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SHORT COMMUNICATION

Oxytocin administration attenuates stress reactivity in borderline personality disorder: A pilot study

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Summary Oxytocin has known stress-reducing and attachment-enhancing effects. We thus hypothesized that oxytocin would attenuate emotional and hormonal responses to stress in borderline personality disorder (BPD). Fourteen BPD and 13 healthy control (HC) adults received 40IU intranasal oxytocin or placebo in double-blind randomized order followed by the Trier Social Stress Test. Subjective dysphoria (Profile of Mood Changes) and plasma cortisol levels were measured. Childhood trauma history, attachment style, and self-esteem were also rated. A significant "Group × Drug × Time" interaction effect for dysphoria ($p = .04$) reflected a proportionately greater attenuation of stress-induced dysphoria in the BPD group after oxytocin administration. Additionally, a marginally significant "Group × Drug" interaction effect for cortisol ($p = .10$) reflected a tendency toward greater attenuation of the stress-induced cortisol surge in the BPD group after oxytocin administration. In the combined sample, the oxytocin-placebo difference in the emotional stress reactivity was significantly predicted by childhood trauma alone ($p = .037$) and combined with self-esteem ($p = .030$), whereas the oxytocin-placebo difference in cortisol stress reactivity was predicted only by insecure attachment ($p = .013$). Results suggest that oxytocin may have a beneficial impact on emotional regulation in BPD, which merits further investigation and could have important treatment implications.
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1. Introduction

The neuropeptide oxytocin (OT) has been implicated in the dampening of hypothalamic-pituitary-adrenal (HPA) axis activation and emotional reactivity at rest and in response to physical or psychological stressors in social mammals, including humans (Carter and Altemus, 1997; Windle et al., 1997; Legros et al., 1984; Suh et al., 1986). OT also promotes healthy attachment to caregiving others (Buchheim et al., 2009), and it has been posited that negative early caregiving experiences may affect brain development in part via the oxytocin—vasopressin system, thus affecting the later formation of secure attachment relationships.

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Indeed, altered OT system sensitivity has been found in adults with histories of childhood abuse or neglect (Heim et al., 2008; Meinslschmidt and Heim, 2007).

Borderline Personality Disorder (BPD) is a psychiatric disorder characterized by major emotional dysregulation, difficulty in interpersonal relationships, and unstable self-esteem (Zeigler-Hill and Abraham, 2006). It is also typically characterized by insecure attachment styles, especially fearful and avoidant (Agrawal et al., 2004). Therefore, the goal of the present pilot study was to investigate whether exogenous OT administration would differentially attenuate emotional and neuroendocrine responses in BPD as compared to healthy individuals, at rest but especially after psychosocial stress. We also hypothesized that the impact of OT on emotional and hormonal responses would be predicted, at least in part, by trauma, attachment, and self-esteem.

2. Methods

2.1. Participants

An adult sample with DSM-IV-TR BPD and a healthy control (HC) sample without lifetime Axis I or II psychiatric disorders participated in the study. The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, and all participants provided written informed consent. Participants were excluded if they had lifetime schizophrenia or bipolar I disorder; mental retardation, or major medical or neurological illnesses; were taking psychotropic or other medications including oral contraceptives within the past 2 weeks (5 weeks for fluoxetine); had current major depression, substance use disorder, or eating disorder; were currently pregnant, lactating, or menopausal; or regularly smoked cigarettes.

2.2. Baseline evaluation

The Structured Clinical Interview for the DSM-IV-TR I and II disorders were used to establish diagnoses (First et al., 2002; First et al., 1994, respectively). Participants completed the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), the Relationship Questionnaire (RQ; Griffin and Bartholomew, 1994), and the Rosenberg Self-Esteem Scale (RSS; Rosenberg, 1965). The CTQ is a 25-item self-report questionnaire rating various childhood interpersonal traumas, the total score indexing the prevalence of traumatic childhood experiences. The RQ rates each of four attachment styles (secure, fearful, preoccupied, dismissive) dimensionally on a seven-point scale; the sum of the three non-secure attachment style scores (i.e., fearful, preoccupied, dismissing) was used to quantify insecure attachment. The RSS is a widely-used 10-item, four-point Likert scale measure of self-esteem, with items rated from "strongly agree" to "strongly disagree," and yields a total score.

2.3. Challenge protocol

Participants were admitted to the General Clinic Research Center on two separate days one to two weeks apart. Upon arrival, participants received a standardized breakfast and were subsequently restricted to bed rest and refrained from eating. At 09:30am, routine laboratory tests were obtained, including urine toxicology and pregnancy testing.

The Profile of Mood States (POMS; McNair et al., 1992) was administered three times throughout the procedure to assess transient, distinct mood states, and the average of its five negative mood factors (i.e., tension-anxiety, depression-rejection, anger-hostility, fatigue-inertia, and confusion-bewilderment) yielded a total "dysphoria" score (the positive factor of vigor-activity was excluded). Plasma cortisol was also assessed at four time points during the challenge.

