Stress
The International Journal on the Biology of Stress

ISSN: 1025-3890 (Print) 1607-8888 (Online) Journal homepage: http://www.tandfonline.com/loi/ists20

Vulnerability to psychogenic non-epileptic seizures is linked to low neuropeptide Y levels

Michael Winterdahl, Alessandro Miani, Moana J. H. Vercoe, Antonia Ciovica, Lori Uber-Zak, Charlotte Ulrikka Rask & Paul J. Zak

To cite this article: Michael Winterdahl, Alessandro Miani, Moana J. H. Vercoe, Antonia Ciovica, Lori Uber-Zak, Charlotte Ulrikka Rask & Paul J. Zak (2017) Vulnerability to psychogenic non-epileptic seizures is linked to low neuropeptide Y levels, Stress, 20:6, 589-597, DOI: 10.1080/10253890.2017.1378638

To link to this article: https://doi.org/10.1080/10253890.2017.1378638

Published online: 19 Sep 2017.

STRESS, 2017
VOL. 20, NO. 6, 589–597
https://doi.org/10.1080/10253890.2017.1378638

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Vulnerability to psychogenic non-epileptic seizures is linked to low neuropeptide Y levels

Michael Winterdahl[a*], Alessandro Miani[a*], Moana J. H. Vercoe[b], Antonia Ciovica[c], Lori Uber-Zak[d], Charlotte Ulrikka Rask[e,f] and Paul J. Zak[b]

[a]Department of Nuclear Medicine and PET Center, Aarhus University, Aarhus, Denmark; [b]Center for Neuroeconomics Studies, Claremont Graduate University, Claremont, CA, USA; [c]Department of Psychiatry, Loma Linda University School of Medicine, Loma Linda, CA, USA; [d]Department of Neurology, Loma Linda University Medical Center, Loma Linda, CA, USA; [e]Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Aarhus, Denmark; [f]Child and Adolescent Psychiatry Center, Aarhus University Hospital, Aarhus, Denmark

ABSTRACT

Psychogenic non-epileptic seizures (PNES) is a conversion disorder that reflects underlying psychological distress. Female patients with PNES often present with a history of prolonged stressors, especially sexual abuse. In the current study, we studied the relationship between neuropeptide Y (NPY) and PNES symptoms in women with a history of sexual abuse. NPY has been associated with resilience to stress and we hypothesized that low levels would increase the extent and severity of PNES symptoms in this patient population. Serum levels of NPY, and related hormones were measured in fifteen female PNES patients and sixty female controls. PNES patients reported more severe abuse histories, feeling of abandonment, and decreased perception of quality of life than controls. Importantly, they also had lower NPY levels. Our analysis indicates that low levels of NPY in PNES may confer greater vulnerability to exhibit seizure-like symptoms and lower quality of life.

ARTICLE HISTORY
Received 19 December 2016
Revised 6 September 2017
Accepted 7 September 2017

KEYWORDS
PNES; NPY; cortisol; ACTH; negative life events; stress

Introduction

Psychogenic non-epileptic seizures (PNES) are paroxysmal events characterized by changes in responsiveness, movements, or behavior that resemble epileptic seizures but are not accompanied by the synchronous electrophysiological signals that characterize epilepsy. Serious sexual, emotional, or physical abuse is reported in the childhood histories of many patients with PNES (Alsaadi & Marquez, 2005).

Perhaps the best-studied component of the stress response in humans is activation of the HPA axis where the anterior pituitary gland produces and secretes adrenocorticotropic hormone (ACTH) into the general circulation, which in turn induces cortisol (CORT) synthesis and release from the adrenal glands. An important feature of a healthy stress response is that it terminates when the stressor has ended. Termination of the stress response is critical because the prolonged activation of the sympathetic nervous system (SNS) and the HPA axis can lead to long-lasting adverse health consequences such as autoimmune diseases and impaired growth (Guilliams & Edwards, 2010). However, stress-related health problems in PNES patients could also be marked by the alteration of other signaling pathways. Higher levels of testosterone (T) and lower levels of oxytocin (OXT) have been found in women with chronic stress and history of abuse (Heim et al., 2009). Estradiol, which modulates the HPA axis, is lower in women during prolonged stressful situations (Hertting & Theorell, 2002). In addition, high levels of prolactin (PRL) have been found to be elevated in post-ictal events in epilepsy (Bauer et al., 1992).

Another component of the SNS, NPY, acts as a neurotransmitter in the brain and in the autonomic nervous system, modulating the HPA axis through release of ACTH from the anterior pituitary. Due to its action on the SNS, NPY may reverse hyperarousal (Ehlers, Somes, Seifritz, & Rivier, 1997). In addition, the interaction of NPY with CORT helps individuals to cope with stress and sustain health, while hyperarousal and decreased NPY are associated with post-traumatic stress disorder (PTSD) symptoms (Rasmusson et al., 2000). The role of NPY in PNES remains to be elucidated.

Here, we focus on the concomitant activity of the SNS and HPA as parts of the stress management system in PNES through the assessment of basal serum levels of NPY, ACTH, CORT, and related hormones. We hypothesize that low NPY levels, due to their important role in resilience to stress, will be diminished in patients with PNES.

Methods

Participants

Fifteen women diagnosed with PNES (mean age 38 years) were recruited from the non-epilepsy outpatient registry at

CONTACT Michael Winterdahl michael.winterdahl@clin.au.dk Associated Professor in Neuroimaging, Department of Nuclear Medicine and PET Center, Aarhus University, Nørrebrogade 44, DK-8000 Aarhus C, Denmark
*These authors contributed equally to this work.

Loma Linda University Medical Center (LLUMC) and participated in the study. A member of the research team telephoned all the women listed on the relevant LLUMC registry and explained to each prospective subject that she was being invited to participate in this research project because she has seizure symptoms. All patients had been diagnosed with PNES using video EEG monitoring by an epileptologist (L.U.-Z.) to rule out organic causes of seizures and were evaluated for psychiatric symptoms by a clinical psychologist (A.C.) following best practices.

The control group of 60 healthy women (mean age 22 years) were randomly recruited from Scripps College and Claremont Graduate University (CGU) through flyers posted around the Claremont Colleges. Based on the self-reported abuse scores (J-NAAP; Jacobs, 2002), the control group was further divided in healthy controls without abuse (HC), and healthy controls with abuse (HA) scoring higher than 0. Only women were tested in this study because the incidence of PNES is three-fold higher than in men (Alsaadi & Marquez, 2005). Women are also more likely to report significant physical and sexual abuse histories (Alsaadi & Marquez, 2005).

