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DECREASED OXYTOCIN PLASMA LEVELS AND OXYTOCIN RECEPTOR EXPRESSION IN BORDERLINE PERSONALITY DISORDER

Running title: Oxytocin levels in borderline personality disorder

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ABSTRACT

Introduction: Borderline personality disorder (BPD) is characterized by intense affective reactions with underlying social and interpersonal cognitive deficits. Oxytocin has largely been associated with both stress regulation and social cognition in psychiatric patients and in non-clinical populations in previous studies. Finally, abnormal oxytocin levels have been preliminary reported in BPD patients.

Methods: 53 patients with moderate-severe BPD and 31 healthy control subjects were investigated for plasma levels of oxytocin and protein expression of oxytocin receptor in blood mononuclear cells. Clinical assessments were made for severity, functionality and comorbidity with axis I and II conditions.

Results: Oxytocin plasma levels were significantly lower in BPD patients compared with controls. In addition, protein expression of oxytocin receptor was significantly reduced in the BPD group. A positive correlation was found between plasma oxytocin levels and the activity index score of the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). Oxytocin receptor protein expression, on the contrary, had a negative correlation with the ZKPQ sociability index score.

Conclusions: Results support the evidence of a dysfunction of the oxytocin system in Borderline Personality Disorder, which could be involved in emotional dysregulation and interpersonal disturbances in these patients.

Keywords: borderline personality disorder, oxytocin, impulsivity, social dysregulation

Significant Outcomes

- Patients with borderline personality disorder show a statistically significant reduction of plasma levels of oxytocin (OXT) compared with the control group.
- Patients with borderline personality disorder present a statistically significant reduction of the OXT receptor protein expression compared with the control group.
- These results support the evidence of a dysfunction of the oxytocin system in patients with borderline personality disorder.

Limitations

- The reduced size of the control group. A greater sample size could probably render statistically significant correlations between neurochemical and clinical variables.
- The possible influence of medications for patients in the neurochemical results. However, we considered that the withdrawal of medication in BPD patients could have a significant rebound effect on the oxytocin levels affecting the results, as well as significant clinical impairment of patients.
- The sample was composed by patients with moderate-severe severity and high dysfunction, so this sample could not represent the average of BPD population.

Data availability statement: The authors confirm that the data supporting the findings of this study are available within the article.

INTRODUCTION

Oxytocin (OXT) is a nine amino acid neuropeptide synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, stored in the pituitary gland and released into the bloodstream (1). At the peripheral level, OXT has important effects on childbirth and lactation (2), while at the central level it acts as a modulator of social and emotional behaviors in animals and humans.

OXT receptors (OXTR) are distributed throughout various brain areas including amygdala, ventromedial hypothalamus, accumbens nucleus, basal brain or cingulate cortex (3, 4). The OXT neuropeptide attenuates amygdala response, modulates the action of stress hormones through the HPA axis and regulates brain activity in areas related to social cognition (5).

Several research studies have proposed the role of OXT in the pathophysiology of disorders with social cognition deficits through its effects on trust, positive social assessment, pro-social behaviors and anxiety (6). OXT deficit has been found in schizophrenia, autism and other disorders in which alterations in social relationships are prominent (7). OXT also seems to influence emotional dysregulation in bipolar II disorder (8). In addition, genetic studies show an association between some oxytocin alleles and life history of suicide attempts (9).

Borderline personality disorder (BPD) is a serious pathology that implies significant emotional, behavioral and relational instability. Interpersonal hypersensitivity, fear of abandonment, or intense and unstable affective relationships are central aspects. At the neurobiological level, BPD has been linked with an abnormal response to stress (10) and neuroimaging studies show structural and functional alterations in the frontolimbic circuits (11), which are both closely related to the central action of OXT. Intranasal Oxytocin has also been proposed as a promising line of drug treatment in this population (12). However, evidence is yet preliminary and there are still more questions than certainties regarding the role of OXT in BPD (13).

