Published in final edited form as:

Brain Res. 2014 September 11; 0: 219–232. doi:10.1016/j.brainres.2013.11.009.

Oxytocin and Postpartum Depression: Delivering on What's Known and What's Not

Sohye Kim^{a,b,c}, Timothy A. Soeken^a, Sara J. Cromer^a, Sheila R. Martinez^{a,b}, Leah R. Hardy^{a,b}, and Lane Strathearn^{a,b,c,d,*}

^aBaylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

^bAttachment and Neurodevelopment Laboratory, Children's Nutrition Research Center, Department of Pediatrics, 1100 Bates Street, Suite 4004, Houston, TX 77030, USA

^cMenninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

^dThe Meyer Center for Developmental Pediatrics, Texas Children's Hospital, 8080 N. Stadium Drive, Houston, TX 77054

Abstract

The role of oxytocin in the treatment of postpartum depression has been a topic of growing interest. This subject carries important implications, given that postpartum depression can have detrimental effects on both the mother and her infant, with lifelong consequences for infant socioemotional and cognitive development. In recent years, oxytocin has received attention for its potential role in many neuropsychiatric conditions beyond its well-described functions in childbirth and lactation. In the present review, we present available data on the clinical characteristics and neuroendocrine foundations of postpartum depression. We outline current treatment modalities and their limitations, and proceed to evaluate the potential role of oxytocin in the treatment of postpartum depression. The aim of the present review is twofold: a) to bring together evidence from animal and human research concerning the role of oxytocin in postpartum depression, and b) to highlight areas that deserve further research in order to bring a fuller understanding of oxytocin's therapeutic potential.

Keywords

postpartum depression; oxytocin; treatment; maternal caregiving; infant

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*Corresponding Author: Dr. Lane Strathearn, MBBS FRACP PhD, Baylor College of Medicine/Texas Children's Hospital, Department of Pediatrics, Attachment and Neurodevelopment Laboratory, Children's Nutrition Research Center, 1100 Bates St, Suite 4004-B, Houston, TX, 77030, USA, Tel: +1 713 798 0351, lanes@bcm.edu.

Conflict of Interest: The authors declare no competing financial interests.

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1. Introduction

Postpartum depression (PPD) is a debilitating disorder affecting at least one in seven American women annually (Gaynes et al., 2005). PPD impairs the mother's capacity for adaptation following childbirth, posing numerous challenges to the mother-infant relationship and the infant's subsequent development (Murray and Cooper, 1997). Despite the increased attention given to PPD over the past several decades, PPD is currently conceptualized and treated in much the same manner as non-postpartum depression, often leading to less than optimal treatment outcomes. In a separate but related line of research, a substantial interest has centered around oxytocin (OT), a neuropeptide hormone critically implicated in the transition to and adjustment during early motherhood. The past two decades have witnessed a surge of clinical trials evaluating OT's therapeutic potential in a wide range of psychiatric disorders, and increasing attention is now directed to PPD as another clinical syndrome for which OT may be of therapeutic benefit. In the present review, we draw upon available data from animal and human research to critically evaluate the potential role of OT in treating PPD. Our goal is to bring together relevant evidence that may elucidate the potential of OT as a therapeutic agent for PPD, while highlighting areas where further research is necessary.

2. Postpartum Depression

2.1 Definition and Diagnosis

PPD is defined as the presence of a major depressive episode following childbirth, although there remains controversy regarding the time criterion pertaining to its onset. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV utilized the specifier "*with postpartum onset*" to limit the diagnosis of PPD to depressive episodes manifesting within 4 weeks post delivery (American Psychiatric Association, 2000), while the newly released DSM-5 uses the specifier "*with peripartum onset*" to encompass depressive episodes present during pregnancy (American Psychiatric Association, 2013). In contrast to the DSM, the International Classification of Diseases (ICD)-10 classifies depression "*as associated with the puerperium*" if the onset is within 6 weeks postpartum (World Health Organization, 1992). In the face of a lack of consensus, two large-scale epidemiological studies have demonstrated that women's risk for psychiatric illness increased from childbirth to approximately 3 months postpartum; the risk increased up to 5 months postpartum specifically for depression (Kendell et al., 1987; Munk-Olsen et al., 2006). In consideration of the epidemiological findings and challenges in practical clinical applications, some experts have recommended that the time criterion be extended to 3 to 6 months postpartum (Elliott, 2000; Wisner et al., 2010).

As with non-postpartum depression, depressive symptoms must be present for more than 2 weeks to warrant the diagnosis of PPD. Common symptoms include depressed mood, loss of interest and energy, changes in sleep or eating patterns, diminished ability to think or concentrate, feelings of worthlessness, and recurrent suicidal ideations. While not currently a part of diagnostic criteria, anxiety is considered a prominent feature of PPD, present in approximately half of women diagnosed with PPD (Ross et al., 2003). In severe cases, PPD

can be accompanied by psychotic features which may include delusions or command hallucinations to harm the infant (American Psychiatric Association, 2013).

