Severe PTSD is marked by reduced oxytocin and elevated vasopressin

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ARTICLE INFO

ABSTRACT

Neuroendocrine analyses of posttraumatic stress disorder (PTSD) have generally focused on hypothalamic-pituitary-adrenal (HPA) axis alterations. In the present analyses, we examine two additional neuroendocrine factors that have been previously implicated in biological stress responses: oxytocin (OT) and arginine vasopressin (AVP). Here we examined basal neuropeptide status in military veterans clinically diagnosed with PTSD (n = 29) and in two non-traumatized comparison groups with previous stress exposure (n = 11 SWAT trainees and n = 21 ultramarathon runners). PTSD patients showed low levels of plasma OT and high levels of AVP. The ratio of AVP/OT robustly related to PTSD status, and emerged as a statistically plausible mediator of relationships between the number of personal traumatic experiences and subsequent PTSD symptom burden. Over the course of behavioral therapy for PTSD, measures of OT showed a significant but modest normalization. Plasma cortisol levels were not statistically different among the three groups. This study suggests that AVP/OT ratios may represent a neuroendocrine predictor of severe PTSD, as well as a potential treatment response biomarker.

1. Introduction

Traumatic experiences can have lasting physical and psychological consequences for personal health, wellbeing, and job performance, but the biological mechanisms of their persisting effects remain poorly understood. When associated increases in depression, anxiety and other psychological and physical symptoms are clinically significant and persistent, they may be characterized as posttraumatic stress disorder (PTSD) [1–5] (Peterson et al., 2021). Research on the neurobiology of traumatic stress has predominately focused on the hypothalamic pituitary-adrenal (HPA) axis in an effort to identify neuroendocrine biomarkers that might predict vulnerability to PTSD or response to therapeutic interventions. Analyses have focused in particular on the adrenal glucocorticoid hormone, cortisol (CORT) [6,7], and corticotropin-releasing hormone (CRH), a neuropeptide that regulates CORT release at the level of the hypothalamus [8,9]. CRH and CORT show marked responses to acute stressors [10], but are less reliably correlated with symptoms associated with chronic stress [11] or post-traumatic stress syndromes such as PTSD [7,12].

In an effort to identify more robust biomarkers of traumatic stress and PTSD, we considered two additional circulating neuropeptides that have previously been implicated in neuroendocrine reactions to acute stress: oxytocin (OT) and arginine vasopressin (AVP) [13–17]. AVP regulates multiple aspects of vertebrate physiology, including water balance, blood pressure, biological rhythms, and various aspects of behavior, as well as activity of the HPA axis [18] (Aguilera & Liu, 2012) and autonomic nervous system. AVP also can amplify the effects of CRH on both behavioral and neural systems with consequences that are not seen in the absence of both peptides [19]. For these and other reasons, an elevation in AVP has been hypothesized as a risk factor or biomarker for PTSD [3,11,19–21], and other mental health disorders [22].

OT also has multiple physiological functions affecting nearly every adaptive function in the mammalian body [13,13,15,23]. In the context of chronic stress, OT appears to buffer physiological stress responses through either direct neuroendocrine influences on physiology or indirectly through increasing social support [24–26]. Previous research on

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PTSD has produced reports of both low OT levels [27,28] and high OT levels [29–32]. These variable results may reflect the modifying effects of developmental life history [33], gender, medical and emotional status of the individuals being study. In addition, differences in the nature of control groups serving as reference points, and the severity of conditions described as PTSD are factors to consider. The methods of data collection and those used to measure OT or AVP also have varied across studies, with results that make comparisons across studies difficult [34, 35]. Thus, many questions remain regarding the possible significance of OT and AVP in PTSD.

In the present observational study, we sought to determine the extent to which basal plasma levels of AVP, OT and CORT might provide reliable neuroendocrine correlates of PTSD.

