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Effects of 7-day continuous D-amphetamine, methylphenidate, and cocaine treatment on choice between methamphetamine and food in male rhesus monkeys

Kathryn L. Schwienteck[a], Matthew L. Banks[a,b,*]

[a] Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA
[b] Institute for Drug and Alcohol Studies, Virginia Commonwealth University, USA

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ABSTRACT

Background: Methamphetamine addiction is a significant public health problem for which no Food and Drug Administration-approved pharmacotherapies exist. Preclinical drug vs. food choice procedures have been predictive of clinical medication efficacy in the treatment of opioid and cocaine addiction. Whether preclinical choice procedures are predictive of candidate medication effects for other abused drugs, such as methamphetamine, remains unclear. The present study aim was to determine continuous 7-day treatment effects with the monoamine releaser D-amphetamine and the monoamine uptake inhibitor methylphenidate on methamphetamine vs. food choice. In addition, 7-day cocaine treatment effects were also examined.

Methods: Behavior was maintained under a concurrent schedule of food delivery (1-g pellets, fixed-ratio 100 schedule) and methamphetamine injections (0–0.32 mg/kg/injection, fixed-ratio 10 schedule) in male rhesus monkeys ($n=4$). Methamphetamine choice dose–effect functions were determined daily before and during 7-day periods of continuous intravenous treatment with D-amphetamine (0.01–0.1 mg/kg/h), methylphenidate (0.032–0.32 mg/kg/h), or cocaine (0.1–0.32 mg/kg/h).

Results: During saline treatment, increasing methamphetamine doses resulted in a corresponding increase in methamphetamine vs. food choice. Continuous 7-day treatments with D-amphetamine, methylphenidate or cocaine did not significantly attenuate methamphetamine vs. food choice up to doses that decreased rates of operant responding. However, 0.1 mg/kg/h D-amphetamine did eliminate methamphetamine choice in two monkeys.

Conclusions: The present subchronic treatment results support the utility of preclinical methamphetamine choice to evaluate candidate medications for methamphetamine addiction. Furthermore, these results confirm and extend previous results demonstrating differential pharmacological mechanisms between cocaine choice and methamphetamine choice.

1. Introduction

Methamphetamine addiction is a significant and global public health problem. For example, methamphetamine was the most frequently identified phenethylamine and the most frequently reported compound by federal Drug Enforcement Agency Laboratories (2014). In addition, the 2013 National Survey on Drug Use and Health, revealed that the number of individuals aged 12 or older who were current users of methamphetamine in 2013 was 595,000 and this number has remained relatively stable over the past decade (SAMHSA, 2014). Currently, there is no Food and Drug Administration (FDA)-approved pharmacotherapy for the treatment of methamphetamine addiction (Brensilver et al., 2013; Carson and Taylor, 2014; Karila et al., 2010). In summary, the prevalence of methamphetamine abuse and absence of effective treatment strategies for methamphetamine addiction suggests a need for preclinical studies in the development and evaluation of potential pharmacotherapies.

One method of preclinical model validation is a reverse translational or "bedside-to-bench" approach where candidate medications have been first evaluated in either human laboratory drug self-administration studies or clinical trials and then

* Corresponding author at: Department of Pharmacology and Toxicology, Virginia Commonwealth University, 410 N. 12th Street, PO Box 980613, Richmond, VA 23298, USA.
E-mail address: mbanks7@vcu.edu (M.L. Banks).

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subsequently tested in preclinical models to determine concordance of results. The most evident example of this approach in the drug addiction literature has been methadone treatment for heroin addiction (Dole et al., 1966; Griffiths et al., 1975; Negus, 2006). A more recent example of this reverse translation approach might be the demonstration of amphetamine treatment efficacy for cocaine addiction (Grabowski et al., 2001; Negus, 2003). Overall, the good concordance between candidate medication efficacy in clinical trials and subchronic candidate medications treatment effects in preclinical drug vs. food choice procedures for opioids (Haney and Spealman, 2008; Negus and Banks, 2013) and cocaine (Banks et al., 2015; Haney and Spealman, 2008) support the potential extension of this approach to other abused drugs, such as methamphetamine.

Because of the relative success of agonist-based pharmacotherapy approaches for opioids and cocaine, agonist-based approaches for methamphetamine addiction have been the most extensively examined (Brensilver et al., 2013; Karila et al., 2010). In particular, the monoamine uptake inhibitor methylphenidate and the monoamine releaser D-amphetamine have been two of the most extensively evaluated candidate medications in clinical trials outside of bupropion. Methylphenidate treatment effects have been equivocal with three clinical trials (Konstenius et al., 2014; Rezaei et al., 2015; Tiihonen et al., 2007) demonstrating a reduction in amphetamine/methamphetamine use and three clinical trials (Konstenius et al., 2010; Ling et al., 2014; Miles et al., 2013) demonstrating no effect on amphetamine/methamphetamine use. Furthermore, D-amphetamine treatment efficacy has not been significant in either clinical trials (Galloway et al., 2011; Longo et al., 2010) or a human laboratory methamphetamine self-administration study (Pike et al., 2014). However, there are two potential reasons for these equivocal or negative clinical results. First, some of these clinical trials did not distinguish between enrolled amphetamine-dependent and methamphetamine-dependent individuals. Given potential differences between amphetamine and methamphetamine interactions at the dopamine transporter (Goodwin et al., 2009), there may also be differential treatment sensitivity between these two drug-dependent populations. Second, candidate medication dosing regimens in clinical trials may be restricted for safety reasons. For example, the largest methylphenidate dose (180 mg/day; ~0.11 mg/kg/h) (Konstenius et al., 2014) examined was also a clinical trial that reported a treatment effect.

