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Alternative reinforcer response cost impacts methamphetamine choice in humans

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ABSTRACT

Methamphetamine use disorders are a persistent public health concern. Behavioral treatments have demonstrated that providing access to non-drug alternative reinforcers reduces methamphetamine use. The purpose of this human laboratory experiment was to determine how changes in response cost for non-drug alternative reinforcers influenced methamphetamine choice. Seven subjects with past year histories of recreational stimulant use completed a placebo-controlled, crossover, double-blind protocol in which they first sampled doses of oral methamphetamine (0, 8 or 16 mg) and completed a battery of subject-rated and physiological measures. During subsequent sessions, subjects then made eight discrete choices between 1/8th of the sampled dose and an alternative reinforcer ($0.25). The response cost to earn a methamphetamine dose was always 500 responses (FR500). The response cost for the alternative reinforcer varied across sessions (FR500, FR1000, FR2000, FR3000). Methamphetamine functioned as a positive reinforcer and produced prototypical stimulant-like effects (e.g., elevated blood pressure, increased ratings of Stimulated). Choice for doses over money was sensitive to changes in response cost for alternative reinforcers in that more doses were taken at higher FR values than at lower FR values. Placebo choices changed as a function of alternative reinforcer response cost to a greater degree than active methamphetamine choices. These findings suggest that manipulating the effort necessary to earn alternative reinforcers could impact methamphetamine use.

1. Introduction

Methamphetamine use remains a persistent public health concern. Data from the National Survey on Drug Use and Health (NSDUH) suggest that 353,000 Americans reported past-month methamphetamine use and 105,000 individuals indicated past-year initiation of methamphetamine use in 2010 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011). Additionally, methamphetamine use is commonly associated with comorbid psychiatric problems and disorders as well as needle sharing and risky sexual behaviors, which can lead to increased risk of contracting HIV (see Semple et al., 2004; Shoptaw et al., 2005, 2006; Zweben et al., 2004). Because of these risks, methods for preventing or reducing methamphetamine use need be investigated.

Efforts to identify a pharmacotherapy for methamphetamine dependence have yet to produce a widely effective medication (see Karila et al., 2010; Rush et al., 2009, for reviews). Behavioral treatments, by contrast, show promise. Contingency management procedures are effective for substance-use disorders in general (see Petry, 2000, for a review) and for methamphetamine-use disorders in particular (e.g., Petry et al., 2005; Reback et al., 2010; Roll et al., 2006a,b; Roll and Shoptaw, 2006). Contingency management programs encourage methamphetamine users to abstain from methamphetamine-taking behavior by using alternative reinforcers to increase objectively verified drug abstinence (e.g., providing drug-negative urine samples). For example, Roll et al. (2006b) assessed the efficacy of a contingency management program relative to the Matrix model in individuals who met DSM-IV criteria for methamphetamine abuse or dependence. Subjects in the contingency management group were allowed to earn tokens, which were exchangeable for prizes. Some of these tokens provided praise for negative samples (i.e., were marked "Good Job"), while others could be exchanged for prizes of differing values (e.g., bus tokens, snacks, compact disc players, telephones). Subjects in the contingency management group submitted significantly more negative samples and had significantly longer periods of abstinence. Contingency management programs not only effectively reduce drug use; they may also reduce some of the behaviors associated with use of drugs like risky sexual behaviors and needle sharing (Hanson et al., 2008; Petry et al., 2010, 2011; Reback et al., 2010; Shoptaw et al., 2005).

Because contingency management programs have proven successful in reducing methamphetamine use and attendant problem

Abbreviations: ANOVA, analysis of variance; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; FR, fixed ratio; h, hours; mg, milligrams; min, minute; SEM, standard error of the mean; US$, United States dollar.

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behaviors associated with use, the parameters of such treatments need be investigated to determine how the efficacy of contingency management can be enhanced. Researchers in preclinical and human laboratories have used drug versus alternative reinforcer choice paradigms as models of contingency management to determine the factors critical to treatment efficacy (Higgins et al., 2004). The outcomes of this research show that schedules with increasing magnitudes of alternative reinforcer value for consecutive drug negative urines that reset for positive tests (Roll and Shoptaw, 2006; Roll et al., 2006a), higher magnitude reinforcers (Nader and Woolverton, 1991; Petry et al., 2004; Rowan-Szal et al., 1994), lower response requirements for alternative reinforcers or higher requirements for drug reinforcers (Nader and Woolverton, 1992), schedules without built-in negative consequences (Iguchi et al., 1988), monetary alternative reinforcers (Stoops et al., 2010a) and schedules without delays to reinforcement or exchange (Roll et al., 2000; Rowan-Szal et al., 1994) are most effective for reducing drug taking. Through the conduct of studies such as these, the optimal parameters of contingency management may be determined, providing clinicians with guidance in developing the most effective means of reducing drug-taking behavior.

