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Effects of Repeated Administration of Cocaine on Schedule-Controlled Behavior of Rats

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WOOLVERTON, W. L., D. A. KANDEL AND C. R. SCHUSTER. *Effects of repeated administration of cocaine on schedule-controlled behavior of rats.* PHARMAC. BIOCHEM. BEHAV. 9(3) 327–337, 1978.—The effects of cocaine (4.0–32 mg/kg) on schedule-controlled behavior of rats were determined before and during a period of repeated administration of cocaine. In rats trained to lever press on a fixed ratio 40 schedule for food delivery, cocaine (8.0–32 mg/kg) initially decreased response rate in a dose-related manner. During the period of repeated administration, the effects of cocaine on response rate and running rate were attenuated in 2 rats and did not change in 2 others. When dose-effect functions of cocaine were redetermined, a shift to the right was observed in several measures indicating the development of tolerance to these effects of cocaine on performance. In rats trained to lever press on a DRL 20″ schedule for food delivery, cocaine (4.0–32 mg/kg) increased response rates, decreased number of reinforcements per session and shifted interresponse time distributions to the left (shorter IRT's in all rats). During the period of repeated administration, the effects of the daily dose of cocaine (16 mg/kg) on all these measures were attenuated. Tolerance to cocaine was further indicated by a shift in the dose effect function of cocaine to the right during the redetermination.

Cocaine Rats Repeated administration Tolerance Fixed-Ratio Differential reinforcement of low rates

A FEW studies have shown the effects of cocaine on schedule-controlled behavior to depend upon the rate of responding under control conditions. Smith [29] administered cocaine (0.1–10 mg/kg) to pigeons responding on a multiple FI 5′ FR 30 schedule for food reinforcement and observed increases in the normally low control rates early in the fixed interval at doses that decreased the normally high control rates late in the interval and in the FR component. Similarly, Barrett [1] observed rate increases early in the interval and rate decreases late in the interval when cocaine was administered to squirrel monkeys responding on a multiple FI 5′ FI 5′ for food delivery and electric shock presentation. Rate increases have also been observed in rats responding for electrical stimulation of the brain [33] and to avoid electric shock (continuous avoidance [9,18]), situations which typically engender relatively low response rates. On the other hand, the administration of cocaine to rats responding on fixed-ratio schedules for food reinforcement [20] or water reinforcement [13] have shown that the relatively high overall response rates were decreased in a dose-dependent manner. The effect of cocaine most often described by these investigators was a dose-related pause in responding followed by a rapid transition to control rates of responding.

The effects of cocaine on schedule-controlled responding cannot, however, be said to be exclusively determined by the control rate of responding and are not always independent of the maintaining event. Johanson [11] trained rhesus monkeys on a 3-ply multiple schedule consisting of FR 30 for food–FR 30 to avoid electric shock–DRL 45″ for food, with a timeout between schedule components. Doses of cocaine that eliminated high rates of responding for food did not affect comparable rates of responding maintained by shock avoidance. Furthermore, the same doses of cocaine that eliminated FR responding for food delivery failed to increase the low response rates in the DRL component. Similar effects were observed following several doses of

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d-amphetamine in the same animals [11]. It is possible that organismic, conditioning or schedule variables contributed to the difference between these data and other reports in the literature.

Although there is a considerable body of literature describing the development of increased sensitivity to some of the effects of cocaine on unconditioned behavior [2, 6, 21, 27, 28], the effects of repeated administration of cocaine on schedule-controlled behavior have not been reported (except aggressive behavior [10]). Tolerance has been reported to the effects of cocaine on milk intake in rats, as has cross-tolerance between cocaine and d-amphetamine [34]. There have, in addition, been numerous reports of the effects of repeated administration of the amphetamines on schedule-controlled behavior. Some of these will be briefly described since amphetamine is often discussed as the prototypical drug of the psychomotor stimulant class. Tolerance to the rate-increasing effects of d-amphetamine on DRL responding for food in rats has been reported [3, 19, 24, 26] while lack of tolerance has been reported to the rate-increasing effects of d-amphetamine in animals responding on a fixed interval schedule for food delivery and for shock avoidance [24]. On the other hand, Tilson and Sparber [32] reported that tolerance did develop to the effects of d-amphetamine in animals responding on a fixed-interval schedule for food delivery. Tolerance to the rate decreasing effects of methamphetamine on fixed-ratio and DRL responding in rhesus monekys has also been reported [8,25]. Furthermore, it has been demonstrated that d-amphetamine must be administered before the experimental session for tolerance to develop. Animals given the drug after the session, so that it does not disrupt responding, did not become tolerant [3,19]. One hypothesis to account for these data was elaborated by Schuster *et al.* [24]. According to their hypothesis, an organism will become tolerant to the effects of a drug that interfere with its ability to meet the contingencies of reinforcement. Thus, tolerance was observed to the rate increasing effects of d-amphetamine on DRL performance but not on FI performance because reinforcement was lost on the DRL but not on the FI. Furthermore, the rate increases observed in animals responding to avoid electric shock decreased the number of shocks received and tolerance did not develop to this effect of the drug.

The present experiments were designed to investigate the effects of single and repeated administrations of cocaine on schedule-controlled behavior as well as the phenomenon of behavioral tolerance. The effects of cocaine were examined in two groups of 4 rats each, one group responding on a schedule that generated a high response rate (FR 40 for food) and the other responding on a schedule that generated low response rates (DRL 20″ for food). The effects of cocaine were found to depend on the control rate of responding and tolerance developed to several effects of the drug.

METHOD

Animals and Apparatus

The animals were 8 experimentally naive male Sprague-Dawley derived albino rats (Holtzman Co., Madison, Wisc.) which weighed between 340–400 grams at the beginning of the experiment. They were housed individually in plastic cages where water was continuously available. Food availability was restricted to 45 mg food pellets (P. J. Noyes Co., Lancaster, New Hampshire) delivered during experimental sessions and supplemental feedings with Teklad Rat and Mouse Diet (Winfield, Iowa). Experimental sessions were conducted in a standard operant chamber for rats (Ralph Gerbrands Co., Arlington, Mass.). On one wall of the chamber was a lever with a stimulus light above it and a food magazine recessed next to it. Programming of stimulus events and recording of response and reinforcement data were accomplished with electromechanical equipment located in an adjacent room.

