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May oxytocin be a trait marker for bipolar disorder?

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Summary There is evidence to suggest that oxytocin is effective in stabilizing mood in humans. Lower plasma oxytocin levels have been reported in patients with major depression. The objective of this study was to investigate serum oxytocin levels during manic and depressive episodes and in the remission period in patients with bipolar disorder. Twenty-two patients in manic episode, 21 in depressive episode, and 24 in remission at the initial phase, ranging from 18 to 65 years of age, who were diagnosed with BD Type I and 24 healthy individuals were included in this study. Blood samples were collected from subjects in the morning at the beginning of the study. A second blood sampling was obtained from manic and depressive patients after response to treatment. MANCOVA was performed to compare the oxytocin values of the groups. The serum oxytocin levels of patients in manic episode were statistically significantly higher than those of the depressive episode and remission groups and of the healthy subjects. The serum oxytocin levels of patients in the depressive episode group and in the remission group were statistically significantly higher than those of the control group. The serum oxytocin levels of the manic episode and depressive episode patients after response to treatment were statistically significantly higher than those of the control group, and there was no statistically significant difference between the patient groups in serum oxytocin levels. The higher oxytocin levels observed in patient groups, compared to the controls, before and after response to treatment suggest that oxytocin may be a trait marker in BD.

1. Introduction

Oxytocin is a nonapeptide hormone well-known for its role in lactation and parturition (Lee et al., 2009). Oxytocin is synthesized mainly in the magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei and is transported on its carrier protein neurophysin

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to the posterior pituitary gland where it is stored to be later released into the circulation. Currently, only one type of oxytocin receptor has been identified (Caldwell et al., 2008).

Oxytocin modulates neuroendocrine response to stress in social interactions and decreases anxiety (Carter et al., 2001; Parker et al., 2005) via its receptors in the limbic system, including the amygdala (Huber et al., 2005). In animal studies, oxytocin has been found to be released within distinct brain regions and into the peripheral circulation in response to physical and psychological stress, and fearful situations (Neumann and Landgraf, 2012). Intracerebral oxytocin inhibits stress-induced hypothalamic—pituitary—adrenal (HPA) axis responsiveness (Neumann et al., 2000a) and modulates the autonomic fear response with its activity in the amygdala (Huber et al., 2005). In rodents, the suckling stimulus by the newborn was found to increase oxytocin release and activate the HPA axis (Heinrichs et al., 2009). In human, however, it was demonstrated that oxytocin can inhibit the basal and stress induced plasma levels of adrenocorticotrophic hormone (ACTH) and cortisol (Heinrichs et al., 2003; Neumann, 2002).

Oxytocin has been investigated in a number of psychiatric disorders due to its physiological effects on human behavior. There is evidence suggesting that oxytocin is effective in stabilizing mood in humans. It is suggested that changes in oxytocin levels are associated with anxiety levels and depression, but the findings of studies related to oxytocin levels in depression are not consistent. It is reported that an association exists between increased oxytocin levels and elevated mood particularly in postpartum women (Lee et al., 2009) and that there is more variability in pulsatile oxytocin release in depressed women compared to nondepressed controls (Cyranowski et al., 2008). Lower plasma oxytocin levels have been reported in patients with major depression than in healthy controls (Pitchot et al., 2008). Oxytocin levels were also found to be negatively correlated with self-reported psychological distress, including depressive symptoms (Gordon et al., 2008). A study in patients with bipolar or unipolar depression reported no significant difference between plasma oxytocin levels before and after antidepressant treatment (Ozsoy et al., 2009). In some animal studies, selective serotonin reuptake inhibitors (SSRIs) increased plasma oxytocin levels (Uvnas-Moberg et al., 1999). Also, in schizophrenic patients, higher serum oxytocin levels were found to be related to prosocial behaviors and less severe positive symptoms (Rubin et al., 2010).

