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Intranasal cocaine functions as reinforcer on a progressive ratio schedule in humans

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Abstract

Cocaine dependence continues to be a worldwide public health concern. Although the majority of individuals reporting cocaine use do so via the intranasal route, relatively few laboratory experiments have examined the reinforcing effects of cocaine administered intranasally. The purpose of this experiment was to measure the reinforcing effects of intranasal cocaine using a progressive ratio schedule in which eight cocaine-using subjects chose between doses of cocaine (4 [placebo], 15, 30 and 45 mg) and an alternative reinforcer (\$0.25). During each session, subjects first sampled the dose of cocaine available that day and then made six choices between that dose and money, which were available on concurrent progressive ratio schedules of responding. Break points for active cocaine doses were higher than those for placebo but no statistically significant active versus placebo dose effects were observed on subject-rated or physiological measures. These data demonstrate that intranasal cocaine functions as a reinforcer under a progressive ratio schedule in humans. Future research should test higher cocaine doses and larger values of the alternative reinforcer. These procedures may be useful for examining the influence of putative pharmacological and behavioral interventions on intranasal cocaine self-administration.

Keywords

Cocaine; Intranasal; Humans; Progressive Ratio

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1. Introduction

Cocaine dependence continues to be a significant public health concern worldwide. Data from the United States indicate that approximately 2 million Americans over the age of 12 report current cocaine use (Substance Abuse and Mental Health Services Administration [SAMHSA], 2009). In the European Union, it is estimated that 1.5 million people report current cocaine use (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2009). Importantly, despite prevention and intervention efforts, prevalence of cocaine use remains stable (e.g., SAMHSA, 2009). Moreover, cocaine use has come to be associated with a host of mental and physical health problems (for reviews see Chen and Lin, 2009; Cregler, 1989). While the use of smoked cocaine (i.e., crack) has received much of the focus of epidemiological research (e.g., SAMHSA 2005; 2007), it is important to recognize that a significant number of cocaine users in the United States and Europe do not smoke cocaine (up to 2/3 of cocaine users; Foltin and Haney, 2004; c.f., Gossop et al., 1994; Prinzleve et al., 2004). In addition, many report their initial experience with cocaine to be *via* intranasal insufflation (Foltin and Haney, 2004; Gorelick, 1992; van der Meer Sanchez and Nappo, 2007).

The pharmacodynamic effects of cocaine have been studied extensively following oral, intranasal, smoked and intravenous administration in humans (e.g., Fischman, 1984; Foltin et al., 1988; 1990; Rush et al., 1999). Cocaine occupies the dopamine transporter regardless of route, which produces increases in positive subjective drug effects, heart rate and blood pressure, but with different rates of onset observed as a function of route of administration (Foltin and Fischman, 1991; Oliveto et al., 1995; Resnick et al., 1977; Volkow et al., 2000). The reinforcing effects of cocaine have also been demonstrated under a number behavioral arrangements (e.g., money versus alternative reinforcer choice, drug versus placebo choice, multiple choice procedure, fixed ratio and progressive ratio schedules), but primarily with smoked or intravenous administration (Donny et al., 2004; Fischman and Schuster, 1982; Haney et al., 1998; 2006; Hart et al., 2007; Sobel et al., 2004; Walsh et al., 2010). The reinforcing effects of intranasal cocaine have not been examined as extensively and have mainly been studied using choice procedures (Higgins et al., 1994; Lile et al., 2004; Rush et al., 2010; Stoops et al., 2010).

The purpose of this experiment was to determine the reinforcing effects of a range of doses of intranasal cocaine (4 [placebo], 15, 30 and 45 mg) on a progressive ratio schedule of responding because cocaine is used intranasally by a significant number of individuals throughout the world and the reinforcing effects of intranasal cocaine have been examined under limited conditions. We hypothesized that cocaine would function as a reinforcer (i.e., engender higher break points than placebo). To more fully characterize the effects of intranasal cocaine, a battery of subject-rated and physiological measures was included.

