD or other mental health disorders are at greater risk for obesity and metabolic syndrome, in part, due to intake of a high fat/high calorie diet, as seen in mice exposed to intense variable stressors and fed a high fat and sugar diet.⁵⁹ This possibility should be investigated. The use of psychotropic medications that contribute to weight gain may also play a role. However, among patients with a variety of mental health disorders on atypical antipsychotics thought to promote metabolic syndrome, PTSD patients showed the greatest risk.⁶⁴ As noted, this raises the possibility that PTSD-associated differences in physiology increase risk for metabolic syndrome. The following analysis of the neurobiology of PTSD, which takes into account individual differences in genetics and neuroendocrine or sympathetic system adaptations that impact PTSD phenotype, provides support for this view.

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

Under baseline conditions, NPY acts presynaptically at NPY-Y₂Rs 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.^{65–71} 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 ~75% of VO₂ maximum,⁶⁹ electroconvulsive therapy,⁷² injection of the α_2 -noradrenergic receptor antagonist yohimbine^{28,43} and mock interrogation exercises during military survival school training.^{41,42} 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 %VO₂ 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 bioenergy 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,^{2,4} and why individuals without PTSD who carry neuroprotective gain-in-function NPY polymorphisms that increase the amplitude of NPY release^{73–75} 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 *over-generalized, conditioned* 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.²⁸ 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.⁵⁹ 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 vasoconstrictor 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.^{76–79} The extent to which such phenomena may contribute to the recently documented increased risk for mortality after surgery in PTSD patients⁸⁰ is yet to be examined.

Stress steroid contributions to the risk for metabolic syndrome

Stress stimulates the synthesis and release of multiple neuroactive steroids from the adrenal gland, gonads and brain. The *ambient balance* of these stress steroids likely affects stress-related behavior, as well as NPY physiology. The following discussion focuses on neuroactive steroids for which the most comprehensive evidence has been assembled in relation to PTSD, depression, NPY physiology and metabolic syndrome (see Figure 1).

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.^{30,81} Allopregnanolone and pregnanolone, 3 α -hydroxy-5 α -pregnan-20-one and 3 α -hydroxy-5 β -pregnan-20-one, respectively, are 3 α -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 3 α -hydroxysteroid dehydrogenase (3 α -HSD) that converts 5 α - or 5 β -dihydroprogesterone (5 α - or 5 β -DHP) to the respective 3 α -reduced steroid. These steroids are the most potent and selective positive endogenous modulators of the action of γ -aminobutyric acid (GABA) at brain GABA_A receptors, enhancing Cl⁻ flux into neurons seven- to 10-fold.^{82,83} Their effects at extrasynaptic GABA_A receptors maintain a tonic inhibitory conductance that moderates gain in neuronal output during periods of increased excitation,^{84–86} as during stress. Multiple studies in animals have demonstrated their potent anxiolytic, sedative and anesthetic effects at nanomolar concentrations,⁸⁷ as well as their capacity to provide negative feedback inhibition of the HPA axis.⁸⁸ In addition, allopregnanolone exerts neuroprotective actions, supporting neurogenesis, enhancing myelination⁸⁹ and reducing apoptosis and inflammation.⁹⁰ Experimental reduction of brain ALLO in rodents has been shown to increase anxious, aggressive and depressive behaviors,⁹¹ and to enhance contextual fear conditioning,⁹² 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.⁵² It is therefore notable that the most potent testosterone metabolite, 5 α -dihydrotestosterone (5 α -DHT), is deactivated by 3 α -HSD,⁹³ the same enzyme that converts 5 α /5 β -DHP to ALLO. In women with PTSD, the ratio of cerebrospinal fluid 5 α -DHP to ALLO is increased,²⁹ suggesting that low ALLO in this population is due to deficient function of 3 α -HSD. Deficient function of 3 α -HSD thus may increase tissue 5 α -DHT levels,⁹¹ 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 lowest²⁹ (see Figure 2). It is also notable that 3 α -HSD gene expression decreases as a result of reductions in testosterone due to gonadectomy in male rodents,⁹⁴ that plasma testosterone levels fall dramatically in male military personnel exposed to extreme stress⁹⁵ and that low testosterone levels in males and females have been associated with depression.⁹⁶ Stress-related reductions in testosterone levels and depression could thus paradoxically be associated with an increase in tissue 5 α -DHT and NPY levels, and increase the risk for metabolic syndrome. These hypotheses are currently under investigation.

