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Oxytocin and Vasopressin Blood Levels in People with Post-Traumatic Stress Disorder

ABSTRACT

Background: The neuroendocrine system and the hypothalamic–pituitary–adrenal axis are among the possible neurobiological factors that may be involved in the emergence and persistence of post-traumatic stress disorder. Here, we determined the levels of vasopressin and oxytocin in the peripheral blood of people with post-traumatic stress disorder, investigating their correlation with post-traumatic stress disorder symptoms.

Methods: The study included patients with post-traumatic stress disorder according to the Diagnostic and Statistical Manual of Mental Disorders Version 4 and healthy controls. People who accepted to participate in the study, who did not have any additional diseases, who had the ability to understand the questionnaires, and who did not use medications during the 3 months preceding the study onset were enrolled. The levels of vasopressin and oxytocin were measured using the enzyme-linked immunosorbent assay.

Results: Twenty-eight subjects with post-traumatic stress disorder and 19 healthy controls were included. The 2 groups were not significantly different in terms of oxytocin blood levels ($P = .481$). However, subjects with post-traumatic stress disorder had a significantly lower vasopressin level than controls ($P < .001$). We found no significant correlations of trauma duration and scale scores with oxytocin or vasopressin levels.

Conclusion: The findings of this study show that blood vasopressin may play a role in post-traumatic stress disorder. Prospective studies based on a larger number of participants are warranted to clarify how neuromodulators may affect the pathogenesis of post-traumatic stress disorder.

Keywords: Post-Traumatic Stress Disorder, oxytocin, vasopressin

Introduction

Post-Traumatic Stress Disorder (PTSD) is a mental disorder in which people re-experience the event after a traumatic experience, avoiding reminiscent stimuli, and increased arousal.[1] Although the traumatic experience represents an essential cause of PTSD, it cannot lead to the development of the disorder without other contributing factors. The lifetime prevalence of a traumatic experience varies between 64% and 90%.[2,3] However, it was reported that only a small minority of people with a traumatic experience develop PTSD. This could be explained by 2 possible hypotheses: the first is a pre-existing neurobiological condition that facilitates the emergence of PTSD, and the second is related to neurobiological changes after exposure to trauma.[4] The PTSD can be initiated and perpetuated by certain neurobiological causes, of which the neuroendocrine system and the hypothalamic–pituitary–adrenal axis (HPA) are plausible candidates.[5-7] Corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol are released to the circulation from the hypothalamus, hypophyseal gland, and surrenal glands, respectively, in response to stress.[8,9] Long-term disruptions of HPA regulation have been demonstrated in PTSD. Under chronic stress, the HPA axis ceases to respond to continuous stimulation, cortisol levels decrease, glucocorticoid receptor sensitivity increases, and negative feedback inhibition is observed.[10,11] In addition, microRNAs are possibly involved in the development of complex disorders such as PTSD.[12,13]

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Glutamate is an important neurotransmitter within the central nervous system. Animal trials have suggested that glutamate could alter stress-related CRH secretion in the hypothalamus, thus affecting HPA and triggering neurobiological events leading to PTSD.[14,15] In addition, studies have shown that a glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist, when administered in advance, reduces stress response as measured by the ACTH level.[16,17] Glutamate is also critical for memory formation, which is an important process in PTSD.[18] However, studies have shown that NMDAreceptor antagonists reduce the development of fear conditioning in hippocampus and amygdala.[19-21] Oxytocin (OT) and vasopressin (AVP) are synthesized in the hypothalamus, transported to the neurohypophysis via an axonal pathway, and stored there. They are then released into the peripheral circulation. They are also secreted into the brain from dendrites semi-independent of axonal release. It is also known that these hormones are secreted in the brain from some differentiated neuron groups to regulate various physiological processes and behaviors.[22]

