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# Effects of menstrual cycle phase on cocaine self-administration in rhesus macaques

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ABSTRACT

Epidemiological findings suggest that men and women vary in their pattern of cocaine use resulting in differences in cocaine dependence and relapse rates. Preclinical laboratory studies have demonstrated that female rodents are indeed more sensitive to cocaine's reinforcing effects than males, with estrous cycle stage as a key determinant of this effect. The current study sought to extend these findings to normally cycling female rhesus macaques, a species that shares a nearly identical menstrual cycle to humans. Dose-dependent intravenous cocaine self-administration (0.0125, 0.0250, and 0.0500 mg/kg/infusion) using a progressive-ratio schedule of reinforcement was determined across the menstrual cycle. The menstrual cycle was divided into 5 discrete phases – menses, follicular, periovulatory, luteal, and late luteal phases – verified by the onset of menses and plasma levels of estradiol and progesterone. Dependent variables including number of infusions self-administered per session, progressive ratio breakpoint, and cocaine intake were analyzed according to cocaine dose and menstrual cycle phase. Analysis of plasma hormone levels verified phase-dependent fluctuations of estradiol and progesterone, with estrogen levels peaking during the periovulatory phase, and progesterone peaking during the luteal phase. Progressive ratio breakpoint, infusions self-administered, and cocaine intake did not consistently vary based on menstrual cycle phase. These findings demonstrate that under the current experimental parameters, the reinforcing effects of cocaine did not vary across the menstrual cycle in a systematic fashion in normally cycling rhesus macaques.



## Introduction

Though epidemiological findings report that cocaine use continues to be more prevalent among men than women (Cotto et al., 2010), the rates of new initiates to cocaine use among the adolescent population have been increasing among females, while remaining constant among males (SAMHSA, 2008). In conjunction with these statistics, women exhibit a more rapid progression from first use to cocaine-related substance use disorders (Carroll et al., 2002; Cotto et al., 2010) and are less successful when seeking treatment for these disorders relative to men due to low rates of treatment retention (Siqueland et al., 2002) or high rates of relapse to cocaine use (Hyman et al., 2007). Over the last decade, complementary preclinical data in laboratory animals have illustrated sex-dependent behavioral effects of cocaine. Many of these studies have demonstrated that laboratory animal models used to assess cocaine's abuse liability can be implemented to further understand the neuroendocrine basis for sex-dependent differences among the human cocaine-using population.

Cocaine self-administration studies in laboratory animals have probed this question by directly comparing behavior between males and females. Overall, these findings indicate that female rats demonstrate greater sensitivity to cocaine's reinforcing effects relative to males with shorter acquisition times (Carroll et al., 2002; Lynch and Carroll, 1999), higher rates of cocaine self-administration (Lynch and Taylor, 2004, 2005; Roberts et al., 1989), and greater resistance to extinction (Kerstetter et al., 2008; Lynch and Carroll, 2000). Studies examining the role of gonadal hormones on cocaine-maintained behaviors found that females demonstrate the greatest sensitivity to cocaine's reinforcing effects (Feltenstein et al., 2009; Hecht et al., 1999; Roberts et al., 1989) and resistance to extinguish responding previously paired with cocaine (Kerstetter et al., 2008; Kippin et al., 2005) during estrus, when circulating estradiol levels are at their highest and progesterone levels are at their lowest. Specifically, plasma progesterone levels appear to predict the behavioral effects of cocaine such that responding was inversely correlated with progesterone plasma levels, with lower progesterone levels predicting greater responding (Feltenstein and See, 2007). Other studies have shown that exogenous progesterone, and its metabolite, allopregnanolone, attenuate acquisition of cocaine self-administration, escalation of cocaine self-administration, and reinstatement of cocaine-seeking (Anker et al., 2007; Feltenstein et al., 2009; Hu and Becker, 2008; Jackson et al., 2006; Larson et al., 2005, 2007; Lynch et al., 2001).