2.2. Prevalence and Risk Factors

Prevalence estimates of PPD range widely from 5 to 25 % (Gavin et al., 2005), primarily due to the variability in the criteria used, particularly the time criterion. However, findings from meta-analytic and systematic reviews converge to point to a more precise estimate of 10 to 15 % (Gaynes et al., 2005; O'Hara and Swain, 1996), translating to approximately 600,000 women in the United States annually. This is distinguished from the postpartum blues, a mild and transient mood disturbance following childbirth, commonly experienced by up to 80% of postpartum women (Beck, 2006; Buttner et al., 2012). The risk of PPD increases with a history of prenatal depression, prenatal anxiety, or PPD (Beck, 2001; Robertson et al., 2004; Wisner and Wheeler, 1994). Stressors during pregnancy and the early postpartum, including perinatal complications, preterm birth, or infant health problems (Blom et al., 2010; Robertson et al., 2004; Sit and Wisner, 2009), also serve to increase the risk of PPD, as do poverty, low social support, and adolescent motherhood (Beck, 2001; O'Hara and Swain, 1996; Robertson et al., 2004; Troutman and Cutrona, 1990; Wang et al., 2011). PPD lasts for more than 7 months in over half of affected women (Sit and Wisner, 2009).

While studies have demonstrated a high heritability of depressive disorders (Sullivan et al., 2000), evidence is less conclusive concerning PPD (Corwin et al., 2010). The only published twin study of PPD is one by Treloar et al. (1999), who demonstrated that genetic factors accounted for 25% of variance in the onset of PPD in 838 Australian female twin pairs. Three family studies exist to date and suggest that the rate of PPD increases in female siblings of women with unipolar (Forty et al., 2006; Murphy-Eberenz et al., 2006) or bipolar depression (Payne et al., 2008). Although informative, these few studies have been criticized by some for methodological shortcomings (e.g., failure to distinguish between PPD and postpartum blues or to control for other psychiatric comorbidity; Corwin et al., 2010), particularly in light of the lack of association shown by other groups between a woman's familial history of depression and her development of PPD (Bloch et al., 2005; Dennis et al., 2004). Studies of genetic markers have also been underway and have highlighted the role of the polymorphisms of three candidate genes, the serotonin transporter, monoamine oxidase A, and catechol-O-methyltransferase genes (Doornbos et al., 2009; Sanjuan et al., 2008), although complex genetic and epigenetic interactions remain to be explored.

2.3. Neuroendocrine Considerations

Elucidating the neuroendocrinology of PPD has been a challenge in the field due to normative and adaptive neuroendocrine changes that take place during pregnancy and postpartum. Gonadal steroid hormones have received attention, as levels of estradiol and progesterone drop drastically following parturition, often coinciding with the onset of postpartum blues or PPD symptoms. A noteworthy study by Bloch et al. (2000) found that the simulation of gonadal withdrawal precipitated depressive symptoms in euthymic women with a history of PPD, supporting the potential contribution of hypogonadism to the onset of PPD. However, the relationship between hypogonadism and PPD has been disputed by

many others (Abou-Saleh et al., 1998; Harris et al., 1996; Klier et al., 2007; Zonana and Gorman, 2005). Currently, there is no consistent evidence that a decrease in absolute concentrations of gonadal hormones triggers PPD, although available data suggest that PPD may manifest in women who are vulnerable to fluctuations in gonadal hormone levels (Workman et al., 2012).

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has also garnered interest for its potential role in the etiology of PPD. The HPA system undergoes numerous changes during pregnancy and postpartum (Lightman et al., 2001; Tu et al., 2006). Adreno-corticotrophic hormone levels increase during pregnancy, and cortisol reaches its peak at the end of pregnancy as the placental corticotropin-releasing hormone (CRH) levels rise, before dropping rapidly at parturition (Kammerer et al., 2006; Yim et al., 2009). There have been reports that women with PPD demonstrate more extreme changes in the activity of the HPA axis during pregnancy and postpartum (Jolley et al., 2007; Taylor et al., 2009), though directionality has been inconsistent, with increased (Lommatzsch et al., 2006; Okano and Nomura, 1992) or decreased cortisol levels being documented (Groer and Morgan, 2007; Jolley et al., 2007). Indeed, some have proposed that different subtypes of PPD may exist, underpinned by distinct genetic predispositions and differential regulation patterns (i.e., hypo- vs. hyper-regulation) of the HPA axis (Kammerer et al., 2006).

