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Monetary alternative reinforcers more effectively decrease intranasal cocaine choice than food alternative reinforcers

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ABSTRACT

Cocaine dependence continues to be a significant public health concern. Contingency management, wherein alternative reinforcers are made available upon cocaine abstinence, has shown promise for decreasing cocaine use. Other research has modeled this effect and demonstrated that alternative reinforcers also reduce cocaine self-administration in the laboratory. Results from both clinical and laboratory studies suggest that the type and value of alternative reinforcers influences their ability to decrease drug choice. The purpose of the present experiment was to determine the effect of money or food alternative reinforcers, valued at $0.01, 0.25, 0.50 and 1.00, on intranasal cocaine (4 [placebo] and 30 mg) choice. Cocaine was chosen to a greater extent than placebo across alternative reinforcer types and values, but the monetary alternative reinforcer suppressed drug choice to a greater degree than the food reinforcer. These results are concordant with previous findings and suggest that money may be a more effective alternative reinforcer for decreasing cocaine use. Future research should determine the sensitivity of this model to specific behavioral aspects of contingency management and whether food could compete with drugs as reinforcers in humans under laboratory conditions.

1. Introduction

Cocaine dependence continues to be a significant public health concern. While no widely accepted pharmacological treatment is available, a number of non-pharmacological treatments for cocaine dependence have been successful for managing cocaine dependence. These include 12 step programs, behavioral and cognitive therapies and psychotherapies (Stitzer and Walsh, 1997). These non-pharmacological treatments seek to increase abstinence from cocaine by modifying drug-related behavior and teaching skills necessary to avoid relapse.

Behavioral treatments based on principles of operant psychology reinforce non-drug related behaviors through approaches like contingency management or the therapeutic workplace (reviewed in Grabowski et al., 1993 and Higgins et al., 2002). With contingency management approaches, non-drug related behaviors are reinforced by the presentation of vouchers for money or products, or chances for vouchers, contingent upon patients' providing cocaine-negative urine samples (e.g., Higgins et al., 1991, 1994b, 2000; Petry et al., 2005, 2007). Although the use of alternative reinforcers has proven generally efficacious in managing cocaine use, there are data to suggest money may more effectively promote drug abstinence than goods (Vandrey et al., 2007) and that medications can enhance the ability of alternative reinforcers to decrease cocaine use (Poling et al., 2006; Schmitz et al., 2008).

Cocaine versus money choice paradigms have been developed to study cocaine self-administration in the presence of alternative reinforcers. Various permutations of these models have demonstrated that cocaine choice is sensitive to dose and pharmacological pretreatment as well as value and type of reinforcer (Donny et al., 2004; Hatsukami et al., 1994; Higgins et al., 1994a, 1996; Hart et al., 2000; Walsh et al., 2001; reviewed in Higgins, 1997). In one series of studies, subjects were allowed to make multiple choices between receiving a cocaine dose or money (Higgins et al., 1994a, 1996). In the first study, four subjects reporting light, recreational cocaine use were allowed to make 10 choices between 10 mg intranasal cocaine and different values of money ($0.00, 0.50, 1.00, or 2.00) (Higgins et al., 1994a). When the options were cocaine or $0.00, subjects took all cocaine available. The number of cocaine choices decreased as a function of the value of monetary reinforcer available, with the highest monetary value available ($2.00) completely suppressing cocaine-taking behavior.

These studies are thought to model contingency management approaches because individuals are making choices between taking

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cocaine and receiving an alternative reinforcer. Findings from the laboratory model mirror those from contingency management studies in that the availability of a non-drug reinforcer decreases cocaine taking. Moreover, as the value of the alternative reinforcer increases, cocaine use decreases substantially. Other studies have extended these results from individuals with recreational cocaine use histories to more experienced, and even dependent, individuals (e.g., Hart et al., 2000; Hatsukami et al., 1994). For example, in the more recent study, six experienced cocaine users were allowed to make six choices between 0, 12, 25 and 50 mg smoked cocaine and a $5 voucher for money or merchandise. Cocaine choices increased significantly with dose, but vouchers for money decreased cocaine choice to a greater degree than vouchers for merchandise (Hart et al., 2000).

