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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