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Effects of 21-day *d*-amphetamine and risperidone treatment on cocaine vs food choice and extended-access cocaine intake in male rhesus monkeys

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ABSTRACT

Background: Clinical trial data suggest amphetamine treatment is most efficacious in moderate to high frequency cocaine users. However, preclinical studies have examined amphetamine treatment effects under relatively limited cocaine access conditions with low to moderate cocaine intakes. This study determined *d*-amphetamine treatment effects on cocaine self-administration in rhesus monkeys under cocaine access conditions allowing for high daily cocaine intake. For comparison and as a negative control, treatment effects with the antipsychotic risperidone were also examined.
Methods: Continuous 21-day treatments with ramping doses of *d*-amphetamine (days 1–7: 0.032 mg/kg/h; days 8–21: 0.1 mg/kg/h, i.v.) or risperidone (days 1–7: 0.001 mg/kg/h; days 8–14: 0.0032 mg/kg/h; days 15–21: 0.0056 mg/kg/h, i.v.) were administered to rhesus monkeys (n = 4) with daily access to two types of cocaine self-administration sessions: (1) a 2-h 'choice' session with concurrent availability of 1-g food pellets and intravenous cocaine injections (0–0.1 mg/kg per injection) and (2) a 20-h 'extended-access' session with 0.1 mg/kg per injection cocaine availability.
Results: Total daily cocaine intake increased >6-fold during extended cocaine access. *d*-Amphetamine significantly decreased total cocaine intake, but not cocaine vs food choice. In contrast, risperidone did not significantly alter either total cocaine intake or cocaine vs. food choice.
Conclusions: These results confirm and extend previous results supporting treatment effectiveness for monoamine releasers, but not dopamine antagonists, to reduce cocaine self-administration. Moreover, these results suggest amphetamine treatment efficacy to decrease preclinical cocaine vs. food choice may depend upon cocaine access conditions.

1. Introduction

Cocaine addiction is a significant and global public health problem, and an estimated 0.4% of the global population has used cocaine at least once (UNODC, 2015). In addition, approximately 6.9% of all substance abuse treatment admissions report that cocaine is the primary abused substance (SAMHSA, 2015). Currently, there is no Food and Drug Administration-approved pharmacotherapy for cocaine addiction (Acri and Skolnick, 2013; Czoty et al., 2016). Taken together, the persistence of cocaine addiction and the absence of effective treatments support continued preclinical research in the development of effective therapeutic strategies.

Over the past decade, "agonist" candidate medications, such as the dopamine and norepinephrine releaser *d*-amphetamine, have emerged as the most promising pharmacotherapeutics for cocaine addiction (Banks et al., 2015b; Negus and Henningfield, 2015; Nuijten et al., 2016; Pérez-Mañá et al., 2011). In contrast, "antagonist" candidate medications, such as the dopamine antagonists flupenthixol or risperidone, have consistently demonstrated poor efficacy to attenuate the abuse-related effects of cocaine in both preclinical (John et al., 2015; Negus, 2003; Woolverton and Balster, 1981) and human laboratory drug self-administration studies (Haney et al., 2001), and clinical trials (for review, see Indave et al., 2016). Overall, this literature supports preclinical research aimed towards improving our understanding of the environmental conditions under which amphetamine treatment decreases cocaine self-administration.

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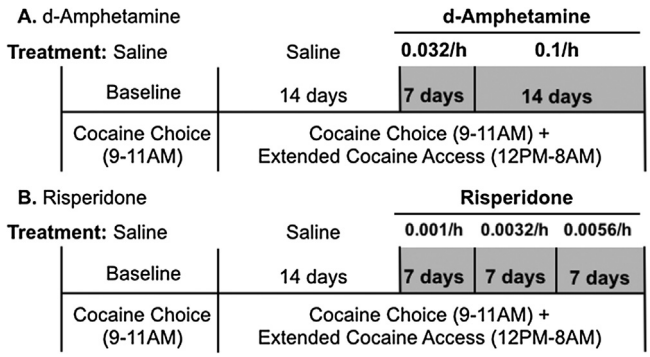

Fig. 1. Experimental timeline. Following a baseline period during which cocaine self-administration was only available during daily 2-h cocaine vs food choice sessions (0900–1100 h), monkeys were subsequently provided access to cocaine during both choice sessions and daily 20-h extended access sessions (1200–0800 h). During extended-access sessions, 0.1 mg/kg/injection cocaine was available under a FR 10/time out 15-min schedule of reinforcement. (A) After 14 days of extended cocaine access, 0.032 mg/kg/h *d*-amphetamine was continuously infused for 7 days, and then the dose was increased to 0.1 mg/kg/h *d*-amphetamine for 14 days for a total of 21 consecutive *d*-amphetamine treatment days. (B) After 14 days of extended cocaine access, 0.001 mg/kg/h risperidone was continuously infused for 7 days, then 0.0032 mg/kg/h for 7 days, and then 0.0056 mg/kg/h for 7 days for a total of 21 consecutive risperidone treatment days.

