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Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure

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Abstract. Rhesus monkeys were trained in a discrete-trials choice procedure and allowed to choose between food delivery (1–16 pellets; 1 g/pellet) and intravenous injections of cocaine (0.03–0.56 mg/kg/injection; $N=4$) or procaine (1.0–10 mg/kg/injection; $N=4$) during daily 3-h sessions. Injections were available as the alternative to food. When the amount of food available as the alternative to drug was held constant and dose of drug was varied, the frequency of drug choice and total drug intake increased in a dose-related fashion for both cocaine and procaine. For both drugs, when the amount of food available as the alternative to drug was increased and the dose of the drug was held constant, the frequency of drug choice and total drug intake decreased. Thus, increases in the magnitude of an alternative non-drug reinforcer decreased cocaine and procaine self-administration. Further, the results suggest that while increasing the magnitude of the alternative reinforcer decreased the potency of cocaine as a positive reinforcer, the reinforcing efficacy of procaine was decreased. Because drug use by humans typically occurs in a context in which other reinforcers are available, the present results are consistent with the hypothesis that drug self-administration by humans can be decreased by increasing the value of alternative positive reinforcers. In addition, these results suggest that the extent to which drug self-administration is sensitive to this manipulation varies across drugs.

Key words: Choice – Self-administration – Cocaine – Procaine – Rhesus monkey

Research with cocaine has consistently demonstrated that it is a highly efficacious positive reinforcer (see Johanson and Fischman 1989). Both human (Fischman and Schuster 1982) and nonhuman (Johanson 1978; Spealman and Goldberg 1978; Griffiths et al. 1980; Woolverton and Nader 1990) subjects self-administer cocaine under a wide variety of conditions. In one experiment, Aigner and Balster (1978) reported that rhesus monkeys given an opportunity to choose between an intravenous injection of cocaine (0.3 mg/kg/injection) and food (5 g) every 15 min, 24 h/day, chose cocaine almost exclusively. This effect was even more impressive considering that the degree of food deprivation increased across days without decreasing the frequency of cocaine choice. The experiment had to be terminated after 8 days because of concern for the monkeys' health. This experiment made it clear that cocaine can, under some circumstances, maintain behavior more effectively than a biologically necessary positive reinforcer.

An understanding of the variables, either pharmacological or environmental, that modify drug self-administration is essential to developing rational approaches to decreasing drug abuse. There has been substantial investigation of pharmacological manipulations (e.g., dose of cocaine, pretreatment with another drug) that can alter cocaine self-administration (e.g., Wilson and Schuster 1972; de Wit and Wise 1977; Roberts et al. 1980; Woolverton 1986; Mello et al. 1989; Carroll et al. 1990). A number of environmental variables have been shown to alter cocaine self-administration as well. For instance, the schedule of reinforcement under which cocaine is available is a critical determinant of rate and pattern of drug-maintained behavior (Johanson 1978; Spealman and Goldberg 1978; Griffiths et al. 1980; Woolverton and Nader 1990). Increasing the number of responses necessary to receive an injection of cocaine (Yanagita 1973; Griffiths et al. 1978), punishment of cocaine self-administration with electric shock (Grove and Schuster 1974; Johanson 1977; Bergman and Johanson 1981), and concurrent access to other drug or non-drug reinforcers (Iglauer and Woods 1974; Johanson and Schuster 1975; Carroll et al. 1989) have all been shown to decrease cocaine self-administration.

The primary purpose of the present experiment was to further investigate the influence of a concurrently

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available non-drug reinforcer on cocaine self-administration. Rhesus monkeys were trained in a discrete-trials choice procedure and allowed to choose between an IV injection of cocaine and delivery of food pellets. The effect on cocaine preference of varying dose and number of food pellets available as the alternative was investigated. A second purpose was to use the identical procedure to investigate a second drug, procaine, that is readily self-administered by monkeys (Ford and Balster 1977; Hammerbeck and Mitchell 1978; Johanson 1980) but is considered to be a less efficacious positive reinforcer than cocaine (Johanson and Aigner 1981). Our first hypothesis was that frequency of drug choice would be decreased by increasing the magnitude of the alternative non-drug reinforcer. Such a result would imply that drug self-administration in an environment in which an alternative positive reinforcer is available can be decreased by increasing the value of the alternative. Our second hypothesis was that procaine self-administration would be more sensitive to this manipulation than cocaine self-administration. This outcome would imply that drugs vary in the extent to which their self-administration can be decreased by increasing the value of an alternative reinforcer.

