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Prenatal and gestational cocaine exposure: Effects on the oxytocin system and social behavior with implications for addiction

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Abstract

Drug abuse during pregnancy is a major public health concern, with negative consequences throughout development. Prenatal cocaine exposure (PCE) in rats produces social behavior deficits with corresponding changes in neuroendocrine and monoaminergic signaling. The relevance of parental care in social behavior maturity cannot be ignored, and gestational exposure to cocaine severely disrupts parental care, thus impacting the early environment of the offspring. Oxytocin (Oxt) is critical in regulating social behaviors and central levels are disrupted following acute and chronic cocaine (CC) treatment in postpartum rat dams, coincident with deficits in maternal care. We will discuss studies aimed to determine the relative contribution of PCE and CC-induced deficits in maternal care to social behaviors and Oxt signaling across development. PCE results in decreased social (including parental) behaviors in adolescence and adulthood. PCE is also associated with increased aggression in adults. Rearing by CC-exposed mothers synergistically increases the behavioral effects of PCE. Rearing by CC-exposed mothers, but not PCE, disrupts Oxt levels and mRNA in regions relevant to social behavior, but does not affect receptors in postpartum adult offspring. Preliminary work indicates PCE/CC rearing has dynamic effects on Oxt levels and receptors in neonatal rat pups, suggesting very early regulation of Oxt signaling. This work highlights how the interactive role of Oxt signaling and behavioral context throughout development can be derailed by drug abuse during pregnancy. The relevance of disrupted Oxt to intergenerational transmission of addiction is briefly discussed.

Keywords

prenatal cocaine; oxytocin; maternal behavior; aggression; addiction; social behavior

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1. Introduction

1.1 Gestational drug exposure has direct and indirect effects on offspring

Increasing evidence indicates many developmental and long-lasting neurological and behavioral effects following prenatal drug exposure (Williams et al., 2011b; Dow-Edwards, 2011; Lester et al., 1998; Lester and Padbury, 2009). Diverse pharmacological substances are known for their neurobehavioral teratological properties; however, prenatal cocaine exposure (PCE) remains one of the most investigated. In addition to the direct effects of drug exposure on the fetus, drug addiction during pregnancy can disrupt the mother's ability to care optimally for her child, and early dysfunctional maternal-infant interactions may compound negative effects of prenatal drug exposure (Williams et al., 2011b; Rutherford et al., 2011; Dow-Edwards, 2011; Strathearn and Mayes, 2010; Lester et al., 1998; Nephew and Febo, 2012; Lester and Padbury, 2009; Strathearn, 2011). Potential mechanisms that underlie the disruptions observed in women who abuse drugs during pregnancy remain elusive; although mounting evidence suggests the neuropeptide oxytocin (Oxt) may be an important contributor. Thus, the following brief review of relevant studies of cocaine's effects on mothers and offspring, highlighting Oxt as a mediating factor, may serve as a helpful guide for future studies.

1.2 Clinical reports of cocaine-induced disrupted maternal care

Chronic drug use and addiction can lead to disrupted parental care (Rutherford et al., 2011; Solis et al., 2012; Wells, 2009). Cocaine-using women are less engaged, less sensitive to infant cues, and have problems feeding their infants (Burns et al., 1991; Eiden et al., 2006; Tronick et al., 2005; Black et al., 1994; Minnes et al., 2005). Problems can persist with toddlers, with cocaine-using mothers exhibiting less interest and more hostility (Johnson et al., 2002; Suchman et al., 2010). Furthermore, these disruptions have been associated with changes in mood, stress response and lower plasma levels of Oxt (Light et al., 2004). Oxt dysregulation and it's interaction with brain reward and stress systems in mothers has been proposed as a likely moderator of neglectful behavior (Light et al., 2004; Strathearn and Mayes, 2010; Rutherford et al., 2011). Unfortunately, women who abuse cocaine often suffer from mood disorders, alcohol and nicotine use, and low socioeconomic status, which can all independently impact parental caregiving. Unfortunately, these drug-use associated parental behaviors result in children being placed in foster care at a rate 20 times higher than children from non-drug using homes (Eiden et al., 2007). These comorbidities make drawing distinct conclusions about cocaine use on parental care difficult in clinical populations.

1.3 Preclinical reports of cocaine-induced disrupted maternal care

Preclinical rodent studies that control for drug dose and regimen as well as gestational and postpartum environments, have allowed for more precise determination of the effects of cocaine on maternal behavior (MB) (see (Nephew and Febo, 2012) for review). Various cocaine treatment regimens (30 mg/kg; acute, intermittent, or chronic) generally disrupt mother-infant interaction dynamics and increase infant neglect during the early postpartum period in the rodent with the extent of disruption dependent on dose, duration and postpartum day of testing (Nelson et al., 1998a; Johns et al., 1997b). Both acute (AC) and chronic cocaine (CC) treatments increased the latency to begin and decreased duration of nursing, reduced licking and nest-building behaviors, and generally disrupted initiation of MB (Zimmerberg and Gray, 1992; Johns et al., 1994; Vernotica et al., 1996; Kinsley et al., 1994). Effects on MB wane as the postpartum period progresses and there is increasing distance from the cocaine exposure (Johns et al., 2005a; Heyser et al., 1992). CC typically increases postpartum maternal aggression (MA) towards a submissive intruder by postpartum day six (PPD6) (Johns et al., 1994; Lubin et al., 2003; McMurray et al., 2008b). Conversely, AC postpartum treatment reduces MA, leaving pups defenseless during an

intruder session (Nelson et al., 1998a; McMurray et al., 2008b). Many of the effects of cocaine treatment during or following gestation have been associated with Oxt system dysregulation in brain regions relevant to MB and MA in rats (Johns et al., 1997a; Nelson et al., 1998a; Johns et al., 1998; Vernotica et al., 1996; 1999; Lubin et al., 2003). In this review we will briefly describe the role of Oxt and its regulation associated with a number of behaviors that are disrupted by gestational cocaine treatment or exposure, and finally how intergenerational effects of cocaine including effects of prenatal exposure or rearing by a cocaine-exposed mother alters Oxt signaling.

2. Oxytocinergic Modulation of Behavior

2.1 Oxytocin Signaling in Socially-Relevant Neurocircuitry

Oxt processes from the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus project to the pituitary for peripheral release into the bloodstream in response to infant-produced or stressful stimuli (Wotjak et al. 1998). In the rodent, Oxt neurons from the PVN also project centrally throughout the forebrain and receptors are concentrated in the medial preoptic area (MPOA), main olfactory bulb (MOB), nucleus accumbens (NAcc), amygdala (AMY), hippocampus (HIPP), and ventral tegmental area (VTA)(Gimpl and Fahrenholz, 2001). Oxt administration or infant suckling (which substantially increases Oxt release) increases the activity of the these regions in rodents (Febo et al., 2005a), and many of these regions mediate behavioral responses relevant to maternal interactions (Numan, 2007). Similarly, clinical studies in parents have shown increased activity in the hypothalamus, VTA, striatum, and medial prefrontal cortex in response to infant auditory and visual stimuli (Strathearn, 2011).

