

Oxytocin and Vasopressin Levels and Related Factors in Adolescents with Social Phobia and Other Anxiety Disorders

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Objective: This study aimed to determine whether a difference exists in plasma oxytocin and vasopressin levels among social anxiety disorder, other anxiety disorders, and healthy control groups in adolescents. The relationship between several psychiatric variables (i.e., state and trait anxiety, social anxiety, childhood trauma, and behavioral inhibition) and oxytocin or vasopressin levels were also investigated in adolescents with anxiety disorders.

Methods: The study included three groups of adolescents: social anxiety disorder (n = 29), those with other anxiety disorders (n = 27), and the control group (n = 28). The participants filled out self-report scales to determine various psychological variables. Oxytocin and vasopressin levels were determined from the blood samples of the participants.

Results: The oxytocin levels did not show a significant difference between the social anxiety disorder group and the other anxiety disorders group. However, the oxytocin levels were significantly higher in the social anxiety disorder and other anxiety disorders groups than in the control group. The vasopressin levels did not show a significant difference among the groups. According to the hierarchical regression analysis, the state and trait anxiety levels predicted oxytocin in opposite directions. Oxytocin showed positive and negative relationship with trait and state anxiety respectively. No predictive factors were found for the vasopressin levels.

Conclusion: We found that the oxytocin levels of adolescents with social anxiety disorder were not different from those of adolescents with other anxiety disorders. Further studies can improve our knowledge of the relationship among anxiety disorders and oxytocin or vasopressin.

KEY WORDS: Anxiety disorders; Behavioral inhibition; Oxytocin; Social phobia; Vasopressin.

INTRODUCTION

Anxiety disorders are frequently seen in children and adolescents, and they cause significant impairments in various areas of their life, including school achievement, social life, and overall quality of life [1,2]. In the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), anxiety disorders in children and adolescent are classified as social anxiety disorder (SoPh), generalized anxiety disorder (GAD), separation anxiety disorder (SAD), panic disorder (PD), selective mutism, and

agoraphobia [3]. The etiology of anxiety disorders is not well known, but various factors may play a role, including genetic, temperamental (i.e., inhibitory temperamental traits), environmental (i.e., parental and family attitudes), and some biological factors [4]. Studies investigating the relationship between anxiety disorders and neurobiological mechanisms indicate that various neuropeptides, neurohormones, and brain structures (i.e., serotonin, dopamine, and the amygdala) may have a role in the etiology of such disorders [5,6]. Although the complex interactions between psychological and biological systems are suspected in this etiology, the exact neurobiological mechanisms underlying these diseases are currently unknown. Recent studies indicate a possible relationship between anxiety disorders and some neuroendocrine hormones, such as oxytocin (OXT) and vasopressin (AVP) [7-9]. However, to date, there have been in-

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sufficient data to confirm this relationship.

OXT and AVP are synthesized from the magnocellular neurons of the supraoptic and paraventricular nuclei in the hypothalamus and transported to the posterior pituitary gland to be released [10,11]. OXT is well known for its physiological role as a hormone involved in lactation and uterine contractions [12]. Recent studies have shown that OXT also has significant effects on attachment, social interaction, stress management, social cognitive function, and mood [10]. Some studies have investigated the potential link between OXT and anxiety disorders, and remarkable data were obtained on this relationship in preclinical studies. Animal studies demonstrate that OXT plays critical roles in fear and anxiety behaviors in systems related to the central nervous system, including the hypothalamic pituitary adrenal (HPA) axis [13]. Most of these studies indicate that OXT has an anxiolytic effect [14]. For example, Neumann *et al.* reported that the HPA axis was suppressed when OXT was administered to rats during stress [15]. Compatible findings have been reported in human studies, indicating that OXT may act as an anxiolytic. Kirsch [16] and Suzuki *et al.* [13] reported that OXT has regulatory effects on fear, social stress, and anxiety, normalizing amygdala activity during stress-causing social behaviors and fear and suppressing the HPA axis to exhibit anxiolytic effects. Supporting the possible anxiolytic effect of OXT, a recent study reported a high level of OXT associated with high social anxiety symptoms in patients with SoPh [9]. However, some studies have found results to the contrary. In a study conducted on adult subjects with SoPh, a positive relationship was reported between the severity of anxiety symptoms and the OXT level, despite the lack of a significant difference between the subjects with SoPh and the controls [8]. However, in their subsequent study, the authors reported a conflicting finding, namely that low levels of peripheral blood OXT were associated with SoPh [17]. Therefore, no consensus has yet been reached on this topic. Moreover, research examining the relationship between OXT and anxiety disorders in humans has been conducted mostly in adults. We have very limited knowledge about this relationship in adolescents. To the best of our knowledge, only one study investigated this relationship in adolescents, reporting that salivary OXT levels and anxiety symptoms have a negative correlation [18], a finding that contradicts the above-mentioned hypothesis that OXT has a positive rela-

tionship with the anxiety level. Based on the contradictory findings in relation to adolescents and in light of the fact that anxiety disorders may arise and manifest differently in adults and adolescents [19], the first aim of the present study was to explore the relationship between OXT and anxiety disorders in adolescents.

