Psychoneuroendocrinology (2013) 38, 1532—1544

Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

The effects of exogenous progesterone on drug craving and stress arousal in cocaine dependence: Impact of gender and cue type

Helen C. Fox [a,*], Mehmet Sofuoglu [b], Peter T. Morgan [a], Keri L. Tuit [c], Rajita Sinha [c]

[a] *The Connecticut Mental Health Center, Yale University School of Medicine, Department of Psychiatry, 34 Park Street, New Haven, CT 06519, USA*
[b] *VA Medical Center, 950 Campbell Ave, # 36, West Haven, CT 06516, USA*
[c] *The Yale Stress Center, Yale University School of Medicine, Department of Psychiatry 2 Church Street South, Suite 209, New Haven, CT 06519, USA*

Received 29 February 2012; received in revised form 21 December 2012; accepted 27 December 2012

KEYWORDS
Progesterone;
Gender;
Cocaine dependence;
Stress;
Drug cue;
Stroop

Summary
Aims: Exogenous progesterone has been shown to attenuate the rewarding effects of cocaine. However, its effects on provoked drug craving, stress arousal and cognitive performance has not been systematically investigated in cocaine dependent men and women. Thus, we conducted a double-blind placebo-controlled study assessing the efficacy of progesterone in reducing provoked drug craving, stress system arousal and improving cognitive performance in cocaine dependent men and women.
Methods: Forty-two early abstinent treatment-seeking cocaine dependent individuals were randomly assigned to either daily doses of placebo (12M/9F) or micronized progesterone (12M/9F) (400 mg/day), for 7 days. Under experimental conditions, all subjects were exposed to three 5-min personalized guided imagery conditions (stress, cocaine cue, relaxing), one per day, consecutively in a random, counterbalanced order. Subjective craving, mood, hypothalamic-pituitary-adrenal (HPA) and cardiovascular output, and a cognitive measure of inhibitory control (Stroop Color Word Task) were assessed pre- and post imagery.
Results: Progesterone relative to placebo significantly decreased cue-induced craving and cortisol responses and increased cue-induced ACTH. In addition, women but not men receiving progesterone reported lower ratings of negative emotion and higher ratings of relaxed mood following stress exposure. Improved Stroop performance was observed in all participants receiving progesterone, across all conditions.

* Corresponding author. Tel.: +1 203 974 7360.
E-mail address: helen.fox@yale.edu (H.C. Fox).

0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2012.12.022

Conclusions: Progesterone was selectively effective in reducing cocaine cue-induced but not stress-related cocaine craving as well as specific measures of the provoked arousal state. Findings suggest that progesterone's effects on drug craving and arousal are moderated by both the type of environmental cue exposure and gender.

1. Introduction

Cocaine dependence is one of the most common and preventable health care problems in the US, with an estimated 1700 initiates per day (SAMHSA, 2010). Moreover, due to changing socioeconomic environments, the number of women dependent on cocaine is rapidly increasing to similar levels as men (SAMHSA, 2006). Coupled with the fact that women also display greater vulnerability in terms of treatment outcome (Quinones-Jenab, 2006; Anker and Carroll, 2011), the need for an FDA approved medication is critical. In view of this, clinical and preclinical studies have shown that the administration of micronized progesterone mediates the acute subjective and physiological reinforcing effects of cocaine more robustly in females compared with males (Evans et al., 2002; Sofuoglu et al., 1999; Russo et al., 2008, 2010 Feltenstein et al., 2009; Evans and Foltin, 2006, 2010; Hudson and Stamp, 2011; Reed et al., 2011; de Wit, 2011). While progesterone demonstrates some efficacy in male rodents by decreasing locomotor activity (Rupprecht, 2003) and in both healthy (Childs et al., 2010) and substance using males (Sofuoglu et al., 2004, 2007) by attenuating negative mood and cardiovascular response, these changes are relatively minimal compared to those observed in females (Quinones-Jenab and Jenab, 2010). Similarly, with regard to motivation for cocaine use, preclinical studies have indicated that both progesterone and its metabolite allopregnanolone inhibit cocaine-primed reinstatement in female, but not male rats (Anker et al., 2007, 2009). Additionally, outpatient treatment studies in humans have shown that exogenous progesterone is not efficacious in reducing consumption in cocaine dependent methadone-maintained men (Sofuoglu et al., 2007).