OT has received less interest than gonadal or stress hormones as a potential etiologic factor in PPD, although it has attracted attention for its involvement in breastfeeding difficulties often present in PPD (Stuebe et al., 2012). It is well known that OT is critically implicated in milk letdown (Pang and Hartmann, 2007). The documented association between breastfeeding difficulties and PPD (Dennis and McQueen, 2009; Taveras et al., 2003; Watkins et al., 2011) is worthy of attention (Skalkidou et al., 2012). To date, only one study (Stuebe et al., 2013) has examined OT as part of the link between lactation failure and PPD. In a group of mothers intending to breastfeed, the authors found that OT levels were inversely correlated with depressive symptoms in both the third trimester and at 8 weeks postpartum, corroborating and extending earlier findings by Skrundz et al. (2011). The authors also documented that OT release was reduced in depressed mothers during breastfeeding compared to non-depressed mothers, although no difference was found between the two groups in breastfeeding duration or intensity. Stress-attenuating effects of breastfeeding deserve consideration here (Heinrichs et al., 2001; Stuebe et al., 2012). Compared to their non-breastfeeding counterparts, breastfeeding women demonstrated attenuated HPA response to stressors (Altemus et al., 1995). Furthermore, cortisol levels decreased in breastfeeding women during lactation (Amico et al., 1994), while mood scores improved following lactation (Heinrichs et al., 2001). Animal models (Neumann, 2003) have suggested that disruptions of the OT system may be implicated in the observed relations between breastfeeding, stress regulation, and mood, which is of particular relevance to PPD given that all three components become disrupted in many affected women (Heinrichs et al., 2001; Stuebe et al., 2012).

3. Maternal Caregiving in Postpartum Depression

PPD is well known to have deleterious effects on the development of the offspring. Reports show that children of depressed mothers are at risk for a wide range of cognitive, emotional, behavioral, and medical problems. Cognitively, they are likely to have lower IQ scores, attention problems, and special educational needs (Hay et al., 2001). Emotionally, they are susceptible to various forms of psychopathology including mood disorders, anxiety disorders, and substance use disorders (Apter-Levy et al., 2013; Murray et al., 2011; Schwartz et al., 1990). Behavioral problems are also prevalent, at times warranting the diagnoses of conduct disorder or oppositional defiant disorder (Alpern and Lyons-Ruth, 1993; Dawson et al., 2003). They are also often high utilizers of pediatric emergency services, while frequently missing outpatient pediatric visits (Flynn et al., 2004). Many of these adverse developmental outcomes have been associated with impaired maternal caregiving behavior in depression, even after controlling for the effects of demographic variables (Azak and Raeder, 2013; NICHD Early Child Care Research Network, 1999).

A large number of studies have highlighted that mothers with PPD are slow to read, decipher, and respond to their infants' signals (see reviews, Field, 2010; Tronick and Reck, 2009). While some depressed mothers are withdrawn, passive, and under-stimulating, others are intrusive, hostile, and over-stimulating (Lovejoy et al., 2000; Malphurs et al., 1996; Weikum et al., 2013). This provides infants with fewer and shorter moments of reciprocal engagement, joint attention, and shared affect (Feldman, 2007; Weinberg and Tronick, 1998). Infants are also given fewer opportunities to experience repair following moments of disrupted engagement (Jameson et al., 1997). Such disruptions in the early mother-infant relationship may serve as a precursor to insecure infant attachment (Mills-Koonce et al., 2008; Stern, 1995), which has longitudinally been linked to numerous adverse developmental outcomes (Sroufe et al., 2005), including the cognitive, emotional, and behavioral outcomes described above. One recent study (Laurent and Ablow, 2013) documented that maternal brain responses were altered in women with PPD. While viewing images of their own infants, mothers with PPD displayed blunted activity in brain regions known to be central for emotional responsiveness, empathy, and reward (e.g., anterior cingulate, orbitofrontal cortex, insula, and striatum).

Frequently, the impaired mother-infant relationship is further compromised by breastfeeding difficulties often experienced in women with PPD. While breastfeeding provides one of the earliest opportunities for the mother to establish an intimate bond with her infant, many depressed mothers report dissatisfaction with breastfeeding (Dennis and McQueen, 2007) and discontinue breastfeeding between 4 to 16 weeks postpartum (McLearn et al., 2006; Paulson et al., 2006).

4. Current Treatment of Postpartum Depression

4.1. Pharmacotherapy

4.1.1. Antidepressant medication—PPD is currently treated in much the same manner as non-postpartum depression, with selective serotonin reuptake inhibitors (SSRIs) as the first-line of pharmacotherapy. As in non-postpartum depression (Cipriani et al., 2007),

SSRIs are efficacious in targeting depressive symptoms in PPD. A review of available randomized controlled clinical trials show that SSRIs improved mood in 43% to 88% of women with PPD (Appleby et al., 1997; Bloch et al., 2012; Misri et al., 2004; Sharp et al., 2010; Wisner et al., 2006; Yonkers et al., 2008), which are similar to rates reported for non-postpartum depression (Kirsch et al., 2008); 37% to 65% of treated women achieved remission of depressive symptoms (De Crescenzo et al., 2013). Despite the demonstrated efficacy, factors unique to pregnancy and the postpartum period complicate the antidepressant treatment of PPD (Ellfolk and Malm, 2010; Yonkers et al., 2009). Many healthcare providers are reluctant to engage patients in pharmacotherapy due to concerns about fetal or infant exposure to antidepressants, and three-quarters of women diagnosed with PPD are indeed left untreated (Bennett et al., 2004). Pregnant or postpartum women similarly show low acceptability of antidepressant medications (Chabrol et al., 2004), with available SSRI trials reflecting high drop-out rates (Appleby et al., 1997; Wisner et al., 2006; Yonkers et al., 2008). Medications may also be prescribed and used at sub-therapeutic doses (Bennett et al., 2004; Epperson et al., 2003), which may be a particular concern since women with PPD require higher doses of antidepressant agents for a longer duration to experience relief of symptoms (Dawes and Chowienczyk, 2001; Hendrick et al., 2000).