As described above, the availability of alternative reinforcers decreases cocaine taking in both naturalistic and laboratory environments. Moreover, study results demonstrate that the type of alternative reinforcer may influence drug choice as a function of its value. The purpose of the present experiment was to investigate further the influence of alternative reinforcer availability, value and type on cocaine choice in experienced cocaine users. To this end, twelve individuals reporting recent cocaine use completed this experiment in which they chose between available cocaine doses (4 [placebo] and 30 mg) and money ($n=6$) or food items ($n=6$) valued at $0.01, 0.25, 0.50 and 1.00.

2. Method

2.1. Subjects

Twelve non-treatment seeking adult subjects with recent histories of cocaine use (i.e., cocaine positive urine at the time of initial screening) who met criteria for cocaine use disorders as determined by a computerized version of the Structured Clinical Interview for the DSM-IV completed this placebo-controlled study. Six of these subjects completed the study with the monetary alternative reinforcers and six completed the study with the food alternative reinforcers as described below. Eleven of these subjects reported smoking cocaine as their primary route of administration. One subject (in the monetary alternative reinforcer group) reported cocaine insufflation as his primary route or administration. Seven additional subjects were enrolled but did not complete the project: four subjects were eliminated because they did not meet cocaine choice criteria to continue in the study proper as described below, one subject experienced ECG abnormalities after administration of placebo cocaine in the active dosing practice session and was removed from the protocol, one subject was removed for failure to comply with study requirements and one subject left the protocol to pursue a job opportunity. Data from these seven individuals were not included in the analyses. The Institutional Review Board of the University of Kentucky Medical Center approved this study and subjects gave their written informed consent before participating. Subjects were paid for their participation.

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, an over-the-counter drug-use questionnaire, the Drug Abuse Screening Test (DAST) (Skinner, 1982) and the Michigan Alcohol Screening Test (MAST) (Selzer, 1971).

A psychiatrist 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 histories of serious physical disease or current 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 substance abuse or dependence, were excluded from participation. Subjects had to meet the following inclusion criteria: (1) self-reported recent cocaine use, (2) confirmation of recent cocaine use by a positive urine screen for cocaine or benzoylecgonine during the initial screening interview and (3) fulfill diagnostic criteria for cocaine use disorder. All subjects were in good health with no contra-indications to stimulants. Table 1 presents the demographic data for these subjects by group.

2.2. General procedures

Subjects were enrolled as outpatients at the University of Kentucky Chandler Medical Center General Clinical Research Center (GCRC) for up to 11 sessions. The first of these sessions was a practice session in which no drugs were administered. Subjects then completed one active dosing practice session and one screening session. If subjects made at least four out of six choices for the active cocaine dose in the screening session, they then completed eight experimental sessions. Subjects were informed that during their participation they would receive intranasal cocaine or placebo. 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 determine how different drugs affect physiology, mood and behavior. Other than this general explanation of purpose, subjects were given no instruction of what they were "supposed" to do or of what outcomes might be expected.

2.2.1. Practice Session

Subjects completed one practice session to familiarize them with experimental measures. Experimental medications were not administered during this session.

2.2.2. Active Dosing Practice Session

Following the practice session, subjects completed one active dosing practice session in which they sampled 4 mg (placebo, labeled Drug A) and 30 mg (labeled Drug B) intranasal cocaine, separated by 45 min. Subjects then made six choices between the two sampled doses at 45 min intervals. The purpose of this session was to familiarize subjects with the experimental measures in the presence of the study drug. This session was essentially identical to the Screening Session, but was included to ensure that the novelty of the experimental setting in combination with drug administration would not influence the data gathered in the Screening and Experimental Sessions.