It is already known that OT and AVP have different and partially contradictory roles in social behaviors, anxiety, and anxiety regulation in rodents and humans.[23,24] It is also known that both these neuropeptides may be involved in gender-dependent social attitudes (e.g., pair-bonding) as well as social cognition modulation and hostile behavior.[25,26] Consistently, OT has been investigated in autism spectrum disorder and schizophrenia, and AVP levels in major depressive disorder.[27-29]As for people with PTSD, there are studies that investigate them together or separately.[30-33] A study that measured OT and AVP levels in the saliva of police officers showed that OT levels were lower in those with PTSD, while no differences in basal salivary OT and AVP levels in women were estimated.[32] Another study in soldiers with PTSD found that plasma AVP and OT levels were not related to PTSD symptoms.[33]

Inconsistent findings are reported in recent studies conducted on OT and AVP in people with PTSD. Nevertheless, studies have employed heterogeneous methods, precluding any comparison between their findings. According to the relevant literature, AVP and OT may be associated with different mental disorders. Our study aimed to contribute to the current debate on this subject by determining AVP and OT levels in the peripheral blood of patients with PTSD and investigating their relationship with PTSD symptoms.

Material and Methods

Study Design and Eligibility Criteria

This research was conducted between 2011 and 2013 in the Inonu University Medicine School Hospital's psychiatry clinic. It enrolled patients over the age of 18 years with a diagnosis of PTSD based on the criteria of Diagnostic and Statistical Manual of Mental Disorders Version 4 (DSM-IV) and healthy controls. The DSM- IV was used since the Diagnostic and Statistical Manual of Mental Disorders Version 5 was not available when this study was performed.[1,34] Detailed medical anamnesis was taken from both patient and control groups, and physical examination and laboratory tests were performed. People who accepted to participate in the study, who did not have any additional diseases, who had the ability to understand the questionnaires, and who did not use medications during the 3 months preceding study onset were enrolled. Some patients (n = 5) were treated with different antidepressants at a fixed dose, but patients who had not used psychotropic drugs during the 3 months preceding the study onset were enrolled in order to have the study data unaffected. Conditions that may potentially affect the results—which included serious disease, seizures, any previous head trauma with resultant loss of consciousness, alcohol or other substance abuse (with the exception of smoking), and being on hormone replacement therapy during the 6 months preceding study onset—were excluded. Exposure to sexual trauma was also an exclusion criterion. Participants with PTSD were administered the Clinician-Administered PTSD Scale (CAPS), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A), as in previous reports. A psychiatrist assessed healthy controls with the Structured Clinical Interview for DSM-IV to exclude any Axis I diagnosis or psychiatric disease in their first-degree relatives. During the study period, healthy controls were recruited from the hospital through flyers and brochures. The study was conducted in accordance with the Declaration of Helsinki after its approval by the Inonu University Ethics Committee (Ethical committee approval number: 2011/28). Before starting the study, an interview was conducted with each participant to provide information about the study protocol. All participants then provided written informed consent.

Data Collection

Socio-Demographic Data Form: This form includes questions about the patients' age, marital status, gender, education, employment, place of residence, and family members.

Clinician-Applied Post-Traumatic Stress Disorder Scale: The validity and reliability of the scale were studied by Aker et al to be used as a screening tool and to determine symptom severity. On the scale, which has a total score between 0 and 136, the higher the score, the higher the PTSD severity. Inter-rater reliability coefficients for the quantitative values of the items are between 0.82 and 0.99, and Kappa values for the qualitative values are between 0.71 and 0.99. Correlation coefficients of CAPS with other clinical scales were found between 0.63 and 0.77. Its subscales include "re-experiencing," "avoidance and blunting," and "hyperarousal." The scale was found to have an internal consistency coefficient (Cronbach's alpha) of 0.91. The re-experiencing, avoidance and blunting, and hyperarousal subscales have internal consistency coefficients of 0.78, 0.78, and 0.82, respectively.[35]

Hamilton Depression Rating Scale: Akdemir et al[36] tested the scale's validity and reliability in 1996. The HAM-D's test–retest reliability coefficient based on a 5-day interval was 0.85; its Cronbach alpha coefficient was 0.75, and a split-half reliability coefficient was 0.76. According to the independent ratings of 4 assessors, the scale had inter-rater reliability coefficients between 0.87 and 0.98.

