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BEHAVIOR CONTROLLED BY SCHEDULED INJECTIONS OF COCAINE IN SQUIRREL AND RHESUS MONKEYS[1]

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Rates and patterns of key-press responding maintained under schedules in which responding resulted in intravenous injections of cocaine were studied in squirrel monkeys and rhesus monkeys. Each injection was followed by a 60- or 100-sec timeout period. Schedule-controlled behavior was obtained at appropriate cocaine doses in each species. Under FR 10 or FR 30 schedules, performance was characterized by high rates of responding (usually more than one response per second) in each ratio. Under FI 5-min schedules, performance was characterized by an initial pause, followed by acceleration of responding to a final rate that was maintained until the end of the interval. Under multiple fixed-ratio fixed-interval schedules, rates and patterns of responding appropriate to each schedule component were maintained. Responding seldom occurred during timeout periods under any schedule studied. At doses of cocaine above or below those that maintained characteristic schedule-controlled behavior, rates of responding were relatively low and patterns of responding were irregular. Characteristic fixed-interval responding was maintained over a wider range of cocaine doses than characteristic fixed-ratio responding. Complex patterns of responding controlled by discriminative stimuli under fixed-ratio or fixed-interval schedules can be maintained by cocaine injections in squirrel monkeys and rhesus monkeys.

Key words: drugs, self-administration, cocaine, FI schedules, FR schedules, multiple schedules, key pressing, squirrel monkey, rhesus monkey

Cocaine has marked effects upon various types of behavior. Appropriate doses of cocaine markedly increase locomotor activity in mice or rats; however, higher doses decrease locomotor activity, and patterns of stereotyped behavior develop (Dews, 1953; Fog, 1969; Randrup and Munkvad, 1970; Scheel-Kruger, 1972; Smith, 1965). Studies of the effects of cocaine upon behavior maintained by presentation of food or electric shock in pigeons and monkeys indicate that average rates of responding under fixed-interval (FI) schedules or second-order schedules are increased by cocaine, whereas average rates of responding under fixed-ratio (FR) schedules are decreased by similar doses of cocaine (Barrett, 1975; Gonzalez and Goldberg, 1974; Smith, 1964; Woods and Tessel, 1974). The behavioral effects of cocaine are qualitatively similar to those of acutely administered amphetamine or related psychomotor stimulants.

In recent years, an increasing number of studies have been concerned with the reinforcement of behavior by cocaine injections. It has been demonstrated repeatedly that responding can be engendered and maintained in rats and monkeys under conditions in which responses result in intravenous injections of cocaine (for example, Deneau, Yanagita, and Seevers, 1969; Goldberg, Hoffmeister, Schlichting, and Wuttke, 1971; Pickens and Thompson, 1968; Schlichting, Goldberg, Wuttke, and Hoffmeister, 1971; Woods and Schuster, 1968). Performances under fixed-ratio and fixed-interval schedules of cocaine injection are of particular interest because each of these schedules can maintain patterns of responding that have reproducible characteristics under diverse conditions (Kelleher

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and Morse, 1968). Under fixed-ratio schedules, at parameter values less than 60, performance is generally characterized by high rates of responding (usually more than one response per second) in each ratio. Under fixed-interval schedules, over a wide range of parameter values, performance is generally characterized by an initial period of no responding (pausing), followed by acceleration of responding to a final rate that is sustained until the end of the interval. Usually, only one-quarter of the total number of responses in each interval have been emitted when 50% or more of the interval has elapsed (Gollub, 1964; Herrnstein and Morse, 1957).

Previous studies of fixed-ratio schedules of cocaine injection have shown that there was generally a period of no responding at the beginning of each fixed ratio (initial pause) followed by an abrupt change to a high rate of responding that was maintained until the drug was injected (Downs and Woods, 1974; Goldberg, 1973*a*; Goldberg, Hoffmeister, Schlichting, and Wuttke, 1971; Goldberg, Kelleher, and Morse, 1975; Pickens and Thompson, 1968; Schlichting, Goldberg, Wuttke, and Hoffmeister, 1971). In studies in which the experimental sessions were relatively long and timeout periods did not follow drug injections, initial pauses were longer and mean response rates were much lower under FR 10, FR 30, or FR 50 schedules of cocaine injection than those that characteristically develop under similar schedules of food presentation (for example, Goldberg *et al.*, 1971). When timeout periods have followed injections, characteristically high average rates of responding (more than one response per second), with little or no pausing, have been maintained under FR 10, FR 30, FR 50, schedules of cocaine injection (Goldberg 1973*a*; Goldberg *et al.*, 1975). Previous studies of fixed-interval schedules of cocaine injection suggest that the characteristic pattern of an initial pause followed by acceleration of responding to a final rate that is maintained until the end of the interval can be maintained in the rat (Dougherty and Pickens, 1973), the rhesus monkey (Balster and Schuster, 1973) or the squirrel monkey (Goldberg *et al.*, 1975).

The present experiments investigated performances maintained under fixed-interval, fixed-ratio, and multiple fixed-interval fixed-ratio schedules of cocaine injection in the squirrel monkey and the rhesus monkey. In some experiments, the dose of cocaine was systematically varied. The results indicate that under appropriate conditions, in both species, the development and maintenance of patterns and rates of responding under schedules of cocaine injection are similar to those under comparable schedules involving other consequent events.