This study was conducted with military veterans diagnosed with PTSD based on a structured diagnostic interview. Behavioral measures included the self-reported PTSD checklist (PCL-5) and Life Experiences Checklist (LEC-5) and were administered to assess prior trauma exposure. We also observed possible changes in these parameters in these same patients during a two-week trauma-focused cognitive-behavioral therapy (CBT) program [4,5]. For comparison, plasma OT, AVP and CORT samples under basal resting conditions also were measured in non-clinical samples of individuals who had encountered significant psychological and/or physiological stress including first responders in training for elite Special Weapons and Tactics (SWAT) teams. SWAT team trainees in the present study reported a history of experiencing or witnessing trauma, but did not report symptoms of PTSD as indexed by a standard self-report psychometric measure (PTSD Checklist PCL-5). In addition, samples were taken from healthy self-trained endurance athletes (RUNNERS) who were preparing for a 100 km ultramarathon endurance race. This population was chosen as a comparison group of individuals who were experiencing an extreme physiological stressor. RUNNERS did not report a significant history of trauma exposure, nor symptoms of PTSD as indexed by the PCL-5. Thus, these comparison groups differed from PTSD patients in having fewer indications of persisting symptomatology, allowing a preliminary assessment of the degree to which basal blood levels of AVP, OT or CORT might serve as neuroendocrine biomarkers of PTSD.

2. Material and methods

Ethics approvals. This research was reviewed and approved by the University of Utah Institutional Review Board under IRB_00112870 (PTSD cohort) and IRB_00110101 (SWAT and RUNNERS).

Recruitment. As reported by Bryan et al. [5], PTSD participants were recruited from community referrals and social media advertisements by the Suicide and Trauma Reduction Initiative for Veterans (STRIVE). STRIVE participants were eligible if they were (1) at least 18 years old; (2) had served in the U.S. military; and (3) met diagnostic criteria for PTSD within the past month, as established by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013), a structured diagnostic interview considered the "gold standard" of PTSD diagnosis administered by master- and doctoral-level mental health professionals and graduate students. Exclusion criteria were (1) current substance use disorder necessitating medical intervention; (2) imminent suicide risk necessitating suicide-focused intervention; (3) a suicide attempt within the past 3 months; or (4) impaired mental status precluding informed consent (e.g., intoxication, psychosis). Participants in the present study were recruited from among this larger pool of STRIVE participants and volunteered for the periodic blood draws during their treatment protocol (n = 29; 5 female). The population of PTSD patients in the STRIVE initiative were predominantly male.

SWAT trainees (n = 11; 1 female) were recruited via emails and in-person appeals prior to a 2020 training exercise conducted in Spanish Fork, Utah, and were financially compensated for their participation. SWAT participants attended a pre-training session on the day prior to the onset of training. RUNNERS (n = 21; 8 female) were recruited via emails

to registrants for a 2020 community ultramarathon in Salt Lake City, UT and also were financially compensated for participation; 21 runners consented to the study and provided baseline blood samples. Participants in all samples provided written informed consent to participate. As with the STRIVE initiative participants from the SWAT and RUNNERS cohorts available for this observational study in self-selected individuals were predominately male.

An additional 4 PTSD (1 female) and 15 SWAT (2 female) participants provided blood samples but these were not included in the primary analysis. The data from the additional subjects are shown in the Supplemental Results S1.

Treatment. The PTSD participants attended 12 1-h sessions of cognitive processing therapy (CPT) for PTSD scheduled daily for 12 consecutive calendar days (i.e., "massed" CPT). CPT is an evidence-based treatment for PTSD that has been shown to significantly reduce PTSD symptom severity and promote recovery from PTSD [36]. In CPT, participants first learn how events, thoughts, and emotions are related and how trauma-related thoughts can maintain their symptoms. Therapists teach participants how to challenge these thoughts and are encouraged to use these skills in their daily lives. Of the 29 PTSD participants included in this study, 25 completed treatment, two terminated therapy early for personal reasons, and two terminated therapy early due to concerns with the COVID-19 epidemic that was emerging at the end of their treatment in March of 2020. Participants completed self-report symptom measures (described below) at the start of every CPT session to monitor treatment response. Participants also consented to blood draws at four time points during the two-week treatment program; blood draws were also collected prior to daily therapy sessions.