Exclusion criteria were: exhibiting clinically significant suicidal ideation; exhibiting psychotic features; substance abuse disorder (per DSM-4 TR) within the past 6 months; any current or past psychiatric disorder that could interfere with diagnostic assessment or study adherence; treatment with psychoactive medications (other than mood stabilizers or Ambien); clinically unstable medical conditions; clinically significant abnormal laboratory results; clinically verified mixed epileptic and non-epileptic seizures; treatment with an experimental drug or device within 60 days of study enrollment. Only participants (PNES and controls) who did not show any depressive tendency, according to an abridged version of the Beck Depression Inventory (BDI), were included. A clinical psychologist (A.C.) interviewed all participants to rule out the above-mentioned co-morbidities prior to inclusion. The Institutional Review Boards of LLUMC, CGU, and Scripps College approved the study. All participants gave written informed consent prior to commencing participation.

Measures

Psychological measures

All participants enrolled in the study completed a shortened version of the Jacobs Neglect, Abandonment, and Abuse Protocol (J-NAAP; Jacobs, 2002) administered by a clinician to determine the presence and severity of abuse/neglect. The J-NAAP assesses traumatic or stressful life events such as loss or abandonment, serious neglect, physical abuse, emotional abuse, and sexual abuse. Participants also completed the Quality of Life in Epilepsy (QOLIE-89) questionnaire (Devinsky et al., 1995). The QOLIE-89 measures overall quality of life, emotional well-being, role limitations due to emotional problems, social support, social isolation, energy/fatigue, worry about seizures medication effects, health discouragement, work/driving/social functions, attention/concentration, language, memory, physical function, pain, role limitations due to physical problems, and health perceptions. Participants also completed the Experiences in Close Relationships-Revised (ECR-R) questionnaire, a 36-item measure of adult attachment style (Fraley, Waller, & Brennan, 2000). The ECR-R measures individuals on two subscales of attachment: avoidance and anxiety. In general, avoidant individuals find discomfort with intimacy and seek independence, whereas anxious individuals tend to fear rejection and abandonment. To control for a possible impact of depression on the HPA response, the BDI (Beck, Ward, Mendelson, Mock, and Erbaugh, 1961) was used. Scores higher than 20 represent clinically relevant depressive symptoms and therefore excluded from the current study. To further check the presence and the nature of traumatic events, the Life Stressor Checklist-Revised (LSC-R; Wolfe & Kimerling, 1997) was administered. The LSC-R focuses on 30 traumatic events relevant to females, such as abortion, sexual abuse, natural disasters, physical abuse, and others. Participants were asked to indicate if each event occurred in their lives, and for those, they were asked to provide additional information about the age at which the event occurred, when it ended, if they felt they were harmed, if they felt helpless about the event, and how upsetting the event was to them.

Serological measurements

All testing was done between 6 pm and 8 pm to control for the diurnal variations of hormones. A total of 28 ml of blood was drawn from an antecubital vein, using two 8-ml EDTA whole-blood tubes and one 12 ml serum-separator tube using Vacutainer® blood collection kits. After phlebotomy, each tube was immediately stored on ice. The tubes were then placed in a refrigerated centrifuge and spun at 1500 rpm at 4 °C for 12 min. Serum was withdrawn and placed into 2-ml polypropylene Fisherbrand screw cap with O-ring microtubes. The microtubes were immediately placed on dry ice and then transferred to a −70 °C freezer until analysis. All tests were performed at the Endocrine Core Laboratory of the Yerkes National Primate Research Center at Emory University, Atlanta, Georgia, USA. Commercial RIA kits from American Laboratory Products Company, Windham, NH (NPY), DiaSorin, Inc., Stillwater, MN (ACTH), Diagnostic Systems Laboratories, Webster, TX (CORT; PRL; estradiol, E), Beckman Coulter, Webster, TX (testosterone, T), Siemens, Los Angeles, CA (progesterone), and Assay Designs, Ann Arbor, MI (OXT), were used. All inter-assay and intra-assay coefficients of variation were within acceptable bounds (<15%).

Statistical analyses

All hormone data were log transformed before analysis and values that deviated more 2.5 standard deviations were considered outliers and removed. A total of 19 outliers were removed (NPY = 2, ACTH = 0, CORT = 1, T = 5, OXT = 2, progesterone = 5, estradiol = 0, PRL = 4). Hormone ratios were calculated by dividing hormone X by hormone Y followed by the log transformation in order to maintain a linear relationship and to avoid problems related to the choice of ratio. Analysis of variances (ANOVAs) were computed to analyze endocrine and psychological measures. All *post hoc* analyses

were performed with Tukey's honestly significant difference (HSD) test. Correlations were computed by Pearson product-moment correlations; no covariates were included in the analysis. For all analyses, the significance level was set at $\alpha = 0.05$. Results are expressed as mean ± the standard error of the mean (SEM).

Results

The PNES group was significantly older than both HA and HC ($p < .0001$), but there was no age difference between HA and HC. Every measure of history of stress (LSC-R), including length and type, was substantially more severe in the patient group, $\chi^2(14) = 81.71$, $p < .0001$ (Table 1). ANOVAs revealed significant differences in abuse ($F_{2,72}=51.69$, $p < .0001$), abandonment ($F_{2,72}=31.62$, $p < .0001$), and QOLIE ($F_{2,63}=11.05$, $p < .0001$) between groups, with PNES patients reporting higher abuse and abandonment (all $p < .001$) and lower QOLIE-89 ($p < .001$) when compared to both HC and HA. Except for abuse ($p < .0001$), HC and HA did not differ in other psychometric measures. PNES patients also scored higher than HC, but not HA, in attachment avoidance ($F_{2,60}=3.77$, $p < .05$), yet no differences were observed for attachment anxiety. Details are reported in Figure 1 and Table 2.

Compared to HC, we found that the PNES group exhibited lower levels of NPY (36%, $F_{2,71}=14.13$, $p < .0001$) and PRL (59%, $F_{2,68}=4.09$, $p < .05$), and higher levels of ACTH (34%, $F_{2,60}=7.04$, $p < .01$). In addition, CORT was lowered of 65% in PNES compared to HA ($F_{2,71}=3.34$, $p < .05$) but not compared to HC (Table 3 and Figure 2). In order to study the balance between the SNS and the HPA axis, ratios were calculated across groups. Altered ratios were found in PNES patients, compared to HC, for NPY/ACTH ($F_{2,60}=15.73$, $p < .0001$), and ACTH/CORT ($F_{2,60}= 9.20$, $p < .001$), but not for NPY/CORT. In addition, we found altered ACTH to PRL (ACTH/PRL, $F_{2,57} = 11.15$, $p < .0001$), CORT to T (CORT/T, $F_{2,69}=3.94$, $p < .05$), ACTH to T (ACTH/T, $F_{2,58}= 4.77$, $p < .05$), and ACTH to estradiol (ACTH/E, $F_{2,59}=4.54$, $p < .05$) ratios.

In the PNES group, ACTH was negatively correlated with NPY, $r(13) = -.68$, $p < .01$, but no significant correlations were found between ACTH and CORT in all three groups. In PNES

Table 1. Life history (LSC-R) for 15 patients with PNES and 60 controls.