Materials and methods

Subjects

Six adult rhesus monkeys *(Macaca mulatta)*, two females (M–8624, M–8712) and four males (M–8703, M–8704, M–8713, M–8802), that weighed between 6.0 and 10 kg under free-feeding conditions, served as subjects. Their body weights were decreased to approximately 90% of free-feeding weights, and maintained at that level for the duration of the experiment, by supplemental feeding of Purina Monkey Chow no sooner than 30 min post-session. In addition, monkeys were given a chewable multiple vitamin tablet 3 days/week and occasionally received fresh fruit. Four monkeys were experimentally naive, while monkeys M–8703 and M–8704 had been initially trained under fixed-interval schedules of drug injections prior to the beginning of this experiment. Monkey M–8802 became ill and had to be removed from the experiment prematurely. Each monkey was fitted with a stainless-steel restraint harness and spring arm which attached to the rear of the cubicle.

Apparatus

Monkeys were individually housed in sound attenuating cubicles (68 cm wide × 84 cm deep × 91 cm high) equipped with two response levers (BRS/LVE, PRL–001, Beltsville, MD), a food pellet dispenser (Ralph Gerbrands Co., Arlington, MA) and a peristaltic infusion pump (Cole-Parmer Co., Chicago, IL) for delivering drug injections. Above each lever were two sets of jewelled stimulus lights. The four lights above the left lever (lever 1) were covered with white lens caps, while two lights above the right lever (lever 2) were covered with red and two with green lens caps. In addition, two houselights, one white and one red, were mounted on the ceiling of the cubicle and were covered with translucent Plexiglas.

Procedure

Surgery. After adaptation to the cubicle and restraint system, each monkey was anesthetized with a combination of ketamine and halothane or a combination of phencyclidine HCl (1.0 mg/kg) and sodium pentobarbital (10–20 mg, IV) and a chronic indwelling venous catheter was surgically implanted. Under sterile conditions, the proximal end of the silicone catheter (0.08 cm inside diameter, Ronsil Rubber Products, Blackstone, VA) was inserted into a jugular vein (internal or external) or a femoral vein, terminating near the right atrium. The distal end of the catheter was threaded subcutaneously and exited through a small incision in the back of the animal.

Training. Monkeys M–8703 and M–8704 had previously been implanted with catheters and were initially trained under the choice procedure to choose between saline injections and food pellet delivery. Experimentally naive monkeys were not implanted with intravenous catheters until they had learned the choice procedure when choosing between food and no injection. When these subjects chose food on nearly 100% of the trials, a catheter was implanted and food-drug choice was studied.

The monkeys were trained to choose between cocaine and food or procaine and food. The procedure was essentially identical to that used by Aigner and Balster (1978) and has been described in detail by Woolverton and Johanson (1984). Daily sessions consisted of a maximum of 15 choice trials. The beginning of a trial was signalled by the illumination of the overhead white houselight, all four white lever 1 stimulus lights and either the red or green stimulus lights above lever 2. Five consecutive responses (fixed-ratio 5; FR 5) on lever 1 changed the stimulus conditions above lever 2 from red to green or vice versa. The red or green stimulus above lever 2 signalled the availability of food or drug contingent upon lever 2 responses. To assure that monkeys were exposed to each stimulus condition at the beginning of each trial, a minimum of three consecutive stimulus switches was required before a lever 2 response would "lock-in" a choice. The first response on lever 2 after the three-switch minimum had been completed extinguished the overhead houselight and the white stimulus lights above lever 1. An additional 29 responses (FR 30) on lever 2 within 2 min (limited hold) resulted in either a 10-s injection (saline, 0.03–0.56 mg/kg/injection cocaine or 1.0–10 mg/kg/injection procaine), accompanied by illumination of the overhead red houselight, or the delivery of food pellets (1–16, 1 g/pellet). A 10-min timeout (TO) separated trials. During the TO the stimulus lights associated with the chosen reinforcer flashed (on-off cycle of approximately 1 s). If 30 responses were not completed within the 2-min limited hold, all stimulus lights were extinguished for the duration of the TO. After 10 min a new trial began with the illumination of the houselight, lever 1 lights and the lights above lever 2 that had been illuminated when the last trial terminated. Sessions ended when (a) 15 trials were completed or (b) 3 h had elapsed or (c) a monkey had received its daily allotment of food (100–120 g/day).

