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Sex differences in reinstatement of cocaine-seeking with combination treatments of progesterone and atomoxetine

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ABSTRACT

Two repurposed medications have been proposed to treat cocaine abuse. Progesterone, a gonadal hormone, and atomoxetine, a medication commonly used to treat attention deficit/hyperactivity disorder, have both been separately shown to reduce cocaine self-administration and reinstatement (i.e., relapse). The goal of the present study was to examine sex differences in the individual effects of PRO and ATO as well as the combination PRO + ATO treatment on cocaine (COC), caffeine (CAF), and/or cue-primed reinstatement of cocaine-seeking. Adult male and female Wistar rats lever-pressed under a FR 1 schedule for cocaine infusions (0.4 mg/kg/inf). After 14 sessions of stable responding in daily 2-h sessions, rats underwent a 21-day extinction period when no drug or drug-related stimuli were present. Rats were then separated into four groups that received PRO (0.5 mg/kg) alone (PRO + SAL), ATO (1.5 mg/kg) alone (VEH + ATO), control (VEH + SAL) or combination (PRO + ATO) treatments prior to the reinstatement condition. Reinstatement of cocaine-seeking to cues and/or drug injections of cocaine or caffeine was tested after extinction. During maintenance, females self-administered more cocaine than males, but no sex differences were seen during extinction. Females showed greater cocaine-seeking than males after a CAF priming injection. Individual treatment with ATO did not decrease reinstatement under any priming condition; however, the combination treatment decreased cocaine-seeking under the COC + CUES priming condition in males, and both PRO alone and the combination treatment decreased cocaine-seeking in the CAF + CUES condition in females. Overall, PRO alone was only effective in reducing reinstatement in females, while the combination treatment was consistently effective in reducing reinstatement in both sexes.

1. Introduction

One of the most difficult challenges in the treatment of drug addiction is relapse to drug use after abstinence (see Shaham and Miczek, 2003 for review). Cocaine users are particularly vulnerable to relapse (Ouimette et al., 2007; Volkow et al., 2006; Alleweireldt et al., 2001; Ciccocioppo et al., 2001), yet there are no effective pharmacological treatments for this phase of cocaine addiction (for review, see Zheng and Zhan, 2012; Mendelson and Mello, 1998). Novel approaches are being tested, such as repurposing other medications like atomoxetine (ATO) and progesterone (PRO), which are FDA-approved for treatment of other uses such as attention deficit/hyperactivity disorder (ADHD) treatment and contraception, respectively (Zlebnik and Carroll, 2015; Jones et al., 2012; Economidou et al., 2011; see Carroll and Anker, 2010; Anker and Carroll, 2011).

An emerging treatment for stimulant dependence, ATO, (Sofuoglu and Sewell, 2009; Somaini et al., 2011) is an FDA-approved medication used to treat ADHD (Bymaster et al., 2002), and it has shown promise in reducing stimulant dependence. In rodents, ATO reduced cocaine reinstatement elicited by cues (Zlebnik and Carroll, 2015; Economidou et al., 2011), nicotine withdrawal symptoms (Davis and Gould, 2007) and conditioned stimulus effects of nicotine (Reichel et al., 2007). In humans, ATO decreased both physiological (e.g., blood pressure increases) and subjective (e.g., pleasurable ratings) responses to D-amphetamine (Sofuoglu et al., 2009). However, in some studies, no effects of ATO on stimulant use have been found (Levin et al., 2009; Walsh et al., 2013; Rush et al., 2011).

