Pharmacology, Biochemistry and Behavior xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Review

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

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ARTICLE INFO

Available online xxxx

Keywords:
Prenatal cocaine
Oxytocin
Maternal behavior
Aggression
Addiction
Social behavior

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 that 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.

Contents

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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0091-3057/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pbb.2013.07.004

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 that 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, and 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 its interaction with brain reward and stress systems in mothers have 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, 1998; Nelson et al., 1998a; 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:2001ua}. Oxt administration or infant suckling (which substantially increases Oxt release) increases the activity of 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,

Please cite this article as: Williams SK, Johns JM, Prenatal and gestational cocaine exposure: Effects on the oxytocin system and social behavior with implications for addiction, Pharmacol Biochem Behav (2013), http://dx.doi.org/10.1016/j.pbb.2013.07.004