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Rats choose cocaine over dopamine agonists in a two-lever self-administration preference test

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Abstract

Rats will self-administer dopamine D_1 and D_2 agonists, alone or in combination. Response rates and patterns for the D_1:D_2 combinations are nearly identical to those induced by cocaine. Here we examine whether rats prefer cocaine over D_1 or D_2 agonists presented alone or in D_1:D_2 combinations. During daily 3-h tests in a two-lever box, cocaine was available at either the right or left lever and the active side was alternated daily. After response rates had stabilized (±10% for 2 days), different groups were offered cocaine (800 μg/kg/injection) at one lever and either another dose (267, 1600, or 2400 μg/kg/injection) of cocaine or a dopamine agonist at the other lever. Animals consistently chose the higher of the presented cocaine doses over the low cocaine dose (267 μg). In choices between cocaine and dopamine agonists, the preferred cocaine dose (800 μg) was chosen over doses of the D_1 (SKF 82958) or D_2 ((+)-PHNO) agonist. However, no preference was shown between 800 μg cocaine and D_1:D_2 agonist mixtures, and the high-dose agonist mixture was preferred to the low cocaine dose. These results suggest that neither D_1 nor D_2 agonists alone fully duplicate the reinforcing actions of cocaine, but agonist combinations may approximate cocaine's reinforcement strength.

Keywords: Cocaine; D_1 agonist; D_2 agonist; D_1:D_2 agonist mixtures; Choice; Two-lever choice; Self-administration; Drug preference

1. Introduction

Most attempts to determine the reinforcing strength of drugs present animals with a Hobson's choice — this drug or none. In standard self-administration experiments, drugs are offered one at a time and the resulting behavior is compared to behavior in tests with other drugs or doses. This method has proven useful in evaluating the pharmacological basis of reinforcement, but it does not permit a direct comparison between the reward value of different drugs or doses. The use of a two-lever choice procedure permits animals to directly choose between two drugs at separate levers in the same test session and thus provides a side-by-side comparison of relative reward strength. However, such a procedure has been hampered in the past by technical problems associated with the delivery of two different drugs in the same test session. Early two-lever drug preference work in primates (Johanson and Schuster, 1975; Meisch and Stewart, 1995) demonstrated that, in general, higher doses of cocaine or methylphenidate were preferred to lower doses, but a similar attempt to study choice behavior in rats (Yokel, 1987) failed to demonstrate such preferences. In the present work, we use a new drug delivery method that permits two drugs to be separately administered through the same intravenous catheter.

Cocaine is believed to produce its rewarding effects mainly by elevating synaptic dopamine levels in the nucleus accumbens (Wise et al., 1995). It has been shown in single-lever tests that rats will self-administer solutions containing selective dopamine D_1 or D_2 agonists alone (e.g., Woolverton et al., 1984; Self and Stein, 1992; Belluzzi et al., 1993; Weed and Woolverton, 1995; Weed et al., 1993; Self et al., 1996; Grech et al., 1996) or in D_1:D_2 mixtures (Belluzzi and Stein, submitted; Belluzzi et al., 1993). Self-administration rates and patterns induced by high doses of a D_1 agonist, or by D_1:D_2 agonist mixtures were similar to those induced by cocaine. If dopamine is the primary mediator of cocaine's

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reinforcing actions, then preference tests comparing cocaine vs. selective dopamine agonists should provide information about the relative importance of D_1-like and D_2-like receptors in reward. Here we report the results of such two-lever preference tests between various doses of cocaine and between cocaine and various doses of D_1 or D_2 agonists, presented alone or in D_1:D_2 agonist mixtures.

2. Method

2.1. Animals

Male albino Sprague–Dawley rats were 90–120 days old (250–300 g) at the start of the experiment. Each animal was housed individually with water available ad libitum. Enough food was provided to maintain a lean, healthy adult body weight (350–400 g) that prevented obesity from developing during long experiments. A 12-h light/dark cycle was maintained with lights on from 0700 to 1900 h in an AAALAC-accredited vivarium maintained by University Laboratory Animal Resources personnel. All experimental procedures were performed in compliance with the requirements of protocols approved by the UCI Institutional Animal Care and Use Committee.

