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Evaluation of serum oxytocin levels in patients with depression, generalized anxiety disorder, panic disorder, and social anxiety disorder: A case-control study

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Abstract

Background/Aim: Oxytocin, an endogenous anti-stress, antidepressant, and anxiolytic hormone, is reported to increase in stressful situations to reduce the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and amygdala for coping with stress and improving social functioning. This study aimed to compare serum oxytocin levels of patients with depression, generalized anxiety disorder (GAD), panic disorder (PD), and social anxiety disorder (SAD) with that of healthy controls.
Methods: The study included 50 patients (25 male, 25 female) with major depression, 26 patients (9 male, 17 female) with GAD, 31 patients (14 male, 17 female) with SAD, and 40 patients (17 male, 23 female) with PD and 30 healthy volunteers. Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Perceived Stress Scale (PSS), and Anxiety Sensitivity Index-3 (ASI-3) were applied to all groups. In addition, Generalized Anxiety Disorder-7 (GAD-7), Panic Disorder Severity Scale (PDSS), and Liebowitz Social Phobia Scale were applied to patients with GAD, panic disorder, and social anxiety disorder, respectively. Serum oxytocin levels were measured by ELISA.
Results: Serum oxytocin levels of patients with depression were significantly lower, and those of patients with generalized anxiety disorder, social anxiety disorder, and panic disorder with agoraphobia were significantly higher compared to the control group (2.46 (2.8) vs. 2.86 (0.72), P=0.004, 11.49 (11.35) vs. 2.86 (0.72), P=0.001, 10.67 (11.32) vs. 2.86 (0.72), P=0.001, and 6.97 (5.01) vs. 2.86 (0.72), P=0.001, respectively).
Conclusion: Lower oxytocin levels in depressed patients and higher oxytocin levels in patients with GAD, and PD with agoraphobia suggest that oxytocin has a role in psychiatric disorders. Further studies are needed to better understand the relationship between depression, anxiety disorders, oxytocin, and the underlying mechanisms.

Keywords: Oxytocin, Depression, Generalized anxiety, Social anxiety, Panic disorder

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Introduction

Oxytocin is a peptide hormone that is known to have a role in birth, breastfeeding, maternal behavior, attachment, and social behaviors [1, 2]. Several studies are conducted on animals to investigate the roles of oxytocin in birth, breastfeeding, reduction of aggression, social behaviors, attachment between the mother and the baby, and partners [1]. Human studies report that oxytocin enhances the sense of attachment, facilitates human interaction, and may have a therapeutic potential in psychiatric patients with social function disorders. Oxytocin is considered a prosocial neuropeptide [2, 3]. It reduces anxiety due to social stress by suppressing cortisol release and amygdala activity [4, 5]. In addition to regulating the reward of the attachment, it makes coping with stress easier. Mother-baby attachment is crucial among mammals and oxytocin enables the emotional functions of this attachment to be regulated during adulthood. Oxytocin suppresses the hypothalamic-pituitary-adrenal (HPA) axis induced by stress [6]. In animal studies, oxytocin was released into the bloodstream and cerebrospinal fluid after stress exposure [7].

Oxytocin has been investigated in various psychiatric disorders due to its potential impacts on psychopathology. The oxytocin system is also affected by early life experiences [8]. A study found out that exposure to emotional abuse was associated with low oxytocin in the cerebrospinal fluid in women [9]. Oxytocin is believed to influence the regulation of stress response, mood, and anxiety disorders by reducing the adrenocorticotropic hormone (ACTH) and basal cortisol levels [10, 11]. It has been reported that there is more variability in the pulsatile release of oxytocin in depressed women compared to non-depressed women [12]. In a study conducted with patients with unipolar and bipolar depression, the oxytocin levels were lower than controls both before and after treatment with antidepressants and ECT [13]. Turan et al. [14] suggested that oxytocin levels were higher both before and after treatment in bipolar disorder patients compared to healthy controls; therefore, oxytocin may be a trait marker for bipolar disorder. In another study, plasma oxytocin levels were lower in schizophrenia patients compared to healthy controls, and oxytocin levels in schizophrenia patients were associated with impairment in metacognitive functions [15].

Taking into consideration the role of the oxytocin in coping with stress, its anxiolytic effects, that it regulates the amygdala response to the social stimuli, reduces anxiety and HPA axis response, we thought that serum oxytocin levels may differ in patients with depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder (PD) and panic disorder with agoraphobia [16]. This study aimed to comparatively investigate the serum oxytocin levels in patients with depression, GAD, SAD, PD, panic disorder with agoraphobia, and healthy controls.