Psychometric measures. Psychometric and trauma history measures were available from 62 of the total study participants across the three study cohorts (PTSD, n = 29; SWAT, n = 11; RUNNERS, n = 21. Assessments for the SWAT and RUNNERS were administered either via mail, in-person, or via electronic mail. Behavioral surveys were completed within one month of the baseline blood draw for all groups. Participants were provided the questionnaires and instructed to fill them out privately at a time when they could focus on the questions and not feel rushed.

The self-report PTSD Checklist (PCL-5) was employed as a measure of *DSM-5* PTSD severity, with high scores indicating greater disturbance, unpleasant feelings, or other emotional difficulties. Participants were directed to report the severity of 20 PTSD symptoms within the preceding 24 h using a scale ranging from 0 to 4. Items are summed to provide an overall metric of PTSD symptom severity, with scores above 30 being indicative of probable PTSD (McDonald and Calhoun, 2010).

The self-report Life Experiences Checklist (LEC-5) was administered to assess prior trauma exposure. The LEC-5 screens for potentially traumatic events in an individual's lifetime and categorizes them according to mode of exposure (i.e., happened to me, witnessed it, learned about it, part of my job, not sure, or doesn't apply). There is no formal scoring methodology for LEC-5, so we scored each of the first four main categories individually, and also formed a "total trauma exposure" score by summing those categories. Results for this measure were only available for 49/65 participants for which baseline hormone measures also were available.

Blood samples. Resting baseline blood samples were collected between 7:00AM and 11:00 a.m., by antecubital venipuncture into EDTA-treated collection tubes which had been pre-chilled at 4°C. After collection, whole blood was stored at 4°C and centrifuged within 30 min of collection for plasma separation (1600 RPM for 15 min at 4°C); 0.5 ml aliquots were frozen at $-20\,^{\circ}$C for up to 12 h before transfer to a $-80\,^{\circ}$C freezer for long-term storage. In the PTSD cohort, in addition to the baseline blood sample collected prior to the start of the treatment program, blood was also sampled an additional three times throughout the two-week NCVS therapy program on days 4, 8, and 12. For the majority of these samples (n = 113), blood was collected less than 1 h prior to the morning therapy session. However, logistical issues led to some

participants being unavailable on certain sessions prior to therapy (13 samples) so blood was instead collected after the morning therapy session. The results from samples collected after therapy sessions did not significantly differ from those collected before therapy and were thus still included in the analysis.

Assay methods. Frozen plasma aliquots were shipped overnight on dry-ice to the Kinsey Institute, Indiana University, Bloomington, IN for hormonal analysis. AVP and OT were assayed by enzyme linked immunosorbent assays (Enzo Life Sciences Arg8-Vasopressin ELISA kit, # ADI-901-017A, and Oxytocin kit, # ADI-901-153A-0001). CORT was assayed with the Arbor Assays Cortisol ELISA kit, #K003–H5. A subset of OT samples was re-assayed using the Arbor Assays Oxytocin ELISA kit, #K048–H5 (Supplement 1). For these assays, blood plasma was diluted in assay buffer (at a ratio of 1:8 for AVP, 1:2 for OT, and 1:100 for CORT) to give results reliably within the linear portion of the standard curve. The ELISA kits used here have been reported by the manufacturers to be highly sensitive (lower limit of detection: 4.10 pg/ml for AVP, 16.38 pg/ml for OT, and 50 pg/ml for CORT) with very little antibody cross-reactivity for other peptides or steroids. All samples were run in duplicate and the inter- and intra-assay coefficients of variation (CV) for AVP were less than 1.6 and 3.5 respectively; for OT less than.