Initially, a low dose of drug was available (cocaine 0.03–0.1 mg/kg/injection; procaine 1.0–3.0 mg/kg/injection) and either one or four pellets was the alternative. When choice was stable ($\pm$15% of the mean for three consecutive sessions, with no trends in behavior) one of three manipulations was performed: drug dose or number of food pellets was changed or the stimulus conditions were reversed to ensure that choice was based upon a reinforcer preference and not a color bias. Experimental conditions were presented in an irregular order and were in effect for at least ten sessions and until choice was stable. If, at a particular quantity of food, drug choice was at least 90%, higher doses of drug were not tested. If, at a particular dose of drug, drug choice was lower than 20%, higher quantities of food were not tested. Each condition was examined at least twice and, in many cases, the replications occurred several months apart. Experiments were conducted 7 days a week at approximately the same time each day. Cocaine-food choice and procaine-food choice were studied in four monkeys each. Two monkeys (M–8624, M–8704) were tested with both cocaine and procaine. M–8624 was first studied with cocaine, whereas M–8704 was first studied with procaine.

Drugs

Cocaine HCl (National Institute on Drug Abuse, Rockville, MD) and procaine HCl (Sigma Chemical Co., St Louis, MO) were dissolved in 0.9% saline for injection. Doses refer to the salt.

Results

When monkeys were allowed to choose between food and an injection of saline, all subjects chose saline on less than 20% of the trials (Figs. 1 and 2). When the number of food pellets/trial was held constant and cocaine dose was varied, the frequency of cocaine choice increased as a function of dose (Fig. 1). For instance, when four food pellets was the alternative to 0.03 mg/kg/injection cocaine, M–8713 chose cocaine on approximately 13% of the trials. When the dose of cocaine was increased to 0.3 mg/kg/injection, the frequency of cocaine choice increased to near 100%. When the number of food pellets available as the alternative to cocaine was varied with a given dose of cocaine, the frequency of cocaine choice decreased with increases in the magnitude of the food reinforcer in all monkeys (Fig. 1). For instance, when 0.3 mg/kg/injection cocaine was the alternative to one food pellet, M–8624 chose cocaine on nearly 100% of the trials. When the number of food pellets was increased to 4 or 16, the frequency of choice of 0.3 mg/kg cocaine decreased to 50% or less. For all monkeys, when four or eight pellets were the alternative to cocaine, the decrease in cocaine choice could be overcome, at least partially, by increasing the dose of cocaine. However, when the number of food pellets/choice was 16, drug choice was not increased above 50% by a higher dose of cocaine in three of the four monkeys.

Frequency of drug choice is based upon the number of trials on which drug was self-administered divided by the total number of trials completed. When choice was between intermediate doses of cocaine (0.1–0.3 mg/kg/injection) and one to eight food pellets, the changes in the frequency of cocaine choice shown in Fig. 1 were generally the result of changes in the total number of completed drug trials among a total of 15 completed trials. However, in some instances the number of completed trials was less than the total of 15 available. For instance, when the number of food pellets available was 16, sessions often ended after fewer than 15 trials because the total food allotment had been delivered. In addition, when 0.56 mg/kg/injection cocaine was the alternative to food, total trials completed per 3-h session decreased to 12 or less. This decrease in total trials completed was especially apparent in two monkeys. For M–8624 and M–8713, the total trials completed within 3 h when 0.56 mg/kg/injection cocaine and four pellets were available ranged between 5 and 8, probably because the high dose of cocaine interfered with responding. To assure that frequency of cocaine choice was a valid measure of preference in these circumstances, the timeout was increased to 30 min to allow drug effects to dissipate and