Data on the effects of antidepressant treatment on maternal functioning are limited. Only one group (Logsdon et al., 2009; Logsdon et al., 2011) has provided relevant data, demonstrating that antidepressants were effective in enhancing maternal role-gratification throughout the first postpartum year, but not maternal self-efficacy, overall maternal role functioning, or the quality of the mother-infant relationship. The literature on fetal or infant exposure to SSRIs is large and growing. As per a recently published report from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG; Yonkers et al., 2009), the accumulated data are in support of small but significant associations between SSRI use during pregnancy and preterm delivery (i.e., < 37 weeks gestation) as well as small-for-gestational-age birth weight (i.e., < 10% of age-adjusted birth weight). Antidepressant use was generally not associated with major congenital malformations in the infant, although use during the third trimester was linked to transient poor neonatal outcomes (e.g., irritability, jitteriness).

4.1.2. Hormonal therapy—Estradiol therapy is a novel treatment that targets the flux of gonadal hormones that may render a subset of women vulnerable to depression in the postpartum period (Bloch et al., 2000; Moses-Kolko et al., 2009). Growing data suggest that estradiol therapy has promising antidepressant properties, with reported response and remission rates exceeding those of SSRIs. Within the first month of a double-blinded, placebo-controlled trial (Gregoire et al., 1996), women treated with estrogen patches showed greater and more rapid improvements in their depressive symptoms compared to those treated with placebo patches. Similar improvements were shown in another study (Ahokas et al., 2001), in which 83% of severely depressed women reached remission within 2 weeks of treatment with sublingual estradiol. Notably, decreases in women's depression scores were inversely correlated with increases in their serum estrogen levels, and available data suggest that estradiol therapy was well tolerated with low dropout rates. However, estradiol therapy may interfere with breastfeeding, a consideration important in the treatment of PPD

(Fitelson et al., 2010; Moses-Kolko et al., 2009). Although early data suggested that synthetic progestones may be therapeutic for PPD, this view has since been challenged and the use of progestones is not recommended (Dennis et al., 2008). Currently, no data exist on the effects of hormonal therapy on maternal behavior.

4.2. Psychological Interventions

Psychological interventions that have been empirically studied for the treatment of PPD include interpersonal psychotherapy (IPT; Grote et al., 2009; Mulcahy et al., 2010), cognitive behavioral therapy (CBT; Chabrol et al., 2002; Wiklund et al., 2010), psychodynamic therapy (Bloch et al., 2012; Cooper et al., 2003), and non-directive counseling (Milgrom et al., 2005; Murray et al., 2003). Several meta-analyses exist to date and suggest that psychological interventions are efficacious in reducing depressive symptoms (Cuijpers et al., 2008; Dennis and Hodnett, 2007; Lumley et al., 2004; Sockol et al., 2011) at rates similar to those of antidepressant medications (De Crescenzo et al., 2013; Sockol et al., 2011). No conclusive data exist to suggest the superiority of one psychotherapy modality to another in the treatment of PPD (Fitelson et al., 2010), although there is some evidence that IPT, which directly addresses interpersonal problems (e.g., role transitions, relational conflicts), may be more efficacious than CBT, which targets maladaptive depressogenic cognitions (Bledsoe and Grote, 2006; Sockol et al., 2011).

However, as with pharmacotherapy, a mere decrease in depressive symptoms is often not enough to enhance maternal functions (Forman et al., 2007; Murray et al., 2003). Psychological interventions without an explicit focus on the mother-infant relationship were effective in reducing maternal parenting stress, without benefiting maternal or infant behavior (Forman et al., 2007; O'Hara et al., 2000). Interventions that actively incorporated the mother-infant relationship as a focus generally yielded some improvement in this domain (Clark et al., 2003; O'Hara and McCabe, 2013; Poobalan et al., 2007). However, therapeutic gains were not sustained on longitudinal follow-ups and did not generalize to infants' cognitive or behavioral outcomes, with the exception of one study in which extensive and prolonged therapy was implemented (Cicchetti et al., 2000).

Current APA and AGOC guidelines recommend psychotherapy as the first-line of treatment for mild to moderate depression, although antidepressant medications are recommended in the presence of moderate to severe depressive symptoms, particularly in women with a history of recurrent depression (Kim et al., 2010; Yonkers et al., 2009). The acceptability of psychotherapy is reported to be high in postpartum women (Chabrol et al., 2004) and psychotherapy is often preferred to antidepressants in this population (Pearlstein et al., 2006; Turner et al., 2008).

5. Oxytocin: A Novel Therapeutic for Postpartum Depression?

As the preceding review suggests, currently available treatments of PPD are promising in reducing depressive symptoms, but are less effective in improving the mother-infant relationship. OT has emerged as a potentially viable treatment option in this context, given its role in regulating the onset and maintenance of maternal behavior, along with its antidepressant and anxiolytic properties.