Given that preclinical studies have both greater control over drug exposure and are able to evaluate both a broader dose range and larger doses than in human drug self-administration studies or clinical trials, the present studies were designed to address these two potential reasons for the equivocal clinical trial results. A concurrent schedule of methamphetamine and food pellet presentation was utilized because preclinical choice procedures have been predictive of candidate medication effects for cocaine (Banks et al., 2015) and heroin (Negus and Banks, 2013). Subchronic 7-day D-amphetamine and methylphenidate treatment effects were determined to model treatment regimens in human laboratory drug self-administration studies and clinical trials. Moreover, to the best of our knowledge, subchronic D-amphetamine or methylphenidate treatment effects on preclinical methamphetamine self-administration have not been previously reported. Furthermore, there are reported differences between cocaine choice and methamphetamine choice in monkeys (John et al., 2015) and the degree to which amphetamine treatment differentially alters cocaine choice vs. methamphetamine choice remains unknown. In addition, we also determined continuous 7-day cocaine treatment effects on methamphetamine choice. Previous studies have demonstrated that methamphetamine treatment reduced cocaine use in a clinical trial (Mooney et al., 2009) and reduced cocaine choice in monkeys (Banks et al., 2011). If cocaine treatment did not attenuate methamphetamine choice, this result would further support dissociation of cocaine choice and methamphetamine choice pharmacological mechanisms.

2. Methods

2.1. Subjects

Studies were conducted in total of five adult male rhesus monkeys (*Macaca mulatta*) surgically implanted with a double-lumen catheter (0.76 mm ID × 2.36 mm OD, STI Flow, Morrisville, NC) inserted into a femoral or jugular vein and had an experimental history (Banks and Blough, 2015). Monkeys were maintained on a diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey Biscuits #5045, PMI Nutrition Inc., St. Louis, MO) delivered in the afternoon post-operant behavioral session. Water was continuously available in the housing chamber and a 12 h light–dark cycle was in effect. Monkeys had visual, auditory and olfactory contact with other monkeys throughout the study. Operant procedures and foraging toys were provided for environmental manipulation and enrichment. Videos or music was also played daily in animal housing rooms to provide additional environmental enrichment. Animal research and maintenance were conducted according to the 2011 Guide for the Care and Use of Laboratory Animals (8th edition) as adopted and promulgated by the National Institutes of Health. 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 environmental enrichment protocol.

2.2. Apparatus

The housing chamber served as the experimental chamber and was equipped with a custom operant panel, a pellet dispenser (Med Associates, Model ENV-203-1000, St. Albans, VT), and two syringe pumps (Model PHM-108, Med Associates). One "self-administration" pump delivered contingent methamphetamine injections through one lumen of the catheter. The second "treatment" pump delivered a 0.1 mL saline, D-amphetamine, methylphenidate, or cocaine noncontingent infusion through the second lumen of the catheter at a programmed rate of every 20 min from 12:00 p.m. each day until 11:00 a.m. the following morning. The intravenous catheter was protected by a customized stainless steel tether and jacket system (Lomir Biomedical, Malone, NY) that permitted monkeys to move freely in the home chamber. Catheter patency was periodically evaluated by intravenous ketamine (5 mg/kg) administration through one lumen of the double-lumen catheter and after any pharmacological manipulation that produced a decrease in methamphetamine vs. food choice. The catheter was considered patent if intravenous ketamine administration produced muscle tone loss within 10 s.

2.3. Methamphetamine versus food choice procedure

Daily experimental sessions were conducted from 09:00 to 11:00 h in each monkey's home chamber as described previously (Banks and Blough, 2015). The terminal choice procedure consisted of five 20-min components, with a different unit methamphetamine dose available during each successive component (0, 0.01, 0.032, 0.1, and 0.32 mg/kg/injection during components 1–5, respectively). Manipulating the injection volume controlled the methamphetamine dose (0, 0.03, 0.1, 0.3, and 1.0 mL/injection, respectively). Components were separated by 5-min timeout periods. During each component, the left, food-associated key was transilluminated red, and completion of the FR requirement (FR100) resulted in 1-g food pellet delivery. The right, methamphetamine-associated key was transilluminated green, and completion of the FR requirement (FR10) resulted in delivery of the intravenous unit methamphetamine dose available during that component. Stimulus lights for the methamphetamine-associated key were flashed on and off in 3 s cycles, and longer flashes were associated with higher methamphetamine doses. Monkeys could complete up to a total of 10 ratio requirements on both the food- and methamphetamine-associated keys. Responding on either key reset the ratio requirement on the other key. Completion of each ratio requirement initiated a 30-s timeout, during which all stimulus lights were turned off, and responding had no programmed consequences. Choice behavior was considered stable when the lowest unit methamphetamine dose maintaining greater than 80% methamphetamine vs. food choice varied by ≤0.5 log units for 3 consecutive days.

Once methamphetamine vs. food choice was stable, test sessions were conducted to determine continuous 7-day D-amphetamine (0.01–0.1 mg/kg/h), methylphenidate (0.032–0.32 mg/kg/h), or cocaine (0.1–0.32 mg/kg/h) treatment effects on methamphetamine vs. food choice. D-Amphetamine and methylphenidate treatments were tested up to doses that either decreased methamphetamine choice or rates of operant responding primarily during components when food was chosen. The 3-day period of saline infusions before each test drug treatment was used as the baseline "+saline." At the conclusion of each 7-day treatment periods, saline infusions were reinstituted for at least 4 days and until methamphetamine vs. food choice had returned to pretreatment levels. D-Amphetamine, methylphenidate, and