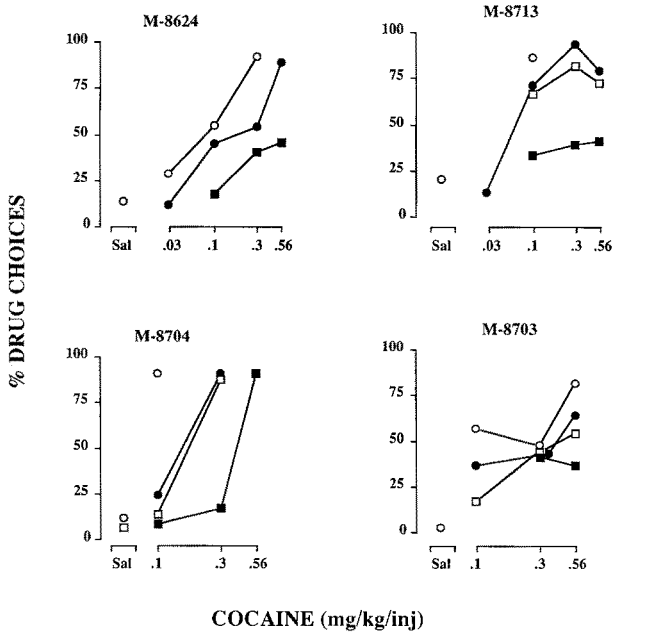

Fig. 1. Percentage of the completed trials in which cocaine was chosen, for each of four monkeys, as a function of cocaine dose (0.03–0.56 mg/kg/inj). Different symbols represent different magnitudes of food reinforcement available (1–16 pellets; 1 g/pellet) as the alternative to cocaine. The last three sessions of a condition were used in data presentation, with each value representing the mean of at least two determinations. Values above *Sal* are from sessions in which saline was available as the drug option. ○ 1 pellet; ● 4 pellets; □ 8 pellets; ■ 16 pellets

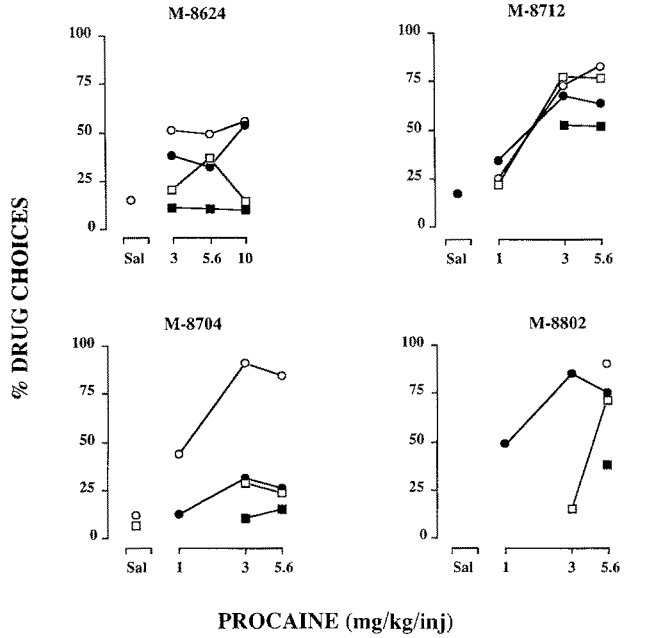

Fig. 2. Percentage of the completed trials in which procaine was chosen, for each of four monkeys, as a function of procaine dose (1.0–10 mg/kg/inj). Different symbols represent different magnitudes of food reinforcement available (1–16 pellets; 1 g/pellet) as the alternative to procaine. Values above *Sal* are from sessions in which saline was available as the drug option. For M–8704, saline data are from Fig. 1. All other details are as described in Fig. 1

the session length was extended to 9 h for these monkeys. This resulted in a doubling of the number of trials completed without changing the frequency of cocaine choice (data not shown).

When the number of food pellets/trial was held constant and procaine dose was varied, the frequency of procaine choice generally increased directly with dose (Fig. 2). The primary exception was M–8624 in which procaine choice never exceeded 50%, regardless of dose. When the number of food pellets available as the alternative to procaine was varied with a given dose of procaine, the frequency of procaine choice decreased with increases in the magnitude of the food reinforcer in all monkeys. This was most striking in M–8704. For this monkey, 3.0 mg/kg/injection procaine was chosen on 90% of the trials when one food pellet was the alternative to drug. However, when the magnitude of the food reinforcer was increased to four, procaine choice decreased to less than 32%. This decrease in drug choice could not be overcome by increasing the dose of procaine to 5.6 mg/kg/injection.

Procaine (1.0–5.6 mg/kg/injection) did not affect the total number of trials completed during the 3-h sessions, with subjects typically completing all 15 trials. For M–8624, the dose of procaine was increased to 10 mg/kg/injection because preference for food or procaine could not be obtained (see Fig. 2). This dose decreased the number of completed trials, with the frequency of drug choice still approximately 50%. The session length was increased to 9 h resulting in a doubling of trials completed without substantially changing the frequency of drug choice.

