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Short communication

Sex differences in guanfacine effects on stress-induced stroop performance in cocaine dependence

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ABSTRACT

Aims: Chronic drug abuse leads to sex-specific changes in drug cue and stress physiologic and neuroendocrine reactivity as well as in neural responses to stress and cue-related challenges and in executive function such as inhibitory control, cognitive flexibility and self control. Importantly, these functions have been associated with high risk of relapse and treatment. Alpha-2 agonism may enhance inhibitory cognitive processes in the face of stress with sex-specific effects, however this has not been previously assessed in cocaine dependence.

Method: Forty inpatient treatment-seeking cocaine dependent individuals (13F/27 M) were randomly assigned to receive either placebo or up to 3mgs of Guanfacine. Three laboratory sessions were conducted following 3–4 weeks of abstinence, where patients were exposed to three 10-min personalized guided imagery conditions (stress, drug cue, combined stress/cue), one per day, on consecutive days in a random, counterbalanced order. The Stroop task was administered at baseline and immediately following imagery exposure.

Results: Guanfacine treated women improved their performance on the Stroop task following exposure to all 3 imagery conditions compared with placebo women ($p = 0.02$). This improvement in cognitive inhibitory performance was not observed in the men.

Conclusions: Enhancing the ability to cognitively regulate in the face of stress, drug cues and combined stress and drug cue reactivity may be key targets for medications development in cocaine dependent women.

1. Introduction

Cocaine dependence is a serious health problem affecting a large number of the world population. Women are steadily increasing their use of cocaine (SAMHSA, 2013), and somewhat alarmingly are more vulnerable than men to the initiation, progression and relapse stages of cocaine dependence (Anker and Carroll, 2010; Quinones-Jenab, 2006). Chronic drug abuse shows differential neuroadaptations in men and women. For example, sex differences have been observed in physiologic and neuroendocrine response to stress and drug cue (Back et al., 2005; Fox and Sinha, 2009) as well as in neural responses regulatory behaviors including inhibitory control, cognitive flexibility and self control (Moeller et al., 2016; Potenza et al., 2012). Notably, these are all measures that have been associated with high risk of relapse and treatment outcomes (Back et al., 2005; Daughters et al., 2009; Fox and Sinha, 2009; Moeller et al., 2016; Sinha et al., 2006; Van Dam et al., 2014). Furthermore, while executive functions such as response inhibition and self control are critical for successful clinical outcome and relapse prevention (Aharonovich et al., 2006; Aharonovich et al., 2003), these functions are known to be most compromised under stress and cue reactivity states. As such, inhibitory control may represent an important process contributing to the association between stress and treatment outcome (Schwabe et al., 2011; Sinha, 2001). Despite this, no previous research has assessed whether stress- and cue-related arousal compromise response inhibition during early abstinence from cocaine, or whether pharmacologic agents that improve prefrontal executive function, such as Alpha-2 adrenergic agonists like Guanfacine (Arnsten, 2009; Arnsten and Jin, 2012), may rescue these executive functions in cocaine dependence.

Preclinical research has shown that Alpha-2 adrenergic agonists such as Guanfacine reduce central norepinephrine, improve executive functioning during stress (Arnsten, 2009), and decrease stress-induced

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reinstatement of drug seeking (Mantsch et al., 2010; Vranjkovic et al., 2012). In nicotine dependent individuals, Alpha-2 adrenergic agonists, such as Clonidine, have been shown to improve smoking cessation outcomes and more so in women than men (Glassman et al., 1993). More recently, we have shown that Guanfacine's ability to strengthen prefrontal function in the face of stress, may play an important role in attenuating motivation for drugs. For example, Guanfacine relative to placebo, improved stress-related self control over smoking in the laboratory and also improved brain prefrontal activation to incongruent stimuli in a Stroop task (McKee et al., 2015). We also previously reported that Guanfacine reduced cue-induced cocaine craving and stress-induced arousal in cocaine dependent individuals and simultanously increased medial and lateral prefrontal activity following stress and drug cue exposure compared with placebo (Fox et al., 2012). Importantly, Guanfacine also displayed sex-specific effects, showing greater efficacy in reducing stress arousal in cocaine dependent women than men (Fox et al., 2014). However, it is not known whether Guanfacine improves inhibitory control during stress and arousal states in cocaine dependent individuals and whether such improvements show sex differences. Thus, the current study examined this possible effect in cocaine dependent men and women treated with 2–3 mg/day of Guanfacine or matching placebo for 3 weeks in a randomized, double blinded manner as reported on previously (Fox et al., 2014). We hypothesized that Guanfacine would improve stress and cue-induced inhibitory control as measured by the Stroop task, and additionally that improvement would be more robust in women relative to men.