Materials and methods

Participants

A total of 177 participants aged between 18 and 65 years were included in this study, as follows: Fifty patients (25 male, 25 female) with major depression, 26 patients (9 male, 17 female) with GAD, 31 patients (14 male, 17 female) with SAD and 40 patients (17 male, 23 female) with PD according to DSM 5 criteria and a healthy control group of 30 (13 male, 17 female) individuals who visited the Psychiatry outpatient clinic of Abant İzzet Baysal University Faculty of Medicine. The patients were not using any psychiatric medications.

Patients who had undergone electroconvulsive therapy within the last six months, patients who had used psychotropic medications within the last month, patients with dementia, schizophrenia, mental retardation, autism, and other comorbid psychiatric disorders such as substance abuse or addiction other than smoking, a history of head trauma, neurological diseases, a known metabolic or endocrine disorders, menstrual irregularities, confirmed pregnancy or patients on contraceptive or hormone therapy were excluded from the study. A total of 30 (13 male, 17 female) healthy individuals who voluntarily participated in the study were also included. The control group had the same age range as the patient groups and no psychiatric, neurologic, endocrine, and metabolic disorders. Exclusion criteria for the control group were the same as the patient group.

This study was supported by Abant İzzet Baysal University Scientific Research Projects Committee (Project No: 2015.08.35.828), approved by the Abant İzzet Baysal University School of Medicine Ethics Board with the Decision No. 2013/22-105 on 02.06.2014, and conducted per the Helsinki Declaration.

Measurements

All patients were diagnosed according to DSM-5 [17]. After the participant filled out the sociodemographic data form, Hamilton Depression Rating Scale (HAM-D) was applied to evaluate the severity of depression. Hamilton Anxiety Rating Scale was used to evaluate the severity of anxiety. Generalized Anxiety Disorder 7-item (GAD-7), Panic Disorder Severity Scale (PDSS), Liebowitz Social Phobia Scale were applied to patients with GAD, PD, and SAD, respectively. The Anxiety Sensitivity Index-3 (ASI-3) and Perceived Stress Scale (PSS-14) were both applied to all groups. To measure the oxytocin serum levels, 10 milliliters of blood samples were collected from the patients and the control group between 08.00 AM and 09.00 AM into the standard vacuumed tube and centrifuged for 15 minutes at 1600 rpm at the biochemistry lab within the first 30 minutes after collection. The serum samples were stored at -70°C until the biochemical analysis.

Hamilton Depression Rating Scale (HDRS): It is an interviewer-filled scale developed by Hamilton to evaluate the severity of depression in patients diagnosed with depression. [18]. There are subgroups such as depressive temperament, suicide, loss of work and activities, retardation, agitation, gastrointestinal symptoms, general somatic symptoms, hypochondriac symptoms, insight, appetite and weight loss, insomnia, and anxiety. Its Turkish validity and reliability study was conducted by Akdemir et al. The internal consistency coefficient of the scale was 0.75 [19].

Hamilton Anxiety Rating Scale (HARS): This scale, developed by Hamilton, was prepared to determine the level of anxiety and symptom distribution in individuals and measure the change in severity. It consists of 14 items that question both mental and physical symptoms [20]. The presence and severity of the items on the scale are evaluated by the interviewer. Its

Turkish validity and reliability study was conducted by Yazıcı et al. [21].

Generalized Anxiety Disorder 7-item test (GAD-7): Developed in 2006 by Spitzer et al. to detect symptoms of common anxiety disorder in primary care, the scale consists of 7 items that individuals will answer based on their self-reports [22]. It is a four-point Likert-type scale, graded between 0 (none) and 3 (almost every day). The higher the scores, the higher the level of anxiety disorder symptoms. The Turkish adaptation and validity-reliability study of the scale were performed by Konkan et al. and the internal consistency coefficient was 0.85 [23].

Panic Disorder Severity Scale (PDSS): As a seven-item, semi-structured scale scored by the physician, PDSS provides a grading of panic frequency, anticipation anxiety, avoidance of physical sensations, and impairment in work and social functionality [24]. Each of these symptoms is graded by the interviewer between 0 and 4. The total score ranges between 0-28. Its Turkish validity, reliability, and standardization study were performed by Monkul et al. The internal consistency coefficient of the scale was 0.92 [25].