2.2.3. Screening Session

Following the active dosing practice session, subjects completed one screening session in which they sampled 4 mg (placebo, labeled Drug A) and 30 mg (labeled Drug B) intranasal cocaine, separated by 45 min. Subjects then made six choices between the two sampled

Table 1
Group demographics. Numerical data are presented as mean (standard error of the mean). Reported *P* values are from *t*-tests comparing the two samples.

Variable	Money	Food	*P* value
Gender distribution	6 male	4 male, 2 female	N/A
Race	6 African American	5 African American, 1 White	N/A
Age	36.3 (1.5)	42.5 (2.5)	0.11
Weight	79.1 (6.2)	78.0 (4.8)	0.90
Number of daily cigarette smokers	6	5	N/A
Cigarettes smoked per day	7 (1.1)	11 (4.3)	0.35
MAST score	12.5 (5.5)	10.7 (3.7)	0.17
DAST score	11.2 (3.0)	15.5 (1.9)	0.80
Days used cocaine in week preceding screening	4.2 (0.8)	3.5 (0.8)	0.57

doses at 45 min intervals. The purpose of this session was to determine if cocaine functioned as a reinforcer (i.e., was chosen to a greater extent than placebo) for subjects prior to enrollment in the study proper. Thus, subjects continued on if they made at least four of six choices for the 30 mg cocaine dose in the screening session. All subjects included in the analysis met this criterion and continued on to Experimental Sessions.

2.2.4. Experimental Sessions

A total of eight experimental sessions were completed and were conducted only on weekdays. Experimental sessions started at 0800 h and lasted 7 h. During each session, subjects sampled the cocaine dose available for that day, 4 mg or 30 mg, and were told the value of the money or the food item available that day. They then made six choices between the available cocaine dose and an alternative reinforcer at 45 min intervals. For six subjects, the alternative reinforcer available was money ($0.01, 0.25, 0.50 and 1.00). For the other six subjects, the alternative reinforcer available was a food item valued to match the monetary reinforcer in the Lexington, KY area (e.g., $0.01 = one piece of chewing gum, 0.25 = one granola bar, 0.50 = one can of tuna fish, 1.00 = one bottle of Gatorade). The six subjects choosing between drug and food selected their most preferred item for each value from a list of five items, but were not explicitly told the value of the items. All subjects received all possible drug and alternative reinforcer value conditions for their respective alternative reinforcer type.

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 tetrahydrocannabinol (THC) prior to experimental sessions. To ensure that subjects were not acutely intoxicated, they had to pass a field sobriety test prior to each session. Subjects had to test negative for all other drug and alcohol use prior to completing the experimental sessions. Females received urine pregnancy tests prior to each session, which had to be negative for participation to continue.

2.2.5. Testing room

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

2.3. Choice procedure

After sampling the dose available in each session, subjects chose between the drug and the alternative reinforcer available. Subjects did this by circling which option they wanted to take (Drug or Alternative Reinforcer [specified as a money value or food item]) on an instruction sheet that was placed in front of them. If a subject chose drug, it was immediately provided to him or her. Alternative reinforcers accrued and were provided to the subject upon completion of the study.

2.4. Subject-rated measures

Subject-rated questionnaires previously shown to be sensitive to the effects of stimulants were administered on a computer in a fixed order (Rush et al., 2003; Stoops et al., 2007). Subjects completed all experimental measures prior to the initial dose administration and 15 min after administration of the sampling dose.

2.4.1. Drug-Effect Questionnaire

The Drug-Effect Questionnaire consists of 20 items and is sensitive to the acute effects of stimulants (Rush et al., 2003). Items are presented on the video screen, one at a time. Subjects rated each item using the computer mouse to point to and select among one of the five response options: Not at All, A Little Bit, Moderately, Quite a Bit and Extremely (scored numerically from 0 to 4, respectively).

