Journal of Psychiatric Research 51 (2014) 30–36

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

# Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol

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ARTICLE INFO

*Article history:*
Received 6 August 2013
Received in revised form
5 December 2013
Accepted 17 December 2013

*Keywords:*
Clinical phenotypes
Cortisol
Gender
Major depression
Plasma oxytocin
Psychotic major depression

ABSTRACT

The neuropeptide oxytocin (OT) promotes social behavior and attenuates stress responsivity in mammals. Recent clinical evidence suggests OT concentrations may be dysregulated in major depression. This study extends previous research by testing whether: 1) OT concentrations vary systematically in depressive disorders with and without hypercortisolemia, 2) gender differences in OT concentrations are observed in depressed vs. healthy control participants, and 3) OT concentrations are predictive of clinical phenotypes. Plasma OT concentrations of psychotic major depressive (PMD; $n = 14$: 10 female, 4 male), non-psychotic major depressive (NPMD; $n = 17$: 12 female, 5 male), and non-depressed, healthy control ($n = 19$: 11 female, 8 male) participants were assayed at 2000, 2400, 0400, and 0800 h. Plasma cortisol concentrations were quantified at 2300 h, and clinical phenotypes were determined. As expected, PMD participants, compared to NPMD and healthy control participants, showed higher plasma cortisol concentrations. Although both depressed groups showed similar OT concentrations, a significant interaction effect between group and gender was observed. Specifically, depressed females exhibited lower mean OT concentrations than depressed males. Further, depressed vs. healthy control female participants exhibited lower mean OT concentrations, whereas depressed vs. healthy control male participants showed a trend in the opposite direction. OT concentrations were also predictive of desirability, drug dependence, and compulsivity scores as measured by the Million Clinical Multiaxial Inventory-III. All findings were independent of cortisol. These data suggest that OT signaling may provide a mechanism by which to better understand female-biased risk to develop depressive disorders and that plasma OT concentrations may be a useful biomarker of certain clinical phenotypes.



## 1. Introduction

Individuals with depressive disorders often exhibit social difficulties, anxiety symptoms, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Heuser et al., 1994). A common feature of HPA axis dysregulation is hypercortisolemia, which is present in 40–60% of depressed patients (Gold et al., 1986; Parker et al., 2003). Depressive disorders are also twice as prevalent in female compared to male patients (Nestler et al., 2002; Young, 1998).

The pathophysiology of depressive disorders and enhanced female risk to develop them are not well understood. It has been hypothesized that the neuropeptide oxytocin (OT) may play a role in these phenomena (Frasch et al., 1995). OT is a neuropeptide of hypothalamic origin with broad ranging central and peripheral nervous system effects. OT is released during positive social interactions (Knox and Uvnas-Moberg, 1998; Young et al., 2008), and exhibits anxiolytic properties in preclinical animal models (Amico et al., 2004). OT also exerts a tonic inhibitory influence over the HPA axis (Neumann et al., 2000). However, stressful social experiences, which are frequent precipitants of depressive disorders, activate the HPA axis. Often these experiences involve social isolation or loss, which may decrease OT signaling, thereby diminishing OT's ability to inhibit HPA axis drive. Females may be particularly vulnerable under these stressful circumstances, as they

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0022-3956/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jpsychires.2013.12.012

respond to social rejection (Stroud et al., 2002) and marital conflict (Kiecolt-Glaser et al., 1996, 1998) with greater HPA axis responses compared to men.

Preliminary research has shown that some depressed patients exhibit lower OT concentrations compared to healthy controls and that OT concentrations are lower in patients with moderate compared to mild depression (Frasch et al., 1995; Garcia et al., 2011; Ozsoy et al., 2009). Several pilot studies have concomitantly measured cortisol and OT concentrations in major depressed patients (Garcia et al., 2011; Parker et al., 2010), but no research has evaluated OT concentrations in patients with psychotic major depression (PMD), who typically exhibit greater depressive severity, and who are more likely to exhibit hypercortisolemia than patients with non-psychotic major depression (NPMD) (Belanoff et al., 2001).

In addition to the well-described roles of OT biology in human behavioral functioning, there is emerging evidence that OT concentrations are also associated with an array of clinical phenotypes and personality traits. For example, cerebrospinal fluid (CSF) OT concentrations are associated with a history of aggression (Lee et al., 2009), childhood trauma (Heim et al., 2009), and suicide intentionality (Jokinen et al., 2012). CSF OT concentrations are likewise negatively correlated with anxiety concentrations in patients with major depression (Scantamburlo et al., 2007) and plasma OT concentrations are lower in female patients with borderline personality disorder compared to healthy female controls (Bertsch et al., 2013). Mothers who used cocaine during pregnancy have lower plasma OT concentrations and greater hostility and depressed mood, as well as less social support and fewer adaptive strategies for dealing with stressful life events compared to cocaine naïve mothers (Light et al., 2004). In contrast, higher plasma OT concentrations are associated with measures of positive personality traits including increased extroversion in healthy male and female participants (Andari et al., 2012) and secure attachment and lower compulsive temperament in first-time mothers (Strathearn et al., 2009, 2012). Increased plasma OT concentrations are also associated with secure attachments and lower plasma cortisol and anxiety concentrations in healthy premenopausal women (Tops et al., 2007).