Further, the relationship of OXT with different types of anxiety disorders is unknown, since studies on this subject generally investigate SoPh or SAD. However, it has not been investigated whether these anxiety disorders differ in terms of their relationship with OXT. In SoPh, the subjects exhibit fear of social situations, which has shown to be associated with the OXT system [20,21]. As OXT is known to be an important molecule in social relationships, discrepancies between studies may be due to differences between other anxiety disorders and SoPh. To our knowledge, no comparison study has yet investigated the differences between subjects with SoPh and those with other anxiety disorders in terms of OXT level, despite the existence of studies reporting confounding findings [8,17,22]. Thus, we hypothesized that the OXT level could be different between SoPh and other anxiety disorders because of its role in social relationships. Therefore, as a second objective, we aimed to explore the OXT levels of adolescents with SoPh, and compare them with those of adolescents with other anxiety disorders, as well as those of healthy adolescents.

The differences of OXT levels in males and females is not clear. In a preclinical study, it has been shown that OXT receptor expression is higher in males than females [23]. Additionally, a study in humans found that women had higher OXT levels than men [24]. However, the relationship between OXT levels and behavior in terms of gender varies considerably between species. It is also suggested that gender differences in behavior are not related to structural changes in the OXT system [25].

AVP is classically known for its role as a hormone involved in homeostasis. Although its association with psychiatric disorders has been investigated in various studies, suggesting that AVP may have a regulatory role in social behaviors [10,26,27], no human studies have explored the relationship between AVP and anxiety disorders directly. OXT and AVP are important regulators of anxiety, stress and social conditions, though usually in opposing directions [28]. There are complementary data from animal studies for the opposing effects of OXT and AVP

on the regulation of anxiety-like and emotional behavior [29]. Particularly, OXT exerts anxiolytic and anti-depressive effects, whereas AVP mainly increases anxiety and depression-related behaviors. Research on the mechanisms of these neuropeptides has demonstrated that OXT and AVP modulate anxiety responses in the amygdala of rats in opposite ways, resulting in an OXT/AVP balance [30–32]. There are also conflict results from studies with intranasal AVP. In a study conducted in rats, it was shown that intranasal AVP has no effect on social recognition and short-term recognition memory [33]. On the other hand, in another study conducted in male adults, it was found that intranasal AVP in individuals with neurotic traits increased responses in various brain regions to negative social interactions and increased insula response to positive social interactions [26]. Considering the literature, mostly based on animal studies, reporting a possible relationship between OXT, AVP, and anxiety disorders, we aimed to explore this relationship in the context of SoPh, since both of these molecules have a clear association with social interaction. Therefore, we aimed to compare the OXT and AVP levels of the adolescents with SoPh, adolescents with other anxiety disorders, and healthy adolescents. We have hypothesized that the OXT and AVP levels of adolescents with SoPh and those with other anxiety disorders would be different, and that the levels of OXT and AVP in these two groups would be different from those of healthy adolescents.

Despite the prevalence of studies focusing on the relationship between anxiety and OXT, to our knowledge, the relationships between OXT and various psychological factors, which are known to be associated with anxiety (i.e., childhood trauma) have not been studied sufficiently. Only one adult study reported lower OXT concentrations in the cerebrospinal fluid of women who experienced early-life abuse [34]. In addition, the relationship between OXT and some anxiety-related constructs (i.e., behavioral inhibition, state and trait anxiety) have not been studied yet. State anxiety and trait anxiety are different concepts, reflecting different mechanisms and features. State anxiety is an emotional state characterized by subjective thoughts and feelings related to worry, apprehension, tension, and nervousness; it varies in intensity and fluctuates over time. In contrast, trait anxiety is an individual personality trait, characterized by a tendency to attend to, experience, and report fears, worries, and anxiety, as reflected

in the frequency with which anxiety states have been experienced in the past and the probability that state anxiety reactions will be experienced in the future [35]. These constructs are known to affect various psychological variables by diverse routes [36]. One study showed a positive relationship between state anxiety and OXT [37], however, relationships between OXT and state and trait anxiety in the same sample were not previously studied. Considering the diversities between these constructs, we have hypothesized that the relationship between OXT and state and trait anxiety are likely to be different. In addition, considering that anxiety is closely related to behavioral inhibition and childhood trauma [34], we have hypothesized that these constructs are also likely to be associated with OXT in adolescents with anxiety disorders.

