Pharmacology Biochemistry and Behavior, Vol. 45, pp. 539–548, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Parameters of Self-Administration of Cocaine in Rats Under a Progressive-Ratio Schedule

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Received 23 September 1992

DEPOORTERE, R. Y., D. H. LI, J. D. LANE AND M. W. EMMETT-OGLESBY. *Parameters of self-administration of cocaine in rats under a progressive-ratio schedule.* PHARMACOL BIOCHEM BEHAV **45**(3) 539–548, 1993.—Progressive-ratio (PR) schedules may provide a more direct measure of drug-reinforcing efficacy than the more traditionally used fixed-ratio schedules. Under a PR schedule, an increasing number of lever presses is required for the delivery of each successive reinforcer. However, there have been few studies of fundamental parameters of cocaine self-administration under a PR schedule. This study was undertaken to assess if PR responding using cocaine reinforcement in rats would: a) be acquired rapidly; b) be maintained on a stable baseline for long periods; and c) provide data on the effect of changing the dose of cocaine that are amenable to statistical analysis. In addition, the effects of pretreatments with SCH23390, a D_1 receptor antagonist, or ondansetron, a 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonist, were tested against several doses of cocaine. Stable performance of PR cocaine self-administration (0.90 mg/kg) was acquired within 10 training sessions and was maintained for over 50 training sessions. Increasing the dose of cocaine from 0.10–2.70 mg/kg resulted in a directly related increase in a) the number of reinforcers obtained, b) the highest ratio completed, and c) the interreinforcer time (IS^RT: time between each cocaine infusion). In terms of statistical analysis, the number of reinforcers obtained was found to be preferable to the highest ratio completed as a measure of breakpoint. Pretreatment with SCH23390 significantly reduced the breakpoint; this reduction was not due to a motor-incapacitating effect of SCH23390 because the IS^RT showed a tendency to be shortened by SCH23390. Pretreatment with ondansetron failed to significantly affect either the number of reinforcers obtained or the IS^RT. These results show that rats can readily acquire the task of self-administration of cocaine under a PR schedule and maintain a stable baseline for an extended period. Further, a PR schedule appears to be suitable for the study of pharmacological treatments that might affect cocaine self-administration. Simultaneous monitoring of the breakpoint and of the IS^RT determines if a decrease in the breakpoint is the result of a motor-incapacitating side effect of the pretreatment.

Cocaine Self-administration Progressive-ratio SCH23390 Ondansetron

DRUG self-administration studies are valuable in part because a high concordance exists between drugs that serve as reinforcers in animals and drugs that humans abuse (10,40,49). Many studies of animal drug taking have used procedures in which drug is available under a simple fixed-ratio (FR) schedule, and often the value of the ratio is relatively low. Such schedules have utility for determining whether drugs can serve as reinforcers, but they provide only nominal information concerning the relative reinforcing efficacy of different drugs (18,20). For example, Katz (20) argued that at best these schedules can only predict that a drug will have abuse potential in humans but that they cannot predict the relative degree of abuse liability that a particular compound might possess.

One procedure that has been claimed to provide an index of reinforcing efficacy is the progressive-ratio (PR) procedure. Initially introduced by Hodos (14) to study liquid reinforcement in rats, this schedule has since been used to assess the reinforcing effects of electrical brain stimulation or drugs using primates, pigs, dogs, and rats as subjects (1,6,11–13,15–17,21,27,31–34,36–38,46,48). Under a PR schedule, each reinforcer is delivered under a ratio schedule, but the ratio value for each successive reinforcer is increased progressively until eventually the subject fails to emit the required number of responses in the designated period (this highest ratio completed within the time limit is usually deemed the breakpoint). The breakpoint maintained by cocaine has been shown generally to increase as a function of cocaine dose (12,13,31–33,48), although at high doses of cocaine this relationship may not hold (1,34). Most of these studies used relatively few subjects and presented data for individual animals without statistical analyses.

More recently, Roberts and co-workers (2,5,7,36–38) and others (17,39) used rats as subjects in the PR procedure. The establishment of the PR procedure in rats has several appealing aspects. For example, rodents are inexpensive as subjects, and it should be easier to obtain data from enough subjects to

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permit statistical evaluation. To date, however, little information is available concerning the parameters of self-administration by rats under this schedule. If dose-effect data from different drugs are to be compared, or if several doses of a blocking drug are to be tested against several doses of cocaine, then it will be critical that baseline stability is maintained across an extended period of time. At least one laboratory reported difficulties in maintaining adequate baseline stability under this procedure (39). Thus, we investigated the acquisition and stability of PR responding using cocaine as a reinforcer to determine the viability of this technique in rats.

When cocaine self-administration is tested under low-value FR schedules, rate of responding is frequently the dependent variable. If this variable is expressed as the time between successive reinforcers (interreinforcer time, IS^RT), then as the dose of cocaine is increased in those procedures the IS^RT also increases. Indeed, in many cases the IS^RT increases with dose such that essentially constant intake of cocaine occurs per unit time, independent of the dose tested (26,29,44). For the PR schedule, little information exists concerning changes that occur in the IS^RT as a function of the dose of drug tested. Most studies using PR methodology simply reported breakpoint (highest ratio completed) data without providing a measure of time between individual reinforcers. Thus, only in the study by Roberts et al. (38), in which the overall rate of cocaine intake was measured during PR responding, has this relationship been examined. Those authors showed that pretreatment with the dopamine antagonist haloperidol resulted in a faster intake of cocaine at the same time that the breakpoint was reduced. However, that study used only a single dose of cocaine, and no studies systematically varied the dose of cocaine to determine the relationship between breakpoint and IS^RT. We studied the effects of a wide range of doses of cocaine on both the number of reinforcers obtained, the highest ratio completed, and the IS^RT. We also determined which of the two measures, the number of reinforcers obtained or the highest ratio completed, would be the most appropriate measure of the breakpoint for statistical analysis.