Although micronized progesterone shows some potential as a pharmacological treatment for cocaine-abusing women (Reed et al., 2011), previous research has typically assessed either the *acute* subjective and physiological responses to cocaine at different phases of the menstrual cycle (MC) (Evans et al., 2002; Sofuoglu et al., 2002) or the *acute* effects of exogenous progesterone administration during the early follicular phase (Justice and de Wit, 1999, 2000; Kouri et al., 2002). Moreover, only a few studies employing these paradigms have compared findings to cocaine dependent men (Sofuoglu et al., 1999, 2004; Mendelson et al., 1999; Evans and Foltin, 2006; Collins et al., 2007). In the current study therefore, we aim to examine whether exogenous micronized progesterone is also able to mediate stress system adaptations known to be related to cocaine craving and relapse (Fox and Sinha, 2009), in both men and women following an abstinence period of four weeks.

During early protracted abstinence from cocaine, dysregulated basal and stress-induced physiological, HPA and emotional changes are strongly associated with increased cocaine craving, cocaine use and relapse (Back et al., 2005; Sinha et al., 2006; Fox et al., 2008a; Fox and Sinha, 2009). These changes include a tonic up-regulation in cortisol and ACTH (Sarnyai et al., 2001; Fox et al., 2008b, 2009) as well as sensitized negative mood, craving, cardiovascular and cortisol output in response to stress and cue (Sinha et al., 2003, 2006; Fox et al., 2005, 2008a, b). As cocaine dependence is a chronic stress state and sex hormones modulate stress system function (Lindheim et al., 1994) exogenous progesterone may mediate components of stress dysregulation during early abstinence.

In support of this hypothesis, previous findings from our own laboratory have highlighted a role for *endogenous* progesterone in reducing some of the chronic stress system adaptations during early abstinence in women. Findings from one study showed that early abstinent women in the mid luteal phase of their MC (high progesterone) demonstrated significant reductions in stress and cue-induced craving as well as cue-induced anxiety and blood pressure compared with women in the early follicular phase (low progesterone) (Sinha et al., 2007). Similarly, cocaine dependent women in their first month of abstinence demonstrated significantly up-regulated salivary cortisol and negative affect along-side enhanced levels of progesterone across the entire MC, suggesting a potentially compensatory role for endogenous progesterone in response to an enhanced distressed state (Fox et al., 2008b).

In addition to having potent anxiolytic and vascular effects on the peripheral nervous system (Sita and Miller, 1996), progesterone may also strengthen prefrontal regulatory mechanisms. This may be due to the actions of its metabolite allopregnanolone on GABA-activated inhibition of neural firing in dopaminergic regions of the striatum, nucleus accumbens (NAc), hippocampus and pre-frontal cortex (PFC) (Becker, 1999; Becker and Hu, 2008; Russo et al., 2008). As optimal levels of dopamine within these mesocorticolimbic systems reduce "noise" in the PFC by suppressing neuronal processing of irrelevant information (Brennan and Arnsten, 2008), progesterone may be a suitable agent for strengthening regulatory processes integral to treatment outcome (Witkiewitz and Marlatt, 2005).

We therefore investigated the subjective, physiological, HPA and cognitive effects of 400 mg/day of exogenous micronized progesterone versus placebo in early abstinent men and women (p.o, b.i.d) for seven days. Dependent measures were assessed at baseline and following exposure to personalized stress and cocaine cue-related imagery. We hypothesized that the progesterone group would demonstrate reduced cocaine craving, negative mood, and cardiovascular output, as well as normalized HPA axis function and improved Stroop performance following stress and cue, compared with placebos. In view of previous research, we also hypothesized that gender would moderate the effects of exogenous progesterone.