METHOD

Subjects and Apparatus

Squirrel monkeys. Five male squirrel monkeys (*Saimiri sciurea*), weighing 600 to 895 g, were generally handled according to procedures reported by Kelleher, Gill, Riddle, and Cook (1963). Surgical procedures for implanting catheters and apparatus were generally similar to those reported by Goldberg (1973*a*) and Herd, Morse, Kelleher, and Jones (1969). During anesthesia with mixtures of halothane and oxygen, under sterile conditions, one end of a polyvinyl chloride catheter (inside diameter 0.38 mm and outside diameter 0.76 mm) was implanted by way of the right or left external jugular vein into the superior vena cava. The distal end of the catheter was passed through the skin in the middle of the monkey's back. The monkeys wore leather jackets at all times to protect the catheters. Each day, the catheters were flushed with saline (0.9% NaCl) and sealed with a stainless-steel obturator.

During experimental sessions, monkeys were individually restrained in a Lucite chair by a waist lock. The chair was enclosed in a sound-attenuating isolation chamber (Model AC-3, Industrial Acoustics Co., Bronx, New York). Extraneous sounds were further masked by continuous white noise. The implanted venous catheter was connected by polyvinyl tubing to a syringe located outside the isolation chamber. The syringe was driven by a 110-V ac motor that could be energized by automatic programming equipment; the motor was held braked by a small dc voltage before and after being energized. Injection duration was approximately 200 msec; volume of each injection was 0.18 ml.

A response key (Lehigh Valley Electronics rat lever, LVE 1352) was mounted on a transparent Lucite wall in front of the monkey. When the monkey pressed the key with a force

of 0.28 N or more, there was an audible relay click and a response was recorded. Two green, two amber, and two red 6-W bulbs, mounted at eye level behind the transparent Lucite wall, could be illuminated and used as visual stimuli. Between experimental sessions, monkeys were kept in individual home cages and had free access to food and water.

Rhesus monkeys. One female and three male rhesus monkeys (*Macaca mulatta*) weighing 4.6 to 6.0 kg were used. The methods were generally similar to those used with squirrel monkeys. The catheter (inside diameter 0.64 mm, outside diameter 1.75 mm) was implanted by way of the right or left internal jugular vein into the superior vena cava. The catheter connections, motor-driven syringe system and injection volume and duration were the same as those used with the squirrel monkey. The monkeys were individually restrained in a Lucite chair by a neck and waist lock (Dews and Herd, 1974). The chair was enclosed in a sound-attenuating isolation chamber (Model AC-5, Industrial Acoustics Co., Bronx, New York), and white noise was continuously present. A response key of the same type used with the squirrel monkeys was mounted on a Lucite strip in front of the monkey at eye level. Two green, two amber, and two white 6-W bulbs were mounted on a transparent Lucite wall 25 cm above the response key. Between experimental sessions, monkeys were kept in the restraining chair and had access to food and water; on weekends the monkeys were kept in individual home cages.

Procedure

The monkeys had been trained to press the key and had responded under various schedules of intravenous cocaine injection before the present study began. The training techniques were generally similar to those described by Goldberg (1973*a*).

Fixed-ratio schedules. In squirrel monkeys, responding was maintained under an FR 10 (S-474) or an FR 30 (S-467) schedule in the presence of a green light. When the fixed-ratio response requirement had been completed, the green light went off, and an intravenous injection occurred with the onset of a 2-sec amber light. A 60-sec timeout period, in which the experimental chamber was dark and responding had no specified consequences, followed presentation of the amber light. Each experimental session lasted 100 min. Initially, performance was studied with injections of 50 μg/kg of cocaine. The dose was subsequently increased and decreased over a range of zero (saline) to 100 μg/kg/injection; each dose was studied for three to six sessions. Squirrel monkey S-474 was then trained under an FR 30 schedule at a dose of 50 μg/kg/injection. Subsequently, the dose was decreased to 25 μg/kg/injection for 10 sessions and 12 μg/kg/injection for six sessions.

In the rhesus monkeys (R-4, R-6, and R-9), fixed-ratio responding was also maintained in the presence of a green light. At the completion of each ratio, the green light went off, and a white light was presented for 2 sec before, and remained on during, the intravenous injection. A 60-sec (R-4 and R-6) or 100-sec (R-9) timeout period followed presentation of the white light. Each experimental session ended after the fiftieth timeout period. After being trained under increasing fixed-ratio response requirements at a cocaine dose of 30 μg/kg/injection, rhesus monkeys R-4 and R-6 were studied under an FR 30 schedule at doses of 30 μg/kg/injection for four sessions and 10 μg/kg/injection for six sessions; R-9 was exposed to a multiple schedule (see below) after only two sessions under the FR 30 schedule.

Fixed-interval schedules. Squirrel monkeys S-467 and S-474 responded under an FI 5-min schedule in the presence of a red light. When each interval was completed, the red light went off, and a cocaine injection occurred with the onset of a 2-sec amber light. A 60-sec timeout period followed presentation of the amber light. Each session ended after the fifteenth timeout period. Initially, performance was studied with injection of 100 μg/kg of cocaine. Subsequently the dose was increased and then decreased over a range of zero (saline) to 200 μg/kg/injection. In squirrel monkeys S-59, S-382, and S-542, responding was maintained under an FI 5-min schedule in the presence of a green light. At the completion of the interval, the green light went off, and an amber light appeared for 2-sec before the first of three cocaine injections, occurring at 10-sec intervals; the amber light remained on until the end of the third injection. A 100-sec timeout period followed presentation of the amber light. Each session ended after the

tenth timeout period. Performances under the fixed-interval schedule were maintained at doses of 3 × 30 μg/kg/injection (S-59 and S-382) or 3 × 100 μg/kg/injection (S-542).