Although the primary purpose of this study was to provide a detailed analysis of the parameters of PR responding, we also assessed the effect of pretreatment with two drugs that we recently tested on cocaine self-administration under a low-value FR schedule (26). In that study, IP pretreatment with the dopamine type-1 receptor (D_1) antagonist SCH23390 (50 and 100 μg/kg) decreased the IS^RT for cocaine self-administration, whereas IP pretreatment with ondansetron, a serotonergic type-3 receptor [5-hydroxytryptamine$_3$ (5-HT_3)] antagonist, had no significant effect upon cocaine self-administration. Based upon these results in the low-value FR procedure, we hypothesized that SCH23390 would reduce the number of reinforcers obtained and shorten the IS^RT for cocaine self-administration under the PR schedule. Consequently, the effect of SC injection of SCH23390 (10 μg/kg) was tested against a 27-fold range of doses of cocaine (0.10, 0.30, 0.90, and 2.70 mg/kg). In addition, SCH23390 was tested at the doses of 5.6, 10, 17.8, and 32 μg/kg, this time against the training dose of cocaine (0.90 mg/kg). The SC route was chosen because SCH23390 has a relatively short duration of action and because a cocaine self-administration session under the type of PR schedule we used typically runs for about twice as long as an FR session for the same dose of infused cocaine. Ondansetron was tested IP at the dose of 0.1 mg/kg against 0.10, 0.30, and 0.90 mg/kg cocaine. Ondansetron was also tested IP, using a 1,000-fold range of doses (0.001-1.0 mg/kg), against a single dose of cocaine (0.90 mg/kg).

METHOD

Animals

Adult, male rats of Fisher F344 strain (Harlan, Indianapolis, IN) were subjects. They were maintained at approximately 270 g body weight (range: 264-291 g) by restricting daily access to food; over the course of the experiments, their weight corresponded to approximately 85% of their free-feeding body weight. Rats were weighed every second day. Body weights were restricted because this procedure produces higher rates of drug intake in self-administration procedures (3).

Apparatus

Lever-press shaping was done with food as a reinforcer in standard two-lever operant chambers (Model E-10-10TC, Coulbourn Instruments, Lehigh Valley, PA) using 45-mg food pellets (BioServ, Frenchtown, NJ). Self-administration experiments were performed in chambers that were custom designed and locally made. They contained a single lever, 5.0 cm above the floor and centered on the back wall, that could be depressed (force of 0.15 N) to close a microswitch. These chambers were also equipped with two stimulus lights (3 W), one located on the ceiling and the other 9 cm above the lever. The ceiling was constructed of Plexiglas and was fitted with a 1.0-cm hole in the center through which a catheter/spring assembly was passed. The arrangement of the counterbalanced swivel was essentially identical to that reported by Dworkin et al. (8). The chambers were placed in sound- and light-attenuating enclosures. Syringe pumps (Razel, Model A; driven at 3.33 rpm) were located outside the enclosures and used to drive 10-ml syringes that contained a cocaine or a saline-vehicle solution. Lines (0.06-in. O.D. Tygon Microbore Tubing, Norton Performance Plastics, Akron, OH) from these pumps were connected via a stainless steel Y connector (part D-TYC-316-20, Small Parts, Miami, FL) placed just before the swivel, and a single line left the Y connector to enter the swivel (Part 50500, Stoelting, Chicago, IL). The exit line from the swivel immediately entered the chamber; this line was protected inside a steel spring that was 24 cm in length and 0.4 cm in diameter. The free end of the spring was ended by a nut that could be locked onto the threaded part of the rat's head mount (see the Surgical Procedure section). All experimental contingencies were controlled and data were recorded via MS-DOS-compatible microcomputers using software described previously (9,41).

Lever-press Shaping

Sixteen rats were first daily trained to press a lever using food (45-mg pellets) as a reinforcer. Under a series of FR schedules, increasing from FR 1 to FR 10 and with no time limit, they were shaped until they emitted at least 200 presses during 1 h under an FR 10 schedule during two consecutive daily sessions. Rats were then trained under a PR schedule, in which a progressively greater number of lever presses had to be emitted for each successive reinforcer (one food pellet). The progression in the number of presses required (ratio) was a modified version of the exponential equation used by Roberts (personal communication):

$$\text{Ratio} = A * \exp(\text{Reinforcer number} * B) - C,$$

where A and C both equal 5 and B equals 0.2. We modified the progression to produce a more rapid increase in the size of

the ratio required by replacing the first six values (1, 2, 4, 6, 9, and 12) with the values 3, 6, and 10, and then continued with the progression given by the equation (15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901, 1,102, and 1,347). The session was ended when a rat failed to complete the ratio for a particular reinforcer within 1 h since the delivery of the previous reinforcer. After seven daily training sessions on this PR schedule, surgery was performed for catheter implantation.

Surgical Procedure

As described in detail in Lane et al. (26), under anesthesia (ketamine, 100 mg/kg; chlordiazepoxide, 20 mg/kg; and nalbuphine, 10 mg/kg) a Silastic catheter (0.025 in. o.d.) was inserted into the right external jugular and its tip advanced into the right atrium. The free end of the catheter was run subcutaneously to an incision in the skin at the top of the skull. This free end was then connected to a modified C313G cannula assembly (Plastic One, Roanoke, VA). The cannula assembly was modified by the vendor such that 5.0 mm of the 22-ga stainless steel cannula guide was left above the plastic threads. Below the plastic threads, this guide cannula was bent at a right angle; the catheter was connected to this bent portion of the 22-ga tube, and the entire unit consisting of catheter, guide cannula, and lower half of the plastic threads was then embedded in dental acrylic cement and fixed to the skull via three stainless steel screws. Immediately following surgery, subjects were injected IV with 0.1 ml of a solution containing 1 U/ml heparin and 1,000 U/ml streptokinase (Kabivitrum, Inc., Franklin, OH) and an antibiotic (ticarcillin plus clavulanate: Timentin, Beecham Laboratories, Bristol, TN), 3.3 mg in 0.1 ml. This treatment was repeated every 12 h for 5 days after surgery. This antibiotic regimen was also administered for 5 days at the start of each month. Catheter patency was assessed immediately before starting each self-administration session by first checking that blood could be drawn into the catheter and second by flushing the catheter with 0.1 ml heparinized saline (10 U/ml). At the conclusion of the session, the catheter was flushed with an additional 0.1 ml heparinized saline (30 U/ml) containing 1,000 U/ml streptokinase.

