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Alternative Reinforcer Response Cost Impacts Cocaine Choice in Humans

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Abstract

Cocaine use disorders are an unrelenting public health concern. Behavioral treatments reduce cocaine use by providing non-drug alternative reinforcers. The purpose of this human laboratory experiment was to determine how response cost for non-drug alternative reinforcers influenced cocaine choice. Seven cocaine-using, non-treatment-seeking subjects completed a crossover, double-blind protocol in which they first sampled doses of intranasal cocaine (5, 10, 20 or 30 mg) and completed a battery of subject-rated and physiological measures. Subjects then made eight discrete choices between the sampled dose and an alternative reinforce (US$0.25). The response cost to earn a cocaine dose was always a fixed ratio (FR) of 100 responses. The response cost for the alternative reinforcer varied across sessions (FR1, FR10, FR100, FR1000). Dose-related increases were observed for cocaine choice. Subjects made fewer drug choices when the FR requirements for the alternative reinforcers were lower than that for drug relative to when the FR requirements were equal to or higher than that for drug. Intranasal cocaine also produced prototypical stimulant-like subject-rated and physiological effects (e.g., increased ratings of Like Drug; elevated blood pressure). These data demonstrate that making alternative reinforcers easier to earn reduces cocaine self-administration, which has implications for treatment efforts.

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Authors Stoops, Lile and Rush designed the study. Authors Hays and Glaser provided medical oversight for the study. Authors Stoops and Rush oversaw the conduct of the research. Author Stoops conducted data analysis. Author Stoops managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Keywords

Cocaine; Humans; Self-Administration; Alternative Reinforcer

1. Introduction

Cocaine use disorders are an unrelenting public health concern. Data from the National Survey on Drug Use and Health (NSDUH) indicate that 1.6 million Americans reported current cocaine use in 2009 (Substance Abuse and Mental Health Services Administration [SAMHSA] 2010). This prevalence makes cocaine the most commonly used illicit stimulant in the United States. Behavioral treatments grounded in operant theory have successfully been implemented to reduce cocaine use (reviewed in Higgins et al. 2004). In essence, these treatments reinforce providing objective evidence of abstinence with non-drug alternative reinforcers (e.g., money, vouchers for goods or services, clinic privileges, written encouragement). Abstinence reinforcement, also known as contingency management, produces dramatic reductions in cocaine use and improves quality of life for cocaine users (Higgins et al. 1991; Petry et al. 2007).

Preclinical and human laboratory studies have modeled abstinence reinforcement interventions by allowing subjects to choose between taking a cocaine dose and receiving a non-drug alternative reinforcer (e.g., Donny et al. 2004; Hart et al. 2000; Higgins et al. 1994; Nader and Woolverton 1991, 1992; Stoops et al. 2010; Thomsen et al. 2008; Vosburg et al. 2010). For example, in early research with monkeys, higher magnitude food alternative reinforcers decreased cocaine self-administration (Nader and Woolverton 1991). Those results were extended in a subsequent study, which demonstrated that fewer drug choices were made when the response requirements for the alternative reinforcers were lower than that for drug (Nader and Woolverton 1992). Findings from human laboratory experiments are concordant with preclinical and treatment results in that the availability of alternative reinforcers of different magnitudes and types suppresses cocaine self-administration (Donny et al. 2004; Hart et al. 2000; Higgins et al. 1994; Stoops et al. 2010; Vosburg et al. 2010).

Although numerous human laboratory and clinical studies have tested how different magnitudes and types of alternative reinforcers impact cocaine taking, we are not aware of any studies that have tested how the “cost” of alternative reinforcers impacts cocaine self-administration in humans. The purpose of the present study was to determine the influence of differential response requirements for monetary alternative reinforcers on cocaine choice. Seven cocaine-using, non-treatment seeking subjects completed a crossover, double-blind protocol in which they first sampled doses of intranasal cocaine (5, 10, 20 or 30 mg) and then made eight discrete choices between the sampled dose and an alternative reinforce (US $0.25). The response cost to earn a cocaine dose was always a fixed ratio (FR) of 100 responses, whereas the response cost for the alternative reinforcer varied across sessions (FR1, FR10, FR100, FR1000). Cocaine choice was hypothesized to increase as a function of dose and be reduced when response requirements for alternative reinforcers were lower than that for drug.