Plasma and serum levels of OXT are usually considered, at the neurobiological level, a biomarker of OXT levels at the central level (14); nevertheless, the validity of this approach is unclear. Some studies have shown no correspondence between central and periphery OXT levels (15). However, a recent meta-analysis has shown a positive correlation between the different OXT concentrations under certain conditions, such as stress or exogenous administration of OXT, but not at baseline conditions (16). Their extraction procedure is not

very intrusive, so many investigations measure the alteration of OXT in blood in relevant populations using commercial immunoassays like RIAs (15,16) or ELISAs (14,17). In 2013 (17), a study showed a reduction in plasma levels of OXT in women diagnosed with BPD, concluding that dysregulation of the oxytocin system can be an important underlying factor in BPD. However, this decrease in blood oxytocin is not found in all samples (16), which suggests that there may be social, psychopathological or biological mediators that are not being taken into account. Some studies try to relate the oxytocin deficit with some biological dimensions such as compassion (18), or with epigenetic factors such as attachment (19), but biological mediators have not yet been sufficiently studied.

Together with oxytocin, some studies have also examined the role of vasopressin (AVP) in human social behaviour, which seems to be mainly involved in social behaviors related to aggression (20), suggesting a potential effect of central AVP in individuals with aggressive impulsive disorder (21).

The objective of this paper is to study oxytocin plasma levels in a sample of BPD patients with a moderate degree of severity. Plasma levels of OXT are known to be similar in men and women, which reinforces the hypothesis of a role of OXT beyond the hormonal function (22). We also investigate in this study the protein expression of the OXT receptor. Through receptor binding studies, it has been observed in animals that its expression in specific brain areas could be related to certain behavioral aspects (23). This receptor is also expressed in peripheral tissues, including lymphocytes (24). Recently, OXTR expression by western blotting has been reported in human PBMC, where children exposed to maltreatment have lower OXTR expression in PBMC, and that was particularly pronounced in a subgroup of insecurely attached mothers compared to the securely attached subgroup (25).

Aims to study: The objective of this paper is to study oxytocin plasma levels and the protein expression of the oxytocin receptor in a sample of BPD patients with a moderate degree of severity.

MATERIAL AND METHODS

53 patients diagnosed with Borderline Personality Disorder according to DSM-IV-TR criteria (26), with a moderate-severe degree of severity (CGI (Clinical Global Impression) > 4) and a moderate level of dysfunction (EEAG (Evaluation Scale for Global Activity) <65) were assessed at the Personality Disorders Unit of the San Carlos University Hospital of Madrid.
Patients between 18 and 55 years of age were included voluntarily in the study and signed written informed consent. The study was approved by the Institutional Ethical Committee
The exclusion criteria included: 1) severe medical conditions possibly affecting oxytocin 2) major depressive disorder or substance abuse at the time of assessment; 3) lifetime diagnosis of organic mental disorder, bipolar disorder or schizophreniform disorders.
A control group of 31 healthy subjects, with similar age, sex and educational level of the group of patients, was also investigated.

Clinical measurements

Clinical interviews were made by experienced psychiatrists and clinical psychologists at the beginning of the study. All patients and controls were interviewed using the Structured Interview for Mental Disorders (SCID-I; 27) and the Structured Interview for Personality Disorders (SCID-II; 28). Severity was measured with the Global Clinical Scale for Personality Disorders (CGI-BPD; 29) and functional impairment was rated with the Global Assessment of Functioning Scale (GAF; 30). Personality features were measured with the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ-III; 31).

Specimen collection and preparation

Venous blood samples (10 mL) were collected between 8:00 and 10:00 h after fasting overnight. Blood tubes were centrifuged (641g × 10 min, 4ºC). The resultant plasma samples were collected and stored at −80ºC. The rest of the sample was 1:2 diluted in culture medium (RPMI 1640, LifeTechnologies) and a gradient with Ficoll-Paque (GE Healthcare) was used to isolate mononuclear cells by centrifugation (800g × 40 min, room temperature -RT-). Peripheral Blood Mononuclear Cell (PBMC) layer was aspired and resuspended in

RPMI and centrifuged (1116 g × 10 min, RT). The supernatant was removed and the mononuclear cell-enriched pellet stored at −80ºC.

Biochemical Determinations in Plasma

Oxytocin levels: were determined through a commercially competitive ELISA-based kit (ref. 500440, Cayman Chemical, Estonia) following the manufacturer's instructions. The absorbance was measured at 405nm (Synergy 2, Biotek). The intra- and interassay CV were 7.2% and 7.0%, respectively. To obtain valid assay results, plasma samples were previously purified using C18 Sep-Pak columns (Waters, UK) to remove molecules that could interfere with the assay (32).