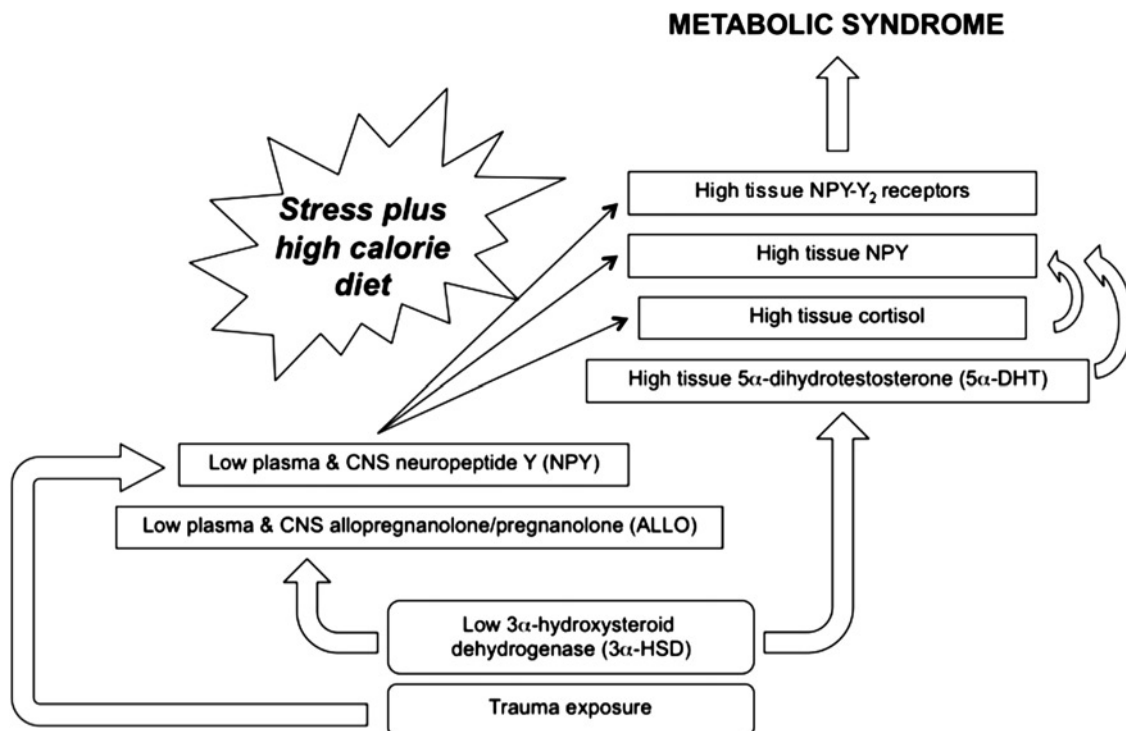


Figure 2 Diagrammatic interactions between trauma or downregulation or dysfunction of the 3 α -hydroxysteroid dehydrogenase (3 α -HSD) gene, the GABAergic neuroactive steroids allopregnanolone/pregnanolone (ALLO), the most potent metabolite of testosterone, 5 α -dihydrotestosterone (5 α -DHT), cortisol and the NPY system in facilitating the development of metabolic syndrome

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. references^{97–99}). As discussed, cortisol reactivity is potentiated by low allopregnanolone levels.⁸⁸ Persons with 3 α -HSD deficits resulting in low allopregnanolone levels, possible high tissue 5 α -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 3 α -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 5 α -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 in adolescents 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 adrenocorticotrophic 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.¹⁰⁴ 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 11 β -HSD-2 (11 β -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.²⁹ 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.^{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.^{120,121} Chronic low-dose DHEA reduces baseline cortisol levels, increases baseline allopregnanolone levels^{122,123} and reduces negative mood and depression in humans, including those refractory to standard antidepressants.^{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 studies¹²⁶ and its administration to elderly men and women in a double-blind, placebo-controlled study reduced visceral and subcutaneous fat and enhanced insulin sensitivity.¹²⁷ The mechanisms for these positive effects include: enhancement of lipolysis,¹²⁸ blockade of NPY-mediated overeating,¹²⁹ upregulation of adiponectin gene expression in human visceral fat¹³⁰ and activation of peroxisome proliferator-activated receptor, which facilitates fatty acid entry into cells and enzymes involved in lipolysis (reviewed in reference¹³⁰).

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 CYPp450 enzymes involved in DHEA metabolism, such as CYP3A4.¹³¹ PXR is activated by stress levels of glucocorticoids, DHEA, DHEA(S), pregnanolone 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 5 α -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. reference¹³²). 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,^{73–75,133,134} while loss-of-function NPY gene polymorphisms have been associated with increased anxiety and emotional reactivity.³⁸ A loss-of-function NPY-Y₂R polymorphism, found thus far in a Swedish population, contributes to slim body habitus and hard bones.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 test¹³⁶ – findings in accordance with work by Michalkiewicz *et al.*¹³⁷ demonstrating the *dominant effect of central NPY-Y₁Rs activation* in restraining blood pressure reactivity over peripheral NPY-Y₁R mediation of vasoconstriction. Possession of a noradrenergic α -2c receptor gene polymorphism (α _{2C}Del_{322–325}) 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.^{138,139}

Numerous genes have polymorphisms that affect either ACTH or cortisol responses to stress.^{140–147} These include polymorphisms of genes for the μ -opioid receptor, catechol-O-methyl-transferase (COMT) and angiotensin I-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 Ashkenazi 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.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.^{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 11 β -HSD-2 that promote glucocorticoid hyper-reactivity.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.^{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.¹⁵³ Perhaps correcting or compensating for underlying biological disturbances with broad impact in such relatively refractory patients (e.g. reference³⁰) will have both psychiatric and medical benefits.^{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-Y₂R gene polymorphism. In contrast, a loss-of-function polymorphism in the 3 α -HSD gene resulting in low allopregnanolone levels could synergize with the noradrenergic autoreceptor α_{2C} Del_{322–325} gene polymorphism and a loss-of-function NPY gene polymorphism or an epigenetically suppressed normal NPY gene (e.g. reference¹⁵⁷) to increase markedly the risk for severe co-morbid PTSD and metabolic syndrome and necessitate the use of multitarget pharmaceuticals.^{158–160} Such combinations of risk and resilience factors could be defined *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.

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^{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.

Author contributions: All authors (AMR, PPS, ZZ, ES and DEF) participated in the writing, critical review and editing of the manuscript.

ACKNOWLEDGEMENTS

The support for this work was provided by the Boston VA Healthcare System, the Veterans Administration National Center for Post-traumatic Stress Disorder (NC-PTSD): Executive, Clinical Neuroscience, and Women's Health Science Divisions, the Center for Naval Analysis, and the

National Institutes of Health Grants HL 055310 and HL067357.