For both cocaine and procaine, the mean dose-response curves for the group shifted to the right with increases in the number of food pellets (Fig. 3, top panels). The dose-response function for cocaine tended to shift parallel to the right while the procaine dose-response also shifted downward. The effects of changes in the number of food pellets on total drug intake (Fig. 3, bottom panels) were similar to the effects seen with percent drug choice. When the number of food pellets was held constant and dose was varied, the total intake per session increased in a dose-related manner, for both drugs. When 16 pellets was the alternative to drug, maximum drug intake was recovered with increases in cocaine dose to 0.56 mg/kg/injection but not with increases in procaine dose to 5.6 mg/kg/injection.

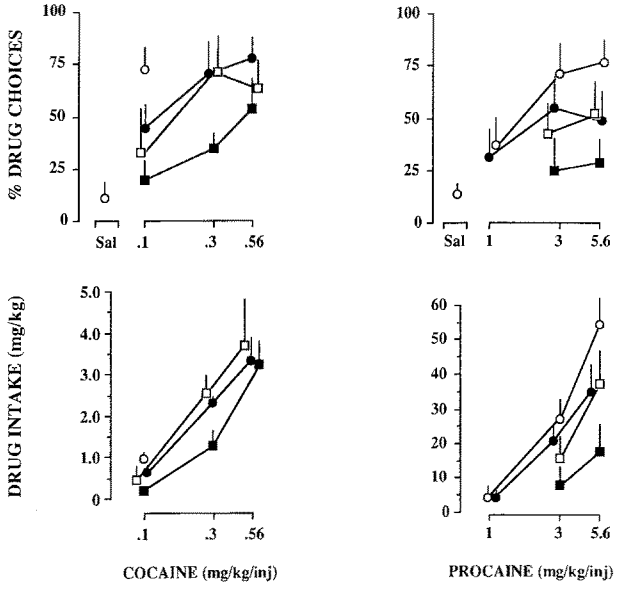

Fig. 3. Mean percentage of the completed trials in which drug was chosen *(top panels)* and total drug intake (mg/kg; *bottom panels*) as a function of drug dose. Different symbols represent different numbers of food reinforcement available (1–16 pellets; 1 g/pellet) as the alternative to cocaine *(left panels)* or procaine *(right panels)*. Each point is the average of three or four monkeys, except procaine 1.0 mg/kg/inj and one food pellet, which is the mean of two monkeys. Vertical lines represent 1 SEM. For symbols see legend of Fig. 1

Discussion

The results of the present experiment confirm previous findings (Woolverton and Balster 1981) that in monkeys allowed to choose between cocaine and food in a discrete-trials choice procedure, the frequency of cocaine choice is a direct function of cocaine dose. At sufficient doses monkeys chose cocaine rather than food on virtually every opportunity. This finding is consistent with the results of Aigner and Balster (1978) using a similar procedure. It should be noted, however, that in the Aigner and Balster (1978) experiment 0.3 mg/kg cocaine was chosen consistently over five food pellets whereas in the present experiment, 0.3 mg/kg cocaine was chosen over four food pellets in two of four subjects. As dose-response functions for cocaine in the present procedure vary across monkeys (see Woolverton and Balster 1981), it seems most probable that individual differences in sensitivity to the reinforcing effects of drug or food were the major determinant of this difference. However, methodological differences between the two experiments may also have contributed. Sessions in the present experiment were limited to 3 h whereas Aigner and Balster (1978) studied cocaine choice in 24-h sessions. In addition, the present experiment was conducted with the monkeys at 90% of free-feeding weight whereas Aigner and Balster (1978) started their experiment with only 23-h food deprivation. It should be noted, however, that at the end of that experiment the monkeys had lost 6–10% of that weight and continued to choose cocaine exclusively. In spite of these caveats, the general conclusion that cocaine is preferred to food under certain conditions is consistent across experiments.