Although there is a rich literature of laboratory studies that have investigated manipulations of drug versus alternative reinforcer choice, no laboratory studies have assessed the impact of "cost" of alternative reinforcers on methamphetamine self-administration. Therefore, the purpose of this study was to assess the extent to which altering response cost requirements for alternative reinforcers (i.e., money) would mediate methamphetamine choice. Seven adults with past-year recreational stimulant use sampled oral doses of methamphetamine (0, 8 or 16 mg). Following sampling sessions, subjects then completed self-administration sessions in which they made eight discrete choices between 1/8th of the sampled dose and an alternative reinforcer (US$0.25). The response cost requirement to earn a dose of methamphetamine was fixed across sessions (FR500), whereas the response cost requirement for the monetary reinforcer varied across sessions (FR500, FR1000, FR2000 or FR3000). We hypothesized that methamphetamine choice would increase as a function of dose and alternative reinforcer response requirement.

2. Materials and methods

2.1. Subjects

Seven non-treatment-seeking adult subjects (5 men, 2 women; 5 Caucasian, 2 African American) with past-year histories of recreational stimulant use completed the protocol. One other subject was enrolled into the protocol but was lost to follow-up before completing. Data from this individual were not included in the analyses. All subjects reported recreational stimulant use in the past year (i.e., mixed salt amphetamine [Adderall], 3,4-methylededioxymethamphetamine [MDMA; ecstasy], methylphenidate or cocaine). Three subjects reported using Adderall; one reported using ecstasy (i.e., 3,4-methylenedioxymethamphetamine [MDMA]); one reported using cocaine, Adderall and Ritalin (i.e., methylphenidate); one reported using cocaine, Adderall, and ecstasy; one reported using Adderall and Ritalin within the past year. Only one subject reported using mixed amphetamine salts during the past month and another subject tested positive for cocaine use during initial screening procedures. Throughout the study, only one subject tested positive for a substance (oxycodone) that prevented him from running an experimental session. This subject was sent home and his session was rescheduled for when he could provide a drug-negative urine. Subjects were 25 (±7) years of age and weighed 75 (±19) kg on average (±SEM). Two of the seven subjects reported daily use of cigarettes (13±4 cigarettes/day) and all reported weekly alcohol use (10±10 drinks/week). In addition to weekly cigarette and alcohol use, subjects reported recent recreational use of other drugs. In the month prior to screening, four subjects used marijuana, four used opioids and two used benzodiazepines. Three subjects met DSM-IV criteria for alcohol abuse and one subject met DSM-IV criteria for cannabis abuse.

The Institutional Review Board of the University of Kentucky Medical Center approved this experiment and all subjects gave their written informed consent prior to participating. Subjects were paid $40 per session and earned an additional $40 per session completion bonus if they finished the study. Subjects underwent extensive screening prior to enrollment (e.g., Sevak et al., 2010). To meet inclusion criteria, subjects had to (1) report past-year recreational use of stimulant drugs (e.g., amphetamine, ecstasy, methylphenidate, cocaine) and (2) be in good health with no contraindications to stimulant medications.

2.2. General Procedures

Subjects reported to the University of Kentucky Laboratory of Human Behavioral Pharmacology (LHBP) at the University of Kentucky Chandler Medical Center for a total of 17 sessions (2 practice and 15 experimental). Subjects were informed that during their participation they would receive methamphetamine or placebo. Other than receiving this general information, subjects were blind to the dose of methamphetamine to be administered during each session. Subjects were told that the purpose of the study was to determine (1) how the drug effects feel and influence mood, (2) the effects of drugs on physiology, and (3) whether subjects like the drug and are willing to take it again. Other than this general explanation of purpose, subjects were not given any information concerning what outcomes might be expected.

For all sessions (practice and experimental), subjects arrived daily at 0800 h to the LHBP. Sessions lasted approximately 7 h. Upon arrival, urine and expired breath samples were collected to confirm drug and alcohol abstinence, respectively. Female subjects also received urine pregnancy tests prior to each session, which were negative throughout their participation. If subjects tested positive for alcohol or other drugs (save THC and tests positive for methamphetamine as a result of experimental administration), they were sent home and their session rescheduled. To ensure that subjects were not acutely intoxicated, subjects had to pass a field sobriety test prior to beginning each session. To further enhance safety, no methamphetamine was administered until at least 2 h after subjects arrived at the laboratory.

Vital signs were recorded at 15 min intervals between 0800 h and 0830 h and subjects were provided a standard breakfast (i.e., 2 Nutri-grain® bars and a juice box or 1 standard single-serving cereal with skimmed milk and a juice box). At approximately 0830 h, subject-rated questionnaires and the choice task (only during practice and experimental self-administration sessions) were completed. Sampling doses or the amount of drug earned on the choice task was administered at 1000 h. For all sessions, subject vitals were recorded and subject-rated questionnaires were administered at 1 h intervals after drug administration (i.e., from 1100 h to 1500 h). Between these measures, subjects were allowed to engage in sedentary, quiet recreational activities (e.g., read newspapers or magazines, complete puzzles, watch television). At 1300 h, subjects were allowed to eat lunch, which was provided by the LHBP. If no drug effects (physiological or behavioral) were detected at 5 h post-administration, subjects were released from the laboratory.

2.2.1. Practice sessions

Subjects completed two practice sessions to familiarize them with (1) subject-rated questionnaires and (2) the methamphetamine versus alternative reinforcer choice task and the different fixed ratio requirements that would be in place in subsequent sessions. These tasks/measures were administered at approximately 0830 h each day. Subject-rated questionnaires and the methamphetamine versus alternative reinforcer choice task were administered on a Macintosh iMac computer (Apple Computer Inc., Cupertino, CA). During the