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Dose–Effect Functions for Cocaine Self-Administration: Effects of Schedule and Dosing Procedure

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SIZEMORE, G. M., T. M. GASPARD, S. A. KIM, L. E. WALKER, S. L. VRANA AND S. I. DWORKIN. *Dose–effect functions for cocaine self-administration: Effects of schedule and dosing procedure.* PHARMACOL BIOCHEM BEHAV **57**(3) 523–531, 1997.—Research related to determining how procedural variables can alter dose–effect functions for cocaine self-administration is limited. Toward clarifying the role of procedural variables, responding was maintained in rats under either variable-interval (VI) or fixed-ratio (FR) schedules of cocaine infusion. In addition to free-operant FR schedules, discrete-trial FR schedules were evaluated. The dose–effect functions were obtained by either substituting a dose for the usual daily dose, instituting a particular dose for several sessions, or making all doses available within a session. Dose–effect functions for response rate (or number of trials with infusions for the discrete-trial FR) were bitonic for the VI and discrete-trial FR schedules but tended to be strictly decreasing for the free-operant FR schedules. Responding was maintained under FR schedules by a low dose (0.083 mg/infusion) if the dose was substituted for a higher daily dose but not when made available daily. Rate of response was higher under ratio schedules at 0.17 mg/infusion when this dose occurred within the context of other higher doses within a session than when the dose was simply substituted for a higher daily dose. These data indicate that procedural variables can alter dose–response curves for cocaine self-administration. © 1997 Elsevier Science Inc.

Cocaine self-administration Dose–effect functions Schedule of reinforcement Dosing procedure

DRUG self-administration procedures provide one of the most direct assessments of drug abuse vulnerability and are routinely used to assess the abuse liability of psychoactive compounds. Although pharmacological variables are of considerable importance in determining the characteristics of responding under such conditions, there has been an increasing awareness of how important nonpharmacological factors can be in the maintenance of behavior by various substances, including cocaine. For the most part, however, studies evaluating the reinforcing effects of cocaine using a self-administration paradigm typically employ either fixed-ratio (FR) or fixed-interval (FI) schedules of drug delivery (12). A considerable amount of research has shown that these two schedules of drug self-administration can be used to provide qualitative information regarding the reinforcing effects and direct effects (i.e., effects that might be expected to occur if the drug was administered response-independently) of potential reinforcing substances (12,13). In general, under both moderate FR and FI schedules of cocaine self-administration, an inverted U-shaped function is obtained for both response rates and number of infusions (12). Moreover, rodents and other species maintain a relatively consistent interinjection interval that is influenced more by dose than by schedule parameters (17). Thus, small to moderate changes in ratio values do not result in significant shifts in the dose–effect curve nor do low to moderate increases in the FI value (4). Fixed-interval values that are less than the mean interinfusion interval result in the same function as an FR 1 (4). A few recent studies, however, have evaluated the effects of increasing either the schedule value or providing extended time-out periods that result in a considerable increase in minimum possible interinfusion intervals. These manipulations have resulted in significant shifts in self-administration dose–effect curves. For example, increases in the time-out between infusions or in the FR value have resulted in clear shifts to the right of the dose–effect curve for cocaine self-administration (21). Thus, low doses that maintain responding with short time-outs or low FR values will no longer maintain self-administration when these

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values are increased. Larger doses that are on the descending limb of the curve with low ratio or short time-out values are on the ascending limb with the larger parameters.

In addition to being affected by manipulation of schedule parameters, dose–effect functions may also be influenced by how doses are presented. The most common method for obtaining dose–effect curves involves maintaining responding under a particular dose and occasionally substituting a different dose for the duration of an experimental session ("probe" or "substitution" procedure). There are several other ways in which dose–effect functions could be obtained. Each of several different doses may, for example, occur in the context of a single session ("within-session" procedure) or, alternatively, each dose may be studied for several sessions ("phase" procedure). The context in which one dose follows another (i.e., large following small or small following large) may influence the self-administration of lower doses of the drug.

Herein we report the effects of using different schedules for evaluating the reinforcing effects of cocaine. This paper describes the effects of altering the dose of cocaine under variable-interval (VI) and FR schedules of cocaine infusion. In the experiments involving FR schedules, dose was manipulated on a probe basis as well as in a within-session arrangement. For some subjects responding under FR schedules, dose was manipulated on both a probe and a phase basis. In addition to these free-operant procedures, FR schedules were investigated in a "discrete trial" type of arrangement.

The general hypothesis tested was that these procedural variables would have an impact on the dose–effect functions that characterize behavior maintained by cocaine infusion. Evaluating such procedural variables is of paramount importance because the dose–effect functions for self-administration comprise the core of animal models of drug addiction.

METHODS

General

Subjects. Twenty-seven male Fischer rats, approximately 90–120 days old at the beginning of the experiments, served as subjects. Each subject was individually housed and had access to water ad lib. Subjects were typically meal-deprived during training (see *Procedure*) but were given access to food ad lib after responding was well established.

Apparatus. Although some specific characteristics of the operant chambers used in each experiment were slightly different, the chambers were all roughly the same size and did not differ from those typically used with rats. Each chamber was located within a sound-attenuating chest (Med Associates) containing, at minimum, a house light (28 V, 100 ma), an exhaust fan, and a Sonalert.

A counterbalanced leash, which consisted of a stainless-steel 11-gauge cylinder centered between two steel springs, was attached to the subject's back and passed through a slot in the ceiling of each chamber. Within the leash was an IV catheter that exited the subject's back (see *Surgical Procedure*) and was attached to a leak-proof swivel affixed to the leash (2). This arrangement allowed virtually complete mobility. Attached to the top of each swivel was a length of polyvinyl tubing that exited the sound-attenuating chest and attached to a syringe operated by a syringe pump (model A, Razel Scientific Instruments, Stamford, CT, USA).