	PNES $n = 15$ (%)	Control $n = 60$ (%)	p (Chi-square)
Abuse history	15 (100.0)	20 (33.3)	<.0001
Prolonged abuse (>2 months)	14 (93.3)	12 (20.0)	<.0001
Molestation (onset):			
0–6 years	3 (20.0)	4 (6.7)	<.05
7–16 years	14 (6.7)	5 (8.3)	<.0001
Rape (onset):			
0–6 years	1 (6.7)	0 (0.0)	<.01
7–16 years	8 (53.3)	3 (5.0)	<.0001
Physical abuse	12 (80.0)	11 (18.3)	<.0001
Emotional abuse	12 (80.0)	9 (15.0)	<.0001
Family violence	13 (86.7)	15 (25.0)	<.0001
Parental divorce	8 (53.3)	18 (30.0)	<.05
Death of close relative	14 (93.0)	36 (60.0)	<.01
Foster care	4 (26.6)	0 (0.0)	<.0001
Miscarriage	8 (53.3)	3 (5.0)	<.0001
Serious physical or mental illness	11 (73.3)	11 (18.3)	<.0001
Serious accident/disaster (disaster, fire, accident)	11 (73.3)	22 (36.7)	<.001

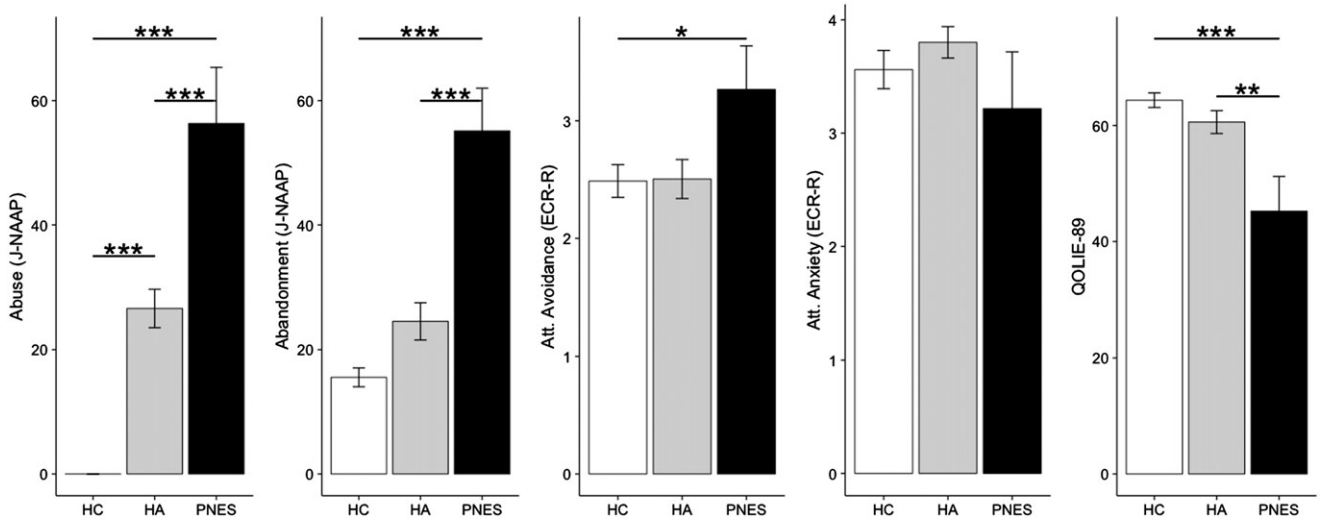

Figure 1. Psychological characteristics of PNES, HC, and HA. Error bars represent SEM; significance codes: $^{***}p < .001$, $^{**}p < .01$, $^{*}p < .05$ (p-adjusted with Tukey HSD).

Table 2. Demographic and psychological characteristics for 15 patients with PNES and 60 healthy controls divided into controls without abuse (healthy controls, HC) and controls with abuse (healthy abused, HA).

	Healthy control, $N = 33$	Healthy abused, $N = 27$	PNES, $N = 15$	F	p
Age	21.72 ± 0.86	22.48 ± 1.13	37.67 ± 4.04	20.46	<.0001
Abuse (J-NAAP)	–	26.63 ± 3.09	56.33 ± 9.01	51.69	<.0001
Abandonment (J-NAAP)	15.55 ± 1.51	24.56 ± 2.99	55.13 ± 6.87	31.62	<.0001
Att. avoidance (ECR-R)	2.49 ± 0.14$^{(27)}$	2.5 ± 0.17$^{(21)}$	3.27 ± 0.37	3.773	<.05
Att. anxiety (ECR-R)	3.56 ± 0.17$^{(27)}$	3.8 ± 0.14$^{(21)}$	3.22 ± 0.5	1.11	ns
QOLIE-89	64.36 ± 1.26$^{(29)}$	60.59 ± 1.97$^{(22)}$	45.22 ± 6	11.05	<.0001

Data are presented as mean ± SEM. Superscript numbers represent sample size. ns: not significant.

Table 3. Basal hormone levels and ratios in controls without abuse (healthy controls, HC), controls with abuse (healthy abused, HA), and PNES patients.

				ANOVA		p adjusted (Tukey HSD)	
	Healthy control (HC), $N = 33$	Healthy abused (HA), $N = 27$	PNES, $N = 15$	F	p	PNES (HC)	PNES (HA)
NPY (pmol/L)	98.91 ± 4.84	92.43 ± 4.07$^{(26)}$	63.45 ± 4.53	11.37	<.0001	<.0000	<.001
ACTH (pg/ml)	21.3 ± 4.57$^{(26)}$	25.57 ± 4.23$^{(22)}$	32.44 ± 2.22	4.56	<.05	<.05	
CORT (μg/dl)	16.67 ± 1.66	18.43 ± 1.84$^{(26)}$	11.2 ± 1.43	3.34	<.05		<.05
PRL (ng/ml)	12.02 ± 0.83$^{(32)}$	12.32 ± 0.94$^{(25)}$	7.54 ± 1.16$^{(14)}$	4.09	<.05	<.05	<.05
Free T (ng/ml)	0.92 ± 0.07$^{(29)}$	0.99 ± 0.52$^{(25)}$	1.07 ± 0.98$^{(14)}$	.59	ns		
OXT (pg/ml)	511.04 ± 58.41 $^{(31)}$	511.16 ± 67.75$^{(25)}$	457.08 ± 76.39	.26	ns		
Progesterone (ng/ml)	702.33 ± 94.26$^{(30)}$	737.6 ± 91.36$^{(25)}$	743.57 ± 168.88$^{(14)}$	.10	ns		
Estradiol (pg/ml)	41.78 ± 13.45	40.52 ± 8.2	19.54 ± 7.06	.78	ns		
NPY/CORT ratio	1.9 ± 0.11	1.68 ± 0.12$^{(25)}$	1.81 ± 0.17	.90	ns		
NPY/ACTH ratio	1.82 ± 0.13$^{(26)}$	1.49 ± 0.14$^{(22)}$	0.66 ± 0.13	15.73	<.0001	<.0001	<.001
ACTH/CORT ratio	0.02 ± 0.27$^{(25)}$	0.05 ± 0.31$^{(22)}$	1.07 ± 0.27	9.20	<.001	<.001	<.01
ACTH/PRL ratio	0.39 ± 0.18$^{(26)}$	0.52 ± 0.11$^{(21)}$	1.13 ± 0.29$^{(14)}$	11.15	<.0001	<.001	<.01
CORT/T ratio	2.72 ± 0.12$^{(32)}$	2.85 ± 0.11$^{(24)}$	2.23 ± 0.1	3.94	<.05	<.05	<.05
ACTH/T ratio	4.18 ± 0.16$^{(25)}$	3.96 ± 0.12$^{(21)}$	3.53 ± 0.09	4.77	<.05	<.01	
ACTH/E ratio	−0.21 ± 0.27$^{(25)}$	0.05 ± 0.31$^{(22)}$	1.07 ± 0.27	4.54	<.05	<.05	
OXT/T ratio	0.72 ± 0.16$^{(30)}$	0.88 ± 0.13$^{(24)}$	1.03 ± 0.16	.96	ns		