Recently, Oxt has been proposed to modulate human brain response to infant stimuli similar to that observed in rodents. Plasma Oxt is correlated with infant-stimuli induced increases in maternal hypothalamic and striatal activity measured with functional magnetic resonance imaging (fMRI) (Strathearn et al., 2009; Strathearn, 2011). Oxt administration decreased activation in the amygdala and increased functional connectivity between the amygdala and the orbitofrontal cortex, cingulated cortex and hippocampus in nulliparous women, suggesting an important role for reducing avoidance of infant stimuli in humans (Riem et al., 2012). Interestingly, increased circulating Oxt or Oxt administration to a mother or father can enhance parental care and raise salivary Oxt in infants (Atzil et al., 2012; Weisman et al., 2012; Feldman et al., 2010). Additionally, genetic variability in the Oxt receptor and the CD38 genes have been correlated with lower plasma Oxt and reduced parental sensitivity (Feldman et al., 2012).

2.2 Oxytocin Signaling in Parental Care and Social Behavior

In rodents, the onset (postpartum day (PPD) 1–4) and maintenance periods (PPD 5–21) of MB are differentiated by their underlying hormonal state (Insel et al. 2001). Oxt and Oxt receptor expression is highly plastic during these phases (Caughey et al., 2011). Central and peripheral Oxt play a significant role in the initiation and maintenance of maternal care toward infants, which has been documented previously (Pedersen et al., 1982; 1992; Pedersen and Boccia, 2002; Ross and Young, 2009; Lee et al., 2009; Numan, 2006; Bosch and Neumann, 2011) Pedersen & Prange 1987, Kendrick et al. 1987, Van Leengoed et al. 1987, Lee et al. 2009, Nemsadze & Silagava 2010). Plasma Oxt is essential for milk ejection, uterine contractions and is associated with stress response (Hashimoto et al. 1989, Kalin et al. 1985, Light et al. 2004). In genetically modified mice that lack Oxt peptide or Oxt receptor, pup survival is reduced because of the loss of lactation (Young et al., 1996; Takayanagi et al., 2005). Specific deletion of the Oxt receptor in the forebrain results in increased pup mortality in the early postpartum period, suggesting a role for Oxt in the

initiation of MB (Macbeth et al., 2010). Central levels of Oxt play a critical role in the onset of rat MB and are likely involved in the maintenance of MB, the extent and direction of which is probably dependent on day of testing.

In addition to its role in parental care, Oxt has been studied extensively for its modulatory role in a variety of social behaviors in clinical and preclinical models (Lee et al., 2009; Yamasue et al., 2012; Lukas and Neumann, 2012; Kumsta and Heinrichs, 2012). Generally, greater Oxt signaling, leads to increased positive or affiliative social behaviors, and less offensive aggression. However, many recent studies have begun to more fully characterize the psychological effects and dose-response curves indicating a complex context-dependent function of Oxt in humans (Guastella et al., 2012; Feldman, 2012). Additionally, animal models have begun better define the neuroanatomical specificity for Oxt's actions (Veenema and Neumann, 2007; Ross and Young, 2009; Macbeth et al., 2010; Lee et al., 2008; Pagani et al., 2011; Dhakar et al., 2012). Specifically, a "social behavior network" including the lateral septum, extended amygdala, preoptic area, several nuclei of the hypothalamus, and the monoaminergic nuclei in the midbrain and hindbrain has been highlighted because of high Oxt receptor expression (Albers, 2012).

2.3 Oxytocin and addiction

Oxt has been shown to modulate the negative aspects of addiction, including reductions in acquisition, withdrawal, and relapse-like drug seeking behavior (McGregor and Bowen, 2011; McGregor et al., 2008; Sarnyai, 1999; 2011)(this issue). The complexity of the neuroanatomical and temporal effects of Oxt and interactions with other signaling systems relevant to social and addictive behaviors is still being studied (Slattery and Neumann, 2008; Yoshida et al., 2009; Yanowitch and Coccaro, 2011; Strathearn, 2011). Nonetheless, disruptions in social behavior and stress responsiveness, as well as vulnerability to drug use are increased by PCE and/or disrupted parenting. The transition into parenthood presents many novel and potentially stressful scenarios. Fortunately, Oxt, which dramatically increases during pregnancy and the postpartum period has been noted to modulate anxiety-like and depressive-like behaviors across reproductive states (Lee et al., 2009; Slattery and Neumann, 2008; Viviani and Stoop, 2008; Rotzinger et al., 2010). We review the literature supporting direct effects of cocaine on Oxt in adults, primarily in females exposed during pregnancy (see Table 1), as well as the impact of maternal gestational exposure to cocaine on offspring Oxt development (Table 2).

3. Cocaine's Effects on Adult Oxytocin Signaling in Rodents

3.1 Acute Cocaine Exposure

Studies investigating the effect of cocaine exposure on Oxt regulation are summarized in Table 1. In males, acute cocaine (AC) decreases Oxt levels in the basal forebrain, but increases Oxt levels in the hypothalamus and HIPP; however these effects are dose-dependent, indicating regional differences in dose-response curves (Sarnyai et al., 1992). AC exposure in a lactating female decreases Oxt levels in the MPOA but not the VTA, AMY or HIPP, on PPD 1; while increases can be seen on PPD 6 in the AMY following several intermittent AC injections. However, repeated AC decreased Oxt levels in the HIPP, hypothalamus and circulating plasma of male rats, and decreased HIPP Oxt in ovarectimized estrogen-treated females (Sarnyai et al., 1992; Johns et al., 1993). Taken together, these reports suggest hormonal state-, sex-, and treatment-specific effects of AC on Oxt signaling (Nelson et al., 1998c; Elliott et al., 2001). The underlying mechanisms controlling these sensitivities remain unknown.

3.2 Chronic Cocaine Exposure decreases Oxt signaling during the initiation phase of MB

Chronic drug use often leads to substantially different neurological changes compared to acute exposures. The majority of investigations of chronic cocaine (CC) exposure on Oxt signaling have been done with pregnant rats in conjunction with studies on disrupted maternal care, with the largest effects observed in the early postpartum period. As previously noted, CC (20 daily treatments) treatment during pregnancy in female rats results in with lower Oxt levels in the MPOA, HIPP and VTA in the early postpartum period (postpartum day (PPD) 1–3), a time when maternal neglect occurs in the chronically treated mothers (Johns et al., 1994; 1997a; Nelson et al., 1998a; Johns et al., 2005a). Interestingly, CC treatment increased Oxt production in the PVN but not SON in PPD 2 rat dams, indicating a specific regional effect of CC. On PPD 5, following a pup retrieval task, CC-exposed mothers had reduced plasma Oxt compared to controls, with no differences in brain Oxt in the MPOA, VTA, HIPP or nucleus accumbens (Williams et al., 2011a). However, CC-exposed mothers have higher baseline plasma levels of Oxt, and enhanced plasma Oxt response to stress (the forced swim test), but no altered HIPP or AMY responses (Williams et al., 2012). This suggests that CC-induced changes in Oxt are sensitive to behavioral context.

