



Cocaine withdrawal influences paternal behavior and associated central expression of vasopressin, oxytocin and tyrosine hydroxylase in mandarin voles



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ABSTRACT

Although the disruptive effects of cocaine on the maternal care are well known, little is known about paternal care in the context of cocaine abuse. Vasopressin (AVP), oxytocin (OT) and dopamine (DA) have been found to regulate paternal behavior and are also involved in cocaine abuse. Mandarin voles (*Microtus mandarinus*) are socially monogamous and display high levels of paternal care. Here, we investigated whether paternal behavior and associated central levels of AVP, OT and DA were altered following 24 h of withdrawal from 4 day administration of 20 mg/kg/day cocaine. Our data shows that vole fathers did not experience altered levels of locomotion during an open field test. However, compared to controls, cocaine attenuated licking/grooming and contact behavior and shortened the latency to crouching, contact and pup retrieval. Last, fewer AVP and OT immunoreactive neurons in the paraventricular nucleus and more tyrosine hydroxylase immunoreactive neurons in the ventral tegmental area were observed in cocaine-treated fathers. These results indicate that cocaine withdrawal disturbs the expression of partial paternal behavior by altering central levels of AVP, OT and DA.

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1. Introduction

Cocaine is a commonly abused stimulant drug. Cocaine impairs the parenting ability of both male and female rats, with and without previous parenting experience (Zimmerberg and Gray, 1992). For example, maternal cocaine exposure disrupts the onset and expression of maternal behavior such as maternal retrieval and crouching (Johns et al., 1994; Kinsley et al., 1994; Nelson et al., 1998). It also goes onto disrupt the maternal behavior of adult offspring (Johns et al., 2005). In humans, maternal cocaine use can lead to child neglect (Kelley et al., 1991), abuse (Murphy et al., 1991), and disrupt the mother–child bond (Burns et al., 1991). For example, cocaine-abusing mothers experience less enthusiasm for and enjoyment from interaction with their infant and are less sensitive to a child's cues and needs (Burns et al., 1991; Barabach et al., 1992).

Clinical and preclinical studies also indicate that males and females differ across several aspects of drug abuse (Lynch et al., 2002; Roth et al., 2004) and that ovarian hormones such as estradiol may contribute to these differences in humans and animals (Lynch et al., 2002; Becker and Hu, 2008; Kerstetter et al., 2012).

It is likely that parental behaviors associated with cocaine use are different between men and women. Although research suggests more fathers than mothers enter drug abuse treatment (McMahon et al., 2005), the vast majority of studies using laboratory models have focused on the effects of drug abuse on maternal behavior. Consequently, very little is known about paternal behavior in the context of drug abuse, and even less is known about the mechanism behind any effect of cocaine on paternal care.

Given the difficulties associated with primate and human experiments (Aragona et al., 2007) and the power of preclinical studies, understanding the neurobiological impact of drug abuse on paternal behavior would be accelerated if rodents with biparental care were studied. Monogamous rodents engage in pair bonding and pre-weaning parental care by fathers (Young et al., 1998; Campbell et al., 2009) and thereby form closer social ties with their offspring than polygamous males. The importance of the father is not primarily protection against infanticidal intruders, but rather the direct care of young (e.g. providing warmth, grooming). For example, the removal of fathers results in lower offspring survival (Gubernick and Teferi, 2000; Campbell et al., 2009). Thus, monogamous species make excellent models for human behavior, in which males are often significant contributors to infant care and potentially incur significant costs (Campbell et al., 2009). The mandarin vole (*Microtus mandarinus*) is a monogamous rodent

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(Smorkatcheva, 1999; Tai et al., 2001; Tai and Wang, 2001), with durable father–offspring recognition (Wang and Tai, 2012) where fathers provide almost exclusive care of offspring, with the exception of nursing (Smorkatcheva, 2003; Wu et al., 2011). Like maternal–offspring attachment, the rewarding properties of offspring are obvious in the father (Wang et al., 2012a). This species is an ideal animal model to examine the link between paternal behavior and drug abuse.

The hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON) play a key role in parental behavior (Bamshad et al., 1993, 1994; Kirkpatrick et al., 1994; Wang et al., 2000; Curley et al., 2011). The neuropeptides arginine vasopressin (AVP) and oxytocin (OT) are synthesized primarily in the PVN and SON. AVP has been shown to influence paternal behavior (Wang et al., 2000; Parker and Lee, 2001) and there is emerging evidence that OT may be also involved in paternal behavior (Insel and Shapiro, 1992; Gubernick et al., 1995; Bales et al., 2004; Song et al., 2010). It has been demonstrated that AVP and OT are correlated with cocaine abuse (Sarnyai et al., 1992; Zhou et al., 2005; McMurray et al., 2008; Rodríguez-Borrero et al., 2010). Therefore, it is possible that AVP and OT are involved in the interaction between cocaine abuse and paternal behavior. Dopamine (DA) has primary effects on paternal behavior (Lonstein, 2002; Young et al., 2011). The ventral tegmental area (VTA) provides the major source of dopaminergic afferents to mesolimbic brain regions (Sharf et al., 2006) and is an important site of drug action and parental motivation (Thompson and Kristal, 1996; Seip and Morrell, 2009). Tyrosine hydroxylase (TH), a rate-limiting enzyme in the synthesis of DA, is an indicator of DA production. Given the involvement of AVP, OT and DA in paternal behavior and drug abuse, we hypothesized that cocaine could affect paternal care and that AVP, OT and/or DA may be involved in the regulation of this effect. To test this hypothesis, we examined the levels of anxiety, locomotion, paternal behavior and the expression of AVP, OT and TH in the PVN, SON and VTA following 24 h of cocaine withdrawal in male mandarin voles.