Procedure

Initial training. The rats were food deprived until they reached 75–80% of their free-feeding body weights and maintained at this weight for the duration of the experiments. Experimental sessions were 1 hr long throughout the experiment. For the initial training sessions, each animal was given an intraperitoneal injection of saline and placed in the operant chamber. Fifteen min later, the stimulus light above the lever was illuminated and a single depression of the lever delivered a 45 mg food pellet (fixed ratio 1; FR 1). Food delivery was accompanied by a 3 sec termination of the light above the lever and the illumination of the feeder light. Responses during this period of time had no programmed consequences.

After 2–3 sessions of responding on FR 1, lever pressing became stable and the animals were divided into two groups. One group of rats (N=4) was designated the FR group and the other group was designated the DRL group (DRL—differential reinforcement of low rates of responding). For the FR rats, the number of lever presses required for food delivery was gradually increased to 40 responses per pellet (FR 40). For the DRL rats, the response requirement for food delivery remained at one response/pellet. However, responses had to be spaced by at least 20 sec in order for food delivery to occur (DRL 20″). Responses occurring before the 20 sec had elapsed were not reinforced and the interval timer was reset. An additional 20 sec had to elapse before reinforcement was again available.

Initial dose-effect determinations. When the number of reinforcements delivered was stable for each rat (less than 10% variation in the mean number of reinforcements delivered for at least 3 consecutive days), dose-effect functions of cocaine on FR 40 or DRL 20″ lever press responding were determined. Single doses of cocaine (4.0, 8.0, 16 and 32 mg/kg) were administered 15 min before the session first in an ascending then in a descending order. All injections were given intraperitoneally and each drug administration was separated by at least 3 days of stable responding when saline was injected before the session.

Repeated administration of cocaine. Following the determination of the effects of single injections of cocaine on responding, a dose of cocaine which decreased the number of reinforcements delivered by at least 25% but did not totally eliminate responding was selected and administered to each animal in both groups 15 min before the session for a period of 92–104 days. The total number of days differed slightly among animals due to variations in the number of days between test doses of cocaine in the dose-effect redeterminations (see below) and failures of the equipment.

Dose-effect redeterminations. After Day 60, cocaine dose-effect functions were redetermined for both groups of rats while they were maintained on the daily cocaine injection regimen. On Day 61, saline was administered before the session. Subsequent administrations of test doses of cocaine

were separated by at least 3 days during which each rat received its usual daily dose of cocaine and responded on the appropriate reinforcement schedule. On test days, only the test doses of cocaine were administered 15 min prior to the session. The number of sessions between test doses of cocaine ranged from 3–5. The effect of each dose was redetermined for each rat first in an ascending then in a descending order.

Drug. Cocaine hydrochloride (Merck Co., Rahway, New Jersey) was used and all drug doses refer to the total salt. The drug was dissolved in physiological saline in a concentration such that injection volumes were 1 ml/kg.

Data Analysis and Presentation

Fixed-ratio performance. The effects of cocaine on the following measures of fixed-ratio performance were calculated.

(1) Initial Pause. The time from the beginning of the session to the delivery of the first pellet. Since once responding began it continued at a high rate until food delivery, this measure is essentially the same as the time to the first response (latency).

(2) Overall Response Rate. The total number of responses in a session/total session time. Data are presented as percent of saline control rates.

(3) Running Rate. The mean rate of responding in a session once responding has begun. This measure is calculated by dividing the total number of responses in a session by the session time minus pause time. Pause time includes the initial pause in the session and the cumulative post-reinforcement pause time for the session.

DRL performance. The effects of cocaine on the following measures of DRL performance were examined.

(1) Overall Response Rate. The total number of responses in a session/total session time. Data are presented as percent of saline control rates.

(2) The total number of reinforcements in a session.

(3) The average interresponse time distribution (IRT's). Interresponse times were recorded in 2 sec bins with the shortest being the 0–2 sec bin and the final bin counting all IRT's greater than 36 sec. The distribution represents the percent of the total number of responses that occurred in each 2 sec bin. Thus, if there were 150 total responses in a session, and 15 of these were spaced by 18–20 sec, the IRT distribution would indicate that 10% (15/150) of the total responses occurred in the 18–20 sec bin. The IRT distribution is thus a representation of response spacing and is presented as a histogram.

The effects of cocaine on each of the above measures were analyzed and compared using an analysis of variance [15] to detect effects of dose, daily treatment and interactions. Where differences were found using the analysis of variance, individual points were tested using Tukey's honestly significant difference test, and a posteriori test for making pair-wise comparisons among means [22] and compared to the observed difference between means. Where significant effects were found, p values are presented.

RESULTS

Fixed-Ratio Performance

Figure 1 shows cumulative response records for a single rat following saline and test doses of cocaine before and during the period of repeated administration of cocaine. Typical fixed-ratio performance [7] was observed following saline injections. As can be seen from the records, the most striking effect of cocaine on responding was the increasing period of no responding early in the session, followed by an abrupt transition to a high rate of responding. The effects of intermediate doses of cocaine on this initial pause time are presented for individual rats in Table 1. As can be seen, the effects of 24 mg/kg in Rats 1 and 2 and the effects of 16 mg/kg in Rats 3 and 4 were similar. On this basis the rats were divided into two groups for repeated administration of cocaine. Group A included Rats 1 and 2 (24 mg/kg cocaine/day) and Group B included Rats 3 and 4 (16 mg/kg cocaine/day).

TABLE 1

EFFECTS OF SALINE, 16 and 24 MG/KG ON THE INITIAL PAUSE TIME OF THE RATS RESPONDING ON A FR 40 SCHEDULE. DURATION OF PAUSE IS EXPRESSED IN MINUTES

Rat	Dose (mg/kg) sal	16	24
1	0.9	16.1	23.2
2	0.8	1.5	22.7
3	0.9	23.4	
4	0.5	38.4	

Initial pause. The effects of single injections cocaine on the mean duration of the initial pause of Group A are shown in Fig. 2A. The average initial pause time following 8.0 mg/kg was not significantly different from that observed following saline while 16, 24 and 32 mg/kg increased pause time in a dose-related manner. Similarly, there was a dose related increase in initial pause for Group B (Fig. 2C). Following 32 mg/kg, all but one animal paused for the entire session.