Cocaine Self-administration Shaping on a Fixed-ratio Schedule

On the fifth day following surgery, subjects were shaped to self-administer cocaine once daily. At the start of each session, a priming injection of cocaine was administered. Subjects were first shaped on an FR 1 schedule with a maximum of 25 self-injections per session and no time limit. The priming injection and each infusion of cocaine consisted of 0.90 mg/kg cocaine in 0.1 ml saline-vehicle delivered over 5.6 s. Priming and each infusion were accompanied by a flashing of the two stimulus lights followed by a 30-s time-out in the dark; a press during this time-out had no consequences. Here and for the progressive-ratio schedule of cocaine self-administration (see below), the 30-s time-out was included to prevent overdose. Once stability in the rate of self-administration was acquired (i.e., the IS^RT did not vary by more than 20% between two consecutive session), rats were switched to a series of FR 2 schedule sessions. Each FR 2 session was limited to 15 self-injections of cocaine (0.90 mg/kg), again with no time limit. The same stability criterion as the one used for the FR 1 schedule was applied before switching rats to the PR schedule. Once rats had been switched to the progressive-ratio schedule, they were never returned to the fixed-ratio schedule.

Cocaine Self-administration Training on a Progressive-ratio Schedule

Rats were trained or tested (see paragraphs below) once daily. The PR schedule used for cocaine self-administration was the same as the one used with food pellets as reinforcers except that at the start of each session a priming injection of cocaine was administered. The priming injection and each infusion of cocaine were in all respect similar to the ones used for the FR schedules. The PR schedule described in the Lever-Press Shaping section governed the relationship between current reinforcer number and ratio to be completed, and there was a 1-h time limit to obtain each reinforcer. Data from each self-administration session were scored as number of reinforcers obtained, highest ratio completed, and IS^RT.

Acquisition and Stability of Cocaine Self-administration Under a Progressive-ratio Schedule

Rats were allowed to self-administer the training dose of cocaine (0.90 mg/kg) for 50 sessions to permit determination of acquisition and stability of the number of reinforcers obtained under the PR schedule. At the end of this 50-training-sessions period, three different doses of cocaine (0.10, 0.30, or 2.70 mg/kg) or saline-vehicle, tested in a randomized order, were substituted for the training dose of cocaine. For these tests, the priming injection consisted of a 0.1-ml volume of the saline-vehicle or of the solution of cocaine (0.10, 0.30, or 2.70 mg/kg) to be tested. Test sessions were separated by at least one training session, and the number of reinforcers obtained during these training sessions had to be within two of the baseline value before subjects were used in the next test session. Failure to meet this criterion resulted in supplemental training sessions until the criterion was fulfilled. This criterion was also applied during the SCH23390 and ondansetron pretreatment experiments.

Relationship Between the Dose of Cocaine Infused, Number of Reinforcers Obtained, Highest Ratio Completed, and IS^RT Recorded

These parameters of cocaine self-administration were determined for saline-vehicle and four doses of cocaine (0.10, 0.30, 0.90, and 2.70 mg/kg) following a saline IP pretreatment, which occurred 30 min prior to the start of the session. Results from this experiment were first analyzed separately to determine the appropriate parameter (i.e., either number of reinforcers obtained or highest ratio completed) for subsequent analysis of the effect of SCH23390 or ondansetron pretreatments. Mean IS^RTs were calculated by first averaging each subject's individual IS^RTs, excluding the first and the last IS^RT. These two IS^RTs were excluded because they were not representative of the general pattern of IS^RTs: The first IS^RT was variable because some rats took longer than others to start self-administering following infusion of the priming dose; the last IS^RT also showed greater variability because at this final ratio value some rats occasionally displayed a pattern of lever pressing in which responding was interrupted by periods of nonresponding.

Effects of Pretreatment with SCH23390 or Ondansetron

Seven rats were used to study the effect of SC pretreatment with saline or SCH23390 (10 μg/kg) against four doses of cocaine (0.10, 0.30, 0.90, and 2.70 mg/kg). Saline or SCH23390 was administered 20 min presession. In addition, the effect of SC pretreatment with saline or SCH23390 (5.6,

10, 17.8, or 32 μg/kg) against the training dose of cocaine (0.90 mg/kg) was evaluated in 10 rats. Saline and SCH23390, as well as the dose of infused cocaine, were tested in a randomized block design.

Six rats were used to determine the effect of saline or ondansetron (0.001, 0.01, 0.1, and 1.0 mg/kg) pretreatment (30 min presession, IP administration) against the training dose of cocaine (0.90 mg/kg). Eight rats were used to assess the effect of 0.1 mg/kg IP ondansetron against 0.10, 0.30, and 0.90 mg/kg cocaine. Saline and ondansetron, as well as the dose of cocaine, were tested in a randomized order.

Drugs

Cocaine HCl (Sigma Chemical Co., St. Louis, MO, and NIDA, Research Triangle Park, NC) was dissolved in saline-vehicle (1.0 U/ml heparinized 0.9% saline) and filtered through 0.22-μm filters (Millipore, Bedford, MA) into sterile 10-ml syringes immediately before use. Ondansetron HCl (gift of Glaxo Group Research, Ware, UK) and SCH23390 HCl (Research Biochemicals, Inc., Natick, MA) were both prepared freshly before each test session and diluted in 0.9% saline.

Data Analysis

All data reported in the text or plotted in the figures are expressed as mean ± SEM except for Fig. 2, where data are plotted as mean ± SD. For the analysis of the cocaine dose–effect data following saline pretreatment, the number of reinforcers obtained, highest ratio completed, and IS^RT recorded were subjected to a Cochran's test (45) to determine whether data violated assumptions of homogeneity of variance. Data that did not violate these assumptions were further subjected to a one-way analysis of variance (ANOVA) for repeated measures. For the SCH23390 and ondansetron experiments that used several doses of cocaine, the number of reinforcers obtained was subjected to a two-way ANOVA for repeated measures, with the dose of cocaine and pretreatment (saline or drug) as the two within factors. For the experiments where several doses of SCH23390 or ondansetron were tested against the training dose of cocaine, the number of reinforcers obtained was subjected to a one-way ANOVA for repeated measures, with the doses of the tested drug as the within factor.

IS^RTs from the SCH23390 or ondansetron experiment were subjected to a two- or one-way ANOVA for repeated measures, respectively. Analysis of IS^RTs for ondansetron was performed on data collected during the experiment where saline or four doses of ondansetron were assessed against the training dose of cocaine, as opposed to using values from the single dose of ondansetron against three doses of cocaine experiment, because this yielded more ondansetron IS^RT values.