Because the studies cited above indicate that oxytocin plays a role in symptoms and behaviors such as anxiety, mood regulation, fear, depression, social interaction disturbance, and dysregulated stress response, which are also seen in patients with bipolar disorder, there may be alterations in the serum oxytocin levels in bipolar disorder. Therefore, we planned to investigate serum oxytocin levels during manic and depressive episodes and the remission period and after response to treatment in bipolar disorder, and to compare levels with those of healthy controls.

2. Subjects and methods

2.1. Subjects

A total of 67 patients (39 male and 28 female) aged between 18 and 65 years, who presented to the Psychiatric Outpatient Department of Erciyes University Medical School and were followed up on either an outpatient or inpatient basis and diagnosed with BD Type I according to DSM-IV-TR diagnostic criteria (American Psychiatric Association, American Psychiatric Association and Task Force on DSM-IV, 2000), were included in this study. Diagnoses were made independently by two psychiatrists using clinical interviews.

Patients who had undergone electroconvulsive therapy (ECT) within the last 6 months, patients with a known metabolic or endocrine disorder, patients with a history of substance use or addiction other than smoking, patients with neurological conditions such as epilepsy or who had suffered head trauma that could result in organic brain disorder, female patients with menstrual irregularity, confirmed or suspected pregnancy, in the lactation or parturition period, and patients on oral contraceptives or hormone therapy were excluded from the study. The control group consisted of a total of 24 healthy individuals from volunteer hospital workers in the same age range as the patient groups, who had no known psychiatric, neurologic, endocrine or metabolic disorder; for female controls, those who had no menstrual irregularity, confirmed or suspected pregnancy, who were not in the lactation or parturition period, and who were not on oral contraceptives or hormone therapy were included.

At the time of the study patients were receiving treatment with at least one drug, such as a mood stabilizing agent (MSA), typical antipsychotic (TAP), atypical antipsychotic (AAP), and antidepressant (AD). In the manic episode group, the treatments were as follows: twelve patients were on MSA and AAP, three patients were on MSA, AAP and TAP, three patients were on AAP and TAP, three patients were on TAP, and one patient was on MSA. In the depressive episode group, the treatments were as follows: nine patients were on MSA and AAP, eight patients were on MSA, AAP and TAP, two patients were on AAP and AD, and two patients were on AAP. In the remission group, the treatments were as follows: thirteen patients were on MSA and AAP, eight patients were on MSA, two patients were on MSA and AD, and one patient was on AAP and AD. Three of the 22 patients in the manic episode group and one of the 21 patients in the depressive episode group were receiving additional benzodiazepine treatment.

Patients and controls were selected by performing physical, psychiatric and neurologic examinations, routine biochemical tests, complete blood counts and thyroid function tests.

This study was approved by the Ethics Committee of Erciyes University Medical School. The objectives and procedures of the study were explained to the patients and controls and their written informed consents were obtained.

2.2. Methods

In the patient groups and the control group, the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were applied to evaluate the severity of depression and mania, respectively.

To measure oxytocin levels, a total of 5 cc blood samples were collected from subjects between 08:00 and 09:00 hours in the morning at the beginning of the study. A second blood sampling was obtained from manic and depressive patients

after a minimum decrease of 50% in YMRS score and HAM-D score, respectively, during follow-up. Blood samples were collected in standard vacuum tubes and centrifuged at 1000 rpm for 15 min at 4 °C within 30 minutes of collection to obtain serum samples which were stored at −70 °C until analysis was performed.

2.3. Biochemical analysis

Serum samples were evaluated at the Biochemistry Research Laboratory of Erciyes University Medical School by means of ELISA test device (Sunrise Basic Tecan, Tecan Austria GmbH).

