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Impact of endogenous progesterone on reactivity to yohimbine and cocaine cues in cocaine-dependent women

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ABSTRACT

Background and objective: Data from clinical and preclinical models of relapse suggest that progesterone attenuates cocaine-seeking behavior. In a recent study, we found that cocaine-dependent women reported greater subjective responses to cues that were preceded by a stressor than cocaine-dependent men. The objective of this study was to examine the impact of endogenous progesterone on the subjective and endocrine responses to a drug-paired cue that was preceded by a stressor in cocaine-dependent women.

Methods: Cocaine-dependent women with low (< 4 ng/ml; n = 16) and high (≥ 4 ng/ml; n = 9) plasma progesterone levels received either the alpha-2 adrenergic receptor antagonist yohimbine (21.6 mg) or placebo before each of two cocaine-cue exposure sessions. Participants were tested under both conditions in a counterbalanced, double-blind fashion. Data were collected after study drug administration, immediately and at 5, 30, and 60 min after the cue.

Results: The anxiety response to the cue was differentially modified by progesterone levels under the two administration conditions (condition × progesterone level interaction, $F_{1,23}$ = 9.8, p = 0.005). Progesterone levels also modified the craving response to the cue differently under the placebo condition as compared to the yohimbine condition (condition × progesterone level interaction, $F_{1,23}$ = 13.9, p = 0.001). In both cases, high progesterone levels attenuated craving and anxiety response to the cue following yohimbine administration. There was no effect of progesterone levels on salivary cortisol or dehydroepiandrosterone under the placebo condition or under the yohimbine condition.

Conclusions: These preliminary data suggest that high levels of endogenous progesterone attenuate subjective responses to drug-cues that are preceded by a stressor. Importantly, these data support a growing literature demonstrating the protective effects of progesterone on the vulnerability to cocaine relapse in women.

1. Introduction

There are significant sex differences in the development and symptomology of substance use disorders, including cocaine dependence. For example, compared to men, women meet criteria for substance use disorders faster and enter treatment programs earlier than men (Anglin et al., 1987; Hernandez-Avila et al., 2004; Westermeyer and Boedicker, 2000). In addition, cocaine-dependent women report higher rates of cocaine use and remain abstinent for shorter periods of time (Griffin et al., 1989). Cocaine-dependent women exhibit significant psychiatric, medical, and psychosocial dysfunction (Brady and Randall, 1999; Najavits and Lester, 2008; Wong et al., 2002). Thus, the effects of short and long-term drug use are particularly formidable for women. Research focused on understanding the neurobiologic factors that underscore sex differences in drug craving and relapse could have important treatment implications for cocaine-dependent women.

Data from clinical and preclinical studies suggests that ovarian hormones are important factors that contribute to sex and gender differences related to stimulant use. For example, estrogen enhances the reinforcing effects of stimulants and may increase the vulnerability of women to drug craving and relapse (Anker et al., 2007; Evans et al., 2002; Justice and de Wit, 1999, 2000; Larson et al., 2005, 2007; Lile et al., 2007; White et al., 2002). Progesterone appears to have the opposite effects on stimulant-seeking behavior. For example, exogenous

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progesterone administered to ovariectomized (OVX) and sham-operated (SH) female rodents attenuated self-administration of cocaine under long-access conditions, suggesting that progesterone attenuates drug binging behavior (Larson et al., 2007). In addition, progesterone treatment reduced cocaine-primed reinstatement in SH female rodents and in OVX female rodents that were treated with estrogen (Anker et al., 2007). Human laboratory studies investigating exogenous progesterone administration have found attenuated cue-induced craving in cocaine-dependent individuals (Fox et al., 2013), and reduced weekly cocaine use in post-partum cocaine-dependent women during a 12-week clinical trial (Yonkers et al., 2014). Studies investigating endogenous progesterone demonstrate similar effects. Elevated levels of progesterone were associated with lower reinstatement responding for cocaine in intact freely-cycling female rodents (Feltenstein and See, 2007). Protective effects of endogenous progesterone have also been found in clinical studies of cocaine-dependent women. Sinha et al. (2007) examined the effects of endogenous progesterone levels on subjective responses to stress and drug cues using an autobiographical imagery paradigm. Cocaine-dependent women with high progesterone levels reported significantly lower cue- and stress-induced craving and lower cue-induced anxiety than cocaine-dependent women with low progesterone levels. Taken together, these data suggest that among cocaine-dependent women, elevated progesterone attenuates craving responses to triggers of relapse and may impact use outcomes.

