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Cerebrospinal fluid neuropeptide Y in combat veterans with and without posttraumatic stress disorder

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Summary

Accruing evidence indicates that neuropeptide Y (NPY), a peptide neurotransmitter, is a resilience-to-stress factor in humans. We previously reported reduced cerebrospinal fluid (CSF) NPY concentrations in combat-related posttraumatic stress disorder (PTSD) subjects as compared with healthy, non-combat-exposed volunteers. Here we report CSF NPY in combat-exposed veterans with and without PTSD. We quantified NPY concentrations in morning CSF from 11 male subjects with PTSD from combat in Iraq and/or Afghanistan and from 14 combat-exposed subjects without PTSD. NPY-like immunoreactivity (NPY-LI) was measured by EIA. The relationship between CSF NPY and clinical symptoms, as measured by the Clinician-Administered PTSD Scale (CAPS) and Beck Depression Inventory (BDI), was assessed, as was the relationship between combat exposure scale (CES) scores and CSF NPY. As compared with the combat-exposed comparison subjects without PTSD, individuals with PTSD had significantly lower concentrations of CSF NPY [mean CSF NPY was 258.6 ± 21.64 pg/mL in the combat trauma-no PTSD group but only 180.5 ± 12.62 pg/mL in PTSD patients ($p = 0.008$)]. After adjusting for CES and BDI scores the two groups were still significantly different with respect to NPY. Importantly, CSF NPY was negatively correlated with composite CAPS score and intrusive (re-experiencing) subscale scores, but did not significantly correlate with CES or BDI scores. Our current findings further suggest that NPY may regulate the manifestation of PTSD symptomatology, and extend previous observations of low CSF NPY concentrations in the disorder. Central nervous system NPY may be a clinically important pharmacotherapeutic target, and/or diagnostic measure, for PTSD.

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Conflict of interest statement

All authors declare that they have no financial or non-financial competing interests.

Keywords

Cerebrospinal fluid (CSF); Neuropeptide Y (NPY); Post-traumatic stress disorder (PTSD); Resilience; Anxiety; Brain; Mood; Depression

1. Introduction

Posttraumatic stress disorder is a trauma-evoked disorder. Since only a fraction of trauma exposed individuals develop PTSD it becomes important to identify neurobiological factors that confer inter-individual differences in “susceptibility” versus “resiliency” to the effects of trauma. Neuropeptide Y (NPY) has gained attention as a resiliency factor in humans that may contribute to inter-individual differences in stress coping and resilience (Zhou et al., 2008).

NPY, a 36-amino-acid transmitter is abundantly expressed in forebrain limbic and brain stem areas that regulate stress and emotional behaviors. Several lines of evidence support a link between NPY and PTSD (see Rasmusson et al., 2010; Sah and Geraciotti, 2013). Pre-clinical studies have shown that NPY and NPY receptors in limbic and brain stem areas play an important role in the regulation of physiological and behavioral responses that may be relevant to PTSD such as stress and anxiety (Heilig, 2004; Kask et al., 2002; Sajdyk et al., 2008) fear (Gutman et al., 2008), learning and memory (Redrobe et al., 1999, 2004), control of blood pressure (Chen et al., 1988; Martin et al., 1989), and sympathetic activity (Zukowska-Grojec, 1995). Administration of NPY or NPY over-expression in rats produces stress resilience (Thorsell et al., 2000; Sajdyk et al., 2008). Moreover, intranasal NPY infusion attenuates development of PTSD-like symptoms to traumatic stress in rats (Serova et al., 2013). In humans, polymorphisms in the NPY gene lead to individual differences in stress response and emotion (Zhou et al., 2008; Witt et al., 2011). Higher plasma NPY concentrations are associated with increased resilience and less psychological distress (Morgan et al., 2000, 2002; Yehuda et al., 2006). Conversely, depleted plasma NPY levels correlate with poorer stress-handling ability and higher dissociation scores. Importantly, as reported in a previous study by our group, individuals with combat PTSD have significantly reduced concentrations of CSF NPY as compared with healthy volunteers (Sah et al., 2009). However, it remains to be determined whether the decrease in CSF NPY is a pathophysiological feature of the disorder or an outcome of exposure to combat trauma. This distinction is clinically relevant since studies in lower animals have reported adaptive responses in CNS NPY expression following stress (McGuire et al., 2011; Makino et al., 2000; Thorsell et al., 1998). Furthermore, previous studies have reported that trauma exposure rather than PTSD is associated with reduced baseline plasma NPY levels in combat veterans (Morgan et al., 2003).

To address this issue we determined CSF concentrations of NPY in male veterans exposed to combat trauma in Iraq/Afghanistan with and without a diagnosis of PTSD. Collectively, our data suggest that NPY may be a pathophysiological feature of PTSD not a determinant of combat trauma by itself or of comorbid depression.

