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Short communication

Reinstatement of methamphetamine seeking in male and female rats treated with modafinil and allopregnanolone

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ABSTRACT

Background: Sex differences in methamphetamine (METH) use (females > males) have been demonstrated in clinical and preclinical studies. This experiment investigated the effect of sex on the reinstatement of METH-seeking behavior in rats and determined whether pharmacological interventions for METH-seeking vary by sex. Treatment drugs were modafinil (MOD), an analeptic, and allopregnanolone (ALLO), a neuroactive steroid and progesterone metabolite.
Method: Male and female rats were trained to self-administer i.v. infusions of METH (0.05 mg/kg/infusion). Next, rats self-administered METH for a 10-day maintenance period. METH was then replaced with saline, and rats extinguished lever-pressing behavior over 18 days. A multi-component reinstatement procedure followed whereby priming injections of METH (1 mg/kg) were administered at the start of each daily session, preceded 30 min by MOD (128 mg/kg, i.p.), ALLO (15 mg/kg, s.c.), or vehicle treatment. MOD was also administered at the onset of the session to determine if it would induce the reinstatement of METH-seeking behavior.
Results: Female rats had greater METH-induced reinstatement responding compared to male rats following control treatment injections. MOD (compared to the DMSO control) attenuated METH-seeking behavior in male and female rats; however, ALLO only reduced METH-primed responding in females. MOD alone did not induce the reinstatement of METH-seeking behavior.
Conclusions: These results support previous findings that females are more susceptible to stimulant abuse compared to males, and ALLO effectively reduced METH-primed reinstatement in females. Further, results illustrate the utility of MOD as a potential agent for prevention of relapse to METH use in both males and females.

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1. Introduction

While fewer females currently use methamphetamine (METH) than males (SAMHSA 2009), females initiate METH use at earlier ages and display more acute dependence (for review, see Dluzen and Liu, 2008). Results from animal studies reflect this pattern, showing that female rats are more sensitive to METH-induced locomotor activity (Milesi-Halle et al., 2007; Schindler et al., 2002), acquire METH self administration at faster rates, and administer greater amounts of METH under fixed- and progressive-ratio schedules of reinforcement (Roth and Carroll, 2004a). While female rats are more prone to stimulant use, they may also be more receptive to pharmacological treatment interventions. For example, Cosgrove and Carroll (2004) found that female rhesus monkeys showed a greater decrease in oral phencyclidine self administration following bremazocine, and Campbell et al. (2002) showed that baclofen, a $GABA_B$ agonist that has been investigated as a treatment for stimulant addiction (Roberts, 2005), was more effective at attenuating rates of acquisition of cocaine self-administration in female rats compared to males. Further, a kappa opioid agonist was more effective at reducing cocaine-induced locomotor activity in female mice compared to male mice (Sershen et al., 1998). While these studies suggest greater treatment receptivity for females, the differential treatment of stimulant abuse with agonist replacements has not been studied during relapse with males vs. females.

Agonist-based treatment is an emerging strategy for stimulant addiction (Hart et al., 2008; Herin et al., 2010, but see Castells et al., 2010). Modafinil (MOD) is an agent of this type and is currently being investigated as treatment for stimulant abuse (Martinez-Raga et al., 2008). Research with non-human primates has indicated that MOD was effective at reducing cocaine-maintained responding (Newman et al., 2010). Further, results from a recent clinical trial

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indicate that MOD treatment was related to increased periods of abstinence in cocaine addicts with comorbid alcohol dependence (Anderson et al., 2009). This finding was supported by an experiment that used a preclinical model of relapse (Reichel and See, 2010) in which MOD was effective at attenuating the reinstatement of METH-seeking behavior in male rats following conditioned cues and drug-priming injections.

Given the sex-differences in treatment response found in previous studies (Campbell et al., 2002; Cosgrove and Carroll, 2004; Sershen et al., 1998) and the exclusive use of male rats in Reichel and See (2010), one aim of the present study was to investigate the possible differential effects of MOD on the reinstatement of METH-seeking behavior between male and female rats. Additionally, growing literature is implicating the role of circulating gonadal hormones in the sex differences observed in substance abuse behaviors (for reviews, see Anker and Carroll, 2010; Carroll and Anker, 2010). Increased risk for stimulant abuse in females has been associated with higher levels of estrogen (Segarra et al., 2010), while these effects are attenuated by the progesterone metabolite and positive $GABA_A$ receptor modulator allopregnanolone (ALLO; Anker and Carroll, 2010). Indeed, ALLO administration attenuated the reinstatement of cocaine-seeking behavior in female, but not male rats (Anker et al., 2009). Thus, a second aim was to investigate the effects of ALLO on the reinstatement of METH-seeking behavior in male and female rats. As female rats respond more during reinstatement following cocaine-priming injections (Anker et al., 2009), the final aim was to investigate sex differences during METH-primed reinstatement.

In the present experiment male and female rats self-administered i.v. infusions of METH and then drug-seeking behavior was extinguished. Subsequently, rats were tested on a multi-component reinstatement procedure in which they received METH priming injections preceded by ALLO, MOD, or control treatments. Since MOD enhances and ALLO inhibits dopamine transmission, both treatments were examined within-subjects to compare potentially sex-mediated effects of these distinct pharmacological approaches to relapse prevention.

