Drug and Alcohol Dependence 181 (2017) 85–93

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

Maintenance on naltrexone + amphetamine decreases cocaine-vs.-food choice in male rhesus monkeys

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ARTICLE INFO

Keywords:
Cocaine
Choice
Amphetamine
Naltrexone
Rhesus monkey
Morphine

ABSTRACT

Background: Cocaine use disorder remains a significant public health issue for which there are no FDA-approved pharmacotherapies. Amphetamine maintenance reduces cocaine use in preclinical and clinical studies, but the mechanism of this effect is unknown. Previous studies indicate a role for endogenous opioid release and subsequent opioid receptor activation in some amphetamine effects; therefore, the current study examined the role of mu-opioid receptor activation in *d*-amphetamine treatment effects in an assay of cocaine-vs-food choice.
Methods: Adult male rhesus monkeys with double-lumen intravenous catheters responded for concurrently available food pellets and cocaine injections (0–0.1 mg/kg/injection) during daily sessions. Cocaine choice and overall reinforcement rates were evaluated during 7-day treatments with saline or test drugs.
Results: During saline treatment, cocaine maintained a dose-dependent increase in cocaine-vs.-food choice. The mu-opioid receptor agonist morphine (0.032–0.32 mg/kg/h) dose-dependently increased cocaine choice and decreased rates of reinforcement. A dose of the mu-selective opioid receptor antagonist naltrexone (0.0032 mg/kg/h) that completely blocked morphine effects had no effect on cocaine choice when it was administered alone, but it enhanced the effectiveness of a threshold dose of 0.032 mg/kg/h amphetamine to decrease cocaine choice without also enhancing nonselective behavioral disruption by this dose of amphetamine. Conversely, the kappa-selective opioid antagonist norbinalorphimine did not enhance amphetamine effects on cocaine choice.
Conclusions: These results suggest that amphetamine maintenance produces mu opioid-receptor mediated effects that oppose its anti-cocaine effects. Co-administration of naltrexone may selectively enhance amphetamine potency to decrease cocaine choice without increasing amphetamine potency to produce general behavioral disruption.

1. Introduction

There are currently no pharmacotherapies approved by the United States Food and Drug Administration for treatment of cocaine use disorder; however, maintenance on the dopamine and norepinephrine releaser amphetamine has been shown repeatedly and across a range of conditions to selectively decrease cocaine self-administration in rats (Chiodo et al., 2008; Thomsen et al., 2012), monkeys (Banks et al., 2013a; Czoty et al., 2011; Negus, 2003; Negus and Mello, 2003), and humans (Greenwald et al., 2010; Rush et al., 2010). Furthermore, clinical trials have demonstrated the effectiveness of amphetamine maintenance to decrease metrics of cocaine use in cocaine-dependent patients (Grabowski et al., 2001; Mariani et al., 2012; Nuijten et al., 2016; Perez-Mana et al., 2011). However, numerous obstacles exist to the clinical deployment of amphetamine as a maintenance medication for treatment of cocaine use disorder (see Negus and Henningfield, 2015).

The mechanism by which amphetamine produces its therapeutic reductions in cocaine-maintained behavior is unknown, but elucidating this mechanism could reveal novel treatment strategies. Although the primary targets of amphetamine are the dopamine and norepinephrine transporters (Rothman et al., 2001), amphetamine also promotes the release of endogenous opioids (Mick et al., 2014). Furthermore, opioid antagonist doses that do not alter abuse-related cocaine effects have been shown to reduce amphetamine effects. For example, naloxone in rodents (Andrews and Holtzman, 1987; Dettmar et al., 1978; Hitzemann et al., 1982; Holtzman, 1974) or naltrexone in monkeys (Winslow and Miczek, 1988) attenuated increases in locomotor activity

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http://dx.doi.org/10.1016/j.drugalcdep.2017.09.020
Received 28 July 2017; Received in revised form 1 September 2017; Accepted 20 September 2017
Available online 13 October 2017
0376-8716/

produced by amphetamine. Furthermore, naloxone blunted the abuse-related effects of amphetamine on intracranial self-stimulation in rats (Esposito et al., 1980; Holtzman, 1976), and naltrexone decreased amphetamine self-administration in monkeys (Jimenez-Gomez et al., 2011), suggesting a role for opioid receptors in mediating at least some behavioral effects of amphetamine. The role of opioid systems in the therapeutic effectiveness of amphetamine maintenance to decrease cocaine use has not been investigated.

