Psychoneuroendocrinology 65 (2016) 44–53

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Effects of progesterone stimulated allopregnanolone on craving and stress response in cocaine dependent men and women

Verica Milivojevic[a,d,*], Helen C. Fox[a,d], Mehmet Sofuoglu[c], Jonathan Covault[b], Rajita Sinha[d]

[a] The Connecticut Mental Health Center, Yale University School of Medicine, Department of Psychiatry, 34 Park Street, New Haven, CT 06519, USA
[b] Alcohol Research Center, Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT 06030, USA
[c] VA Medical Center, 950Campbell Ave, # 36, West Haven, CT 06516, USA
[d] The Yale Stress Center, Yale University School of Medicine, Department of Psychiatry 2 Church Street South, Suite 209, New Haven, CT 06519, USA

ARTICLE INFO

Article history:
Received 21 October 2015
Received in revised form
11 December 2015
Accepted 11 December 2015

Keywords:
Progesterone
Allopregnanolone
Cocaine dependence
Stress
Drug cue
Craving

ABSTRACT

Objectives: Fluctuations in progesterone levels during the menstrual cycle have been shown to affect physiological and subjective effects of cocaine. Furthermore, our laboratory has demonstrated that following drug-cue exposure, cocaine dependent women with high levels of circulating progesterone display lower diastolic and systolic blood pressure responses and report lower levels of anxiety and drug craving compared to cocaine dependent women with low levels of progesterone. In the current study we examined the role of the progesterone derived neuroactive steroid allopregnanolone (ALLO) on stress arousal, inhibitory control and drug craving in cocaine dependent subjects.
Methods: Plasma levels of ALLO were measured using GC/MS in 46 treatment-seeking cocaine dependent men and women on day 5 of a 7-day treatment regimen of micronized progesterone (15M/8F) (400 mg/day) or placebo (14M/9F) administered in a double blind, randomized manner. As a control, levels of the testosterone derived neurosteroid androstanediol (ADIOL) were also measured. All subjects participated in laboratory sessions on days 5–7 of progesterone/placebo administration in which they were exposed to a series of 5-min personalized guided imagery of either a stressful situation, cocaine use or of a neutral setting and dependent variables including subjective craving, mood, Stroop task as a measure of inhibitory control performance and plasma cortisol were assessed. Participants were grouped by high or low ALLO level and levels of dependent variables compared between ALLO groups.
Results: Progesterone relative to placebo significantly increased ALLO levels with no sex differences. There were no effects of micronized progesterone on the testosterone derived ADIOL. Individuals in the high versus the low ALLO group showed decreased levels of cortisol at baseline, and a higher cortisol response to stress; higher positive mood scores at baseline and improved Stroop performance in the drug-cue and stress conditions, and reduced cocaine craving across all imagery conditions.
Conclusions: As expected, cocaine dependent individuals administered progesterone showed significantly higher ALLO plasma levels. High levels of ALLO appeared to normalize basal and stress response levels of cortisol, decrease cocaine craving and also contribute to improvements in positive emotion and Stroop performance in response to stress and drug-cue exposures. These findings suggest that the neuroactive steroid ALLO plays a significant role in mediating the positive effects of progesterone on stress arousal, cognitive performance and drug craving in cocaine dependence.

1. Introduction

Cocaine dependence is a common and serious health problem (SAMHSA, 2007) for which there are currently no approved medications. Early abstinence from cocaine is marked by dysregulated basal and stress-induced physiological, hypothalamic–pituitary–adrenal (HPA) axis and emotional changes, which 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). As sex steroid hormones play a key role in modulating these relapse-related stress responses, we aim to examine the underlying mechanism

* Corresponding author.
E-mail address: verica.milivojevic@yale.edu (V. Milivojevic).

http://dx.doi.org/10.1016/j.psyneuen.2015.12.008
0306-4530/

more clearly by assessing the role of allopregnanolone (ALLO) in ameliorating stress-induced craving in early abstinent cocaine dependent men and women.

Preclinical and clinical research has shown that fluctuations in endogenous progesterone levels during the menstrual cycle can affect physiological and motivational aspects of cocaine, both following acute intake of the drug, as well as during early recovery from cocaine (for review see Festa and Quinones-Jenab, 2004). For example, cardiovascular and positive-subjective responses to cocaine in women were reduced during the luteal phase of the menstrual cycle, i.e., when progesterone levels are high, compared to the follicular phase when progesterone levels are low (Sofuoglu et al., 1999; Evans et al., 2002; Evans and Foltin, 2006). Previous research from our laboratory also showed that women with high levels of circulating progesterone demonstrated lower diastolic and systolic blood pressure responses to cue and reported lower levels of anxiety and drug craving compared to women with low endogenous levels of progesterone (Sinha et al., 2007). Similarly, cocaine dependent women in their first month of abstinence demonstrated significantly up-regulated salivary cortisol and negative affect alongside enhanced levels of progesterone across the entire menstrual cycle, suggesting a potentially compensatory role for endogenous progesterone in response to an enhanced distressed state (Fox et al., 2008b). New clinical evidence also suggests some benefit in cocaine use outcomes from progesterone treatment in post-partum women with a cocaine use disorder (Yonkers et al., 2014).