Surgical procedure. Under pentobarbital-induced anesthesia (50 mg/kg), all subjects were implanted with chronic indwelling jugular catheters (Tygon microbore tubing, 5-54-HL) using the method described by Weeks (19,20). The catheter, which was anchored to tissue surrounding the right interior jugular vein, in which it was placed, continued subcutaneously to the back, where it exited through a plastic plate. This plate was covered with teflon mesh and implanted in the skin between the scapulae. Attached to the backplate were two nylon screws to which the leash was attached.

Procedure. All subjects were first implanted with indwelling jugular catheters (see *Surgical procedure*) and were then exposed to an FR 1 schedule of cocaine infusion (0.33 mg/infusion except were otherwise noted). With the exception of the within-session dosing procedure (see below), cocaine was always infused for 5.6 s duration (a volume of 0.2 ml). Thus, the dose of cocaine was manipulated by changing the concentration of cocaine in the syringe. Under the within-session dosing procedure, dose was manipulated by changing the duration of the infusion. In all portions of the experiment, infusions of cocaine were accompanied by a tone and the house light was illuminated while the lever light was extinguished. This set of stimulus conditions was in effect for 20.0 s following initiation of the infusions.

Experiment 1: Free-Operant Fixed-Ratio Schedules of Cocaine Infusion: Within-Session Dosing

Subjects. Four subjects were used.

Apparatus. Four identical chambers (28.2 × 21.0 × 21.0 cm) were used. Mounted and centered horizontally on each of the side walls and the back wall of the chamber was a retractable lever. Only the lever (4.5 × 2.0 cm) mounted on the back wall was used. This lever was approximately 7.4 cm above the grid floor (which was composed of 4.0-mm-diameter stainless steel bars separated by 1.5 cm). Centered above this lever was a jeweled lens cap (2.7 cm in diameter), the center of which was located about 5.9 cm above the lever, which could be transilluminated by a light source (28 V, 100 mA). There were also lens caps centered above the levers on the side walls; these levers always remained retracted and the lever lights were never illuminated. There was, additionally, a circular recess (3.0 cm diameter) for the delivery of fluids via dipper and a stainless steel circular feeder pan on, respectively, the left and right walls. The feeder pan (6.0 mm deep) projected into the chamber perpendicular to the wall and was approximately 4.0 cm in diameter. The bottom was 1.2 cm above the grid floor.

Procedure. Following the establishment of responding under the FR 1 schedule, the ratio value was raised gradually across sessions to FR 10, where it remained for the duration of this portion of the experiment. Unlike the other experiments, the subjects were exposed to more than one dose per session (0.17, 0.33, and 0.67 mg/infusion), and these three doses were present from the beginning of the experiment. Each dose was available for 1 h and the dose order was pseudorandom. The different components were separated by 10-min blackouts, and each one began with a response-independent infusion. At the beginning of each session, approximately 10 min elapsed from the time the subject was placed in the chamber until the time the session began. Sessions always ended after 3 h had elapsed from the beginning of the session (not counting time in the between-component blackouts).

Experiment 2: Free-Operant Fixed-Ratio Achedules of Cocaine Infusion: Between-Session Dosing

Subjects. Four subjects were used.

Apparatus. Four identical operant chambers (28.1 × 21.0 × 21.0 cm) were used. The two small walls (left and right

sides) were made of stainless steel and the back, front, and top were made of Plexiglas. On the right-hand side wall of each chamber were mounted two retractable levers (Med Associates) that could be inserted into the chamber. The lever (4.5 × 2.0 cm) closest to the back of the chamber (1.4 cm from back wall to the leftmost edge of the lever) was used. When extended, the lever was approximately 7.2 cm from the top of the bars of the grid floor (4.0-mm-diameter stainless steel bars separated by 1.5 cm). The other lever (1.9 cm from front wall) was always retracted. Centered above each lever was a jeweled lens cap (2.7 cm in diameter; center 5.7 cm above the lever) that could be transilluminated from behind by a light source (28 V, 100 mA). The center of the lens cap above the lever used in the experiment was 3.8 cm from the back wall.

Procedure. Following the establishment of responding under the FR 1 schedule, the ratio value was raised gradually across sessions to FR 10, where it remained for the duration of this portion of the experiment. Subjects were trained with a dose of 0.33 mg/infusion and, when responding was stable, were exposed to different doses (0.17 and 0.67 mg/infusion) for one session at a time. Subjects were typically exposed to these doses more than once, and at least one session in which the dose was 0.33 mg/infusion intervened between exposures to the other two doses. At the beginning of each session, approximately 10 min elapsed from the time the subject was placed in the chamber until the time the session began. Sessions always began with an infusion and the accompanying stimuli (see *General Procedure*). The light above the lever was illuminated after the termination of this 20-s stimulus complex and was illuminated for the rest of the session, except for 20 s following the initiation of infusions. Sessions always ended after 3 h had elapsed from the initiation of the first infusion.

Experiment 3: Discrete-Trial Fixed-Ratio 10 Schedules of Cocaine Infusion

Subjects. Six subjects were used.

Apparatus. Six identical operant chambers (23.5 × 19.0 × 22.0 cm) were used. Mounted and centered horizontally on the right wall was a retractable lever (4.5 × 2.0 cm; Med Associates) that when extended was 2.0–2.5 cm above the grid floor (3.0-mm-diameter bars separated by 1.5 cm). Centered above the lever, approximately 7.2 cm from the floor, was a jeweled lens cap that could be transilluminated from a light source behind the wall (28 V, 100 mA).