OT is a nonapeptide synthesized in magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei of the hypothalamus and released into the bloodstream from the neurohypophysis (Gimpl and Fahrenholz, 2001; Insel, 2010). OT receptors are located throughout the brain including regions known to be critical for the expression of maternal behaviors, such as the ventromedial nucleus of the hypothalamus, central nucleus of the amygdala, medial preoptic area (MPOA), bed nucleus of the stria terminalis (BNST), and ventral tegmental area (VTA). OT is also secreted in small amounts by numerous peripheral tissues such as the uterus, placenta, corpus luteum, testis, and heart (Gimpl and Fahrenholz, 2001). For many decades, OT was well recognized for its peripheral actions, including uterine contraction in parturition and milk ejection during lactation (Insel, 2010; Ross and Young, 2009), though it is now regarded a key neuroregulator implicated in social and stress-related disorders on one hand and maternal behavior on the other (Bartz and Hollander, 2006; Neumann and Landgraf, 2012). To assist in evaluating the potential of OT as a therapeutic agent for PPD, we examine available animal and human research on the role of OT in a) anxiety- and depressive-like behavior and in b) maternal functioning.

5.1. Antidepressant and Anxiolytic Effects of Oxytocin

5.1.1. Animal studies—An antidepressant effect of OT was first reported by Arletti and Bertolini (1987), who demonstrated that acute and repeated intra-peritoneal injections of OT in mice reduced the immobility time in the forced swim test, a commonly used index of depressive behavior in animals. Similarly, subcutaneous OT infusions in rats reduced the escape failures in the learned helplessness test, another widely used animal model of depression (Nowakowska et al., 2002). Recently, these results were replicated following intracerebral administrations of OT (Ring et al., 2010), suggesting that central or peripheral administrations of OT may have anti-depressant properties (Slattery and Neumann, 2010b). In rats, OT has also been shown to improve other features of depression (Neumann and Landgraf, 2012), including anhedonia (Liberzon et al., 1997), sexual dysfunction (Melis et al., 2007), and sleep disturbance (Lancel et al., 2003).

Anxiolytic and stress-attenuating effects of OT have also been well documented. Anxiogenic stimuli are understood to increase central OT release in the PVN of the hypothalamus (Nishioka et al., 1998), central nucleus of the amygdala (Ebner et al., 2005), and lateral septum (Ebner et al., 2000), which subsequently functions to dampen stress response by modulating the activity of the HPA axis (Engelmann et al., 2004; Neumann et al., 2000). OT knockout mice showed increased stress-induced fos expression in the medial amygdala and BNST, heightened CRH mRNA expression in the PVN, and elevated corticosterone release following exposure to stressors (Amico et al., 2008; Nomura et al., 2003). Furthermore, intracerebroventricular infusions of OT decreased the molecular and neuroendocrine responses of the HPA axis and attenuated anxiety-like behaviors in female rats, while administration of the OT receptor antagonist produced opposite results (Slattery and Neumann, 2010a; Windle et al., 2004).

While mechanisms of the antidepressant and anxiolytic effects of OT remain to be further elucidated, available evidence suggests that the effects may be produced in part by the interactions between the serotonergic, corticotropin-releasing factor (CRF), and OT systems

(Neumann and Landgraf, 2012). OT release is understood to activate OT receptors in serotonergic neurons of the raphe nuclei to yield antidepressant and anxiolytic effects (Yoshida et al., 2009), whereas stimulation of serotonin release activates CRF and OT neurons in the hypothalamus (Javed et al., 1999), a mechanism that may underlie antidepressant properties of the SSRIs (Emiliano et al., 2007).

5.1.2. Human studies—OT-related dysfunctions have been examined in depressed patients, although results remain inconclusive. Some groups have shown that peripheral OT concentrations were lower in depressed patients, particularly female patients (Ozsoy et al., 2009), compared to controls (Frasch et al., 1995; Zetsche et al., 1996). Another report showed that the severity of patients' depression and anxiety symptoms was inversely correlated with their plasma OT levels (Scantamburlo et al., 2007). However, other studies of plasma OT (Cyranowski et al., 2008; van Londen et al., 1997) and a few available studies of cerebrospinal fluid (CSF) OT (Demitrack and Gold, 1988; Pitts et al., 1995) failed to document reduced OT levels in depressed patients. Notably, these studies found a greater variability of OT concentrations in the patient group (Cyranowski et al., 2008; van Londen et al., 1997); in one study, a trend toward reduced OT was found only in a subgroup of patients (Pitts et al., 1995).