REFERENCES

- Heppner PS, Crawford EF, Haji UA, Afari N, Hauger RL, Dashevsky BA, Horn PS, Nunnick SE, Baker DG. The association of posttraumatic stress disorder and metabolic syndrome: a study of increased health risk in Veterans. *BMC Med* 2009;7. See: <http://www.biomedcentral.com/1741-7015/7/1> (last checked 22 July 2010)
- Weathers FW, Keane TM, Davidson JRT. Clinician-administered PTSD Scale: a review of the first ten years of research. *Depress Anxiety* 2001;13:132–56
- Violanti JM, Fekedulegn D, Hartley TA, Andrew ME, Charles LE, Mnatsakanova A, Burchfiel CM. Police trauma and cardiovascular disease: association between PTSD symptoms and metabolic syndrome. *Int J Emerg Mental Health* 2006;8:227–37
- Breslau N, Davis GC, Peterson EL, Schultz LR. A second look at comorbidity in victims of trauma: the posttraumatic stress disorder-major depression connection. *Biol Psychiatry* 2000;48:902–9
- Glover DA, Stuber M, Polan RE. Allostatic load in women with and without PTSD symptoms. *Psychiatry* 2006;69:191–203
- McEwen BS, Wingfield JC. What is in a name? Integrating homeostasis, allostasis and stress. *Hormones Behav* 2010;57:105–11
- Schnurr PP, Green BL. *Trauma and Health: Physical Health Consequences of Exposure to Extreme Stress*. Washington, DC: American Psychological Association, 2004
- Schnurr PP, Jankowski MK. Physical health and post-traumatic stress disorder: review and synthesis. *Semin Clin Neuropsychiatry* 1999;4:295–304
- Das SR, Kinsinger LS, Yancy WS Jr, Wang A, Ciesco E, Burdick M, Yevich SJ. Obesity prevalence among veterans at Veterans Affairs medical facilities. *Am J Prev Med* 2005;28:291–4
- Vieweg WVR, Bates JDA, Quinn III, Fernandez A, Hasnain N, Pandurangi A. Posttraumatic stress disorder as a risk factor for obesity in male military veterans. *Acta Psychiatr Scand* 2007;116:483–7
- Cwikel J, Abdelgani A, Goldsmith JR, Quastel M, Yvelson II. Two-year follow-up study of stress-related disorders among immigrants to Israel from the Chernobyl area. *Environ Health Perspect* 1997;105(Suppl. 6):1545–50
- Davidson JRT, Hughes DC, Blazer DG, George LK. Post-traumatic stress disorder in the community: an epidemiological study. *Psychol Med* 1991;21:713–21
- Kibler JL, Joshi K, Ma M. Hypertension in relation to posttraumatic stress disorder in the US National Comorbidity Survey. *Behav Med* 2008;34:125–31
- O'Toole BI, Catts SV. Trauma, PTSD, and physical health: an epidemiological study of Australian Vietnam veterans. *J Psychosom Res* 2008;64:33–40
- Sawchuk CN, Roy-Byrne PP, Goldberg J, Manson SM, Noonan C, Beals J, Buchwald DS. The relationship between post-traumatic stress disorder, depression and cardiovascular disease in an American Indian tribe. *Psychol Med* 2005;35:1785–94
- Emdad R, Söndergaard HP, Agartz I, Theorell T. Cardiovascular reactivity in posttraumatic stress disorder (PTSD) patients undergoing magnetic resonance imaging (MRI). *Stress Trauma Crisis* 2004;7:243–55
- Kang HK, Bullman TA, Taylor JW. Risk of selected cardiovascular diseases and posttraumatic stress disorder among former World War II prisoners of war. *AEP* 2006;16:381–6
- Santic Z, Lukic A, Sesar D, Milicevic S, Ilakovac V. Long-term follow-up of blood pressure in family members of soldiers killed during the war in Bosnia and Herzegovina. *Croat Med J* 2006;47:416–23
- Schnurr PP, Spiro A III, Paris AH. Physician-diagnosed medical disorders in relation to PTSD symptoms in older male military Veterans. *Health Psychol* 2000;19:91–7
- Granada NS, Smith TC, Swanson GM, Harris RB, Shahar E, Smith B, Boyko EJ, Wells TS, Ryan MA. Newly reported hypertension after military combat deployment in a large population-based study. *Hypertension* 2009;54:966–73