Procedure. In this experiment, the response criterion for reinforcement (ultimately FR 10) had to be met within 10 min. If the criterion was not met, the intertrial interval (ITI; a period during which the lever light was extinguished and responses had no programmed responses) was initiated. If an infusion was obtained, the ITI began immediately after termination of the stimuli correlated with infusion.

Following the establishment of responding under an FR 1 schedule, the ratio was raised across sessions to FR 10. During this training period, the ITI was 10.0 min. Trial duration was always a maximum of 10.0 min. Once responding was reasonably stable under the FR 10 schedule, the ITI was shortened to 3.0 min, where it remained for the duration of this experiment. When responding was stable under this latter set of conditions, determination of the dose–effect function was undertaken. The dose of the cocaine reinforcer (0.083, 0.17, 0.33, 0.67, and 0.83 mg/infusion) was changed before each session in an ascending fashion. This series of doses occurred at least twice for all of the subjects whose data are reported here. Five of the six subjects were exposed to this series of doses, followed, within a few sessions, by some number of consecutive sessions in which the consequence of responding was the infusion of saline. All of the subjects of this experiment were subsequently exposed to at least two more of these ascending series of doses, and it is these latter manipulations that are considered here. Sessions ended after the 10th trial.

Experiment 4: Variable-Interval 4.89-min Schedule of Cocaine Infusion

Subjects. Eight subjects were used: six to obtain dose–effect functions and two exposed to saline extinction.

Apparatus. Six nearly identical chambers (25.4 × 17.6 × 17.6) were used, and subjects were housed in the same cages in which experimental sessions were conducted. The cages were placed in the sound-attenuating chest immediately before experimental sessions. One of the small walls and the floor were a continuous piece of wire mesh (1.5-mm-diameter wire; 1.3-cm squares). The other three walls were made of stainless steel. Cut into the small sheet-metal wall, which was oriented to the right when the cage was placed in the sound-attenuating chest, was a rectangular hole through which a lever could be inserted. The center of the hole was approximately 4.0 cm above the floor; its leftmost edge was about 11.3 cm from the back wall and its rightmost edge about 3.7 cm from the front wall. The length of the hole was about 2.6 cm. The hole had a roughly circular portion cut (approximately 1.3 cm in diameter) in the center of the rectangular portion to accommodate the motion of the lever. The lever consisted of a cylinder (4.0 mm in diameter, 2.0–2.5 cm long) mounted on, and perpendicular to, a flat piece of metal (width 4.0 mm) attached to a microswitch. The cylinder was, thus, parallel to both the floor and the wall through which it protruded. The center of the cylinder was about 3.5 cm from the wall. Centered above the lever was a jeweled lens cap that could be transilluminated from a light source (28 V, 100 mA) behind the wall. The center of the lens cap was about 7.8 cm above the floor.

Procedure. After establishment of responding under the FR 1 schedule, subjects in this experiment were exposed, in consecutive sessions, to VI 30 s, 60 s, 180 s, and finally, 4.89 min. The VI schedule remained at this value for the remainder of the experiment. Each dose was studied for between 3 and 28 sessions (usually 6–11 sessions). The order of the doses administered was not systematic across subjects. There was a 5.0-min time-out following the initiation of infusions. During this period, the chambers were dark and responses had no scheduled consequences. At the beginning of each session, approximately 10 min elapsed from the time the subject was placed in the chamber until the time the session began. Sessions always began with an infusion and the accompanying stimuli. Sessions always ended 3 h from the beginning of the session unless the 5.0-min blackout duration was in effect, in which case the session ended immediately succeeding the termination of the timeout period. Each response operated the relay mounted in the sound-attenuating chest, producing an audible click.

Experiment 5: Comparison of Probe Versus Phase Dosing Procedures under FR 10 Schedules of Cocaine Infusion

Subjects. Five subjects were used.

Apparatus. Two identical operant chambers (23 × 21.5 × 19.0 cm) were used. The two small walls (left and right sides) were made of stainless steel, and the back, front, and top were made of Plexiglas. The floor of the chamber consisted of

stainless steel bars (1.2 mm in diameter) separated by 2 cm. On the right-hand side wall of each chamber was mounted a lever. The lever (5.7 × 2.5 cm) was mounted closest to the front of the chamber (3.0 cm from front wall to the rightmost edge of the lever). The lever was approximately 2.5 cm from the top of the bars of the grid floor. The other lever (1.9 cm from front wall) was always retracted. Centered above the lever was a jeweled lens cap (1.4 cm in diameter; center 4.8 cm above the lever) that could be transiluminated from behind by a light source (28 V, 100 mA).

Procedure. After establishment of responding under FR 1 (0.33 mg/infusion) schedules of reinforcement, the ratio was increased gradually to FR 10. In contrast to the other free-operant FR procedures described above, there were no response-independent infusions programmed. When responding was stable under 0.33 mg/infusion, a dose of 0.083 mg/infusion was substituted occasionally for the usual dose. This substitution could take place as frequently as every other session provided that responding under 0.33 mg/infusion was similar to that observed during baseline. Each session lasted 2 h and 40 min. Following at least three determinations of the effects of 0.083 mg/infusion, this dose was examined on a phase basis. This procedure was then followed by a dose of 0.17 mg/infusion.

Drugs. Cocaine hydrochloride was dissolved in isotonic saline that contained heparin (1.7 units/ml). Concentrations and doses are, throughout, given in terms of the salt.