2.2. Catheter construction

A chronically indwelling catheter was implanted into the external jugular vein of each animal by a method similar to that described by Caine et al. (1993). Catheters were assembled from 12.5-cm lengths of Silastic tubing (0.012 in. ID × 0.025 in. OD, Dow Corning, Midland, MI) attached to a 22-gauge stainless steel guide cannula (Plastics One, Roanoke, VA). Prior to catheter assembly, the tubing was cleansed with 1 ml of a hexane/heptane/toluene (1:1:2) solution, flushed with 1 ml TDMAC heparin to inhibit clot formation after catheter implantation, and allowed to dry for 24 h. Guide cannulas were bent to right angles. The Silastic tubing was expanded in HEMO-De (Fisher Scientific, Pittsburgh, PA) and slid onto the guide cannula. An additional 2-cm length of large tubing (64 μm ID × 120 μm OD) was expanded and slid over the small tubing to protect the more fragile smaller tubing near the base of the catheter. After flushing with double-distilled water and drying for several hours, the cannula was embedded in a cranioplastic cement molding (Plastics One). A 3.0-cm^2 patch of Marlex mesh (Bard, Billerica, MA) was attached to the base of the catheter with cranioplastic cement. A small patch of Mersiline mesh (Ethicon, Somerville, NJ) was glued to the tubing 3.25 cm from the end to serve as a marker for catheter insertion. The assembled catheters were inspected for leaks by flushing with water between each step. Implanted catheters were flushed daily with 0.2 ml of a heparinized saline solution (20 U heparin/ml) to maintain patency.

2.3. Surgery

Rats were anesthetized with equithesin (2.5 ml/kg ip). Two small skin incisions were made for implantation of the catheter: one (about 2 cm) on the animal's back and the second (about 1 cm) on its neck above the jugular vein. After isolation of the vein, the catheter was passed under the skin of the back and the small tubing was inserted into the jugular vein until the tip reached the right atrium. Care was taken to avoid penetration of the right atrium. Surgical thread was tied around the vein and to the Mersiline mesh to secure the tubing. The neck incision was closed, thus securing the tubing subcutaneously. The Marlex mesh was similarly secured by closing the back incision. Antiseptic ointment (Neosporin) was applied to both incisions and Baytril (2.5 mg/kg im) was injected. Rats were allowed 3 days of postoperative recovery before beginning the experiments.

2.4. Lever-press training

Prior to surgery, food intake was restricted while animals were trained to lever-press for 45-mg food pellets in daily 20-min sessions in chambers identical to those used for drug self-administration tests. Next, rats were trained to alternate between the two levers. During alternation training, a light above the active lever signaled food availability and remained lighted until the animal responded. Responses at the other lever had no consequences. After each correct lever-press, a food pellet was delivered and the active side (and light) was switched to the opposite lever. After the animals had obtained 50 pellets on each lever (100 pellets per session) in three consecutive sessions, the self-administration tests began.

2.5. Self-administration preference test

Animals were tested in six identical Plexiglas chambers (28 × 25 × 30 cm) that were individually housed in ventilated, sound-resistant enclosures. Each chamber contained two levers (Gerbrands, Model G6314) mounted on the rear wall of the test chamber 1.5 cm above the floor and 10.5 cm apart. Three 10-ml glass syringes, each mounted in an infusion pump (MED Associates, Model PHM-100), were individually connected by polyethylene tubing (PE 50) to different ports of a four-way multiport "+" connector (Omnifit, Model 1004, Teflon PTFE, 1.5 mm bore). The fourth port was attached by polyethylene tubing (PE 50) to a single-channel feed-through swivel (Instech Model 375) that was connected (PE 20) to the catheter assembly on the animal's back inside a steel spring to protect the tubing (Fig. 1). Two syringes contained test solutions and the third contained saline. In initial experiments, each 6-s, 100-μl injection of test solution was followed by a 4-s injection of saline to purge the system of residual drug. In later experiments, an additional 6-s saline flush was introduced 10 s after the first flush. Each injection was followed by a 3-min

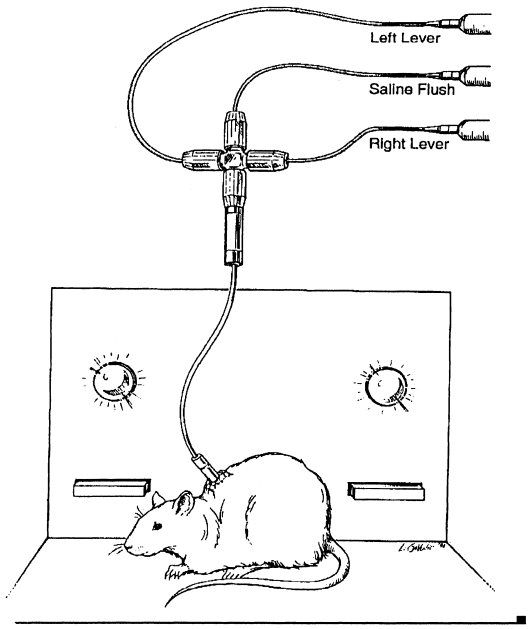

Fig. 1. Diagram of the self-administration delivery system used to separately inject two different drugs through the same intravenous catheter. Syringes are loaded into three injection pumps and attached with polyethylene tubing to the "+" connector that in turn is attached to the catheter on the rat's back. A response on either lever delivers 100 μl of the solution in that pump. Then the saline pump is operated to flush the drug out of the catheter (see Methods section for details).

time-out period during which all stimuli were turned off and both levers were inactive, but responses in the time-out period were recorded. The 180-s time-out period approximated the single-lever interresponse interval for the lowest cocaine dose (267 μg/kg/injection) and was intended to ensure that no animal would spend time without a drug injection that would otherwise have been taken if no time-out existed. At the end of the time-out, a white cue light came on over the active lever or levers, and a 1-s tone sounded to signal drug availability for the next trial.