Another repurposed pharmacological treatment that has shown promise in decreasing stimulant addiction is PRO. Progesterone is used in oral contraceptives and in the maintenance of pregnancies (Jones et al., 2012). Initial evidence showed that, during stages of the estrous cycle when PRO is high and estradiol is low, cocaine self-administration was lower, and rats exhibited less cocaine-induced hyperactivity than during estrous stages when estradiol was high and progesterone was low (Lynch et al., 2000; Jackson et al., 2006; Sell et al., 2000). In humans, exogenous administration of PRO attenuated cocaine use and relapse to cocaine (Yonkers et al., 2014). In rodents, PRO treatment reduced reinstatement of cocaine-seeking (e.g., Anker et al., 2009;

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Feltenstein et al., 2009; for a review, see Carroll and Anker, 2010; Anker and Carroll, 2011), prevented the escalation of cocaine self-administration (Larson et al., 2007), decreased cocaine-induced stereotyped behaviors (Souza et al., 2014) and reduced impulsivity for cocaine self-administration (Smethells et al., under review).

Combination therapies, both behavioral and pharmacological, may be effective strategies for reducing cocaine dependence and relapse (Verrico et al., 2013; Smith et al., 2014), especially when employing medications that show efficacy when used alone (Stoops and Rush, 2014). Recent work in our laboratory indicated that combining a behavioral intervention (i.e. concurrent running in an attached exercise wheel) with PRO was more successful in preventing reinstatement to cocaine-seeking than either treatment alone (Zlebnik et al., 2014). In fact, the combination of wheel-running and ATO produced an additive effect of PRO and ATO on reinstatement of cocaine-seeking behavior (Zlebnik and Carroll, 2015). The purpose of this study was to extend these findings and examine a potential combined effect of ATO and PRO on reinstatement of cocaine-seeking. We hypothesized that ATO and PRO would produce a greater attenuation of reinstatement to cocaine (COC), caffeine (CAF) and/or cue primes than either pharmacological treatment alone.

Additionally, sex-specific effects of ATO, PRO, and their combination were examined. Sex differences were previously reported in the effects of PRO on cocaine dependence in humans, with PRO producing greater effects in females than males (Fox et al., 2013; Evans and Foltin, 2006; for review, see Quinones-Jenab and Jenab, 2010). Animal work with exogenous PRO similarly showed greater effects in females than males (Anker et al., 2009; Zlebnik et al., 2014). While there has been little research on sex differences in treatment effects of ATO on cocaine dependence, some studies involving the therapeutic potential of ATO on ADHD showed different treatment responsivity between sexes (Marchant et al., 2011; Robison et al., 2008). For example, women reported greater improvement on measures of ADHD symptoms than men, and in general, female animals were more responsive than males to treatments for drug-seeking behaviors (see reviews by Anker and Carroll, 2011; Carroll and Anker, 2010).

The goal of the present study was to examine sex-specific effects of ATO, PRO and combination PRO + ATO treatments on reinstatement of cocaine-seeking behavior generated by cues-, cocaine- and caffeine-priming conditions, and a drug + cues condition. Caffeine and caffeine + cues were used as priming conditions, as caffeine produced robust reinstatement of cocaine-seeking (Regier et al., 2014; Weerts and Griffiths, 2003; Green and Schenk, 2002; Schenk et al., 1996; Worley et al., 1994). However, it is not known whether there are sex differences in response to this priming condition. It was hypothesized that females would be more sensitive to the priming effects of caffeine and caffeine with cues, as female rats generally show enhanced sensitivity to drug and/or cue-induced reinstatement compared to males (Anker et al., 2009; Kerstetter et al., 2008; Lynch and Carroll, 2000; Anker and Carroll, 2010). These results will provide useful information for designing sex-specific treatments to prevent relapse to drug-seeking. It was also predicted that females would be more responsive to single PRO and ATO treatments as well as their combinations, as in previous studies female rats showed greater responsivity to drug abuse treatments than males (see reviews by Anker and Carroll, 2011; Carroll and Anker, 2010).