METHODS

Participants

The study groups were recruited from the outpatient clinic for child and adolescent psychiatry at a university hospital. They were treatment-naïve adolescents aged 12–18 years who were diagnosed with SoPh, GAD, SAD, or PD, based on the DSM-5 criteria. The exclusion criteria were the presence of major physical, endocrinological, or neurological diseases, autism spectrum disorder, psychotic disorder, bipolar disorder, substance use disorder, severe head trauma, and intellectual disability—evaluated via clinical interview. Patients who had used psychotropic drugs within the previous six months or smoked, alcohol and other substance used within the six months prior to admission were also excluded from the study. The control group consists of healthy adolescents between the ages of 12–18, who do not have any known disease and who meet the inclusion and exclusion criteria and volunteer to participate in the study. No other specific criteria considered except for the inclusion and exclusion criteria. The psychiatric evaluation of the control group was carried out one day before blood samples were taken. The same inclusion and exclusion criteria were applied to the control group. Moreover, the subjects who had any anxiety disorder in the control group were excluded from the study. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS-PL) was applied for the patients and control subjects by an experienced child and adoles-

cent psychiatrist [38]. The diagnoses of SoPh, GAD, SAD, and PD were made according to the DSM-5 criteria [39]. The K-SADS-PL is a semi-structured interview form developed by Kaufman *et al.* to identify the past and present mental disorders of children and adolescents [40]. The K-SADS-PL is implemented through face-to-face interviews with parents and the child or young person, and all data are finalized by evaluating the information received from the sources (parents, children, and schools). If a discrepancy exists in the data obtained from different sources, the clinician uses his/her clinical judgment to settle the issue. The validity and reliability of this interview form for our nation were established [38]. The study for adapting the K-SADS to DSM-5 was also conducted [39].

The study was approved by the local ethics committee of the university (no. 2016/505) and all the procedures were in accordance with the Declaration of Helsinki and local laws and regulations. The participants and their parents gave their written informed consent after the investigators explained the purpose and course of the study. Oral assent was also obtained from all subjects. In the patient groups, 60 children were approached, but four were excluded on the basis of the exclusion criteria. In the control group, 36 children were approached, but eight were excluded.

Procedures

To determine the adolescents' depression and anxiety levels, the participants completed the Children's Depression Inventory (CDI) and the State-Trait Anxiety Inventory for Children (STAIC) [41,42]. The adolescents were also asked to complete the Childhood Trauma Questionnaire (CTQ) to measure their childhood trauma and the Social Anxiety Scale for children (SAS) to evaluate their social anxiety levels [43,44]. In addition, the adolescents filled out the Behavioral Inhibition System and Behavioral Activation System Questionnaire (BIS/BAS) to assess their behavioral inhibition (BI) levels [45]. The reliability and the validity of all questionnaires were previously established for the Turkish population. All psychiatric assessments, including the diagnostic interview and self-report evaluations, were administered to the subjects in a separate quiet room designed for psychiatric assessment. The day after completion of the psychiatric assessments, the participants were invited to the hospital for a phlebotomy procedure. After 30 minutes of acclimatization, periph-

eral venous blood samples for OXT and AVP were drawn from an antecubital vein in a sitting position between 8:00 AM and 10:00 AM. Subjects were requested to fast for 12 hours and to avoid heavy exercise prior to the blood sampling. In this way, possible changes induced by circadian variations or by previous meals were minimized. The participants had not seen the phlebotomy room before the procedure. Blood samples were taken by a licensed phlebotomist in the phlebotomy room, in the presence of the interviewer (NU). The parent escorting the participant was requested to wait in a different room. Psychiatric evaluation and blood sampling of the control group were carried out in a similar manner.

The blood samples of the participants and the controls were extracted and collected in appropriate tubes. The tubes were centrifuged at 4,000 rpm for 5 minutes at 4°C. Then, the plasma was stored at -80°C in Eppendorf tubes until analysis. Enzyme-linked immunosorbent assay (ELISA) kits were used for the plasma analyses of OXT (Cayman, Ann Arbor, MI, USA) and AVP (Elabscience, Wuhan, China). The plasma levels of OXT and AVP were measured using ELISA kits following the manufacturer's protocols. The patient and control samples were run together in the same plates.

Children's Depression Inventory

The CDI is a self-assessment scale used to measure the level of depression in children and adolescents [46]. It consists of 27 items and can be used with individuals aged 6–17 years. Each item of the scale contains three statements designed to evaluate the state of the individual in the previous two weeks. The total scores obtained from the statement points constitute the total score of the scale. The higher the total score, the more severe the depression level. The highest score on the scale is 54, and the cut-off point is 19. In our study, Cronbach's coefficient alpha for CDI was 0.85, which was very similar to a previously reported study with adolescents (0.86) [47]. This scale was adapted for our nation and Cronbach's alpha for CDI in our nation was previously reported as 0.80 [41].