Rhesus monkey R-75 also responded under an FI 5-min schedule. When the interval was completed, the green light went off, and a white light was presented for 2-sec before, and remained on during, the injection of 30 μg/kg of cocaine. A 60-sec timeout period followed each injection. This monkey was initially trained under an FR 1 schedule of cocaine injection and then changed to the FI 5-min schedule.

Multiple fixed-ratio fixed-interval schedules. In squirrel monkey S-467, responding was initially maintained under a multiple schedule composed of an FR 30 component in the presence of a green light and an FI 5-min component in the presence of a red light. Each component ended with an intravenous injection of 50 μg/kg cocaine at the onset of a 2-sec amber light and was followed by a 60-sec timeout period. Each session began with a fixed-interval component; fixed-ratio and fixed-interval components alternated throughout the session. Each session ended after the thirtieth timeout period. The dose of cocaine was increased and then decreased over a range of 6 to 100 μg/kg/injection. Each dose was studied for three to five sessions.

In rhesus monkeys (R-4, R-6, and R-9), the multiple schedule was composed of an FR 10 component in the presence of a green light and an FI 5-min component in the presence of an amber light. Each component ended with a white light presented for 2-sec before, and remaining on during, the injection of cocaine. A 100-sec timeout period followed each component. The session always began with a fixed-ratio component; fixed-ratio and fixed-interval components alternated. Each session ended after the fifteenth timeout period. Rhesus monkeys R-4 and R-6 responded under various fixed-ratio and fixed-interval schedules before being changed to the multiple schedule, whereas R-9 had responded only under fixed-ratio schedules. The doses of cocaine were 30 to 300 μg/kg/injection for R-4, 30 to 600 μg/kg/injection for R-6, and 30 μg/kg/injection for R-9.

Drugs. Cocaine HCl was dissolved in saline (0.9% NaCl). All doses are expressed as the salt.

Analysis of results. Average rates of responding (responses per second) during fixed-ratio, fixed-interval, and timeout periods in each session were computed from digital counters and elapsed-time meters. The total number of responses in each fifth (S-467 and S-474) or each tenth (S-59, S-382, and S-542) of the fixed-interval duration was recorded over the entire session. These data were used to compute quarter-life values. The quarter life, calculated by linear interpolation, is the average time taken to complete the first quarter of the responses in the fixed-interval. This estimated quarter-life value provides an indication of the temporal patterning of responding, which is relatively independent of rate of responding (Gollub, 1964; Herrnstein and Morse, 1957). Responding was also recorded on cumulative response recorders. Average rates of cocaine intake (μg/kg/minute) were computed by dividing total cocaine intake in a session by total time spent in a session including timeout periods.

RESULTS

Fixed-ratio schedules. In both squirrel and rhesus monkeys, characteristic fixed-ratio patterns and rates of responding were maintained in the presence of the green light at appropriate doses of cocaine, whereas responding seldom occurred during timeout periods. In the squirrel monkey, as the dose of cocaine was increased, average rates of responding increased and then decreased, with maximal rates occurring at 25 μg/kg/injection; however, the rate of cocaine intake was directly related to dose over the range of doses studied (Figure 1). Representative cumulative response records show that high rates of responding were maintained throughout most of each session at 25 μg/kg/injection (Figure 2). Lower doses maintained only irregular responding, especially in the early part of each session; with higher doses, periods of no responding became increasingly frequent as the session progressed. In the rhesus monkey, average rates of responding were about the same at the only two doses studied (Table 1); these high rates were maintained throughout each session (Figure 3).

Fixed-interval schedules. Again, in both species of monkeys, characteristic fixed-interval patterns of responding were maintained at

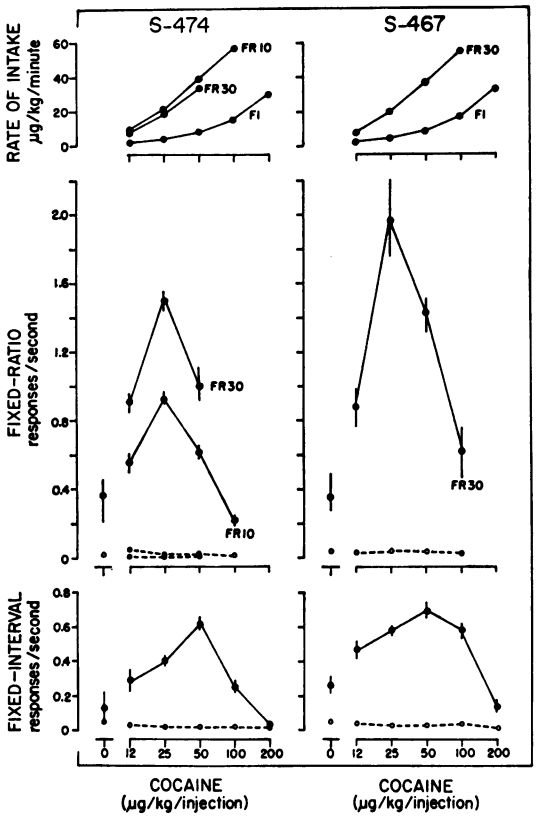

Fig. 1. Effects of cocaine dose on rates of cocaine intake and rates of responding of squirrel monkeys (S-474 and S-467) under fixed-ratio or fixed-interval schedules of cocaine injection. *Upper graphs.* Ordinate: rate of cocaine intake; abscissa: dose of cocaine per injection, log scale. *Middle and lower graphs.* Ordinate: rate of responding; abscissa: dose of cocaine per injection, log scale. Each point is the mean of three observations; vertical lines indicate range of observations. Solid-circles: rates of responding when schedule was in effect; open circles: rates of responding during timeout periods. Note that the rate of cocaine intake was directly related to dose under both schedules; that the maximal rates of responding under fixed-ratio schedules were greater than and to the left of those under fixed-interval schedules; and that responding was near zero during timeout periods.