4.1 and 7.2 respectively; and for CORT less than 2.6 and 7.2 respectively. Samples with CV > 20 % were eliminated from the results (affecting n = 10 samples across all assays). All assays were performed by the same researcher (HPN), blinded to sample identity.

Statistical analysis. Data were analyzed using base R, with differences between groups assessed by standard linear model analyses followed by planned pairwise-contrasts. Mixed effect linear model analyses were used to analyze repeated measurements during PTSD treatment. In addition to comparing the raw hormone levels (in pg/ml for OT and AVP; ng/ml for CORT), a ratio statistic was also computed to quantify the inverse relationship between AVP and OT while controlling for any correlated influences [24]. Due to a shortage of sample, CORT was only measured in baseline samples.

3. Results

3.1. PTSD symptoms and trauma exposure

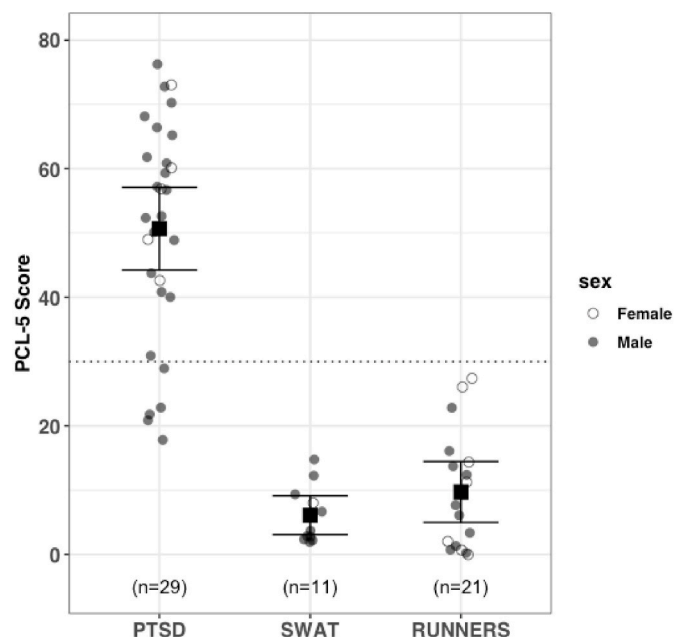As anticipated based on their clinical diagnosis, the PTSD group

showed significantly elevated PCL-5 scores compared to both groups of stressed-but-not-traumatized controls ($p < .001$, Fig. 1). The majority in the PTSD group showed PCL-5 scores above the PCL-5 clinical cutoff score of 30, whereas none of the SWAT or RUNNER controls showed scores above that value. PCL-5 scores did not differ significantly for the SWAT vs RUNNER comparison groups.

In parallel analyses of trauma exposure history, as assessed by the Life Experiences Checklist (LEC), trauma exposure scores were significantly elevated for both the PTSD and SWAT groups relative to the RUNNER control group ($p < .001$, and $p < 0.01$, respectively) (Fig. 2). The PTSD and SWAT groups showed no significant difference in lifetime trauma exposure ($p = 0.74$), underscoring the utility of the SWAT group for comparisons of previous trauma exposure while isolating the effects of symptoms associated with an ongoing post-traumatic stress disorder.

3.2. Baseline hormone levels

As shown in Fig. 3, PTSD patients showed significantly lower baseline plasma OT levels and significantly higher baseline plasma AVP levels relative to both SWAT and RUNNER comparison groups ($p < 0.001$ in both comparisons, for both hormones). These differences were substantial in absolute magnitude, exceeding 2-fold for both OT and AVP. By contrast, CORT levels did not differ significantly across groups ($p = 0.183$), with means varying by 20 % or less between groups (Fig. 3). The ratio of AVP to OT was particularly effective in distinguishing the PTSD group from the SWAT and RUNNER comparison groups, generating virtually non-overlapping distributions (Fig. 3). Similar results emerged in analyses that controlled for participant age and sex (OT: $p < 0.001$; AVP: $p < 0.001$; AVP:OT ratio: $p < 0.001$; Cortisol: $p = 0.526$).