Accumulating research demonstrates an important interaction between stress and drug cues in relapse. For example, stress potentiates cue-induced reinstatement of cocaine-seeking behavior in rodents (Banna et al., 2010; Buffalari and See, 2009; Feltenstein et al., 2011; Liu and Weiss, 2002). Of note, compared to male rodents, female rodents exposed to the pharmacological stressor yohimbine exhibit greater stress potentiation of cue-induced cocaine seeking behavior (Feltenstein et al., 2011). Compared to cocaine-dependent men, cocaine-dependent women exhibited significantly greater craving and anxiety to drug cues that were preceded by yohimbine (Moran-Santa Maria et al., 2014). Thus, stress may enhance the salience of drug cues in cocaine-dependent women. To date, the effects of endogenous progesterone on reactivity to drug cues that are preceded by a stressor have yet to be explored in a clinical population. The aim of this study was to assess the impact of endogenous progesterone on reactivity to yohimbine and drug cues in cocaine-dependent women. Yohimbine was used as it is a reliable pharmacological stressor in both human and animal models. We hypothesized that cocaine-dependent women with high progesterone levels would exhibit lower reactivity to yohimbine and the drug cue than cocaine-dependent women with low progesterone levels.

2. Methods

2.1. Participants

This study is a secondary analysis of a larger study designed to determine if cocaine-dependent subjects would have altered craving following yohimbine administration and drug cues as compared to placebo (Moran-Santa Maria et al., 2014). Only cocaine-dependent women were included in the present analysis. Cocaine-dependent women were recruited via advertisements over a 48-month period. Written informed consent was obtained from each participant before the study assessments were administered. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and received Institutional Review Board (IRB) approval. Inclusion criterion included (1) Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for cocaine-dependence in the 90-days prior to the study. Exclusion criterion included (1) DSM-IV criteria for substance dependence except caffeine, nicotine, alcohol or marijuana within the past 60 days; (2) pregnancy, nursing, or ineffectual means of birth control; (3) premenstrual dysphoric disorder; (4) history/current hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological diseases; (5) history/current psychotic, panic, eating, or bipolar affective disorders; (6) current depression or PTSD; (7) history/current medical diseases that could affect HPA axis hormones; (8) synthetic glucocorticoid or exogenous steroid therapy within 30 days of testing; (9) psychotropic medications (with the exception of selective serotonin reuptake inhibitors), opiates or opiate antagonists, benzodiazepines, antipsychotics, b-blockers and other medications that might interfere with HPA axis hormones; (10) acute illness or fever; (11) body mass index > 35; and (12) aversion or inability to remain abstinence from alcohol and other drugs of abuse (except nicotine) for three days prior to the study procedures.

2.2. Assessment

Participants meeting pre-screening criteria were evaluated for study eligibility with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The substance use module of the Structured Clinical Interview for DSM-IV (SCID-IV) was used to assess current and lifetime substance use disorders (First et al., 1994). Substance use in the ninety days prior to the study was assessed using the Time-Line Follow-Back (Sobell and Sobell, 1992). A medical history and physical examination were completed to assess for medical exclusions. Participants meeting inclusion criteria and no exclusion criteria were scheduled to complete the study procedures.

2.3. Study procedures

Subjects participated in two cue reactivity sessions on consecutive days. On day 1 of testing, participants arrived at the Medical University of South Carolina's Clinical and Translational Research Center (CTRC) at 10:00 a.m. Upon arrival, urine pregnancy tests were administered. All participants were practicing some form of non-hormonal birth control (e.g. condoms, barriers, abstinence) throughout the study. Smokers were provided with a nicotine patch. Self-reports, urine drug screens (Roche Diagnostics, Indianapolis, Indiana), and breathalyzer tests (AlcoSensor III, Intoximeters, Inc., St. Louis, Missouri) were used to assess abstinence. If the pregnancy and drug tests were negative (with the exception of THC), study procedures continued.

The study utilized a double-blind placebo-controlled design. At 11:00 a.m. on the morning of the first study visit, a blood sample was collected. This blood sample was used to assay ovarian hormone levels (see *assays* below). Salivary cortisol and dehydroepiandrosterone (DHEA) samples were also collected at 11:00 a.m. using the passive drool method (Salimetrics, LLC, State College, PA). One hour later (12:00 p.m.), participants received either yohimbine or a matching placebo capsule (see *medication administration* below). Study participants were provided with a standard lunch and were seated in a CTRC testing room where they were allowed to read until the testing procedures began. Subjective and endocrine response data were collected at 1:40 p.m. and again at 1:55 p.m. The cue reactivity session began at 2:00. The session started with a scripted imagery exercise. Briefly, the participants were instructed to release any tension in the shoulders, back and neck and to breathe deeply. Afterwards, the participants were asked to remember a time when they were using cocaine, and to recall as much detail as possible including their physical response (increased heart rate and breathing) and the “rush” at the first hit of cocaine. Participants were then asked to view and handle cocaine cues. For those who use crack cocaine, this consisted of a small bag of simulated crack cocaine, a crack pipe, a lighter, and a $20 bill. For powder or intravenous users, cues consisted of simulated cocaine, a mirror, a razor, and a $20 bill. Participants examined and handled the cues for two-minutes. Afterwards, the subjects watched a five-minute film depicting cocaine use. This combination of “in-vivo” cues and cocaine use depiction has produced significant craving and physiologic activity in previous studies (Coffey et al., 2002; Saladin et al., 2003). Data were