2. Methods

2.1 Subjects

Seven non-treatment seeking adult subjects (5 men, 2 women; 5 Black, 1 of Mixed Race, 1 Hispanic) with recent histories of cocaine use who met criteria for cocaine dependence as determined by a computerized version of the Structured Clinical Interview for the DSM-IV and verified by study physicians completed the protocol. Four of these subjects reported

smoking crack cocaine as their preferred route, two subjects reported insufflating powder cocaine as their preferred route and one subject preferred smoking crack cocaine and insufflating powder cocaine equally. Subjects were 38 (±4) years of age and weighed 78 (±6) kg on average (±SEM). All subjects reported daily use of cigarettes (11±3 cigarettes/day) and six of the seven reported weekly alcohol use (10±3 drinks/week). In addition to cocaine use in the week prior to screening (4±1 days of use totaling US$218±$132 spent on cocaine in the past week), subjects reported recent recreational use of other drugs. All subjects reported marijuana use, two subjects reported benzodiazepine use and two subjects reported opioid use in the month prior to screening. Six subjects reported marijuana use and one subject reported benzodiazepine use in the week prior to screening. One other subject was enrolled into the protocol but was discontinued after the screening session for failing to meet predetermined criteria for entry into the study proper (see below). Data from this individual were not included in the analyses.

The Institutional Review Board of the University of Kentucky Medical Center approved this experiment and subjects gave their written informed consent before participating. Subjects were paid $40 per session and earned an additional $40 per session completion bonus if they finished the study. Prior to participation, all potential subjects underwent a comprehensive physical- and mental-health screening. The screening measures that were used included a medical-history questionnaire, a general-health questionnaire, a mini-mental status examination, a drug-use questionnaire, the Drug Abuse Screening Test (DAST) (Skinner 1982) and the Michigan Alcohol Screening Test (MAST) (Selzer 1971). A study physician interviewed and examined each potential subject and deemed him or her to be appropriate for the study. Routine clinical laboratory blood chemistry tests, vital signs assessment and an electrocardiogram were also conducted. Potential subjects with current or past serious physical disease (e.g., impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizure, head trauma or CNS tumors) or current or past histories of serious psychiatric disorder (i.e., Axis I, DSM IV), other than cocaine use disorders that in the opinion of the physician would interfere with participation were excluded from the study. Aside from cocaine dependence, subjects did not meet DSM-IV criteria for psychoactive substance dependence on any drug. Two subjects did meet criteria for alcohol abuse. To meet inclusion criteria, subjects had to: (1) report recent cocaine use, (2) provide a urine sample positive for cocaine or benzoylecgonine during the initial screening process and (3) fulfill diagnostic criteria for a cocaine use disorder. All subjects were in good health with no contraindications to cocaine administration.

2.2 General Procedures

Subjects were admitted as outpatients at the University of Kentucky Chandler Medical Center Clinical Research and Development Operations Center (CRDOC) for a total of 18 sessions. Subjects were informed that during their participation they would receive intranasal cocaine. Other than receiving this general information, subjects were blind to the dose of cocaine to be administered in each session. Subjects were told that the purpose of the study was to (1) determine how the drug effects feel and influence mood, (2) determine the effects of the drug on performance of laboratory tasks, (3) determine whether subjects like the drug and are willing to take it again and (4) determine the effects of drug on physiology.

2.2.1 Practice Session—Subjects completed one practice session to familiarize them with experimental measures including the cocaine versus alternative reinforcer choice task and the different FR responses that would be in place in subsequent sessions. These responses were described as extra small (i.e., FR1), small (i.e., FR10), medium (i.e., FR100) and large (FR1000), but the actual number of responses was not disclosed to subjects. Experimental medications were not administered during this session.