- 21 Andersen J, Wade M, Possemato K, Ouimette P. Association between posttraumatic stress disorder and primary care provider-diagnosed disease among Iraq and Afghanistan veterans. *Psychosomatic Med* 2010;**72**:498–504
- 22 Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol Bull* 2007;**133**:725–46
- 23 Buckley TC, Kaloupek DG. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosom Med* 2001;**63**:585–94
- 24 Beckham JC, Feldman ME, Barefoot JC, Fairbank JA, Helms MJ, Haney TL, Hertzberg MA, Moore SD, Davidson JR. Ambulatory cardiovascular activity in Vietnam combat Veterans with and without posttraumatic stress disorder. *J Consult Clin Psychol* 2000;**68**:269–76
- 25 Beckham JC, Flood AM, Dennis MF, Calhoun PS. Ambulatory cardiovascular activity and hostility ratings in women with chronic posttraumatic stress disorder. *Biol Psychiatry* 2009;**65**:268–72
- 26 Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallett AJ. A meta-analytic review of research on hostility and physical health. *Psychol Bull* 1996;**119**:322–48
- 27 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. Washington, DC: American Psychiatric Association, 1994
- 28 Rasmusson AM, Hauger RL, Morgan CA III, Bremner JD, Charney DS, Southwick SM. Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) in combat-related posttraumatic stress disorder. *Biol Psychiatry* 2000;**47**:526–39
- 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
- 30 Rasmusson AM, Pinna G, Paliwal P, Weisman D, Gottschalk C, Charney DS, Krystal J, Guidotti A. Decreased cerebrospinal fluid allopregnanolone levels in women with PTSD. *Biol Psychiatry* 2006;**60**:704–13
- 31 Gill J, Vythilingam M, Page GG. 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
- 32 Britton KT, Southerland S, Van Uden E, Kirby D, Rivier J, Koob G. Anxiolytic activity of NPY receptor agonists in the conflict test. *Psychopharmacology* 1997;**132**:6–13
- 33 Britton KT, Akwa Y, Southerland S, Koob GF. Neuropeptide Y blocks the 'anxiogenic-like' behavioral action of corticotropin-releasing factor. *Peptides* 2000;**21**:37–44
- 34 Heilig M, Soderpalm B, Engel J, Widerlov E. Centrally administered neuropeptide Y (NPY) produces anxiolytic-like effects in animal anxiety models. *Psychopharmacology* 1989;**98**:524–9
- 35 Heilig M, McLeod S, Brot M, Heinrichs S, Menzaghi F, Koob G, Britton K. Anxiolytic-like action of neuropeptide Y: mediation by Y1 receptors in amygdala, and dissociation from food intake effects. *Neuropsychopharmacology* 1993;**8**:357–63
- 36 Kask A, Rago L, Harro J. Anxiogenic-like effect of the neuropeptide Y Y1 receptor antagonist BIBP3226: antagonism with diazepam. *Eur J Pharmacol* 1996;**317**:R3–4
- 37 Kask A, Rago L, Harro J. Alpha-helical CRF9-41 prevents anxiogenic-like effect of NPY Y1 receptor antagonist BIBP3226 in rats. *NeuroReport* 1997;**8**:3645–7
- 38 Howell OW, Silva S, Scharfman HE, Sosunov AA, Zaben M, Shatya A, McKhann G II, Herzog H, Laskowski A, Gray WP. Neuropeptide Y is important for basal and seizure-induced precursor cell proliferation in the hippocampus. *Neurobiol Dis* 2007;**26**:174–88
- 39 Hansel DE, Eipper BA, Ronnett GV. Neuropeptide Y functions as a neuroproliferative factor. *Nature* 2001;**410**:940–4
- 40 Zhou Z, Zhu G, Hariri AR, Enoch MA, Scott D, Sinha R, Virkkunen M, Mash DC, Lipsky RH, Hu XZ, Hodgkinson CA, Xu K, Buzas B, Yuan Q, Shen PH, Ferrell RE, Manuck SB, Brown SM, Hauger RL, Stohler CS, Zubieta JK, Goldman D. Genetic variation in human NPY expression affects stress response and emotion. *Nature* 2008;**452**:997–1001
- 41 Morgan CA, Wang S, Southwick SM, Rasmusson A, Hazlett G, Hauger RL, Charney DS. Plasma neuropeptide-Y concentrations in humans exposed to military survival training. *Biol Psychiatry* 2000;**47**:902–9
- 42 Morgan CA III, Rasmusson AM, Wang S, Hoyt G, Hauger R, Hazlett G. Neuropeptide Y and subjective distress in humans exposed to acute stress: replication and extension of previous report. *Biol Psychiatry* 2002;**52**:136–42
- 43 Rasmusson AM, Southwick SM, Hauger RL, Charney DS. Plasma neuropeptide Y (NPY) increases in response to the α_2 antagonist yohimbine. *Neuropsychopharmacology* 1998;**19**:95–8
- 44 Yehuda R, Brand S, Yank RK. Plasma neuropeptide Y concentrations in combat exposed veterans: relationship to trauma exposure, recovery from PTSD and coping. *Biol Psychiatry* 2005;**59**:660–3
- 45 Antonijevic IA, Murck H, Bohlhalter S, Frieboes RM, Holsboer F, Steiger A. Neuropeptide Y promotes sleep and inhibits ACTH and cortisol release in young men. *Neuropharmacology* 2000;**39**:1474–81
- 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. *Psychoneuroendocrine* 2006;**31**:100–7
- 47 Shih C-D, Chan JYH, Chan SHH. Tonic suppression of baroreceptor reflex response by endogenous neuropeptide Y at the nucleus tractus solitarius of the rat. *Neurosci Lett* 1992;**148**:169–72
- 48 Ergene E, Dunbar JC, Barraco RA. Visceroendocrine responses elicited by neuropeptide Y in the nucleus tractus solitarius. *Brain Res Bull* 1993;**32**:461–5
- 49 Potter EK, Ulman LG. Neuropeptides in sympathetic nerves affect vagal regulation of the heart. *NIPS* 1994;**9**:174–7
- 50 Shine J, Potter EK, Biden T, Selbie LA, Herzog H. Neuropeptide Y and regulation of the cardiovascular system. *J Hypertension* 1994;**12**(Suppl. 10):S41–5
- 51 Ulman LG, Potter IK, McCloskey DI, Morris MJ. Post-exercise depression of baroreflex slowing of the heart in humans. *Clin Physiol* 1997;**17**:299–309
- 52 Zukowska-Grojec Z. Neuropeptide Y. A novel sympathetic stress hormone and more. *Ann NY Acad Sci* 1995;**771**:219–33
- 53 Zukowska-Grojec Z, Karwatowska-Prokopczuk E, Fisher TA, Ji H. Mechanisms of vascular growth-promoting effects of neuropeptide Y: role of its inducible receptors. *Regul Peptides* 1998;**75**–76:231–8
- 54 Pons J, Kitlinska J, Ji H, Lee EW, Zukowska Z. Mitogenic actions of neuropeptide Y in vascular smooth muscle cells: synergistic interactions with the beta-adrenergic system. *Can J Physiol Pharmacol* 2003;**81**:177–85
- 55 Zukowska-Grojec Z. Neuropeptide Y: an adrenergic cotransmitter, vasoconstrictor, and a nerve-derived vascular growth factor. *Adv Pharmacol* 1998;**42**:125–8
- 56 Yang L, Scott KA, Hyun J, Tamashiro KL, Tray N, Moran TH, Bi S. Role of dorsomedial hypothalamic neuropeptide Y in modulating food intake and energy balance. *J Neurosci* 2009;**29**:179–90
- 57 Billington CJ, Briggs JE, Harker S, Grace M, Levine AS. Neuropeptide Y in hypothalamic paraventricular nucleus: a center coordinating energy metabolism. *Am J Physiol* 1994;**266**:R1765–70
- 58 Kapio K, Kallio J, Pesonen U. Mitochondrial targeting signal in human neuropeptide Y gene. *Biochem Biophys Res Commun* 2005;**337**:633–40
- 59 Kuo LE, Kitlinska JB, Tilan JU, Li L, Baker SB, Johnson MD, Lee EW, Burnett MS, Fricke ST, Kvetnansky R, Herzog H, Zukowska Z. Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. *Nat Med* 2007;**13**:803–11
- 60 Colmers W, Bleakman D. Effects of neuropeptide Y on the electrical properties of neurons. *TINS* 1994;**17**:373–9
- 61 Corder R, Castagne V, Rivet J-M, Mormede P, Gaillard RC. Central and peripheral effects of repeated stress and high NaCl diet on neuropeptide Y. *Physiol Behav* 1992;**52**:205–10
- 62 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
- 63 Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolauuo A, Heninger GR, Charney DS. Abnormal noradrenergic function in posttraumatic stress disorder. *Arch Gen Psychiatry* 1993;**50**:266–74
- 64 Jin H, Lanouette NM, Mudaliar S, Henry R, Folsom DP, Khandrika S, Gloriosio DK, Jeste DV. Association of posttraumatic stress disorder with increased prevalence of metabolic syndrome. *J Clin Psychopharmacol* 2009;**29**:210–15