Serum oxytocin levels were assayed with ELISA (CUSABIO Human Oxytocin ELISA Kit) (assay range: 6—400 μIU/ml, sensitivity: <14 μIU/ml). Three samples of known concentration were tested in twenty assays to assess the intra-assay precision (precision within an assay): CV% <15%. Three samples of known concentration were tested twenty times on one plate to assess the inter-assay precision (precision between assays): CV% <15%. The obtained optic density values were converted into serum concentration values according to the formula calculated from linear regression analysis.

2.4. Statistical analysis

The Kolmogorov—Simirnov test was used to evaluate whether the data were normally distributed. The gender distribution of the groups was compared using the chi-square test. For the comparison of the demographic and clinical data, the independent samples *t*-test was used for data with normal distribution, and the Kruskal—Wallis test was applied for data without normal distribution. The post hoc Mann—Whitney *U* test was used when intergroup differences were found. For the comparison of the pre-treatment and post-treatment data of the manic and depressive patients, the paired *t*-test and Wilcoxon test were used for data with normal and non-normal distribution, respectively.

MANCOVA was performed, with the number of cigarettes smoked, age, gender and body mass index (BMI) as the covariates, to compare the oxytocin values of the groups. Bonferroni correction was used to avoid type 1 error. Then, with the same covariates, serial ANCOVAs were carried out to find out which group differed from the other(s) when there were statistically significant differences. The scores of the MANCOVA and Wilcoxon tests are presented in Tables 2 and 3, respectively. Other relevant statistical results are presented within the text. Spearman's correlation test was used because the oxytocin levels were distributed non-normally.

3. Results

3.1. Sociodemographic and clinical characteristics of the patient and control groups

This study included a total of 67 patients with bipolar disorder: twenty-two in manic episode, 21 in depressive episode, and 24 in remission at the initial phase. After a follow-up period of one to six months, a minimum decrease of 50% in HAM-D and YMRS scores in 14 depressive ($n = 14$) and manic ($n = 14$) patients, respectively, was considered as response to treatment and these patients were assessed in the study again.

There was no significant difference between the patient groups and the control group in age, duration of education, body mass index (BMI), gender and number of cigarettes smoked per day (Table 1).

3.2. Comparison of the oxytocin levels of the manic episode, depressive episode, remission and control groups

When age, gender, BMI and the number of cigarettes smoked per day were taken as the covariates, the serum oxytocin levels of patients included in the study during manic episode were statistically significantly higher than those of patients during depressive episode, of patients in the remission group and of healthy subjects in the control group ($F = 9.072$; df = (1, 41); $p = 0.005$, $F = 5.506$; df = (1, 44); $p = 0.024$ and $F = 66.590$; df = (1, 44); $p < 0.001$, respectively). The serum oxytocin levels of patients in the depressive episode group and in the remission group were statistically significantly higher than those of the control group ($F = 7.693$; df = (1, 43); $p = 0.008$ and $F = 8.145$; df = (1, 46); $p = 0.007$, respectively). When age, gender, BMI and the number of cigarettes smoked per day were taken as the covariates, the serum oxytocin levels of the manic episode and depressive episode patients measured after response to

Table 1 Sociodemographic and clinical characteristics of the groups included in the study.

Demographic data	Manic episode group $n = 22$ (mean ± SD)	Depressive episode group $n = 21$ (mean ± SD)	Remission group $n = 24$ (mean ± SD)	Control group $n = 24$ (mean ± SD)	Comparison
Age (years)	33.14 ± 12.40	36.19 ± 12.51	36.00 ± 11.40	34.42 ± 8.30	$\chi^2 = 1.919$; $p = 0.589$
Duration of education (years)	11.41 ± 2.94	11.38 ± 2.99	10.67 ± 3.94	12.25 ± 4.19	$\chi^2 = 2.868$; $p = 0.413$
BMI (kg/m^2)	26.01 ± 5.94	27.41 ± 4.96	26.78 ± 4.25	25.78 ± 3.04	$\chi^2 = 0.888$; $p = 0.828$
Number of cigarettes per day	8.23 ± 11.78	6.86 ± 8.88	7.13 ± 9.17	9.96 ± 13.79	$\chi^2 = 0.177$; $p = 0.981$
Gender: Male/female	10/12	13/8	16/8	14/10	$\chi^2 = 2.295$; $p = 0.513$
Duration of disease (months)	107.68 ± 119.26	116.00 ± 66.74	123.08 ± 94.05	—	$\chi^2 = 2.171$; $p = 0.338$

n: Number of subjects, mean ± SD: mean ± standard deviation, BMI: Body mass index.