3.3. Effects of PTSD treatment

The PTSD subjects reported generally positive emotional outcomes from the treatment protocol. There was a decline in the PCL over the therapy treatment in PTSD symptoms (Fig. 4). Over the course of the 14-day treatment protocol for PTSD, participants showed a significant increase in OT levels ($p = 0.009$). AVP levels did not change significantly ($p = 0.248$) as a function of the PTSD treatment, and were markedly more variable than OT. The AVP/OT ratio declined significantly over the course of treatment ($p = 0.003$). However, changes in plasma OT or AVP did not statistically correlate with the changes reported PTSD symptoms (see Fig. 5).

4. Discussion

The present results identify substantial elevations in plasma AVP and
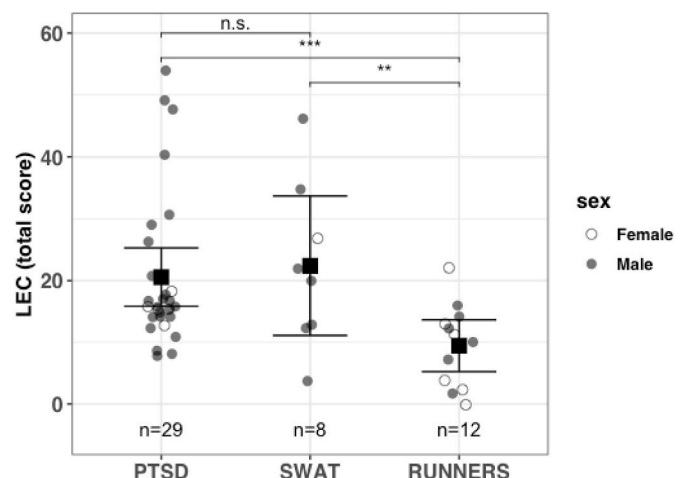

Fig. 1. PTSD symptoms by group.

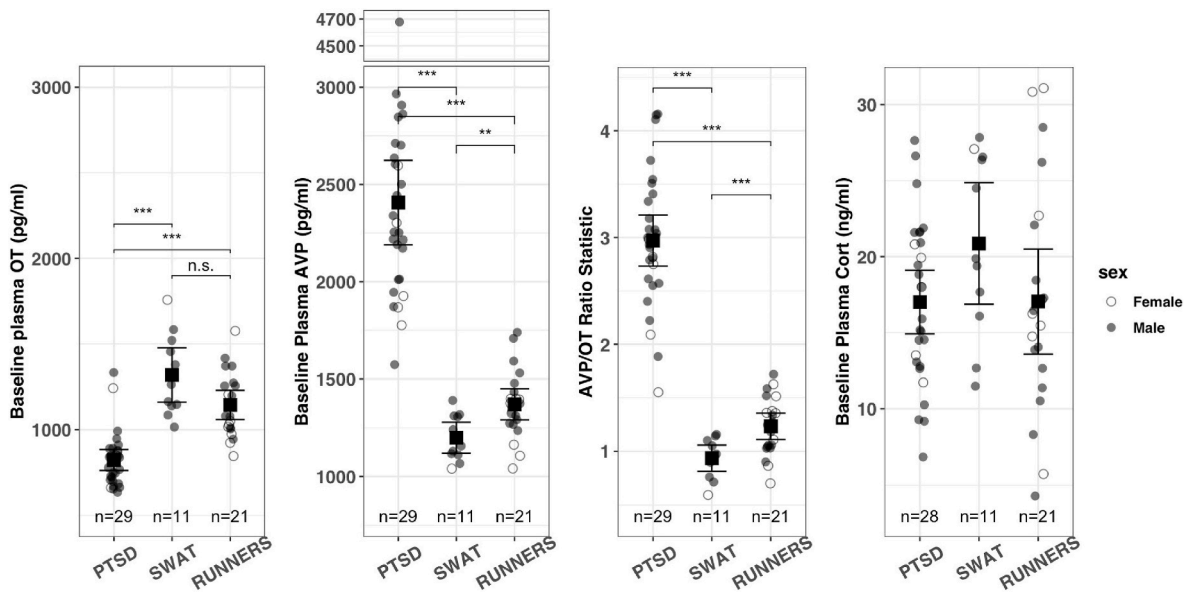**Fig. 2.** Trauma history (total events) by group.