- 65 Archelos J, Xiang J, Reinecke M, Lang R. Regulation of release and function of neuropeptides in the heart. *J Cardiovasc Pharmacol* 1987;**12**:S45–50
- 66 Dahlof P, Tarizzo V, Lundberg J, Dahlof C. Alpha- and beta-adrenoceptor-mediated effects on nerve stimulation-evoked release of neuropeptide Y (NPY)-like immunoreactivity in the pithed guinea pig. *J Auton Nerv System* 1991;**35**:199–210
- 67 Haass M, Cheng B, Richardt G, Lang R, Schomig A. Characterization and presynaptic modulation of stimulation-evoked exocytotic co-release of noradrenaline and neuropeptide Y in guinea pig heart. *Naunyn-Schmiedeberg Arch Pharmacol* 1991;**339**:71–8
- 68 Lundberg J, Rudehill A, Sollevi A. Pharmacological characterization of neuropeptide Y and noradrenaline mechanisms in sympathetic control of pig spleen. *Eur J Pharmacol* 1989;**163**:103–13
- 69 Pernow J. Co-release and functional interactions of neuropeptide Y and noradrenaline in peripheral sympathetic vascular control. *Acta Physiol Scand* 1986;**568**:1–56
- 70 Pernow J, Lundberg J. Modulation of noradrenaline and neuropeptide Y (NPY) release in the pig kidney *in vivo*: involvement of alpha 2, NPY and angiotensin II receptors. *Naunyn-Schmiedeberg Arch Pharmacol* 1989;**340**:379–85
- 71 Kallio J, Pesonen U, Kaipio K, Karvonen MK, Jaakkola U, Heinonen OJ, Uusitupa MI, Koulou 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**:1242–4
- 72 Nikisch G, Mathé AA. CSF monoamine metabolites and neuropeptides in depressed patients before and after electroconvulsive therapy. *Eur Psychiatry: J Assoc Eur Psychiatrists* 2008;**23**:356–9
- 73 Uusitupa MI, Karvonen MK, Pesonen U, Koulou M. Neuropeptide Y: a novel link between the neuroendocrine system and cholesterol metabolism. *Ann Med* 1998;**30**:508–10
- 74 Karvonen MK, Valkonen VP, Lakka TA, Salonen R, Koulou M, Pesonen U, Tuomainen TP, Kauhanen J, Nyyssönen K, Lakka HM, Uusitupa MI, Salonen JT. 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 van Rossum CT, Pijl H, Adan RA, Hoebee B, Seidell JC. Polymorphisms in the NPY and AGRP genes and body fatness in Dutch adults. *Int J Obes* 2006;**30**:1522–8
- 76 Boscarino JA. Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. *Psychosomatic Med* 1997;**59**:605–14
- 77 Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention. *Psychosomatic Med* 2008;**70**:668–76
- 78 Brass LM, Page WF. Stroke in former prisoners of war. *J Stroke Cerebrovasc Dis* 1996;**6**:72–8
- 79 Dobie DJ, Kivlahan DR, Maynard C, Bush KR, Davis TM, Bradley KA. Posttraumatic stress disorder in female veterans: association with self-reported health problems and functional impairment. *Arch Intern Med* 2004;**164**:394–400
- 80 Brzezinski M. (unpublished findings) Reported at the annual meeting of the American Society of Anesthesiologists, October 17–21, New Orleans, 2009. See: www.asahq.org/news/2009AM_Brzezinski_FINAL.pdf (last checked 22 July 2010)
- 81 Uzunova V, Sheline Y, Davis J, Rasmusson A, Uzunova D, Costa E, Guidotti A. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci USA* 1998;**95**:3239–44
- 82 Lambert JJ, Belelli D, Peden DR, Vardy AW, Peters JA. Neurosteroid modulation of GABA_A receptors. *Prog Neurobiol* 2003;**71**:67–80
- 83 Puia G, Mienville J-M, Matsumoto K, Takahata H, Watanabe H, Costa E, Guidotti A. On the putative physiological role of allopregnanolone on GABA_A receptor function. *Neuropharmacology* 2003;**44**:49–55
- 84 Mitchell SJ, Silver RA. Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron* 2003;**38**:433–45
- 85 Mody I, Pearce RA. Diversity of inhibitory neurotransmission through GABA_A receptors. *TINS* 2004;**27**:569–75
- 86 Semyanov A, Walker MC, Kullmann DM, Silver RA. Tonically active GABAA receptors: modulating gain and maintaining the tone. *TINS* 2004;**27**:262–9
- 87 Paul SM, Purdy RH. Neuroactive steroids. *FASEB J* 1992;**6**:2311–22
- 88 Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvatoni C, Tonetti A, Nappi RE, Luisi S, Palumbo M, Purdy RH, Luisi M. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. *J Clin Endocrinol Metab* 1998;**83**:2099–103
- 89 Ghomari AM, Ibanez C, El-Etr M, Leclerc P, Eychenne B, O'Malley BW, Baulieu EE, Schumacher M. Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. *J Neurochem* 2003;**86**:848–59
- 90 VanLandingham JW, Cekic M, Cutler S, Hoffman SW, Stein DG. Neurosteroids reduce inflammation after TBI through CD55 induction. *Neurosci Lett* 2007;**425**:94–8
- 91 Guidotti A, Dong E, Matsumoto K, Pinna G, Rasmusson AM, Costa E. The socially-isolated mouse: a model to study the putative role of allopregnanolone and 5 α -dihydroprogesterone in psychiatric disorders. *Brain Res Rev* 2001;**37**:110–15
- 92 Pibiri F, Nelson M, Guidotti A, Costa E, Pinna G. Decreased corticolimbic allopregnanolone expression during social isolation enhances contextual fear: a model relevant for posttraumatic stress disorder. *Proc Natl Acad Sci USA* 2008;**105**:5567–72
- 93 Penning TM, Burczynski ME, Jez JM, Hung C-F, Lin H-K, Ma H, Moore M, Palackal N, Ratnam L. Human 3 α -hydroxysteroid dehydrogenase isoforms (AKR1C1–AKR1C4) of the aldo-ketoreductase superfamily: functional plasticity and tissue distribution reveals roles in the inactivation and formation of male and female sex hormones. *Biochem J* 2000;**35**:67–77
- 94 Mitev YA, Darwish M, Wolf SS, Holsboer F, Almeida OF, Patchev VK. Gender differences in the regulation of 3 α -hydroxysteroid dehydrogenase in rat brain and sensitivity to neurosteroid-mediated stress protection. *Neuroscience* 2003;**120**:541–9
- 95 Morgan CA, Wang S, Mason J, Southwick SM, Fox P, Hazlett G, Charney DS, Greenfield G. Hormone profiles in humans experiencing military survival training. *Biol Psychiatry* 2000;**47**:891–901
- 96 Ebinger M, Sievers C, Ivan D, Schneider HJ, Stalla GK. Is there a neuroendocrinological rationale for testosterone as a therapeutic option in depression? *J Psychopharmacol* 2009;**23**:841–53
- 97 Rasmusson AM, Vythilingam M, Morgan CA III. The neuroendocrinology of PTSD – new directions. *CNS Spectrums* 2003;**8**:651–67
- 98 Yehuda R. Current status of cortisol findings in post-traumatic stress disorder. *Psychiatric Clin N Am* 2002;**25**:341–68
- 99 Young EA, Breslau N. Cortisol and catecholamines in posttraumatic stress disorder: an epidemiologic community study. *Arch Gen Psychiatry* 2004;**61**:394–401
- 100 Hou YT, Lin HK, Penning TM. Dexamethasone regulation of the rat 3 α -hydroxysteroid/dihydrodiol dihydrogenase (3 α -HSD/DD) gene. *Mol Pharmacol* 1998;**53**:459–66
- 101 Raison CL, Miller AH. When not enough is too much. The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry* 2003;**160**:1554–65
- 102 Charmandari E, Chrousos GP. Metabolic syndrome manifestations in classic congenital adrenal hyperplasia: do they predispose to atherosclerotic cardiovascular disease and secondary polycystic ovary syndrome? *Ann NY Acad Sci* 2006;**1083**:37–53
- 103 Livadas S, Dracopoulou M, Lazaropoulou C, Papassotiropoulos I, Sertedaki A, Angelopoulos GN, Chrousos GP, Dacou-Voutetakis C. A favorable metabolic and antiatherogenic profile in carriers of CYP21A2 gene mutations supports the theory of a survival advantage in this population. *Hormone Res* 2009;**72**:337–43
- 104 Witchel S, Lee P, Suda-Hartman S, Trucco M, Hoffman E. Evidence for a heterozygote advantage in congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 1997;**82**:2097–101
- 105 Yehuda R, Bierer LM. Transgenerational transmission of cortisol and PTSD risk. *Prog Brain Res* 2008;**167**:121–35
- 106 Rosenfeld RS, Hellman L, Roffwarg H, Weitzman ED, Fukushima DK, Gallagher TF. Dehydroisoandrosterone is secreted episodically and synchronously with cortisol by normal man. *J Clin Endocrinol* 1971;**33**:87–92