On PPDs 2–6, mid- and high- dose treated CC dams exhibit significantly increased threatening and attack behavior (Lubin et al., 2001a; Nelson et al., 1998b; Johns et al., 1994; 1998), and measurements of AMY Oxt levels immediately following aggression are lower in CC dams (Johns et al., 1995). An Oxt antagonist infused in the AMY, but not the VTA, of non-drug treated lactating rats also significantly increased levels of MA towards intruders on PPD 6 relative to control rats, similar to that seen in CC-treated rats strongly implicating Oxt involvement in MA behavior (Lubin et al., 2003). However, no baseline differences in Oxt levels were found on PPD 5–11 (Lubin et al., 2001a; Johns et al., 1998; Nelson et al., 1998b). Interestingly, virgin females injected with the CC regimen showed slightly decreased aggression associated with a slight decrease in HIPP Oxt levels, but no change in AMY (Lubin et al., 2001b). Taken together, these data suggest the importance of the endocrine state and time point of collection in Oxt response to CC exposure.

3.3 Repeated Cocaine Exposure Effects Can Be Long-Lasting

Dysregulation in baseline Oxt levels in the MPOA, VTA, AMY, and HIPP dissipates by PPD 11 (Nelson et al., 1998c) and remains stable at PPD 22 (Johns et al., 2005a). This return to typical Oxt levels in CC dams observed in the mid-lactational period is associated with reduced Oxt receptor binding in the bed nucleus of the stria terminalis and ventromedial hypothalamus but not the central nucleus of the AMY as shown with autoradiographical methods (Jarrett et al., 2006b). Additionally, higher receptor occupancy and affinity was also observed in the whole AMY at PPD 6 in rat dams (Johns et al., 2004). However, when faced with a stressful situation over 2 weeks following pup weaning, female rats exhibit decreased Oxt levels in the MPOA; this was associated with increased aggression following a competitive water task (Johns et al., 2010). Taken together, these results indicate the complexity by which cocaine can impact Oxt signaling in females across the reproductive cycle. Additionally, it highlights how drug-induced changes in stress-responsiveness can be enduring. These disruptions are brain-region-, dose-, time-, context-, and hormonal state dependent. Much more work is need to understand the intricate ways by which cocaine is altering Oxt signaling in light of how these changes can contribute negatively to maternal care during a critical developmental period for the optimal neurobehavioral welfare of the offspring.

3.4 Potential Monoaminergic Mechanism for Cocaine's Effects

Mechanistic pathways underlying these cocaine-induced changes in Oxt (and perhaps neglect) have not been fully elucidated. Oxt synthesis and release and Oxt receptor regulation are modulated by a number of signaling pathways (Gimpl and Fahrenholz, 2001; McMurray et al., 2008a). As cocaine blocks reuptake of dopamine, serotonin and norepinephrine, studies looking at drugs which similarly effect these neurotransmitter systems offer insight into selective neurotransmitter involvement in drug-induced Oxt system changes and maternal care. Chronic fluoxetine (a selective serotonin reuptake inhibitor) treatment throughout pregnancy results in decreased maternal care toward pups on PPD 1, increased MA on PPD 6 and increased Oxt receptor number and affinity in the AMY, with no change in Oxt levels in MPOA, AMY or HIPP in the maintenance phase of MB (Johns et al., 2004; 2005b). When the gestational fluoxetine treatment was combined with amfonelic acid (AFA: a specific dopamine transporter blocker) decreased Oxt levels in the HIPP and increased VTA Oxt levels were observed on PPD 6 (Johns et al., 2005b). Similarly, HIPP Oxt levels were decreased when AFA was administered alone, although no increase in MA was observed. Amytryptiline, a combined norepinephrine and serotonin transporter blocker produces decreased crouching and aggression but increased licking behavior, and decreased HIPP Oxt levels on PPD 6 (Cox et al., 2011). Similarly, when the specific norepinephrine transporter blocker, desipramine, was given chronically throughout pregnancy, decreases in MB and MA along with reduced HIPP Oxt levels were observed. These data suggest that disruption in all three neurotransmitter systems or another pharmacological effect of cocaine is required to see the increased MA observed in cocaine-exposed dams. However, chronic transporter inhibition disruption of dopamine or norepinephrine alone is enough to decrease basal Oxt levels in the HIPP. The effects of chronic monoamine blockade on Oxt levels during the initiation phase of MB have not yet been investigated, but we would predict lower Oxt in the MPOA given the behavioral changes observed.

3.5 Drugs of Abuse may Generally Disrupt Maternal Care and Oxytocin

Studies investigating changes in MB and Oxt following chronic alcohol or other drug exposure remain sparse. Acute alcohol administration studies suggest a similar impact on MB compared to cocaine (Pepino et al., 2002; Ponce et al., 2011; Pueta et al., 2008; Subramanian, 1999). In pregnant, lactating and estrous cycling women, acute alcohol reduces plasma Oxt levels (Fuchs and Fuchs, 1981; Fuchs et al., 1982; Coiro et al., 1992; Mennella et al., 2005; Mennella and Pepino, 2006). Combined gestational exposure to both chronic alcohol and chronic nicotine showed decreased MB and reduced Oxt levels in the MPOA and the VTA on PPD 1 (McMurray et al., 2008c), similar to what is observed in CC exposure. However, similar treatment did not induce changes in MA (McMurray et al., 2007). Chronic exposure studies in both animal models and clinical investigations are needed to determine whether the effects observed with cocaine exposure are similar to other drugs of abuse.

3.6 Summary

Exposure to drugs of abuse, in particular cocaine, during pregnancy has multiple effects on Oxt signaling that are dependent on the pharmacology, measurement taken, time of drug exposure and abstinence period, and endocrine state. A great deal more work is needed to fully understand how cocaine and other drugs of abuse impact Oxt signaling in adults. Foremost, future studies should focus on how multiple classes of drugs of abuse impact Oxt release and receptor expression in adult estrus-cycling females and further characterization of the male response should be completed. Additionally, the exact mechanism of how these various drugs are capable of disrupting Oxt remains elusive, further studies with more specific pharmacological and regional approaches can hope to answer this question.