Endogenous OT released during breastfeeding (Chiodera et al., 1991) has been understood to underlie the attenuated HPA responsiveness and reduced anxiety behavior shown in lactating women (Heinrichs et al., 2001). However, exogenous OT administrations in humans have produced equivocal findings. Intranasal OT was reported to decrease stress responsiveness and anxiety in healthy men (Heinrichs et al., 2003), reduce levels of salivary cortisol during couple conflict in heterosexual couples (Ditzen et al., 2009), and attenuate fear-related amygdala reactivity in healthy males and patients with social anxiety (Kirsch et al., 2005; Labuschagne et al., 2010). However, these studies failed to document direct effect of intranasal OT on mood (Kirsch et al., 2005; Labuschagne et al., 2010). Furthermore, while the majority of the studies were conducted in men, intranasal OT was shown to enhance fear-related amygdala reactivity in healthy women (Domes et al., 2010; but see Rupp et al., 2012 for results in nulliparous women only), while producing null effects in healthy postpartum women (Rupp et al., 2012). Notably, the only available study on PPD demonstrated that intranasal OT worsened self-reported mood ratings in this group of women (Mah et al., 2013). A study observing the use of OT to aid the progress of labor further showed that OT administration during labor did not reduce the incidence of PPD in first-time mothers (Hinshaw et al., 2008).

5.2. Oxytocin and Maternal Behavior

5.2.1. Animal studies—A large body of research supports the role of OT in the onset and maintenance of maternal behavior across species. Intracerebroventricular injections of OT induced a full range of maternal behavior in female virgin rats (Pedersen and Prange, 1979; Pedersen et al., 1982), whereas infusions of OT antagonist inhibited the emergence of maternal behavior in parturient rat dams (Pedersen et al., 1994; van Leengoed et al., 1987). Similar results were found in mice (McCarthy, 1990) and sheep (Kendrick et al., 1987; Keverne and Kendrick, 1992). These findings are in line with the report that lesions of the

PVN, a main site of OT production in the brain, disrupted the onset of maternal behavior in rats (Insel and Harbaugh, 1989). Impaired maternal behavior was similarly found in female OT knockout mice (Ragnauth et al., 2005; Takayanagi et al., 2005) and postpartum mutant female mice with reduced OT neurons in the PVN (Li et al., 1999). Other prominent sites of OT receptors have also been examined in relation to the expression of maternal behavior. OT receptor density in the central nucleus of the amygdala and BNST was shown to be correlated with the quality of maternal care in rats (Francis et al., 2000); OT receptor binding density in the nucleus accumbens was similarly associated with the amount of time prairie voles spent crouching over pups (Olazabal and Young, 2006).

Another important line of research in this area concerns the modification of the OT system by early caregiving experiences (Champagne, 2008; Meaney, 2001). A series of experimental and cross-fostering studies demonstrated that female rats reared by low licking-and-grooming and arched-back nursing (LG-ABN) mothers showed a reduced density of OT receptors in brain regions critical for the expression of maternal behavior, including the MPOA, PVN, and lateral septum (Champagne et al., 2001; Champagne et al., 2003b; Champagne et al., 2006). Just like their mothers, the female rat pups were subsequently seen to display low levels of LG-ABN behavior with their offspring when they reached the postpartum period (Champagne et al., 2003; Francis et al., 1999). Similarly, non-maternal rearing in rhesus monkeys was associated with reduced CSF OT levels across the first three years of life (Winslow et al., 2003).

Studies on OT-related maternal functions are continuing to expand. The current understanding is that OT circuits interact closely with dopaminergic circuits to regulate the expression of maternal behavior (Shahrokh et al., 2010; Strathearn, 2011). OT neurons in the PVN and MPOA of the hypothalamus project to the VTA and nucleus accumbens (Numan and Smith, 1984; Ross et al., 2009a), and the connections and signals between these regions increase with the quality of maternal behavior (Champagne et al., 2004; Shahrokh et al., 2010). The OT-dopamine interactions are thought to mediate the rewarding and reinforcing properties of the mother-infant interaction.

5.2.2. Human studies—Over the past decade, many important advances have been extended from animal models to humans, elucidating the central role of OT in human mothering. Peripheral OT levels in mothers have been consistently associated with naturally occurring variations in maternal behavior, with high OT levels during pregnancy and postpartum predicting enhanced maternal behavior (Atzil et al., 2011; Feldman et al., 2007; Gordon et al., 2010a; Gordon et al., 2010b). Following the work of Meaney (2001) and Champagne (2008), research in this area has underscored the interindividual variability of OT-related functions in mothers. Interactions with infants stimulate OT release in mothers, but only in a subgroup of mothers who demonstrate secure attachment (Strathearn et al., 2009), display sensitivity to emotions and physical sensations (Strathearn et al., 2012), or exhibit synchronous and affectionate forms of mothering (Feldman et al., 2010a; Kim et al., in press). Maternal OT increase during mother-infant interaction has further been correlated with the concurrently measured OT increase in the infant, supporting an intergenerational link between the OT functions of mother and infant in humans (Feldman et al., 2010b). Evidence continues to grow supporting the understanding that women's OT functions may

be modified by their early caregiving experiences. Inverse associations have been reported between women's levels of CSF OT and the severity and duration of abuse and neglect to which they were exposed in childhood (Heim et al., 2009). Studies have further documented low plasma OT levels in individuals who reported receiving low levels of parental care (Feldman et al., 2011; Gordon et al., 2008).