For all ANOVAs, when F values showed a significant effect ($p < 0.05$) a planned comparison analysis was performed, with significance reported whenever the p values were less than 0.05 (for clarity sake, the F and p values for the posthoc tests are not reported in the text). All ANOVAs were performed with SYSTAT software (43).

RESULTS

Acquisition and Stability of Cocaine Self-administration Under a PR Schedule

Stable self-administration of cocaine (training dose of 0.90 mg/kg) under a PR schedule was acquired within approximately 10 sessions (Fig. 1). Once PR responding was acquired, there was a high degree of stability in the number of reinforcers obtained over the period covering the next 41 sessions; the average number of reinforcers obtained during these last 41 sessions was 19.0 ± 0.1. In addition, for each individual session over this period the SEMs ranged from 0.8–1.8 reinforcers. The low values of these SEMs reflect the small inter-subject differences in the number of reinforcers obtained within the same training session.

Relationship Between the Dose of Cocaine Infused, the Number of Reinforcers Obtained, and the Highest Ratio Completed

Varying the dose of infused cocaine over a 27-fold range (from 0.10–2.70 mg/kg) resulted in a 2.7-fold dose-related increase in the number of reinforcers obtained [Fig. 2, top; $F(3, 30) = 46.57$, $p < 0.001$]. However, this was not a linear effect across the entire range of doses. Tripling the training dose (from 0.90 to 2.70 mg/kg) did not markedly increase the number of reinforcers obtained but instead the curve plateaued. All but the 0.90- and 2.70-mg/kg doses differed significantly from one another. Substituting the saline-vehicle solution for the training dose of cocaine yielded a low number of reinforcers obtained (1.1 ± 0.3). Note that the average number of reinforcers earned under the 0.90-mg/kg dose (19.5 ± 1.2) was close to the average calculated for the period covering the last 41 training sessions (19.0 ± 0.1; see Fig. 1).

As the dose of cocaine increased, the highest ratio completed also increased (Fig. 2, bottom). Increasing the dose of cocaine from 0.10 to 2.70 mg/kg resulted in a 16.6-fold increase in the highest ratio completed. However, as shown by the different magnitudes of SDs in the figure, these data violate assumptions of homogeneity of variance [Cochran's test,

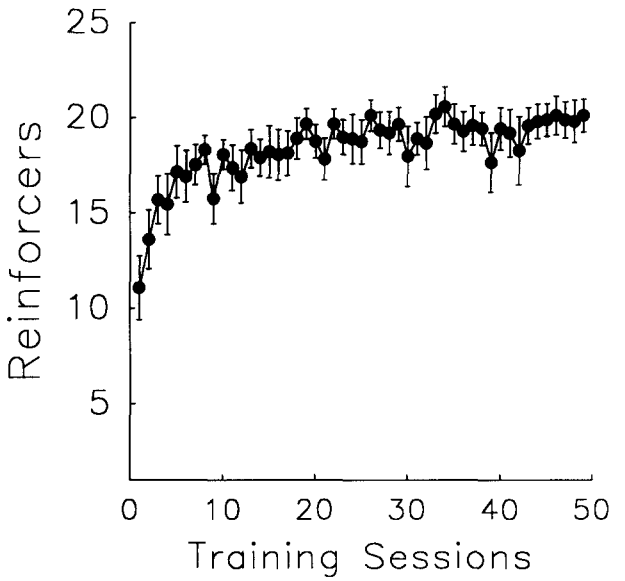

FIG. 1. Acquisition and stability of self-administration of cocaine under a progressive-ratio (PR) schedule. Abscissa, training session number; ordinate, number of reinforcers obtained during the training session. Each circle represents the average number of reinforcers obtained as a function of the training session shown on the abscissa. The dose of cocaine infused as a reinforcer was 0.90 mg/kg. Vertical bars represent SEMs. $n = 13$.

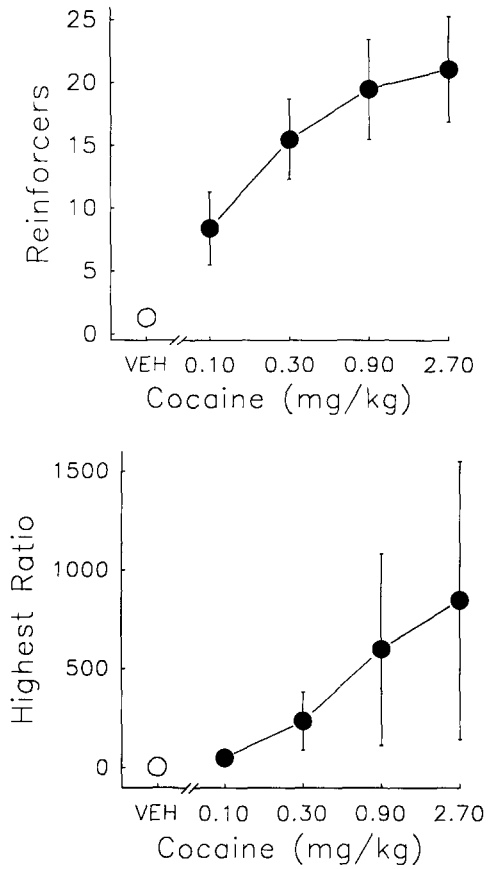

FIG. 2. Relationship between the dose of cocaine infused and the number of reinforcers obtained (top panel) or the highest ratio completed (bottom panel). Top panel: abscissa, dose of cocaine available for self-administration; ordinate, number of reinforcers obtained during the session. Each filled circle represents the average ± SD. (○), average number of reinforcers obtained when saline-vehicle (VEH) in a volume of 0.1 ml per infusion was substituted for cocaine. Bottom panel: same legend as top panel except for the ordinate, which is the highest ratio completed during the session. Refer to the Lever-Press Shaping section for the relationship between reinforcer number and the associated ratio. For both panels, some SD bars do not show because they are smaller than the symbol size. n = 11.

C = 0.70, $p < 0.01$]. Violation of homogeneity of variance can be a serious confound in an ANOVA for repeated measures (45), and for this reason the highest ratio completed was not considered further for statistical analysis. When a data set violates assumptions of homogeneity of variance, a means of circumventing this problem is to transform the data through square root or logarithmic calculation (45). Here, the number of reinforcers obtained is a natural logarithmic function of the highest ratio completed, and the reinforcer data do not violate assumptions of homogeneity of variance. For these reasons, subsequent data analyses for the SCH23390 and ondansetron experiments were performed on the number of reinforcers obtained instead of the highest ratio completed.