The current data suggest that cocaine exposure before, during or after pregnancy is altering the natural plasticity that the female brain undergoes during the transition from pregnancy to motherhood. These naturally occurring changes in neurochemistry are critical for the transition from avoidance of offspring to the complete dedication to offspring that is necessary for their survival. Hence cocaine-induced Oxt changes in brain regions associated with reward and learning (i.e. VTA, HIPP, AMY, and prefrontal cortex) and social behavior (MPOA, HIPP, and AMY), could be an underlying cause of the behavioral deficits observed. Naturally occurring changes in MPOA and VTA activity, associated with changes in Oxt levels, are important for motivation to care for pups and the transitions between MB stages {Pereira:2011dr, Pereira:2010dp}{Shahrokh:2010ch}. The observed reductions in Oxt in these regions following both AC and CC indicate that future studies should focus on how to prevent these cocaine-induced deficits or return typical functioning during the postpartum period. Similarly, the Oxt levels in the HIPP during the maintenance phase of MB are sensitive to many manipulations, suggesting another area of interest to study.

Alternatively, Oxt changes in the mother may be a result of altered stress-response neurocircuitry. Oxt can inhibit brain and hypothalamic-pituitary-adrenal (HPA) stress response by directly antagonizing corticotropin-releasing factor activity in the brain (Bülbül et al., 2011; Dabrowska et al., 2011; Legros, 2001). Oxt administration reduces stress-induced cortisol release in adult humans (Cardoso et al., 2012; Quirin et al., 2011) and corticosterone in male rats (Petersson et al., 1999). Additionally, Oxt signaling is associated with increased parasympathetic activity (Gamer and Büchel, 2012; McCall and Singer, 2012). This modulation of stress reactivity may be important not only for stressful social situations such as the peripartum period, but also drug response and addiction. Furthermore, addiction-related increases in anxiety and depression are thought to be partially mediated by overactive stress systems in the brain (Rotzinger et al., 2010; Logrip et al., 2011). The changes in brain and plasma Oxt following cocaine exposure suggest that other social behaviors, stress reactivity or responsiveness to drugs may be altered in chronically drug exposed females which may help explain relapse into addiction or increased postpartum mood disorders observed in these clinical populations (Williams et al., 2012; Rutherford et al., 2011).

4. Prenatal Exposure to Cocaine and Oxytocin System Development

4.1 The role of Oxytocin in Development

The multitude of effects caused by gestational cocaine exposure on the mother suggest that PCE may also alter Oxt signaling in offspring (see Table 2 for all effects). The ontogeny of Oxt signaling provides a time frame for PCE to cause a disruption. Oxt receptors can be found as early as embryonic day 14 in rats (Tribollet et al., 1989). The relevance of the activation of these receptors can be observed as early as birth with Oxt protecting the brain from excitotoxicity during birth (Khazipov et al., 2008; Ceanga et al., 2010). Additionally, Oxt during birth can have an analgesic effect on the newborns (Mazzuca et al., 2011). A single exposure to an Oxt receptor antagonist given on the fist day of life can decrease maternal-separation-induced vocalizations in female vole pups, while repeated administration increases vocalizations on postnatal day 8, indicating the dynamic develop of Oxt on infant behaviors (Kramer et al., 2003). Administration of Oxt on the day of birth also increased territorial aggression in adult females, but not males, suggesting the life-long impact of early Oxt dysregulation and a female specific vulnerability (Bales and Carter, 2003). Recent work has also implicated neonatal Oxt manipulation in the development of the serotonergic system,, potentially providing a mechanism for changes in aggression (Eaton et al., 2012; Hashemi et al., 2013). These data suggest that short-term Oxt disruptions in early in life may have long-term consequences for the developing social behavior network.

Post-weaning deletion of forebrain Oxt receptors results in reduced fear conditioning, but no changes in aggression and only minor deficits in maternal care, unlike what is observed in mice with life-long Oxt receptor deletion (Pagani et al., 2011; Macbeth et al., 2010; Dhakar et al., 2012). Chronic overstimulation of Oxt receptors during adolescence can inhibit typical social bonding in voles, however in rats with similar treatments a decrease in anxiety and ethanol consumption was observed (Bales et al., 2012; Bowen et al., 2011). The developmental time-course of Oxt receptor expression is brain-region specific and can be influenced by maternal separation (Lukas et al., 2010). Experience of a stressful childhood (abuse and neglect) results in lower plasma Oxt levels in adult men and cerebral spinal fluid levels in women, associated with higher levels depressive and anxiety scores (Opacka-Juffry and Mohiyeddini, 2012; Heim et al., 2009). These data indicate the importance of early life environment (primarily through maternal care) might alter the Oxt system and affect Oxt modulated behaviors such as aggression or drug abuse.

4.2 Prenatal Cocaine Exposure Affects Oxytocin-Modulated Behaviors

Prenatal exposure to drugs of abuse results in a multitude of behavioral and neurobiological changes that are still being actively investigated and the scope of which is beyond this review (see these reviews) (Glatt et al., 2000; Chae and Covington, 2009; Buckingham-Howes et al., 2013; Behnke et al., 2013). Overall many of the disruptions, particularly following PCE in rodents, and also sometimes in humans are often age, dose and sex-specific (Overstreet et al., 2000; Liu and Lester, 2011; Lambert and Bauer, 2012; Riley and LaFiette, 1996; Williams et al., 2011b; Johns and Noonan, 1995). Many of the behaviors that are altered in PCE children and rodent offspring have been shown to be modulated by Oxt signaling such as neuroendocrine stress response, agonistic and affiliative social interactions, and increased likelihood of drug abuse. Additionally, in children of women who abuse drugs during pregnancy, the risk of disruptions is enhanced. Drug abusing women are more likely to neglect their children, and child neglect has independently been shown to impact many of the same behaviors affected by prenatal exposure (Wells, 2009; Niccols et al., 2012; De Bellis, 2005; Cahill et al., 1999). This has made conclusions about the direct impact on PCE compared to early environmental stress on offspring behavior challenging. A series of preclinical cross-fostering studies was performed to better understand the contribution of prenatal exposure and an early-life environment of rearing by a drug-exposed mother. These studies often highlighted the combined exposure caused the greatest disruptions (Johns et al., 2007; 2005a; McMurray et al., 2008a; 2008b; Goodwin et al., 1992). We will review PCE-induced effects compared to those caused by being reared by a cocaine-exposed mother throughout developmental stages below.