Only a handful of studies have examined the role of OT in maternal brain responses. Strathearn et al. (2009) found that mesocorticolimbic dopaminergic reward regions (i.e., ventral striatum, medial prefrontal cortex) as well as the hypothalamic OT regions were activated when securely attached mothers viewed images of their own infants. Similar results were reported by Atzil et al. (2011), who demonstrated that mothers who displayed synchronous forms of mothering showed activation of the nucleus accumbens, a key reward region, while viewing video clips of their own infants. Notably, activations in these brain regions were correlated with the peripheral measures of OT in these mothers (Atzil et al., 2011; Strathearn et al., 2009). Brain responses of breastfeeding mothers have also attracted attention, given the role of breastfeeding in endogenous OT production (Chiodera et al., 1991). The only pertinent study to date is that by Kim et al. (2011), who found that breastfeeding mothers showed greater activation of the brain regions critical for the expression of maternal behavior, including the striatal reward region, in response to their own infants' cries.

Studies have recently begun to examine the role of exogenous OT administrations in maternal brain responses. Intranasal administrations of OT were shown to increase the incentive salience of an unknown infant's laughter in a group of women, as evidenced by the enhanced connectivity observed between the amygdala and emotion regulation regions (Riem et al., 2012). Conversely, in response to an unknown infant's cry, intranasal OT decreased the women's negative emotional arousal, as reflected by reduced amygdala signals, while increasing activations in the empathy-related regions (Riem et al., 2011). It is important to note that intranasal OT further decreased the women's handgrip force in response to hearing infant's cry, although the effect was present only in women without early experiences of harsh parenting (Bakermans-Kranenburg et al., 2012).

5.3. Oxytocin in the Treatment of Psychopathology

In addition to its role in regulating the expression of maternal behavior as reviewed above, a large body of literature has implicated OT in a much broader range of social behaviors (Benarroch, 2013; Meyer-Lindenberg et al., 2011), including pair bonding (Ross et al., 2009b; Schneiderman et al., 2012), interpersonal trust (Kosfeld et al., 2005; Van IJzendoorn and Bakermans-Kranenburg, 2012), emotion recognition (Lischke et al., 2012; Perry et al., 2013), and empathy (Hurlemann et al., 2010; Rodrigues et al., 2009), to name a few. Due to its seemingly widespread prosocial effects, along with its antidepressant and anxiolytic properties, OT has gained widespread popularity over the past decade in the study of normative and psychiatric populations. A sizable number of trials have investigated its therapeutic potential in many psychiatric disorders, and many more trials are underway. To date, clinical trials in which OT has demonstrated therapeutic benefit over placebo include those of autism spectrum disorder (Anagnostou et al., 2012; Andari et al., 2010; Guastella et

al., 2010), schizophrenia (Averbeck et al., 2011; Feifel et al., 2010; Modabbernia et al., 2013; Pedersen et al., 2011), social anxiety (Guastella et al., 2009; Labuschagne et al., 2010), and post-traumatic stress disorder (Yatzkar and Klein, 2009).

Despite the considerable excitement that these results have generated, a more complicated and nuanced picture emerges upon careful examination of the available data. Effects of OT reported in many social domains (e.g., social cognition, prosociality) are often inconsistent or, more precisely, are moderated by contextual and personal factors (Bartz et al., 2011b; Guastella and MacLeod, 2012; Macdonald and Macdonald, 2010). The context-dependent nature of the effects of OT is well demonstrated in a series of studies conducted on trust, in which exogenous administrations of OT increased participants' trust of individuals perceived as part of the in-group, but increased non-cooperation toward out-group members who were perceived as potential threats (De Dreu et al., 2010; De Dreu et al., 2012). The person-dependent nature of the effects of OT is well captured in a growing number of studies that demonstrate null effects of exogenous OT in individuals with adverse early caregiving experiences, whether assessed by reported severity of childhood abuse, neglect, or loss (Meinlschmidt and Heim, 2007), memories of parental love-withdrawal (Riem et al., 2013; van IJzendoorn et al., 2011), or recollections of harsh parenting experiences (Bakermans-Kranenburg et al., 2012). Considering that the development of one's OT system is critically modified by the quality of early caregiving one receives (Champagne, 2008; Meaney, 2001), it is possible that the OT system may have been altered at a more fundamental level, possibly at the level of receptors, in individuals with early adverse experiences. The resulting alterations in OT receptor density, affinity, or functions may underlie the decreased responsivity that is seen in these individuals upon exogenous administrations of OT (Bakermans-Kranenburg and van IJzendoorn, 2013).