Relationship Between the Dose of Cocaine Infused, the Reinforcer Number, and the Interreinforcer Time

The relationship between the dose of cocaine infused, the number of reinforcers obtained, and the IS^RT is presented in the 3-D graph of Fig. 3. Two relationships concerning the IS^RT can be seen in this graph: First, the IS^RT increases as a function of the dose of cocaine infused; second, for any given dose of cocaine the IS^RT increases during the session from reinforcer to reinforcer.

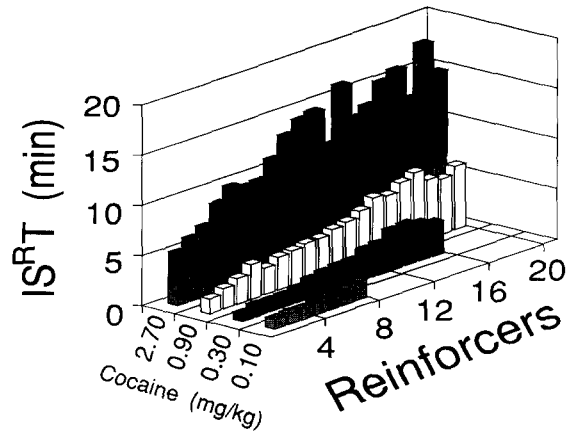

FIG. 3. Relationship between the dose of cocaine infused, the reinforcer number, and the interreinforcer time. X-axis, reinforcer number; Y-axis, dose of cocaine available for self-administration; Z-axis, interreinforcer time (IS^RT) in min. Each column represents the mean IS^RT. IS^RTs were calculated for individual subjects by excluding the first and the last IS^RT; resulting data for each remaining reinforcer were then averaged across subjects. For each dose of cocaine, the number of IS^RTs plotted corresponds to the average number of reinforcers obtained rounded to the nearest integer (see Fig. 2, top). For clarity, SEMs have been omitted. n = 11.

The mean IS^RT (Table 1) increased 7.7-fold, $F(3, 30)$ = 157.71, $p < 0.001$, as the dose of infused cocaine increased 27-fold, and all four mean IS^RTs were significantly different from one another. Note that IS^RTs obtained under saline-vehicle were not analyzed because most subjects (10 of 11) took less than three reinforcers.

Effect of Pretreatment with Saline or SCH23390 on the Number of Reinforcers Obtained and the Interreinforcer Time

For all four doses of cocaine, pretreatment with SCH23390 (10 μg/kg) decreased the highest ratio completed (data not shown and not amenable to statistical analysis; see above) as well as decreased the number of reinforcers obtained [Fig. 4, top; $F(1, 6)$ = 32.66, $p < 0.001$]. The ability of SCH23390 to decrease the number of reinforcers obtained was significant for the three lowest doses of cocaine. The significant interac-

TABLE 1

RELATIONSHIP BETWEEN THE DOSE OF COCAINE INFUSED AND THE MEAN INTERREINFORCER TIME (IS^RT)

	Dose of Cocaine (mg/kg)			
	0.10	0.30	0.90	0.27
IS^RT	1.57 ± 0.16	2.35 ± 0.13	4.65 ± 0.52	12.14 ± 0.58

Values are expressed as mean (min) ± SEM. IS^RTs were calculated by first averaging each subject's individual IS^RTs, excluding the first and the last IS^RT (see the Method section). n = 11.

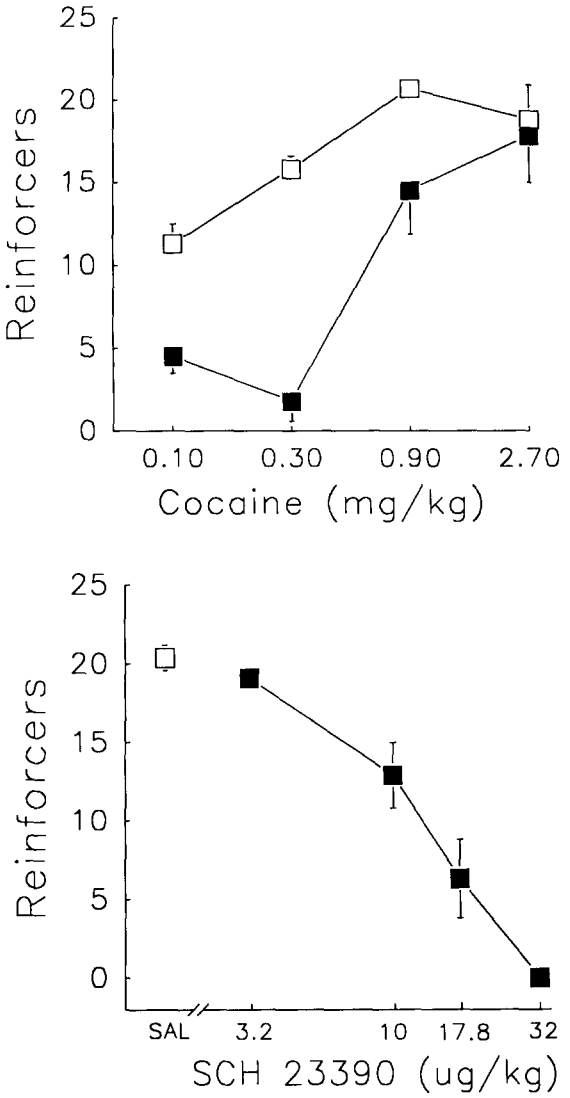

FIG. 4. Effect of SCH23390 pretreatment on the number of reinforcers obtained. Top panel: Abscissa and ordinate same as in top panel of Fig. 2. Each symbol represents the average number of reinforcers obtained in a session with pretreatment of saline (□) or SCH23390 (10 μg/kg, SC; ■). Vertical bars represent SEMs. n = 7. Bottom panel: abscissa, dose of SCH23390; ordinate, number of reinforcers obtained during the session. Each symbol represents the average number of reinforcers obtained in a session with SC pretreatment of saline (□) or SCH23390 (■). Saline or SCH23390 were tested against the training dose of cocaine (0.90 mg/kg). Vertical bars represent SEMs. n = 10.

tion between the dose of cocaine infused and the pretreatment, $F(3, 18) = 7.14$, $p < 0.01$, suggests that SCH23390 or saline pretreatment affected the cocaine dose-effect curve in a different way. This differential effect of SCH23390 can be seen in the graph, where the SCH23390 pretreatment curve is not parallel to the saline pretreatment curve.