MAIN POINTS

- *The levels of oxytocin in the plasma of people with post-traumatic stress disorder (PTSD) are comparable to those of healthy subjects.*
- *Plasma vasopressin level was lower in people with PTSD as compared with healthy controls.*
- *No significant relationship was found between trauma duration, scale scores, and oxytocin/vasopressin levels in participants with PTSD.*

Hamilton Anxiety Rating Scale: This scale's validity and reliability were tested in Turkish by Yazici et al.[37] The average reliability coefficient of HAM-A was found to be 0.72, and the reliability coefficient for the total score was 0.94.

Biochemical Analysis

The fasting blood samples were obtained via the antecubital vein between 8.00 AM and 10.30 AM and put into biochemistry. The tubes were then subjected to centrifuge at 3000 rpm for 10 minutes to obtain the serum, which was then stored at −70°C until biochemical tests (maximum 1 year). These were used for human AVP and OT level measurements using commercial enzyme-linked immunosorbent assay kits (Cusobio) 2 times on the same day in order to overcome technical and personal bias according to the instructions.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (Chicago, IL, USA) software package was used for statistical analyses. Frequencies with percentages were used for descriptive statistics. Descriptive statistics for continuous variables included mean and standard deviation and median with minimum and maximum values. The normality of data distribution was tested using the Shapiro–Wilk test. Because of the non-normal distribution of age, the Mann–Whitney *U*-test was used to compare these variables between the groups. Gender was compared between the groups using the Pearson chi-square test. The Mann–Whitney *U*-test was used to compare the non-normally distributed variables of AVP and OT levels between the groups. The nonparametric test (i.e., the Spearman correlation coefficient, which is used when the data do not show normal distribution) was used to evaluate the correlation between AVP and OT levels with scale scores. Statistical significance was set at $P < .05$.

Results

The study included 28 subjects with PTSD (11 females and 17 males) and 19 healthy controls (7 females and 12 males).

The socio-demographic data of the groups are shown in Table 1. There was no significant difference between the groups in terms of age ($P = .847$) and gender ($P = .866$) (Table 1). No statistically significant difference was found between patient and control groups concerning marital status and education level ($P > .05$). The groups showed a homogeneous distribution according to marital status and education (Table 1).

The mean length of illness was 41.5 (SD = 54.4) months. The median exposure duration to trauma was 36 months (min-max: 1-204). The median scale score indicators of disease severity were as follows: CAPS = 78.50 (min-max: 33-99), HAM-D = 20 (min-max: 12-34), and HAM-A = 28 (min-max: 16-34).

The patient and the control groups showed no significant differences in terms of OT blood levels ($P = .481$). On the other hand, individuals with PTSD had significantly lower AVP levels compared to the control group ($P < .001$) (Table 2). No gender differences in terms of AVP levels were found in PTSD ($P = .746$), whereas the OT levels were significantly lower among males ($P = .003$) (Table 3).

No significant correlations were detected between trauma duration, scale scores, and OX-AVP levels in PTSD.

Discussion

In this study, OT and AVP blood levels of patients with PTSD were compared with the blood levels of healthy volunteers. We found that OT levels were not correlated with PTSD, whereas AVP levels

Table 1. Socio-Demographic Characteristics of Patient and Control Groups

Demographic Characteristics			Patient Group (n = 28)	Control Group (n = 19)	*P*
Gender (male/female)			17/11	12/7	.866
Age (years) (Mean (SD))			34.42 (SD = 9.94)	33.84 (SD = 10.44)	.847
Education level	Primary school	n (%)	7 (25.0)	2 (10.5)	.220
	Middle school	n (%)	6 (21.4)	7 (36.8)	
	High school	n (%)	11 (39.3)	4 (21.1)	
	College	n (%)	3 (10.7)	3 (15.8)	
	University	n (%)	1 (3.6)	3 (15.8)	
Marital status	Married	n (%)	17 (60.7)	12 (63.2)	.963
	Single	n (%)	9 (32.1)	6 (31.6)	
	Divorced/deceased	n (%)	2 (7.1)	1 (5.3)	

n, number of subjects; SD, standard deviation.