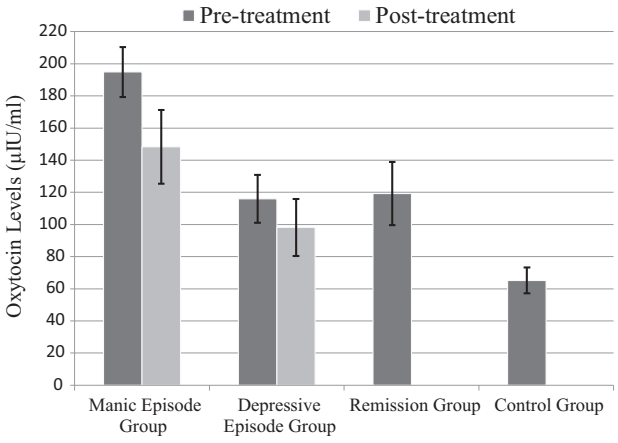

Figure 1 Comparison of oxytocin levels between groups. Error bars represent the standard error of mean (SEM).

treatment were statistically significantly higher than those of the control group ($F = 14.713$; df = (1, 36) $p = 0.001$ and $F = 5.048$; df = (1, 36) $p = 0.032$, respectively), and there was no statistically significant difference among the patient groups in terms of serum oxytocin levels (Table 2 and Fig. 1).

3.3. Comparison during episode and after response to treatment

When age, gender, BMI and the number of cigarettes smoked per day were taken as the covariates, the serum oxytocin levels measured during manic episode were significantly higher than the post-treatment levels ($Z = 2.158$, $p = 0.031$). There was no statistically significant difference between the serum oxytocin levels measured during the depressive episode and those measured after response to treatment in the same group (Table 3).

3.4. Correlation analysis

There was a negative correlation between the serum oxytocin levels measured in the manic episode group and the total duration of the disease ($r_s = 0.462$, $p = 0.015$). There was individual stability between oxytocin levels measured before and after treatment for patients with manic and depressive episodes ($r_s = 0.514$, $p = 0.025$; $r_s = 0.686$, $p = 0.007$; respectively).

No significant correlation was found as a result of analyzing the characteristics of the course of the disease and oxytocin levels in the depressive episode and remission groups.

4. Discussion

To the best of our knowledge, this is the first study to investigate the serum oxytocin levels of patients during manic episode and remission periods. Nevertheless, there is evidence in the literature that oxytocin is effective in improving mood in humans. Among these studies there is evidence that oxytocin plays a role in modulating responses to stress by modulation of the HPA axis, that irregularities in oxytocin levels are associated with anxiety and depression, and that high levels of oxytocin result in elevated mood (Lee et al., 2009).

4.1. Oxytocin during manic episode

It is known that some of the symptoms that occur during manic episode are particularly related to elevated dopamine levels in the limbic system (Akiskal, 2009). There is evidence from recent animal studies suggesting that cells expressing hypothalamic oxytocin modulate dopamine receptors and that oxytocin and dopamine increase together in the same

Table 2 Comparison of oxytocin levels between groups.