When tested against the training dose of cocaine (0.90 mg/kg), SCH23390 was found to decrease the number of reinforcers in a dose-dependent manner [Fig. 4, bottom; $F(3, 27) = 14.18$, $p < 0.001$]. A dose of 32 μg/kg SCH23390 completely blocked self-administration of 0.90 mg/kg cocaine. Differences in the number of reinforcers were significant for all pairs of doses of SCH23390 and saline compared except for two pairs: the saline vs. 3.2 μg/kg and the 17.8 μg/kg vs. 32 μg/kg. For all subjects, SCH23390 markedly decreased the number of reinforcers obtained in a dose-dependent manner.

SCH23390 at the dose of 10 μg/kg showed a tendency to reduce the IS^RT (Table 2), but this tendency was not significant, nor was the interaction between the dose of infused cocaine and pretreatment. The 0.10- and 0.30-mg/kg doses of cocaine were not included in this table because when these doses of cocaine were combined with SCH23390, three (0.10 mg/kg) and four (0.30 mg/kg) of the seven rats did not self-administer cocaine. These subjects were omitted from the whole IS^RT analysis because missing data points in a within-subjects ANOVA prevent analysis.

Effect of Pretreatment with Saline or Ondansetron on the Number of Reinforcers Obtained and the Interreinforcer Time

For the three doses of cocaine tested (0.10, 0.30, and 0.90 mg/kg), pretreatment with 0.1 mg/kg ondansetron failed to significantly affect the number of reinforcers obtained (Fig. 5, top). Indeed, this dose of ondansetron had virtually no effect on the number of reinforcers obtained. Interaction between the dose of cocaine infused and the pretreatment was not significant. Ondansetron was not tested against the dose of 2.70 mg/kg cocaine because the cocaine dose-response relationships obtained under saline in the SCH23390 experiment showed that 0.90 and 2.70 mg/kg yielded comparable numbers of reinforcers obtained (see Fig. 4, top).

When tested against the training dose of cocaine (0.90 mg/kg), pretreatment with ondansetron, over a 1,000-fold range

TABLE 2

EFFECT OF SALINE OR SCH23390 (10 μg/kg) PRETREATMENT ON THE MEAN INTERREINFORCER TIME (IS^RT)

	Dose of Cocaine (mg/kg)		
	0.30	0.90	2.70
Saline	N.C.	2.60 ± 0.46	5.97 ± 1.05
SCH23390	N.C.	2.37 ± 0.22	5.04 ± 1.09

Values are expressed as mean (min) ± SEM. IS^RTs were calculated by first averaging each subject's individual's, excluding the first and the last IS^RT (see the Method section). In addition to excluding these two IS^RTs, the IS^RT distribution was further truncated for each subject such that equal numbers of IS^RTs were available for comparison for a given dose of cocaine. For example, if a subject tested under the 0.90-mg/kg dose of cocaine obtained 20 and 15 reinforcers under saline and SCH23390 pretreatment, respectively, then the calculation of the mean IS^RT would use only reinforcer 2 to 14 for both pretreatments. This was done to have identical numbers of IS^RTs for each subject across both pretreatments for a given dose of cocaine. If this procedure is not adopted, the additional IS^RTs occurring under saline bias the data by making the saline IS^RTs appear to be longer than is actually the case. Mean IS^RTs were not calculated (N.C.) for the 30-mg/kg dose of cocaine because four of the seven rats did not self-administer this dose of cocaine in combination with SCH23390. n = 7.

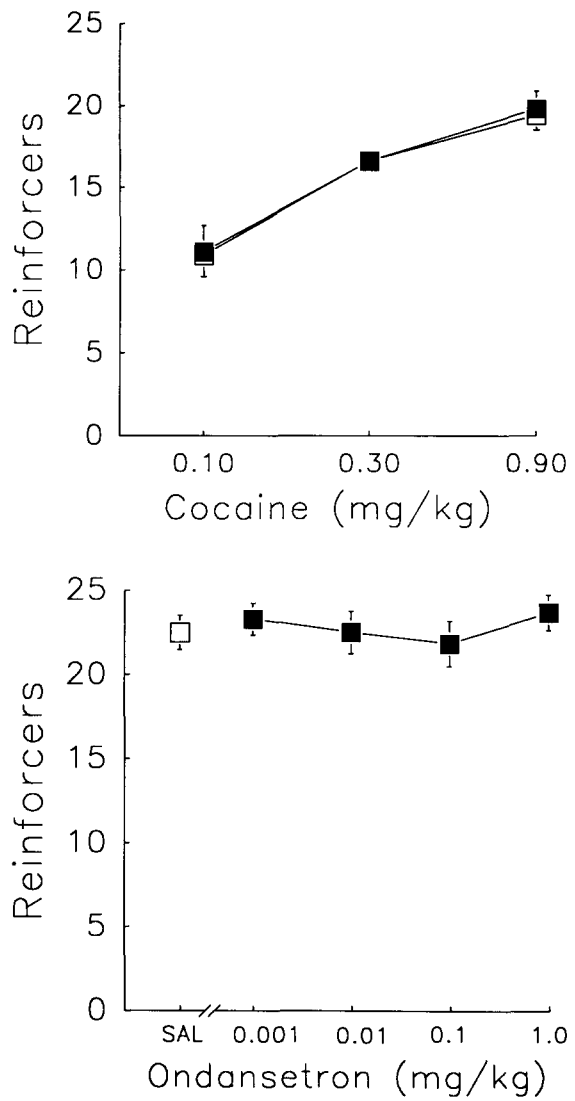

FIG. 5. Effect of ondansetron pretreatment on the number of reinforcers obtained. Top panel: Abscissa and ordinate same as in top panel of Fig. 2. Each symbol represents the average number of reinforcers obtained in a session with saline (□) or ondansetron (0.1 mg/kg, IP; ■) pretreatment. Vertical bars represent SEMs. $n = 6$. Bottom panel: abscissa, dose of ondansetron; ordinate, number of reinforcers obtained during the session. Each symbol represents the average number of reinforcers obtained in a session with IP pretreatment of saline (□) or ondansetron (■). Saline or ondansetron were tested against the training dose of cocaine (0.90 mg/kg). Vertical bars represent SEMs. $n = 8$.

of doses, neither increased nor decreased significantly the number of reinforcers obtained (Fig. 5, bottom). For all four doses of ondansetron, the number of reinforcers obtained was changed by a maximum of 5% as compared to control (saline pretreatment).