State-Trait Anxiety Inventory for Children

The STAIC is used to measure anxiety levels in children [48]. Developed by Spielberger, this scale has two multiple-choice subscales with 20 questions for state (CSAI) and trait (CTAI) anxiety. Each item is scored 0, 1, or 2, ac-

ording to the severity of the indication. State anxiety can change according to external factors and defines the anxiety that the individual feels in certain circumstances at a certain time. Trait anxiety describes how the individual feels in general and reflects the individual's general anxiety predisposition. In a study conducted in adolescents, Cronbach's alpha of total STAIC was 0.91 [49]. Our sample demonstrated similar values (CSAI: 0.92, CTAI: 0.91). The validity and reliability study for our population was conducted. Cronbach's coefficient alpha for CSAI and CTAI in our nation was reported previously as 0.82 and 0.81, respectively [42].

Childhood Trauma Questionnaire

The CTQ was developed by Bernstein *et al.* [50] to investigate the trauma experiences of adolescents. It has 40 items in a five-point Likert scale. Higher scores indicate a higher frequency of childhood traumatic experiences. The CTQ has three subscales: emotional abuse and emotional neglect, physical abuse, and sexual abuse. A previous adolescent study reported Cronbach's alpha for CTQ as 0.97 [51], compared with 0.87 in our study. The validity and reliability of the CTQ for our nation was established with a high Cronbach's alpha value (0.96) [43].

Social Anxiety Scale for Children

The SAS for children was developed by La Greca and Stone [52] to assess children's social anxiety levels. It consists of 18 questions and evaluates two components of social anxiety, namely fear of negative evaluation and distress and discomfort in the social environment. Cronbach's coefficient alpha for SAS was 0.96 in our study. The validity and reliability study for our nation was conducted and reporting a Cronbach's alpha value of 0.81 [44].

Behavioral Inhibition System and Behavioral Activation System Questionnaire

The BIS/BAS was developed by Carver and White [53]. The behavioral inhibition subscale and the behavioral activation heading consist of a total of 4 subscales and 24 items: there is a behavioral inhibition-related and there are three behavioral activation-related scales (reward responsiveness, drive, fun seeking). There are seven items on the behavioral inhibition subscale, four on the entertainment-seeking subscale, five on the susceptibility subscale, and four on the impulsive subscale. The partic-

ipants evaluate themselves on a four-point Likert scale for each item (1: I totally agree, 2: I slightly agree, 3: I slightly disagree, 4: I do not agree at all). Although there are 24 items in the scale, evaluation is made over 20 items. In scoring, all items except items 2 and 22 are calculated by reversing. Cronbach's coefficient alpha for BIS/BAS was 0.76 in our study. The validity and reliability study for our nation was conducted, and we used the behavioral inhibition subscale of the BIS/BAS in this study, which was reported to have a Cronbach's alpha value of 0.69 [45].

Statistical Analysis

Statistical analyses were performed with SPSS 20.0 statistical software (IBM Co., Armonk, NY, USA). The variables were presented as a number (n), percentage (%), mean \pm standard deviation, or frequency. All of the variables were checked for normality using the Kolmogorov-Smirnov test. MANOVA tests were used to compare the differences in the three groups (SoPh, other anxiety disorders, and control) in terms of the demographic and clinical characteristics. To compare the OXT and AVP levels of the groups, a multivariate analysis of covariance (MANCOVA) was conducted to avoid the risk of type II errors related to the multiple testing effect and to control for possible confounding factors (i.e., age and sex). After determining that the MANCOVA test yielded a significant difference among the groups, a one-way analysis of covariance (ANCOVA) was separately performed on the outcome variables. Before the MANCOVA and ANCOVA tests, variables showing non-normal distributions (i.e., age and OXT) were logarithmically transformed. Bonferroni post hoc tests were conducted, with corrections for multiple testing. A new group (a whole anxiety disorder group) was formed, including the participants with SoPh and other anxiety disorders, to conduct the correlation and regression analyses. Pearson or Spearman's correlation analyses were used for variables showing normal or non-normal distribution features, respectively, to determine the association between the clinical and psychological variables in the whole anxiety disorder group. A hierarchical regression analysis was conducted to determine the variables predicting the OXT and AVP levels in the same group. Possible predicting variables were put in the analysis step by step, and the coefficient of determination (R^2) changes were explored to determine the steps, resulting in an incremental contribution to the analysis.

The significance level of the 95% confidence interval in the analyses was set to less than 0.05, except for the correlation analyses. To avoid the type II error related to multiple testing, the p value was set to less than 0.01 for the correlation analyses.

RESULTS

The final study population consisted of 29 adolescents with SoPh, 27 with other anxiety disorders, and 28 healthy controls. In the other anxiety disorders group, there were 16 adolescents with GAD, 9 adolescents with SAD and 2 adolescents with PD. Table 1 presents and compares the descriptive data and the clinical variables of the study groups. As shown in the table, no significant between-group difference was found for age or gender distribution of the groups. CDI, CSAI, CTAI, and BIS/BAS scores were statistically significantly higher in SoPh and other anxiety groups compared to the control group. However, no statistically significant difference was found between SoPh and other anxiety groups. SAS scores were statistically significantly higher in SoPh group than other anxiety group and control group. Also, SAS scores were statistically significantly higher in other anxiety group compared to the control group. There was no statistically significant difference between the study groups in terms of CTQ scores.