Liebowitz Social Phobia Scale (LSPS): The validity and reliability study of the scale, developed by Liebowitz (1987), was conducted by Heimberg et al. [26]. There are a total of 24 items on the scale. LSAS was developed to evaluate situations in which individuals with social phobia exhibit fear and/or avoidance behavior. The Turkish validity and reliability studies of the Liebowitz Social Anxiety Scale were conducted by Soykan, Özgüven, and Gençöz in 2003 [27].

Anxiety Sensitivity Index-3 (ASI-3): The ASI measures anxiety sensitivity, or fear of anxiety-related emotions. A new version of the ASI, the ASI-3, consists of 18 items [28]. It evaluates the three most cantilevered AS domains: Social, cognitive, and physical. The score that could be obtained from the scale ranges between 0 and 72. Mantar et al. demonstrated the validity and reliability of the Turkish version of the ASI-3. The internal consistency coefficient of the scale was 0.93 [29].

Perceived Stress Scale (PSS-14): The PSS-14 is designed to assess an individual's perceived stress. The total score from the scale ranges from 0 to 56 [30]. Its Turkish validity and reliability study was conducted by Eskin et al. [31] and the internal consistency coefficient was 0.84.

Biochemical analysis

Serum samples were analyzed via ELISA (Sunrise Basic Tecan, Tecan Austria GmbH) device at Erciyes University School of Medicine Central Biochemistry Laboratory. Serum oxytocin level was measured via enzyme-linked immune-sorbent assay (ELISA) (Phoenix Human Oxytocin ELISA Kit) kit (Measurement range: 0- 100 ng/ml, Sensitivity: 0.09 ng/ml). The optic density values were transformed into serum concentration values via an absorbance/concentration curve that draws a reverse sigmoidal shape shown on the QC data plate, as per the prospectus of the oxytocin kit.

Statistical analysis

The normality of the distribution of continuous variables was evaluated by the Shapiro-Wilk test. The Mann-Whitney U test was used to compare non-normally distributed numerical data between two groups. Chi-square test and Bonferroni correction were used for categorical variables. Mean (SD), median and interquartile ranges were given as descriptive statistics. Statistical analysis was performed with SPSS for Windows version 24.0 and a *P*-value <0.05 was considered statistically significant.

Results

No significant difference was found between the depression, panic disorder, panic disorder with agoraphobia groups in terms of age. The generalized anxiety group was older, and the social phobia group was younger than the control group. The groups significantly differed in terms of marital status and education level ($P<0.001$, for all), and were similar in terms of gender, daily smoking, and family history of psychiatric illness ($P=0.910$, $P=0.503$, $P=0.900$, respectively) (Table 1).

Serum oxytocin levels of patients with depression were significantly lower, and those of patients with generalized anxiety disorder, social anxiety disorder, and panic disorder with agoraphobia were significantly higher compared to the control group (2.46 (2.8) vs. 2.86 (0.72), $P=0.004$, 11.49 (11.35) vs. 2.86 (0.72), $P=0.001$, 10.67 (11.32) vs. 2.86 (0.72), $P=0.001$, and 6.97 (5.01) vs. 2.86 (0.72), $P=0.001$, respectively). Patients with panic disorders without agoraphobia had insignificantly higher serum oxytocin levels compared to the control group ($P=0.147$).

Table 1: Comparison of demographic data and family history of psychiatric diseases of all study participants