Controlled human laboratory studies have also investigated the extent to which cocaine's effects vary between males and females. Findings from early human studies investigating sex-dependent differences in the subjective effects of cocaine have been mixed (Evans et al., 1999; Haney et al., 1998; Kosten et al., 1996), challenging

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the generalizability of cocaine's sex-dependent differences observed in rodent models. However, these studies varied with respect to the route of cocaine administered and they did not control for menstrual cycle phase. Several studies have directly investigated the extent to which menstrual cycle phase contributes to sex differences in the subjective response to cocaine (Collins et al., 2007; Evans and Foltin, 2006a; Evans et al., 2002; Lukas et al., 1996; Mendelson et al., 1999; Sofuoglu et al., 1999), but again, the results have been inconsistent, particularly among studies that administered intranasal cocaine (Collins et al., 2007; Lukas et al., 1996). In contrast, studies with smoked cocaine have revealed a clearer contribution of menstrual cycle phase to cocaine's subjective effects. The subjective effects of smoked cocaine are similar between men and women tested during the follicular phase, when estradiol levels are high and progesterone levels are low (Evans and Foltin, 2006a; Sofuoglu et al., 1999), whereas during the luteal phase (when progesterone levels are high) the subjective response to smoked cocaine is decreased relative to females tested during the follicular phase (Evans and Foltin, 2006a; Evans et al., 2002; Sofuoglu et al., 1999; but see Reed et al., 2011) or to men (Evans and Foltin, 2006a; Sofuoglu et al., 1999). Further, administration of exogenous progesterone decreased subjective responses to smoked cocaine in females during the follicular phase (Evans and Foltin, 2006a; Sofuoglu et al., 2002), but not in men (Evans and Foltin, 2006a). Exogenous progesterone also decreased the subjective ratings of 'high' produced by intravenous cocaine in a sample of men ($n=6$) and women ($n=4$) tested during the follicular phase (Sofuoglu et al., 2004). Despite these differences in subjective response to cocaine, and in contrast to the preclinical literature in rodents, no studies in humans have observed differences in cocaine self-administration as a function of sex (Lynch et al., 2008; Sofuoglu et al., 1999, 2004), menstrual cycle phase (Reed et al., 2011; Sofuoglu et al., 1999), or progesterone administration (Reed et al., 2011; Sofuoglu et al., 2004). Thus, it remains unclear whether differences in the subjective response to cocaine between men and women, possibly due to naturally occurring fluctuations of gonadal hormone levels, contribute to differences in the reinforcing effects of cocaine. There are inherent limitations of human-subjects research, such as constraints on study length, restriction on the number and range of cocaine doses that can be tested, and inability to control for variability between participants that present obstacles for systematically investigating the role of gonadal hormones on cocaine's behavioral effects in humans. To overcome these limitations, the current study investigated the effects of menstrual cycle phase on cocaine self-administration in non-human primates, a species that can perhaps provide the most generalizable findings to predict factors that contribute to human drug abuse and dependence (Weerts et al., 2007).