Data Evaluation

For all subjects responding under the free-operant procedures (Experiments 1, 2, and 4), rate of response and rate of cocaine intake were analyzed. For subjects responding under the discrete-trial procedure (Experiment 3), number of trials with infusions, total cocaine intake, and mean latency to respond on trials with infusions were analyzed. Response rates for Experiments 1, 2, and 4 were analyzed using one-way repeated-measures analysis of variance (ANOVA), as were intake rates for Experiments 1 and 2. Response rates were compared across procedures at the doses common to them all using Kruskal–Wallis one-way ANOVA on ranks and Dunn's method of pairwise comparisons. Number of infusions and latency to respond under the discrete-trial experiment (Experiment 3) was also analyzed using one-way repeated-measures ANOVA.

RESULTS

Figure 1 shows response rate (left panel) and rate of drug intake (right panel) as a function of dose for Experiments 1, 2, and 4 (free-operant FRs and VI) averaged across subjects. Over the range of doses tested, response rate was an inverse function of dose under both free-operant FR procedures and was a bitonic function under the VI schedule. Dose was a statistically significant variable (one-way repeated-measures ANOVA) within each procedure type: VI [$F(4, 126) = 37.186$, $p < 0.0001$], within-session dosing [$F(2, 19) = 759.9$, $p < 0.0001$], and between-session dosing [$F(2, 15) = 27.3$, $p < 0.0001$]. For the VI procedure, the variance for the lowest (0.083 mg/infusion) and the highest doses (0.83 mg/infusion) differed from normality. Response rates were further analyzed by comparing them across procedures at each of the three common doses (0.17, 0.33, and 0.67 mg/kg) using the Kruskal–Wallis one-way ANOVA on ranks. Type of proce-

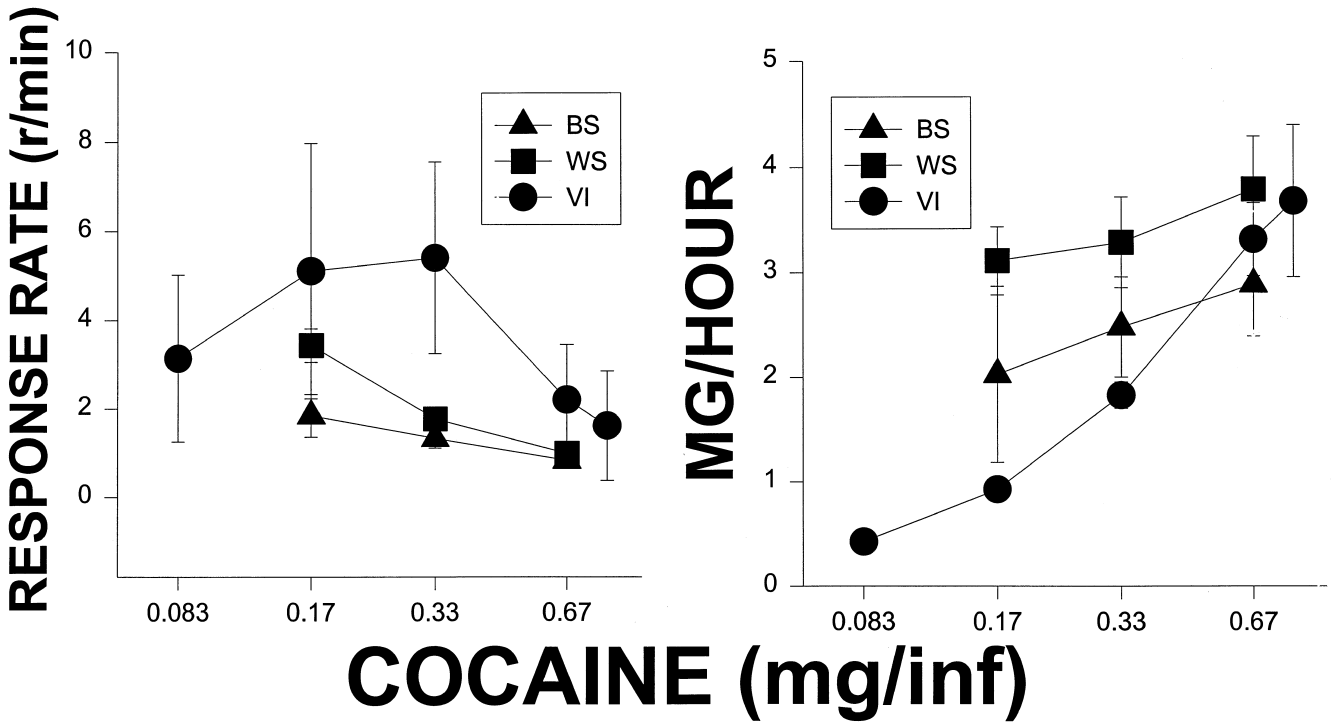

FIG. 1. Response rate (left panel) and rate of intake (right panel) as a function of dose of cocaine for Experiments 1, 2, and 4. Circles show data from the VI schedule (Experiment 4), squares from the within-session (WS) dosing FR (Experiment 1), and triangles from the between-session (BS) dosing FR (Experiment 2). Error bars are standard deviations. x-axis, dose of cocaine (mg/infusion); y-axes, response rate (responses/min; left panel) and rate of intake (mg/h; right panel).

dure produced a statistically significant difference at every dose. For 0.17, 0.33, and 0.67 mg/infusion, respectively, $H(2) = 20.1$, 79.8, and 22.3. These p-values are all <0.0001. Dunn's method of pairwise comparisons revealed that response rates for the two FR procedures were similar but were significantly higher for the within-session dosing group at a dose of 0.17 mg/kg ($Q = 2.99$, $p < 0.05$). Average rate of responding was higher under the interval schedule than under both of the free-operant FR procedures except at 0.17 mg/kg; rate of responding was not significantly different at this dose when compared with that of the within-session dosing procedure. For the comparison of VI to the within-session dosing FR, $Q = 1.84$, 6.3, and 3.52, for 0.17, 0.33, and 0.67 mg/infusion, respectively; the latter two p-values are <0.05. For the comparison of VI to the between-session dosing FR, $Q = 4.45$, 7.06, and 3.9, for 0.17, 0.33, and 0.67 mg/infusion, respectively; p-values are all < 0.05.