Data are presented as mean ± SEM; superscript numbers represent sample size. ns: not significant.

but not in HA and HC, NPY negatively correlated with levels of abuse, $r(13) = -.56$, $p < .05$. Such correlation was even stronger when PNES were grouped with HA individuals, $r(39) = -.55$, $p < .001$. Only in the PNES patients, NPY had a tendency to increase with age, $r(13) = .51$, $p = .0506$, while ACTH was negatively correlated with age, $r(13) = -.54$, $p < .05$. A linear regression analysis was used to test whether NPY, ACTH, and age significantly predicted self-reported levels of abuse for the overall population (PNES, HA, and HC). Results indicated that the three predictors explained 44.4% of the variance (Table 4).

Discussion

An altered SNS and HPA axis in PNES patients, marked by lowered basal levels of NPY and CORT as well as higher basal levels of ACTH, were the key findings of this study. We interpret our results in the light of resilience. Resilience is the capacity to cope with adversities, traumas, and tragedies. Greater resilience is associated with better health, so genetic and neurobiological factors might contribute to resilience to stress (Southwick, Southwick, & Charney, 2012). Transgenic rats with overexpression of NPY in the hippocampus show greater resilience (Thorsell et al., 2000). Special Forces soldiers trained to be resilient to stress had significantly higher NPY levels than typical soldiers after the Prisoners of War experience (Morgan et al., 2000). In a stress study with healthy subjects, resilience was positively correlated with urinary CORT and negatively correlated with childhood trauma (Simeon et al., 2007).

Our findings suggest that the endocrine dysregulation is perhaps derived from a long-term exposure to stress consistent with patients' self-reported abuse. Despite a significant number of PNES patients having been subjected to abuse (Alsaadi & Marquez, 2005), most previous studies did not report the life history of abuse exposure. PNES patients often suffer from chronic stress as a consequence of severe physical and emotional abuse, and our findings indicate that PNES patients may experience permanent damages to the HPA axis. Approximately half of individuals with PNES have co-morbid psychological disorders associated with trauma, including PTSD, anxiety, and depression (Alsaadi & Marquez, 2005). Moreover, the physical manifestation of PNES may be a result of psychological distress (Alsaadi & Marquez, 2005) perhaps driven by physiologic dysfunctions we document here. However, despite the fact that PNES patients were not depressed at the time of the study, we did not check for other co-morbidities such as PTSD or anxiety.

Hormone levels

A key finding from this study is that serum levels of NPY were lower in PNES patients than in the control groups (Table 2). Low NPY levels have previously been reported in individuals with PTSD (Charney, 2004; Rasmusson et al., 2000), but, in line with our results, such a reduction was

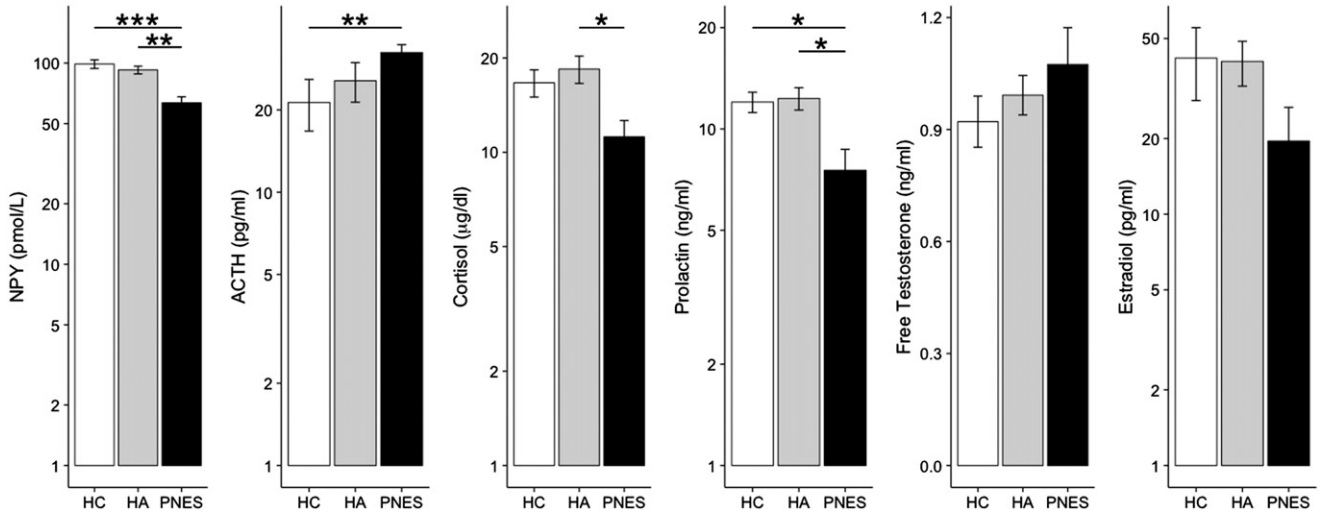

Figure 2. Hormone levels of PNES, HC, and HA. Error bars represent SEM; significance codes: $^{***}p < .001$, $^{**}p < .01$, $^{*}p < .05$ (p-adjusted with Tukey HSD).

more accentuated following trauma exposure rather than with PTSD *per se* (Morgan et al., 2003). Blunted NPY may be linked to the development of stress-related conditions such as PTSD (Rasmusson et al., 2000) or PNES, as in our case, for vulnerable individuals. NPY is also linked to depression (Charney, 2004). Yet, despite a well-known link between depression and PNES (Alsaadi & Marquez, 2005), the patients in our study were not depressed at the time of data collection as confirmed by both the BDI and the lack of depressive symptoms during clinical evaluation. However, given the potential antidepressant action of NPY in the brain (Morales-Medina, Dumont, & Quirion, 2010), the low NPY in the PNES population might have contributed to decreasing their resilience to stress and accentuating the consequences of their traumatic experiences, manifesting as conversion disorder. Interestingly, low NPY has been also linked a higher incidence of epileptic seizures; by reducing neuronal excitability (Reibel et al., 2001), NPY has been found effective in suppressing epileptic seizures in animal models (Stroud, O'Brien, Jupp, Wallengren, & Morris, 2005). We do not exclude that other pathological pathways are operating in PNES, but to our knowledge no studies to date have investigated NPY in PNES, therefore it is possible that lowered NPY levels might have contributed to the emergence/occurrence of PNES symptoms.