2. Materials and methods

2.1. Animals

Forty-five female and forty-three male adult Wistar rats (weighing 200–224 and 250–274 g on arrival and with age ranges of 63–77 days) from Harlan Sprague-Dawley Inc. (Madison, WI, USA) were used in the present study. Initially, rats were pair-housed in plastic cages and allowed ad libitum access to food (Teklad 2018, Harlan Laboratories, Madison, WI, USA) and water. They were habituated to the facility for at least 3 days before being beginning the experiment. All experiments took place during the light phase of the cycle (lights on from 0600 to 1800 h). Rooms were maintained at 24 °C with 40–50% humidity.

Once the experiments began, rats were transferred to the operant conditioning chambers, where they were single-housed for the duration of the study. Rats were allowed free access to water, but they were restricted to 16 g (female) or 20 g (male) of food per day based on previous work (Zlebnik et al., 2014). Experimental sessions were started at 0900 h, and food was given post session at 1515 h. Body weights were recorded weekly, and rat health was checked daily. All experiments were approved by the Institutional Animal Care and Use Committee (Protocol #1307-30762A) in compliance with the Guide for the Care and Use of Animals (National Research Council, 2011).

2.2. Apparatus

Rats were housed in custom-built octagonal operant conditioning chambers previously described by Anker et al. (2007) and each chamber was contained in a sound-attenuating wooden box with a ventilation fan. There were two levers on opposite sides of the chamber with LED stimulus lights above each lever along with a house light (4.76 W) in an upper corner. A syringe pump (PHM-100, Med Associates. St. Albans, VT) delivered cocaine infusions via a swivel-tether system (375/22PS, Instech, Plymouth Meeting, PA, USA; C313CS-MN, Plastics One, Roanoke, VA, USA). The tether was attached to the rat by a harness (CIH95AB, Instech). MED-PC IV software running on PC computers controlled all experiments and collected data.

2.3. Drugs

Cocaine HCl (National Institute of Drug Abuse, Research Triangle Institute, Research Triangle Park, NC) was dissolved in sterile saline to a concentration of 1.6 mg cocaine HCl/1 ml saline. Heparin (5 USP/ml) was added to enhance catheter patency. Cocaine was infused at 0.025 ml/s, and the duration of the infusion was set based on the weight of the rat (1 s/100 g), resulting in a delivery of a standard 0.4 mg/kg dose. Progesterone (Sigma-Aldrich, St. Louis, MO) was dissolved in peanut oil (Sigma-Aldrich, VEH, 0.625 mg/ml) and administered subcutaneously (s.c.) at a final dose of 0.5 mg/kg that produced physiologically-relevant levels of PRO in previous studies (Jackson et al., 2006; White and Uphouse, 2004) and previously decreased drug-seeking behaviors in our laboratory (Zlebnik et al., 2014; Anker et al., 2012). Additionally, in a dose-response study, 0.5 mg/kg PRO significantly decreased cocaine-induced hyperlocomotion (Niyomchai et al., 2005). Atomoxetine HCl (ATO, Tocris Biosciences, Bristol, UK) was dissolved in sterile saline to reach a concentration of 3 mg/ml and administered intraperitoneally (i.p.) at a final dose of 1.5 mg/kg. This dose was chosen based on our previous work in both female and male rats showing that ATO at 1.5 mg/kg reduced cocaine-induced reinstatement in both high and low-impulsive rats (Zlebnik and Carroll, 2015), and similar doses affected the reinforcement value of cocaine but not food (Economidou et al., 2011). Both treatment drugs (PRO and ATO) and their corresponding vehicles (peanut oil and saline [SAL], given s.c. and i.p. respectively) were acutely administered 30 min prior to session (08:30) on priming sessions, and treatment was not given before saline priming sessions. Reinstatement doses of cocaine (COC, 10 mg/kg) and caffeine (CAF, 5 mg/kg) were administered i.p. at the start of the session (09:00).

2.4. Surgical procedures

Rats were surgically implanted with a chronic indwelling jugular catheter in a procedure developed by Weeks (1972) and modified by Carroll et al. (1981), Lynch and Carroll (1999) and Zlebnik et al.