Table 2. Comparison of Oxytocin and Vasopressin Levels Between Patient and Control Groups

	PTSD Group (n = 28)		Control Group (n = 19)		
Variable	Mean (SD)	Median (Min-Max)	Mean (SD)	Median (Min-Max)	*P*
Oxytocin (ng/mL)	72.38 (SD = 60.98)	53.42 (9.82-297.66)	60.29 (SD = 43.18)	44.36 (21.18-221.73)	.481
Vasopressin (ng/mL)	179.99 (SD = 215.85)	120.19 (52.88-1035.48)	1115.38 (SD = 898.65)	881.85 (186.98-3000.00)	<.001*

Max, largest value observed; min, smallest value observed; n, number of subjects; PTSD, post-traumatic stress disorder; SD, standard deviation.
*Statistically significant difference between groups.

Table 3. Comparison of Oxytocin and Vasopressin Levels by Gender in Patient and Control Groups

Group	Variable	Subgroup	Mean (SD)	Median (Min-Max)	*P*
PTSD group (n = 28)	Oxytocin (ng/mL)	Female	104.88 (SD = 72.29)	82.88 (44.36-297.66)	.003*
		Male	51.61 (SD = 42.92)	49.17 (9.82-205.43)	
	Vasopressin (ng/mL)	Female	187.57 (SD = 207.78)	135.84 (52.88-787.69)	.746
		Male	175.07 (SD = 227.10)	119.24 (54.16-1035.48)	
Control group (n = 19)	Oxytocin (ng/mL)	Female	60.57 (SD = 19.05)	58.26 (43.82-88.4)	.128
		Male	60.13 (SD = 53.41)	40.19 (21.18-221.73)	
	Vasopressin (ng/mL)	Female	916.56 (SD = 497.99)	881.85 (223.09-1519.4)	.933
		Male	1231.36 (SD = 1070.7)	947.91 (186.98-3000)	

Max, largest value observed; min, smallest value observed; n, number of subjects; PTSD, post-traumatic stress disorder; SD, standard deviation.
*Statistically significant difference between groups.

were lower in patients with PTSD diagnosis as compared to healthy subjects.

The PTSD is among the diseases induced by stress, and it was reported that the HPA axis is stimulated by acute stress, increasing cortisol secretion from the adrenal cortex. Cortisol activates energy and prepares the body to cope with the traumatic event.[38] However, it was found that when the co-activation of the OT system compensated for the stress, cortisol levels decreased. [39,40,41] It was also reported that when the effect of CRH is stimulated by AVP, it is inhibited by OT.[42] Low AVP levels may cause under-stimulation of CRH in PTSD patients and for this reason, adequate cortisol, which prepares the person to cope with the traumatic event, is not secreted, which causes symptoms to appear. In other studies reporting that HPA axis activation continues in chronic stress, it was observed that OT is also activated, and there is no decrease in OT levels with the continuation of stress, which is similar to the response found in our study.[43,44] These data show that OT is important in the chronicity of disease in PTSD or that a disorder in the modulation of the HPA axis may play a role in its pathogenesis. It was also found in comparative studies conducted on OT peptide synthesis that OT expression is generally high in women, and receptor expression is high in men.[45] Herein, we failed to detect any significant difference between control and patient groups regarding OT levels. However, men outnumbered women in our study. We attribute the lack of anticipated increase in OT levels to differences between genders. It is already known that gender differences, positive or negative life events, and social experiences—which are individual factors—can cause changes in OT levels. Studies also reported that the expression of genes of OT and its receptors, basal OT levels, sensitivity, number, and location of OT receptors, and the OT system may interact with other systems differently in every individual.[43]