During the period of repeated administration of cocaine (24 mg/kg) to Group A, initial pause time decreased from an average of 27 min on Days 1–5 to 9 min for Days 55–60 (Fig. 2B). In the initial dose-effect determination, 24 mg/kg resulted in a 23 min pause, while on Days 59–60, the animals paused an average of 9 min following this dose. When the dose-effect function of cocaine on initial pause was redetermined during the period of repeated administration, there was again a dose-related increase in initial pause (Fig. 2A). In addition, the shift to the right in the redetermination of the dose-effect function was found to be significant ($p<0.05$). The effects of 24 and 32 mg/kg on initial puase were attenuated during the period of repeated administration ($p<0.05$). For Group B, initial pause time during repeated cocaine administration decreased from an average of 15 min on Days 1–5 to an average of 8 min on Days 55–60 (Fig. 2D). In the initial dose-effect determination 16 mg/kg cocaine resulted in a 30 min initial pause whereas following this dose on Days 59–60 the animals paused an average of 11 min. In the dose-effect redetermination there was a dose-related increase in initial pause (Fig. 2C). The shift to the right in the dose-effect function was significant at the 0.05 level.

Overall response rate. In the initial dose-effect determinations, single injections of cocaine decreased the overall response rate of the rats in Group A (Fig. 3A). The effect of 8.0 mg/kg was not significantly different from saline while 16, 24 and 32 mg/kg produced dose-related decreases in response rate. Similarly, Fig. 3C shows the effects of single injections of cocaine on the response rate of the rats in

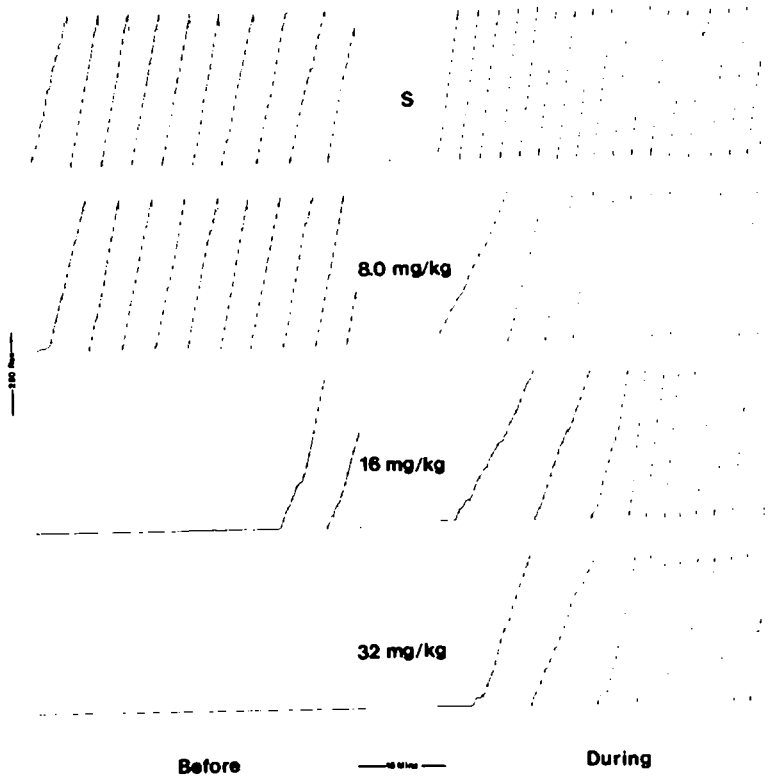

FIG. 1. Cumulative response records for a representative rat (No. 4) responding on a FR 40 schedule of food delivery. Ordinate: Responses; Abscissa: Time. Diagonal pips represent food delivery. The effects of saline (S) and 3 doses of cocaine on responding are shown. On the left are response records following these doses of cocaine in the initial dose-effect determinations. On the right are response records following these doses of cocaine in the dose-effect redeterminations. The daily dose of cocaine was 16 mg/kg.

Group B. Rates following 8.0, 16 and 32 mg/kg were all significantly different from saline.

Figure 3B shows the change in response rate following 24 mg/kg cocaine for Group A between Days 1–60 of repeated cocaine administration. The solid line between the initial effect of 24 mg/kg and the effects on Days 59–60 indicates that response rate increased during this period. However, this line should be compared to the dotted line which connects the point representing the initial control rate of responding and the control rate observed following saline injections given on Day 61. Since these lines are parallel, the change in response rate between Days 1–60 can be accounted for as a shift in control rate of responding rather than an attenuation of the effects of cocaine on response rate during this period. In the dose-effect redetermination (Fig. 3A), there was again a dose-related decrease in overall response rate. Relative to the initial dose-effect determination, a two-way analysis of variance revealed no change in effect of cocaine as a result of the daily treatment regimen.

Figure 3D shows the change in response rate of the rats in Group B during the period of repeated administration (16 mg/kg). The solid line which connects the initial effect of 16 mg/kg and the effect on Days 59 and 60 indicates that response rate increased during this period. This line should be compared to the dotted line which connects the point representing initial control rate and the control rate observed following saline injections on Day 61. Rate following 16 mg/kg increased faster than did control rate indicating that there was likely an attenuation of the effects of 16 mg/kg cocaine during this period. Test doses of cocaine produced a dose-related decrease in response rate when the effects of these doses were redetermined during the period of repeated administration. A two-way analysis of variance revealed a significant effect of daily administration ($p<0.001$) and a significant interaction ($p<0.001$). When comparisons were made between individual means, no change was seen in the effects of 8.0 and 32 mg/kg relative to that observed initially. However, the effect of 16 mg/kg on response rate was attenuated during the period of repeated administration ($p<0.05$).

Running Rate

In the initial dose-effect determination, cocaine had no effect on the running rate of the rats in Group A. There was, however, a dose-related decrease in running rate of the rats in Group B. The effect of 8.0 mg/kg was not significantly different from saline while 16 and 32 mg/kg produced dose-related decreases in running rate.