	Depression (n=50)	Panic disorder (n=20)	Gen. Anxiety dis. (n=25)	Social phobia (n=20)	Panic dis. + Agoraphobia (n=20)	Control (n=30)	*P*-value
Age (Mean (SD))	28.4 (5.88)	27.9(6.29)	32.08(6.74)	24.55(4.19)	28.55 (6.03)	28.4(5.15)	0.001[1]
Gender							0.910
Female	25(50%)	12 (60%)	16 (64%)	17(54.8%)	11 (55%)	17 (56.7%)	
Male	25(50%)	8 (40%)	9 (36 %)	14 (45.2%)	9 (45%)	13(43.3%)	
Marital status							0.001*
Married	23 (46%)	7 (35%)	17 (68%)	4 (12.9%)	8 (40%)	5 (16.7%)	
Widow	0 (0%)	0 (0%)	0 (0 %)	1 (3.2%)	0 (0%)	5 (16.7%)	
Divorced	4 (8%)	3 (15%)	0 (0%)	2 (6.5%)	1 (5%)	0 (0%)	
Single	23 (46)	10 (50%)	8 (32%)	24(77.4%)	11 (55%)	20(66.7%)	
Education status							0.001*
Primary school	2 (4%)	0 (0%)	0 (0%)	1 (3.2%)	4 (20%)	0 (0%)	
High school	25 (50%)	12 (60%)	12 (48%)	4 (12.9%)	10 (50%)	6 (20%)	
Higher education	23 (46%)	8 (40%)	13 (52%)	26 (83.9%)	6 (30%)	24 (80%)	
Smoking							0.503
No	27 (54%)	14 (70%)	19 (76%)	24(77.4%)	14 (70%)	20(66.7%)	
1-10 cigarettes	17 (34 %)	5 (25%)	5 (20%)	5 (16.1%)	5 (25%)	4 (13.3%)	
10-20 cigarettes	5 (10%)	1 (5%)	1 (4%)	2 (6.5%)	1 (5%)	6 (20%)	
20> cigarettes	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Family history of psychiatric disease							0.900
Yes	10 (20%)	2 (10%)	3 (12%)	5 (16.1%)	3 (15%)	4 (13.3%)	
No	40 (80%)	18 (90%)	22 (88%)	26(83.9%)	17 (85%)	26(86.7%)	

* Significant at $P<0.05$, Chi-square test, [1] Significant at $P<0.05$, Kruskal-Wallis test

The mean scores of psychological scales applied to patients with depression and the control group are presented in Table 2. The mean panic disorder severity scale scores of panic disorder patients without and with agoraphobia were 11.4 (3.7) and 14.75 (4.72), respectively (Tables 3 and 4). Panic disorder severity and anxiety sensitivity were significantly higher in panic disorder patients with agoraphobia than in those without (P=0.018 and P=0.016, respectively) (Table 5).

Table 2: Comparison of oxytocin levels and scale scores between depressed patients and healthy controls

	Depression (n=50)	Control (n=30)	*P*-value
Oxytocin	2.46 (2.8)	2.86 (0.72)	0.004*
Hamilton anxiety scale	13.6 (6.33)	1.73 (2.21)	0.001*
Hamilton depression scale	24.82 (5.45)	0.73 (1.53)	0.001*
Anxiety sensitivity index	23.44 (14.97)	13.8 (6.26)	0.010*
Perceived stress scale	24.32 (12.25)	14.5 (8.22)	0.001*

* Significant at P<0.05, Mann-Whitney U test

Table 3: Comparison of oxytocin levels and scale scores between panic disorder patients and healthy controls

	Panic disorder (n=20)	Control (n=30)	*P*-value
Oxytocin	2.98 (2.21)	2.86 (0.72)	0.147
Hamilton anxiety scale	25.15 (5.91)	1.73 (2.21)	0.001*
Hamilton depression scale	7.7 (4.54)	0.73 (1.53)	0.001*
Anxiety sensitivity index	29.65 (6.52)	13.8 (6.26)	0.001*
Perceived stress scale	34.35 (5.16)	14.5 (8.22)	0.001*
Panic disorder severity scale	11.4 (3.7)		

* Significant at P<0.05, Mann-Whitney U test

Table 4: Comparison of oxytocin levels and scale scores between panic disorder patients with agoraphobia and healthy controls

	Panic disorder with agoraphobia (n=20)	Control (n=30)	*P*-value
Oxytocin	6.97 (5.01)	2.86 (0.72)	0.001*
Hamilton anxiety scale	28.15 (6.01)	1.73 (2.21)	0.001*
Hamilton depression scale	10.75 (5.13)	0.73 (1.53)	0.001*
Anxiety sensitivity index	35.55 (7.85)	13.8 (6.26)	0.001*
Perceived stress scale	37.6 (6.15)	14.5 (8.22)	0.001*
Panic disorder severity scale	14.75 (4.72)		

* Significant at P<0.05, Mann-Whitney U test

Table 5: Comparison of oxytocin levels and scale scores between panic disorder patients with and without agoraphobia

	Panic disorder with agoraphobia (n=20)	Panic disorder without agoraphobia (n=20)	*P*-value
Oxytocin	6.97 (5.01)	2.98 (2.21)	0.01*
Hamilton anxiety scale	28.15 (6.01)	25.15 (5.91)	0.09
Hamilton depression scale	10.75 (5.13)	7.7 (4.54)	0.05
Anxiety sensitivity index	35.55 (7.85)	29.65 (6.52)	0.016*
Perceived stress scale	37.6 (6.15)	34.35 (5.16)	0.06
Panic disorder severity scale	14.75 (4.72)	11.4 (3.7)	0.018*

* Significant at P<0.05, Mann-Whitney U test

The mean Generalized Anxiety Disorder-7 scale score of patients with GAD was 13.08 (2.29), and the mean total Liebowitz social anxiety scale score of patients with SAD was 102.81 (13.81). The comparison of the scores of these patient groups with the control group is presented in Tables 6 and 7.