4.3 Infancy is a sensitive period

In infancy, PCE toddlers showed less negative response to separation from their mothers, and differ in their response to the Still-Face task, a measure of interpreting social cues (Lewis et al., 2009; Molitor et al., 2003). These infants are often reported to be more reactive, harder to sooth and their mothers have an exaggerated response to the infant's reactivity (Schuetze et al., 2012). Similarly, in rodents, PCE infant rats are less capable of eliciting appropriate maternal care from normal rat mothers as well as CC mothers (Johns et al., 2005a), although this seems to be limited to the very early neonatal period (Heyser et al., 1992). These changes in reactivity and social responsiveness may be tied to neuroendocrine responses. Although the HPA axis is typically hypo-responsive during infancy, neonatal brain stress circuitry is responsive to maternal separation (Levine et al., 1991; Dallman, 2000). Preliminary evidence suggests that in PCE/CC reared infant rat pups on postnatal 5, there is no difference in basal or maternal separation induced plasma or brain Oxt levels; however pups at this age show lower Oxt receptor binding (Williams et al., 2010). Interestingly, PCE pups have similar Oxt receptor binding compared to controls on the day

of birth, but have lower brain Oxt levels (Williams et al., 2010). Given the ability of small changes in Oxt signaling can have effect on other neurotransmitter systems that are known to be disrupted by PCE, such as serotonin (Williams et al., 2011b; Eaton et al., 2012), future studies are warranted to understand the exact time course of PCE effects. These data suggest that the impact of PCE may occur very early in life and can be temporally specific even, in the early neonatal period. Future studies will need to investigate the effect of PCE or rearing by a CC-exposed mother at these early time points to determine the contribution of each factor at these early stages.

4.4 Prenatal Cocaine Affects Oxytocin-Modulated Juvenile and Adolescent Behavior

During childhood and adolescence, continued PCE-induced deficits in stress reactivity can be seen in both clinical and preclinical studies (Williams et al., 2011b; Chae and Covington, 2009; Liu et al., 2011). Males in particular seem to be affected in both human and rodent studies, although dysregulation in behavioral stress response appears during adolescence in females with PCE. Higher anxiety-like behavior is also observed in both PCE male and female adolescent rodents (Overstreet et al., 2000). PCE is correlated with increased aggressiveness in males of both human children and young rodents (Wood and Spear, 1998; Bendersky and Lewis, 1998). PCE male and female rats spend less time interacting with conspecifics at PND 30, and they are less capable of eliciting positive social interaction from age-matched controls (Wood et al., 1995; 1994). Juvenile males were tested for pup-induced parental behavior, and those exposed to rearing by intermittently cocaine-exposed mother were less likely to perform the task to completion (Johns, 2010; Jarrett et al., 2006a); however, no changes in Oxt levels in the AMY or HIPP were in either PCE or cocaine-reared offspring. Since there are typical changes in regional Oxt receptor expression during childhood and adolescence, and these developmental stages are critical for learning socially–appropriate behavior, future studies should focus on understanding how prenatal drug exposure or exposure to drug-using parents may influence Oxt signaling and behavior at these time points.

4.4 Prenatal Cocaine Increases Aggression While Rearing by a Cocaine-Exposed Mothers Disrupts Adult Oxytocin Regulation

The large majority of studies investigating adult rodents with PCE show increased depression and anxiety-like behaviors, and these changes have been tied to changes in HPA signaling and serotonin; however Oxt can directly modulate those systems and should be investigated in the future (Salas-Ramirez et al., 2010; Sobrian et al., 2003; Sobrian and Holson, 2011; Overstreet et al., 2000; Williams et al., 2011b). Changes in anxiety and depression are often correlated with increased aggression and PCE generally increases aggression in adult rodents. Male PCE rats showed increased aggression in water competition and resident intruder tasks (Wood and Spear, 1998; Johns, 2010; Johns and Noonan, 1995). Intermittent PCE also results in increased aggressive behavior towards an intruder male (Johns, 2010). Males with combined PCE and rearing by a CC mother show the most intense aggression in a water-competition task suggesting combined prenatal and rearing influences. Simply being reared by a CC dam was sufficient to increase aggression and reduce AMY Oxt levels in adult male rats (Jarrett et al., 2006a; Johns, 2010; Goodwin et al., 1992).

Interestingly, PCE females also exhibit increased aggression in social interactions with other females (Johns and Noonan, 1995). Both prenatal exposure and rearing by a CC-exposed mother increased MA, although the treatment schedule of cocaine exposure resulted in slightly different outcomes. Interestingly, only rearing by cocaine mother, but not PCE, reduced Oxt levels in the AMY of females on PPD 9, similar to what is observed in male water-competition aggression (McMurray et al., 2008b). These data indicate effects of

cocaine-rearing are maintained through adulthood and major hormonal changes associated with pregnancy and lactation.

4.5 Rearing by a Cocaine-Exposed Mothers Disrupts Adult Oxytocin Regulation and Positive Social Behaviors

Adult rats with PCE show decreased duration of social interaction and increased avoidance with unfamiliar rats as adults (Estelles et al., 2006; Overstreet et al., 2000; Johns and Noonan, 1995). Interestingly, PCE effects on aggression and social interactions can be mediated by the housing condition of the adult offspring (Estelles et al., 2005), suggesting that the regulation of the "social neuropeptides" may be playing a role. Adult males who were reared by CC exposed mothers were less likely to exhibit pup-induced parental care than controls. There was no effect of PCE alone on this task indicating the importance maternal care on adult social behavior. When PCE males were reared by CC treated mothers the outcome was worse than in either situation alone with the interaction effect much more significant (Johns et al., 2007). Additionally it was observed that in the group of males reared by CC mothers that did meet the criteria, had much higher levels of Oxt in the HIPP and AMY compared to control animals that behaved similarly. This is in comparison to males reared by CC mothers that competed in the water competition task who had reduced AMY Oxt levels (Jarrett et al., 2006a; Johns, 2010). These differences could indicate different levels of resilience to the effects of PCE combined with varying levels of disrupted MB, and that in order to typically perform social behavior an over-compensation of Oxt is needed in these offspring. Alternatively, these behavioral results suggests that perhaps Oxt receptors are down-regulated in many males reared by CC mothers, however this has not yet been empirically tested.

Female parental care was impacted by both prenatal and rearing influences. PCE disrupted pup retrieval on PPD 1, and females reared by CC-exposed mothers took longer to begin and had shorter sustained bouts of nursing (Johns et al., 2005a). Interestingly, the pattern of crouching frequency was extremely similar between females that been exposed to cocaine during pregnancy and females who had been reared by those cocaine–exposed mothers, even though they had no cocaine treatment during their own pregnancies. CC-reared females had significantly higher Oxt levels in the MPOA compared to females reared by other groups. This is similar to the increased AMY Oxt observed in CC reared males needed for pup-induced parental care, again suggesting that CC reared animals may need to over compensate for reductions in Oxt receptors. However, the impact of rearing by a CC exposed dam on offspring adult Oxt receptor binding has not yet been investigated.

4.6 Rearing by a Cocaine-Exposed Mother and Vulnerability to Addiction

PCE and cocaine rearing both result in overlapping behavioral changes in offspring; however, the molecular mechanisms underlying theses changes are not necessarily the same. These studies indicate that PCE has direct effects on the neonatal Oxt production, but does not by itself seem to cause long-term changes in adolescent or adult Oxt signaling. However, a thorough examination of all relevant brain regions in both sexes across development is needed to fully determine the long-term effects. The data support instead that rearing by a cocaine-exposed mother can have developmental, time point- and brain region- specific effects on Oxt signaling. These alterations in Oxt were tied to deficits in several social behaviors, and it is possible that other Oxt-dependent behaviors, such as drug addiction, are altered as well.