- 107 Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. *Front Neuroendocrinol* 2000; **21**:1–56
- 108 Morfin R, Starka L. Neurosteroid 7-hydroxylation products in the brain. *Int Rev Neurobiol* 2001; **46**:79–95
- 109 Balazs Z, Schweizer RA, Frey FJ, Rohner-Jeanrenaud F, Odermatt A. DHEA induces 11 β -HSD2 by acting on CCAAT/enhancer-binding proteins. *J Am Soc Nephrol* 2008; **19**:92–101
- 110 Sondergaard HP, Hansson LO, Theorell T. Elevated blood levels of dehydroepiandrosterone sulphate vary with symptom load in posttraumatic stress disorder: findings from a longitudinal study of refugees in Sweden. *Psychother Psychosom* 2002; **71**:298–303
- 111 Maes M, Lin AH, Delmeire L, Van Gastel A, Kenis G, de Jongh R, Bosmans E. Elevated serum interleukin-6 (IL-6) receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biol Psychiatry* 1999; **45**:833–9
- 112 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**:253–5
- 113 Schuld A, Mullington J, Freiss E, Hermann DM, Galanos C, Holsboer F, Pollmacher T. Changes in dehydroepiandrosterone (DHEA) and DHEA-sulfate plasma levels during experimental endotoxemia in healthy volunteers. *J Clin Endocrinol Metab* 2000; **85**:4624–9
- 114 Spivak B, Maayan R, Kotler M, Mester R, Gil-Ad I, Shtaiif B, Weizman A. Elevated circulatory level of GABA A-antagonistic neurosteroids in patients with combat-related post-traumatic stress disorder. *Psychol Med* 2000; **30**:1227–31
- 115 Yehuda R, Brand SR, Golier JA, Yang RK. Clinical correlates of DHEA associated with post-traumatic stress disorder. *Acta Psychiatr Scand* 2006; **114**:187–93
- 116 Morgan CA III, Southwick S, Hazlett G, Rasmusson A, Hoyt G, Zimolo Z, Charney D. Relationships among plasma DHEA(S), cortisol, symptoms of dissociation and objective performance in humans exposed to acute stress. *Arch Gen Psychiatry* 2004; **61**:819–25
- 117 Morgan CA III, Rasmusson A, Pietrzak RH, Coric V, Southwick SM. Relationships among plasma dehydroepiandrosterone and dehydroepiandrosterone sulfate, cortisol, symptoms of dissociation and objective performance in humans exposed to underwater navigation stress. *Biol Psychiatry* 2009; **66**:334–40
- 118 Kudielka BM, Hellhammer J, Hellhammer DH, Wolf OT, Pirke K-M, Varadi E. Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a two-week DHEA treatment. *J Clin Endocrinol Metab* 1998; **83**:1756–61
- 119 Deuster PA, Faraday MM, Chrousos GP, Poth MA. Effects of dehydroepiandrosterone and alprazolam on hypothalamic-pituitary responses to exercise. *J Clin Endocrinol Metab* 2005; **90**:4777–83
- 120 Bertagna X, Escourolle H, Pinier JL, Coste J, Raux-Demay MC, Petal P. Administration of RU486 for 8 days in normal volunteers: antiglucocorticoid effect with no evidence of peripheral cortisol deprivation. *J Clin Endocrinol Metab* 1994; **78**:375–80
- 121 VanHaarst AD, Oitzl MS, Workel JO, DeKloet ER. Chronic brain glucocorticoid receptor blockade enhances the rise in circadian and stress-induced pituitary–adrenal activity. *Endocrinology* 1996; **137**:4935–43
- 122 Kroboth PD, Amico JA, Stone RA, Folan M, Frye RF, Kroboth FJ, Bigos KL, Fabian TJ, Linares AM, Pollock BG, Hakala C. Influence of DHEA administration on 24-hour cortisol concentrations. *J Clin Psychopharmacol* 2003; **23**:96–9
- 123 Genazzani AD, Stomati M, Bernardi F, Pieri M, Rovati L, Genazzani AR. Long-term low-dose dehydroepiandrosterone oral supplementation in early and late postmenopausal women modulates endocrine parameters and synthesis of neuroactive steroids. *Fertility Sterility* 2003; **80**:1495–501
- 124 Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L. Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 2009; **156**:646–9
- 125 Schmidt PJ, Daly RC, Bloch M, Smith MJ, Danaceau 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
- 126 Rabijewski M, Papierska L, Kozakowski J, Zgliczynski W. The relationship between androgens concentrations (testosterone and dehydroepiandrosterone sulfate) and metabolic syndrome in non-obese elderly men. *Endokrynol Pol* 2007; **58**:496–504