The Trier Social Stress Test (TSST; Kirschbaum et al., 1993) was used as the acute psychosocial stressor. The TSST has been reliably shown to induce mild to moderate HPA axis, cardiovascular, and psychological stress responses in various clinical and non-clinical samples. Administration took 15 min, with a 5-min preparation phase and a 10-min public speaking and mental arithmetic task phase, performed and audiotaped in front of a trained audience. The speech and math task were slightly modified for Day 2, with comparable difficulty.

Challenge day timeline was as follows: 11:00am: POMS1 (baseline); 11:30am: plasma cortisol (CORT1; baseline), then 40IU dose of intranasal OT (Syntocinon, Novartis) or placebo (PL) in double-blind randomized order; 12:00pm: POMS2, CORT2. 12:30pm: CORT3, then TSST; 12:50pm: POMS3, CORT4.

2.4. Statistical analyses

Two repeated-measures analyses of covariance (ANCOVAs) were conducted, one for dysphoria and one for plasma cortisol, covarying for age and gender. For subsequent simple comparisons, independent and paired Student's *t*-tests were employed; "resting" analyses used POMS 1 and 2 scores for dysphoria and CORT 1 and 2 levels for cortisol, and "stress" analyses used POMS 2 and 3 scores for dysphoria and CORT 3 and 4 levels for cortisol.

In order to examine the influence of trauma, attachment, and self-esteem on OT responses in the combined sample, two separate hierarchical linear regressions were conducted. The dependent variable was the difference in dysphoria or cortisol stress response between OT and PL, with childhood trauma, secure attachment, and insecure attachment entered in a stepwise fashion in block one, followed by self-esteem in block two. All analyses were two-tailed.

3. Results

3.1. Participants

BPD patients ($N = 14$) were 35.1 ± 8.0 and healthy participants ($N = 13$) were 34.5 ± 8.9 years old ($t = 0.21$, $p = .84$). The groups did not differ significantly in gender (BPD: 6 females, HC: 9 females, $\chi^2 = 0.90$, $p = .34$). BPD participants had the following current comorbid diagnoses: dysthymia ($n = 2$), social anxiety disorder ($n = 3$), panic disorder ($n = 3$), posttraumatic stress disorder ($n = 3$), and generalized anxiety disorder ($n = 1$). All 13 HC participants and 10 of 14 BPD participants completed both testing days. Of the four BPD participants who only completed the first challenge day, 3 did not receive OT and 1 did not receive placebo; they were

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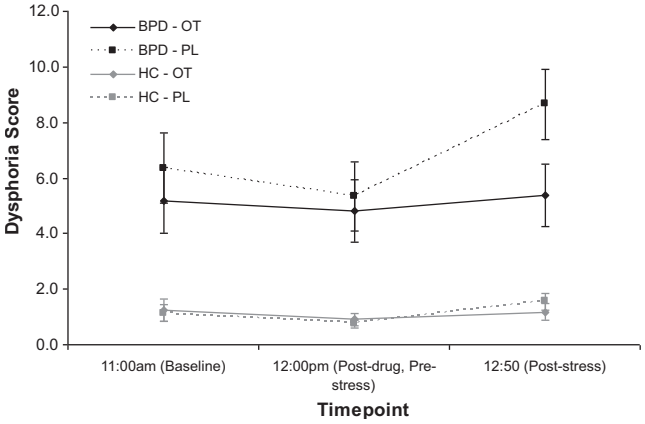

Figure 1 POMS Dysphoria ratings at three time points in the BPD and HC groups as a function of oxytocin/placebo administration and psychosocial stress testing.

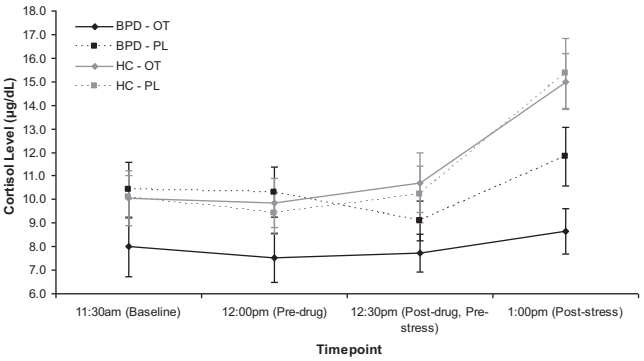

Figure 2 Plasma cortisol levels at four time points in the BPD and HC groups as a function of oxytocin/placebo administration and psychosocial stress testing.

excluded from all analyses. Two HC participants had one missing POMS rating for the PL day, and were excluded from all dysphoria analyses.

3.2. Emotional responses to oxytocin in the BPD and HC groups

ANCOVA analysis revealed a significant Group (BPD vs. HC) × Drug (OT vs. PL) × Time (baseline vs. post-drug, pre-stress vs. post-stress) interaction for dysphoria (Huynh—Feldt corrected $F = 3.81$, $df = 1.70$, $p = .04$; Fig. 1). There were no other significant interaction effects. Simple comparisons demonstrated no significant within-group or between-group changes in dysphoria after OT or PL administration at rest. Under stress, both groups exhibited a significant increase in dysphoria after PL (BPD: paired $t = 3.56$, $df = 9$, $p = .006$; HC: paired $t = 2.58$, $df = 10$, $p = .03$) but not after OT (BPD: paired $t = 0.58$, $df = 9$, $p = .57$; HC: paired $t = 0.85$, $df = 10$, $p = .41$) administration. Notably compared to the HC group, the BPD group demonstrated a significantly greater increase in dysphoria only after PL ($t = 2.85$, $p = .01$) but not after OT ($t = 0.27$, $p = .79$).