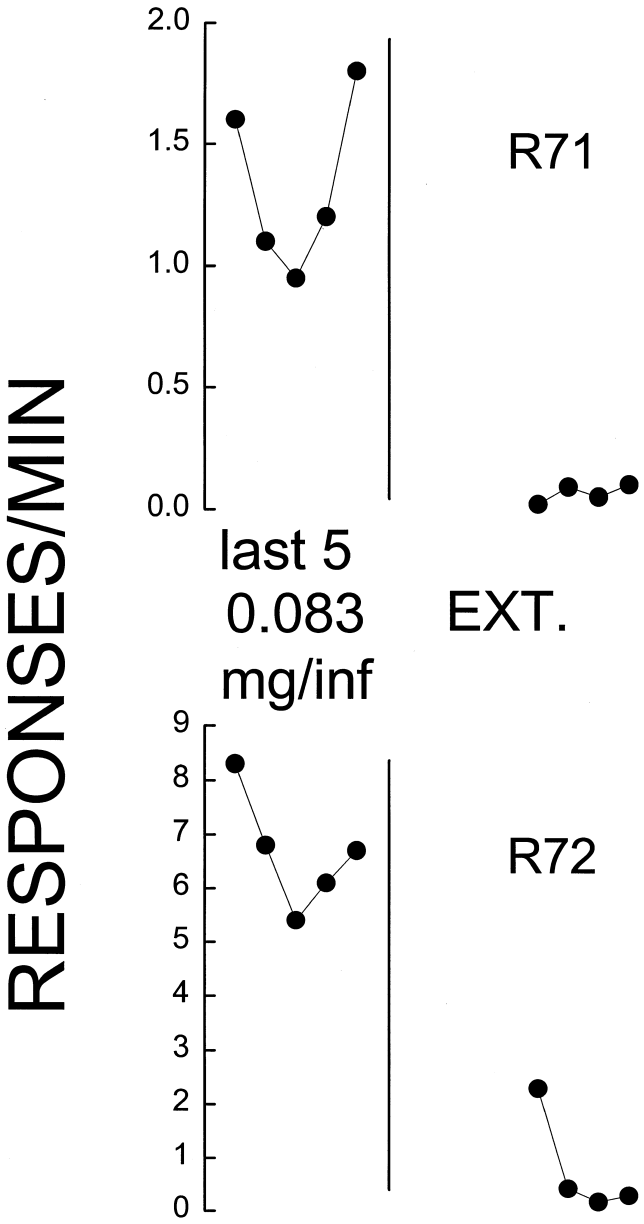

FIG. 2. Response rate during last five sessions of 0.083-mg/infusion phase (VI schedule) and during saline extinction for two rats. x-axis, consecutive sessions; y-axis, response rate (responses/min).

There was a further difference between the interval- and ratio-schedule data that is not observable in the averaged response-rate data of Fig. 1. For all of the subjects on the FR schedule, the highest rates of response occurred when the dose of cocaine was 0.083 (see Fig. 5 below) or 0.17 mg/infusion, but this was not the case for subjects on the VI schedule. For three of five subjects, 0.33 mg/infusion produced the highest rates observed for each subject. For these same subjects, however, 0.33 mg/infusion could, at a different time in the experiment, produce rates of response more comparable to 0.67 mg/infusion. Only one subject showed clearly higher rates of response at 0.17 than at 0.33 mg/infusion.

Over the range of doses tested, rate of drug intake (right-hand panel) was a direct function of dose in all three of the experiments depicted in Fig. 1. Although the functions for the FR schedules were relatively flat, dose was a significant variable (one-way repeated-measures ANOVA) under both conditions: for the within-session subjects [$F(19, 2) = 27.5$, $p < 0.01$] and for the between-session subjects [$F(15, 2) = 5.97$, $p < 0.05$].

Figure 2 shows the last five sessions under 0.083 mg/infusion and four consecutive sessions under saline for two additional rats. Responding was almost eliminated under the saline condition, indicating that the effects of extinction can be observed by the second session.

Data presented in Fig. 3 are from rats studied using the discrete-trial procedure. The left-hand panel shows number of infusions (out of 10 possible), and the right-hand panel drug intake, as a function of dose. Number of infusions was a bitonic function of dose, first increasing up to about 0.33 mg/infusion and then decreasing. Dose was a statistically significant variable when analyzed using a one-way repeated-measures ANOVA [$F(4, 12) = 10.773$, $p < 0.0001$]. Because of unequal numbers of treatments for one subject, a nonparametric repeated-measures test could not be used despite the fact that variances were not normal for doses of 0.17, 0.33, 0.67, and 0.83 mg/infusion. Drug intake (right panel) was a direct, S-shaped function of dose. As dose was increased, the amount of drug taken increased up to 0.67 mg/infusion. There was little difference between 0.67 and 0.83 mg/infusion in terms of the amount of drug taken.

Latency to respond in trials in which an infusion occurred was a bitonic function of dose (Fig. 4). Latencies increased up to a dose of 0.67 mg/infusion, but tended to decrease at 0.83 mg/infusion. Dose was a statistically significant variable when analyzed using a one-way repeated-measures ANOVA [$F(4, 12) = 37.087$, $p < 0.0001$].