OXT levels were 211.4 ± 69.1 pg/ml in the SoPh group, 216.2 ± 75.9 pg/ml in the other anxiety disorders group and 166.2 ± 52.7 pg/ml in the control group. AVP levels

were 38.1 ± 12.6 pg/ml in the SoPh group, 39.4 ± 19.6 pg/ml in the other anxiety disorders group and 50.6 ± 25.4 pg/ml in the control group. MANCOVA analysis yielded that there were significant differences among the groups (Pillai's Trace $V = 0.198$, $F [2, 79] = 4.34$, $p = 0.002$, $np^2 = 0.099$) in terms of OXT and AVP. Separate univariate ANCOVA was conducted after being adjusted for age and sex, and the OXT and AVP levels of the three groups were compared. The analyses showed significantly higher OXT levels in the SoPh and other anxiety disorder groups compared to the controls ($F [2, 81] = 5.24$, $p = 0.007$, $np^2 = 0.117$); (Fig. 1) however, the AVP levels were not significantly different among groups ($F [2, 81] = 2.83$, $p = 0.065$, $np^2 = 0.067$) (Fig. 2). Averages of

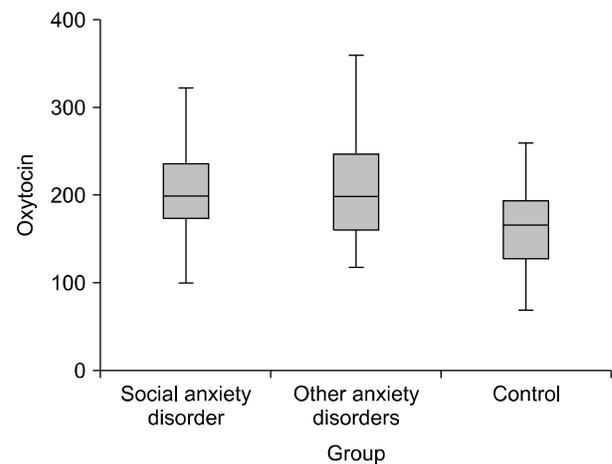


Fig. 1. Box plots representing the distribution of serum oxytocin levels in study groups.

Table 1. Demographic and clinical characteristics of the participants

Variables	Social anxiety disorder (n = 29)	Other anxiety disorders (n = 27)	Control group (n = 28)	Statistical analysis			Post-hoc analysis ^a
				χ^2	F	p value	
Sex (M/F)	11 (38)/18 (62)	13 (48)/14 (52)	13 (46)/15 (54)	0.689		0.709	
Age	14.74 ± 1.9	13.77 ± 1.5	15.04 ± 1.7		2.84	0.06	
CDI	19.8 ± 8.37	17.5 ± 8.22	11.6 ± 5.78		9.505	< 0.001	1 > 3, 2 > 3
SAS	68.03 ± 9.22	39.23 ± 12.86	27.21 ± 7.38		117.6	< 0.001	1 > 2 > 3
CTQ	61.62 ± 17.02	61.30 ± 15.29	56.85 ± 14.69		1.205	0.305	
CSAI	42.77 ± 9.5	45.03 ± 10.3	34.57 ± 10.59		9.674	< 0.001	1 > 3, 2 > 3
CTAI	41.22 ± 9.27	40.76 ± 10.15	32 ± 9.29		9.044	< 0.001	1 > 3, 2 > 3
BIS/BAS-BI	22.11 ± 2.42	22.69 ± 2.94	20.21 ± 3.37		5.402	0.006	1 > 3, 2 > 3

Values are presented as number (%) or mean \pm standard deviation.

CDI, Children's Depression Inventory; SAS, Social Anxiety Scale for Children; CTQ, Childhood Trauma Questionnaire; BIS/BAS-BI, Behavioral Inhibition System and Behavioral Activation System Questionnaire Behavioral Inhibition Subscale; CSAI, State Anxiety Inventory for Children; CTAI, Trait Anxiety Inventory for Children.

^a1: social anxiety disorder, 2: other anxiety disorders, 3: control group.

the OXT and AVP levels are given in Table 2.