Adult mice and rats with PCE are more likely to acquire self-administration of cocaine and exhibit increased ethanol consumption (Rocha et al., 2002; Hecht et al., 1998; Kelley and Middaugh, 1996; Kelley et al., 1997). Although they will consume more drugs, PCE animals

do not show the same learned preference for the experience, as measured by conditioned place preference (Estelles et al., 2006; Gulley et al., 1999), indicating a heightened reward threshold must be met by other drugs. Prenatal cocaine use along with parental negativity can predict cocaine use in teenagers (Delaney-Black et al., 2011). Although no studies have been performed to directly investigate the role of rearing by cocaine-exposed mothers on vulnerability to addiction, our prediction is that similar changes in Oxt signaling would occur and thus an increase in this behavioral disruption. The few studies that have investigated other drug exposure on later Oxt regulation indicate that the effect is sex and age specific, and may contribute to social behavior and drug-seeking behavior (McMurray et al., 2008c; Kelly et al., 2009; Williams et al., 2009). It is an open question whether changes have also occurred in the Oxt receptor following either PCE or cocaine-exposed mother rearing, which may find more stable changes.

5. Conclusions

We have focused primarily on the complex interaction of cocaine and Oxt as it relates to maternal, social and aggressive behavior with a possible role of Oxt as a mediator of some effects. It is clear that cocaine and likely other drugs of abuse can affect Oxt signaling at different time points. Oxt has a growing reputation for its role in the multiple effects of drugs abuse, which is covered in much greater detail elsewhere in this issue. Some of these effects have been tied to direct effects on dopamine signaling within the reward circuitry, potentially through direct dopamine-oxytocin receptor heteromers (Febo et al., 2005b; Qi et al., 2008; Baracz and Cornish, 2012; Kovacs et al., 1990; Love et al., 2012; Douglas, 2010; Shahrokh et al., 2010; Johns et al., 1994; Romero-Fernandez et al., 2012). Although, these interactions are likely species, sex, and age specific, so further work is necessary to fully understand these interactions.

Oxt signaling has been proposed to be one mechanism that underlies how the quality and quantity of parental care received can directly influence the type of maternal care performed in next generation rodent mothers (Pedersen and Boccia, 2002). The role of rodent maternal care in the neurodevelopment of offspring has been systematically studied, indicating that behavioral changes in the mother can produce epigenetic changes in the infant brain that in turn alter adult behavioral patterns (McGowan et al., 2011; Matthews and Phillips, 2012; Pedersen and Boccia, 2002; Champagne, 2012). Given the importance of the early dyadic relationship between mother and infant to health and well-being of both the infant and the mother, a better understanding of disruptions to this system is needed. Furthermore, changes in Oxt signaling in the mother may predispose her to relapse and drug-taking behavior; which can in turn cause longer-lasting deficits in MB creating a more tumultuous environment for her children.

Developmental changes in the Oxt system, combined with the multitude of other PCE-induced teratologies, contribute to numerous altered behavioral phenotypes including increased stress reactivity, decreased/disrupted social behavior and increased risk of drug abuse (see Figure 1). We have presented studies here that indicate that cocaine can significantly alter maternal care and various aspects of aggression intergenerationally, perhaps through cocaine's effects on the Oxt system in mothers and subsequently through altered development of the offspring's Oxt system dynamics either through prenatal exposure or rearing effects. There is the potential that Oxt plays a significant role both in drug reward circuitry and continued vulnerability to addiction in the mothers. Additionally, the multiple effects on offspring exposed to altered maternal care and drug related effects are likely mediated by epigenetic controls and can initiate a continuing cycle of intergenerational drug abuse. This highlights the need for future Oxt intervention studies

along with continued work to discover the mechanisms by which drug abuse interacts with development and function of the Oxt system.

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Abbreviations

PCE	prenatal cocaine exposure
Oxt	oxytocin
AC	acute cocaine
CC	chronic cocaine
MB	maternal behavior
MA	maternal aggression
PPD	postpartum day
MPOA	medial preoptic area
VTA	ventral tegmental area
AMY	amygdala
HIPP	hippocampus
PVN	paraventricular nucleus
SON	supraoptic nucleus
AFA	amfonelic acid
HPA	hypothalamic-pituitary-adrenal

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Highlights

- Gestational cocaine exposure disrupts maternal care and oxytocin in the postpartum
- Prenatal cocaine alters the oxytocin-driven aggression, stress and parental care.
- Exposure to cocaine-exposed mothers disrupts offspring social behavior and oxytocin
- Altered maternal care and oxytocin may lead to intergenerational transmission of drug abuse

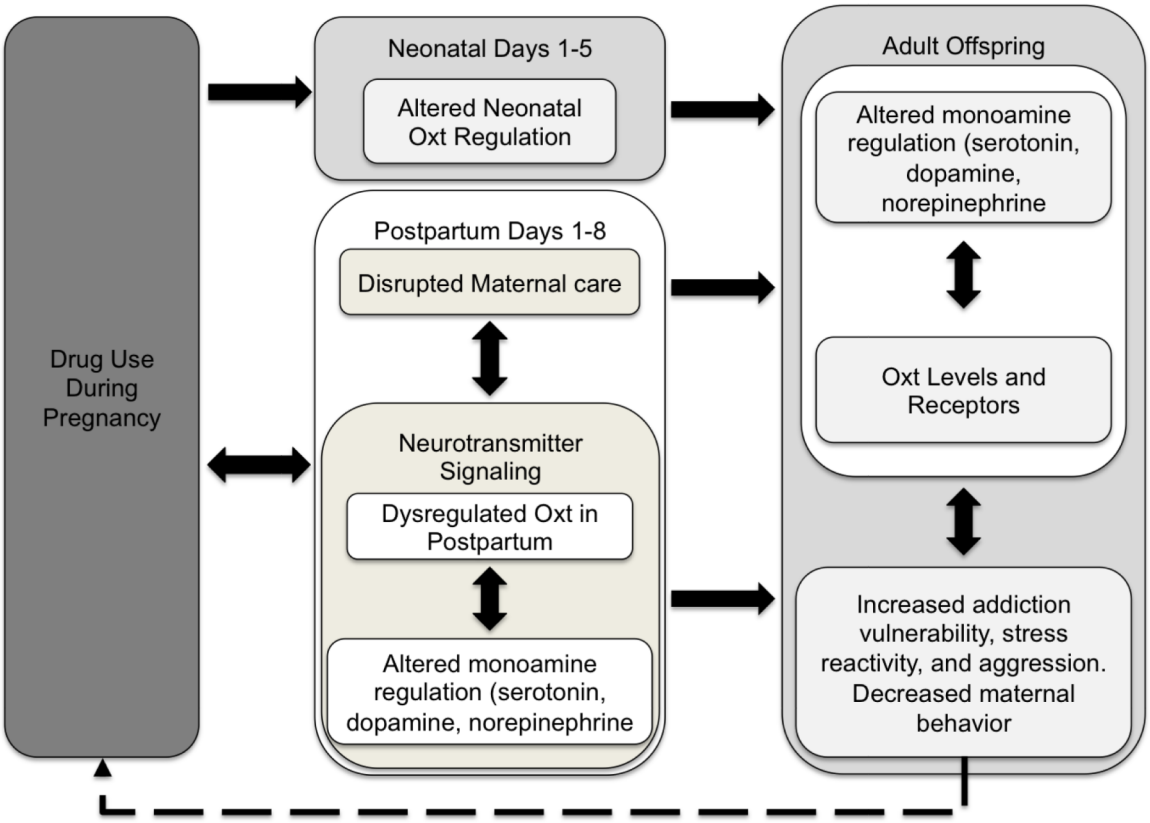

Figure 1.