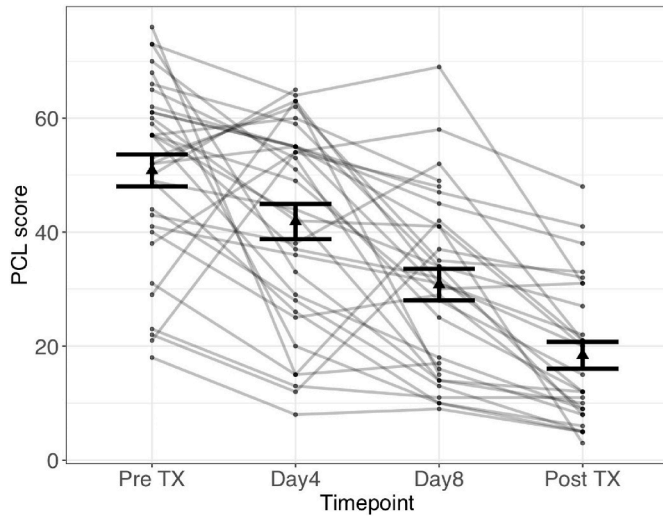**Fig. 3.** Group differences in baseline plasma hormone levels.

Fig. 4. PCL changes throughout PTSD therapy (with mean + 95%CI).

reductions in plasma OT among PTSD patients when compared to individuals who were also exposed to high levels of stress but who showed no indications of clinical PTSD symptomatology (i.e., SWAT team trainees, and long-distance RUNNERS). By contrast, we observed no significant difference in plasma CORT levels in PTSD patients in comparison to the other two stress-exposed groups (Fig. 3). These results suggest that plasma AVP/OT ratios may represent a more specific and robust indicator of PTSD pathophysiology (i.e., distinct from stress or previous trauma exposure) than the more typically analyzed measures of HPA axis activity such as plasma CORT. Moreover, plasma biomarkers of OT, and AVP/OT ratio all showed significant normalization over the course of a 14-day behavioral therapy intervention that reduced PTSD symptomatology. Collectively, these findings suggest that AVP/OT ratios may constitute a promising neuroendocrine biomarker for future analyses of PTSD pathophysiology, as well as PTSD clinical screening and intervention response assessment.

4.1. Do OT and AVP play a role in PTSD?

Based on their neurobiology and association with stress and the HPA axis, both AVP and OT have previously been hypothesized to contribute to PTSD and other chronic stress disorders [18,24,37,38].
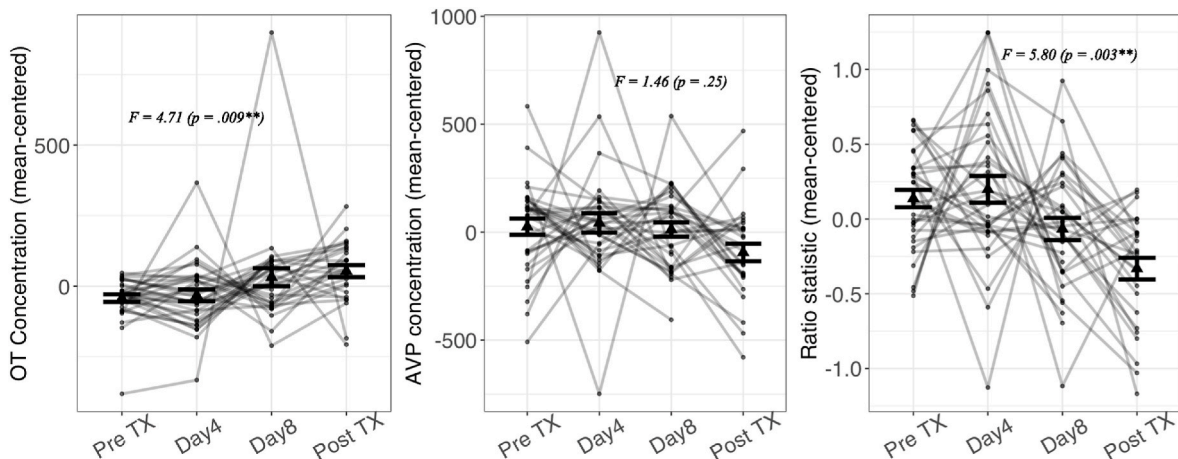