Three-hour test sessions were conducted 6 days per week. Two successive daily single-lever sessions, in which animals had access to each of the drug solutions alone, were followed by one two-lever choice session where both drug solutions were simultaneously available. In a second three-session sequence, the side and order of drug availability were reversed to control for side preferences or recency effects on drug choices. Throughout all six sessions of each choice test, one drug was associated with a flashing light and intermittent low-intensity 2900-Hz tone (Sonalert, Model SC628; 500-ms duty cycle); the other drug was associated with a continuous light and tone. Both signal lights came on prior to each choice and the appropriate tone was sounded during the 6-s drug injection and 4-s flush. The side of the initial drug, order of drug presentation, and drug–stimulus association were randomly assigned to each animal in a test group. A fixed-ratio 1 schedule of reinforcement was in effect during all sessions.

Cocaine doses (267, 800, 1600, and 2400 μg/kg/injection) were chosen to span the effective dose range of cocaine in self-administration tests. Doses of the D_1 agonist SKF 82958 (3, 10, and 30 μg/kg/injection) also spanned the dose–effect curve for SKF 82958 self-administration. Doses of the D_2 agonist (+)-PHNO (1, 3, and 10 μg/kg/injection) were chosen to be one-third the doses of SKF 82958 based upon earlier results that had demonstrated optimal effects with these dose ratios.

2.6. Drugs

The following drugs were used: cocaine HCl (National Institute on Drug Abuse, Research Triangle Park, NC). SKF

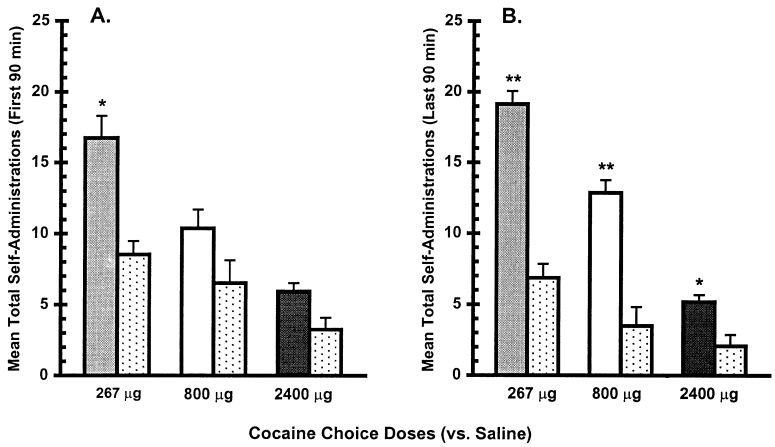

Fig. 2. Mean (±S.E.M.) total self-administrations during both two-lever choice sessions for each drug offered during the first half (A) and second half (B) of the 180-min choice sessions. A cocaine dose (in μg/kg/injection) was available at one lever and saline (Sal) at the other lever in each choice session. Lever-drug pairings were reversed during the second choice session. Animals responded significantly more for cocaine than for saline (stippled bars) at all cocaine doses tested, * $P<.05$ vs. saline; ** $P<.01$; $n=6–7$ per choice.

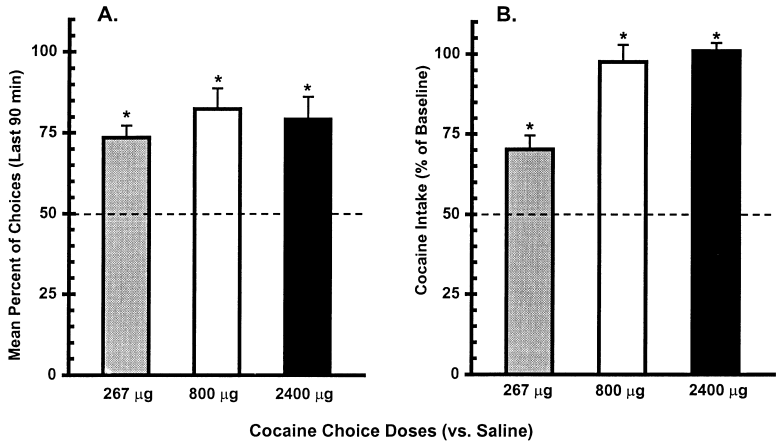

Fig. 3. (A) Mean (±S.E.M.) percent of choices for each dose of cocaine (in μg/kg/injection) during the last 90 min of choice tests offering saline vs. the cocaine dose indicated. Responding for all cocaine doses was significantly greater than would be expected by chance, * $P<.05$; $n=6-7$ per choice. (B) Total cocaine intake (percentage of single-lever baseline) for each dose of cocaine during saline vs. cocaine choice tests. Intake was nearly identical to that obtained during baseline sessions for the higher cocaine doses, and all three levels of intake were significantly greater than would be expected by chance, * $P<.05$; $n=6-7$ per choice.