It remains unclear if OT and AVP peripheral levels may be surrogate markers of OT and AVP central levels.[24,46] Although some studies reported a relationship between plasma and cerebrospinal fluid OT levels,[47] some studies did not confirm this trend. For example, in a study on suicidal patients, no correlation was detected between cerebrospinal fluid and plasma OT levels.[48] In a study that compared plasma OT and plasma AVP levels with cerebrospinal fluid levels, it was determined that both were not associated.[49] In addition to these, there are also conflicting data regarding the levels of AVP and OT in plasma, saliva, and urine.[50,51] The measurement methods of these metabolites are questioned because the data are not consistent. Few studies have investigated the reliability and validity of the methods used to measure these metabolites.[52,53] In this study, some of the patients reported that they used antidepressant drugs for a while during certain periods of the disease. In a study by Atmaca et al[54] regarding PTSD and pituitary volumes, it was reported that psychotropic drugs can affect pituitary volume. Use of psychotropic drugs can affect pituitary volume as well as pituitary functions.[54]

It is already known that the frequency of PTSD varies depending on age and gender. Being a young adult may be a significant risk factor for PTSD.[55] There are studies which report that trauma can contribute to the appearance of PTSD (symptoms) in military personnel in the younger age group.[56,57] Moreover, PTSD occurs more commonly in women than men with a ratio of 2 : 1.[2] Nonetheless, in our study, the patient group was mainly composed of males. We attribute this to the fact that participants in our study had types of trauma which differed from those of other studies in this field. The National Comorbidity Survey reported that the most prevalent trauma type is as experiencing and witnessing war-related traumas in men and being raped or sexually abused in women.[58] Similarly, in a study in the USA, the most common causes of PTSD were found to be war, severe injury, or witnessing severe injury or death in men, and the most common cause was rape and sexual harassment in women. Conversely, patients who were exposed to sexual trauma were not included in our study. It was reported that patients developing PTSD after sexual harassment tended to have more severe symptoms and presented to medical care longer after the exposure than those developing the condition after non-sexual trauma.[59,60]

There were some limitations that affected the results of our study. First, pre- and post-disease comorbidities and childhood traumas were not investigated. These traumatic experiences may affect the severity of the disease or have effects on the development of PTSD. Second, the number of cases included in our study is limited. Third, we did not evaluate patients in the acute period of PTSD. In addition, no information on polyuria or polydipsia, which are conditions that may affect AVP levels in both groups, was collected. Finally, the cross-sectional nature of the study prevented us from making interpretations on causal relationships between tested variables.

The findings of the present study imply that AVP levels may play a role in the pathophysiology of PTSD. However, no such data were obtained for the OT. Prospective studies with larger samples and investigating acute and persistent cases are warranted for a more robust understanding of how neuromodulators may affect the pathogenesis of PTSD.

Ethics Committee Approval: *This study was approved by Ethics Committee of Inonu University (Approval No: 28, Date: 2011).*

Informed Consent: *Written informed consent was obtained from the patients who agreed to take part in the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – E.P.Z., A.B.K., S.Ö., Ş.K.; Design – E.P.Z., Ş.K.; Supervision – E.P.Z ., Ş.K.; Resources – E.P.Z., Ş.K.; Materials – E.P.Z., A.B.K., S.Ö., Ş.K.; Data Collection and/or Processing – E.P.Z., A.B.K., S.Ö., Ş.K.; Analysis and/or Interpretation – E.P.Z., A.B.K., S.Ö., Ş.K; Literature Search – E.P.Z., A.B.K., Ş.K.; Writing – E.P.Z.; Critical Review – E.P.Z., A.B.K., S.Ö., Ş.K.*

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