2.2.2 Screening Session—Following the practice session, subjects completed one screening session in which they sampled 5 mg (labeled Drug A) and 30 mg (labeled Drug B) intranasal cocaine, separated by 30 min. Subjects then made eight choices between the two sampled doses at 30 min intervals. The purpose of this session was to determine if the high cocaine dose functioned as a reinforcer (i.e., was chosen to a greater extent than the low dose) for subjects prior to enrollment in the study proper. Subjects continued on if they made at least six of eight choices for the 30 mg cocaine dose in the screening session. As noted above, only one subject was eliminated from further participation for failing to choose the high cocaine dose to a greater extent than the low cocaine dose.

2.2.3 Experimental Sessions—A total of sixteen experimental sessions (i.e., one for each combination of cocaine dose and FR condition; order of conditions was randomly determined) were completed and were conducted only on weekdays. Experimental sessions started at 0800 h and lasted 7.5 h. Urine and expired breath samples were collected prior to each session to confirm drug and alcohol abstinence, respectively. Subjects occasionally tested positive for cocaine and THC prior to experimental sessions. To ensure that subjects were not acutely intoxicated, subjects had to pass a field sobriety test prior to beginning each session. To enhance safety, no cocaine was administered until at least 2 h after subjects arrived at the laboratory. Subjects had to test negative for all other drug and alcohol use prior to completing experimental sessions because no other drugs were administered experimentally, and unlike marijuana, drugs like opioids and benzodiazepines are generally not detectable in urine for a significant period after use. The female subjects received urine pregnancy tests prior to each session, which were negative throughout their participation.

During each session, subjects sampled the cocaine dose available for that day, 5, 10, 20 or 30 mg. The cocaine dose was constant within each session but varied across sessions. Physiological measures were recorded 15 and 30 min after the sampling dose. Subject-rated measures were completed 15 min after the sampling dose. Immediately after the 30 min physiological measures, subjects entered the choice phase in which they made eight forced, discrete choices between the available cocaine dose and an alternative reinforcer (US$0.25) at 30 min intervals. The amount of money earned during each session was determined by the number of alternative reinforcer choices; subjects could earn a maximum of $2.00 each session if they made all eight choices for money. During the 30 min intervals, after receiving their chosen option, subjects completed the subject-rated and physiological measures 15 min after dosing and were then allowed to engage in sedentary, quiet recreational activities (e.g., read newspapers or magazines, complete puzzles).

Subjects were instructed that the drug dose would always require a medium response (i.e., FR100), while the alternative reinforcer would require an extra small (i.e., FR1), small (i.e., FR10), medium (i.e., FR100) or large (i.e., FR1000) response. The FR response for the alternative reinforcer was constant within each session but varied across sessions.

2.2.4 Testing Room—The testing room for all sessions consisted of a table and chair for the research assistant and nurse, a cushioned reclining chair for the subject, an Apple iBook laptop computer (Apple Computer Inc., Cupertino, California), a computer mouse and an automated ECG and blood pressure monitor (Dinamap Pro 1000 Vital Signs monitor, Critikon Company L.L.C., Tampa, Florida). A crash cart was available in case of a medical emergency.

2.3 Cocaine Versus Alternative Reinforcer Choice Procedure

After sampling the dose available in each session, subjects made eight discrete choices between the drug and the alternative reinforcer (US$0.25) at 30 min intervals. Subjects did

this by selecting one of two options presented to them on a computer screen ("Dose" or "Money"). After making a choice, subjects were then required to complete a number of responses using the computer mouse to earn that choice (i.e., 100 responses for a dose or 1, 10, 100 or 1000 responses for money). If a subject chose drug, it was immediately provided to him or her after completing the required number of responses. If a subject chose money, he or she was immediately provided with a token marked $0.25 after completing the required number of responses and the amount of money earned was added to his or her payment at the end of the session.

2.4 Subject-Rated Measures

Subject-rated questionnaires were administered periodically throughout session on a computer in a fixed order.