During the period of repeated administration of cocaine, the average running rate of the rats in Group A increased. However, the control running rate increased similarly during this time. Thus, there was no change in sensitivity to the effects of

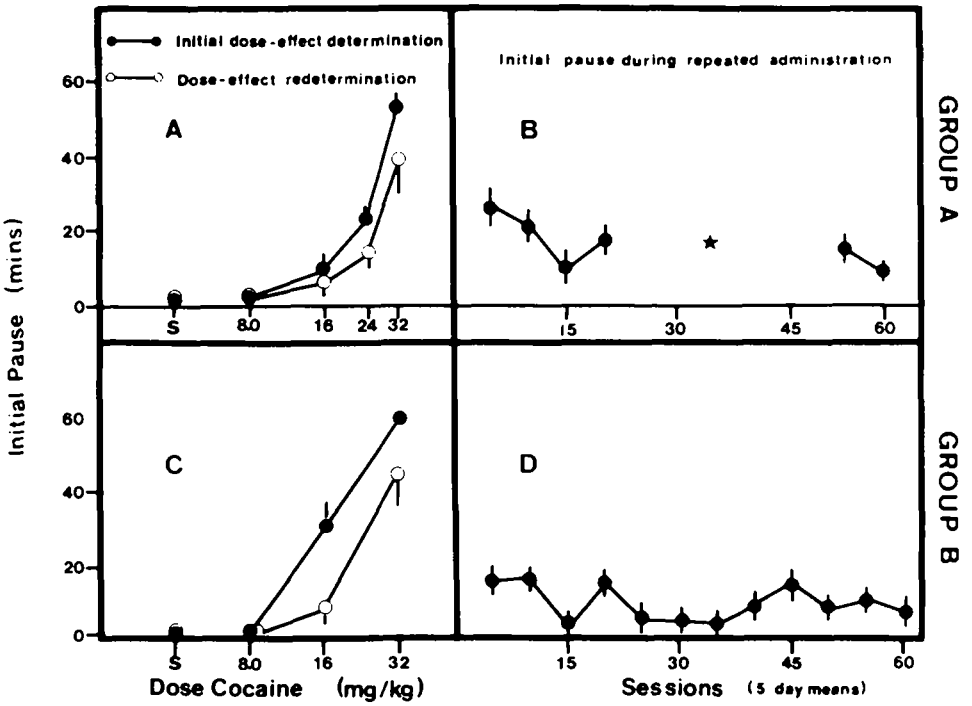

FIG. 2. Effects of single and repeated injections of cocaine on the mean duration of the initial pause in the session for rats responding on a FR 40 schedule of food delivery. *Upper Left Panel (A):* The dose-effect function of cocaine before (●——●) and during (○——○) repeated administration of cocaine (24 mg/kg) to the rats in Group A. Ordinate: time in minutes. Abscissa: dose of cocaine. The points above S represent the effects of saline pretreatment on initial pause. *Upper Right Panel (B):* The effects of repeated administration of cocaine (24 mg/kg) on the mean duration of the initial pause for the rats in Group A from session 1 to session 60 of repeated administration. Each point is the mean of 5 consecutive sessions. *Lower Left Panel (C):* The dose-effect function of cocaine before (●——●) and during (○——○) repeated administration of cocaine (16 mg/kg) to the rats in group B. *Lower Right Panel (D):* The effects of repeated administration of cocaine (16 mg/kg) on the mean duration of the initial pause for the rats in Group B from session 1 to session 60 of repeated administration. Each point is the mean of 5 consecutive sessions. In all cases, vertical lines represent the standard error of the mean.

24 mg/kg cocaine during this period. In addition, there was no shift in the cocaine dose-effect function when it was redetermined during the period of cocaine administration. In contrast, for the rats in Group B the running rate following 16 mg/kg increased somewhat faster during this period than did control running rate indicating that there was an attenuation of the effects of 16 mg/kg cocaine on running rate. When the effects of test doses of cocaine on the running rate of these rats were redetermined during the period of repeated administration, there was no change in the effect of 8.0 and 32 mg/kg relative to that observed initially. However, there was an attenuation of the effect of 16 mg/kg on running rate ($p<0.05$), indicating tolerance development to this effect of this dose.

DRL Performance

Figure 4 shows cumulative response records for a representative rat before and during the period of repeated administration of cocaine. Control DRL performance is characterized by a low response rate as shown in the record of responding following saline injection. Interresponse time distributions following saline injections (Fig. 7) showed the bimodal distribution typical of this schedule of reinforcement with a peak between 0–2 sec representing response bursting and a second peak consisting of IRT's between 20–22 sec, the minimum spacing required for reinforcement [7]. The most striking effect of cocaine on DRL performance was to increase responding and decrease the number of reinforcements delivered. At the two highest doses of cocaine (16 and 32 mg/kg) an initial pause in responding was observed; however, in no case was responding eliminated for the entire session.

Response rate. The effects of single injections of cocaine (4.0, 8.0, 16 and 32 mg/kg) on the average response rate of these rats are shown in Fig. 5A. In contrast to fixed-ratio performance, the effect of cocaine was to increase response rate on the DRL schedule. The effect of 4.0 mg/kg was not significantly different from saline while 8.0 and 16 mg/kg produced significant increases in responding. The effect of 32 mg/kg was to increase responding in some rats and to decrease responding in others.