2. Materials and methods

2.1. Subjects

Mandarin voles used in this study were laboratory-reared F3 generation animals that originated from a wild population in Henan province, China. Animals were reared in conventional plastic cages (length × width × height, 44 cm × 22 cm × 16 cm). Cotton wool and wood shavings were provided for nesting material and changed weekly. The colony room was illuminated on a 14:10 light–dark cycle (lights on 20:00 h) and the temperature was maintained at 23 ± 2 °C. Lighting was maintained at 200 lux. Water, carrots and standard rabbit chow (Xian Jiaotong University Laboratory Animal Center, Xian, China) were freely available. Immediately after weaning at the age of 21 days, pups were separated from parents and housed with peers. At the age of 45 days they were divided into male and female groups. At 70–80 days of age, virgin females and males were paired. Twenty days after pairing, females were checked daily for signs of labor. The day of birth was denoted postnatal day (PND) zero (day of birth = day 0). Animal care followed guidelines of the National Institute of Health and was approved by the Shaanxi Normal University Institutional Animal Care and Use Committee.

2.2. Behavioral testing

2.2.1. Open-field test

It is known that four consecutive days of reinforcement can induce a conditioned place preference (CPP) to cocaine in mandarin

voles (Wang et al., 2012a). Therefore, three days after the birth of their offspring mandarin vole fathers were assigned to two groups: fathers receiving four consecutive days of physiological saline injection, FS ($n = 10$); or fathers receiving four consecutive days of cocaine injection at 20 mg/kg, FC ($n = 8$).

Drug administration Cocaine-hydrochloride (Northwest Pharmaceutical Co., Ltd. Sinopharm, Xian, China) was used in this experiment, diluted in saline. At 0900 h in the colony room, vole received 20 mg/kg/d subcutaneously (s.c.) via a single injection of cocaine or saline in the dorsal caudal flank region. Cocaine doses were chosen on the basis of previous studies on effects of cocaine on CPP and locomotion in female mandarin voles (Wang et al., 2012b). Voles were held for a short time with a leather glove outside the cage and the injection site was massaged. Because the voles were frequently handled, they become well-adapted to the procedure. In addition, massaging the injection site reduces stress. Fathers were placed back in the home cage with pups immediately after the injection process.

Tests were conducted 24 h following the last injection. On the morning of the next day motor activity and anxiety-like behavior were assessed in an open field chamber between 0900 and 1100 h. The chamber was a brightly and evenly illuminated square arena (1 × w × h, 50 cm × 50 cm × 25 cm) made of white glacial polyvinyl chloride and illuminated by four 60 W lamps mounted 1.5 m above the box (400 lux in the center of arena). The area was divided into 16 quadrants (four central and 12 peripheral) (Fiore and Ratti, 2007). Voles were placed individually in the center of the open field left to explore for 5 min and videotaped under white illumination. After the test trial was completed, the open field was thoroughly cleaned with 70% ethanol solution. To assess anxiety-like behavior, the time spent in the center of the open field was measured. The number of crossings between quadrants was used to assess locomotion. In addition, rearing (raising on the hind legs sniffing into the air or the wall of the box), self grooming (licking own fur, sometimes using forepaws, passing them over the nose with a series of brief, horizontal movements) and central vs total walking duration ratio were recorded. The frequency and total duration of these behaviors were later scored by a researcher blind to experimental treatment using Observer 5.0 (Noldus, Netherlands).

2.2.2. Paternal behavior test

After the open field test, paternal behavior was conducted between 1500 and 1700 h. Paternal responsiveness was assessed through behavioral testing following Smorkatcheva et al. (2010), with some modification. Specifically, the testing aquarium was of similar dimensions to the subject's home cage and was initially divided with a removable partition into two sections. The section where the male was placed contained soiled bedding from his home cage, a small amount of food and nesting material. The vole father was placed in the testing arena and allowed to habituate to the new environment for 5 min. Voles perceived this place as a nest area or safe shelter. While wearing a glove, the experimenter placed one pup from the vole father's litter in the opposite corner of the aquarium from where the father was sitting. Once the partition was removed, a video-recorder mounted 70 cm above the apparatus monitored paternal behavior for 15 min. We recorded four of the most common paternal behaviors directed towards pups: *hover crouching* (sitting over the pups with an arched-back posture at least 3 s; Stern and Johnson, 1990), *licking/grooming the pups (L/G)*, *pup contact* (sitting flat on a pup or next to it, while touching, but without an arched back; Bales et al., 2006), and *pup retrieval* (vole father using its mouth to move the pup to the section where the male was placed). The frequency, latency and total duration of these behaviors were later scored by a researcher blind to experimental treatment using Observer 5.0 (Noldus, Netherlands).

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