2.4.1 Drug-Effect Questionnaire—This questionnaire consisted of 20 items that were presented one at a time (see Rush et al., 2003 for the items rated) on a 0–100 Visual Analog Scale.

2.4.2 Adjective-Rating Scale—This questionnaire consisted of 32 items and contained two subscales: Sedative and Stimulant (Oliveto et al. 1992), with each item rated on 0–4 Likert-type scale.

2.5 Physiological Measures

Heart rate, blood pressure and oral temperature were recorded immediately prior to the first dose administration and periodically thereafter until the subject met release criteria at the end of session. Cardiac rhythmicity was recorded continuously throughout experimental sessions. If heart rate exceeded 130 beats per minute, systolic blood pressure exceeded 180 mmHg, diastolic blood pressure exceeded 120 mmHg or clinically significant ECG changes occurred following administration of cocaine at any point during the experiment, participation was terminated. No subjects were excluded from further participation for exceeding these parameters, nor were any doses withheld.

2.6 Drug Administration

Cocaine was administered in a double-blind fashion. Cocaine doses (5, 10, 20 and 30 mg) were prepared by combining the appropriate amount of cocaine HCl (Mallinckrodt, St. Louis, Missouri) with lactose to equal a total of 60 mg powder.

During each administration, a nurse presented the subject with the powder, a mirror and a single edged razor blade. The subject was instructed to divide the powder into two even "lines" and insufflate one line of powder through each nostril using a 65-mm plastic straw within 2 min.

2.7 Data Analysis

Effects were considered significant for $p < 0.05$. Data from the Cocaine Versus Alternative Reinforcer Choice Procedure were analyzed as number of drug choices. Choice data were analyzed using a two-factor, repeated-measures ANOVA with Cocaine Dose (5, 10, 20 and 30 mg) and Alternative Reinforcer FR Requirement (1, 10, 100 and 1000 responses) as the factors (StatView, Cary, North Carolina). F statistics were used to interpret the ANOVA outcomes.

Subjects made differing choices between cocaine and money following the sampling dose, so only physiological and subject-rated data recorded prior to the choice period were

analyzed (i.e., peak effect [maximum number recorded at either 15 or 30 min after the sampling dose] for physiological data and the single observation 15 min after the sampling dose for subject-rated data). Physiological and subject-rated data were averaged across all FR values and analyzed using a one-factor, repeated-measures ANOVA with Cocaine Dose (5, 10, 20 and 30 mg) as the factor (StatView, Cary, North Carolina). F statistics were used to interpret the ANOVA outcomes.

3. Results

3.1 Cocaine Versus Alternative Reinforcer Choice Procedure

Significant main effects of Cocaine Dose ($F_{3,18} = 3.58$, $p = 0.03$) and Alternative Reinforcer FR Requirement ($F_{3,18} = 4.07$, $p = 0.02$) were observed on number of drug choices from the Cocaine Versus Alternative Reinforcer Choice Procedure. Figure 1 shows that dose-related increases were observed for intranasal cocaine choice. Fewer drug doses were generally chosen under the FR1 and FR10 schedules relative to the FR 100 and FR 1000 schedules (i.e., when the alternative reinforcer required less responses than the dose).

3.2 Subject-Rated Measures

Significant main effects of Cocaine Dose ($F_{3,18}$ values > 3.25, p values < 0.05) were observed on 9 items from the Drug-Effect Questionnaire: Active/Alert/Energetic, Any Effect, Good Effects, High, Like Drug, Rush, Stimulated, Willing to Pay For and Willing to Take Again. Figure 1 shows data for 1 representative measures: Like Drug. In general, ratings on these measures increased as a function of dose. No significant effects were observed on the Adjective Rating Scale.

3.3 Physiological Measures

Significant main effects of Cocaine Dose ($F_{3,18}$ values > 3.23, p values > 0.05) were observed for systolic and diastolic blood pressure. Dose-dependent increases were observed on systolic and diastolic blood pressure (data not shown). No significant effects were observed for heart rate or oral temperature.