2. Methods

This study was approved by the IRB of the University of Cincinnati and by the Research and Development Committee of the Cincinnati Veterans Affairs Medical Center (VAMC). Written informed consent was obtained from participants prior to inclusion in the study.

2.1. Subjects

Eleven male patients with combat-related PTSD from deployment to Iraq and/or Afghanistan (“Operation Iraqi Freedom” [OIF] and/or “Operation Enduring Freedom” [OEF]) were enrolled, along with 15 subjects matched for combat deployment (with the exception of one control subject who served in Kosovo) (Table 1). At the time of study, PTSD patients were aged 30.7 ± 2.7 years and control subjects 32.1 ± 1.4 years (mean $\pm$ SEM). The body mass indices in the PTSD patients and controls were, respectively, 27.9 ± 1.3 and 25.9 ± 1.1 . Nine of 11 PTSD patients were white, the other two were African-American, and 13 of 14 control subjects were white, one African-American. Seven of 11 PTSD patients smoked as did 5 of 14 controls.

All subjects were evaluated using the Structured Clinical Interview for the DSM-IV in addition to exploratory clinical interviews. All subjects were without substance abuse for at least 3 months prior to study, although one control subject was positive for urine cannabinoids. Table 2 shows subject co-morbidities and/or histories thereof. All subjects were free of medication for at least 10 disappearance half-lives at the time of enrollment into this study. Most had never taken psychotropic medication. The combat exposure scale (Lund et al., 1984) was 24.36 ± 2.829 in the PTSD veterans and 16.86 ± 1.334 in the no-PTSD veterans. The day before CSF collection, the mean Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995) and Beck Depression Index (Beck et al., 1961) were administered.

2.2. CSF collection procedures

Subjects were admitted to the Clinical Psychoneuroendocrinology Unit of the Cincinnati VAMC the day before CSF collection. At 2000 h, patients ate a standard 665-cal mixed meal and fasted thereafter, with the exception of water ingestion until 2400 h. At midnight, all subjects were confined to bed rest. In the case of the smoking participants, no further pre-procedure smoking was permitted.

The next morning, using strict sterile technique and 1% intradermal and subcutaneous xylocaine anesthesia, CSF was obtained by lumbar puncture with subjects in the seated position. Subjects remained at bedrest during the entire CSF collection interval. The first post-lumbar puncture aliquot, 1–2 mL, was used for NPY assay.

2.3. CSF neuropeptide Y assay

NPY-like immunoreactivity (NPY-LI) was measured in CSF samples in duplicate using a competitive enzyme immunoassay (EIA) (Peninsula Laboratories Inc., Bachem, San Carlos, CA) as we previously reported (Sah et al., 2009). All samples were assayed in a single run; the intra-assay variability was 4%.

2.4. Statistical analysis

We provided summary statistics (means, SD's, 95% confidence intervals) for each of the two groups on the demographic variables, age, height, weight, and BMI, as well as NPY and the PTSD diagnostic scores (CAPS, intrusiveness, avoidance, arousal) as well as, combat exposure scores (CES) and BECK scores. The overall levels for each of these were tested between the two groups using both a Student's *t*-test and the Wilcoxon Rank-Sum test. Correlations were also derived between NPY and the CAPS total and subscale, CES, and BDI scores using both Pearson and Spearman correlation coefficients. Lastly, an analyses of covariance (ANCOVA) was conducted where NPY was the response variable, patient group (PTSD or control) was the independent class variable, and each of the diagnostic scores was the independent continuous variable, i.e., a separate ANCOVA for each of these latter variables. Additionally, in order to take into account the many zero responses among symptom scores, each variable was dichotomized to two groups: those with a zero response and those with a positive response. For each behavior the two groups were compared using a Student's *t* test as well the Wilcoxon Rank-Sum test as a check. Outcomes of these analyses were in agreement with the non-dichotomized data analysis.

3. Results

3.1. Age, body mass index, and smoking

There were no significant differences between PTSD subjects and controls in either age or body mass index. CSF NPY-LI correlated with neither age ($r = 0.027$; $p = 0.89$) nor BMI ($r = -0.012$; $p = 0.55$). Independent of diagnosis, CSF NPY concentrations were 225 ± 21.36 in smokers and 223.1 ± 22.65 in non-smokers, which were not statistically different ($p = 0.94$).

3.2. CAPS and BDI scores in combat-exposed PTSD and combat-exposed no-PTSD veterans

Mean CAPS scores of combat-exposed PTSD subjects (57.5 ± 4.8) were significantly higher as compared with combat-exposed no PTSD subjects (7.11 ± 2.2); [$t(23) = 10.35$, p -value = 0.0001]. BDI scores of combat-PTSD subjects (14.9 ± 1.5) and combat-no PTSD subjects (3.3 ± 1.0) were also significantly different ($p = 0.0001$, $t = 6.01$, $df = 23$).