A trend, although non-significant, was found for ACTH that increased with abuse scores across the three groups (Figure 2), with PNES patients having significantly higher ACTH than HC. When compared to epilepsy, patients with PNES have a higher risk of developing PTSD (Dikel, Fennell, & Gilmore, 2003). Previous studies reported no difference in basal ACTH levels in PTSD patients when compared to healthy controls, even though CORT levels were significantly lower (Kanter et al., 2001). Yet, interestingly, women who experienced a history of sexual abuse without having developed major depression—as in our patient population—produce more ACTH and lower CORT in response to CRH compared to controls and women without sexual abuse but with major depression (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). Given that our patients also reported significantly higher rates of sexual abuse, but they did not develop major depression, we suggest that a history of sexual abuse *per se* might be a causative factor for an increased ACTH in PNES patients. Lower NPY levels may exacerbate this vulnerability.

We also found significantly decreased CORT levels in PNES patients. The literature is inconsistent when testing CORT in PNES subjects; it has been reported as increased (Bakvis et al., 2010) or equal (Bakvis, Spinhoven, & Roelofs, 2009) to that of healthy controls. Bakvis et al. (2010) found increased basal diurnal CORT in PNES patients with history of sexual abuse compared to both controls and PNES without abuse. Inconsistencies might be caused by sampling (saliva versus serum), time of the day (early versus late afternoon), number of measures (single versus multiple), group size, and sex ratio (only women versus men and women). An alternative explanation for such conflicting results could be that the high-CORT phase that follows an intensely stressful situation may last years before resulting in hypocortisolism (Guilliams & Edwards, 2010). Thus, CORT levels may depend on the time between the stressful event and CORT assessment, or with the intensity of abuse. Accordingly, our HA group had higher CORT levels than HC, though not significantly. We thus speculate that our low CORT levels might be due to the early and extended (>2 months) occurrence of abuse in our patients (Table 1). In line with our results, women with a history of intimate partner violence and rape have lower plasma CORT levels than controls (Seedat, Stein, Kennedy, & Hauger, 2003). Hypocortisolism may therefore be a result of traumatic early life experiences (Gunnar & Vazquez, 2001).

We found lower PRL in PNES patients compared to HC and HA subjects. Peripheral PRL can cross the blood–brain barrier and can act as a neuropeptide in the brain protecting the hippocampus from the anti-proliferative effects of glucocorticoids (Torner et al., 2009). PRL has been found to attenuate hormonal and neuronal responses to stressors reducing gastric ulcers and protecting neurogenesis in chronically stressed mice (Torner et al., 2009). Low peripheral PRL levels have been found in women with post-partum depression compared to non-depressed post-partum women (Abou-Saleh, Ghubash, Karim, Krymski, & Bhai, 1998). As such,

lowered levels of PRL in PNES patients might result from chronic stress and decreased resilience to stress.

Hormone interactions

In healthy individuals, the balance between hormones within the SNS and HPA systems is maintained by negative feedback. Because of this interaction, a change in a single hormone produces a cascade of effects within the same system and/or between the SNS and HPA axis. We found an increased ACTH to CORT (ACTH/CORT) ratio in PNES patients (Table 3 and Figure 2). Dissociations in the HPA axis are quite common, especially when patients face high stress (Bornstein, Engeland, Ehrhart-Bornstein, & Herman, 2008). Consistent with other findings (Yehuda, Golier, Halligan, Meaney, & Bierer, 2004), we did not detect a correlation between ACTH and CORT in any of the groups. In fact, factors other than pituitary ACTH—such as other neuropeptides, neurotransmitters, and sexual hormones—might affect CORT secretion, leading to dissociations between ACTH and CORT (Bornstein et al., 2008).

The interaction between SNS and the HPA axis and their feedback is consistent with the reduced NPY and CORT, and higher ACTH in PNES patients. A possible explanation is that NPY and CORT cease to be (fully) regulated by ACTH. Indeed, besides the endocrine ACTH-mediated mechanism, CORT production can be stimulated by both neural and immune pathways (Bornstein et al., 2008). Hypothalamic NPY neurons are equipped with glucocorticoid receptors (Härfstrand et al., 1989), and when dexamethasone (a selective glucocorticoid receptor agonist) is administered, hypothalamic NPY levels increase in rats (Corder et al., 1988). In this fashion, a negative feedback may occur between NPY and CORT: the low CORT contributes to lower NPY levels, which in turn further reduces CORT production. Indeed, the adrenal glands are connected to the SNS through the splanchnic nerve, on which activation depends on the production and release of both NPY (Renshaw & Hinson, 2001) and CORT (Bornstein et al., 2008).

Although not significant, we found decreased estradiol levels in PNES participants. When the ACTH to estradiol (ACTH/E) ratio was computed, PNES patients showed significantly lower values than HC but not HA. Chronic stress has been shown to reduce estradiol levels (Hertting & Theorell, 2002). At the same time, protecting the hippocampus, estradiol modulates psychosocial stress (Albert, Pruessner, & Newhouse, 2015). In addition, estradiol is able to modulate CORT and ACTH in response to stress (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). Lastly, it has been suggested that estrogens and progesterone might promote resilience in women (Charney, 2004). Thus, it appears that the balance between HPA and hypothalamic–pituitary–gonadal (HPG) axis, measured by the ACTH/E ratio, may be a resilience marker.

PNES subjects had an altered CORT to T (CORT/T) ratio though not higher free T compared to controls. In women, T is produced in equal quantity by both adrenal zona fasciculata and ovarian stroma, cumulatively contributing to 50% of the total circulating T (Burger, 2002). Although the relationship between T and physical/psychological stress remains to be elucidated, some studies found diminished T in PTSD (Charney, 2004). Yet, in soldiers, when PTSD was not accompanied by other comorbid conditions, T levels were reported to be higher than controls as well as soldiers with both PTSD and major depression (Karlović et al., 2012). This finding is consistent with an elevated CORT/T, a phenomenon that follows a prolonged period of stress in which the CORT/T ratio is high (Doan, Newton, Kraemer, Kwon, & Scheet, 2007). Deriving from the same biochemical precursor (cholesterol), an increase of one corresponds to a decrease of the other because of a competitive reaction process (Lee et al., 2016). In addition, CORT may reduce T production by blocking T effects in target tissues. In turn, T may reduce CORT levels through the hypothalamus (Romero-Martínez, González-Bono, Lila, & Moya-Albiol, 2013).

Adrenal selective damages?