As the SoPh and other anxiety groups were similar in terms of both OXT and AVP levels, we combined these groups to conduct further (correlation and hierarchical regression) analyses. Thus, we investigated the relationship between the psychological variables and the OXT and AVP levels in this new group, which comprised SoPh and

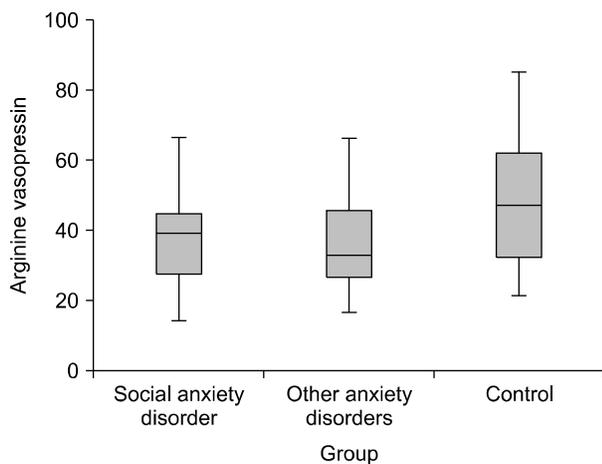


Fig. 2. Box plots representing the distribution of serum vasopressin levels in study groups.

other anxiety disorder groups ($n = 56$). According to the correlation analyses, no correlations were observed between the psychological variables and the OXT and AVP levels (Table 3). The psychological variables predicting the OXT levels were determined using a hierarchical regression analysis. As shown in Table 4, only the last step of the analysis (including CSAI and CTAI) was statistically significant and made an incremental contribution to the analysis ($R^2 = 0.27$, $p = 0.04$, R^2 change = 0.13, $p = 0.02$), indicating that only CSAI (negatively) and CTAI (positively) predicted OXT levels of the subjects with anxiety disorders. The same analysis was performed to determine the factors predicting the AVP levels of the same group. However, no predictive factors were found in the regression analysis ($p = 0.44$).

DISCUSSION

This study was the first to investigate the plasma OXT and AVP levels in adolescents with SoPh alone, those with other anxiety disorders (SAD, GAD, and PD), and healthy controls to elucidate the possible roles of these neuroendocrine hormones in the neurobiological background of anxiety disorders. The analyses demonstrated

Table 2. ANCOVA for oxytocin and vasopressin levels among the groups controlling for age and sex

Variable	Social anxiety disorder ($n = 29$)	Other anxiety disorders ($n = 27$)	Control group ($n = 28$)	Statistical analysis		Post-hoc test ^a
				F	p value	
Oxytocin (pg/ml)	211.4 ± 69.1	216.2 ± 75.9	166.2 ± 52.7	5.24	0.007	1 > 3, 2 > 3
Vasopressin (pg/ml)	38.1 ± 12.6	39.4 ± 19.6	50.6 ± 25.4	2.83	0.065	

Values are presented as mean ± standard deviation.

ANCOVA: Analysis of Covariance.

^a1: social anxiety disorder, 2: other anxiety disorders, 3: control group.

Table 3. Correlations of the oxytocin and vasopressin levels with psychological variables

Variables	1	2	3	4	5	6	7	8
1 Oxytocin	1							
2 Vasopressin	0.10	1						
3 CDI	0.04	-0.22	1					
4 SAS	0.01	0.12	0.24	1				
5 CTQ	0.04	-0.17	0.08	-0.07	1			
6 BI	0.17	0.15	0.17	0.02	-0.11	1		
7 CSAI	-0.25	-0.18	0.64*	-0.02	0.09	0.16	1	
8 CTAI	-0.01	-0.30*	0.67*	0.13	0.11	0.04	0.79*	1

CDI, Children's Depression Inventory; SAS, Social Anxiety Scale for Children; CTQ, Childhood Trauma Questionnaire; BI, behavioral inhibition; CSAI, State Anxiety Inventory for Children; CTAI, Trait Anxiety Inventory for Children.

* $p < 0.01$.

Table 4. Factors predicting oxytocin levels according to the hierarchical regression analysis

Variables	B	SE	t	<i>p</i> value	<i>p</i> change	R ² change	F change
(Constant)	343.767	76.658	4.484	0.000	0.153	0.068	1.947
Sex	-26.000	19.400	-1.340	0.186			
Age	-6.219	5.260	-1.182	0.242			
(Constant)	341.700	76.428	4.471	0.000	0.251	0.024	1.348
Sex	-36.593	21.381	-1.711	0.093			
Age	-6.850	5.271	-1.300	0.199			
CDI	1.502	1.294	1.161	0.251			
(Constant)	473.476	123.994	3.819	0.000	0.418	0.051	0.962
Sex	-33.902	21.468	-1.579	0.121			
Age	-7.074	5.339	-1.325	0.191			
CDI	1.759	1.354	1.298	0.200			
SAS	0.134	0.541	0.247	0.806			
CTQ	-0.098	0.617	-0.158	0.875			
BIS/BAS-BI	-6.181	3.700	-1.670	0.101			
(Constant)	452.560	117.236	3.860	0.000	0.023	0.127	4.085
Sex	-37.999	20.876	-1.820	0.075			
Age	-5.320	5.532	-0.962	0.341			
CDI	2.455	1.627	1.509	0.138			
SAS	-0.272	0.533	-0.510	0.612			
CTQ	-0.065	0.593	-0.110	0.913			
BIS/BAS-BI	-3.848	3.603	-1.068	0.291			
CTAI	3.827	1.716	2.231	0.030			
CSAI	-4.553	1.657	-2.748	0.008			

Variable: Oxytocin.