Among depressed patients, the serum oxytocin levels, and HAM-A, ADI-3 and PSS scores were significantly correlated (r=0.647, P<0.001; r=0.734, P=0.001; r=0.760, P=0.001, respectively). There was no significant correlation between oxytocin levels and HAM-D scores (P>0.05). In GAD patients, serum oxytocin levels and HAM-D scores were significantly negatively correlated (r=-0.427, P=0.033), while there was no correlation with GAD-7, HAM-A, ADI-3, and PSS scores. In those with panic disorders with and without agoraphobia, serum oxytocin levels and PSS, HAM-D, HAM-A, ADI-3, and PSS scores were not correlated (P>0.05 for all). There was no significant correlation between oxytocin levels and LSPS social anxiety, LSPS avoidance, and LSPS total scores, HAM-D, HAM-A, ADI-3, and PSS scores in patients with social phobia (P>0.05) (Tables 8 and 9).

Table 6: Comparison of oxytocin levels and scale scores between generalized anxiety disorder patients and healthy controls

	Generalized Anxiety Disorder (n=25)	Control (n=30)	*P*-value
Oxytocin	11.49 (11.35)	2.86 (0.72)	0.001*
Hamilton anxiety scale	25.64 (6.62)	1.73 (2.21)	0.001*
Hamilton depression scale	12.16 (3.1)	0.73 (1.53)	0.001*
Generalized anxiety disorder scale	13.08 (2.29)	1.87 (2.01)	0.001*
Anxiety sensitivity index	42.96 (8.76)	13.8 (6.26)	0.001*
Perceived stress scale	35.92 (6.69)	14.5 (8.22)	0.001*

Table 7: Comparison of oxytocin levels and scale scores between patients with social phobia and healthy controls

	Social Phobia (n=20)	Control (n=30)	*P*-value
Oxytocin	10.67 (11.32)	2.86 (0.72)	0.001*
Hamilton anxiety scale	15.84 (4.65)	1.73 (2.21)	0.001*
Hamilton depression scale	7.42 (3.39)	0.73 (1.53)	0.001*
Liebowitz social phobia- anxiety	52.39 (6.81)	34.83 (9.54)	0.001*
Liebowitz social phobia-avoidance	50.42 (7.14)	34.27 (8.35)	0.001*
Liebowitz social phobia-Total	102.81 (13.81)	69.1 (17.55)	0.001*
Anxiety sensitivity index	28.84 (6.7)	13.8 (6.26)	0.001*
Perceived stress scale	35.58 (8.94)	14.5 (8.22)	0.001*

* Significant at P<0.05, Mann-Whitney U test

Table 8: Correlations between oxytocin levels and HAM-A, HAM-D, PSS, ADI-3, PDSS, LSPS, GAD-7 scores in patient groups

		Panic disorder Oxytocin	GAD Oxytocin	Depression Oxytocin	Panic disorder with agoraphobia Oxytocin	Social phobia Oxytocin
HAM-A	r	0.172	0.183	0.647**	0.024	0.252
	P	0.467	0.381	0.000	0.920	0.171
	n	20	25	50	20	31
HAM-D	r	0.285	-0.427*	0.093	0.164	0.064
	P	0.224	0.033	0.520	0.490	0.731
	n	20	25	50	20	31
PDSS	r	-0.362			-0.234	
	P	0.117			0.321	
	n	20			20	
GAD-7	r		-0.069			
	P		0.744			
	n		25			
ADI-3	r	-0.044	-0.019	0.734**	0.253	0.189
	P	0.855	0.930	0.001	0.282	0.307
	n	20	25	50	20	31
PSS	r	0.143	0.264	0.760**	-0.174	0.287
	P	0.549	0.203	0.001	0.463	0.117
	n	20	25	50	20	31

r: Spearman Rank Correlation Coefficient, * Significant at P<0.05, ** Significant at P<0.01