Inhibited negative feedback from ACTH to CORT might be an inadequate explanation for our results as a previous study found that the dexamethasone suppression test did not reduce CORT in PNES patients (Bakvis et al., 2010). Indeed, the CORT negative feedback has not been associated with an altered ACTH/CORT ratio (Yehuda et al., 2004). An alternative explanation is reduced adrenal sensitivity, when the adrenal glands become unresponsive to ACTH and do not release enough CORT. Low circulating CORT is then an insufficient signal to the pituitary to stop producing ACTH. Considering this as a valid alternative explanation for our findings, further evidence comes from the primary adrenal insufficiency that is characterized by high ACTH and low CORT levels (Arlt & Allolio, 2003). Women with adrenal insufficiency are at increased risk for the development of immune-related disorders or pain syndromes (Heim et al., 2001). It has also been reported that adrenal insufficiency might lead to some forms of seizure (Arlt & Allolio, 2003). Although it has been suggested that NPY is unlikely a product of the adrenal glands (Renshaw & Hinson, 2001), our results are somewhat inconsistent with the literature showing that central NPY stimulates ACTH production and inhibits secretion of PRL (Crowley, 2004). If it was so, the lowered NPY would not have signaled ACTH production as well as PRL reduction. The fact that NPY production in the adrenal glands is modulated by ACTH in the zona glomerulosa and by glucorticoids in the inner zones and medulla (Renshaw & Hinson, 2001), and that T is likely to be stimulated by an action of ACTH —accounting for the 25% of circulating T— in the adrenal zona fasciculata (Burger, 2002), we suggest that selective damages to the adrenal glands might have occurred due to over production of tissue-specific hormones, as already seen in other stress-related pathologies such as anorexia nervosa (Lanfranco et al., 2004).

Aging, NPY, and self-reported abuse

Several studies report higher NPY levels in older versus younger healthy individuals (Baranowska, Radzikowska, Wasilewska-Dziubinska, Roguski, & Polonowski, 2000).

Table 4. Regression results using abuse as the criterion for the overall population (PNES, HA, and HC).

Predictor	*b*	*b*, 95% CI [LL, UL]	β	β, 95% CI [LL, UL]	sr^2	sr^2, 95% CI [LL, UL]	*r*	Fit
(Intercept)	157.62**	[60.69, 254.54]						
Age	0.71*	[0.15, 1.26]	.26	[0.06, 0.46]	0.06	[−0.03, 0.15]	0.41**	
NPY	−41.89**	[−60.91, −22.87]	−.45	[−0.66, −0.25]	0.19	[0.03, 0.34]	−0.56**	
ACTH	10.89*	[1.63, 20.15]	.24	[0.04, 0.44]	0.05	[−0.03, 0.14]	0.36**	
								$R^2 = 0.444$**
								95% CI [0.23, 0.57]

*$p < .05$. **$p < .01$. A significant *b*-weight indicates the β-weight and semi-partial correlation are also significant. *b* represents unstandardized regression weights; β indicates the standardized regression weights; sr^2 represents the semi-partial correlation squared; *r* represents the zero-order correlation. LL and UL indicate the lower and upper limits of a confidence interval, respectively.

We found a positive correlation between NPY and age in the PNES group, but not in the control groups. This absence of correlation could be due to a significant difference in age distribution in our groups. We also found that in the PNES group ACTH decreased with age. In accordance with previous literature (Heuser et al., 1994), we did not find a decrease of ACTH in healthy controls. Consistent with the linear regression (Table 4) in which age, NPY, and ACTH levels predict abuse, we suggest that as the endocrine profile moves towards normal values with age, the self-reported level of abuse is perceived to be less severe. We interpret our results as the increased NPY and decreased ACTH in PNES patients indicates that with age these two indices of SNS and HPA axis tend to move toward normal values, perhaps suggesting a natural but long recovery from trauma. While we are unable to test this hypothesis, it is consistent with changes in recalled traumatic memories over time in PTSD patients (Vanderkolk et al., 1995).

Limitations and further studies

Some limitations of the present study must be addressed. First, there is a selection bias in our participant sample as only female patients were recruited from an outpatient clinic and volunteered for the study. Since we could not perform a random assignment to condition, PNES patients may have pre-abuse vulnerabilities that explain our findings. Another limitation is our sample size and age distribution. This could be a reason why we did not find hormonal changes in response to age in the control group as other studies have reported. Yet, this weakness disappeared when the whole population was considered, and the regression model revealed indeed an effect of age as well as NPY and ACTH on abuse history, suggesting a more robust and generalizable effect of NPY and ACTH on self-reported levels of abuse. We also acknowledge that single-point measures of CORT and ACTH are not sufficient to extensively assess the HPA axis tone. Contemporary assessment of HPA axis activity typically includes consideration of daily rhythms, with a special emphasis placed on the waking response that is strongly linked to pathology (see e.g. Bakvis et al., 2010).

We also did not take into account the phase of the menstrual cycle and/or hormonal contraceptive use. This might have hindered finding significant differences in estradiol, progesterone, OXT, and testosterone. However, NPY appears unaffected by menstrual cycle (Lewandowski et al., 1998) and no ACTH and CORT differences are evident between luteal and follicular phase of the menstrual cycle (Kirschbaum et al., 1999). Future studies obtain additional measures of hormones, especially for HPG hormones that depend on the ovarian cycle.

Unfortunately, we did not record the onset and duration of illness, the frequency of seizures or the time of the initial abuse. It would also be of interest to check whether hormone levels and ratios are modulated by the time since the trauma(s) and illness occurred as well as a correlation with seizure frequency. Following a traumatic experience, CORT rises and remains stable for a certain amount of time, after which it falls below typical physiological levels (Guilliams & Edwards, 2010) perhaps due to an adrenal tissue damage. This likely affects other SNS and HPA hormones due to feedback effects. Thus, fluctuating interactions within the hormonal environment are expected and most likely depend on when the stressor occurred.

Lastly, given that in our study NPY, PRL, and estradiol seemed to characterize PNES itself, while ACTH and T seemed to vary with the levels of abuse, testing those hormones and their ratios in PNES patients without history of abuse against PNES with abuse would be important in discriminating distinctive features of PNES (see e.g. Bakvis et al., 2010).

Conclusions

The SNS and HPA axis appear to be altered in our cohort of PNES patients. Specifically, PNES patients, compared to healthy controls with and without exposure to abuse, had lower NPY and CORT and increased ACTH plasma levels. The vulnerability to PNES appears to be linked to low NPY levels, indicating that NPY could be a potential biomarker of PNES, while ACTH and CORT might be related to the level of abuse. Thus, we hope that future testing of hormones in the clinic may aid in the detection of PNES among patients presenting with epileptic-like symptoms, and at a lower cost than vEEG. Measuring hormones may also help move PNES patients into appropriate treatment more rapidly to alleviate suffering. Future larger studies involving subjects of both sexes and patients with epileptic seizures are warranted.