CSF NPY concentrations are significantly reduced in combat-exposed PTSD subjects compared with combat-exposed subjects without PTSD.

As shown in Fig. 1, CSF NPY concentrations were significantly lower in the combat veterans with PTSD than in the combat veterans who were without PTSD. NPY concentrations averaged 258.6 ± 21.64 in the control group, but only 180.5 ± 12.62 pg/mL in the combat PTSD patients ($p = 0.008$, $t = 2.901$, $df = 23$).

To assess whether combat exposure had an effect on CSF NPY differences between the groups, we performed an analysis of covariance (ANCOVA) wherein NPY was the response while diagnostic group (PTSD or no-PTSD) and combat exposure scale (CES) were the independent variables. Since the interaction term between diagnostic group and CES was not statistically significant ($F_{(1,21)} = 0.68$, p -value = 0.42) it was dropped from the ANCOVA

and the resulting simpler, linear model without this term was used. After adjusting for CES, the mean NPY difference between the diagnostic groups was still significant ($p = 0.029$, $t = 2.33$, $df = 23$). It should be noted the CES was not statistically significant in this model ($F(1,21) = 0.14$, p -value = 0.71).

3.3. Inverse correlation of CSF NPY with PTSD symptom measures

In our entire cohort of combat veterans, CSF NPY-LI showed a significant inverse correlation with total CAPS score ($r = -0.41$, $p = 0.04$) as shown in Fig. 2a, as well as with the intrusive (re-experiencing) subscale scores ($r = -0.54$, $p = 0.006$, Fig. 2b). Correlation of CSF NPY with avoidance subscale score showed statistical trends ($r = -0.38$, $p = 0.069$) while hyperarousal subscale scores were not statistically significant ($r = -0.2426$, $p = 0.253$). Interestingly, CSF NPY-LI did not significantly correlate with either BDI ($r = -0.27$, $p = 0.20$) or CES scores ($r = -0.30$, $p = 0.14$) (see Fig. 3). Importantly, after adjusting for combat exposure scale and BDI scores, the inverse correlation between NPY and intrusive scores was still significant ($p < 0.05$).

4. Discussion

In veterans from the recent wars in Iraq and/or Afghanistan (OEF/OIF), we found that low CSF NPY concentrations are associated with combat-related PTSD and PTSD symptomatology. Importantly, CNS NPY concentrations correlated negatively with total CAPS scores, and with the re-experiencing subscale score in particular. The current findings extend and support our previous observations of reduced CNS NPY in Vietnam combat veterans with chronic PTSD (Sah et al., 2009). Thus, in two cohorts from different combat eras, we observe significant central nervous system reductions of the putative resiliency hormone NPY in individuals with PTSD.

Our finding of a direct link between reduced CSF concentrations of NPY and PTSD symptomatology is supported by several lines of evidence, as recently reviewed (Wu et al., 2011; Sah and Geraciotti, 2013). NPY plays an important role in the regulation of physiological and behavioral responses that are of relevance to the clinical syndrome of PTSD, including stress and anxiety, fear, learning and memory, control of blood pressure, and sympathetic nervous system activity. Clinically, intrusive emotionality, anxiety, and sympathetic overdrive in PTSD patients may emerge from dysregulation of the physiological balance between stress-regulatory neurotransmitters in the CNS. The NPY system has been shown to operate as a physiological “brake” system which dampens the CNS activity of the stress-signaling transmitters corticotropin-releasing hormone (CRH) and norepinephrine (NE) in the amygdala, bed nucleus of stria terminalis (BNST) and brain stem (Morris et al., 1997; Kash and Winder, 2006; Giesbrecht et al., 2010). In this regard, CNS abnormalities in both CRH and NE are observed in PTSD patients (for example, Baker et al., 1999; Geraciotti et al., 2001, 2008).

Although it is speculative to connect our CSF findings with NPY activity in discrete brain regions, that re-experiencing symptoms were those most closely related to NPY concentrations may suggest that forebrain and limbic areas that regulate fear conditioning, such as the amygdala – and are closely linked with higher brain areas subserving memory

and cognitive structures – are preferentially disinhibited by low NPY, whereas the brainstem, which is likely to subserve hyperarousal symptoms, is perhaps slightly less vulnerable to relative NPY decrements.

PTSD is frequently co-morbid with major depression (Kessler et al., 1995), and the two syndromes have overlapping symptoms. CSF NPY concentrations have been found to be reduced (Heilig et al., 2004; Nikisch et al., 2005; Widerlov et al., 1988) or elevated (Martinez et al., 2012) in studies of patients with major depression in comparison with healthy subjects. In our entire cohort of combat veterans, CSF NPY did not significantly correlate with depression ratings, but did with PTSD symptom scores, suggesting that reduced CSF NPY may be more tightly associated with PTSD than with accompanying depression. Yet, in a preliminary correlation analysis within our PTSD patient cohort (not large enough to achieve statistical validity), CSF NPY concentrations were positively associated with depressive symptoms, despite the lower NPY concentrations in this population (data not shown).