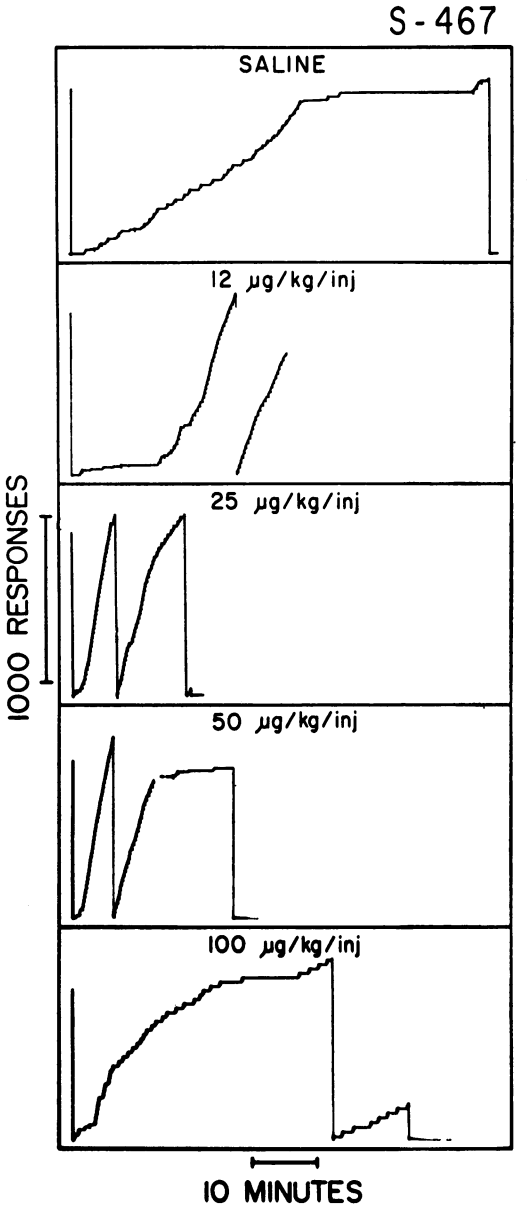

Fig. 2. Representative performances of a squirrel monkey (S-467) under an FR 10 schedule at various doses of cocaine. Ordinate: cumulative responses; abscissa: time. The recording pen reset to the baseline whenever 1100 responses had accumulated and at the end of each experimental session. Short diagonal strokes on the record indicate cocaine injections; the recorder did not run during the 1-min timeout period following each injection. Note the decreased rates of responding in the latter parts of each session as the dose of cocaine was increased.

appropriate doses of cocaine. As the dose of cocaine was increased (squirrel monkeys S-467 and S-474), mean rates of responding increased and then decreased, with maximal rates of 0.6 to 0.7 responses per second at 50 µg/kg/injection (Figure 1). Responding seldom occurred during timeout periods. Rate of cocaine intake was directly related to dose, but increased less rapidly than under the fixed-ratio schedule. Rates of responding in individual fixed-interval components within experimental sessions were more variable than mean rates of responding in different sessions (Figure 4). Such variability in fixed-interval components within

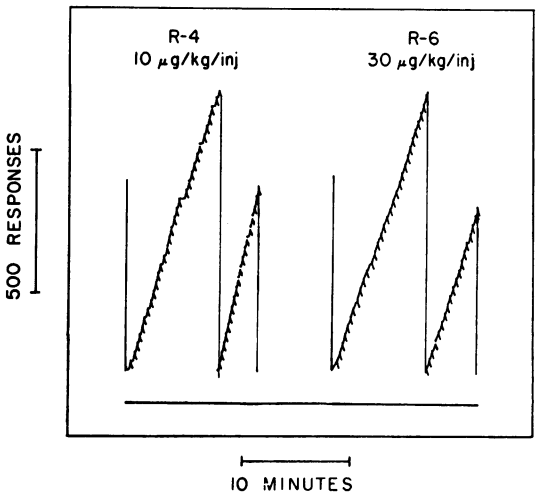

Fig. 3. Characteristic performances of rhesus monkeys (R-4 and R-6) under an FR 30 schedule of cocaine injection. Recording as in Figure 2. Note the brief pause followed by an abrupt change to a high rate of responding in each fixed-ratio component.

Table 1

Mean rates of responding (responses per second ± SE) of rhesus monkeys under an FR 30 schedule of cocaine injection.

	Cocaine μg/kg/injection	
Monkey	*10*	*30*
R-4	1.49 ± 0.17	1.56 ± 0.43
R-6	0.80 ± 0.17	1.10 ± 0.48

an experimental session is commonly observed under fixed-interval schedules of food presentation (Ferster and Skinner, 1957). In another three squirrel monkeys, which had extensive experience under various schedules of cocaine injection, stable patterns of responding were maintained under FI 5-min schedules of cocaine injection (Figure 5). Average quarter-life values ranged from 56% to 65%.

The rhesus monkey developed similar patterns of responding under an FI 5-min schedule of cocaine injection (Figure 6). Average quarter-life value was more than 60%.

Multiple fixed-ratio fixed-interval schedules. As the dose of cocaine was increased in squirrel monkey S-467, mean rates of responding increased and then decreased, with maximal response rates occurring under both schedule components at 50 μg/kg/injection (Figure 7). The ascending and descending limbs of the dose-response curves had steeper slopes under the fixed-ratio schedule than under the fixed-interval schedule. A similar difference was observed when the fixed-ratio and fixed-interval schedules were studied separately (see Figure 1).