Table 9: Correlations between oxytocin levels and LSPS scores in patients with social phobia

		Social phobia Oxytocin
LSPS-anxiety	r	0.189
	P	0.309
	n	31
LSPS-avoidance	r	0.213
	P	0.250
	n	31
LSPS-total	r	0.197
	P	0.289
	n	31

Discussion

In this study, we first aimed to compare serum oxytocin levels in patients with depression and healthy controls and investigate the relationship between oxytocin levels and depression severity, anxiety severity, perceived stress, and anxiety sensitivity. Second, we aimed to compare serum oxytocin levels in patients with generalized anxiety disorder, social anxiety disorder, panic disorder, and panic disorder with agoraphobia and healthy controls. We found decreased serum oxytocin levels among patients with depression, and increased oxytocin levels in panic disorder patients with agoraphobia, SAD, and GAD. In patients with PD with agoraphobia, oxytocin levels were significantly higher than in PD patients without agoraphobia. Oxytocin regulates stress response by regulating the HPA axis, which plays a key role in depression and anxiety disorders [16].

Oxytocin is secreted via psychosocial stimuli and stimulates social attachment and social recognition [32]. It also suppresses HPA activity induced by stress and reduces anxiety. The nerve fibers containing oxytocin reaching out to the amygdala, hippocampus, and lateral septum, which are centers related to the emotional regulation and stress adaptation, from parvicellular cells reveals the importance of oxytocin in depression pathophysiology [5]. In a study by Frasch et al. [33], in which they compared twelve patients with major depression and twelve control group individuals in terms of nocturnal oxytocin level, nocturnal oxytocin level was significantly lower in patients with major depression.

Lower plasma oxytocin levels were detected in 14 fibromyalgia patients with comorbid depression compared to 25 female fibromyalgia patients without depression and 30 healthy controls; oxytocin levels were negatively correlated with daily depression, pain, and stress scores [34]. In another study, serum oxytocin levels were lower in 40 patients hospitalized due to unipolar and bipolar depression compared to the control group. Antidepressant treatment did not alter oxytocin levels [35]. Likewise, a negative correlation was reported between oxytocin levels and HAM-D scores in patients with depression [36]. Mean saliva oxytocin level was lower in women with chronic depression [37]. Contradictory results are available in the literature. A study conducted by Van Londen et. al. [38] on 52 patients with major depression and 37 healthy controls found no difference between plasma oxytocin levels. Parker et al. [33] stated that nocturnal oxytocin peak was evident in patients with depression following plasma oxytocin measurement from 6 pm to 9 am, and their oxytocin levels were higher than those of the control group. The differences in the results might be associated with the limited sample size, differences in patient selection, heterogeneous patient groups (unipolar depression, bipolar depression, fibromyalgia, etc.), unmatched patients with regards to age, gender, BMI and menopause periods, the inclusion of patients taking psychotropic medications, disregard of the attachment type and childhood trauma, the differences in blood sample collection time, conduction of a cross-sectional evaluation with a single measurement and anxiety symptoms accompanying depression.

In animal depression models, oxytocin shows anxiolytic and stress-reducing effects similar to antidepressants [39]. Reduction in oxytocin might contribute to the HPA axis irregularity because oxytocin suppresses HPA axis activity induced by stress [4]. Serotonergic and noradrenergic pathways have known roles in the development of depression. Oxytocin fibers cause serotonin secretion by stimulating the raphe nuclei directly. Reduction in oxytocin levels might affect serotonin secretion and lead to depression [36]. Norepinephrine, which has a prominent role in depression pathophysiology, is one of the regulators of oxytocin secretion. Norepinephrine fibers facilitate oxytocin secretion from the hypothalamus and hippocampal oxytocin enhances mRNA expression and plasma oxytocin levels [40]. When oxytocin receptors are blocked, the amount of norepinephrine secreted as a response to stress is reduced. There is a close interaction between oxytocin and the dopamine system, which modulates mother-baby attachment, attachment between partners, social cognition, sexual behavior, and reward systems. For example, oxytocin receptors are intense in the mesocorticolimbic pathways which contain PFK, and in the nucleus accumbens. Dopamine also affects the oxytocin receptor expression in the amygdala [41]. Oxytocin activates the MAP kinase pathway and hippocampal neural plasticity by enhancing CREB phosphorylation, induces BDNF expression, and weakens hippocampal shrinkage induced by glucocorticoids or stress. It is thought that activation of this pathway is how oxytocin shows its antidepressant effect [42]. Oxytocin also weakens proinflammatory cytokine response by diminishing the HPA axis response to stress in depression and limits the depressive symptoms [43].