4. Discussion

Intranasal cocaine produced dose-related, stimulant-like effects. Moreover, cocaine choice was sensitive to differential response requirements for a monetary alternative reinforcer. Subjects generally made fewer drug choices when the FR requirements for money were low (i.e., FR1 or FR10) relative to when the FR requirements were equal to or higher than those for drug (i.e., FR100 or FR1000). Higher drug doses were selected more than 75% of the time for the FR100 and FR1000 response requirements, although the number of drug choices for the 20 mg cocaine dose was also nearly maximal under the FR10 response requirement. The greatest difference between low (i.e., 5 mg) and high (i.e., 20 and 30 mg) dose drug choices was observed under that response requirement as well.

These human laboratory findings translate those of earlier preclinical research that examined how the response “cost” for a food alternative reinforcer impacted cocaine self-administration in monkeys. In a study that mirrors the conditions of the present study, increasing the response requirement to obtain food from an FR30 to FR240 or FR480 resulted in nearly maximal cocaine choice (Nader and Woolverton 1992). In another preclinical study, pairing a histamine punisher with cocaine delivery reduced cocaine self-administration whereas pairing the histamine punisher with food delivery increased cocaine self-administration (Negus, 2005). Taken together, these outcomes suggest that increasing

cost of the alternative reinforcer, either by increasing the work required to earn money or food, or pairing the alternative reinforcer with punishment, increases drug taking.

The current results extend previous research examining cocaine and alternative reinforcer choice in humans (e.g., Donny et al. 2004; Hart et al. 2000; Higgins et al. 1994; Stoops et al. 2010; Vosburg et al. 2010). Those studies tested various parameters that might influence cocaine choice in the presence of alternative reinforcers, demonstrating that the value of the alternative reinforcer, the type of the alternative reinforcer and altering the probability of receiving reinforcement all impact cocaine self-administration. For example, in one study, cocaine choice was suppressed to a greater degree when the chance to receive alternative reinforcers was increased (i.e., when subjects could pull more balls from a bingo wheel; Vosburg et al. 2010). The present findings contribute further by demonstrating that the response cost for the alternative reinforcer also impacts cocaine self-administration.

The finding that the availability of alternative reinforcers, particularly those that are easier to obtain than drug, reduces drug choice is concordant with previous clinical findings and has clinical relevance. Treatments employing contingency management consistently demonstrate that reinforcing drug abstinence with alternative reinforcers substantially reduces cocaine and other drug taking (reviewed in Higgins 1997; Higgins et al. 2004). However, certain individuals do not respond to contingency management treatments (García-Fernández et al. 2011). Perhaps making alternative reinforcers easier to obtain would increase the percentage of individuals who respond to contingency management. The results of previous clinical research support this notion and suggest that reducing the effort necessary to receive alternative reinforcers (e.g., starting with easier requirements to earn vouchers or providing reinforcement for reductions in cocaine metabolite levels in urine samples as opposed to for cocaine-negative urines) can improve treatment outcomes (Kirby et al., 1998; Preston et al., 2001). Importantly, such shaping procedures also reduce cigarette smoking, demonstrating the generalizability of this effect (Lamb et al., 2010).

Several limitations of the present experiment associated with modeling drug use in a controlled laboratory environment warrant mentioning. First, we observed effects of low magnitude following the sampling doses of cocaine (i.e., subject ratings averaged less than 20 on a 100 point scale and heart rate was not significantly increased). Low unit doses of cocaine were selected to permit subjects to make a range of choices between cocaine and the alternative reinforcer and minimize the possibility of having to withhold doses; however, the use of lower doses could limit the generalizability of the results. Second, overall drug choice was relatively high (i.e., subjects made more than 4 choices for drug on average under all FR conditions) and suppression of drug taking by reduced FR requirements for alternative reinforcers was modest (i.e., subjects made approximately 2 fewer choices on average for 10 mg cocaine under the FR10 condition relative to the FR1000 condition, which is the largest reduction in choice observed). The robust reinforcing effects of cocaine, and the difficulty of attenuating cocaine use in the laboratory and natural environment are well documented, so it is not surprising that doses were chosen at such a high level. Third, due to the small sample size, the route of administration that was not a preferred route for four of seven subjects and the poly-drug use of the subjects (see Martinotti et al., 2009) these findings may have limited generalizability.