Fig. 5. Changes in OT and AVP throughout PTSD therapy (with mean + 95%CI).

Experimental data from animal models reveals that both OT and AVP modulate stress response pathways [13,15,24,28,39]. However, human clinical studies have reported mixed results in analyses testing for OT or AVP differences in PTSD [21,40]. In contrast, the results of the present study in patients diagnosed with severe PTSD documented a markedly lower OT and an elevation in AVP, as well as an increased AVP/OT ratio.

Our study differs from previous research in two major ways: 1) the use of stressed comparison groups, allowing us to consider the effects of acute stress and/or trauma exposure and focus specifically on post-traumatic stress symptoms at the time of testing, and 2) the assay of total blood OT and AVP (including plasma protein-bound neuropeptides) rather than a focus on the protein-unbound "free" neuropeptide fraction. Extraction procedures may remove a substantial fraction of circulating OT, and in some assays can result in low or undetectable neuropeptide measurements. These differences depend on the assay system and antibodies in use [26,34,35,40].

Assays conducted in our laboratory, using unextracted samples, have detected functional relationships between OT and behavioral measures in dozens of studies [33,41,42]. Human research studies done in other laboratories also have reported that the relationships between OT and behavior were stronger in assays using unextracted samples [43,44]. The present findings suggest that unextracted neuropeptide levels can show strong associations with PTSD symptomatology, a finding that was not detected in previous analyses of extracted samples [21,40].

AVP is a plausible neuroendocrine indicator of PTSD pathophysiology as it has repeatedly been linked to acute and chronic stress [3,8, 11,18,20,21,37,45–47]. Similarly, OT has previously been implicated in multiple aspects of "resilience neurobiology" including affiliative behaviors [26,48]. OT can be anxiolytic, anti-inflammatory [17], and analgesic [23,49,50]. Thus, OT may physiologically protect against the consequences of traumatic experiences and extreme stress, thus limiting the effects of PTSD, and helping to build resiliency to future challenges [51].

In existing studies, when OT has been associated with PTSD, OT has tended to be lower than comparison groups [32,52]. However, young women with psychological, dissociative symptoms showed very high levels of OT [30].

4.2. Reciprocal actions of AVP and OT

Genes regulating OT and AVP are located on the same chromosome (human chromosome 20) and are linked in their functions [53]. Located in the same hypothalamic nuclei, but in distinct neuronal populations, are magnocellular neurons that synthesize and release either OT or AVP [54]. OT can be released under many of the same conditions as AVP [55], operates in many of the same organs, tissues, and physiological systems, and can even bind to AVP's receptors, albeit with lower affinity [56]. Despite similarities in morphology and signaling mechanics, OT's regulatory functions are typically distinct from AVP's and these peptides can potentially moderate the functions of the other [26,45].

AVP supports a mobilized defense strategy, of particular importance under conditions of acute stress [15,15,45]. Although OT may be released by acute stressors [55], it is especially protective during chronic conditions, in particular when social relationships and reproduction are involved. Under some conditions, OT and AVP have opposite consequences, possibly reflecting the evolutionary history of these molecules [49,57].