2. Methods

2.1. Subjects

Male ($n = 10$) and female ($n = 9$) Wistar rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN) weighing 350–400 g and 250–300 g, respectively, were used in the present study. Estrous cycle was allowed to vary randomly in females so that the effects of fluctuating hormones on drug-seeking behavior would generalize to female rats regardless of cycle phase. Rats were pair-housed in plastic cages upon arrival in the laboratory, and they had ad libitum access to food and water. Next, chronic, indwelling catheters were implanted in the jugular vein as previously described by Carroll and Boe (1982). After they recovered from surgery, rats were placed in operant conditioning chambers where they remained for the duration of the study. Throughout the experiment, they were given free access to water and 20 g (males) or 16 g (females) of ground food per day. Rats were housed under a constant light/dark cycle (12/12-h with room lights on at 6:00 am) in humidity- and temperature- (24 °C) controlled holding rooms. The experimental protocol (1008A87755) was approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC), and the experiment was conducted in accordance with the Principles of Laboratory Animal Care (National Research Council, 2003) in laboratory facilities accredited by the American Association for the Accreditation of Laboratory Animal Care.

2.2. Self-administration, extinction, and reinstatement

The drug self-administration apparatus was identical to that described by Roth and Carroll (2004b). Briefly, operant chambers were stainless steel and octagon-shaped. They contained a drinking spout, recessed food receptacle, 2 stimulus lights, one active and one inactive lever, and a house light. During self-administration sessions the house light was illuminated, and a response on the active lever resulted in the delivery of an i.v. infusion of METH and activated the stimulus lights above the lever for the length of the infusion. Responses on the inactive lever illuminated the stimulus light above the lever but did not result in an infusion. Initially, rats were trained to lever press for i.v. infusions of METH (0.05 mg/kg/infusion) during 6-h daily sessions (9:00 am to 3:00 pm). Sessions ended at 3:00 pm or when rats achieved 40 infusions, whichever came first. Once they self-administered 40 infusions for 3 consecutive days, rats continued responding for METH during 2-h daily sessions (9:00 am to 11:00 am) for 10 days, but infusions were unlimited. Next, METH was replaced with saline, and rats extinguished lever responding for a period of 18 days. The house light, stimulus lights and drug infusion pump were unplugged one day prior to the reinstatement procedure and remained unplugged for the remainder of the experiment. During reinstatement, control treatments for ALLO (15 mg/kg, s.c.) and MOD (128 mg/kg, i.p.) were peanut oil (V, s.c.) and dimethyl sulfoxide (DMSO, i.p.), respectively. These treatments were administered 30 min before a METH (1 mg/kg, i.p.) priming injection that was given at the onset of session. Additionally, MOD and DMSO priming injections were administered alone at the beginning of the session to determine if MOD induced reinstatement of drug-seeking behavior. The following is an example of the 6 conditions in the reinstatement procedure; however, priming conditions were randomized across rats to counter possible ordering effects: V + METH, ALLO + METH, DMSO + METH, MOD + METH, DMSO, MOD. Each of these conditions was preceded by a daily session that commenced with a saline-priming injection (S).

2.3. Drugs

d-Methamphetamine HCL (METH) was supplied by the National Institute of Drug Abuse (Research Triangle Institute, Research Triangle Park, NC) and was dissolved in sterile 0.9% NaCl saline at a concentration of 0.2 mg METH/mL saline and refrigerated. ALLO was purchased from Sigma–Aldrich (St. Louis, MO) and was dissolved in peanut oil (20 mg allopregnanolone/mL peanut oil). MOD was synthesized in the laboratory of Dr. T. E. Prisinzano (Department of Medicinal Chemistry, The University of Kansas, Lawrence, KS) and dissolved in DMSO (Sigma–Aldrich) at a concentration of 100 mg MOD/mL DMSO.

2.4. Data analysis

Active and inactive responses and infusions during maintenance and extinction, as well as active and inactive responses made during reinstatement, served as dependent measures. Responses and infusions were averaged across two 5-day blocks for the 10-day maintenance phase, and two 9-day blocks during the 18-day extinction phase. Between-group comparisons of active and inactive responses and infusions during maintenance and extinction were analyzed using a 2-factor repeated-measures ANOVA. Between-group comparisons of responses during reinstatement were analyzed separately with 2-factor repeated-measures ANOVAs, as shown in the separate panels in Fig. 2. Inactive lever pressing during reinstatement was similarly analyzed. Post hoc comparisons were made between group means using Fisher's LSD protected *t*-test.

3. Results

3.1. Maintenance and extinction

As shown in Fig. 1, there were no significant differences between males and females in active lever pressing throughout the maintenance [mean (±SEM) males = 53.3 (±4.4), females = 52.0 (±3.0)] or extinction [mean (±SEM) males 11.3 (±1.6), females = 15.0 (±1.8)] phases. Responding was stable throughout the maintenance phase for both groups. In both groups, responding declined over the first 6 extinction sessions and remained at low and stable levels for the remaining 12 days. There were no significant differences in responses on the inactive lever during either phase.

3.2. Reinstatement

Fig. 2 shows mean responses on the lever previously associated with METH during the 3 components of the reinstatement procedure. For the MOD component, there were main effects for treatment ($F_{2,32} = 36.99$, $p < 0.001$) and sex ($F_{1,36} = 12.40$, $p = .0028$), as well as an interaction between these factors ($F_{2,53} = 8.89$, $p < 0.001$). Female rats showed higher responding following DMSO + METH compared to males ($ps < 0.01$), while both males and females responded more following DMSO + METH compared to MOD + METH and S conditions (males, $ps < 0.05$; females $ps < 0.01$). For the ALLO component, there were main effects for both treatment ($F_{2,34} = 14.34$, $p < 0.001$) and sex ($F_{1,38} = 6.02$, $p = .025$), as well as an interaction between sex and treatment ($F_{2,56} = 5.69$, $p = 0.007$). Female rats responded more than males following V + METH