Figure 5 shows rate of response as a function of dose for the five rats in which the probe- and phase-dosing procedures were compared. Rate of response was, for four of the five rats, a monotonic decreasing function of dose under probe conditions (filled circles), with a dose of 0.083 mg/infusion producing the highest rate of response. When 0.083 mg/infusion was available for consecutive sessions, however, this dose maintained much less responding in these four rats. For rats R31 and R33, 0.083 mg/infusion maintained rates of response equal to or less than saline, and for R29 and R30, it maintained rates of response slightly above those maintained by saline. For R27, there was little difference between rates of response under 0.083 mg/infusion in probe and phase conditions. For all subjects there was essentially no difference be-

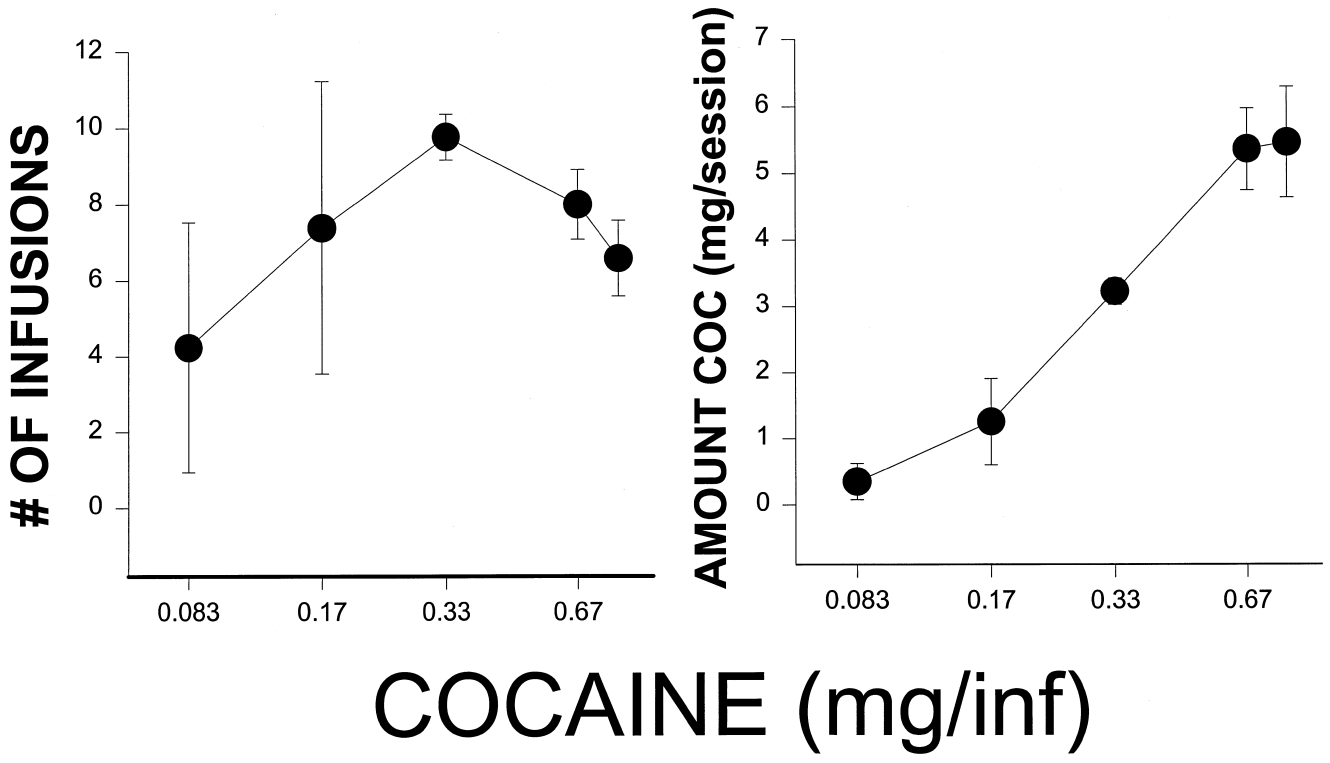

FIG. 3. Number of infusions (left panel) and amount of cocaine (right panel) as a function of dose of cocaine (Experiment 3). Error bars are standard deviations. x-axis, dose of cocaine (mg/infusion); y-axes, number of infusions (left panel) and amount of cocaine (mg/session; right panel).

tween the effects of probe versus phase procedures at doses other than 0.083 mg/infusion. For one subject (R33), 0.17 mg/infusion was not examined under phase conditions.

DISCUSSION

Cocaine self-administration was examined by using a variety of procedures that generated dose–effect functions that differed in certain respects. The most striking difference among the dose–effect functions concerned the dose at which the highest rate of responding (or largest number of trials with infusions, in the discrete-trial procedure) occurred. In the probe portion of Experiment 5, this dose was, for four of five rats, 0.083 mg/infusion (Fig. 5). Under the VI schedule, however, the peak of the average response-rate dose–effect function was around 0.17–0.33 mg/infusion (Fig. 1). Under the discrete-trial procedure, the peak of the average dose–effect function (trials with infusions) was 0.33 mg/infusion (Fig. 3). In the phase portion of Experiment 5, the highest rates of response tended to be at a dose of 0.17 mg/infusion. In Experiments 1 and 2, 0.17 mg/infusion maintained the highest rates of response, but this was the lowest dose examined.

A second difference among the dose–effect functions involves the rates of response generated. Not only were there differences in the dose that generated the highest rates, there were differences in the rates produced. The highest rates of response occurred under the VI schedule. Over the range of doses where comparison is possible (0.17–0.67), the within-session dosing procedure tended to produce higher rates of response than under the FR procedures in which only a single dose was available.