Cerebrospinal fluid NPY concentrations were reduced in our PTSD subjects and related with PTSD symptomatology even after controlling for combat exposure scores (CES) scores. Although this finding does not rule out contributions from possible pre-combat trauma or adversity in the PTSD group, it does suggest that traumatic experiences during combat are not alone sufficient to cause the disorder. It also suggests that combat trauma exposure in and of itself is not the primary contributor to low CSF NPY in the PTSD group. In apparent contrast, a previous study reported trauma exposure rather than PTSD diagnosis to be associated with plasma NPY (Morgan et al., 2003), but this study quantified peripheral NPY and not NPY in the CNS. Given the lack of correlation between NPY levels in CSF and NPY levels in circulating blood (Dotsch et al., 1997; Baker et al., 2012), this divergence with our results is not surprising. However, CSF NPY concentrations in the trauma exposed no-PTSD group in the current study were lower than those found in the healthy volunteers in our previous study (Sah et al., 2009). A shortcoming of the current study was the absence of a healthy control group. Although a direct comparison cannot be made between different study cohorts, it is possible that exposure to combat trauma produces a decrement in NPY expression. However, as suggested by our data, this decrease, if present, does not by itself appear to be significant enough to result in pathophysiological outcomes leading to PTSD.

What might contribute to lower NPY in individuals with PTSD? It is possible that our veterans with PTSD had reduced NPY prior to combat trauma due a genetic predisposition. The most commonly studied single nucleotide polymorphism (SNP) in the NPY gene is the rs16147 –399T>C that resides in the promoter region. rs16147 is associated with low NPY expression (30% decrease in –399C allele carriers), higher amygdalar and hippocampal activation in response to threat-related facial expressions, lower recruitment of the opioid system after a painful stressor, and higher trait anxiety (Zhou et al., 2008). rs16147 also confers significantly higher amygdala activation to angry faces and slows response to antidepressant treatment in patients with anxious depression (Domschke et al., 2010). Another possibility is that exposure to early life adversity or chronic stress results in dysregulation of CNS NPY, at least in certain individuals, and, superimposed with combat trauma exposure, leads to PTSD. In this regard, the NPY gene is regulated by stress and

preclinical studies in rats have reported reduced NPY following both acute and chronic stress exposure (Thorsell et al., 2000; Sergeyev et al., 2005). An enduring reduction in amygdalar NPY peptide levels has also been observed in rats during recovery from chronic variable stress (CVS) (McGuire et al., 2011). Clinical studies are needed to clarify the role of genetics and early life adversity on both NPY expression and on the vulnerability to developing PTSD.

In conclusion, our data support an association between central NPY and PTSD pathophysiology and underscore the need to perform clinical trials of CNS-penetrating NPY or NPY analogs in PTSD.

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Fig. 1. Cerebrospinal fluid concentrations of neuropeptide Y in combat veterans with and without posttraumatic stress disorder. * $p = 0.008$ versus combat no PTSD group.

Fig. 2.

Cerebrospinal fluid neuropeptide Y (NPY) levels in combat veterans are negatively correlated with (a) Clinician-Administered PTSD Scale (CAPS) score ($r = -0.4128$, $p = 0.0403$), (b) re-experiencing (intrusive) subscale score ($r = -0.543$, $p = 0.006$), (c) avoidance subscale score ($r = -0.377$, $p = 0.069$) showed trends while (d) hyperarousal subscale score ($r = -0.252$, $p = 0.235$) did not show significant correlation with NPY. Data points shown: PTSD (circles), no PTSD (triangles).

Fig. 3.

Cerebrospinal fluid neuropeptide Y (NPY) concentrations in combat veterans do not correlate with (a) combat exposure scores (CES) score ($r = -0.304$, $p = 0.140$) or (b) Beck Depression Index (BDI) scores ($r = -0.266$, $p = 0.198$). Data points shown: PTSD (circles), no PTSD (triangles).

Table 1

Military branch of participants.

	Combat PTSD patients	Combat controls
Army	8/11	10/14
Marines	2/11	2/14
Air force	1/11	1/14
Navy	0/11	1/14

Table 2

Comorbidities, or history thereof, in participants.

	Combat PTSD patients	Combat controls
Major depression	4/11	2/14 (history only)
Panic attacks	2/11	1/14 (history only)
History of transient, PTSD-related psychosis	2/11	0/14
History of alcohol abuse	7/11	2/14
History of cannabis abuse	3/11	3/14
History of other drug abuse	1/11	0/14