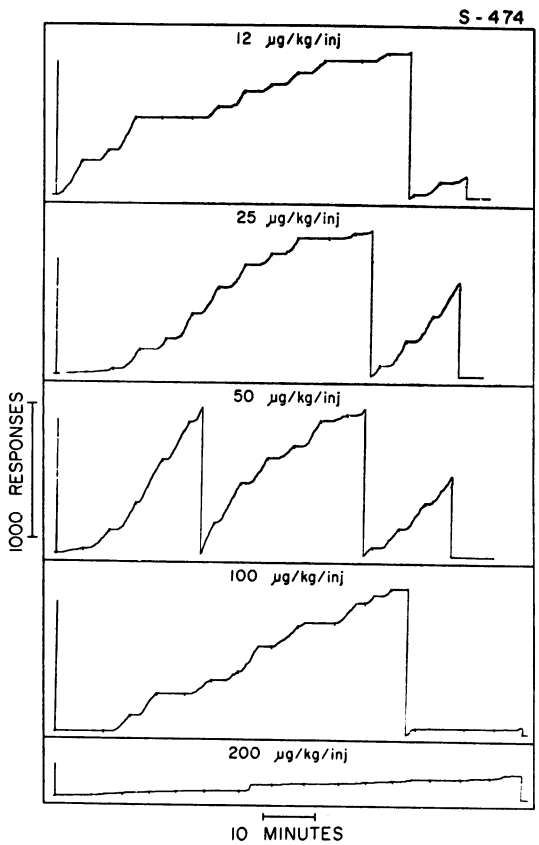

Fig. 4. Effects of cocaine dose on performance of a squirrel monkey (S-474) under an FI 5-min schedule of cocaine injection. Recording as in Figure 2. Note the initial pause followed by increasing responding in most fixed-interval components at 25 or 50 μg/kg/injection of cocaine and the disruption of this pattern at higher doses.

In rhesus monkey R-9, the transition from an FR 30 schedule to a *mult* FR 10 FI 5-min schedule is shown in Figure 8. Responding in the fixed-interval component was initially negatively accelerated (upper frame), then relatively constant throughout each interval (middle frame), and finally was characterized by an initial pause followed by acceleration of responding to a final rate that was maintained until the end of the interval (lower frame). As the dose of cocaine was varied, characteristic performance under the multiple schedule was maintained at 30 or 100 μg/kg/injection with

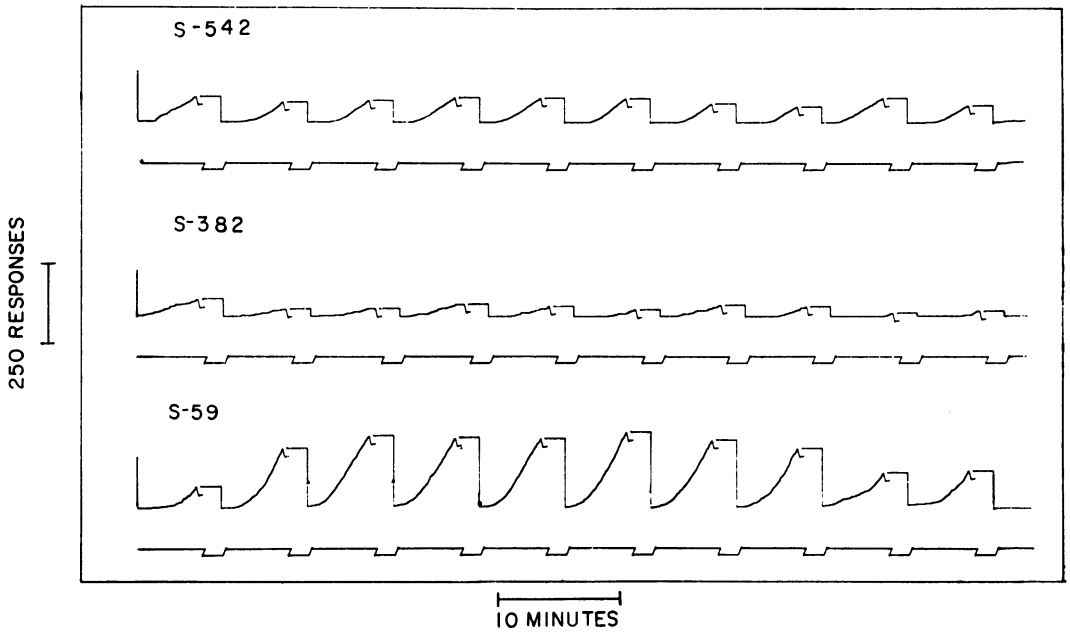

Fig. 5. Characteristic performances of squirrel monkeys (S-542, S-382, and S-49) under an FI 5-min schedule of cocaine injection. Ordinate: cumulative responses; abscissa: time. The recording pen was offset during three successive injections at 10-sec intervals of 100 μg/kg (S-542) or 30 μg/kg (S-382 and S-59) of cocaine and reset to the baseline at the end of the timeout period. The event pen was offset during each 100-sec timeout period.