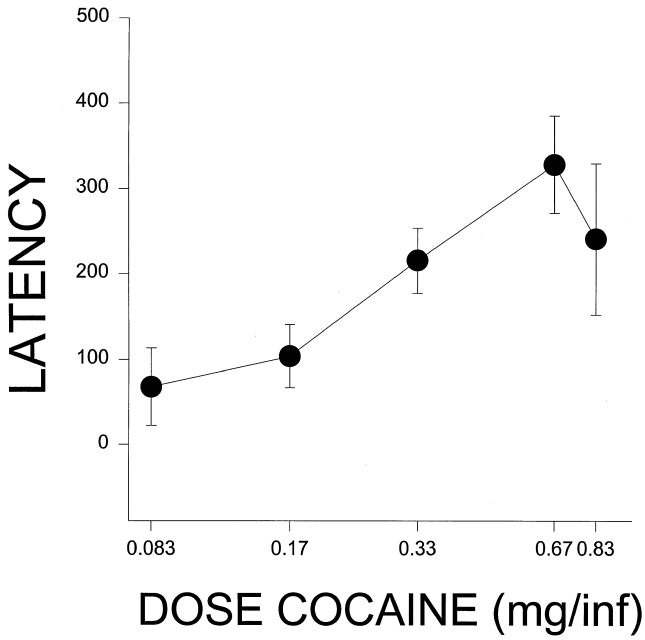

FIG. 4. Latency to respond as a function of dose of cocaine (Experiment 3). Error bars are standard deviations. x-axis, dose of cocaine (mg/infusion); y-axis, latency (s).

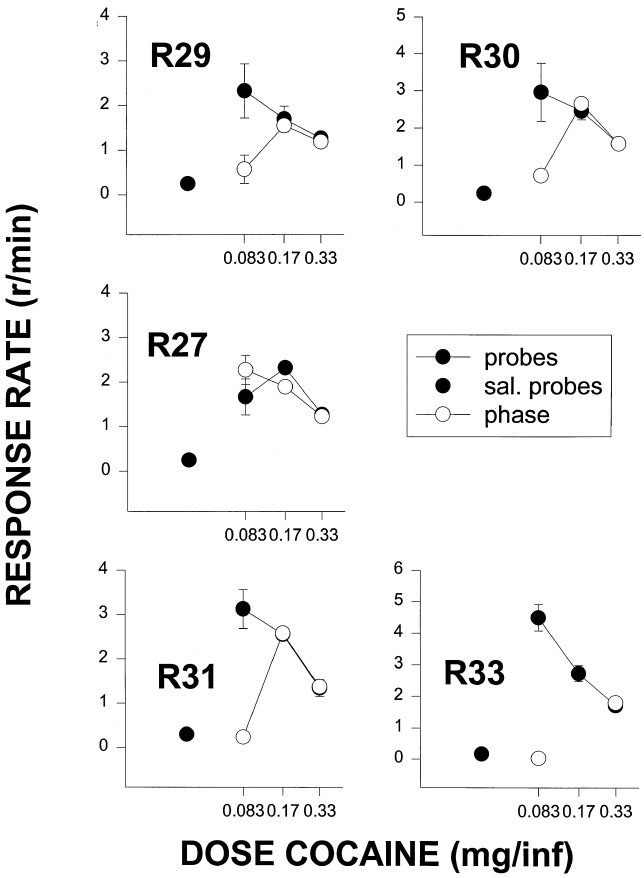

FIG. 5. Response rate as a function of dose of cocaine (Experiment 5). Filled symbols show data from the probe sessions and open symbols data from the phase portion. Error bars are standard deviations. x-axis, dose of cocaine (mg/infusion); y-axis, response rate (responses/min).

A third notable difference among the dose–effect functions concerns their overall shape. From data presented here and elsewhere (7), it seems clear that the dose that maintains peak responding may be altered substantially by merely changing aspects of the procedure. What is not clear is which of the procedural variables shift the dose–effect function in a parallel fashion, alter its height, or produce some other alteration. A comparison of the VI-schedule functions with those from the phase portion of Experiment 5 suggests that certain manipulations alter the shape of the dose–effect function considerably. It appears that the ascending limb under small FR schedules must be located between a very narrow range of doses—so narrow, in fact, that it may be difficult to observe response rates intermediate between those maintained by saline and those maintained at the peak of the dose–effect function (as in the present Experiment 5). The ascending limb of the VI-schedule dose–effect function was located over a wider range of doses. Some subjects, during the phase portion of Experiment 5, stopped responding altogether at 0.083 mg/infusion and others responded at rates only slightly above those maintained by saline. Under the VI schedule, in contrast, responding was maintained by 0.083 mg/infusion in all subjects. Thus, under the free-operant FR procedure employed in the phase portion of Experiment 5, responding was not reliably maintained at a dose that maintained responding under the VI schedule, but the peak of the FR-schedule dose–effect function occurred at a dose lower than under VI. That is, the curves were shaped differently. It is not clear from the present data which procedural aspects and associated controlling variables are responsible for the difference between these two dose–effect functions. From a procedural standpoint there are two possibilities: schedule type (interval vs. ratio) or presence versus absence of postinfusion time-outs. Both of these procedural differences affect, among other things, the maximum amount of drug that can be self-administered per unit time. The dose that maintains the highest rate of response is a direct function of time-out duration when this variable is manipulated within the context of FR schedules (21). There do not seem to have been many studies involving parametric manipulation of interval schedules, so the effects of manipulation of minimum interinfusion interval by this method are unknown. The interinfusion interval may also be manipulated indirectly by changing the number of responses required (i.e., FR value) and the dose at the peak of the response-rate dose–effect function is, here too, a direct function of ratio value (3,21). The maximum possible rate of drug infusion is probably the variable responsible for the tremendous diversity of reported dose–effect functions for cocaine self-administration (see below). In addition to procedural differences yielding differences in maximum possible rate of drug infusion, schedule type is probably the next most important variable in explaining the reported differences in dose–effect functions.