82958 ((±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine HBr) was purchased from Research Biochemical International (Natick, MA). (+)-PHNO ((+)-4-propyl-9-hydroxynapthoxazine) was provided by Merck, Sharp and Dohme (Rahway, NJ). Drugs were dissolved in 0.9% saline and sterile-filtered immediately before testing (0.2-μm Acrodisc, Gelman Sciences, Ann Arbor, MI).

2.7. Statistical analysis of the data

Total mean self-injections for each experiment were analyzed using a two-way ANOVA with Drug × Dose and Bonferroni post hoc comparisons. Cocaine intake and percent of choices values were analyzed using Bonferroni-corrected single-group *t* tests with mean of 50. All analyses were performed using SYSTAT 9.0 statistical software.

3. Results

When animals were offered cocaine and saline at different levers, they chose cocaine over saline at all doses tested [$F(1,17)=49.4603$, $P<.0001$; Fig. 2]. Self-injection rates at both levers decreased substantially with increases in the cocaine dose due to the long interinjection intervals associated with higher cocaine doses. However, the ratio of cocaine to saline choices remained relatively constant at greater than

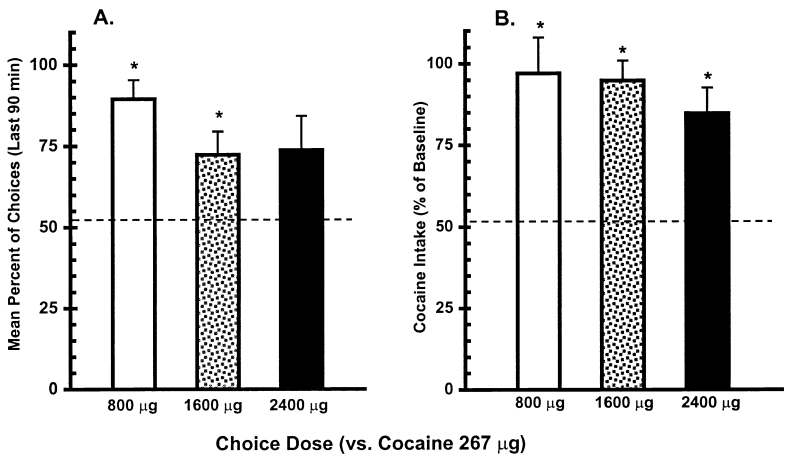

Fig. 4. (A) Mean (±S.E.M.) percent of choices for each dose of cocaine (in μg/kg/injection) during the last 90 min of choice tests offering cocaine (267 μg/kg/injection) vs. the cocaine doses indicated. * Significantly different from 50%, $P<.05$; $n=6-8$ per choice. (B) Total cocaine intake (percentage of baseline) for each dose of cocaine during cocaine (267 μg/kg/injection) vs. cocaine dose choice tests. Intake was nearly identical to single-lever baseline sessions for the two lower doses. * Significantly different from 50%, $P<.05$; $n=6-7$ per choice.