2.4.2. Stimulant-Sensitive Adjective-Rating Scale

The Stimulant-Sensitive Adjective-Rating Scale consists of 21 items and is sensitive to the acute effects of stimulants. Subjects rated each item on the scale identical to that described above. Responses to individual items are summed to create a composite score, with a maximum total score of 84.

2.5. Physiological measures

Heart rate and blood pressure were recorded immediately prior to each cocaine dose administration and at 15 min intervals thereafter for 45 min. Cardiac rhythmicity was recorded continuously throughout the experimental sessions. If the heart rate exceeded 130 bpm, systolic blood pressure exceeded 180 mm Hg, diastolic blood pressure exceeded 120 mm Hg or clinically significant ECG changes occurred following administration of cocaine at any point during the experiment, participation was terminated. No subject was excluded from participation for exceeding these parameters nor were any doses withheld.

2.6. Drug administration

All drugs were administered in a double-blind fashion. Cocaine doses (4 mg [placebo], and 30 mg) were prepared by combining the appropriate amount of cocaine HCl (Mallinckrodt, St. Louis, MO) with lactose to equal a total of 40 mg powder. An active placebo (i.e., 4 mg cocaine) was used in an attempt to increase subject "blindness". Cocaine HCL (4 mg) produces nasal numbing, but no discernible blood levels and is routinely used as the placebo dose in human laboratory studies involving intranasal drug administration (e.g., Higgins et al., 1990; Javaid et al., 1978).

During each administration, a nurse presented the subject with the powder, a mirror and a standard 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

Choice data from the Screening Session were analyzed as number of drug choices using a two-factor mixed ANOVA with alternative reinforcer type (money or food) as the between-subjects factor and cocaine dose (4 [placebo] and 30 mg) as the within-subjects factor. Choice data from Experimental Sessions were analyzed as number of drug choices using a three-factor mixed ANOVA with alternative reinforcer type (money or food) as the between-subjects factor and cocaine dose (4 [placebo] and 30 mg) and alternative reinforcer value ($0.01, 0.25, 0.50 and 1.00) as the within-subject factors (StatView, Cary, NC).

For physiological data, peak effect (maximum value observed 15–45 min after dosing) following the sampling dose was analyzed. For subject-rated data, data collected 15 min after the sampling dose were analyzed. These data were analyzed in a fashion identical to that described for Screening Session choice data above, with individual subject data averaged across alternative reinforcer value. Data gathered during the active dosing practice session and after subjects made choices between drug and alternative reinforcers in experimental sessions were not analyzed statistically. For all analyses, F values were used to interpret the outcomes of the analyses and effects were considered significant for $p \leq 0.05$. For brevity, significant main effects are not reported if interactions were observed.

3. Results

3.1. Drug choice

A significant main effect was observed for cocaine dose ($F_{1,10}=1225.0$) on drug choice during the Sampling Session. For the monetary alternative reinforcer group, cocaine was chosen over placebo 5.8 times out of 6 and for the food alternative reinforcer group, cocaine was chosen over placebo 6 times out of 6 during this session.

Significant main effects were observed for alternative reinforcer type ($F_{1,10}=8.4$), cocaine dose ($F_{1,10}=13.5$) and alternative reinforcer value ($F_{3,30}=2.9$) on drug choice during Experimental Sessions. The number of drug choices was lower for the monetary alternative reinforcer group relative to the food alternative reinforcer group. Cocaine was chosen over the available alternative reinforcer more often than placebo. For the monetary alternative reinforcer group, cocaine choice was generally stable across values and placebo choice was completely suppressed by higher values. For the food group, the $0.50 value produced the greatest suppression of cocaine choice and placebo choice was generally stable across values. Fig. 1 displays these results.