Acknowledgements

We thank staff at LLUMC out-patient epilepsy clinic for assistance and Dr Carlos Fayard for advice.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

This work was supported by a John Templeton Foundation to Paul J. Zak.

ORCID

Michael Winterdahl http://orcid.org/0000-0002-8790-7574

References

Abou-Saleh, M.T., Ghubash, R., Karim, L., Krymski, M., & Bhai, I. (1998). Hormonal aspects of postpartum depression. *Psychoneuroendocrinology*, *23*, 465–475. https://doi.org/10.1016/S0306-4530(98)00022-5

Albert, K., Pruessner, J.C., & Newhouse, P. (2015). Estradiol levels modulate brain activity and negative responses to psychosocial stress across the menstrual cycle. *Psychoneuroendocrinology*, *59*, 14–24. https://doi.org/10.1016/j.psyneuen.2015.04.022

Alsaadi, T.M., & Marquez, A.V. (2005). Psychogenic nonepileptic seizures. *American Family Physician*, *72*, 849–856. http://www.aafp.org/journals/afp.html

Arlt, W., & Allolio, B. (2003). Adrenal insufficiency. *Lancet (London, England)*, *361*, 1881–1893. https://doi.org/10.1016/S0140-6736(03)13492-7

Bakvis, P., Spinhoven, P., Giltay, E.J., Kuyk, J., Edelbroek, P.M., Zitman, F.G., & Roelofs, K. (2010). Basal hypercortisolism and trauma in patients with psychogenic nonepileptic seizures. *Epilepsia*, *51*, 752–759. https://doi.org/10.1111/j.1528-1167.2009.02394.x

Bakvis, P., Spinhoven, P., & Roelofs, K. (2009). Basal cortisol is positively correlated to threat vigilance in patients with psychogenic nonepileptic seizures. *Epilepsy & Behavior*, *16*, 558–560. https://doi.org/10.1016/j.yebeh.2009.09.006

Baranowska, B., Radzikowska, M., Wasilewska-Dziubinska, E., Roguski, K., & Polonowski, A. (2000). Relationship among leptin, neuropeptide Y, and galanin in young women and in postmenopausal women. *Menopause*, *7*, 149–155. doi: 10.1097/00042192-200007030-00004

Bauer, J., Stefan, H., Schrew, U., Uhlig, B., Landgraf, S., Neubauer, U., … Burr, W. (1992). Serum Prolactin Concentrations and Epilepsy. *European Archives of Psychiatry and Clinical Neuroscience*, *241*, 365–371. doi: 10. 1007/BF02191962

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004

Bornstein, S.R., Engeland, W.C., Ehrhart-Bornstein, M., & Herman, J.P. (2008). Dissociation of ACTH and glucocorticoids. *Trends in Endocrinology & Metabolism*, *19*, 175–180. https://doi.org/10.1016/j.tem.2008.01.009

Burger, H.G. (2002). Androgen production in women. *Fertility and Sterility, 77(Suppl. 4)*, S3–S5. https://doi.org/10.1016/S0015-0282(02)02985-0

Charney, D.S. (2004). Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptations to extreme stress. *American Journal of Psychiatry*, *161*, 195–216. https://doi.org/10.1176/foc.2.3.368

Corder, R., Pralong, F., Turnill, D., Saudan, P., Muller, A.F., & Gaillard, R.C. (1988). Dexamethasone treatment increases neuropeptide Y levels in rat hypothalamic neurones. *Life Sciences*, *43*, 1879–1886. doi: 10. 1016/S0024-3205(88)80005-5

Crowley, W.R. (2004). Neuroendocrine actions of neuropeptide Y. In M. C. Michel (Ed.), *Neuropeptide Y and related peptides* (pp. 185–220). Berlin: Springer.

Devinsky, O., Vickrey, B.G., Cramer, J., Perrine, K., Hermann, B., Meador, K., & Hays, R.D. (1995). Development of the quality of life in epilepsy inventory. *Epilepsia*, *36*, 1089–1104. https://doi.org/10.1111/j.1528-1157.1995.tb00467.x

Dikel, T.N., Fennell, E.B., & Gilmore, R.L. (2003). Posttraumatic stress disorder, dissociation, and sexual abuse history in epileptic and nonepileptic seizure patients. *Epilepsy & Behavior*, *4*, 644–650. https://doi.org/10.1016/j.yebeh.2003.08.006

Doan, B.K., Newton, R.U., Kraemer, W.J., Kwon, Y.-H.H., & Scheet, T.P. (2007). Salivary cortisol, testosterone, and T/C ratio responses durinq a 36-hole golf competition. *International Journal of Sports Medicine*, *28*, 470–479. https://doi.org/10.1055/s-2006-924557

Ehlers, C.L., Somes, C., Seifritz, E., & Rivier, J.E. (1997). CRF/NPY interactions: A potential role in sleep dysregulation in depression and anxiety. *Depression and Anxiety*, *6*, 1–9. https://doi.org/10.1002/(SICI)1520-6394(1997)6:1 < 1::AID-DA1>3.0.CO;2-J

Fraley, R.C., Waller, N.G., & Brennan, K.A. (2000). An item response theory analysis of self-report measures of adult attachment. *Journal of Personality and Social Psychology*, *78*, 350–365. https://doi.org/10.1037/0022-3514.78.2.350

Guilliams, T.G., & Edwards, L. (2010). Chronic stress and the HPA axis: Clinical assessment and therapeutic considerations. *The Standard*, *9*, 1–12. http://www.pointinstitute.org/

Gunnar, M.R., & Vazquez, D.M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology*, *13*, 515–538. https://doi.org/10.1017/S0954579401003066

Harfstrand, A., Cintra, A., Fuxe, K., Aronsson, M., Wikstrom, A.C., Okret, S., … Agnati, L.F. (1989). Regional differences in glucocorticoid receptor immunoreactivity among neuropeptide Y immunoreactive neurons of the rat brain. *Acta Physiologica Scandinavica*, *135*, 3–9.

Heim, C., Newport, D.J., Bonsall, R., Miller, A. H., & Nemeroff, C.B. (2001). Altered pituitary-adrenalaxis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry*, *158*, 575–581. https://doi.org/http://dx.doi.org/10.1176/appi.ajp.158.4.575

Heim, C., Young, L.J., Newport, D.J., Mletzko, T., Miller, A.H., & Nemeroff, C.B. (2009). Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Molecular Psychiatry*, *14*, 954–958. https://doi.org/10.1038/mp.2008.112

Hertting, A., & Theorell, T. (2002). Physiological changes associated with downsizing of personnel and reorganisation in the health care sector. *Psychotherapy and Psychosomatics*, *71*, 117–122. https://doi.org/10.1159/000049355

Heuser, I.J., Gotthardt, U., Schweiger, U., Schmider, J., Lammers, C.H., Dettling, M., & Holsboer, F. (1994). Age-associated changes of pituitary-adrenocortical hormone regulation in humans: Importance of gender. *Neurobiology of Aging*, *15*, 227–231. https://doi.org/10.1016/0197-4580(94)90117-1

Jacobs, D.F. (2002). *Jacobs neglect, abandonment and abuse protocol (J-NAAP)*. Redlands, CA: Author.