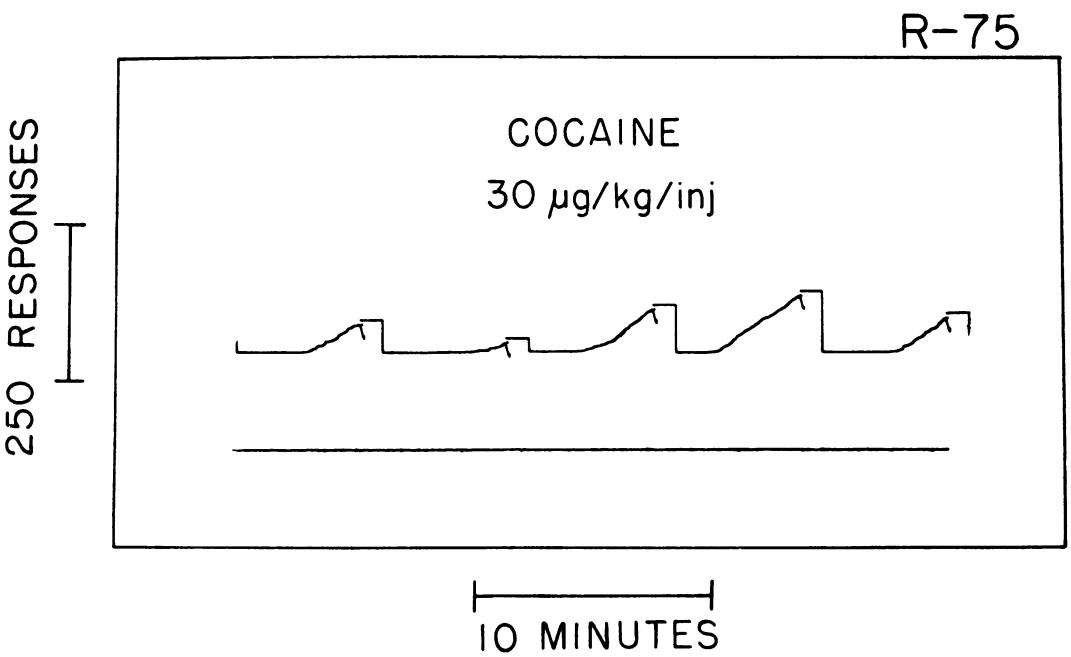

Fig. 6. Characteristic performance of a rhesus monkey (R-75) under an FI 5-min schedule of cocaine injection. Ordinate: cumulative responses; abscissa: time. Each diagonal stroke on the record indicates an injection of cocaine. The recording pen reset to the baseline after the 1-min timeout period that followed each injection.

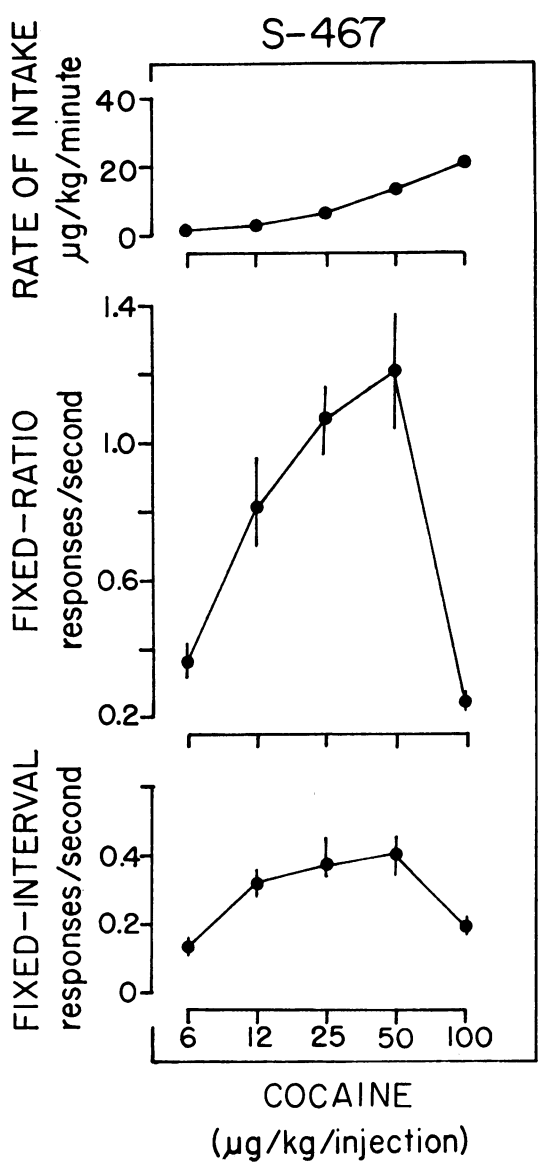

Fig. 7. Effects of cocaine dose on rates of cocaine intake and rates of responding under fixed-ratio and fixed-interval components of a multiple schedule of cocaine injection (squirrel monkey S-467). *Upper graph.* Ordinate: rate of cocaine intake; abscissa: dose of cocaine per injection, log scale. *Middle and lower graphs.* Ordinate: rate of responding; abscissa: dose of cocaine per injection, log scale. Each point is the mean of three observations; vertical lines indicate range of observations. Note that the dose-response curve is flatter for fixed-interval than for fixed-ratio responding.

R-4 and at 30 to 300 μg/kg/injection with R-6 (Table 2). Rates of responding decreased at higher doses for each animal (Figure 9).