3.2. Subject-rated measures

A significant main effect of cocaine dose ($F_{1,10}$ values ≥ 5.0) was observed for eleven items from the Drug-Effect Questionnaire: Active, Alert or Energetic; Any Effect; Good Effects; High; Like Drug; Nauseated; Rush; Stimulated; Talkative; Willing to Pay For and Willing to Take Again (data not shown). Cocaine increased ratings on these measures relative to placebo independent of alternative reinforcer type. A significant interaction of alternative reinforcer type and cocaine dose ($F_{1,10}=5.7$) was observed for subject ratings of Bad Effect from the Drug-Effect Questionnaire (data not shown). Cocaine increased ratings on this item in the monetary alternative reinforcer group whereas placebo increased ratings on this item in the food alternative reinforcer group.

A significant main effect of cocaine dose ($F_{1,10}=15.2$) was observed on the Stimulant-Sensitive Adjective-Rating Scale (data not shown). Cocaine increased ratings on this measures relative to placebo independent of the alternative reinforcer type.

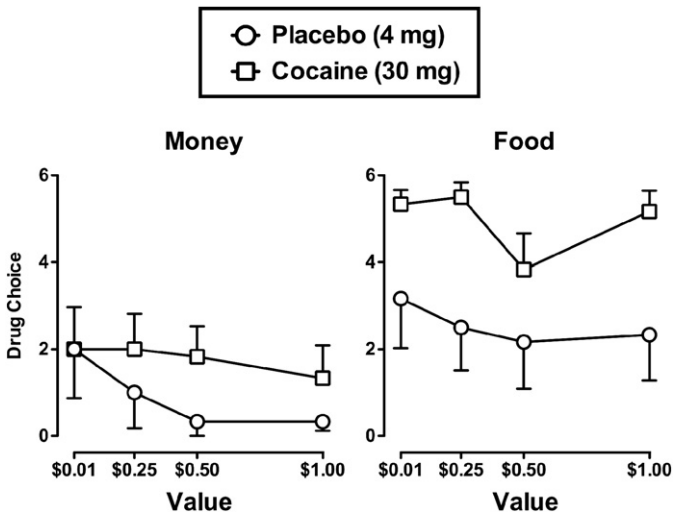

Fig. 1. Drug choices for cocaine (squares) and placebo (circles) when money (left) and food (right) were available. *X*-axis: value of alternative reinforcer. Brackets indicate one SEM. Unidirectional brackets were used for clarity.

3.3. Physiological measures

Significant main effects of alternative reinforcer type ($F_{1,10}$ values >5.0) were observed on systolic blood pressure and heart rate (data not shown). These measures were higher in the monetary alternative reinforcer group than in the food alternative reinforcer group independent of drug dose.

4. Discussion

This experiment demonstrated that intranasal cocaine functioned as a reinforcer (i.e., it was chosen over placebo during the Screening Session) and the availability of food and monetary alternatives reduced the relative reinforcing effectiveness of cocaine. This effect was most pronounced in the presence of monetary reinforcers, which could have implications for behavioral treatments like contingency management. Specific alternative reinforcer values (e.g., $0.50 in the food reinforcer group) suppressed drug taking to a greater extent than others and this was not an orderly function of value.

These data are concordant with a number of previous studies demonstrating that availability of specific alternative reinforcers decreases cocaine taking in nonhuman animal and human laboratory studies, as well as in clinical trials (e.g., Higgins et al., 1991; 1994a; Hart et al., 2000; Nader and Woolverton, 1991). For example, in one study, the relative reinforcing effectiveness of cocaine was decreased to a greater extent by vouchers for money than by vouchers for goods (Hart et al., 2000). Importantly, decreases in cocaine taking are usually a function of alternative reinforcer value (e.g., Nader and Woolverton, 1991) but that effect was not observed in the present experiment. These data are also discordant with findings of studies that show that much higher alternative reinforcer values are necessary to suppress intravenous or smoked cocaine choice (e.g., Donny et al., 2004; Hart et al., 2000). The reason for these discrepancies is not known, but it is possible that the route of administration used in the present study contributed to this inconsistency or that the cohort enrolled in the monetary alternative reinforcer condition was particularly sensitive to money as a reinforcer.