SE, standard error; CDI, Children's Depression Inventory; SAS, Social Anxiety Scale for Children; CTQ, Childhood Trauma Questionnaire; BIS/BAS-BI, Behavioral Inhibition System and Behavioral Activation System Questionnaire Behavioral Inhibition Subscale; CSAI, State Anxiety Inventory for Children; CTAI, Trait Anxiety Inventory for Children.

^aMales and females were coded as 1 and 2 respectively in the dataset of the study.

that the OXT levels were significantly higher in both the SoPh and the other anxiety disorders group than in the control group. Nevertheless, no significant difference was found in the OXT levels between the SoPh group and the other anxiety disorders group. Nor did the groups differ in terms of AVP levels. The hierarchical regression analyses revealed that the AVP levels were not predicted by any psychological variables when controlled for age, sex, and other psychological variables. Unlike AVP, the OXT levels were predicted, according to the hierarchical regression analysis, by the state and trait anxiety levels of the subjects with anxiety disorders. Interestingly, the state and trait anxiety predicted the OXT levels in opposite directions: whereas trait anxiety predicted OXT positively, state anxiety predicted it negatively. However, we found that the behavioral inhibition levels and the previous trauma levels did not predict the OXT or AVP levels.

Comparison studies conducted on clinical samples on the OXT levels of anxiety disorders are limited, and they reveal inconsistent findings. Hoge *et al.* [8] reported two

contrasting findings in different adult studies: one found that individuals with SoPh and the control group did not differ, whereas the other found that low levels of peripheral blood OXT were associated with SoPh [17]. Despite the discrepancies in the results of comparison studies, OXT is used for anxiolytic purposes, based on the findings of animal studies, thus indicating that OXT has anxiolytic effects by regulating the hypothalamus-pituitary axis system [15,54-56]. The OXT receptor system is activated by anxiogenic and stressful stimuli, as reflected by the stimulated release of peripheral and intracerebral OXT. For example, exposure to novelty, forced swimming, or social defeat increased OXT release into rats' blood [57]. On the other hand, the anxiogenic effects of OXT were reported in some human studies [58,59]. Some authors claimed that these inconsistent findings arose from context-dependent factors [60]. In contrast to the suggestion that OXT has an anxiolytic effect, we found that the subjects with anxiety disorders had higher OXT levels than the controls. This finding can be explained by the notion

that the OXT receptor system can be regulated by the stress response system. Specifically, because of the anxiety or stress that these subjects experienced, which could be an adaptation strategy, the OXT receptors could have downregulated and resulted in an increase in OXT levels. Supporting this hypothesis, the OXT receptor system has been shown to be epigenetically regulated according to the attachment style [61]. Moreover, the OXT receptor system is epigenetically downregulated in rhesus monkeys with early maternal deprivation [62].

However, the existing literature is based on adult studies and, to our knowledge, research on the relationship between OXT and anxiety disorder in adolescents is very limited. As mentioned in the introduction section, only one study reported a negative correlation between OXT and anxiety levels [18], which is partially compatible with our finding that OXT is negatively predicted by state anxiety. We suggest that researchers bear in mind the previous contradictory findings in adolescents and our finding that OXT has a variable relationship with state and trait anxiety.

The inconsistent findings in the literature on the relationship between OXT and anxiety have been attributed to the unstable and changeable nature of OXT. It is well known that any physical or mental stress changes OXT quickly. To minimize this effect, we completed the psychiatric evaluations one day prior to the phlebotomy procedure. However, all psychiatric evaluation and phlebotomy procedures were conducted in the psychiatry clinic of a hospital and it was the first experience of being in a psychiatry clinic for most of our subjects. This situation may, of itself, have caused stress and have slightly affected the results of the study.

OXT is known to be involved in several psychological concepts (i.e., attachment, trust, social reward, stress, depression, and anxiety) [10]. Although some relationships between OXT and anxiety disorders have been discovered, the findings in the literature are not consistent. Moreover, the differences between SoPh and other anxiety disorders are not known. We hypothesized a difference between SoPh and other anxiety disorders in terms of OXT levels, as SoPh is characterized by attentional biases focused on fear of social situations [63], which is not the focus of other anxiety disorders. On the basis of the literature indicating that OXT is known to enhance social cognition [54], which may be impaired among in-

dividuals with SoPh [64], we considered SoPh to differ in terms of OXT levels because the frightening situations are the social conditions, contrary to other anxiety disorders that do not include a fear of a social situation. Although the OXT levels of the SoPh group were higher than those of the controls, the SoPh group was similar to the other anxiety disorders group in terms of OXT levels. Moreover, the correlation and regression analyses revealed no relationship between the severity of SoPh symptoms and OXT levels. According to the findings of this study and in contrast to our second hypothesis, we assume that OXT is related to any fear in anxiety disorders, rather than fear of a social situation.