AVP is the evolutionarily older molecule, which evolved from vasotocin around 400 million years ago. Vasopressin retains many primitive features associated with vasotocin and vasopressin receptors are more ancient than the primary OT receptor [58]. AVP and OT have particular relevance to the adaptive and temporally different role of social experiences in the endocrine, autonomic and immune management of reactions to different types of stressors [59] and with different consequences for inflammation [17]. AVP may respond quickly during the management of acute challenges and defensive behaviors. OT also is released by acute challenges, but may be especially adaptive under conditions of chronic challenge, when the benefits of social support and lasting relationships are most apparent [60].

4.3. Do these observations have clinical relevance?

OT and AVP have previously been suggested as factors in depression including PTSD [9,18,37]. Endogenous OT may help to regulate the autonomic nervous system and encourage calm states during which regeneration, sleep, and other conditions of rest can exist [15]. For example, deficient OT could alter the body's ability to experience such states, which might explain, in part, hyperarousal and sleep difficulties, which are frequent issues in PTSD patients [61]. The low circulating OT levels among individuals with PTSD also might increase the vulnerability for these individuals to trust and connect with others, possibly leading to the increased feelings of isolation, loneliness and discomfort in public places, experiences often reported by PTSD patients (Peterson et al., 2021).

4.4. Limitations and strengths of the present study

The present findings support a plausible role for OT and AVP in PTSD. However, the current results are based on an observational comparison of three small convenience samples, and therefore cannot establish a causal role for either OT or AVP in PTSD.

Previous experimental administration of OT has not reliably reduced PTSD symptoms or other chronic stress symptoms [25,62]. However, many issues are associated with the usefulness of exogenous OT [15,63].

Furthermore, the previous studies may have involved more acute forms of trauma or less severe forms of PTSD. OT and/or AVP may represent physiological correlates or consequences of PTSD pathophysiology rather that causal biological mechanisms.

The use of groups of from the STRIVE study, as well as the ultra-marathon RUNNERS and SWAT trainees was opportunistic and all groups were male biased based on self selection of participants. Future studies should include a broader range of challenging conditions and more female subjects. Although in the present study ancillary analyses controlled for group differences in age and sex, other variables were not measured and could potentially confound the observed comparison across groups (e.g., exposure to early life adversity, or other genetic or biological vulnerability factors). Age, gender, trauma history, disease severity and receptor sensitivity are major co-variants, among several, that will need deeper study before strong conclusions are possible regarding the role of OT or AVP in PTSD.

The present study's psychometric and neuroendocrine analyses were cross-sectional and retrospective, and therefore cannot determine whether altered OT or AVP emerged after trauma exposure and/or PTSD development, or represented pre-existing vulnerability factors. However, the trend toward a reduced AVP/OT ratio over the course of PTSD therapy is consistent with psychobiological connections between PTSD symptoms and peptide concentrations, indexed here by blood levels of OT and AVP. The present study did not assess receptor activity for AVP or OT or any other aspect of neural function, and thus the neurobiological significance of these differences in plasma hormone levels remains to be defined in future research.

5. Summary

PTSD is associated with minimal differences in basal plasma CORT levels but apparent downregulation of OT and upregulation of AVP. In the present study plasma measurements of AVP, OT and an AVP/OT ratio emerged as robust biomarkers of PTSD status. Furthermore, in PTSD patients both the AVP/OT ratio and individual OT measures showed some normalization following 14 days of intensive behavioral therapy. The findings from this observational study support the emerging hypothesis that measures of AVP, OT or the AVP/OT ratio may

have value as neuroendocrine indicators of PTSD pathophysiology and in the description of the effectiveness of various therapies.

CRediT authorship contribution statement

Alexander J. Horn: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Steve Cole:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Hans P. Nazarloo:** Writing – original draft, Methodology, Data curation, Conceptualization. **Nazarloo Parmida:** Data curation, Formal analysis. **John M. Davis:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation, Conceptualization. **David Carrier:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Craig Bryan:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **C. Sue Carter:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2024.100236.

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