Although ondansetron showed a tendency to shorten the mean IS^RT (Table 3), this was not statistically significant. The mean IS^RT for the training dose of 0.90 mg/kg (5.44 min) is higher than the one reported in Table 2 for the SCH23390 experiments (2.60 min) because the mean IS^RTs in the SCH23390 experiments were calculated on the basis of a smaller number of reinforcers (see Table 2 for more information).

DISCUSSION

Self-administration of cocaine by rats under this PR schedule presented several interesting features. Its acquisition was rapid and it showed long-term stability. This study provides data analysis showing that for statistical purposes the number of reinforcers obtained instead of the highest ratio completed is the appropriate measure of the breakpoint. As the dose of cocaine is increased, both the breakpoint and the interreinforcer time (IS^RT) increase in an orderly manner. The breakpoint was found to be sensitive to the effects of SCH23390, a drug previously shown to increase the rate of cocaine self-administration in other schedules, and was not affected by ondansetron, a drug that has not previously been shown to affect cocaine self-administration in rats. Finally, monitoring of the IS^RT along with the breakpoint allows for control of motor-incapacitating effects of drug pretreatment on cocaine self-administration without having to resort to controls using other schedules or others reinforcers such as food. Our data overall suggest that the rat is an excellent subject for the production of PR schedule data amenable to statistical analysis.

Stability of cocaine self-administration under this PR paradigm can be maintained routinely for more than 3 mo, allowing one to conduct a series of parametric experiments. To our knowledge, long-term stability of PR responding, particularly for large groups of animals, has not been demonstrated before. This study also shows that changing the dose of infused cocaine, with or without pretreatment with SCH23390 or ondansetron, does not affect baseline stability of PR responding. This is particularly important if one wants to conduct multiple drug tests against several doses of infused cocaine rather than solely against the training dose of cocaine. In addition, rapid acquisition of cocaine self-administration under this type of PR schedule allowed testing to begin within 2 weeks of initiation of training. We attribute the longevity and viability of subjects to semisterile surgical procedures and postoperative care and to a fastidious regimen of anticoagulants and antibiotics that was designed to minimize infection and maximize catheter patency (see the Surgical Procedure section).

Both the number of reinforcers obtained and the highest ratio completed increased in an orderly manner as a function of an increase in the dose of infused cocaine. These increases are thought to reflect an increase in the reinforcing efficacy of the reinforcer (14). However, at the 2.70-mg/kg dose in the SCH23390 experiment we observed that under saline pretreatment the number of reinforcers was slightly lower than that for the 0.90-mg/kg dose. Inverted U-shaped curves have been observed by others at the highest doses of drug intake (12,34,46,48). Doses of cocaine above 2.70 mg/kg were not used in this study because of the inherent toxicity of the drug (e.g., in pilot studies when doses of 3.7 mg/kg and above were used, seizures and/or death were occasionally observed).

Independent of the highest dose utilized, the values for the highest ratio completed were routinely higher in this study than the values reported by others using rats as subjects. For example, Roberts et al. (38) reported average highest ratios of 38 and 92 for doses of cocaine of 0.30 and 0.90 mg/kg, respectively. Hubner and Moreton (17) reported two different averages for a 0.225-mg/kg dose of cocaine: In one, the high-

TABLE 3

EFFECTS OF SALINE OR ONDANSETRON PRETREATMENT ON THE MEAN INTERREINFORCER TIME (IS^RT)

	Dose of Ondansetron (mg/kg)				
	Saline	0.001	0.01	0.1	1.0
IS^RT	5.44 ± 0.27	5.00 ± 0.20	4.84 ± 0.26	4.98 ± 0.24	4.55 ± 0.12

Values are expressed as mean (min) ± SEM. Saline or Ondansetron was tested against the training doses of cocaine (0.90 mg/kg). IS^RTs were calculated by excluding the first and the last IS^RT (see the Method section). $n = 6$.

est ratio was 88 and in the other the highest ratio was 168. In contrast, our animals reached average highest ratio values of 599 and 848 for 0.90 and 2.70 mg/kg, respectively. We do not know why our animals worked to such high values, but perhaps the difference between our results and those of Hubner and Moreton (17) may be found in differences between paradigms (i.e., progression of the ratio, force required to produce a lever-press, duration of the time-out, etc.) or differences in the strains, ages, and body weights of rats. However, a difference in the progression of the ratio is unlikely to account for differences between this study and that of Roberts et al. (38), who used essentially the same progression.

As a rate measure, interreinforcer time (IS^RT, in minutes) was used. The IS^RT increased approximately eightfold and in a direct relationship to the dose of cocaine tested. For example, for cocaine doses of 0.90 and 2.70 mg/kg associated IS^RTs were approximately 4.5 and 12 min, respectively. Interestingly, the IS^RT value found with the training dose of cocaine (0.90 mg/kg) is similar to the IS^RT found in an FR 2 procedure (IS^RT: 4.5 min) for this same dose in our laboratory (26). From data in which an FR 5 was used with a cocaine dose of 0.75 mg/kg (17), we calculated that these authors obtained an IS^RT of approximately 3.4 min; and, similarly, using an FR 1 schedule and a 0.5-mg/kg dose, we calculated that Peltier and Schenk (28) obtained an IS^RT of approximately 4.8 min. Although additional data are necessary to reach a firm conclusion, the available data suggest that independent of the schedule that governs cocaine delivery rats respond such that across strains and different laboratories cocaine self-injections occur at comparable average intervals that are a function of the dose of cocaine. We would further note, however, that the average IS^RT in this PR procedure could be misleading because IS^RTs are not uniformly distributed across the session.