Based on data presented here and in Winger's (21), Goldberg and Kelleher's (7), and Caine and Koob's (3) papers, as well as what is known about schedules of nondrug reinforcement, some tentative statements concerning how dose–effect functions are determined by procedural variables are possible. Response-rate dose–effect functions under ratio schedules with no postinfusion time-outs consist primarily of a descending limb, and the dose that maintains maximum rates of response will tend to be low with respect to interval schedules. This "peak dose" will, however, be relatively close to doses that are ineffective at maintaining responding, i.e., the range of doses over which an ascending limb can be observed is very narrow. Increasing the duration of postinfusion time-outs will tend to shift the curve to the right and will also tend to increase response rates (i.e., the height of the function changes). It is not clear whether the range of doses over which an ascending limb can occur will increase. Changing from a probe- to a phase-dosing procedure shifts the peak dose to the right and lowers peak response rates. This would not be expected to alter the narrow range of doses over which an ascending limb could be observed. It is probably true that low doses tend to maintain higher rates of responding when they occur in the context of higher doses, as in the probe procedure, but also when higher doses precede lower doses in within-session procedures.

Response-rate dose–effect functions for interval schedules of cocaine infusion will be clearly bitonic, with a relatively broad range of doses constituting the ascending limb. Responding will be maintained at doses lower than those that maintain responding under ratio schedules. Increasing values of postinfusion time-out will increase rate of response except at very short intervals with very small doses. Adding time-outs to rather long intervals would be expected to have little effect on the peak dose but would, presumably, alter it when added to short intervals. It is not clear what effect different dosing procedures might have under interval schedules.

There have been a variety of different response-rate dose–effect curves reported for cocaine. Some authors have reported that increasing the dose of cocaine decreases rats' and

monkeys' rates of response under free-operant FR schedules of cocaine infusion (6,17,24). Other researchers using primates, however, have reported bitonic functions (6,8,23) and increasing functions (22).

That rate of response under interval schedules of cocaine presentation is a bitonic function of dose is, also, partially consistent with the literature. Under FI schedules of cocaine infusion, strictly decreasing (4), bitonic (1,6), and strictly increasing (1) functions of dose have been reported.

There are few published data with which to compare our data for the discrete-trial procedure. Dworkin, Mirkis, and Smith (5), however, investigated concurrent chained FR 1 FR 10 schedules of food, water, and cocaine presentation in the three terminal components. Although there were many differences between Dworkin et al.'s procedure and the one utilized in the present experiment, the curves relating trials with infusions to dose are comparable. The present study demonstrates that the conditional probability measure (trials with infusions displayed in Fig. 3 is equal to the conditional probability $\times$ 10.0), which was made possible by limiting the duration of the trial, was sensitive to changes in dose.

The interpretation most readers are likely to draw from the discrepancies in the literature is that a large enough range was not investigated in the studies that did not report a bitonic function. Although this is, to a great extent, true, there are several caveats. One is that not all dose–effect functions *must* be continuous over the range of the function. There is some reason to believe that for small FR schedules of cocaine infusion (with no time-outs), the ascending limb of the response-rate dose–effect function may not be continuous because of the nature of the feedback between amount of cocaine infused and response rate. Another caveat is that even if dose–effect curves under ratio and interval schedules are both bitonic and continuously differentiable, they are still—apparently—shaped differently.

The data from the current experiments and from some of the literature cited are similar to those reported for nondrug reinforcers. The differences between the response-rate dose–effect functions under interval and ratio schedules observed here parallel those found when concentration of a sucrose solution was manipulated in the context of FR and FI schedules (16). In those studies, the rate of response was essentially flat over the range of concentrations under FI schedules but strictly decreasing under FR schedules. Other researchers have also found a strictly decreasing function under FR schedules when sucrose concentration was manipulated (11). Also consistent with the differences in dose–effect functions is that, under FI schedules, manipulation of the magnitude of nondrug reinforcers tends to produce increases in the rate of response (9) or to produce flat functions (14). Taken together, these studies suggest that one is more likely to observe an increasing portion and a flat portion on the function relating rate of response to magnitude under interval schedules, but to observe strictly decreasing functions under FR schedules. It is, however, not quite so simple; increasing response-rate magnitude functions have also been observed with FR schedules (18).

Also similar to interval- versus ratio-schedule differences observed here is the finding that responding tends to be maintained under interval schedules with reinforcer magnitudes that do not maintain responding under ratio schedules or ratio-like schedules (10). This finding seems to be related to the "regenerative" properties of interval schedules (25).

Finally, there are data consistent with some of those discussed earlier (21) regarding dose–effect functions and changes in FR value (15). These researchers found that the function relating overall response rate to magnitude of food reinforcement was an inverted U-shaped function. Increasing the FR value caused the "magnitude–effect" functions to shift to the right just as the dose–effect functions did. These data, and the data from studies involving nondrug reinforcers presented above, suggest that some of the effects produced when procedural variables are manipulated in drug self-administration studies are common to those involving nondrug reinforcers.

The diversity of reported dose–effect curves for cocaine self-administration reflects the tremendous power of procedural variables to alter dose–effect curves, and this remains true whether or not all of these functions are ultimately described as bitonic. Care must be taken, however, when interpreting these effects—they may reflect processes that are not unique to the self-administration of drugs.

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