The major finding of the present experiment was that an increase in the magnitude of an alternative non-drug reinforcer decreased the frequency of cocaine choice and total cocaine intake. It has previously been reported (Carroll et al. 1989) that making a non-drug positive reinforcer (a glucose + saccharin solution) concurrently available could decrease cocaine self-administration in rats. On the other hand, Dworkin et al. (1990) reported that cocaine self-administration was unchanged by the

concurrent availability of food reinforcement and that responding maintained by food or water was only slightly affected by changes in cocaine dose. By varying the magnitude of each reinforcer, the present experiment demonstrated an interaction between drug and a non-drug reinforcer that was systematically related to the magnitude of reinforcement. It seems likely that the larger decreases in cocaine intake seen in the present experiment were primarily the result of increasing the magnitude of the alternative to drug. However, it is also likely that differences in experimental conditions were also important determinants of the differences between experiments. In the Carroll et al. (1989) and the Dworkin et al. (1990) experiments, reinforcers were simultaneously available (concurrent access) whereas in the present experiment the choice was mutually exclusive (discrete-trials choice). That is, in the present experiment, choosing to self-administer a drug had an additional consequence of terminating availability of an alternative reinforcer which it did not have in the Carroll et al. (1989) and Dworkin et al. (1990) experiments. Nevertheless, it is clear that the availability of alternative reinforcers is an environmental variable that, like punishment and response cost, can substantially alter cocaine self-administration. Therefore, although cocaine is a highly efficacious positive reinforcer, cocaine self-administration can be decreased by environmental manipulations that also decrease behavior maintained by other drug and non-drug positive reinforcers.

The present results with procaine extend the conditions under which procaine can function as a positive reinforcer and demonstrate that procaine self-administration can also be decreased by increasing the magnitude of an alternative positive reinforcer. One important consideration in the design of the present experiment was to determine whether procaine choice was more sensitive than cocaine choice to manipulation of the alternative reinforcer. The analysis of the group data in Fig. 3 suggests that this is the case. The apparently parallel shift to the right in the cocaine dose-response function is in contrast to the primarily downward shift in the procaine dose-response function in response to the same manipulations. In pharmacological terms, this result suggests that potency of cocaine as a positive reinforcer decreased while the efficacy of procaine as a reinforcer was decreased. This conclusion must be drawn with some caution, since full effect of cocaine was not recovered with the increase in dose to 0.56 mg/kg; higher doses were not tested out of concern for the monkeys' health. Similarly, full effect of procaine was not recovered with an increase in dose to 5.6 or 10 mg/kg/injection, an increase that is consistent with the 10-fold potency difference between cocaine and procaine reported in other experiments (Woolverton and Balster 1982, 1983). Nevertheless, our results do suggest that drugs vary in the extent to which their self-administration is sensitive to modification by the availability of alternative reinforcers. Moreover, they support the notion that it is useful to characterize drugs in terms of their relative efficacy as positive reinforcers (Griffiths et al. 1979; Woolverton and Nader 1990; but see Katz 1990).

Several other issues should be considered in evaluating the present results. Since food deprivation can alter the reinforcing effects of not only food but also drugs (Carroll et al. 1979; Meisch and Carroll 1987), it may have contributed to the results of the present experiment. However, since food deprivation enhances the reinforcing effects of both food and drugs, it seems likely that any effect that did occur did not differentially modify the effects of one reinforcer or the other. In addition, since body weights were virtually constant throughout the experiment, any effect of food deprivation was constant across conditions and the functional relationship between reinforcers should have been constant. It is also possible that the anorectic effects of cocaine decreased the efficacy of food as a positive reinforcer as dose of cocaine was increased. This seems unlikely, however, since increases in the magnitude of the food reinforcer decreased cocaine choice, even at the high doses.

Although no clinical studies have explicitly examined the effects of increasing the value of alternative positive reinforcers on cocaine self-administration in cocaine abusers, there is evidence that avoiding the loss of other valuable positive reinforcers can decrease cocaine self-administration in humans (Crowley 1984). Indeed, such an effect may have played a role in the present results because of the mutually exclusive nature of the choice alluded to previously: to choose one option eliminated, at least temporarily, access to the other. It has been demonstrated, on the other hand, that in controlled laboratory settings in which drug abusers could chose between drug and money, increasing the value of the monetary reinforcer decreases the frequency of alcohol choice (Vuchinich and Tucker 1983, 1988) and opiate choice (Stitzer et al. 1980, 1983) in humans. Taken together with the present results, the implication of these experiments is that cocaine self-administration by humans could be decreased by increasing the value of appropriate alternative positive reinforcers.

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