Given the similarity in menstrual cycle in terms of duration and hormonal fluctuations between female macaques and humans (Appt, 2004; Shimizu, 2005), macaques are an ideal species to use for attempting to elucidate the role of fluctuations of gonadal across the menstrual cycle on cocaine reinforcement. Despite these similarities between humans and non-human primates, only 3 studies, all from the same laboratory, have been conducted to evaluate the reinforcing effects of intravenous cocaine in non-human primates as a function of sex, menstrual cycle phase, and administration of exogenous gonadal hormones (Mello et al., 2007, 2008, 2011). In one study (Mello et al., 2007), 4 gonadally intact, cycling female and 2 gonadally intact male cynomolgus monkeys (*Macaca fascicularis*) self-administered intravenous cocaine using a progressive ratio schedule of reinforcement. In that study, menstrual cycle phase did not consistently alter responding in female monkeys, although females reached a higher progressive ratio breakpoint than males for all doses tested, demonstrating a clear sex difference. Mello et al. also showed that exogenous estradiol failed to consistently affect cocaine self-administration in female rhesus monkeys (2 gonadally intact and 2 ovariectomized; Mello et al., 2008), whereas exogenous progesterone decreased intravenous cocaine self-administration of 0.01 mg/kg/injection in female rhesus monkeys (4 gonadally intact and 1 ovariectomized: Mello et al., 2011). These findings are important since they bridge the results in rodents with the results in humans. Therefore, the present study had two objectives. Since the majority of non-human primate research related to the reinforcing effects of cocaine have been conducted in rhesus monkeys (Mello and Negus, 1996), the first objective was to extend the results obtained in female cynomolgus monkeys (Mello et al., 2007) to rhesus monkeys, by determining whether cocaine's reinforcing effects varied as a function of menstrual cycle phase using a progressive ratio schedule of cocaine self-administration. The second objective was to relate these findings to studies conducted in human female cocaine abusers (Evans and Foltin, 2006a; Evans et al., 2002; Reed et al., 2011).

## Methods

### *Subjects*

Five adult female rhesus monkeys (*Macaca mulatta*), weighing 6.0 to 10.0 kg, were housed unrestrained as described below for the duration of the study in a room that was maintained on a 12 h light/dark cycle, with lights on at 7 AM. Each day, monkeys received fruit, a daily vitamin, and monkey chow to maintain stable body weight; approximately 7–9 chow (105–135 g; High protein monkey diet #5047, 3.37 kcal/g; LabDiets®, PMI Feeds, Inc., St. Louis, MO). In addition, monkeys periodically received various food treats such as raisins, cookies, candy and fruit-flavored juices. Monkeys were housed in customized, squeeze-capable, rack-mounted, non-human primate cages (Hazleton Systems, Inc., Aberdeen, MD) in the AAALAC-approved animal care facility of The New York State Psychiatric Institute. Each monkey had access to 2 identically sized chambers (61.5 cm wide × 66.5 cm deep × 88 cm high) connected by a 40 cm × 40 cm opening. Water was freely available from spouts located on the back panels of both chambers. Four of the five monkeys had participated in previous studies assessing the pharmacokinetics of cocaine across the menstrual cycle (Evans and Foltin, 2004, 2006b). Investigators and veterinarians routinely monitored the health of the monkeys. Cages were positioned to allow all monkeys to have visual, auditory and olfactory social contact with other monkeys, the animal caretakers and other staff. In addition to the operant procedures, when self-administration sessions were not in progress, monkeys had other various forms of environmental enrichment including: music, cartoon videos (e.g., Scooby Doo and Nemo), a puzzle box, a mirror, and other tactile and chew toys. Lastly, monkeys had multiple positive interactions each day with the primary caregivers, as well as with the Investigators, who were knowledgeable about environmental enrichment, primate behavior and the evaluation of primate behavior. All study procedures and aspects of animal maintenance complied with the US National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the New York State Psychiatric Institute Animal Care and Use Committee.

### *Surgery*

For long-term intravenous drug administration, monkeys were surgically implanted with a chronic indwelling catheter (Access Technologies, Skokie, IL) that terminated in a subcutaneous vascular access port (VAP) (Wojnicki et al., 1994). An outside veterinary team with extensive expertise in VAP surgeries performed all of the VAP surgeries. Briefly, intravenous propofol was administered before an intertracheal tube was inserted. The monkey was connected to isoflurane gas, the anesthesia level was monitored and maintained within physiological limits throughout the surgery, and an angiocath was placed in the saphenous vein, allowing an intravenous fluid line to be established. Under aseptic surgical conditions, a subcutaneous VAP connected to a silicone rubber-rounded-tip (intinsil tip) catheter was implanted in the right atrium through a femoral or jugular vein and was anchored to the vein with sutures. The VAP was anchored