	Manic	Depressive	Remission	Control	Comparison
Initial assessment					
n	22	21	24	24	
mean ± SD (μIU/ml)	194.86 ± 72.85[a]	115.93 ± 68.37[b]	119.24 ± 95.96[b]	65.15 ± 39.42	$F = 12.698$; df = (3.72); $p < 0.001$
Assessment after response to the treatment					
n	14	14	24	24	
mean ± SD (μIU/ml)	148.33 ± 88.98[b]	98.18 ± 66.53[b]	119.24 ± 95.96[b]	65.15 ± 39.42	$F = 8.605$; df = (3.72); $p < 0.001$

n: Number of subjects.
[a] Higher than depressive episode, remission, and control groups.
[b] Higher than control group.

Table 3 Comparison of oxytocin levels during episode and after response to the treatment.

	During episode	After response to the treatment	Comparison
Oxytocin levels (μIU/ml)			
Mania ($n = 14$)	193.96 ± 72.07	148.33 ± 88.98[a]	$Z = 2.158$, **$p = 0.031$**
Depression ($n = 14$)	119.00 ± 47.97	98.18 ± 66.53	$Z = 1.475$, $p = 0.140$

n: Number of subjects.
[a] Lower than during episode

brain regions (Liu and Wang, 2003; Smeltzer et al., 2006; Succu et al., 2007). The relationship between oxytocinergic neurons and mesolimbic dopaminergic neurons in particular was associated with bonding and sexual behavior. Oxytocin-rich hypothalamic nuclei are innervated by dopaminergic fibers and are regulated by dopamine via D2-like dopaminergic receptors. Oxytocin is released to the hippocampus, amygdala, ventral tegmental area, and the spinal cord via axonal projections of magnocellular neurons within the PVN and SON and contributes to the regulation of several physiological and behavioral functions including reproductive and sexual behaviors, anxiety and social behaviors (Baskerville and Douglas, 2010; Bosch and Neumann, 2012; Feldman, 2012; Knobloch et al., 2012). When the information in the literature and the findings from this study, namely that oxytocin levels increase during manic episode, are evaluated together, it is likely that increased dopamine as well as oxytocin may play a role in the occurrence of euphoria, distractibility, excessive involvement in pleasurable activities that have a high potential for painful consequences, hypersexuality, socially incompatible behavior and cognitive dysfunction which are seen during manic episodes in bipolar disorder.

It is thought that psychotropic drugs such as mood stabilizers and antipsychotics, which are used in manic episode, increase peripheral oxytocin levels (McGregor and Bowen, 2012). From this point of view, it is conceivable that high levels of oxytocin during manic episode may be associated with psychotropic drugs. Oxytocin levels during manic episode, which have been found to be significantly higher than those seen after response to treatment despite the use of drugs from the same class, suggest that the higher oxytocin levels observed during manic episode cannot solely be explained by drug use. If increased oxytocin levels had been due to drugs alone, the oxytocin levels would have been expected to remain high after response to treatment as well. In addition, if we consider that the oxytocin levels of the manic episode group were found to be higher than those of the other patient groups, it can be said that there is an association between manic episode and oxytocin levels, and this can be interpreted that the oxytocin levels decrease as relief from manic symptoms begins.

4.2. Oxytocin during depressive episode

In this study, similar to the manic episode group, the serum oxytocin levels of the patients in the depressive episode group were also higher than those of the control group. In a study consistent with this finding, Parker et al. found that the plasma oxytocin levels in patients with major depression (unipolar or bipolar) were significantly higher than those of healthy controls and suggested that while the reason for this was not yet known, oxytocin may be a biomarker of emotional distress and impaired social relationships in depressive patients (Parker et al., 2010). In early studies, while no difference was found between the CSF oxytocin levels of depressed patients and those of the control groups, postmortem examinations of patient groups with bipolar and unipolar depression demonstrated enlargement in vasopressin and oxytocin producing PVN in both groups. This finding may be associated with increased synthesis of vasopressin and oxytocin (Marazziti and Catena Dell'osso, 2008). While there are also studies that found decreased plasma oxytocin levels in patients with unipolar depression (Pitchot et al., 2008), the postmortem examinations of patients with melancholic depression demonstrated increased oxytocin mRNA levels in PVN, which was associated with increased synthesis of oxytocin (Bao et al., 2008).