This therapeutic effect of progesterone may be mediated by the neuroactive steroid (3α,5α)-3-hydroxypregnan-20-one (a.k.a. allopregnanolone; ALLO), which is synthesized from progesterone. ALLO potentiates the GABA induced opening of the $GABA_A$ receptor chloride channel at nanomolar concentrations, and produces anxiolytic, anticonvulsant and hypnotic effects similar to those induced by other $GABA_A$ receptor potentiating drugs (Lambert et al., 2001; Majewska et al., 1986). Most notably, fluctuations in peripheral and brain ALLO levels have been associated with motivational mood-related changes during pregnancy, menopause, and a number of psychiatric disorders, including depression, premenstrual dysphoric disorder, schizophrenia and bipolar disorder (Barbaccia et al., 1996; Concas et al., 1998; Girdler et al., 2001; Marx et al., 2006a,b; Uzunova et al., 2006).

Recent evidence suggests that progesterone derived neuroactive steroids could also be important in mediating regulatory cognitive function (Milivojevic et al., 2014b) and stress-associated relapse, as supported by the finding that the HPA axis is largely under GABAergic control (Herman et al., 2004). Acute stress has been shown to down-regulate GABA-ergic transmission (Biggio et al., 2007) and increase neuroactive steroid levels in the brain and periphery (Purdy et al., 1991). In addition, intraperitoneal (i.p.) injections of CRF and ACTH in rats increase brain and plasma levels of allopregnanolone (Torres et al., 2001). These findings indicate that neuroactive steroids may play a crucial compensatory role in mediating homeostasis in response to stress (Biggio et al., 2007; Crowley and Girdler, 2014; Sarkar et al., 2011).

In support of this, preclinical studies have found that ALLO administration decreased cocaine primed reinstatement in female, but not in male rats (Anker et al., 2009). In addition, ALLO administration decreased yohimbine-induced cocaine reinstatement in female rats only (Anker and Carroll, 2010), suggesting that ALLO may attenuate stress-induced reinstatement of cocaine seeking in females. More extensive research has examined the role that neuroactive steroids play in alcohol's effects (Morrow et al., 1999; Morrow et al., 2001). For example, acute alcohol increases levels of neuroactive steroids in plasma (VanDoren et al., 2000) and brain (Sanna et al., 2004), and blockade of neuroactive steroid production by the 5α-reductase (5α-R) inhibitor finasteride attenuated acquisition of alcohol preference in mice (Ford et al., 2008). In humans, the plasma concentration of ALLO was increased following severe intoxication (Torres and Ortega, 2003, 2004), but not moderate intoxication (Holdstock et al., 2006; Nyberg et al., 2005; Pierucci-Lagha et al., 2006). Importantly, chronic alcohol exposure reduces both plasma and brain levels of ALLO (Morrow et al., 2001). Clinical studies have also demonstrated that variation in genes that encode neuroactive steroid synthesis enzymes was associated with alcohol dependence (Milivojevic et al., 2011) and subjective effects of alcohol (Milivojevic et al., 2014a), which may modulate risk for the development of dependence. Moreover, neuroactive steroids may be mediating nicotine effects, as nicotine has been found to increase neuroactive steroids (Porcu et al., 2003). Unlike alcohol dependence, their levels were found to be higher in smokers, in whom levels of allopregnanolone positively correlated with nicotine dependence severity (Marx et al., 2006a,b). The role that neuroactive steroids may play in cocaine effects in humans is still largely unclear and has not been systematically examined.

In a previous study we showed that administration of 400 mg/day of exogenous progesterone across 7 days demonstrated some selective efficacy in attenuating cortisol response and cocaine craving following drug cue as well as negative mood in women (Fox et al., 2013). However, the reason for these effects of progesterone are not clear and the extent to which ALLO was a contributing element, is unknown. Moreover, it is not clear whether ALLO has modulatory effects on inhibitory cognitive function. Thus, we examined the effects of the progesterone metabolite ALLO in a larger group of the cocaine dependent individuals recruited for this study (Fox et al., 2013) in order to assess this further. ALLO levels were assayed on day 5 of the 7-day progesterone/placebo treatment regimen to generate high and low ALLO groups. Based on existing preclinical findings, we hypothesized that high ALLO relative to low ALLO will improve mood and inhibitory cognitive control, as assessed using the Stroop task, and decrease cocaine craving and stress response during acute stress and drug cue imagery exposure in a controlled laboratory experiment with progesterone versus placebo treated cocaine dependent men and women. Androstanediol (ADIOL), a neuroactive steroid derived from testosterone was assessed as a control measure to ensure that any observed effects were specific to progesterone stimulated increases in ALLO and not other potent neuroactive steroids, such as the testosterone derived ADIOL. We predicted that ADIOL will not be different by ALLO groups and hence will not have an impact on stress, drug craving and inhibitory control in CD subjects in this laboratory paradigm.

2. Methods

2.1. Participants

Forty six treatment-seeking cocaine dependent individuals (29M/17F) were recruited through local advertisements. All subjects from Fox et al., (2013) were included in the current analysis, and the current sample included 4 more participants over the parent study. Participants met DSM-IV criteria for current cocaine dependence and tested positive for cocaine in urine toxicology screens upon entry into inpatient treatment and study at the Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center (CMHC) for a 3–4 week inpatient stay. The CNRU is a locked inpatient treatment facility with no access to alcohol or drugs and very limited access to visitors. Alcohol and drug testing was conducted 3 times per week, to ensure drug abstinence. Participants were excluded if they met criteria for any other current psychiatric disorder or current and/or lifetime dependence on substances other than cocaine, alcohol or nicotine, determined using the Structured Clinical Interview for the Diagnostic and