Oxytocin has been widely investigated in anxiety disorders, as well [44, 45]. In our study, serum oxytocin levels in patients with GAD, SAD, and panic disorder with agoraphobia were significantly higher than the control subjects. Interestingly, oxytocin levels in patients with panic disorder with agoraphobia were significantly higher than the panic disorder patients without agoraphobia. A study conducted with 24 patients with generalized SAD found no difference in oxytocin levels when compared with healthy controls and reported that high social anxiety scores were associated with high oxytocin levels [44]. Yet another study stated that oxytocin levels which were similar to the control group initially, were lower when compared with healthy controls after the completion of the trust game task with the partner [45]. Oxytocin reduces anxiety and stress by activating GABAergic interneurons in the amygdala. In a study in which brain activities of the SAD patients were examined via fMRI by showing emotional faces to them, amygdala hyperactivity, found in SAD patients, normalized following a single dose of intranasal oxytocin. However, no changes occurred in the subjective anxiety symptoms reported by the patients [46]. Stressful stimuli increase oxytocin levels directly by stimulating the oxytocin synergic fibers in the amygdala.

There may be several reasons why oxytocin levels are high in patients with anxiety disorders. Oxytocin is an endogenous anti-stress neuropeptide and has a role in stress response [47]. Increased stress exposure and anxiety levels in patients with anxiety disorders may have contributed to the high oxytocin levels. Also, HPA activity induced by stress stimulates oxytocin release and increases oxytocin levels [7]. Similarly, in our study, perceived stress level and anxiety sensitivity were significantly higher in patients with GAD, SAD, PD, and panic disorder with agoraphobia than in healthy controls. Anticipation anxiety, avoidance behaviors, and chronic stress arising out of avoidance might have triggered the oxytocin secretion in patients with anxiety disorders. There is a reciprocal interaction between oxytocin and CRH. CRH stimulates ACTH and oxytocin secretion. It was reported that oxytocin secretion is reduced in anxiety-related behaviors in rats that received CRH-1 receptor antagonists, and CRH receptor stimulation was required for oxytocin secretion [48]. Oxytocin suppresses the HPA axis, reduces saliva cortisol levels, and suppresses amygdala activity. In lactating rats with high oxytocin levels, stress response declined considerably [49]. In the mice with deleted oxytocin genes, corticosterone response to psychogenic stressors increased remarkably [50]. While oxytocin secretion, which increases following acute stress in rats, is normalized after 24 hours, in

chronic stress exposure, oxytocin level cannot be normalized [51]. Exposure to chronic stress of patients with GAD, SAD, and patients with agoraphobia might account for the non-normalization of the oxytocin levels increased with stress. In parallel with the literature, in our study when all groups were analyzed together, oxytocin level was positively correlated with perceived stress.

Another cause of high oxytocin levels in anxiety disorder patients might be the change in oxytocin receptor function following chronic stress exposure. Deletion of the oxytocin gene increases anxiety in rodents [52]. Chronic stressors reduce the mRNA expression of oxytocin receptors; accordingly, oxytocin levels are elevated to compensate [53]. Perhaps increased oxytocin levels in anxiety disorders may be a part of the compensatory physiological mechanism to suppress the hyperactivity of the HPA axis.

Limitations

Our study had some limitations. First, it was a cross-sectional study, so a causality relationship could not be established. Second, the sample size was small. Third, anxiety sensitivity and perceived stress levels were evaluated with self-report scales. Therefore, the results may have been affected by participants' bias. Also, the fact that all patients and controls are from the hospital population may have caused selection bias. Fourth, serum oxytocin levels may not reflect central oxytocin levels. Fifth, childhood trauma, attachment styles, genetic variations in oxytocin receptors that may affect oxytocin levels were not evaluated [54]. Sixth, oxytocin secretion changed situationally and during the daytime, but we measured serum oxytocin levels once and cortisol levels that affect oxytocin were not measured.

Conclusion

Oxytocin is an important marker for depression and anxiety disorders. Prospective studies with large samples, including childhood traumas and attachment styles, are warranted to determine the role of oxytocin in the pathophysiology of depression and anxiety disorders.

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