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Oxytocin and HPA stress axis reactivity in postpartum women

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Summary
Background: Lactation is thought to buffer stress reactivity via oxytocin (OT). Dysregulation of the HPA axis has been reported in women with postpartum depression (PPD). The co-occurrence of PPD and lactation failure suggests that abnormalities in OT signaling may play a role in PPD. We hypothesized that abnormal OT signaling is implicated in dysregulated HPA axis reactivity among postpartum women with mood symptoms. In a prospective perinatal cohort, we tested associations between OT levels during breastfeeding and stress reactivity.
Methods: We recruited 52 pregnant women who intended to breastfeed, among whom 47 underwent a standardized stressor, the Trier Social Stress Test (TSST), at 8 weeks postpartum. 39 were breastfeeding at time of TSST. We assessed mood symptoms using validated instruments and defined as symptomatic women with EPDS $\geq$ 10 and/or Spielberger $\geq$ 34. Following IV placement for blood draws, women breastfed their infants and then underwent the TSST. Mothers' hormone responses were quantified.
Results: Among symptomatic breastfeeding women ($N = 11$; asymptomatic $N = 28$), we found lower OT levels during breastfeeding ($p < 0.05$) and higher CORT levels ($p < 0.05$) both during breastfeeding and the TSST, as compared to asymptomatic breastfeeding women. In a mixed effects model examining CORT reactivity by symptom group and OT AUC, we observed a paradoxical response in symptomatic breastfeeding women during the TSST (group $\times$ time $\times$ OT AUC $p < 0.05$); higher OT AUC was associated with higher CORT.
Conclusions: In all breastfeeding women, the surge of OT during feeding appears to buffer subsequent stress-induced CORT secretion. However, in symptomatic breastfeeding women, we found a positive correlation between OT AUC and CORT, instead of the expected negative correlation, which we found among asymptomatic women.

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1. Introduction

Postpartum depression (PPD) and early, undesired weaning attributed to lactation dysfunction (disrupted lactation) are two common public health problems following childbirth. PPD is defined by the DSM-5 as a major depressive episode with onset beginning during pregnancy or within the first 4 weeks postpartum (American Psychiatric Association, 2013). PPD affects between 10 and 15% of all mothers and is the greatest risk factor for maternal suicide and infanticide (Lindahl et al., 2005). PPD is often accompanied by severe anxiety or ruminating thoughts (Bernstein et al., 2008; Putnam et al., in press). It has also been shown to significantly compromise mother-infant attachment and impairs maternal implementation of recommended parenting practices that provide a safe and stimulating environment for appropriate child growth and development (Flynn et al., 2004).

Breastfeeding is recommended by all major medical groups for the first year of the child's life to protect the infant from infection and development of chronic diseases; however, early, undesired weaning attributed to problems with lactation physiology remains very common in the US and has been estimated to occur in one out of eight women (Stuebe et al., 2014). In addition to increased child morbidity, early weaning also impacts maternal health, as curtailed breastfeeding is associated with higher maternal rates of ovarian and breast cancers, type 2 diabetes, hypertension and myocardial infarction (AHRQ, 2007). PPD has been associated with undesired weaning including reduced breastfeeding duration and alterations in lactation physiology (Groer and Davis, 2006; Dennis and McQueen, 2009; Figueiredo et al., 2013; Kendall-Tackett et al., 2013; Paul et al., 2013). In a recent report that examined data from the Infant Feeding Practices II Study, early, undesired weaning was more common among women with symptoms of PPD, affecting 56% of women with depressive symptoms at 2 months postpartum, compared with 44% of women without depressive symptoms (Stuebe et al., 2014).

Oxytocin (OT) is a neuroendocrine hormone that is essential for normal breastfeeding physiology, as it stimulates breast myoepithelial cell contraction, which transfers milk to the areola for the infant (Pang and Hartmann, 2007). OT has been implicated in maternal behavior and in forming and maintaining social bonds, particularly in its interaction with dopamine (Pedersen et al., 1994; Pedersen, 1997; Numan et al., 2005; Aragona et al., 2006). In an investigation of lactating rats and maternal behavior, Shahrokh et al. demonstrated a direct effect of OT on dopamine release within the mesocorticolimibic dopamine system; OT neurons in the medial preoptic area (mPOA) were shown to regulate dopamine function in the ventral tegmental area (VTA), thereby determining the rewarding properties of a pup (Shahrokh et al., 2010). It is possible that with improper OT signaling, reward properties are altered, which could lead to changes in maternal behavior and mood.

The literature is small and conflicted regarding OT abnormalities in major depression, with studies showing that OT has different effects on different individuals (Meinlschmidt and Heim, 2007; Cyranowski et al., 2008; Parker et al., 2010; Chen et al., 2011; Mah et al., 2013; Thombs et al., 2014). Genetic variations in the OT receptor have been implicated in PPD and decreased breastfeeding duration (Jonas et al., 2013). Disruption of normal OT physiology has been linked to a dysregulated stress response and poor feeding outcomes in animal models (Lonstein and Stern, 1998). Recent work by our research group suggests that there is a relationship between symptoms of depression and anxiety and differences in OT response and effect during breastfeeding, thereby also implicating possible abnormalities in OT signaling in PPD (Stuebe et al., 2013).

In addition to the possible abnormalities in OT signaling, dysregulation of the hypothalamic pituitary adrenal (HPA) stress axis, including insufficient glucocorticoid signaling and impaired feedback regulation of relevant stress response systems, has been demonstrated in women with PPD (Greenwood and Parker, 1984; Magiakou et al., 1996; Wisner and Stowe, 1997; Bloch et al., 2003; Bloch et al., 2005; Groer and Davis, 2006; Jolley et al., 2007). For example, Jolley et al. studied postpartum women who underwent a physical stressor (maximal treadmill test) and measured mood, ACTH and cortisol (CORT) responses to the stressor. They reported a significant difference in within-subject ACTH levels predicting CORT regression slopes in postpartum women with and without depression at both 6 and 12 weeks postpartum; non-depressed postpartum patients exhibited a normal regulated feedback relationship of the HPA axis, with CORT levels rising in response to increasing levels of ACTH, while depressed postpartum patients exhibited an atypical and dysregulated pattern whereby higher levels of ACTH did not result in increased levels of CORT (Jolley et al., 2007).

Prior work suggests that breastfeeding immediately before a social stressor buffers CORT response (Heinrichs et al., 2001). In male subjects, both OT and social support blunt HPA axis activation (Heinrichs et al., 2003). To date, no studies to our knowledge have quantified the relationship between the HPA axis, OT, and PPD symptoms. Thus, in the present study, we sought to assess the relationship between OT and HPA reactivity in breastfeeding women with and without postpartum depression symptoms. A well validated measurement of HPA stress reactivity is the Trier Social Stress Test (TSST), introduced by Kirschbaum et al. (1993) as a standardized protocol for inducing and studying the psychosocial stress response and dysregulation of the HPA axis in the laboratory setting (Kirschbaum et al., 1993). The TSST has been shown to reliably induce a well-characterized HPA axis response (Kudielka et al., 2007). Therefore, we administered the TSST to symptomatic and asymptomatic lactating mothers. We hypothesized that the TSST would induce a differential stress response in mothers with symptoms of depression and anxiety versus euthymic mothers. We further hypothesized that the dysregulation of HPA stress reactivity in women with PPD may reflect deficient OT signaling, which could be assessed under breast feeding-induced stimulation and which might be reflected by the loss of expected associations between OT and CORT in women with PPD symptoms.

2. Materials and methods

We recruited women in the third trimester of pregnancy who intended to breastfeed for a longitudinal study of