2. Materials and methods

2.1 Subjects

Eight non-treatment seeking adult subjects (7 men, 1 woman; 7 Black, 1 White) with recent histories of cocaine use (i.e., cocaine positive urine during initial screening) who met criteria for cocaine dependence as determined by a computerized version of the Structured Clinical Interview for the DSM-IV completed the protocol. Seven of these subjects reported smoking cocaine as their primary route of administration. One subject reported cocaine insufflation as her primary route of administration. Subjects were 40 (± 3) years of age and weighed 82 (± 5) kg on average. Aside from reporting cocaine use in the week prior to screening (mean = 2.3 days $\pm$ 0.7 days using; US \$120 $\pm$ \$61 spent on cocaine per week), subjects reported recent use of other drugs; all subjects reported marijuana use and two subjects reported

benzodiazepine use in the month prior to screening. Seven subjects reported daily tobacco cigarette use. 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.

Another three subjects signed consent and were screened for the protocol but did not complete. Two were lost to follow up before beginning the study proper and one was discharged from the protocol after ECG abnormalities following administration of 45 mg intranasal cocaine. These abnormalities were deemed likely to be artifact from movement and unrelated to study procedures by the attending physicians (LRH and PEAG). Data from these three individuals were not included in the analyses.

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 psychiatrist (LRH or PEAG) 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. 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 enrolled as outpatients at the University of Kentucky Chandler Medical Center Clinical Research and Development Operations Center (CRDOC) for 5 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 1) how different drugs affect physiology, mood and behavior and 2) whether they would be willing to take the drug they sampled in each session again. 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 including the Progressive Ratio Procedure. Experimental medications were not administered during this session.

2.2.2 Experimental Sessions—A total of four 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, 15, 30 or 45 mg. They then made six choices between the available cocaine dose and an alternative reinforcer (\$0.25) at 30 min intervals. After making a choice, subjects then had to complete a response requirement (see Progressive Ratio Procedure below) to earn that choice.

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, subjects had to pass a field sobriety test prior to 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. The female subject received urine pregnancy tests prior to each session, which were negative throughout her participation.

2.2.3 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, CA), a computer mouse 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 Progressive Ratio Procedure

After sampling the dose available in each session, subjects made six choices between the drug and the alternative reinforcer available at 30-minute 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 then were required to complete a number of responses using the computer mouse to earn that choice. Cocaine and the alternative reinforcer were available on concurrent progressive ratio schedules such that the ratio for the next choice only increased for the previously chosen option. The initial response requirement was 400 and ratios increased by 200 responses for each subsequent choice (i.e., 600, 800, 1000, 1200 and 1400). These ratios were selected based on recent findings from our laboratory demonstrating a larger effect size for d-amphetamine self-administration compared to ratios we had used previously (Sevak et al., Under Review). If a subject chose drug, it was immediately provided to him or her. If a subject chose money, he or she was provided with a token marked \$0.25 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 previously shown to be sensitive to the effects of stimulants, including intranasal cocaine, were administered on a computer in a fixed order (Rush et al., 2003; Stoops et al., 2008). Subjects completed all experimental measures prior to the initial dose administration and 15 minutes after each dose administration.

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). Participants rated each item on a 0–100 Visual Analog Scale anchored with “not at all” under the left anchor and “extremely” under the right anchor.

2.4.2. Adjective-Rating Scale—This questionnaire consisted of 32 items and contained two subscales: Sedative and Stimulant (Oliveto et al., 1992). Participants selected among one of five response options: Not at All, A Little Bit, Moderately, Quite a Bit, and Extremely (scored numerically from 0 to 4, respectively).

2.5 Physiological Measures

Heart rate, blood pressure and oral temperature were recorded immediately prior to the first dose administration and at 15-minute intervals thereafter until 30 minutes following the last choice. 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, except the one noted above for ECG artifact, were 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 [placebo], 15, 30 and 45 mg) were prepared by combining the appropriate amount of cocaine HCl (Mallinckrodt, St. Louis, MO) with lactose to equal a total of 60 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 minutes.

2.7 Data Analysis

Effects were considered significant for $P < 0.05$. Data from the Progressive Ratio Procedure were analyzed as break point (i.e., the last ratio subjects completed to earn cocaine or money). Subjects made differing choices between cocaine and money following the sampling dose, so only subject-rated and physiological data gathered 15 minutes after the sampling dose were analyzed. All data were analyzed using a one-factor, repeated-measures ANOVA with cocaine dose (4 [placebo], 15, 30 and 45 mg) as the factor (Prism 5 for Mac OS X, GraphPad Software, La Jolla, CA). If a significant effect was observed on the ANOVA, Dunnett's *post hoc* tests were used to compare the effects of each active dose to placebo.