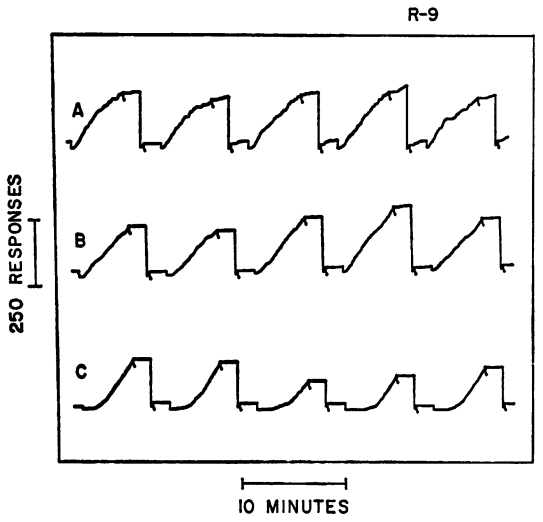

Fig. 8. Performance of a rhesus monkey (R-9) during the transition from an FR 30 schedule to a *mult* FR 10 FI 5-min schedule of cocaine injection. Records A, B, and C show the first, second, and twelfth sessions on the multiple schedule. Ordinate: cumulative responses; abscissa: time. Short diagonal strokes on the record indicate injections of cocaine (30 μg/kg). Each injection was followed by a 100-sec timeout period. The recording pen reset to the baseline at the end of each timeout period. Note the change in fixed-interval performance from negatively accelerated to positively accelerated responding with increasing exposure to the multiple schedule.

DISCUSSION

Schedule-controlled patterns of responding can be highly reproducible under diverse conditions and are of particular interest because comparable performances can be maintained in different species by a variety of consequent events. In the present experiments, the fixed-interval patterns of responding maintained by intravenous injections of cocaine were comparable to previously reported fixed-interval patterns of responding maintained in various species by presentation of food or water (Kelleher and Morse, 1968) and in squirrel monkeys by presentation of electric shock (McKearney, 1968, 1969), or by termination of a stimulus associated with occasional electric shocks (Kelleher and Morse, 1964; Morse and Kelleher, 1966). Also, the rates and patterns of fixed-ratio responding that were maintained by intravenous injection of cocaine in the present experiments and some previous experiments (Downs and Woods, 1974; Goldberg, 1973*a*; Goldberg *et al.*, 1975) were comparable to previously reported rates and pat-

Table 2

Effects of cocaine dose on rates of responding (responses per second ± SE) of rhesus monkeys under a *mult* FR 10 FI 5-min schedule of cocaine injection.

Monkey	Schedule Component	Cocaine (μg/kg/injection) 30	100	300	600
R-4	FR	1.93 ± 0.25	2.13 ± 0.36	0.04 ± 0.01	–
	FI	0.24 ± 0.03	0.20 ± 0.01	0.08 ± 0.01	–
R-6	FR	0.86 ± 0.17	0.78 ± 0.04	1.07 ± 0.09	0.35 ± 0.09
	FI	0.50 ± 0.06	0.42 ± 0.04	0.52 ± 0.05	0.40 ± 0.08

terns of fixed-ratio responding maintained in various species by presentation of food or water and in squirrel monkeys by termination of a stimulus associated with occasional electric shocks (Kelleher and Morse, 1964; Morse and Kelleher, 1966). Thus, injections of cocaine can be included among the various consequent events that can maintain comparable performances when they are scheduled in comparable ways.

As with other consequent events, the scheduling of cocaine injections in different ways engenders different rates and patterns of responding. In the present experiments, injections of cocaine maintained high steady rates of responding under fixed-ratio schedules; moderate rates of responding were maintained under fixed-interval schedules, and performance was characterized by an initial pause followed by acceleration of responding to a

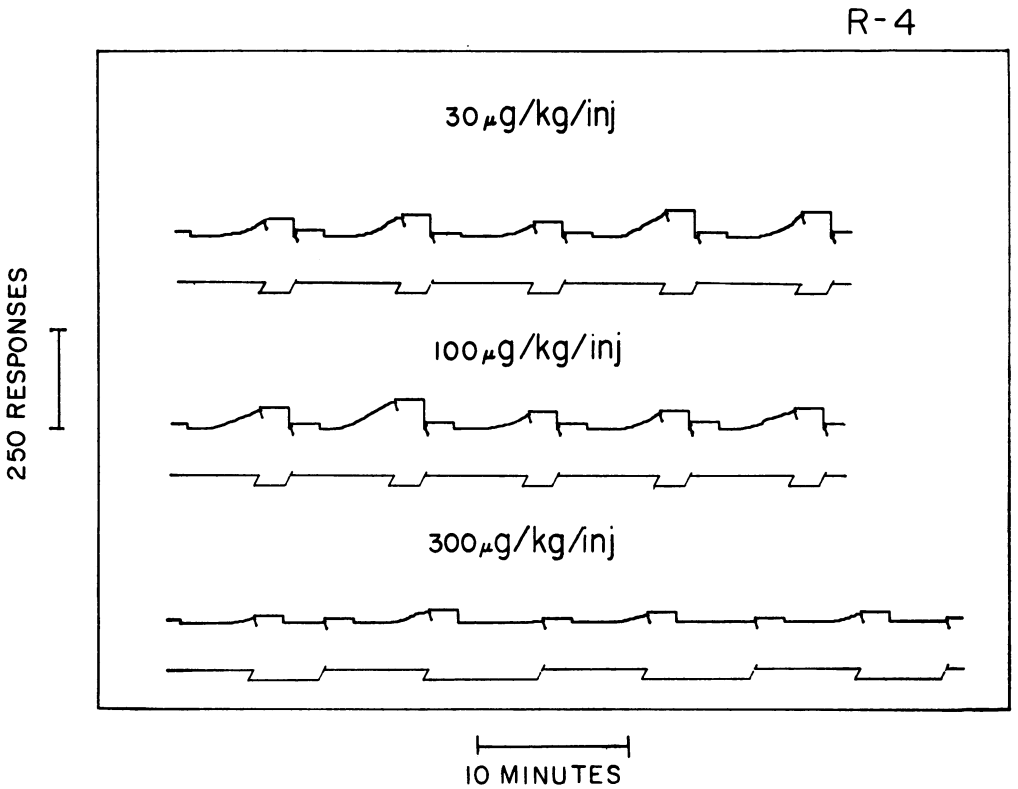

Fig. 9. Representative performances of a rhesus monkey (R-4) under a *mult* FR 10 FI 5-min schedule at various doses of cocaine. Ordinate: cumulative responses; abscissa: time. Short diagonal strokes on the cumulative record indicate cocaine injections. The recording pen reset to the baseline at the end of the 100-sec timeout period following each injection. The event pen remained offset during the timeout period after each fixed-interval component and during the next fixed-ratio component. Note the decrease in fixed-ratio responding at 300 μg/kg/injection.