A dose of 16 mg/kg was chosen for repeated daily injections since it produced comparable effects in all rats. Figure 5B shows the change in response rate between Days 1 and 60 of repeated cocaine administration. During this period, rate decreased from 178.3% (± 16.1%SEM) of control levels for Days 1–5 to 115.5% (± 7.4% SEM) of control levels for Days 55–60. Furthermore, response rate following 16 mg/kg cocaine decreased from 215.4% (± 21.8% SEM) of control levels in the initial dose effect determination to 125% (± 12.1% SEM) of original control rate following this dose on Days 59–60 (solid line, Fig. 5B). The decrease in respond-

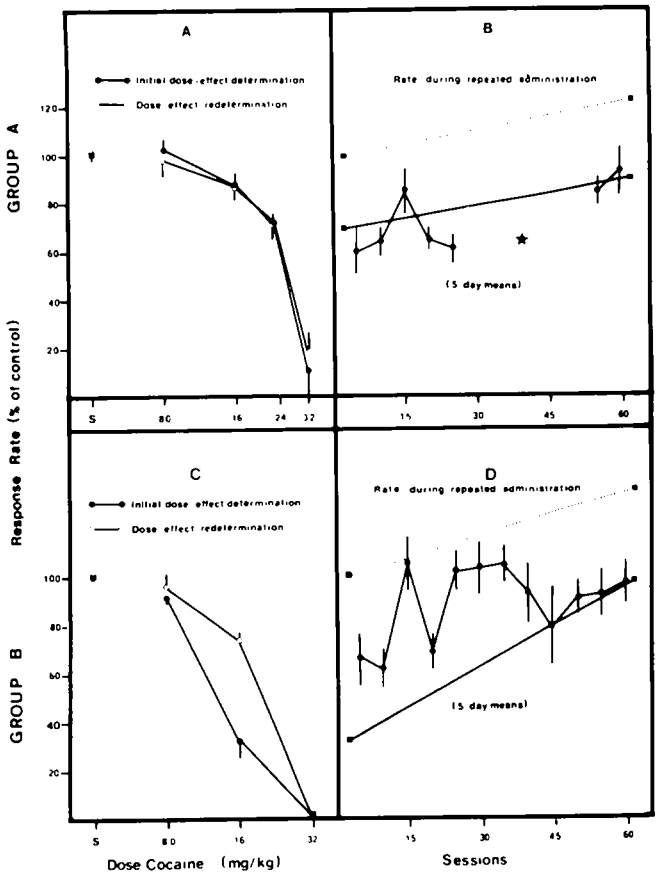

FIG. 3. Upper Left Panel (A): Effects of single injections of cocaine on the overall response rate of rats in Group A before (●——●) and during (○——○) a period of daily injections of cocaine (24 mg/kg). Drug effects on rate are expressed as percent of nondrug control rates. For the initial dose-effect determinations control values were the mean rate following saline injections given between test doses of cocaine (71.6 res/min). For the redeterminations, control rates were the mean response rate following test injections of saline given on Day 61 (88.8 res/min). The points above S represent the effects of saline injection on rate. Vertical lines represent the standard error of the mean. *Upper Right Panel (B):* Effects of repeated administration of cocaine (24 mg/kg) on the mean response rate of rats in Group A during the period of repeated administration of cocaine. Each point is the mean of 5 consecutive sessions. The solid line (■——■) connects the point representating the initial effects of this dose with the point representing the mean rate on Days 59 and 60. The dotted line (■- -■) connects the point representing the initial effect of saline with the point representing the rate observed following saline injections given on Day 61. Control values were the same as in the initial dose-effect determinations.★ Points are omitted. Rat 2 stopped responding due to an abscess in one foot, which was treated with penicillin. He was injected daily but was not tested during this period. *Lower Left Panel (C):* Effects of single injections of cocaine on the overall response rate of rats in Group B before (●——●) and during (○——○) a period of daily injections of cocaine (16 mg/kg). For the initial dose-effect determinations, control values were the mean rate following saline injections given between test doses of cocaine (81.8 res/min). For the redeterminations, control rates were the mean response rate following test injections of saline given on Day 61 (103.5 res/min). The points above S represent the effect of saline on rate. Vertical lines represent the standard error of the mean. *Lower Right Panel (D):* Effects of repeated administration of cocaine (16 mg/kg) on the mean response rate of rats in Group B during the period of repeated administration of cocaine. Each point is the mean of 5 consecutive sessions. The solid line (■——■) connects the point representing the initial effects of this dose with the mean rate of Days 59 and 60. The dotted line (■- -■) connects the point representing the initial effect of saline with the point representing the rate observed following saline injections given on Day 61. Control values were the same as in the initial dose-effect determination.

ing was maximal by about Day 40 and stable thereafter. The average response rate following saline injections was slightly higher on Day 61 than initially (Fig. 5B, dotted line).

In the redetermination of the dose-effect function (Fig. 5A) there was no effect of cocaine (4.0–32 mg/kg) on response rate. Relative to the initial dose-effect function, a two-way analysis of variance revealed a significant interaction between dose and daily treatment indicating nonparallel dose-effect curves before and during daily administration. Further analysis revealed that changes observed at 4.0, 8.0 and 32 mg/kg were not significant due to high variability in the effects of these doses in different rats during the redetermination. However, the decrease in responding observed following 16 mg/kg was significant ($p<0.05$).

Reinforcements per session. In the initial dose-effect determination, single injections of cocaine (4.0–32 mg/kg) decreased the number of reinforcements /session (Fig. 6A). The 4.0 mg/kg dose was not different from saline, while 8.0, 16 and 32 mg/kg all produced decreases in the number of reinforcements per session.

The change in mean number of reinforcements per session over the first 60 days of daily cocaine injections is shown in Fig. 6B. During this period, reinforcements per session increased from 51.1 (± 6.0 SEM) for Days 1–5 to 59 (± 5.4 SEM) for Days 55–60. Furthermore, in the initial dose-effect determinations, reinforcements per session averaged 32.5 (± 2.5 SEM) while an average of 57 (± 9.4 SEM) food pellets were delivered for sessions 59 and 60. The increase in number of reinforcements per session was maximal at about Day 40 and relatively stable thereafter.

When the dose-effect function of cocaine was redetermined (Fig. 6A), there was no effect of dose of cocaine on the number of reinforcements per session. Relative to the initial dose-effect function, a two-way analysis of variance revealed a significant effect of daily treatment and a significant interaction between daily treatment and dose of cocaine ($p<0.05$; $p<0.01$, respectively) indicating nonparallel shifts in the dose effect function during the period of repeated administration. Comparisons of individual points revealed no change in the number of reinforcements per session following injections of saline, 4.0 and 8.0 mg/kg. However, a significantly greater number of reinforcements were delivered at 16 and 32 mg/kg during the dose-effect redeterminations ($p<0.01$ in both cases).

IRT Distributions

Figure 7A shows the effects of single injections of cocaine on the interresponse time distributions in the initial dose-effect determinations. Cocaine produced a dose-dependent shift to the left in IRT's, that is toward shorter non-reinforced IRT's, and more response bursting (i.e., responses with IRT's of less than 2 sec) was observed.