2. Methods

2.1. Participants

Forty treatment-seeking cocaine dependent individuals (13F/27 M) were recruited from the local area using newspaper and on-line advertisements. Current cocaine dependence was determined using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID IV – First et al., 1995) as well as positive urine toxicology screens collected upon entry into inpatient treatment. Exclusion criteria included DSM-IV dependence for any drug other than cocaine, alcohol or nicotine. Participants using prescribed medications for any psychiatric or medical disorders were also excluded, and all individuals underwent stringent medical assessments including electrocardiography and laboratory tests of renal, hepatic, pancreatic, hematopoietic and thyroid function. Results from the parent study on Guanfacine effects on cue reactivity from this sample are previously published (Fox et al., 2014). Written and verbal consent were obtained from all participants and the procedures were approved by the Human Investigation Committee of the Yale University School of Medicine.

2.2. Guanfacine dosing

Subjects were randomly assigned to either Guanfacine (2 mgs or 3 mgs) or placebo in a randomized, double blind manner and five days after inpatient admission were initiated on a twelve-day tapered medication schedule, similar to that used in previous human studies (Biederman et al., 2008; Chappell et al., 1995; Handen et al., 2008; Scahill et al., 2001). As such, participants who were randomized to the dose of Guanfacine 2 mg started dosing on days 1–3 (0.5 mg evening), on days 4–13 (0.5 mg morning and 1.0 mg evening), and weeks 2 onwards (1.0 mg morning and 1.0 mg evening). Participants who were randomized to the dose of Guanfacine 3 mg started dosing on days 1–2 (0.5 mg evening), on days 3–5 (0.5 mg morning and 1.0 mg evening), on days 6–8 (1.0 mg morning and 1.0 mg evening), on days 9–11 (1.0 mg morning and 1.5 mg evening), and on day 12 onwards (1.5 mg morning and 1.5 mg evening). Placebo was administered exactly as the Guanfacine group dosing, and all pills appeared identical. All laboratory sessions were conducted in week 3-4, approximately 21 days after admission. Following the laboratory sessions, and on completion of inpatient stay (5 weeks) all participants underwent a standard 5-day taper (Strang et al., 1999). Randomization procedures were conducted by the Connecticut Mental Health Center (CMHC) research pharmacist, experienced in Urn randomization procedures (Stout et al., 1994).

2.3. Laboratory sessions

Subjects participated in three laboratory sessions conducted at the Clinical Neuroscience Research Unit (CNRU) of the CMHC in week 3–4 of inpatient stay. In the laboratory sessions, participants were exposed to 10-min personalized stress/stress, drug cue/drug cue and stress/drug cue imagery scripts, one imagery condition per day, across three consecutive days in a randomized and counterbalanced order. Imagery script development procedures are based on methods developed by Lang and his colleagues (Lang et al., 1980,1983; Miller et al., 1987), and further adapted in our previous studies (Sinha et al., 1999; Sinha et al., 2000; Sinha et al., 1992; Sinha and Parsons, 1996). Procedures are presented in previous studies (Bergquist et al., 2010; Sinha, 2009; Sinha et al., 2006; Sinha et al., 2005; Sinha et al., 2003) and also in a published manual (Sinha and Tuit, 2012). The imagery conditions were: i) stress (5 mins)/stress (5 mins) (2 separate stress scripts), ii) cue (5 mins)/cue (5 mins) (2 separate drug cue scripts), iii) combined stress (5 mins)/cue (5 mins) (one stress and one drug cue script).

2.4. Cognitive inhibitory performance

Cognitive inhibitory performance was measured using the Stroop Color/Word Test (Golden, 1976), which has been used extensively in both clinical and experimental fields to assess the ability to inhibit incongruent competing conflicts. On the initial trial participants are given 45 s to read as quickly as possible a list of 100 color words (red, green, blue) randomly arranged and printed in black ink. On the second trial participants have 45 s to identify as quickly as possible the color of 100 "XXXX" printed in either red, green or blue ink. The final trial consists of the 100 words presented in the initial trial in the colors presented in the second trial. In all cases, the word (i.e., red) is different from the color it is printed in (i.e., blue. (e.g., "red"). Subjects are given 45 s to name the color of the ink as quickly as possible. The number of raw items read for each trial is recorded and converted to standardized T scores. In the current study, participants practiced the Stroop task during intake assessments, and then completed the Stroop at baseline (pre-imagery) and immediately following imagery period on each experimental day.

2.5. Statistical analyses

Linear Mixed Effect (LME) models (Laird and Ware, 1982) were implemented to analyze the data, both at baseline and following imagery exposure, using SPSS software (version 19). Within-subjects factors of Imagery Condition (stress/stress, cue/cue, combined stress/cue), Time-point (pre- and post- imagery) and Between-subjects factors of Medication Group (Guanfacine vs Placebo) and Gender (Males vs Females) were the fixed effects. Subjects represented the random effect. Baseline data were used as covariates in all analyses in order to account for variability across each testing day. T-tests were used to compare the medication groups on demographic and drug use variables. Chi-squares were applied to all categorical variables including gender and racial distribution across groups.

3. Results

3.1. Sample characteristics

The placebo and Guanfacine groups were statistically matched in terms of demographic and drug use variables (see Table 1).