Biochemical Determinations in peripheral blood mononuclear cell (PBMC)

To carry out all biochemical determinations, PBMC samples were first fractionated in cytosolic and nuclear extracts as in previously published articles (33, 34).

The protein levels from cytosolic extracts were measured using the Bradford method, based on the protein-dye binding.

Western Blot, 15 µg of cytosolic extracts were loaded into an electrophoresis gel. Once separated on the basis of molecular weight, proteins from the gels were blotted onto a nitrocellulose membrane (Transfer Pack, BioRad) with a semi-dry transfer system (Bio-Rad) and were blocked in 5% BSA for 1.5hr, then the membranes were incubated overnight at 4ºC with specific antibodies against: OXTR (1:750 BSA0.5%, sc515809, SCB), and β-actin (1:15000, A5441, Sigma). After washing with a TBS-Tween solution the membranes were incubated with the respective horseradish peroxidase-conjugated secondary antibodies for 90 min at room temperature and revealed by ECL™-kit following manufacturer's instructions (Amersham Ibérica, Spain). Blots were imaged using an Odyssey® Fc System (Li-COR Biosciences) and quantified by densitometry (NIH ImageJ® software). β-actin was used as loading controls (the blots are shown in the respective figures). All blots were performed at least 3 times in separate assays and the densitometries are expressed in % from control group.

Statistical Analysis

Biochemical data are expressed as mean ± SEM. The ROUT method was performed with a significance Q set at 1% for the detection of outliers. Data were analysed using the D'Agostino & Pearson normality test, those with a normal distribution were analysed with an Unpaired two-tailed t test comparing controls vs BPD, and a two-tailed t test with Welch's correction was employed when samples did not have equal standard deviations. In those cases, in which the data did not follow a normal distribution, a nonparametric Mann-Whitney test was performed. To investigate oxytocin association with clinical features of BPD, linear correlation between neurochemical variables and severity (CGI), functionally (GAF) and personality traits (Zuckerman-Kuhlman Personality Questionnaire, ZKPQ-III). In all cases, a p value < 0.05 was considered statistically significant.

RESULTS

Demographic and clinical features

Demographic and clinical features are shown in table 1.

Oxytocin markers in controls and BPD patients.

Patients with BPD showed 1) a significant reduction of plasma oxytocin (OXT) levels (figure 1A) and 2) a decreased protein expression of the OXT receptor (OXTR) in blood mononuclear cells, compared with the control group (figure 1B).

Correlations of neurochemical and clinical measurements

Correlations of neurochemical variables and social functioning (GAF) did not render statistically significant results (table 2). Regarding severity, however, a statistically significant positive correlation was found between oxytocin (OXT) plasma levels and CGI score at the time of the study (p=0.028) (table 2).

Although correlations of neurochemical variables and personality traits (Zuckerman-Kulhman Personality Questionnaire, ZKPQ) were not statistically significant (table 3), some positive correlations at a tendency level could be remarkable, including a positive association of OXT plasma levels and scores of the ZKPQ activity index (r=0.213; p=0.258) and an inverse association between oxytocin receptor (OXTR) expression and the scores of the ZKPQ sociability index (r=-0.335; p=0.072).

DISCUSSION

Our study supports previous reports of anomalies of the oxytocin system in men and women with BPD, by demonstrating decreased levels of plasma OXT and decreased protein expression of the OXT receptor in our patients compared to healthy controls. The oxytocin deficit could influence the abnormal response to stress and the bottom-up and top-down dysregulation of emotional systems characteristic of Borderline Personality Disorder (35).

Low oxytocin action at the limbic system would generate an unusually high amygdala activation in these patients (5), not sufficiently modulated by the prefrontal cortex, resulting in interpersonal hypersensitivity, emotional dysregulation and impulsive behavior. These findings are also compatible with a down-regulation process of the oxytocin system in these patients in response to early infant negative experiences associated with disorganized attachment styles as previously described by Jobst et al., (19).