Animal studies have shown the antidepressant-like and anxiolytic effects of oxytocin and oxytocin receptor agonists (McGregor and Bowen, 2012; Neumann et al., 2000b). In relation to this effect, the effect of antidepressants on oxytocin levels has become a research subject. A study by Ozsoy et al. (2009) suggested that serum oxytocin levels were not affected by antidepressant use in patients with unipolar or bipolar depression. On the other hand, there are other studies in the literature suggesting that antidepressants increase central oxytocin levels. It is suggested in these studies that an increase in central oxytocin levels may be one of the underlying causes for the activities of antidepressants such as SSRIs, SNRIs and TCAs (Rotzinger et al., 2010; Uvnas-Moberg et al., 1999). Besides antidepressants, lithium has also been shown to potently stimulate hypothalamic oxytocinergic circulation (McGregor and Bowen, 2012). It is suggested that the use of antipsychotics such as clozapine in patients with schizophrenia significantly increases plasma oxytocin levels and that oxytocin may act as a natural antipsychotic (Lee et al., 2009; Uvnas-Moberg et al., 1992). The higher serum oxytocin levels in the depressive episode group, as compared to the control group, may be related to the antidepressant, antipsychotic or lithium therapy that the patients were receiving and it may also result from the compensatory increase in the endogenous release of oxytocin in order to utilize its anxiolytic and antidepressant effects. As a matter of fact, the PVN hypertrophy detected in postmortem examinations of unipolar patients may well be limited to oxytocin producing cells alone (Meynen et al., 2007).

4.3. The relationship between remission in BD and oxytocin

To the best of our knowledge there is no study in the literature on serum oxytocin levels during a period of remission in bipolar disorder. As indicated before, high levels of oxytocin, which also persist during remission, are probably related to the use of psychotropic drugs such as mood stabilizers (particularly lithium), antidepressants or antipsychotics. However, the possibility should not be ruled out that the endogenous release of oxytocin could have been increased to stabilize mood.

4.4. Assessment of the oxytocin levels in the manic episode group after response to treatment

While the serum oxytocin levels of patients in the manic episode group during the episode were significantly higher than those of the depressive and remission groups, this significant difference disappeared after response to treatment. In other words, it is possible to say that the serum oxytocin levels of all groups with bipolar disorder after response to treatment are comparable. Based on these findings, it may well be said that in the future oxytocin levels may

be an applicable parameter in the clinical follow-up of manic episode, and be one of the hormonal criteria that indicate remission in bipolar disorder. Although the use of oxytocin agonistic or antagonistic agents is still at the experimental stage, the use of these agents in the maintenance treatment of BD or during episodic periods may be an appropriate option.

In conclusion, oxytocin may play an important role in the pathophysiology of bipolar disorder. The finding of higher oxytocin levels in patient groups than in controls before and after treatment response suggests that oxytocin may be a trait marker in BD. Investigation of oxytocin levels in larger groups of patients with bipolar disorder will make a major contribution to a better understanding of this disorder and to the development of therapeutic options.

4.5. Limitations of the study

The results of this study need to be interpreted with caution, because serum levels of oxytocin might not reflect central release (Neumann and Landgraf, 2012). The target number of the patients included in the study could not be achieved. It was not possible to contact all the patients included in the manic episode and depressive episode groups after response to treatment assessment. All of the patients who could be contacted met the criteria for response to treatment after a follow-up period of one to six months. It was not possible to define the condition of patients who were lost to clinical follow-up. Among those patients who did not respond to treatment, if any, were those whose hormone levels could not be assessed. All of the patients evaluated during episodes were previously taking psychotropic drugs. A patient group without psychotropic drug use could not be formed. Therefore, it was not possible to prevent drug effect on oxytocin levels.

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Conflict of interest

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