3. Results

3.1 Break point

A significant effect of cocaine dose was observed on break point for cocaine and break point for money from the Progressive Ratio Procedure ($F_{3, 21}$ values > 7.25 , P values < 0.01 ; Fig. 1 shows break point for cocaine). *Post hoc* analysis revealed that 15 and 45 mg cocaine significantly increased break point for cocaine and significantly decreased break point for money.

3.2 Subject-Rated Measures

A significant effect of cocaine dose was observed on one item from the Drug-Effect Questionnaire: Sluggish, Fatigued or Lazy ($F_{3, 21} = 3.12$, $P < 0.05$). *Post hoc* analysis did not reveal any significant active versus placebo dose effects. Visual inspection of the data indicates that 30 mg cocaine increased ratings on this measure, although not to a statistically significant degree. Trends toward significance were observed in the ANOVA for scores on the Stimulant subscale of the Adjective Rating Scale and two items from the Drug-Effect Questionnaire: Good Effects and Restless ($F_{3, 21}$ values ≥ 2.50 , P values < 0.09).

3.3 Physiological Measures

No significant effects were observed on physiological measures. A trend towards significance was observed in the ANOVA for Systolic Blood Pressure ($F_{3, 21} = 2.61$, $P = 0.08$).

4. Discussion

The results of the present experiment demonstrate that intranasal cocaine functions as a reinforcer on a progressive ratio schedule of reinforcement in humans. Trends were observed for cocaine to dose-dependently increase several subjective measures (i.e., scores on the Stimulant subscale of the Adjective Rating Scale and ratings of Good Effects). Cocaine doses were safe and well tolerated.

A number of other studies have shown that intranasal cocaine is chosen to a greater degree than placebo or available alternative reinforcers (Higgins et al., 1994; Rush et al., 2010; Stoops et al., 2010), but the present results extend those findings by demonstrating that intranasal cocaine functions as a reinforcer when an operant response is required to obtain a cocaine dose. Importantly, the arrangement tested here first required a choice between cocaine and an alternative reinforcer, which mimics naturalistic drug-taking and abstinence reinforcement treatments (for a review see Higgins, 1997). The arrangement then required responses for the chosen option on a progressive ratio schedule of reinforcement, which is considered a measure of motivation to take drugs (for reviews see Katz, 1990; Richardson and Roberts, 1996).

The findings are also concordant with a number of other studies that have evaluated the reinforcing effects of other stimulants on progressive ratio schedules (for a review see Stoops, 2008). Other studies have demonstrated the reinforcing effects of intravenous cocaine on progressive ratio schedules (Haney et al., 1998; Walsh et al., 2010), but to our knowledge, this is the first study to test the reinforcing effects of intranasal cocaine on this schedule. The results of those previous studies support the predictive validity of using progressive ratio schedules both in terms of medications development and naturalistic drug taking behavior. For example, pergolide did not change the reinforcing effects of cocaine nor was it effective in managing cocaine dependence (Haney et al., 1998; Malcolm et al., 2000). Likewise, cocaine dependent individuals self-administer more cocaine than cocaine abusing individuals in a laboratory setting (Walsh et al., 2010). Laboratory measures of drug-self administration in humans are increasingly being recognized as important models for testing pharmacological and behavioral therapies (Comer et al., 2008; Haney and Spealman, 2008; Stoops, 2008). That the results from the present study using intranasal administration are in agreement with prior research using smoked and intravenous cocaine suggests that these methods might also serve as a valuable research tool, particularly considering that intravenous cocaine administration is more invasive and smoked cocaine administration is technically challenging. Additional studies are needed, however, to demonstrate the predictive validity of the present procedures.

In this experiment, only trends toward significant cocaine dose effects were observed on subject-rated and physiological measures. A number of other studies have demonstrated significant effects of intranasal cocaine doses comparable to those we tested on both subject-rated and physiological measures and the reason for the discrepancy observed here is unknown (Foltin and Haney, 2004; Oliveto et al., 1995). For example, the second highest dose tested in the study by Foltin and Haney (0.69 mg/kg intranasal cocaine) roughly corresponds to the highest dose tested here (45 mg or 0.63 mg/kg in a 70 kg human). In that study, 0.69 mg/kg produced both subject-rated and physiological effects that were of greater magnitude than placebo (e.g., increased blood pressure and street value estimates). In the