With this PR schedule, increasing doses of cocaine resulted in a greater number of responses emitted (highest ratio completed) and reinforcers obtained. Historically, breakpoint under a PR schedule has been arbitrarily defined as the highest ratio completed (14). However, the use of the highest ratio completed as a measure of the breakpoint presents a problem for statistical analysis. Because the enormous range of ratio values produces unequal variance across different doses of the reinforcer, the highest ratio completed is not amenable to ANOVA. This difficulty with analyzing PR data may have been recognized previously; for example, although Roberts *et al.* (38) present data in the form of highest ratio completed they note that the data were log-transformed for statistical analysis. In the present case, the reinforcer number is a natural logarithmic function of the ratio value, and indeed the reinforcer data in the top panel of Fig. 2 are amenable to ANOVA because they do not violate assumptions of homogeneity of variance. If the PR schedule is to be used for parametric statistical comparisons of the effects of pretreatments, then the logarithmic transformation of the highest ratio completed appears to be the appropriate measure of breakpoint. We suggest that an exponential formula should be used to construct the relationship between ratio and reinforcer number because the reinforcer number then provides a ready logarithmic transformation of the ratio value.

Cocaine is thought to act at dopamine and serotonin transporter sites (30,35), which suggests that compounds interacting with the receptors for these neurotransmitters might be expected to modify the rate of cocaine self-administration. A substantial body of evidence is accumulating that implicates brain dopamine in the reinforcing effects of cocaine [for a review, see (24)]. Consistent with this putative role of dopamine is the observation that both dopamine D_1 (17,22,23, 26,47) and D_2 (17,23,28,47) antagonists are efficacious in shifting cocaine self-administration to faster intake under low-value FR procedures. Using a second-order schedule, Bergman et al. (2) have also shown that SCH23390 blocks the reinforcing effects of cocaine. Because faster intake of cocaine is associated with lower doses of cocaine in FR schedules, these shifts to faster intake of cocaine have been interpreted to mean that D_1 and D_2 antagonists block the reinforcing effects of cocaine.

Little work has been published concerning effects of dopamine antagonists under PR schedules. Using a single dose of cocaine, Roberts et al. (38) reported that haloperidol reduced the highest ratio completed and increased the rate of cocaine intake. Hubner and Moreton (17) reported that SCH23390 and the D_2 antagonist spiperone also decreased the highest ratio completed. In the present study, SCH23390 decreased the breakpoint (number of reinforcers obtained) over the whole range of doses of cocaine tested. This would suggest that SCH23390 blocked the reinforcing effects of cocaine. This is also in agreement with the well-documented action of dopamine in the initiation and/or maintenance of cocaine self-administration (19,42), and the results of these studies provide evidence that the PR schedule is sensitive to the blocking effects of drugs interfering with dopamine transmission on cocaine self-administration.

One alternative explanation for the observed decrease in the number of reinforcers earned under SCH23390 could be that SCH23390 simply blocked the discriminative properties of cocaine. According to this hypothesis, the priming dose would provide a discriminative stimulus that would be necessary for the initiation of self-administration. Thus, under SCH23390 some rats would have failed to self-administer (no reinforcers earned) while other rats would have self-administered a number of reinforcers comparable to control (saline

pretreatment) levels. As the dose of SCH23390 increased, one would have expected to see an increasing number of rats failing to initiate self-administration. Instead, we found that for each rat as the dose of SCH23390 increased the number of reinforcers obtained was progressively decreased. This pattern of results with SCH23390 argues in favor of a blocking effect of cocaine self-administration rather than a blocking effect of a cocaine discriminative cue.

Like Hubner and Moreton (17), we also observed in a previous study that SCH23390 increased the rate of responding in rats self-administering cocaine under a low-value FR schedule (26). On the basis of our previous data and those of Hubner and Moreton, one hypothesis is that SCH23390 blocks the effects of cocaine by making a bigger dose of cocaine have the effects of a smaller dose. Thus, SCH23390 would be expected to produce shorter IS^RTs (as found in low-value FR procedures) and reduce the number of reinforcers obtained (as found in PR procedures). This simple hypothesis, however, is not supported by the present set of IS^RT data. In the absence of SCH23390, the effect of lowering the cocaine dose is to produce shorter IS^RTs. Although SCH23390 decreased the number of reinforcers, it showed no capacity to significantly shorten the IS^RT under this PR schedule.

On the other hand, SCH23390 did not reduce the breakpoint simply because of motor impairment. Had that been the case, we might have expected to see longer IS^RTs, whereas we observed that the IS^RT showed a tendency to be shortened by SCH23390. Hubner and Moreton (17) proposed that in their group of rats trained on a PR schedule SCH23390 did not decrease the highest ratio completed through motor impairment. Those authors drew their conclusion regarding PR responding indirectly from the observation that SCH23390 increased the rate of responding in a separate group of rats trained to self-administer cocaine on an FR 5 schedule. In the present study, simultaneous monitoring of both the number of reinforcers obtained and the IS^RT allowed us to reach this conclusion directly, in the same animals, and using solely the PR procedure.

Ondansetron, a selective 5-HT_3 antagonist, had no significant effect either on the number of reinforcers or on the IS^RT. An absence of effect of ondansetron on cocaine self-administration using low-value FR procedures has been reported by Lane et al. (26), as well as Peltier and Schenk (28). Using a PR procedure, Lacosta and Roberts (25) provided preliminary evidence that another selective 5-HT_3 antagonist, MDL 72222, was without effect on the highest ratio completed in their PR procedure. We provide evidence that ondansetron, across a 1,000-fold range of doses tested against the training dose of cocaine, as well as at the dose of 0.1 mg/kg tested against three doses of cocaine (0.10, 0.30, or 0.90 mg/kg), has no significant effect on either the number of reinforcers or the IS^RT. The range of doses investigated more than spanned the doses that have been reported to be active via the IP route in other behavioral tests (5,28). Thus, if serotonergic mechanisms are indeed important in cocaine self-administration (4, 27) it is likely the case that these mechanisms do not involve the 5-HT_3 site.

ACKNOWLEDGEMENTS

This work was supported by NIDA Grant RO1 4137 (MWE-O), State of Texas Advanced Technology Program Grants 3711 and 9768 (JDL), and by GLAXO Group Research, Ltd. (MWE-O). The authors appreciate the technical assistance of Clay Pickering, Mickey Hooper, Doug Lytle, and Scott Boone.

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