Kanter, E.D., Wilkinson, C.W., Radant, A.D., Petrie, E.C., Dobie, D.J., McFall, M.E., … Raskind, M.A. (2001). Glucocorticoid feedback sensitivity and adrenocrotical responsiveness in posttraumatic stress disorder. *Biological Psychiatry*, *50*, 238–245.

Karlović, D., Serretti, A., Marčinko, D., Martinac, M., Silić, A., & Katinić, K. (2012). Serum testosterone concentration in combat-related chronic posttraumatic stress disorder. *Neuropsychobiology*, *65*, 90–95. https://doi.org/10.1159/000329556

Kirschbaum, C., Kudielka, B.M., Gaab, J., Schommer, N.C., & Hellhammer, D.H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine*, *61*, 154–162. https://doi.org/0033-3174/99/6102-0154

Lanfranco, F., Gianotti, L., Picu, A., Fassino, S., Abbate Daga, G., Mondelli, V., … Arvat, E. (2004). The adrenal sensitivity to ACTH stimulation is preserved in anorexia nervosa. *Journal of Endocrinological Investigation*, *27*, 436–441. https://doi.org/10.1007/BF03345287

Lee, J.-M., Colangelo, L.A., Schwartz, J.E., Yano, Y., Siscovick, D.S., Seeman, T., … Greenland, P. (2016). Associations of cortisol/testosterone and cortisol/sex hormone-binding globulin ratios with atherosclerosis in

middle-age women. *Atherosclerosis*, *248*, 203–209. https://doi.org/10.1016/j.atherosclerosis.2016.03.028

Lewandowski, J., Pruszczyk, P., Elaffi, M., Chodakowska, J., Wocial, B., Switalska, H., … Zukowska-Grojec, Z. (1998). Blood pressure, plasma NPY and catecholamines during physical exercise in relation to menstrual cycle, ovariectomy, and estrogen replacement. *Regulatory Peptides*, *75–76*, 239–245. https://doi.org/10.1016/S0167-0115(98)00074-3

Morales-Medina, J.C., Dumont, Y., & Quirion, R. (2010). A possible role of neuropeptide Y in depression and stress. *Brain Research*, *1314*, 194–205. https://doi.org/10.1016/j.brainres.2009.09.077

Morgan, C.A., Rasmusson, A.M., Winters, B., Hauger, R.L., Morgan, J., Hazlett, G., & Southwick, S.M. (2003). Trauma exposure rather than posttraumatic stress disorder is associated with reduced baseline plasma neuropeptide-Y levels. *Biological Psychiatry*, *54*, 1087–1091. https://doi.org/10.1016/S0006-3223(03)00433-5

Morgan, C.A., Wang, S., Southwick, S.M., Rasmusson, A.M., Hazlett, G., Hauger, R., & Charney, D.S. (2000). Plasma neuropeptide Y concentration in exposed to military survival training. *Biological Psychiatry*, *47*, 902–909.

Rasmusson, A.M., Hauger, R.L., Morgan, C.A., Bremner, J.D.D., Charney, D.S., & Southwick, S.M. (2000). Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. *Biological Psychiatry*, *47*, 526–539. https://doi.org/10.1016/S0006-3223(99)00185-7

Reibel, S., Nadi, S., Benmaamar, R., Larmet, Y., Carnahan, J., Marescaux, C., & Depaulis, A. (2001). Neuropeptide Y and epilepsy: Varying effects according to seizure type and receptor activation. *Peptides*, *22*, 529–539. https://doi.org/10.1016/S0196-9781(01)00347-3

Renshaw, D., & Hinson, J.P. (2001). Neuropeptide Y and the adrenal gland: A review. *Peptides*, *22*, 429–438. https://doi.org/10.1016/S0196-9781(01)00353-9

Romero-Martínez, A., González-Bono, E., Lila, M., & Moya-Albiol, L. (2013). Testosterone/cortisol ratio in response to acute stress: A possible marker of risk for marital violence. *Social Neuroscience*, *8*, 240–247. https://doi.org/10.1080/17470919.2013.772072

Seedat, S., Stein, M.B., Kennedy, C.M., & Hauger, R.L. (2003). Plasma cortisol and neuropeptide Y in female victims of intimate partner violence. *Psychoneuroendocrinology*, *28*, 796–808. https://doi.org/10.1016/S0306-4530(02)00086-0

Simeon, D., Yehuda, R., Cunill, R., Knutelska, M., Putnam, F.W., & Smith, L.M. (2007). Factors associated with resilience in healthy adults. *Psychoneuroendocrinology*, *32*, 1149–1152. https://doi.org/10.1016/j.psyneuen.2007.08.005

Southwick, S., C.D., Southwick, S.M., & Charney, D.S. (2012). The science of resilience: Implications for the prevention and treatment of depression. *Science*, *338*, 79–82. https://doi.org/10.1126/science.1222942

Stroud, L.M., O'brien, T.J., Jupp, B., Wallengren, C., & Morris, M.J. (2005). Neuropeptide Y suppresses absence seizures in a genetic rat model. *Brain Research*, *1033*, 151–156. https://doi.org/10.1016/j.brainres.2004.11.022

Thorsell, A., Michalkiewicz, M., Dumont, Y., Quirion, R., Caberlotto, L., Rimondini, R., … Heilig, M. (2000). Behavioral insensitivity to restraint stress, absent fear suppression of behavior and impaired spatial learning in transgenic rats with hippocampal neuropeptide Y overexpression. *Proceedings of the National Academy of Sciences*, *97*, 12852–12857. https://doi.org/10.1073/pnas.220232997

Torner, L., Karg, S., Blume, A., Kandasamy, M., Kuhn, H.-G., Winkler, J., … Neumann, I.D. (2009). Prolactin prevents chronic stress-induced decrease of adult hippocampal neurogenesis and promotes neuronal fate. *Journal of Neuroscience*, *29*, 1826–1833. https://doi.org/10.1523/JNEUROSCI.3178-08.2009

Vanderkolk, B.A., Fisler, R., van Der Kolk, B.A., Fisler, R., Vanderkolk, B.A., & Fisler, R. (1995). Dissociation and the fragmentary nature of traumatic memories: Overview and exploratory-study. *Journal of Traumatic Stress*, *8*, 505–525. https://doi.org/10.1002/jts.2490080402

Wolfe, J., & Kimerling, R. (1997). Gender issues in the assessment of posttraumatic stress disorder. In J. Wilson & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD* (pp. 192–238). New York: Guilford.

Yehuda, R., Golier, J.A., Halligan, S.L., Meaney, M.J., & Bierer, L.M. (2004). The ACTH response to dexamethasone in PTSD. *The American Journal of Psychiatry*, *161*, 1397–1403. https://doi.org/10.1176/appi.ajp.161.8.1397