The aim of the current study was to evaluate the role of mu-opioid receptors in mediating amphetamine treatment effects on cocaine self-administration using a cocaine vs. food choice procedure in rhesus monkeys (Negus, 2003). The choice procedure was chosen for three primary reasons (Banks and Negus, 2012, 2017; Czoty et al., 2016; Heyman, 2009; Jones and Comer, 2013). First, drug choice procedures provide a dependent measure of drug reinforcement (i.e., percent drug choice) that is relatively independent of treatment effects on overall rates of responding or reinforcement. Second, drug choice procedures provide a simplified preclinical model of natural environments that contain both drug and non-drug reinforcers, and these procedures can be used to study determinants of behavioral allocation toward or away from drug use. Specifically, clinical drug abuse treatments seek not only to reduce drug use but also to promote more adaptive behaviors maintained by non-drug reinforcers, and preclinical choice procedures provide a useful tool to examine effects of candidate treatments on behavioral allocation. Finally, drug choice procedures are also widely used in human laboratory studies, so their use in preclinical research enhances preclinical-to-clinical translation. To examine the role of mu-opioid receptor activation in the therapeutic effects of amphetamine, we first tested the hypothesis that mu receptor activation would be sufficient to mimic amphetamine-induced decreases in cocaine choice by treating monkeys with the mu agonist morphine (Bowen et al., 2002; Emmerson et al., 1994). Morphine maintenance increased rather than decreased cocaine choice, suggesting that any mu receptor-activating effects of amphetamine might oppose rather than contribute to amphetamine-induced decreases in cocaine choice. Accordingly, follow-up studies evaluated the effects of co-administering amphetamine and the opioid antagonist naltrexone to test the hypothesis that blockade of mu receptors would enhance amphetamine-induced decreases in cocaine choice. Naltrexone was selected as the opioid antagonist for two reasons. Firstly, it is moderately selective for mu vs. other opioid receptors, its relative potency and selectivity as a mu antagonist in monkeys are well established, and more selective reversible and systemically active mu antagonists are not currently available (Bidlack and Matthews, 2009; Bowen et al., 2002; Emmerson et al., 1994; Ko et al., 1998). Secondly, naltrexone is approved as a maintenance medication for treatment of opioid and ethanol abuse, and it showed some effectiveness as a candidate medication for treatment of amphetamine abuse (Anton, 2009; Jayaram-Lindstrom et al., 2008; Severino and Kosten, 2009). Nonetheless, because naltrexone has only modest ($\leq$10-fold) selectivity for mu vs. kappa opioid receptors (Emmerson et al., 1994; Ko et al., 1998), the effects of amphetamine were also examined in combination with the kappa-selective antagonist norbinaltorphimine (Butelman et al., 1998, 1993).

2. Methods

2.1. Subjects

A total of 11 adult male rhesus monkeys (*Macaca mulatta*) were housed individually and had extensive behavioral and drug histories, including exposure to a range of monoaminergic compounds (e.g., *d*-amphetamine, pimavanserin, lorcaserin, and lisdexamphetamine), as well as more limited exposure to opioid and nicotinic compounds. Monkeys weighed 8.3–13.6 kg and were maintained on a diet of primate chow (LabDiet High Fiber Monkey Biscuits; PMI Feeds, St. Louis, MO) and fresh fruit and vegetables. They had continuous access to water in the home chamber and were maintained under controlled temperature on a 12/12-h light-dark cycle (lights on from 0600 to 1800 h). Environmental enrichment was provided on a daily basis. The maintenance and experimental use of animals was carried out in accordance with the 2011 Guide for Care and Use of Laboratory Animals (National Research Council Committee for the Update of the Guide for the Care and Use of Laboratory, 2011). The facility was accredited by the AAALAC international and all experimental protocols were approved by the Institutional Animal Care and Use Committee.

2.2. Surgery

Monkeys were treated with intramuscular (IM) ketoprofen (2 mg/kg/day; Zoetis Inc., Kalamazoo, MI) for a total of 5 days, beginning the day before surgery. On the day of surgery, monkeys were initially anesthetized with ketamine (10 mg/kg IM; Vedco Inc., St. Joseph, MO), followed by injections of cefazolin (30 mg/kg IM; WG Critical Care LLC, Paramus, NJ), xylazine (1 mg/kg IM; Lloyd Laboratories, Shenandoah, IA) and atropine (0.04 mg/kg IM; Med-Pharmex Inc., Pomona, CA); anesthesia was maintained by isoflurane (1–3%; Zoetis Inc.). A double-lumen intravenous (IV) catheter (Tygon 3350 i.d. = 0.76 mm, o.d. = 2.36 mm; STI Components, Roanoke, VA or silicone extruded i.d. = 0.76 mm, o.d. = 2.36 mm; Reiss Manufacturing, Blackstone, VA) was surgically implanted into a femoral or jugular vein and secured to the vessel with sutures (Ethibond Excel 3-0; Ethicon Inc., Somerville, NJ). The catheter extended from the vessel to an exit point at the midscapular region of the back.

2.3. Apparatus

Each housing chamber was equipped with a customized operant response panel, which had two response keys that could be illuminated red or green, and a pellet dispenser (ENV-203–1000; Med Associates Inc., St. Albans, VT) that delivered 1 g banana-flavored food pellets (Grain-Based Non-Human Primate Tablet; TestDiet, St. Louis, MO) to a receptacle below the operant panel. The externalized portion of the catheter was routed through a custom jacket and tether system connected to a dual-channel fluid swivel (Lomir Biomedical, Quebec, Canada) on the chamber top and then to two safety syringe pumps (PHM-108; Med Associates Inc.), one for each lumen of the double-lumen catheter. One pump was used to deliver contingent cocaine injections through one lumen of the double-lumen catheter. The second pump was used to deliver noncontingent saline or drug treatments through the second lumen at a programmed rate of 0.1 ml injections every 20 min from 12:00 p.m. each day until 11:00 a.m. the next morning.

2.4. Cocaine vs. food choice procedure

Behavioral sessions were conducted seven days a week from 9:00 a.m. to 11:00 a.m. as described previously (Banks et al., 2013a,b, 2011). Under the terminal schedule, each session consisted of five 20-min components separated by 5 min time-out periods, and a maximum of 10 reinforcers could be earned in each component. During each component, the left key was illuminated red and completion of a fixed-ratio (FR) 100 resulted in delivery of a food pellet. In addition, completion of an FR 10 on the right key resulted in delivery of the unit cocaine dose available during that component (0, 0.0032, 0.01, 0.032, or 0.1 mg/kg per injection for components 1–5, respectively). The cocaine-associated key was not illuminated during the first component, and during subsequent components, it was transilluminated with green stimulus lights that flashed on and off in 3 s cycles (i.e., longer flashes associated with higher cocaine doses). Ratio requirement completion on either key initiated a 3-s timeout, during which all stimulus lights were turned off, and responding had no scheduled consequences. Behavior was considered stable when the lowest unit cocaine dose maintaining