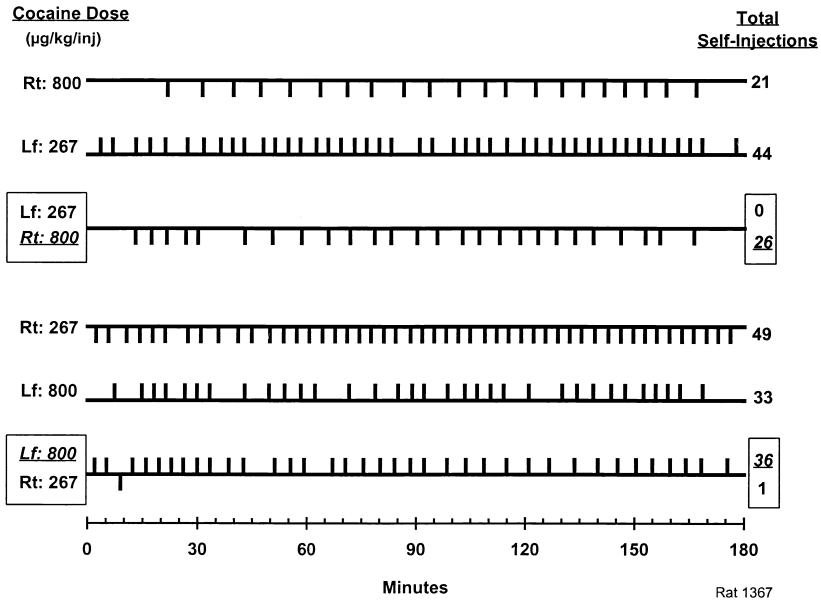

Fig. 5. Representative rat showing cocaine self-administration during the six-session choice procedure. Each line represents a 180-min session with lever side and cocaine dose (in μg/kg/injection) on the left and total self-injections in 3 h on the right. The third and sixth horizontal lines are two-lever choice sessions where self-injections are shown for both the left (up-ticks) and right (down-ticks) levers. The remaining lines represent single-lever baseline sessions for each dose separately.

2:1 across cocaine doses (Fig. 2). To compensate for differences in baseline self-administration rates at different cocaine doses, and to weight each subject equally in group averages, choice data were recalculated for each rat as a percentage of total choices. Fig. 3A shows that the selection of cocaine over saline was significantly greater than would be expected by chance (50%) at all cocaine doses tested. Since drug preferences were generally more clear-cut during the latter half of the self-administration session, Fig. 3A presents data for the last 90 min of the 180-min session (animals sample both levers during initial choice trials apparently to confirm which lever delivers which test solution due to the counterbalanced design). There was a significant increase in percentage of cocaine choices when the second 90-min period was compared to the first [$F(1,23)=9.9575$, $P=.0044$]. Cocaine intake approached single-lever baseline intake levels at the higher doses (Fig. 3B), again supporting the idea that the rats were not responding randomly at the two levers. Because

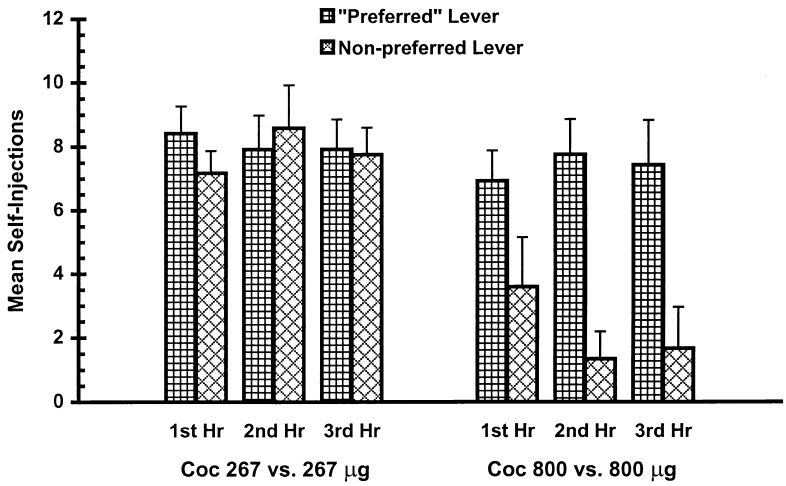

Fig. 6. Mean (±S.E.M.) hourly self-injections for identical cocaine doses (in μg/kg/injection) on both levers in the two-lever choice procedure. Mean responses during the two choice sessions were computed for the lever receiving the most (“preferred”) and fewest (“nonpreferred”) responses during the first 3-h choice session. Animals working for the low cocaine dose (267 μg/kg/injection) alternated between levers within each choice session, whereas animals working for the higher dose (800 μg/kg/injection) tended to stay at one lever in both sessions.

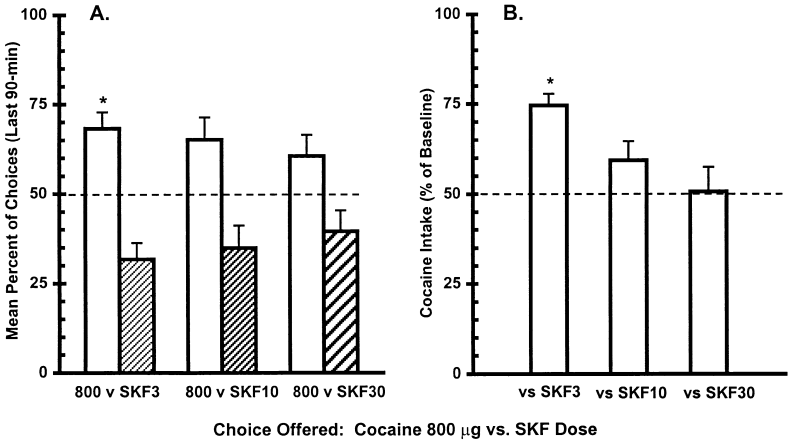

Fig. 7. Mean (±S.E.M.) percent of choices for each drug pair during the last 90 min of choice tests offering cocaine (800 μg/kg/injection) and a dose (in μg/kg/injection) of D_1 agonist SKF 82958 (SKF). (A) Animals responded significantly more for cocaine only at the low D_1 agonist dose (3 μg/kg/injection). (B) Total cocaine intake (percentage of 800-μg single-lever baseline) during cocaine vs. SKF 82958 choice tests. Cocaine intake was reduced to 50% as the SKF 82958 dose was increased. * Significantly different from 50%, $P<.05$; $n=7-12$ per choice.