The average IRT distributions for the group during the redetermination of the dose-effect function are shown in Fig.

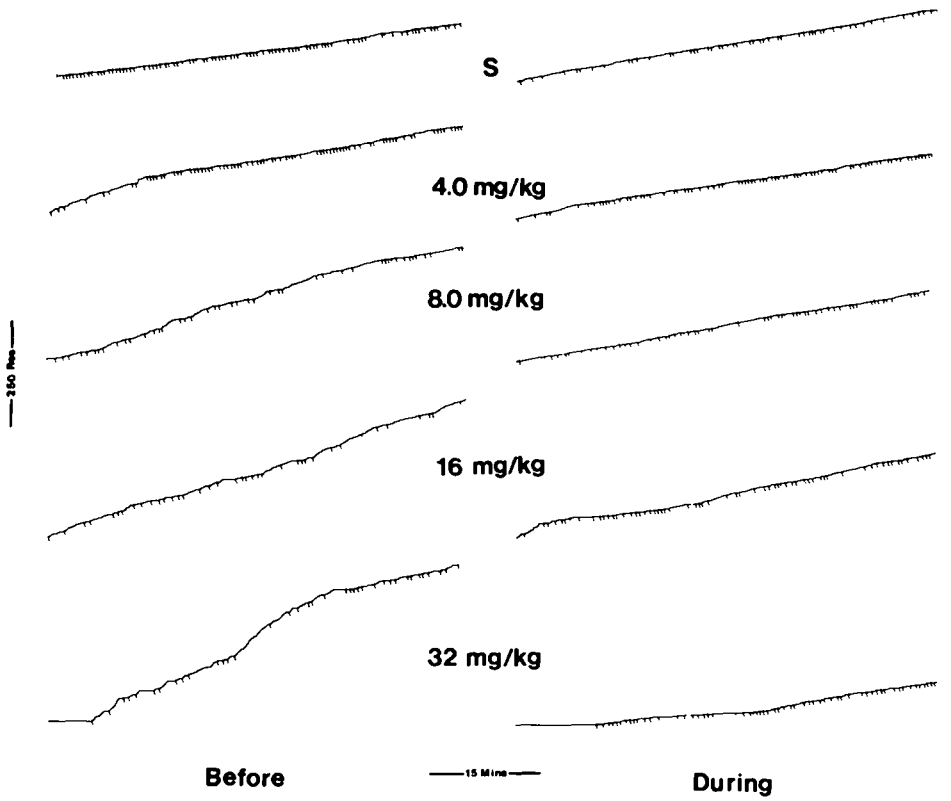

FIG. 4. Cumulative response records for a single rat (No. 3) responding on a DRL 20″ schedule of food delivery. Ordinate: Responses; Abscissa: Time. Diagonal pips represent food delivery. The effects of saline and 4 doses of cocaine on responding are shown. On the left are response records following these doses of cocaine in the initial dose-effect determinations. On the right are response records following these doses of cocaine in the dose-effect redeterminations. The daily dose of cocaine was 16 mg/kg.

7B. Consistent with the response and reinforcement data presented above, there is little noticeable effect of dose of cocaine on the IRT distribution during the redetermination. Relative to the initial dose-effect data, the IRT's following saline injection were shifted slightly to the left as were IRT's following 4.0 mg/kg. Following 8.0 mg/kg, there was some shift in the IRT's toward the 20–22 sec bin, but the percent of IRT's that were reinforced remained the same as was observed initially. Following 16 and 32 mg/kg, there was a distinct shift in the IRT distribution to the right relative to those observed initially indicating a decrease in response bursting and a higher percentage of reinforced IRT's.

DISCUSSION

Single injections of cocaine produced dose-related changes in schedule-controlled behavior in rats. In the animals maintained on a fixed-ratio 40 schedule of food presentation, 8.0 mg/kg cocaine had little effect on responding while higher doses (16 and 32 mg/kg) produced dose-related decreases in response rate. Decreases in rate were found to be the result of a period of no responding early in the session (initial pause), the duration of which was a function of the dose of drug. Further, response rate decreases in two rats (Group B) were also a function of disruption of the fixed-ratio run performance, as measured by running rate. In the two other rats, cocaine had no effect on running rate. That is, once responding began, it continued at control rates. The effects of cocaine on pausing and response rate confirm the effects of cocaine on fixed-ratio performance which have been previously reported [13,20]. On the other hand, DRL responding was increased by doses lower than those producing any effects in the rats responding on an FR 40 schedule. Doses of 4.0, 8.0 and 16 mg/kg all increased DRL responding, while 32 mg/kg decreased responding in some rats responding on the DRL 20″ schedule and increased it in others. Although 32 mg/kg most often eliminated fixed-ratio responding, this effect was never observed on DRL performance. The effects of cocaine on the interresponse time distributions was to shift them to the left, i.e., toward shorter nonreinforced IRT's, and more response bursting was observed.

These data are consistent with the observations of other experimenters who have found the effects of cocaine to depend upon control response rates. Specifically, the response rate decreasing effects of cocaine in animals responding on an FR schedule were the same as reported elsewhere [13,20]. Further, the rate increases found here were similar to those reported by Smith [29] and Barrett [1] using FI schedules. In another experiment using rhesus monkeys and a multiple schedule of food presentation and shock avoidance, rate in-