3.3. Hormonal responses to oxytocin in the BPD and HC groups

ANCOVA analysis revealed a marginally significant Group (BPD vs. HC) × Drug (OT vs. PL) interaction effect for plasma cortisol (Huynh—Feldt corrected $F = 2.83$, $df = 1$, $p = .10$; Fig. 2). There was also a significant Cort × Group ($p = .04$) and Cort × Age ($p = .03$) interaction. No other interaction effects were significant. Simple comparisons demonstrated no significant within-group or between-group changes in plasma cortisol after OT or PL administration at rest. Under stress, BPD participants demonstrated a trend significant cortisol surge after PL (paired $t = 2.17$, $df = 9$, $p = .06$) but not OT (paired $t = 1.26$, $df = 9$, $p = .24$), whereas HC participants showed significant increases in plasma cortisol after both PL (paired $t = 3.44$, $df = 12$, $p = .005$) and OT (paired $t = 2.94$, $df = 12$, $p = .01$). Under stress and compared to the HC group, the BPD group showed a trend significant smaller cortisol response after OT ($t = 2.05$, $df = 21$, $p = .06$) but not PL ($t = 0.99$, $df = 21$, $p = .33$).

3.4. Combined sample: influence of trauma, attachment and self-esteem on oxytocin-mediated stress response

The placebo-oxytocin difference in stress-induced dysphoria was significantly predicted by childhood trauma ($F = 5.12$, $R^2 = 0.23$, $df = 1,17$, $p = .04$) and by childhood trauma + self-esteem ($F = 4.41$, $R^2 = 0.36$, $df = 2,17$, $p = .03$); the additional contribution of self-esteem to the prediction was marginally significant (change $R^2 = 0.12$, $p = .10$). Secure and insecure attachment did not contribute to the prediction.

The placebo-oxytocin difference in stress-induced cortisol surge was significantly predicted by insecure attachment alone ($F = 7.55$, $R^2 = 0.30$, $df = 1,18$, $p = .01$). Childhood trauma, secure attachment, and self-esteem did not significantly contribute to the prediction.

Of interest, there was no significant relationship in the combined sample between the dysphoria and the cortisol stress response, for oxytocin ($r = -0.27$, $p = .21$) or for placebo ($r = -0.02$, $p = .92$).

4. Discussion

To our knowledge, this is the first pilot study demonstrating that OT administration affects emotional and neuroendocrine responses to psychosocial stress in BPD. Compared to HC participants, single-dose OT administration in the BPD group resulted in differentially greater attenuation of the dysphoric emotional response to stress, as well as a tendency toward a more dampened cortisol response to stress. Interestingly, childhood trauma was the strongest predictor of oxytocin's effect on the emotional response to stress, possibly mediated in part through its negative impact on self-esteem. On the other hand, insecure attachment was the strongest predictor of oxytocin's effect on the HPA axis response to stress. These diverging relationships, as well as the absence of a relationship between dysphoria and cortisol responses to stress, may suggest that the impact of OT on emotion and HPA axis occur via partly independent neural pathways. Our findings are in

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line with the scant OT literature in relation to trauma and attachment disturbances in adult samples, albeit not in BPD. It was recently shown that in healthy volunteers that a single dose of oxytocin induced a significant increase in a task-based objective measure of attachment security in insecurely attached adults (Buchheim et al., 2009). Two other studies (Heim et al., 2008; Meinslschmidt and Heim, 2007) in adults with major childhood trauma (in which attachment was not examined), reported altered OT sensitivity but did not examine attachment styles.

The present pilot study was limited by its small sample size, which did not allow for the statistical examination of the relationship between comorbid diagnoses and stress reactivity. It is conceivable, for example, that social anxiety or posttraumatic stress symptoms may have in part influenced emotional and hormonal responses to the psychosocial stressor. On the other hand BPD is always highly comorbid with Axis I psychopathology, so the current sample may be more representative of the BPD population at large thus enhancing the generalizability of the findings. In addition, the limited scope of this study did not allow us to control for other sampling factors such as body mass index or menstrual cycle timing, nor to use a comprehensive interview assessment of attachment style. Furthermore, a challenge protocol more directly related to attachment and trauma would also be of particular of interest in this disorder.

Currently available pharmacological treatments for BPD are of modest efficacy and primarily target the symptom clusters of impulsive aggression, affective instability, and psychoticism. Thus, investigation of novel agents that may more directly target stress reactivity is of great interest in BPD, and OT warrants further study in this disorder both in larger and more rigorously controlled challenge studies and in the form of treatment trials.

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Conflict of interest statement

Dr. Hollander has applied for a patent for oxytocin in autism and related conditions. All other authors have no conflicts of interest to declare.

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