Studies focusing social relationships and trust in investigating the role of OXT on emotions have not reported any contradictory results on the OXT levels and the state and trait anxiety concepts, which indicate momentary and sustained anxiety, respectively. Our study is the first to indicate opposing ways to predict OXT levels for the state and trait anxiety levels. Limited studies investigated the relationships between both state and trait anxiety and OXT. For example, Lawson analyzed the relationships between trait and state anxiety levels and OXT levels in subjects with anorexia nervosa before and after eating and reported a positive relationship between OXT levels and trait anxiety and pre- and post-eating state anxiety [65].

However, the results of the regression analyses of the present study should be interpreted with caution, since highly correlated factors were put into the analyses as co-variables (i.e., depression, state and trait anxiety) which could have resulted in a suppression effect. Although the relationship between state and trait anxiety and depression is well known—and found in the correlation analyses of our study, as expected—we conducted regressions to see the univariate effects of these variables on OXT and AVP. We conducted a separate regression analysis including only age, gender, and state and trait anxiety levels to test the suppression effect of state and trait anxiety on OXT levels ($R^2 = 0.22$, $p = 0.013$) and found that OXT was still negatively predicted by state anxiety ($B = -4.2$, $p = 0.007$), and positively predicted by trait anxiety ($B = 4.6$, $p = 0.005$). This finding supports the notion that state and trait anxiety act as suppressors for each other in predicting OXT levels. On the other hand, since the R^2 of the regression analysis is not particularly high (0.27), we think that the suppression effect is not substantial.

Our findings did not reveal any relationship between OXT levels and the childhood trauma and behavioral inhibition levels of the subjects with anxiety disorders. Studies have reported inconsistent results on the relationship between OXT levels and childhood trauma [34,60]. In a recent study, childhood trauma was not related to plasma OXT levels but was negatively correlated with OXT receptor protein expressions in peripheral blood mononuclear cells [66]. This study indicates that the OXT system, rather than plasma levels, can be changed in the receptor regulation process. Furthermore, because the childhood trauma levels of our sample were not sufficiently high in our study, their effect on the OXT level may have not been so explicit. This issue should be elucidated in future studies.

The AVP levels did not show any difference among the groups in the comparison analysis and were not related to any psychological variable, according to the regression analysis. However, although the difference is not statistically significant in the dual comparisons, it can be seen that the controls had a higher level of AVP than the anxiety disorder groups (50 vs. 38 and 39 pg/ml). The non-significant result may be related to the small sample size, which could have hampered the statistical analyses.

Although many animal studies have indicated that AVP has an anxiogenic effect [28] contrary to our findings, human studies on this topic are limited. The explanation for these findings may be similar to that for the findings obtained from the comparison analysis of the OXT levels in the present study. Specifically, an upregulation in the AVP receptors of the subjects with anxiety could have resulted in lower levels of AVP. Supporting the hypothesis, the AVP gene expression could be changed by stress in rats [67]. Further studies with a larger sample could yield more informative data on this topic.

The present study has several limitations. First, our study sample was small, and we evaluated the psychological variables using self-reporting scales. Secondly, OXT levels may present high variability within the same subject. For this reason, this condition should be taken into consideration when evaluating the results. However, this is a common limitation due to the measurement method in studies on OXT. Also, since the BIS/BAS and SAS have been validated in adults and children respectively, and no validity studies conducted in adolescents, we had to rely on these scales. On the other hand,

the menstrual histories and estradiol levels which affects OXT levels of the female participants were not evaluated in our study. Finally, participants completed the scales one day before the phlebotomy procedure, which may have given rise to contradictory relationships between CSAI and CTAI. However, since our study design did not contain an intervention to measure the effect of an anxiogenic condition on OXT or AVP, but instead aimed to test the relationship between these variables in a non-stressful setting, we deliberately scheduled the exercise of completing the scales before the phlebotomy to avoid the traumatic (and possibly anxiogenic) effect of the procedure.

In conclusion, we found that the OXT levels of adolescents with SoPh were not different from those of adolescents with other anxiety disorders. However, the OXT levels of all anxiety disorders were higher than those of the healthy controls. The OXT levels were predicted by the state and trait anxiety levels in opposite directions. Moreover, we evaluated the AVP levels of the subjects but could not find any significant difference among the groups nor a significant relationship in the regression analysis of the anxiety group. Further studies with a larger sample can improve our knowledge of the relationship among anxiety disorders, OXT, and AVP.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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