The present study extends previous research efforts in several respects. We measured plasma OT and cortisol concentrations in both male and female PMD, NPMD, and healthy control participants to test whether OT concentrations differ in participants with PMD vs. NPMD, or in depressed participants with and without hypercortisolism (regardless of depressive subtype). We also sought to examine whether female and male depressed participants differed in OT concentrations, and whether cortisol concentrations influenced these differences. Finally, we explored whether OT concentrations were associated with depression severity and anxiety symptomology (Hamilton Depression Rating Scale), as well as personality and clinical syndromes (Million Clinical Multiaxial Inventory-III) in depressed participants.

## 2. Materials and methods

### 2.1. Study participants

Adult participants were recruited through Stanford University Medical Center, as well as through online and print advertisements, as part of a larger research program, which investigates HPA axis physiology in depressive disorders. The present study was initiated after the completion of two recruitment rounds of a larger parent study, and resulted in available samples from 50 participants: 14 PMD (10 female, 4 male), 17 NPMD (12 female, 5 male), and 19 healthy controls (11 female, 8 male). Participants enrolled in the present study did not overlap with those in our previously published OT and depression study (Parker et al., 2010). However, participants' cortisol data have been reported previously (Keller et al., 2006; Schatzberg et al., 2013). This research was conducted in accordance with the Declaration of Helsinki, and the Stanford University Institutional Review Board approved the study design. Informed written consent was obtained from all participants after the study procedures had been fully explained.

All PMD and NPMD participants met DSM-IV-TR criteria for a current major depressive episode, with or without psychotic features and provided Hamilton (1960) Depression Rating Scale (HDRS) scores ranging from severe to very severe depression. PMD participants were required to have a minimum score of 5 on the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). This subscale consists of the following four items: conceptual disorganization, suspiciousness, hallucinations, and unusual thought content. Healthy control participants were required to have a score $<6$ on the HDRS, have no psychotic symptoms as measured by the BPRS positive symptom subscale, and have no history of Axis I disorders as determined by the Structured Clinical Interview for DSM-IV-TR (First et al., 1997). Depressed participants were allowed to remain on psychiatric medications (see Table 1) provided the dose had not been adjusted in the last week. Healthy control participants were free of psychiatric medications. Additional study exclusion criteria for all participants were as follows: electroconvulsive shock therapy or substance abuse problems in the last six months, current drug use (evaluated by urinary toxicology screening), major medical illness, history of seizures, major head trauma, abnormal clinical laboratory tests, unstable or untreated hypertension, cardiovascular disease, endocrine disorders, pregnancy, or lactation.

### 2.2. Blood collection procedures

Participants were admitted to the Stanford University Hospital General Clinical Research Center at 1500 h. At 1600 h, an intravenous line, kept patent with saline infusion, was started in one arm and 4 mL of whole blood was drawn into heparinized vacutainer tubes once every hour between 1800 and 0900 h. Participants were required to be supine in bed 15 min prior to each blood sample collection. No food or sleep restrictions were imposed. Blood samples were subsequently centrifuged and the plasma fraction was stored at $-70$ °C prior to hormone quantification. Blood aliquots were available for OT analyses at four time points (2000, 2400, 0400, and 0800 h).

### 2.3. Plasma hormone quantification

Plasma OT concentrations were quantified using a commercially available enzyme immunoassay kit (Enzo Life Sciences, Inc.,

**Table 1**
Concomitant psychiatric medications for participants with non-psychotic major depression (NPMD) and psychotic major depression (PMD).

| | NPMD ($N = 14$) | PMD ($N = 13$) |
|---|---|---|
| No psychiatric medications | 2 | 8 |
| Antidepressant only | 3 | 4 |
| Antidepressant and antipsychotic | 1 | 0 |
| Antidepressant and anxiolytic | 1 | 1 |
| Antidepressant and mood stabilizer | 0 | 1 |
| Antidepressant, antipsychotic, and anxiolytic | 3 | 0 |
| Antidepressant, antipsychotic, and mood stabilizer | 3 | 0 |
| Antipsychotic and mood stabilizer | 1 | 0 |
| *Breakdown of psychiatric medications* | | |
| Any antidepressant | 10 | 6 |
| Any antipsychotic | 8 | 0 |
| Any anxiolytic | 4 | 1 |
| Any mood stabilizer | 4 | 1 |