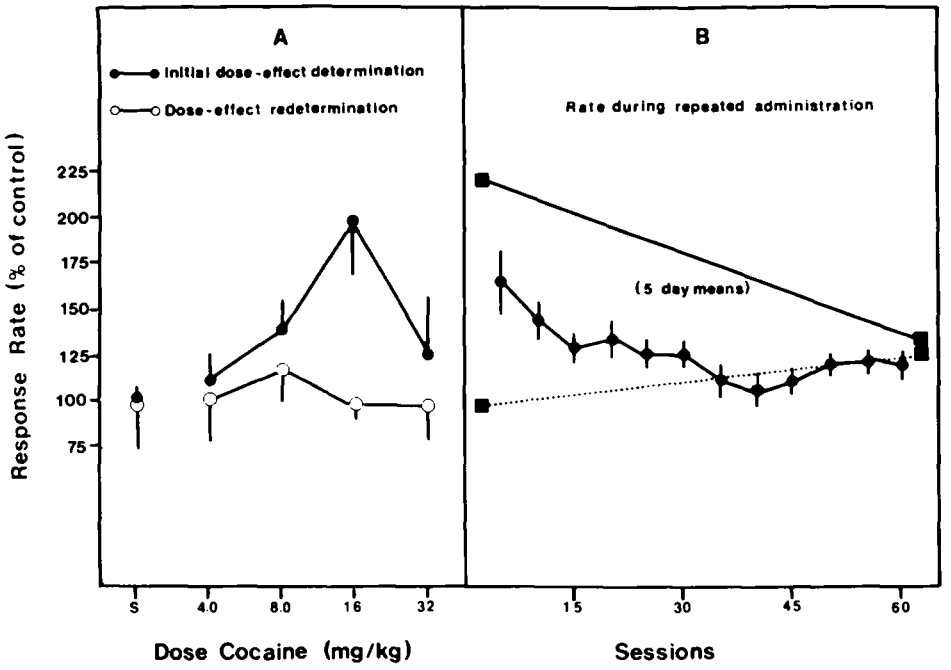

FIG. 5. *Left Panel (A):* Effects of single injections of cocaine on the mean response rate of the rats responding on a DRL 20" schedule for food delivery (N=4) before (●——●) and during (○——○) a period of daily injection of cocaine (16 mg/kg). On the ordinate is reponse rate as percent of control and on the abscissa are doses of cocaine. For the initial dose-effect determination, control values were the mean rate following saline injections given between test doses of cocaine (2.8 res/min). For the redetermination control rate was the mean response rate when saline was given on Day 61 (3.5 res/min). The points above S represent the effects of saline injection on responding. Vertical lines represent the standard error of the mean. *Right Panel (B):* Effects of repeated administration of cocaine (16 mg/kg) on responses/session for these rats (DRL 20" schedule) during the period of repeated administration. Each point is the mean of 5 consecutive sessions. Control value was the same as in the initial dose-effect determination. The solid line (■——■) connects the point representing the initial effect of 16 mg/kg cocaine with the mean rate on Days 59 and 60. The dotted line (■- -■) connects the point representing the initial effect of saline with the point representing the rate following saline injections given on Day 61.

creases were not observed in the DRL component for food following cocaine pretreatment [11]. Possible sources of the difference between these experiments may be the fact that rats were used here rather than rhesus monkeys, the fact that a multiple schedule was used by Johanson rather than a single schedule used here and/or the extended training (more than 1 year) for the rhesus monkeys. Any one or a combination of these factors may have altered the effects of cocaine on behavior in the Johanson study [11].

The effects of cocaine on schedule-controlled responding seen here are very similar to the effects of other psychomotor stimulant drugs described by other investigators. Decreases in the rate of fixed-ratio responding have been observed in animals following the administration of d,l-amphetamine, d-amphetamine, l-amphetamine, methamphetamine and have been seen to be the result of both disruption of the fixed-ratio run and increased pause time [5, 8, 14, 17]. Furthermore, increases in DRL responding with consequent decreases in number of reinforcements delivered and shifts to the left in IRT distributions have been reported following d-amphetamine, methamphetamine and methylphenidate [8, 19, 24, 26].

The repeated administration of cocaine resulted in an attenuation of several of the effects of cocaine on responding. Tolerance developed to the effects of cocaine on the duration of the initial pause in fixed-ratio responding. Two rats (Group B) became tolerant to the effects of cocaine on overall response rate. In these rats not only was pause time decreased but disruption of the fixed-ratio run was attenuated. Although the rats in Group A became tolerant to the effects of cocaine on initial pause, they were not tolerant to the effects on overall response rate. This would seem paradoxical since less pausing should mean more responding and a higher response rate. An explanation for this discrepancy can be found in the fact that cocaine initially increased running rate slightly in these rats, an effect that was attenuated during the period of repeated administration. Thus, although more time was spent responding, running rate was diminished relative to that observed initially resulting in no increase in overall rate.

In the rats responding on a DRL 20" schedule, the repeated administration of 16 mg/kg cocaine resulted in an attenuation of the increase in rate of responding and consequent decrease in number of reinforcements produced initially by this dose. When the dose-effect function was redetermined, tolerance was observed to the effects of 16 and 32 mg/kg on