Intergenerational Transmission of Addiction through Disrupted Oxytocin. Drug use during pregnancy results in negative outcomes for neonatal pups (Top box in center) as well as disrupted Oxt signaling and poor maternal care. Independently, either of these outcomes can be responsible for altered Oxt and monoaminergic signaling and resulting behavioral deficits in adult offspring. Phenotypes of offspring could result in addiction and drug use during pregnancy in the next generation, perpetuating a cycle of oxytocin deficits (dashed arrow).

Table 1

Cocaine and Monoamine Transport Blockade Effects on Oxytocin Signaling. The majority of studies have been performed when adminstration of drugs occurred during pregnancy.

Cocaine and Monoamine Transport Blockade Effects on Oxytocin Signaling								
Drug	**Drug Exposure Type**	**Days Since last drug exposure**	**Measurement Timing**	**Gender/Reproductive State**	**Measurement**	**Measured Area**	**Effect**	**Reference**
Cocaine	Chronic	5	Baseline, Stress-induced	F/Lact	Oxt Levels	Plasma	↑	Williams et al. 2012
Cocaine	Sub-chronic	0		M	Oxt Levels	Plasma	↓	Sarnyai et al. 1992
Cocaine	Chronic	5	Baseline	F/Lact	Oxt Levels	Plasma	↓	Williams et al. 2011
Cocaine	intermittent	0	Baseline	F/Lact	Oxt Levels	AMY	↑	Elliot et al. 2001
Cocaine	Acute	1	Baseline	F/OVX/E (2days)	Oxt Levels	AMY	↓	Johns et al. 1993
Cocaine	Chronic	6	Post-Aggression	F/Lact	Oxt Levels	AMY	↓	Johns et al. 1995
Cocaine	Sub-chronic, Chronic	0, 5	Baseline	M, F/Lact	Oxt Levels	Basal Forebrain	-	Sarnyai et al. 1992; Williams et al. 2011
Cocaine	Acute	0	Baseline	M	Oxt Levels	Basal Forebrain	↓ (med & high dose)	Sarnyai et al. 1992
Cocaine	Chronic	5	Baseline	F/Lact	Oxt Levels	HIPP	↑	Lubin et al. 2001
Cocaine	Chronic	6	Baseline	F/Lact	OxtR Bmax	HIPP	↑	Johns et al. 2004
Cocaine	Acute	0	Baseline	M	Oxt Levels	HIPP	↑ (low dose)	Sarnyai et al. 1992
Cocaine	Sub-chronic	0	Baseline	M	Oxt Levels	HIPP	↓	Sarnyai et al. 1992
Cocaine	Chronic	2	Baseline	F/Lact	Oxt Levels	HIPP	↓	Johns et al. 1997
Cocaine	Chronic	6	Baseline	F/Lact	OxtR (kd)	HIPP	↓	Johns et al. 2004
Cocaine	Chronic	6	Baseline	F/Lact	OxtR (kd)	HIPP, MPOA, VTA	-	Johns et al. 2004

Cocaine and Monoamine Transport Blockade Effects on Oxytocin Signaling								
Drug	**Drug Exposure Type**	**Days Since last drug exposure**	**Measurement Timing**	**Gender/Reproductive State**	**Measurement**	**Measured Area**	**Effect**	**Reference**
Cocaine	Chronic	2	Baseline	F/Lact	OxtR Binding	HIPP, MPOA, VTA	-	McMurray et al. 2008b
Cocaine	Chronic	6	Baseline	F/Lact	OxtR Binding	BNST, VMH	↓	Jarrett et al. 2006
Cocaine	Chronic	6	Baseline	F/Lact	Oxt mRNA	Paraventricular Nucleus of Hypothalamus	-	Jarrett et al. 2006
Cocaine	Chronic	2	Baseline	F/Lact	Oxt mRNA	Paraventricular Nucleus of Hypothalamus	↑	McMurray et al. 2008b
Cocaine	Chronic	2,6	Baseline	F/Lact	Oxt mRNA	Supraoptic Nucleus of Hypothalamus	-	Jarret et al. 2006, McMurray et al. 2008b
Cocaine	Acute	0	Baseline	M	Oxt Levels	Anterior Hypothalamus	↑(med & high dose)	Sarnyai et al. 1992
Cocaine	Sub-chronic	0	Baseline	M	Oxt Levels	Anterior Hypothalamus	↓	Sarnyai et al. 1992
Cocaine	Acute	0	Baseline	F/Lact	Oxt Levels	MPOA	↓	Elliot et al. 2001
Cocaine	Chronic	1	Baseline	F/Lact	Oxt Levels	MPOA	↓	Johns et al. 97
Cocaine	intermittent	36	Baseline	F/Cycle	Oxt Levels	MPOA	↓	Johns et al. 2010
Cocaine	Intermittent, Chronic	I: 0, 2, 22; C: 2, 5, 22, 36	Baseline	F/Lact	Oxt Levels	MPOA	-	Elliot et al. 2001; Johns et al. 1997, 2005, 2010; Williams et al.2011, 2012;
Cocaine	Chronic	6	Baseline	F/Lact	OxtR Bmax	MPOA, VTA	↓	Johns et al.2004
Cocaine	Chronic	2	Baseline	F/Lact	Oxt Levels	VTA	↓	Johns et al. 1997
Cocaine	Acute, Intermittent, Chronic	A: 0,1; I: 0,1 0,1,22,	Baseline	F/Lact, F/Cycle	Oxt Levels	VTA	-	Elliot et al. 2001; Johns et al. 1997, 2005, 2010; Williams et al. 2011;