cocaine is a psychomotor stimulant, it is possible that responses at the cocaine lever resulted from drug-induced stereotypy. However, analysis of response rates during the 3-min time-out periods revealed remarkably low levels (3-h mean responses = 0.04 ± 0.04) even at the highest cocaine dose (2400 g). The absence of responding during the time-out periods would appear to eliminate drug-induced stereotypy as a factor in the observed preferences for cocaine over saline.

In choice tests between the low cocaine dose (267 μg/kg/injection) and higher doses, the animals responded significantly more for the higher doses (Fig. 4A). Total cocaine intake at the higher dose lever approximated single-lever baseline levels and was significantly greater than intake expected from random responding (Fig. 4B). Fig. 5 shows that when a cocaine dose was presented alone in single-lever sessions, response rates and patterns typical of that dose were obtained. When two doses were offered simultaneously in two-lever choice sessions, the rates and response patterns of the preferred dose approximated those of the single-lever sessions irrespective of the side or recency of the baseline test. For the nonpreferred low cocaine dose, neither the single-lever baseline rate nor pattern was maintained in the choice test. When the higher cocaine doses (800 vs. 2400 μg) were compared, animals displayed a nonsignificant preference for the 800-μg dose suggesting the possibility that the preference curve peaked at about 800 μg/kg/injection. However, total intake measures indicated that approximately 50% of the single-lever intake was self-administered at each dose.

When animals were offered identical doses of cocaine at each lever in choice tests, response patterns were dependent on the dose. If both cocaine doses were low (267 μg),

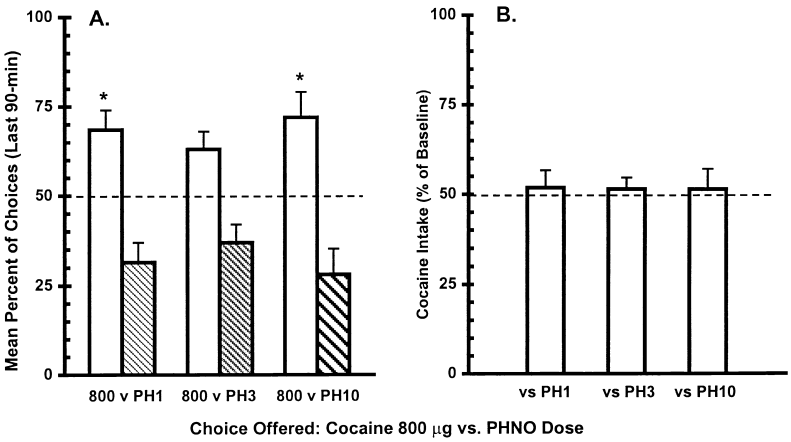

Fig. 8. Mean (±S.E.M.) percent of choices for each drug pair during the last 90 min of choice tests offering cocaine (800 μg/kg/injection) and a dose (in μg/kg/injection) of D_2 agonist (+)-PHNO (PH). (A) Animals responded significantly more for cocaine at the low and high D_2 agonist doses. (B) Total cocaine intake (percentage of 800-μg single-lever baseline) during cocaine vs. (+)-PHNO choice tests. Cocaine intake was reduced to 50% at all (+)-PHNO doses. * Significantly different from 50%, $P<.05$; $n=6-12$ per choice.