To our knowledge, this is the first study showing a decrease of protein expression of the OXT receptor in BPD patients. A reduced protein expression may be a biological mediator of some aspects of the psychogenesis and the psychopathology of BPD., since most of the effects of oxytocin at the central level depends on the dynamics and the distribution of its receptor in the different brain areas (36). It has been suggested that both plasma OXT levels and OXTR expression might modulate the impact of child rearing disturbances on adult life psychopathology (37). In fact, rearing and attachment problems have been proposed as central for the genesis of BPD and could be a psychosocial mediator between oxytocin dysfunctions and BPD psychopathology at adolescence. Therefore, decreased protein expression of the OXTR could be related with disorganized attachment styles frequently found in BPD patients. In this sense, a gene-environment interaction of genetic polymorphisms of OXTR and negative experiences in childhood converging and creating a general factor of vulnerability has been suggested (5). However, this can only be determined with more developmental studies that investigate the way environmental factors influence down-regulation of OXTR expression in these BPD subjects.

Despite the large number of studies trying to link peripheral OXT levels to psychiatric disease states, there is no reliable evidence to support the correlation between peripheral and central oxytocin levels at baseline conditions. Even OXT cerebrospinal fluid levels might not reflect activity in specific neurocircuitries. This limitation is mainly due to the lack of consistent and reproducible methodologies that allow the measurement of OXT. Current immunoassays detect not only OXT but also OXT fragments derived from its degradation, multiple forms of OXT, and non-OT immunoreactive molecules due to cross-reactivity. Some of these problems could be resolved through a previous process of plasma purification. So, the study of the OXTR could be crucial for the understanding of the OXT pathway in this context.

This study also supports the idea that reduction of oxytocin function is common to a number of mental conditions characterized by social deficits, such as schizophrenia or autism (38). Significantly low levels of plasma OXT are consistently found in autism, where the communication deficits and social isolation are central features (39). Borderline personality disorder is characterized by behavioral and social disturbances derived from interpersonal extreme sensitivity and misinterpretations, and OXT dysfunction could probably explain part of the disturbed social cognition in these patients (40).

Besides social cognition, dysfunction of the oxytocin system is involved in emotional dysregulation, another of the central aspects of BPD. Plasma levels of oxytocin are lower in depressed women than in controls (41) and are increased in bipolar patients, especially in the manic phase (42) and in type II bipolar patients compared with patients with major depressive disorder (8). BPD patients in our study, although not suffering from major depression or hypomania, did have affective instability due to emotional dysregulation and increased limbic reactivity which could be partially explained by reduced oxytocin function (5).

Deficits of social cognition in BPD have been described and are subject of research in the last years (43), and some evidence indicates that autistic traits could even be prominent in a group of BPD patients (44). In this sense, preliminary treatment trials in BPD patients with intranasal oxytocin have demonstrated positive effects on social approach and social trust (45).

Finally, the interactions of OXT at central and peripheral levels with other neurotransmitters also involved in social and emotional dysfunctions in BPD should be investigated in future studies since there is some evidence of interactions with vasopressin, testosterone, dopamine or serotonin (5). Vasopressin is associated with social aggression (20), but there is insufficient knowledge of how oxytocin and vasopressin interact in the experience of social reward, social frustration and aggressive response (5). Regarding the importance of studying the genes for the OXT receptor in future studies, it is becoming increasingly clear that when evaluating complex human behaviors it may be more appropriate to study gene networks than single genes (46). Recently, genetic studies found a contribution of a vasopressin receptor subtype (Avpr-1a) in social behaviour and several studies have shown an association between the Avpr1a receptor gene and autism (21).

It seems clear that expanding the knowledge on the role of oxytocin in the complex developmental neurobiology of BPD can contribute to novel pharmacological approaches to the disorder and also help to define biomarkers in order to improve the efficacy of psychotherapies (47).

Conclusions

The present study provides data that supports the evidence of a dysfunction of the oxytocin system in patients with Borderline Personality Disorder. It confirms low plasma levels of OXT and finds, for the first time, a decreased protein expression of oxytocin receptor in BPD. Next steps should address the intermediate effects of factors such as attachment and rearing, which are known to be related with oxytocin function, in the relation of oxytocin deficits and BPD psychopathological features.

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Table 1. Sociodemographic and function variables of patients and controls.

