Psychoneuroendocrinology (2013) 38, 2343—2353

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Sex differences in methamphetamine seeking in rats: Impact of oxytocin☆

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Received 28 February 2013; received in revised form 2 May 2013; accepted 6 May 2013

KEYWORDS
Methamphetamine;
Self-administration;
Oxytocin;
Sex differences;
Reinstatement;
Progressive ratio

Summary Previous evidence in an animal model of drug self-administration and drug seeking showed that acute oxytocin decreased methamphetamine (meth) seeking in male rats, suggesting potential clinical efficacy for the treatment of psychostimulant addiction. However, based on the well-established role of oxytocin in reproduction and pair bond formation, it is important to know how this effect extrapolates to females. Here, we tested whether oxytocin (1 mg/kg, IP) would decrease meth seeking in female rats across various stages of the estrous cycle (Experiment 1). Freely cycling Long Evans female rats self-administered meth (IV) in 2-h daily sessions, followed by daily extinction sessions. Following extinction, rats received oxytocin (0, 0.3, or 1 mg/kg, IP) 30 min before a meth priming injection (1 mg/kg, IP) to assess reinstatement of meth seeking. Next, we examined the effects of oxytocin on motivated meth- and sucrose-taking and seeking in male and female rats. In separate experiments, males and females self-administered meth (Experiment 2) or sucrose (Experiment 3) until responding was stabilized along a fixed ratio (FR) 5 schedule of reinforcement. Subsequently, rats received either oxytocin or vehicle prior to self-administration along a progressive ratio (PR) schedule of reinforcement. Rats were subsequently tested for cue-, meth-, and stress-induced reinstatement after pretreatment with oxytocin or vehicle. While oxytocin reduced meth seeking in females, we found that estrous cycle stage (as determined from vaginal cytology) did not influence meth-primed reinstatement or the ability of oxytocin to decrease reinstatement of meth seeking. Oxytocin reduced PR responding for meth only in females. Females responded more than males during cue-induced reinstatement of meth and sucrose seeking, and oxytocin reduced this responding only in meth females. In both sexes, oxytocin attenuated meth seeking in response to a meth prime and yohimbine (a pharmacological stressor). The results suggest that oxytocin may have efficacy as a treatment of meth addiction in both sexes; however, females may show greater response to oxytocin treatment for the prevention of relapse.

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http://dx.doi.org/10.1016/j.psyneuen.2013.05.005

1. Introduction

Oxytocin is an endogenous peptide that is primarily synthesized in magnocelluar neurons of the supraoptic and paraventricular nuclei of the hypothalamus and is secreted through the posterior pituitary for systemic circulation. In addition, oxytocin is produced in parvocelluar neurons in the paraventicular nucleus, which project to various brain regions. Oxytocin binds to the Gq class of G protein-coupled receptors activating phopholipase C and subsequently increasing neuronal firing and neurotransmitter release through this second messenger cascade (Gimpl and Fahrenholz, 2001). In both males and females, central oxytocin regulates social and sexual bonding, as well as other behaviors such as aggression, stress, and anxiety (Baskerville and Douglas, 2010). In females, systemic oxytocin plays an important role in reproduction by inducing uterine contractions for childbirth and facilitating lactation. Oxytocin receptors are distributed throughout the brain (Gimpl and Fahrenholz, 2001), including regions of the mesocorticolimbic dopamine system critically involved in reward processing (Baskerville and Douglas, 2010). For example, oxytocin fibers innervate dopamine-containing nuclei in the ventral tegmental area. Cell bodies of dopamine neurons that make up the mesocorticolimbic dopamine pathways originate in this area, suggesting that oxytocin may subsequently affect dopamine release into target regions (e.g., nucleus accumbens, amygdala, prefrontal cortex). Additionally, hypothalamic oxytocin cells express dopamine receptors (Baskerville et al., 2009), suggesting that dopamine may mediate oxytocin release. Combined, this extensive interaction of the dopamine and oxytocin systems has expanded the interest in the role of oxytocin in drug addiction.

