Hormones and Behavior 59 (2011) 227–235

Contents lists available at ScienceDirect

Hormones and Behavior

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

The effects of oral micronized progesterone on smoked cocaine self-administration in women

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ARTICLE INFO

Article history:
Received 20 September 2010
Revised 15 December 2010
Accepted 17 December 2010
Available online 28 December 2010

Keywords:
Cocaine
Cardiovascular effects
Humans
Progesterone
Menstrual cycle
Self-administration
Subjective effects
Women

ABSTRACT

There are currently no FDA-approved pharmacotherapies for cocaine abuse. Converging preclinical and clinical evidence indicates that progesterone may have potential as a treatment for cocaine-abusing women, who represent a growing portion of cocaine users. We have previously shown that oral progesterone reduced the positive subjective effects of cocaine in female cocaine users during the follicular phase of the menstrual cycle, when endogenous progesterone levels were low. To extend these findings, the present study assessed the effects of oral progesterone (150 mg BID) administered during the follicular phase on smoked cocaine self-administration in women relative to the normal follicular and luteal phases. Healthy, non-treatment seeking female cocaine smokers ($N = 10$) underwent three 4-day inpatient stays, during: 1) a normal follicular phase; 2) a normal luteal phase; and 3) a follicular phase when oral progesterone was administered. During each stay, participants completed 4 self-administration sessions in which they first smoked a "sample" dose of cocaine (0, 12, 25 or 50 mg) and then had 5 opportunities at 14-minute intervals to self-administer that dose at a cost of $5 per dose. Expected cocaine dose effects on self-administration, subjective effects, and cardiovascular effects were observed. However, there was no effect of oral progesterone administration or menstrual cycle phase on cocaine self-administration. Thus, oral progesterone was not effective in reducing cocaine use in women under the current conditions. However, based on previous literature, further research assessing the role of oral progesterone for the treatment of cocaine dependence in women is warranted.

Introduction

Cocaine abuse continues to be a prominent public health problem, with an estimated 1.9 million current cocaine users in the United States (SAMHSA, 2009). Although cocaine abuse remains more prevalent among men, the gender gap is narrowing (SAMHSA, 2008). Based on the 2006 Treatment Episode Data Set (TEDS) the majority (71%) of all cocaine treatment admissions were for smoked cocaine, and of those, 42% were women (SAMHSA, 2008). Women who exhibit more rapid progression from initiation of use to cocaine dependence (O' Brien and Anthony, 2005; Ridenour et al., 2005), are more likely to be dependent on cocaine (Wu et al., 2010), and have poorer treatment outcomes than men (Tuchman, 2010). For instance, women drop out of treatment (Siqueland et al., 2002; Sayre et al., 2002) and relapse to cocaine use (Hyman et al., 2008) earlier than men. These findings highlight the need for better treatment strategies for cocaine-abusing women.

Numerous studies have shown that, in laboratory animals, females are more vulnerable to the behavioral effects of cocaine than males (e.g., Carroll et al., 2002; Hu et al., 2004; Hecht et al., 1999; Lynch and Carroll, 1999; Roberts et al., 1989). Many of these sex differences are due, in part, to fluctuations in gonadal hormones (Becker et al., 2001; Carroll et al., 2004a; Festa and Quiñones-Jenab, 2004; Becker and Hu, 2008). For instance, during the rat estrus phase of the estrous cycle, when progesterone levels are minimal, females work harder to self-administer cocaine (Roberts et al., 1989; Hecht et al., 1999), show greater disruptions in the regulation of cocaine self-administration (Lynch et al., 2000), and show greater cocaine-seeking behavior (Feltenstein and See, 2007) than they do during other phases of their cycle. More recently, several preclinical studies have shown that progesterone administration reduces the reinforcing effects of cocaine, and may reduce reinstatement of drug-self administration ("relapse"), particularly in female rats (Frye, 2007; Evans and Foltin, 2010; Anker and Carroll, 2010a; Hudson and Stamp, 2011). For example, progesterone attenuated cocaine-induced increases in locomotor activity (Niyomchai et al., 2006), cocaine-induced conditioned place preference (Russo et al., 2008), reinstatement of cocaine-seeking behavior (Anker et al., 2007; Feltenstein et al., 2009), and cocaine self-administration (Jackson et al., 2006; Larson et al., 2007) in female rats. In contrast, progesterone failed to reduce cocaine-induced locomotor activity or conditioned place preference in male rats (Russo et al., 2010). Similarly, an active metabolite of

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0018-506X/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.yhbeh.2010.12.009

progesterone, allopregnanolone, reduced both cocaine-induced (Anker et al., 2009) and stress-induced (Anker and Carroll, 2010b) reinstatement of cocaine seeking in female, but not male, rats.

Sex differences in response to cocaine, and the involvement of gonadal hormones in such differences, have also been demonstrated in humans and non-human primates (e.g., Lynch et al., 2002; Mello and Mendelson, 2002; Terner and de Wit, 2006; Carroll and Anker, 2010; Evans and Foltin, 2010). However, existing evidence on the effects of progesterone on cocaine in humans is limited (Evans, 2007; Anker and Carroll, 2010a). In a previous study (Evans and Foltin, 2006), we showed that oral micronized progesterone attenuated the positive subjective effects of smoked cocaine in women, but not in men. Two studies by Sofuoglu and colleagues have also demonstrated that oral progesterone reduced some subjective effects of smoked cocaine in women (Sofuoglu et al., 2002) and intravenous (i.v.) cocaine in a mixed male and female sample (Sofuoglu et al., 2004).