study by Oliveto and colleagues, the second lowest dose tested (40 mg/70 kg intranasal cocaine) also roughly corresponds to the highest dose tested here. That dose also produced prototypical stimulant-like effects (e.g., increased ratings of Good Effects). While it is possible that the doses tested in the present study were too low to produce statistically significant subject-rated and physiological effects, it is also possible that analyzing data from only a single post-drug time point (i.e., 15 minutes after the sampling dose) accounts for the limited effects observed. However, other research has demonstrated that the effects of intranasal cocaine peak approximately 15 minutes after administration (Volkow et al., 2000). Another possibility is that due to the heavy cocaine use in the study population (i.e., all subjects met cocaine dependence criteria), these individuals were tolerant to the subject-rated and physiological effects of cocaine. Regardless of the reason for the general lack of statistically significant differences between placebo and active doses for subject-rated and physiological measures in the present experiment, the reinforcing effects of cocaine were clearly evident. The results of previous research have also demonstrated the reinforcing effects of drugs in the absence of subject-rated effects (Lamb et al., 1991). The present findings contribute to and extend the growing body of literature demonstrating the dissociation between the reinforcing and subject-rated effects of drugs of abuse (for further discussion, see Stoops, 2008).

There are a number of limitations that need to be acknowledged for the present study. First, the reinforcing effects of intranasal cocaine were not dose-dependent. The dose-response curve was essentially flat. It is possible that the reinforcing effects observed for the low dose (15 mg) cocaine are unique to this study; future work should seek to replicate this finding. Moreover, the 30 mg cocaine dose did not engender break points significantly higher than placebo, so future studies should determine whether this dose of intranasal cocaine can function as a reinforcer on a progressive ratio schedule. Other research has shown similar curves for active cocaine doses, so it is possible that humans are insensitive to cocaine dose in the relatively limited range that can be safely administered in the laboratory (Haney et al., 1998; 2006; Hart et al., 2007; Rush et al., 2010). Human studies generally test a three- to four-fold range of active cocaine doses in self-administration procedures, whereas nonhuman animal studies have tested 100-fold or higher ranges (Collins et al., 2007; Haney et al., 1998; Lile et al., 2005; Rowlett and Woolverton, 1997; Walsh et al., 2010).

Another limitation to the present study is that only one alternative reinforcer of relatively low value was tested. Previous research in our laboratory has shown that the value tested (\$0.25) substantially decreases cocaine taking in a simple drug versus alternative reinforcer choice procedure (Stoops et al., 2010). The impact of the alternative reinforcer value on cocaine break points cannot be determined from the present results, but future research should test the influence of other alternative reinforcer values on progressive ratio responding. Lastly, this study tested the effects of intranasal cocaine in a population that reported smoking cocaine as their primary route of administration. Given that the route tested here produces slower onset than the route typically endorsed by our subjects, which can be an important determinant of the reinforcing effects of drugs (reviewed in Lile, 2006), it is possible that the effects observed are of smaller magnitude than what would be observed if we tested bioequivalent doses of smoked cocaine. Subjects made four of six choices on average (i.e., break points of approximately 1000) for 15 and 45 mg intranasal cocaine and only one of six choices for placebo (i.e., break points of approximately 400). Thus, cocaine functioned as a reinforcer even when administered in a route different from that typically used. While break point for cocaine was higher than for placebo, it was not maximal (i.e., 1400 responses was the maximum break point). This finding leaves room for enhancement or attenuation of the reinforcing effects of cocaine with putative behavioral or pharmacological treatments in this model.

5. Conclusion

Intranasal cocaine functioned as a reinforcer on a progressive ratio schedule of responding in the present study, which is consistent with the results of previous studies with intravenous cocaine. Drug self-administration seems to be the best predictor from the human laboratory of treatment success (Haney and Spealman, 2008), thus, methods similar to those reported here can be used to test potential behavioral and pharmacological therapies for cocaine dependence. Moreover, these results suggest that intranasal cocaine functions as a reinforcer in a group that largely reported smoking cocaine, indicating that this model is a valid measure of reinforcement regardless of a subject's naturalistic route of administration. Future research should test other values of alternative reinforcer and demonstrate the predictive validity of this model by examining how known effective behavioral and pharmacological treatments change intranasal cocaine taking under the conditions tested here.

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Fig. 1. Mean break point for cocaine for 8 subjects. Filled symbols indicate a significant difference ($P < 0.05$) from placebo. X-axis: cocaine dose. Brackets indicate one S.E.M.