- 127 Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men: a randomized controlled trial. *JAMA* 2004; **292**:2243–8
- 128 Hernandez-Morante JJ, Perez-de-Heredia F, Lujan JA, Zamora S, Garaulet M. Role of DHEA-S on body fat distribution: gender- and depot-specific stimulation of adipose tissue lipolysis. *Steroids* 2008; **73**:209–15
- 129 Navar D, Saulis D, Corll 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
- 130 Hernandez-Morante JJ, Milagro F, Gabaldon JA, Martinez JA, Zamora S, Garaulet M. Effect of DHEA-sulfate on adiponectin gene expression in adipose tissue from different fat depots in morbidly obese humans. *Eur J Endocrinol* 2006; **155**:593–600
- 131 Lamba V, Yasuda K, Lamba JK, Assem M, Davila J, Strom S, Schutetz EG. PXR (NR112) splice variants in human tissues, including brain, and identification of neurosteroids and nicotine as PXR activators. *Toxicol Appl Pharmacol* 2004; **199**:251–65
- 132 Amato MC, Galluzzo A, Merlino S, Mattina A, Richiusa P, Criscimanna A, Giordano C. Lower insulin sensitivity differentiates hirsute from non-hirsute Sicilian women with polycystic ovary syndrome. *Eur J Endocrinol* 2006; **155**:859–65
- 133 Ding B, Kull B, Liu Z, Mottagui-Tabar S, Thonberg H, Gu HF, Brookes AJ, Grundemar L, Karlsson C, Hamsten A, Arner P, Ostenson CG, Efendic S, Monne M, von Heijne G, Eriksson P, Wahlestedt C. Human neuropeptide Y signal peptide gain-of-function polymorphism is associated with increased body mass index: possible mode of function. *Regul Peptides* 2005; **127**:45–53
- 134 Nordman S, Ding B, Ostenson CG, Karvestedt L, Brismar K, Efendic S, Gu HF. Leu7Pro polymorphism in the neuropeptide Y (NPY) gene is associated with impaired glucose tolerance and type 2 diabetes in Swedish men. *Exp Clin Endocrinol Diabetes* 2005; **113**:282–7
- 135 Lavebratt C, Alpman A, Persson B, Arner P, Hoffstedt J. Common neuropeptide Y2 receptor gene variant is protective against obesity among Swedish men. *Int J Obesity* 2006; **30**:453–9
- 136 Wang L, Rao F, Zhang K, Mahata M, Rodriguez-Flores JL, Fung MM, Waalen J, Cockburn MG, Hamilton BA, Mahata SK, O'Connor DT. Neuropeptide Y1 receptor NPY1R. Discovery of naturally occurring human genetic variants governing gene expression in cells as well as pleiotropic effects on autonomic activity and blood pressure *in vivo*. *J Am Coll Cardiol* 2009; **54**:944–54
- 137 Michalkiewicz M, Zhao GQ, Jia Z, Michalkiewicz T, Racadio MJ. Central neuropeptide Y signaling ameliorates N(omega)-nitro-L-arginine methyl ester hypertension in the rat through a Y1 receptor mechanism. *Hypertension* 2005; **45**:780–5
- 138 Neumeister A, Charney DS, Belfer I, Geraci M, Holmes C, Sharabi Y, Alim T, Bonne O, Luckenbaugh DA, Manji H, Goldman D, Goldstein DS. Sympathoneural and adrenomedullary functional effects of alpha_{2C}-adrenoreceptor gene polymorphism in healthy humans. *Pharmacogen Genomics* 2005; **15**:143–9
- 139 Neumeister A, Drevets WC, Belfer I, Luckenbaugh DA, Henry S, Bonne O, Herscovitch P, Goldman D, Charney DS. Effects of a alpha 2C-adrenoreceptor gene polymorphism on neural responses to facial expressions in depression. *Neuropsychopharmacology* 2006; **31**:1750–6
- 140 Hernandez-Avila CA, Wand G, Luo X, Gelernter J, Kranzler HR. Association between the cortisol response to opioid blockade and the Asn40Asp polymorphism at the mu-opioid receptor locus (OPRM1). *Am J Med Genet* 2003; **118B**:60–5
- 141 Oswald LM, McCaul M, Choi L, Yang X, Wand GS. Catechol-O-methyltransferase polymorphism alters hypothalamic-pituitary-adrenal axis responses to naloxone: a preliminary report. *Biol Psychiatry* 2004; **55**:102–5
- 142 Baghai TC, Schule C, Zwanzger P, Minov C, Zill P, Ella R, Eser D, Oezer S, Bondy B, Rupprecht R. Hypothalamic-pituitary-adrenocortical axis dysregulation in patients with major depression is influenced by the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene. *Neurosci Lett* 2002; **328**:299–303
- 143 Wust S, Van Rossum EF, Federenko IS, Koper JW, Kumsta R, Hellhammer DH. Common polymorphisms in the glucocorticoid