In combination, these findings in laboratory animals and humans suggest that progesterone may have potential as treatment for cocaine abuse, particularly in women. However, although oral progesterone has been shown to attenuate the positive subjective effects of cocaine, particularly in women, it remains unclear whether progesterone administration would also decrease cocaine use in humans. Similar to cocaine self-administration procedures used in laboratory animals, human cocaine self-administration studies can assess both the reinforcing effects of cocaine and the ability of potential pharmacotherapies to reduce cocaine taking (e.g., Haney, 2009; Haney and Spealman, 2008). This is important because the effect of a medication on self-reported cocaine craving or the subjective effects of cocaine may differ from its ability to decrease cocaine self-administration in the laboratory or in clinical applications (e.g. Haney et al., 1998, 2005, 2006; Hart et al., 2004, 2007). Moreover, the effect of medication on self-administration in the laboratory has good predictive validity with regards to efficacy in the clinic (see Haney, 2009). Only one study has assessed whether oral progesterone alters cocaine self-administration in the laboratory in humans (Sofuoglu et al., 2004) and one other study has evaluated its efficacy in a clinical setting (Sofuoglu et al., 2007). In the laboratory study, although oral progesterone (200 mg) reduced subjective ratings of "high", participants self-administered the same number of i.v. cocaine doses regardless of whether they were pretreated with progesterone or placebo. There were no reported differences between men (n = 6) and women (n = 4; Sofuoglu et al., 2004). In addition, the one placebo-controlled clinical trial undertaken to date failed to show that oral progesterone (600 mg/day) was more effective than placebo for reducing cocaine use among opioid- and cocaine-abusing men maintained on methadone (n = 45; Sofuoglu et al., 2007). Both of these studies used either a mixed-gender sample or only men; it therefore remains unknown whether oral progesterone would decrease cocaine use in a sample of cocaine-abusing women.

The purpose of the present study was to extend the findings of our previous study (Evans and Foltin, 2006) to determine whether oral progesterone administration would not only reduce the positive subjective effects of cocaine, but would also decrease cocaine self-administration using a cocaine self-administration procedure developed in our laboratory. Since existing literature suggests that progesterone is more effective at altering the behavioral effects of cocaine in females than in males, this study was conducted only in a sample of non-treatment seeking cocaine-abusing women. We used a design similar to our previous study (Evans and Foltin, 2006); women were tested twice in the follicular phase (once in the presence of oral micronized progesterone and once during a normal follicular phase) and once in the normal midluteal phase of the menstrual cycle. A full dose–response function of smoked cocaine (0, 12, 25 and 50 mg cocaine base) was assessed during each phase. Further, since a previous study (Hart et al., 2008) demonstrated that modafinil significantly reduced cocaine self-administration when participants had to purchase the cocaine doses with their own study earnings, this methodological modification to our previous laboratory self-administration procedures (e.g., Evans et al., 1998a; Haney et al., 2006) was used in the present study. We hypothesized that cocaine self-administration and the subjective and cardiovascular effects of cocaine would be 1) lower in the normal luteal phase compared to the normal follicular phase and 2) within the follicular phase, attenuated by oral progesterone compared to placebo.

Methods

Participants

Ten female research volunteers (9 Black and 1 Native American), 36–43 (mean = 41) years of age, with current reports of smoking cocaine were solicited through newspaper advertisements in New York, NY. Females reported currently spending an average of $258/week on cocaine (range of $65–450/week), currently smoking cocaine an average of 5 days each week (range of 3–7 days/week), and smoking cocaine for an average of 19 years (range of 7–25 years). Seven women reported smoking tobacco cigarettes, an average of 7 cigarettes/day. Women had a mean education level of 12 years (range of 10–14 years) and a mean body mass index (BMI) of 27 (range of 18–35). All participants were medically healthy based on a physical examination, electrocardiogram, chest X-ray, complete blood chemistries (including pseudocholinesterase levels), and urinalysis. None of the participants was using hormonal contraceptives, or any other prescription medication. Participants were not pregnant (based on blood pregnancy tests) or nursing, nor had they undergone an abortion or been pregnant within the previous 6 months. All participants had normal menstrual cycles. Psychiatric status was assessed with the structured clinical interview for DSM-IV Axis I disorders (SCID I; First et al., 1995). No participants suffered from premenstrual dysphoric disorder or other major mood or anxiety disorders. None were receiving psychiatric treatment or seeking treatment for their drug use.

Each participant signed a consent form, approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI). The consent form described the study, outlined possible risks, and indicated that during inpatient phases, there would be opportunity for cocaine self-administration, possibly on a daily basis. Participants were paid for their participation at the end of the study in multiple weekly payments of up to $300 each week.

Design and experimental procedures

Participants were informed that the purpose of the study was to assess the effects of the hormone progesterone on their response to smoked cocaine at different phases of the menstrual cycle. After providing informed consent, all participants began filling out daily rating forms as outpatients (see Evans et al., 1998b for details); they were paid to report to the laboratory twice a week to return completed forms and collect new forms. This ensured consistent outpatient contact and allowed us to monitor the menstrual cycle for accurate timing of inpatient phases. Using the forms, participants reported on various aspects of daily mood and physical symptoms known to vary across the menstrual cycle and indicated whether or not they were menstruating. Participants were prospectively tracked for several weeks before the first inpatient admission, and throughout the study, to determine menstrual cycle length and time of ovulation. They were instructed to notify the research nurse when menstruation started. During the midfollicular phase, participants provided daily urine samples to determine the time of ovulation using OvuQuick® (QUIDEL Corp., San Diego, CA; Martini et al, 1994). This test is simple to use and is 96–99% accurate at detecting luteinizing hormone (LH)