One important environmental determinant of medication treatment efficacy may be cocaine access conditions and corresponding cocaine intake. For example, a recent clinical trial suggested that amphetamine in combination with topiramate treatment efficacy varied according to baseline cocaine use frequency, such that amphetamine treatment was most effective in patients who reported the most frequent cocaine use (Mariani et al., 2012). Consistent with this clinical trial, preclinical studies have also suggested differential treatment sensitivity to acute pharmacological manipulations as a consequence of baseline cocaine self-administration rates (Wee et al., 2009). Previous studies from our laboratory (Banks et al., 2013b, 2015a; Negus, 2003) and others (Thomsen et al., 2013) have demonstrated *d*-amphetamine treatment efficacy to attenuate cocaine vs food choice under 2-h cocaine access conditions that allow for limited (~1.2 mg/kg) cocaine intake. Whether *d*-amphetamine treatment retains efficacy to decrease preclinical cocaine vs food choice under extended cocaine access conditions allowing for high daily cocaine intake remains to be empirically determined.

Accordingly, the present study aim was to determine *d*-amphetamine treatment effects on cocaine vs. food choice under cocaine access conditions allowing for high daily cocaine intake. Specifically, 21-day *d*-amphetamine treatment effects were examined under conditions that allowed cocaine access 22 h/day during two types of cocaine self-administration sessions: (1) a 2-h cocaine vs. food choice sessions to assess pharmacological treatment efficacy to reallocate behavior away from cocaine choice and towards food choice, and (2) a 20-h extended cocaine access session to assess treatment efficacy during high daily cocaine intakes (Fig. 1). For comparison, and as a negative control, we also determined risperidone treatment effects under the same experimental conditions. Although risperidone has been extensively evaluated as a candidate medication for cocaine addiction in clinical trials (Grabowski et al., 2000; Loebl et al., 2008; Smelson et al., 2004), risperidone treatment on cocaine self-administration has not been determined in preclinical studies. We hypothesized that *d*-amphetamine treatment would attenuate both cocaine vs food choice and extended cocaine access self-administration. Furthermore, we hypothesized risperidone treatment would fail to attenuate both cocaine vs. food choice and extended cocaine access self-administration consistent with previous human laboratory and clinical trial results.

2. Methods

2.1. Animals

A total of six adult male rhesus monkeys (*Macaca mulatta*) of either Indian or Chinese origin served as subjects and were surgically implanted with a double-lumen catheter (Reiss Manufacturing, Blackstone, VA or STI Flow, Raleigh, NC) inserted into a major vein (femoral or jugular). All subjects had prior cocaine self-administration histories (Banks et al., 2013a; Hutsell et al., 2016). Monkeys weighed 9–13 kg and were maintained on a diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey Biscuits no. 5045; PMI Nutrition, St. Louis, MO) provided after daily choice sessions. Water was continuously available via an automatic watering system. A 12-h light-dark cycle was in effect (lights on from 0600 to 1800 h).

Animal research and maintenance were conducted according to the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011) and the ARRIVE guidelines (Kilkenny et al., 2010). Animal facilities were licensed by the United States Department of Agriculture and accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved the research and enrichment protocols. Monkeys had visual, auditory, and olfactory contact with other monkeys throughout the study. Operant procedures and foraging devices were provided for environmental manipulation and enrichment. Videos were played daily in animal housing rooms to provide additional environmental enrichment.

2.2. Apparatus and catheter maintenance

Monkeys were housed individually in well-ventilated, stainless steel chambers that also served as experimental chambers. Each chamber was equipped with a custom operant panel mounted on the front wall. Three square translucent response keys were arranged in a horizontal row, and only the left and right keys were used in the present study. Each chamber was also equipped with a pellet dispenser (Model ENV-203-1000; Med Associates, St Albans, VT) and two syringe pumps (Model PHM-108; Med Associates), one for each lumen of the double lumen catheter. One syringe pump (the "self-administration" pump) delivered response-contingent cocaine injections. The second syringe pump (the "treatment" pump) delivered noncontingent saline, *d*-amphetamine, or risperidone injections through the second lumen of the catheter at a programmed rate of 0.1-ml infusions every 20 min from 1200 to 1100. The intravenous catheter was protected by a tether and jacket system (Lomir Biomedical, Malone, NY) that allowed the monkeys to move freely. Catheter patency was periodically evaluated by intravenous (i.v.) ketamine (3 mg/kg) administration through the catheter lumen, and after any treatment that decreased cocaine vs food choice. The catheter was considered patent if ketamine produced a loss of muscle tone within 10 s.

2.3. Behavioral procedures

Initially, monkeys responded in daily 2-h choice sessions (0900–1100 h) that consisted of a five-component concurrent schedule of food pellet and i.v. cocaine availability as previously described (Negus, 2003). During each component, responses on the left key were reinforced with food (1-g banana-flavored pellet; Test Diets, Richmond, IN) according to a fixed-ratio (FR) 100 schedule, and responses on the right key were reinforced with i.v. cocaine (0–0.1 mg/kg/injection) according to an FR 10 schedule. A response on one key reset the ratio requirement on the alternative key. Each reinforcer delivery was followed by a 3-s timeout during which all stimulus lights were extinguished, and responding