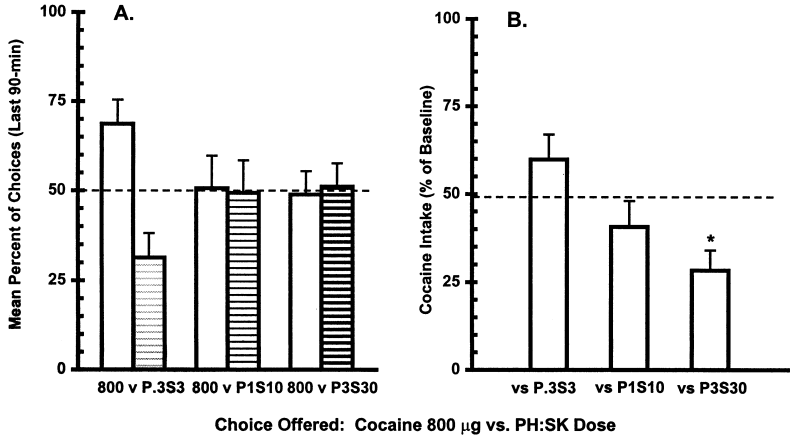

Fig. 9. Mean (±S.E.M.) percent of choices for each drug pair during choice sessions offering cocaine (800 μg/kg/injection) of cocaine (Coc) and mixtures of D_2 agonist (+)-PHNO (P) and D_1 agonist SKF 82958 (S) in the 1:10 dose ratios (in μg/kg/injection) shown. (A) Animals showed no significant preference for any drug solution offered. (B) Total cocaine intake (percentage of 800-μg single-lever baseline) during choice tests offering cocaine vs. (+)-PHNO/SKF 82958 mixtures. Cocaine intake was dramatically reduced at all (+)-PHNO/SKF 82958 doses. * Significantly different from 50%, $P<.05$; $n=6-12$ per choice.

responses were alternated between both levers within each choice session such that there was no difference in the number of responses at either lever [$F(1,5)=0.0461$, $P=.8385$; Fig. 6, left]. However, if both levers delivered the preferred middle dose (800 μg), the animals responded significantly more at the lever on their "preferred" side in both choice sessions [$F(1,5)=8.2230$, $P=.0351$; Fig. 6, right] and this side preference increased over the 3-h choice session [$F(2,10)=5.6226$, $P=.0231$; Fig. 6, right].

In choice tests where cocaine and the dopamine D_1 agonist SKF 82958 were offered, the animals selected the previously preferred dose (800 μg) of cocaine (Fig. 7A). Cocaine intake was significantly greater than chance only when compared to the lowest dose of SKF 82958 (Fig. 7B). When offered the previously less-preferred cocaine dose (267 μg) the animals showed no cocaine preference over any dose of SKF 82958 (data not shown). Choice tests between cocaine and the D_2 agonist (+)-PHNO produced similar results: animals chose the higher cocaine dose (800 μg) over all doses of (+)-PHNO [$F(1,30)=16.4261$, $P=.0003$; Fig. 8A], but displayed no such preference for the 267-μg cocaine dose [$F(1,20)=1.0802$, $P=.3110$]. In the (+)-PHNO comparisons, a few rats had high response rates in the time-out period suggesting that stereotypy may have interfered with drug selection. However, exclusion of these rats did not change the results or conclusions of this choice test. Intake of the 800-μg cocaine dose in choice tests was cut in half at all doses of (+)-PHNO (Fig. 8B). In preference tests offering cocaine and D_1:D_2 agonist mixtures, rats no longer preferred the 800-μg cocaine dose over the various D_1:D_2 agonist mixtures (Fig. 9A), and cocaine intake was strongly suppressed (Fig. 9B). However, there was a preference for the high-dose agonist mixture (PHNO 3 μg + SKF 30 μg) when compared to the low cocaine dose (Fig. 10A), and intake of the 267-μg cocaine dose also was significantly suppressed (Fig. 10B).

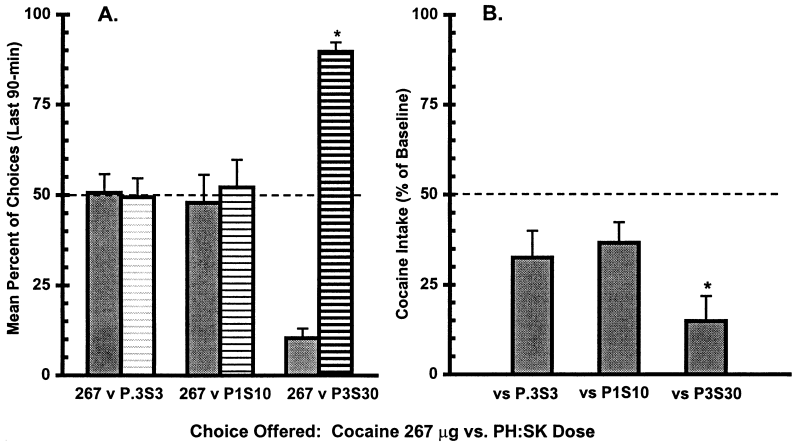

Fig. 10. Mean (±S.E.M.) percent of choices for each drug pair during choice sessions offering the low cocaine dose (267 μg/kg/injection) and mixtures of D_2 agonist (+)-PHNO (P) and D_1 agonist SKF 82958 (S) in the 1:10 dose ratios (in μg/kg/injection) shown. (A) Animals showed a significant preference for the high-dose agonist mixture over the low cocaine dose. (B) Total cocaine intake (percentage of 267-μg single-lever baseline) during choice tests was dramatically reduced at all (+)-PHNO/SKF 82958 doses. * Significantly different from 50%, $P<.05$; $n=6-12$ per choice.