This is of particular relevance in considering the use of OT in psychiatric patients, since early adverse experiences are rather common in this population. Not surprisingly, a review of data suggests that psychiatric patients have produced variable results in response to exogenous OT administrations, ranging from improvement (Guastella et al., 2010; Pedersen et al., 2011) to worsening of symptoms (Bartz et al., 2011a; Mah et al., 2013), along with some null findings (Epperson et al., 1996; Pitman et al., 1993). In some cases, exogenous administrations of OT have yielded opposing patterns of results for psychiatric and healthy groups (e.g., Bartz et al., 2011a; Pincus et al., 2010). This divergence is well reflected in the results of recent meta-analyses of available clinical trials, which demonstrated that, when taken together, exogenous OT administrations did not improve symptoms of psychiatric disorders with the exception of autism spectrum disorder, although weak to moderate beneficial effects were found for healthy controls (Bakermans-Kranenburg and van IJzendoorn, 2013). While meta-analytic results are discouraging, more research is necessary given that the number of clinical trials available for the meta-analyses were small for many psychiatric conditions.

5.4. Can Exogenous Oxytocin Benefit the Treatment of Postpartum Depression?

While data from animal models suggest that OT may have potential in the treatment of PPD, the future of exogenous OT in human psychiatric disorders remains unclear. To date, limited

data exist on the antidepressant or anxiolytic effects of exogenous OT in women, and a small number of available studies have demonstrated null (Rupp et al., 2012) or negative results (Domes et al., 2010; Mah et al., 2013). The role of exogenous OT in human mothering has received more direct support (Riem et al., 2011; Riem et al., 2012), although growing evidence suggests that its effects are critically moderated by women's early caregiving experiences (Bakermans-Kranenburg et al., 2012). While we are cautiously optimistic about OT's therapeutic potential, we believe that there are many questions that remain to be answered. Here, we highlight some of these remaining questions for future research.

First, it would be of great importance to identify individual differences among PPD patients that may moderate the effects of exogenous OT. PPD patients are likely a heterogeneous group of individuals demonstrating a large variability in OT receptor function, endogenous OT production, and early caregiving experiences. As these factors are understood to alter one's responsivity to exogenous OT, careful investigation of these intraindividual characteristics and identification of relevant neurobiological and behavioral markers are of paramount interest. Given the pattern of results reviewed, it is possible that exogenous OT may yield beneficial effects only in a subgroup of PPD patients. Such results may not be apparent and may even be obscured in between-group designs, where effects are averaged across individuals and within-group individual differences are overlooked (Guastella and MacLeod, 2012). We concur with others (e.g., Guastella and MacLeod, 2012) that the imperative next step in OT translational research is to develop cognitive, behavioral, and neurobiological markers that can index the degree to which patients may be responsive to exogenous administrations of OT.

Second, gender is an important consideration given the differences in the endogenous OT levels between men and women. Furthermore, gonadal hormones, estrogen in particular, are understood to be critically involved in the regulation of OT, whether endogenously produced or exogenously administered. It is in this regard that a relative dearth of clinical trials in women is particularly problematic. It is not yet clear to what degree the extant findings obtained in men can be generalized to women, and particularly to postpartum women who undergo significant hormonal changes. It is also unclear how, and to what extent, menstrual cycle and accompanying fluctuations in gonadal hormones moderate the effects of exogenously administered OT and contribute to divergent results (e.g., see Domes et al., 2010 vs. Rupp et al., 2012). It is important that future studies recruit female participants, and specifically postpartum women, to examine the effects of OT in this unique population.

Third, for therapeutic use of exogenous OT, it would be important to systematically address questions of dosage, timing, and side effects associated with long-term administration. All clinical trials to date have used low doses (18 to 40 IU) for a short span of time, with minimal reported side effects (MacDonald et al., 2011). Future research should examine the safety of high-dose long-term use of OT. It would be critical to understand how chronic exogenous administrations of OT may affect endogenous OT production as well as complex neuroendocrine functions in the postpartum period.

Fourth, it remains to be determined whether exogenous OT should be used as a stand-alone treatment or should better be integrated with other therapies. Most available clinical trials have excluded patients undergoing medication treatment, and there is currently limited data from which to draw conclusions about the safety and efficacy of OT as an augmentation agent (MacDonald et al., 2011). Furthermore, anxiolytic and prosocial effects of OT have led some to believe that exogenous OT administrations may help aid the process of psychotherapy. This would be a fruitful area for future investigation.

6. Conclusions

While OT initially appeared to offer much promise, the pattern of results that has thus far emerged is more nuanced and inconsistent than it appeared to be at first. The literature reviewed in preceding sections suggest that studies are beginning to shed light upon the complex context- and person-dependent nature of OT effects. We propose that future studies attend to individual variations that may be present among mothers with PPD, rather than looking for the uniform effect across all mothers. We underscore that focused studies that tease apart OT-related individual variations are necessary to fully evaluate the therapeutic potential of OT in the treatment of PPD.

Acknowledgments

Funding Sources: This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development [R01HD065819]; and the National Institute on Drug Abuse [R01DA026437]. The content is solely the responsibility of the authors and does not necessarily represent the official views of these institutes or the National Institutes of Health.

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- PPD not only affects the mother but also her relationship with her infant
- Maternal brain response and behavior are compromised in PPD
- OT is implicated in regulation of mood as well as maternal behavior
- OT may be a viable treatment option targeting both depression and maternal behavior
- Future study should address individual variations that moderate the effect of OT