		BPD group (n=49)	Control group (n=33)
Age (mean ± SD)		29.8 ± 9.293	30.5 ± 8.810
Gender (percentage)	Male	12.2%	6.3%
	Female	87.8%	93.8%
Disease duration (years)		17.67	0
Pharmacological treatment	Antidepressants	67.4%	0%
	Antipsychotic	34.8%	0%
	Anti-epileptic	34.8%	0%
	Benzodiazepines	69.6%	0%
CGI (mean ± SD)		5.29 ± 0.913	
GAF (mean ± SD)		58.94 ± 6.589	

BPD group= borderline personality disorder group; CGI= Global Clinical Scale; GAF= Global Assessment of Functioning Scale

Table 2. Results of correlations of neurochemical variables and severity (CGI) and functionally (GAF).

	CGI	GAF
	Statistical analysis *r*; *p*-value	Statistical analysis *r*; *p*-value
Oxytocin	r=0.314; p=0.028	r=-0.220; p=0.137
OXTR	r=-0.147; p=0.325	r=-0.048; p=0.755

Oxytocin=oxytocin levels; OXTR= Oxytocin receptor; CGI= Global Clinical Scale; GAF= Global Assessment of Functioning Scale

Table 3. Correlations of neurochemical variables and Zuckerman-Kuhlman Personality Questionnaire (ZKPQ-III).

	ZKPQ Impulsivity	ZKPQ Anxiety	ZKPQ Aggressiveness-hostility	ZKPQ Activity	ZKPQ Sociability
	Statistical analysis *r*; *p*-value	Statistical analysis *r*; *p*-value	Statistical analysis *r*; *p*-value	Statistical analysis *r*; *p*-value	Statistical analysis *r*; *p*-value
Oxytocin	r=0.069; p=0.715	r=-0.027; p=0.889	r=0.147; p=0.437	r=0.213; p=0.258	r=-0.006; p=0.977
OXTR	r=0.101; p=0.594	r=0.021; p=0.912	r=0.160; p=0.398	r=0.125; p=0.509	r=-0.334; p=0.072

Oxytocin=oxytocin levels; OTR= Oxytocin receptor; ZKP Impulsivity= ZKPQ impulsivity index; ZKP Anxiety= ZKPQ anxiety index; ZKPQ Aggressiveness-hostility = ZKPQ aggressiveness-hostility index; ZKPQ Activity= ZKPQ activity index; ZKPQ Sociability= ZKPQ sociability index

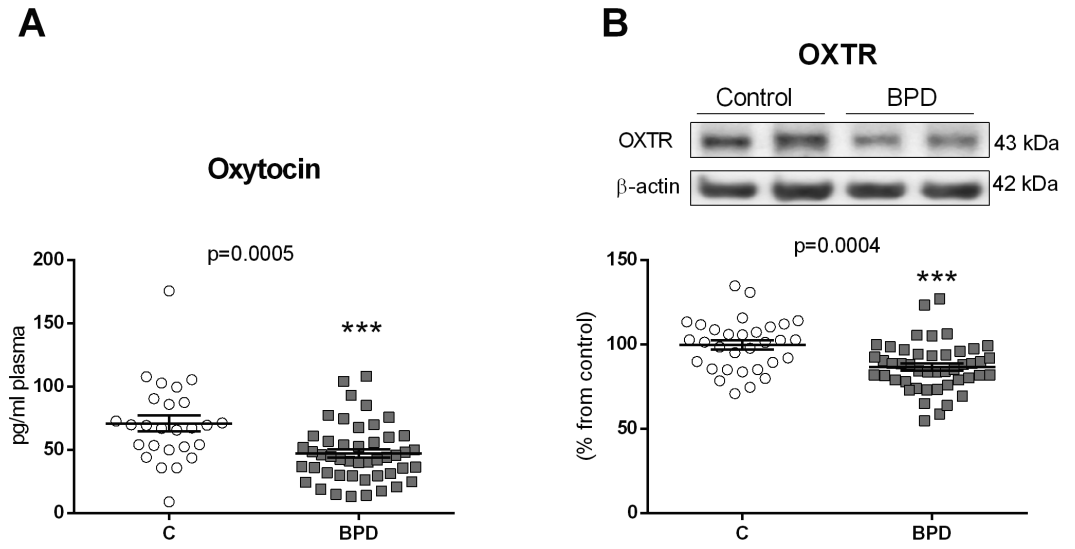

Figure 1. BPD= borderline personality disorder group; Oxytocin=oxytocin levels in plasma; OXTR= expression of Oxytocin receptor in peripheral blood mononuclear cells.