Other limitations of this study related to the self-administration procedures should be noted. The alternative reinforcer value (US$0.25) available at each choice might have been insufficient to reduce cocaine choice to a substantial degree. Moreover, the actual alternative reinforcer was not provided until the end of session, which could have further reduced its reinforcing efficacy. Future research should determine whether alternative reinforcers with higher value paid immediately suppress drug choice to a greater degree under this

arrangement. Alternative reinforcer magnitude and the immediacy of reinforcement both impact reinforcing efficacy (Gleeson and Lattal, 1987; Nader and Woolverton, 1991). In addition, this study did not include an inactive placebo control condition. Cocaine produces peripheral cues like nasal numbing (e.g., Johnson et al., 2003), so providing an inactive placebo that would not produce peripheral cues would negatively impact the study blind. A low cocaine dose (5 mg) was included in the place of a placebo as similar doses produce nasal numbing without engendering significant behavioral effects (Collins et al., 2007; Foltin et al., 1988; Higgins et al., 1990; 1994; Javaid et al., 1978; Oliveto et al., 2001). Finally, this study did not include a condition in which subjects could only earn cocaine (i.e., a no alternative reinforcer condition), which would have provided information about cocaine taking in the absence of a competing non-drug reinforcer. However, given that the focus of the study was to determine how response cost of alternative reinforcers impacted cocaine choice, inclusion of a no alternative reinforcer condition would have increased the study length and subject attrition and not necessarily have contributed information to the primary research question.

5. Conclusion

Drug choice was reduced when the response cost to earn an alternative reinforcer was less than that to earn a cocaine dose, consistent with preclinical and clinical treatment results. These findings have implications for the use of contingency management in cocaine use disorders because they suggest that making alternative reinforcers easier to earn could further decrease cocaine use or increase the percentage of individuals who respond to treatment. Conversely, these findings are also important because they demonstrate that increased drug use could be expected when non-drug alternatives are more difficult to obtain.

Highlights

- This study tested how alternative reinforcer response cost impacts cocaine choice.
- Dose-related increases were observed for cocaine choice.
- Fewer drug choices were made at lower alternative reinforcer response costs.
- Making alternative reinforcers easier to earn could reduce cocaine use.

Abbreviations

ANOVA	Analysis of Variance
CNS	Central Nervous System
CRDOC	Clinical Research Development and Operations Center; cocaine HCl cocaine hydrochloride
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
DAST	Drug Abuse Screening Test
ECG	electrocardiogram
FR	fixed ratio
h	hours
kg	killigrams

MAST	Michigan Alcohol Screening Test
mg	milligrams
mm	millimeter
mmHG	millimeters of mercury
min	minute
NSDUH	National Survey on Drug Use and Health
SEM	Standard Error of the Mean
SAMHSA	Substance Abuse and Mental Health Services Administration
THC	tetrahydrocannabinol
US$	United States Dollar

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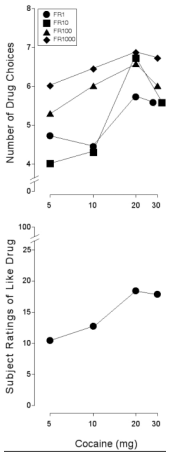

Fig. 1.

Top Panel: Mean number of drug choices for 7 subjects. X-axis: cocaine dose. Symbols represent the FR values for the alternative reinforcer: FR1 (circles), FR10 (squares), FR100 (triangles), FR1000 (diamonds). Symbols for FR1 and FR10 at the 30 mg dose overlapped so they are offset for clarity.

Bottom Panel: Mean subject ratings for Like Drug for 7 subjects. X-axis: cocaine dose. Data are collapsed across FR values and come from measures completed 15 min after intranasal cocaine administration.

Error bars are omitted due to the repeated measures design of the study.