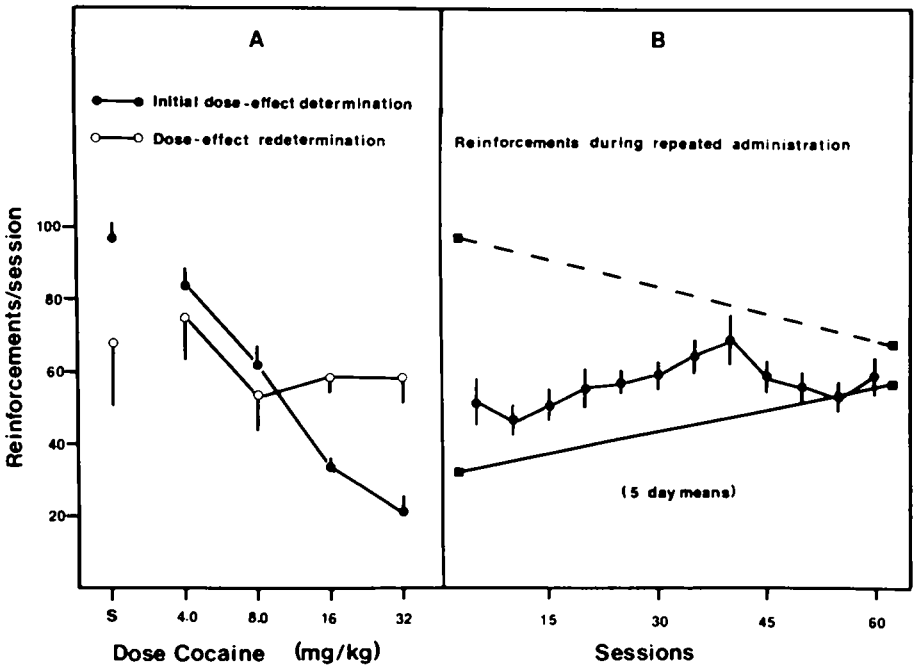

FIG. 6. *Left Panel (A):* Effects of single injections of cocaine on the mean number of reinforcements per session for the rats responding on a DRL 20″ schedule for food delivery (N=4) before (●——●) and during (○——○) a period of daily injections of cocaine (16 mg/kg). On the ordinate are reinforcements per session and on the abscissa are doses of cocaine. The points above S represent the effects of saline injection on number of reinforcements. Vertical lines represent the standard error of the mean. *Right Panel (B):* Effects of repeated administration of cocaine (16 mg/kg) on number of reinforcements/session for these rats (DRL 20″ schedule) during the period of repeated administration. The solid line (■——■) connects the effect of 16 mg/kg cocaine in the initial determination to that observed on Days 59–60. The dotted line (■--■) connects the point representing the initial effect of saline to that observed on Day 61.

these measures. Furthermore, the IRT distributions were shifted to the right at these doses in the redetermination relative to the distributions observed initially. Surprisingly, responding was disrupted in two rats when saline was administered on Day 61, though the average effect of saline was not significantly different from that observed initially. There was also some indication of this effect following 4.0 and 8.0 mg/kg. It may be that after such prolonged exposure to cocaine in the experimental situation, the drug becomes a stimulus necessary for appropriate performance, and that changes from this stimulus (e.g., saline) disrupted responding. Similar effects have been observed elsewhere. Carey [4] reported that when animals trained on a DRL 22″ schedule for 19 days under the influence of 1.0 mg/kg d-amphetamine were tested on Day 20 with saline injections, DRL performance was disrupted. Furthermore, when animals were trained to use drug induced internal states as cues for responding, Overton [16] reported that animals trained in a task in the drug state fail to respond appropriately in the nondrug state.

The present data lend further support to the theory of behavioral tolerance [24]. Animals given cocaine so that it interfered with their ability to meet the contingencies required for food delivery, became tolerant to these effects. It should be pointed out that in the case of the rats which did not become tolerant to cocaine (FR 40 schedule, Group A), the initial effect of the dose that was later administered on a daily basis was only to decrease the number of pellets delivered by 20% whereas, in all other animals, the daily dose (16 mg/kg) initially decreased the number of pellets delivered by at least 50%. However, the fact that rats in Group A received a higher dose of cocaine during the daily injection regimen and that Rat 2 was not tested for a portion of this period may also have contributed to the lack of tolerance development in these rats. Nevertheless, it is interesting to note that the animals that showed tolerance were the same ones that showed a large initial effect of the daily dose on number of reinforcements.

In view of the numerous reports of increased sensitivity to the effects of cocaine on behaviors such as stereotypy [6, 12, 21, 30, 31], it is important to note that in no case was increased sensitivity to cocaine observed in the present experiments. Any changes in sensitivity observed here were all in the direction of tolerance.

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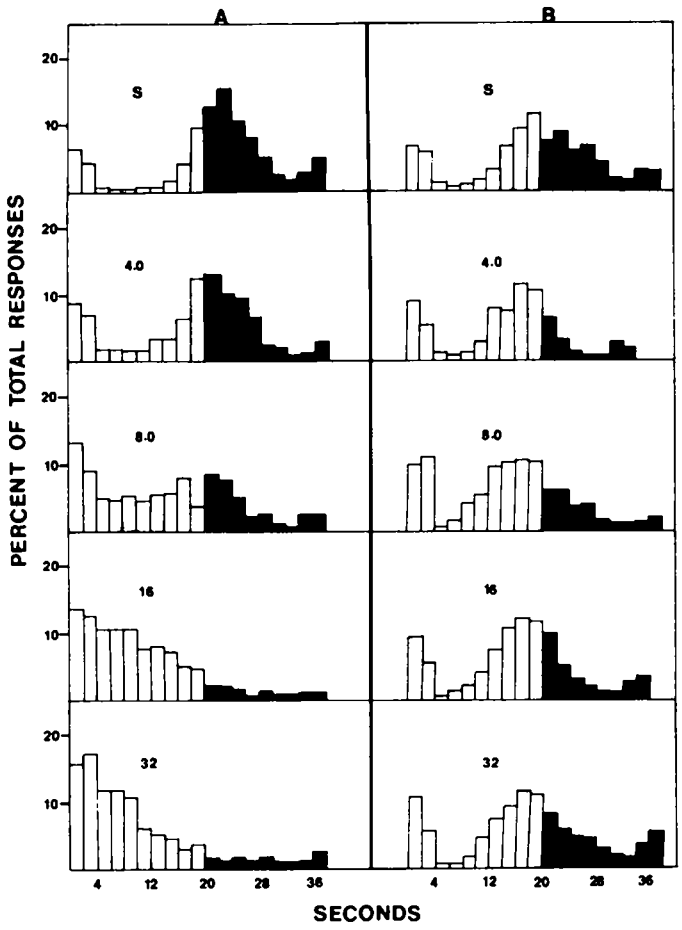

FIG. 7. *Left Panel A:* Effects of single injections of cocaine on the IRT distribution of rats responding on a DRL 20″ schedule for food delivery before the period of repeated administration of cocaine (16 mg/kg). Each IRT histogram is divided into 2 sec bins, the shortest being the percent of total responses that were spaced 0–2 sec, the longest being all responses spaced by more than 36 sec. Each bin contains the percent of the total responses per session that occurred in that bin. Each histogram is the mean of two determinations of the effects of each dose in all 4 rats. The exception is the IRT distribution following saline injection (S) which is the mean of 10 randomly selected sessions with saline pretreatment between test doses of cocaine. Doses of cocaine (mg/kg) are indicated on the left side of each bin. Solid bins are >20″ and represent reinforced IRT's. *Right Panel B:* Effects of single injections of cocaine on the IRT distributions of these rats (DRL 20″ schedule) during the period of repeated administration of cocaine (16 mg/kg). Histograms are as above. Each is the mean of two redeterminations of the effects of each dose in all 4 rats. The exception is the IRT distribution following saline (S) which is the mean of one administration of saline for all 4 rats (Day 61).

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