Based on such evidence, oxytocin has potential for treatment of psychostimulant addiction (McGregor and Bowen, 2012) and may play a regulatory role in attenuating drug tolerance, dependence, and withdrawal via actions in the mesolimbic dopamine reward pathways (Baskerville and Douglas, 2010). Oxytocin blocked cocaine-induced dopamine release in the nucleus accumbens (Kovacs et al., 1990) and decreased cocaine intake during self-administration (Sarnyai and Kovacs, 1994). Additionally, recent preclinical evidence suggests that oxytocin may have therapeutic benefits in preventing relapse to methamphetamine (meth) use (Carson et al., 2010a). Of particular note, oxytocin decreased meth seeking in an animal model of addiction (Carson et al., 2010a) and reduced meth-conditioned reward (Qi et al., 2009; Baracz et al., 2012) in males. Oxytocin may be a critical regulator in drug addiction via modulation of dopaminergic transmission in corticolimbic structures (Baskerville and Douglas, 2010; Sarnyai and Kovacs, 1994). For example, oxytocin decreased dopamine release and receptor binding in mesolimbic brain structures (Sarnyai and Kovacs, 1994). Support for the use of oxytocin as an addiction treatment has gained momentum, due in part to the ability of some drugs to enhance social interactions (McGregor et al., 2008; Dumont et al., 2009). Further, neural circuits mediating social bonding and drug reward may overlap (Burkett and Young, 2012).

To date, the ability of oxytocin to ameliorate meth seeking or conditioned reward in female rats is unknown. However, this is an important question given that gonadal hormones regulate oxytocin's binding affinity and receptor density in various brain regions (Schumacher et al., 1990; Patchev et al., 1993). Further, progesterone and estrogen fluctuate throughout the estrous cycle in female rats, rendering studies with females a necessity to determine oxytocin's full potential as a pharmacotherapeutic treatment for meth addiction. Clinical research in meth addiction indicates numerous sex differences in terms of meth use patterns and response to treatment (reviewed in Dluzen and Liu, 2008). For example, women tend to initiate meth use at a younger age (Dluzen and Liu, 2008), transition faster to dependence, exhibit greater dependence (Rawson et al., 2005), and have greater comorbidity with other neuropsychiatric disorders (Hser et al., 2005; Yen and Chong, 2006). While clinical evidence has shown gender differences, preclinical research investigating meth addiction and potential pharmacotheraputic treatments has primarily focused only on male subjects. This pattern is problematic, as females may respond differently to treatments when compared to males, suggesting a need for gender-specific therapies. Consistent with clinical populations, animal models indicate that female rodents have an increased sensitivity to meth's psychomotor stimulating effects (Schindler et al., 2002; Milesi-Halle et al., 2007).

Animal models of drug self-administration incorporate various aspects of the addiction cycle, including motivation to consume a drug and/or drug seeking behavior in the absence of reinforcement. Self-administration models require animals to learn to press an operandum (typically a lever) for an intravenous drug infusion. In these models, more female rats acquire meth self-administration relative to males (Roth and Carroll, 2004), exhibit higher meth intake (Reichel et al., 2012), and exert more effort for meth as a primary reward (Roth and Carroll, 2004). Meth seeking can be inferred by the reinstatement of lever responding following a period of non-reinforced responding. These reinstatement tests incorporate various trigger factors (e.g., cues, drug-priming, or stress) for the testing of pharmacotherapies that may block reinstatement (Yahyavi-Firouz-Abadi and See, 2009).

Here, we assessed whether systemic oxytocin may be a potential treatment for meth addiction in females and males. To this end, we first determined the effects of oxytocin (0.3 and 1 mg/kg) on meth-primed reinstatement of meth seeking throughout the various stages of the estrous cycle in female rats. Second, we determined whether oxytocin (1 mg/kg, the dose previously shown to reduce meth-primed reinstatement in females) would impact motivation for meth in both males and females during meth self-administration and in response to meth associated cues, meth priming, or pharmacological stress (yohimbine) induced reinstatement. We utilized yohimbine (an α_2-adrenergic receptor antagonist) as a pharmacological stressor as it can elicit anxiety states in clinical studies (Bremner et al., 1996), craving in drug dependent subjects (Greenwald et al., 2013), and reinstatement of drug seeking in rats (See and Waters, 2010). Finally, we determined whether oxytocin effects would extend to natural reinforcement (i.e., sucrose pellets) in males and females.