These results are also consistent with previous studies which suggest that money may be more effective at decreasing drug taking or more preferable to treatment seeking clients than other alternative reinforcers, and extend those findings from voucher reinforcers to food reinforcers (Hart et al., 2000; Reilly et al., 2000; Vandrey et al., 2007). Importantly, in the present experiment, all drug taking (i.e., placebo or cocaine) was lower in the monetary alternative reinforcer group than the food alternative reinforcer group. These data indicate that the relative reinforcing effectiveness of cocaine is lower when compared to money than when compared to food, or put another way, that money is a more effective alternative reinforcer than food. This is consistent with the results of a previous study demonstrating that money suppressed beer choice to a greater degree than pizza did (Zacny et al.,1992). It should be noted that Bad Effect ratings were increased following 30 mg cocaine administration in the monetary reinforcer group. It is possible that these ratings resulted in the lower levels of drug taking, however, these ratings were very small in magnitude (i.e., an average of 0.13 on a five point scale) compared to the other subject-rated measures.

Intranasal cocaine produced prototypical subject-rated and effects (e.g., increased ratings of stimulated). Worth noting is that the magnitude of the subject-rated effects of intranasal cocaine was small, albeit significantly different from placebo. The effects of cocaine alone on the Drug-Effect Questionnaire, for example, were less than 1.5 on a five-point scale ranging from 0 to 4. However, the magnitude of the effect of cocaine observed in the present experiment was comparable to that observed previously with similar doses administered by various routes (e.g., oral, intranasal, intravenous and smoked) (e.g., Collins et al., 2006; Haney et al., 2005; Rush, 1999; Stoops et al., 2007).

There are a number of limitations to this study that need to be acknowledged. First, this study used a between group design, so it is possible that some unmeasured group difference contributed to the difference observed in drug taking. However, the groups were generally well matched on demographic characteristics (Table 1) and reported similar subject-rated effects following cocaine administration. Admittedly, the groups did vary in terms of cardiovascular measures, so it is possible that these effects influenced cocaine choice. Future research should examine the influence of money and food alternative reinforcers using a within-group design. Second, this experiment only tested a single, relatively low dose of intranasal cocaine. Future research should determine how higher doses of cocaine administered by different routes influence drug versus alternative reinforcer choice in the laboratory. This has been evaluated previously with monetary alternatives (e.g., Donny et al., 2003), but the assessment of varying values of other reinforcer modalities has received less attention. Third, for the food alternative reinforcer group, cocaine choice did not decrease as an orderly function of value and did not suppress cocaine taking appreciably. It is possible that the value difference between various items (e.g., between a granola bar [0.25] and a bottle of Gatorade [1.00]) is not as readily apparent as the difference between actual money values. Future research should include higher value, more obviously different food items. Fourth, the delivery of cocaine when it was chosen was immediate, whereas delivery of the alternative reinforcer when it was chosen was delayed. This delay could have resulted in increased cocaine choice due to devaluation of the delayed alternative reinforcer (Bickel and Marsch, 2001). However, cocaine choice was generally low when the money alternative reinforcer was available, indicating that the delay did not increase choice in that condition. Regardless, future research should determine how immediate delivery of alternative reinforcers influences cocaine choice.

Taken together, the results of this experiment contribute to and expand on available literature demonstrating that availability of alternative reinforcers decreases cocaine-taking behavior. These results also suggest that drug versus monetary alternative reinforcer choice studies in human laboratories produce results consistent with contingency management and thus may be a model of this type of treatment. Further research is needed to confirm the validity of this model, particularly in terms of determining whether food can compete with drugs as reinforcers in humans (e.g., under conditions of moderate food deprivation or with higher value food options). In addition, the sensitivity of this model to specific behavioral aspects of contingency management (e.g., reset of available alternative reinforcer value after drug taking) or to the synergistic effects observed when contingency management is combined with pharmacotherapies remains to be determined (Poling et al., 2006; Schmitz et al., 2008).

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