4. Discussion

It is clear that rats prefer all test doses of cocaine over saline, and higher cocaine doses over lower. Our findings confirm earlier reports of primate preferences for higher doses (Johanson and Schuster, 1975; Meisch and Stewart, 1995) and may help to explain an earlier failure to find a preference for higher cocaine doses in rats (Yokel, 1987). In the early study, rats did not receive sufficient single-lever baseline self-administration training, the comparison doses (500 and 1500 μg) may have been too high and/or too close together, and time-out periods were not presented after each self-injection. When these procedures were introduced in the present study, preferences for higher cocaine doses were quite clearly demonstrated.

Preferences between different cocaine doses above 800 μg/kg/injection were not observed. Since interinjection intervals are directly related to cocaine dose, one difficulty is the reduced number of choice opportunities in these high-dose choice tests. This limitation could make it more difficult for animals to demonstrate clear choices for high drug doses, but future tests could be partially compensated by use of longer sessions. However, in spite of this limitation, several high-dose vs. low-dose choices produced significant preferences for the high dose. A second difficulty is the necessity for rats to sample both levers in order to identify the location of the preferred drug. More clear-cut preference behavior in the second half of the self-administration session supports this inference. Also, one cannot discount the influence of drug interactions on choice behavior. It may be more rewarding to deliver both available drugs in certain cases, rather than selecting only the preferred drug solution to the exclusion of the other. On the other hand, the development of side preferences with 800-μg cocaine presented on both levers, but not with the 267-μg dose, suggests that the animals are making a choice to explore for higher rewards when only low rewards are available, but not when the reward on either lever is sufficiently high. This indirectly indicates that the 800-μg dose was near optimal since the animals discontinued alternation behavior after sampling both levers early in the session.

The generality of the results may be constrained by methodological factors. For example, the time-out period following each drug injection may significantly affect drug preferences. The time-out was introduced to ensure careful choice behavior by increasing the cost of ''incorrect'' responses. Nevertheless, rats self-administering the 267-μg cocaine dose during single-lever sessions did not self-administer the maximum amount of cocaine available and took less cocaine under the 3-min time-out than rats in previous experiments took without the time-out. This reduced intake may be due to schedule-induced changes in sensitivity to the drug. The reduced intake of cocaine during the 267-μg cocaine–saline choices also may reflect this changed sensitivity to cocaine. In addition, since each response for saline prevented cocaine intake for 3 min, overall cocaine intake was lower than predicted from baseline sessions.

The demonstration that animals prefer high cocaine doses over dopamine agonists suggests that the agonists alone do not duplicate all of cocaine's reinforcing actions. It should be noted, however, that animals failed to prefer the low cocaine dose (267 μg) over either agonist. This result suggests that the maximum reinforcement strength of the agonists is approximately equal to the low cocaine dose, but additional dopamine agonists must be tested to generalize this finding. The demonstration that the high-dose D_1:D_2 mixture was preferred over the low cocaine dose is an intriguing indication that some dopamine agonist dose combinations might be more reinforcing than cocaine. The selected agonist doses were based on earlier work that indicated they covered the most important part of the self-administration dose–effect curve. The dose ratios selected for the D_1:D_2 mixtures also were based on previous work but clearly do not exhaust possible combinations that may have different reinforcing actions. Also, the low response rates observed for these combinations, as well as for the high dose of SKF alone, may have complicated the demonstration of preferences. In any event, it seems likely that there are important differences between the pharmacological actions of the agonists and cocaine that could affect the relative reinforcing strength of these drugs. First, cocaine acts indirectly by blocking the presynaptic reuptake of dopamine — thus enhancing the phasic actions of endogenous dopamine — whereas, the agonists act primarily on postsynaptic dopamine receptors and effectively bypass the effects of endogenous dopamine. Indeed, D_2 agonists may act at presynaptic dopaminergic autoreceptors to inhibit dopamine release. Second, it is known that cocaine blocks the reuptake of transmitters other than dopamine, in particular serotonin reuptake. These actions may contribute to the overall reinforcing effect of cocaine and may distinguish it from reinforcing actions at dopamine receptors alone.

Our choice method appears to be suitable for examining preferences among other drugs of abuse, both within classes (e.g., stimulants) and between classes (e.g., stimulants vs. opiates). However, the method is not without complications. As noted, one cannot discount the influence of total drug intake on choice behavior. In addition, the problem of drug mixing cannot be totally discounted. Even the use of a 3-min interinjection time-out period does not necessarily eliminate residual drug effects of previous injections and could alter choice behavior in unexpected ways. This problem can be mitigated by the use of even longer time-out periods after self-injections. Another concern is the influence of conditioned reinforcement due to the counterbalancing of stimuli during single-lever self-administration sessions. Such conditioned reinforcement might interact with drug preferences in unpredictable ways and should be considered in the interpretation of negative results. However, the counterbalancing of factors such as side bias, recency effects, etc., in the present experiments increases

our confidence in the demonstration of the drug and dose preferences we observed.

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