Cocaine and Monoamine Transport Blockade Effects on Oxytocin Signaling								
Drug	**Drug Exposure Type**	**Days Since last drug exposure**	**Measurement Timing**	**Gender/Reproductive State**	**Measurement**	**Measured Area**	**Effect**	**Reference**
		36; C: 1, 5, 22, 36						Lubin et al. 2001
Cocaine,	Acute, Repeated, intermittent. Chronic	A: 0, 1; I:1, 22, 36; C: 1, 2, 5, 11, 22, 36	Baseline	F/Lact, F/Cycle, M	Oxt Levels	AMY	-	Johns et al. 1997, 1998, 2004, 2005, 2010; Lubin et al. 2001; Williams et al. 2011, 2012; Sarnyai et al. 1992; Elliot et al. 2001; Nelson et al. 1998
Cocaine, FLU	Acute, intermittent, Chronic	A: 0,1; I: 0, 1, 22, 36; C: 1, 11, 22, 36; F: 7	Baseline	F/Cycle, F/Lact	Oxt Levels	HIPP	-	Elliot et al. 2001; Johns et al. 1997, 1998, 2005, 2010
Cocaine, FLU	Chronic	6	Baseline	F/Lact	OxtR (kd), OxtR Bmax	AMY	↑	Johns et al. 2004
Cocaine, AFA/FLU	Chronic	6	Baseline	F/Lact	OxtR Binding	AMY	-	Jarrett et al. 2006; Johns et al. 2004
AFA/FLU, AFA, AMIT, DES, FLU	Chronic	7	Baseline	F/Lact	Oxt Levels	VTA	-	Cox Jarret et al. 2011; Johns et al. 2005
AFA/FLU, AFA, AMIT DES, FLU	Chronic	7	Baseline	F/Lact	Oxt Levels	AMY	-	Johns et al. 2005; Cox, Jarrett et al. 2011
AFA/FLU, AFA, AMIT, DES, FLU	Chronic	7	Baseline	F/Lact	Oxt Levels	MPOA	-	Cox, Jarret et al. 2011; Johns et al. 2005
AFA/FLU, AFA, AMIT, DES	Chronic	7	Baseline	F/Lact	Oxt Levels	HIPP	↓	Johns et al. 2005
AFA/FLU, FLU	Chronic	6	Baseline	F/Lact	OxtR Bmax	HIPP, MPOA, VTA	-	Johns et al. 2004
AFA/FLU, FLU	Chronic	7	Baseline	F/Lact	OxtR (kd)	AMY	-	Johns et al. 2005

Cocaine and Monoamine Transport Blockade Effects on Oxytocin Signaling								
Drug	**Drug Exposure Type**	**Days Since last drug exposure**	**Measurement Timing**	**Gender/Reproductive State**	**Measurement**	**Measured Area**	**Effect**	**Reference**
AFA/FLU	Chronic	7	Baseline	F/Lact	Oxt Levels	VTA	↑	Johns et al. 2005
AMIT	Chronic	7	Baseline	F/Lact	Oxt Levels	MPOA	↑ (low dose)	Cox, Jarrett et al. 2011

Baseline

FLU: fluoxetine, AFA: Amfonelic acid, AMIT: Amitriptyline, DES: Desipramine. Acute exposure implies drug was still in measurable quntities in the blood stream. Letters in the third column (A,I,C) refer to the drug regimen (acute, intermittent, or chronic respectively). M:Male, F: Female, LACT: Lactating/postpartum, OVX: ovariectomized, E: estrogen, Cycling: Females were experiencing normal estrous cycling. Arrows indicate significant change from controls for each study (primarily compared to saline-injected or untreated controls).Oxt: oxytocin, OxtR: oxytocin receptor, Kd: Receptor Affinity, Bmax: Receptor Occupancy. MPOA:medial preoptic area of hypothalamus, VTA: ventral tegmental area, BNST: bed nucleus of stria terminalis, VMH: ventromedial hypothalamus. AMY: amygdala, HIPP: hippocampus

Table 2

Effects of Developmental Drug Exposure on Oxytocin Signlaing. The majority of studies have been performed when adminstration of drugs occurred during pregnancy of the mother.

Effects of Developmental Drug Exposure on Oxytocin Signlaing								
Drug	**Drug Exposure Type**	**Days since last drug exposure/ Age**	**Measurement Timing**	**Gender/Reproductive State**	**Measurement**	**Measured Area**	**Effects**	**Reference**
Cocaine	Prenatal	1	Baseline	M, F	OxtR Binding	Whole Brain	-	Williams et al. 2011
Cocaine	Prenatal	1	Baseline	M, F	Oxt Levels	Whole Brain	↓	Williams et al. 2011
Cocaine	Prenatal	60–80	Following Aggression Test	M	Oxt Levels	AMY, HIPP	-	Jarrett et al. 2006; Johns et al. 2007
Cocaine	Prenatal	60–80 (PPD1)	Baseline	F/Lact	OxtR Binding	MPOA, HIPP, AMY, VTA	-	McMurray 2008b
Cocaine	Prenatal	60–80 (PPG6, 9)	Baseline	F/Lact	Oxt Levels	MPOA, HIPP, AMY, VTA	-	Johns et al. 2005, McMurray et al. 2008
Cocaine	Prenatal/Rearing	5	Baseline, Following Maternal Separation	M, F	Oxt Levels	Whole Brain	-	Williams et al. 2011b
Cocaine	Prenatal/Rearing	5	Baseline, Following Maternal Separation	M, F	Oxt Levels	Plasma	-	Williams et al. 2011b
Cocaine	Prenatal/Rearing	5	Baseline	M, F	OxtR Binding	Whole Brain	↓	Williams et al. 2011b
Cocaine	Rearing Dam	60–80	Following Aggression Test	M	Oxt Levels	HIPP	-	Jerrett et al. 2006
Cocaine	Rearing Dam	60–80	Following Pup-exposure	M	Oxt Levels	HIPP	↑	Jarrett et al. 2006
Cocaine	Rearing Dam	60–80	Following Pup-exposure	M	Oxt Levels	AMY	↑	Jarrett et al. 2006
Cocaine	Rearing Dam	60–80	Following Aggression Test	M	Oxt Levels	AMY	↓	Jarrett et al. 2006
Cocaine	Rearing Dam	60–80 (PPD5)	Baseline	F/Lact	Oxt Levels	HIPP, AMY, VTA	-	Jarrett et al. 2006
Cocaine	Rearing Dam	60–80 (PPD5)	Baseline	F/Lact	Oxt Levels	MPOA	↑	Jarrett et al. 2006
Cocaine	Rearing Dam	60–80 (PPG9)	Baseline	F/Lact	Oxt Levels	MPOA, HIPP, VTA	-	McMurray et al. 2008
Cocaine	Rearing Dam	60–80 (PPG9)	Baseline	F/Lact	Oxt Levels	AMY	↓	McMurray et al. 2008

Arrows indicate significant change from controls for each study (primarily compared to saline-injected or untreated controls). M:Male, F: Female, LACT: Lactating/postpartum, PPD: postpartum. Females were tested on differing days of thier own lactating period following maternal care experiments. Oxt: oxytocin, OxtR: oxytocin receptor. MPOA:medial preoptic area of hypothalamus, VTA: ventral tegmental area, AMY: amygdala, HIPP: hippocampus