- receptor gene are associated with adrenocortical responses to psychosocial stress. *J Clin Endocrinol Metab* 2004;**89**:565–73
- 144 Slawik M, Reisch N, Zwermann 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**:3131–7
- 145 Gonzalez-Gay MA, Hajeer AH, Garcia-Porrúa C, Dababneh A, Amoli MM, Botana MA, Thomson W, Llorca J, Ollier WE. Corticotropin-releasing hormone promoter polymorphisms in patients with rheumatoid arthritis from northwest Spain. *J Rheumatol* 2003;**30**:913–17
- 146 Smoller JW, Rosenbaum JF, Biederman J, Kennedy J, Dai D, Racette SR, Laird NM, Kagan J, Snidman N, Hirshfeld-Becker D, Tsuang MT, Sklar PB, Slaugenhaupt SA. Association of a genetic marker at the corticotropin-releasing hormone locus with behavioral inhibition. *Biol Psychiatry* 2003;**54**:1376–81
- 147 Challis BG, Luan J, Keogh J, Wareham NJ, Farooqi IS, O'Rahilly S. Genetic variation in the corticotrophin-releasing factor receptors: identification of single-nucleotide polymorphisms and association studies with obesity in UK Caucasians. *Int J Obes Relat Metab Disord* 2004;**28**:442–6
- 148 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**:1291–305
- 149 Yehuda R, Cai G, Golier JA, Sarapas C, Galea S, Ising M, Rein T, Schmeidler J, Müller-Myhsok B, Holsboer F, Buxbaum JD. Gene expression patterns associated with posttraumatic stress disorder following exposure to the World Trade Center attacks. *Biol Psychiatry* 2009;**66**:708–11
- 150 Seckl JR, Meaney MJ. Glucocorticoid 'programming' and PTSD risk. *Ann NY Acad Sci* 2006;**1071**:351–78
- 151 Rauch SA, Grunfeld TE, Yadin 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
- 152 Galovski TE, Monson C, Bruce SE, Resick PA. Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? *J Trauma Stress* 2009;**22**:197–204
- 153 Nishith P, Nixon RD, Resick PA. Resolution of trauma-related guilt following treatment of PTSD in female rape victims: a result of cognitive processing therapy targeting comorbid depression? *J Affective Dis* 2005;**86**:259–65
- 154 Kimerling R. An investigation of sex differences in nonpsychiatric morbidity associated with posttraumatic stress disorder. *J Am Med Womens Assoc* 2004;**59**:43–7
- 155 Otis JD, Keane TM, Kerns RD. An examination of the relationship between chronic pain and post-traumatic stress disorder. *J Rehab Res Development* 2003;**40**:397–405
- 156 Otis JD, Keane TM, Kerns RD, Monson C, Scioli E. The development of an integrated treatment for veterans with comorbid chronic pain and posttraumatic stress disorder. *Pain Med* 2009;**10**:1300–11
- 157 Schuebel K, Chen W, Cope L, Glockner SC, Xuzuki H, Yi J-M, Chan TA, Van Neste L, Van Crieckinge W, van den Bosch S, Van Engeland M, Ting AH, Jair K, Yu W, Toyota M, Imai K, Ahuja N, Herman JG, Baylin SB. Comparing the DNA hypermethylation with gene mutations in colorectal cancer. *PLoS Genet* 2007;**3**:e157
- 158 Goldstein LE, Rasmusson AM, Bunney BS, Roth RH. Role of the amygdala in the coordination of behavioral, neuroendocrine and prefrontal cortical monoamine responses to psychological stress in the rat. *J Neurosci* 1996;**16**:4787–98
- 159 Southwick SM, Rasmusson AM, Barron J, Arnsten A. Neurobiological and neurocognitive alterations in PTSD: a focus on norepinephrine, serotonin, and the HPA axis. In: Vasterling J, Brewin C, eds. *Neuropsychology of PTSD*. New York: Guilford Publications, 2005:27–58
- 160 Arnsten AF. Stress signaling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci* 2009;**10**:410–22
- 161 Cohen BE, Marmar C, Li R, Bertenthal D, Seal KH. Association of cardiovascular risk factors with mental health diagnoses in Iraq and Afghanistan war veterans using VA health care. *JAMA* 2009;**302**:489–92