final rate that was sustained until the end of the interval. Moreover, depending on whether the discriminative stimuli associated with the fixed-ratio schedule or the discriminative stimuli associated with the fixed-interval schedule were present under the multiple schedule, these different performances alternated repeatedly in individual monkeys within each session, indicating both stimulus control and schedule control of responding. The present results provide further evidence that the way behavior is controlled by consequent events may depend more upon the schedule than the type of event maintaining the behavior.

Balster and Schuster (1973) studied rhesus monkeys responding under an FI 9-min schedule of intravenous cocaine injection, with 15-min timeout periods separating successive fixed-interval components and with responding in every fourth fixed-interval component being maintained by food presentation. Quantitative indices of fixed-interval curvature and representative cumulative response records in their study indicate that characteristic fixed-interval performances were maintained at doses varying from 50 to 200 μg/kg/injection. In the present study, characteristic performances under FI 5-min schedules were maintained in rhesus monkeys over a similar range of cocaine doses. Balster and Schuster also found that mean response rate of one rhesus monkey increased as dose was increased from 25 to 800 μg/kg/injection, whereas mean response rate of a second rhesus monkey increased as dose was increased from 25 to 400 μg/kg/injection, but sharply decreased when dose was increased to 800 μg/kg/injection; higher doses were not studied. Although changes in cocaine dose had similar effects in both the Balster and Schuster experiments with rhesus monkeys and the present experiments with squirrel and rhesus monkeys, the range of doses over which mean fixed-interval response rates increased was greater in the Balster and Schuster experiments. This difference can probably be attributed to differences in frequency of cocaine injection. In the Balster and Schuster study, the maximum frequency of injection was about once per 32 min. In the present study with rhesus monkeys, the fixed interval was a component of a multiple schedule in which the maximum frequency of injection was almost once per 4 min.

As the dose of cocaine per injection was increased, mean rate of responding first increased and then decreased under the fixed-ratio schedules, the fixed-interval schedules, and the multiple schedules. In other experiments, key-press responding has been maintained by such diverse events as presentation of heat to subjects in a cold environment (Weiss, 1957; Weiss and Laties, 1960), electrical stimulation of the brain (Olds, Travis, and Schwing, 1960; Plutchik, McFarland, and Robinson, 1966; Reynolds, 1958), presentation of food (Goldberg, 1973*a*), and intravenous injection of drugs (for example, Goldberg, 1973*a;* Woods and Schuster, 1968). In each case, response rate increased and then decreased as the parameter of the event maintaining behavior was increased. Increasing response rates with increases in parameter of different consequent events may simply reflect the need for some minimal dose or amount of the event to maintain optimal responding. It would be wrong, however, to assume that decreases in response rate with further increases in the parameter of different consequent events necessarily reflect common processes. For example, when the amount of cocaine injected or food presented is relatively large under fixed-ratio schedules, similar progressive decreases in responding occur during each session (Goldberg, 1973*a*). It seems likely, however, that the cumulative dose of cocaine would disrupt behavior controlled by other events, such as termination of a stimulus associated with electric shock, whereas the cumulated food intake would not. The precise mechanisms underlying changes in response rates as a function of changes in the parameter of the consequent events remain to be determined.

Performances under fixed-ratio schedules were more markedly altered by changes in dose of cocaine than were performances under fixed-interval schedules. Under the fixed-ratio schedules, frequency of injection was directly related to rate of responding up to a maximum of almost once per minute. In contrast, under the FI 5-min schedule, frequency of injection was relatively independent of rate of responding and could reach a maximum of only once per 6 min. Thus, the relatively high sensitivity of fixed-ratio performances to changes in dose of cocaine probably depend in part on the greater dependence of rate of cocaine intake on rate of responding.

That schedule factors other than rate of cocaine intake are also important in determining these functions is suggested by the results obtained with multiple schedules. Although the alternation of fixed-interval and fixed-ratio components in these schedules results in a similar average rate of cocaine intake under each schedule, fixed-ratio rates of responding were again more readily affected than fixed-interval rates of responding by changes in dose of cocaine. In the squirrel monkey, for example, under the multiple schedule, where fixed-interval and fixed-ratio components alternated—resulting in similar average injection frequencies—changes in injection dose of cocaine also produced greater changes in fixed-ratio response rates than in fixed-interval rates. Increasing cocaine dose from 12 to 50 μg/kg/injection increased fixed-ratio response rate about 50% but increased fixed-interval response rate only 25%; an increase in cocaine dose from 50 to 100 μg/kg/injection decreased fixed-ratio response rate about 80% but decreased fixed-interval response rate only 50%. Although overall rate of cocaine intake was the same under each component of the multiple schedules, there may have been local effects of the cocaine injections that were greater during fixed-ratio components because the duration of exposure to the fixed-ratio component was usually much shorter than to the fixed-interval component.

Further evidence that the schedule of drug injection can be an important determinant of the functions relating injection dose to response rate is provided by comparisons of the present results under fixed-interval schedules of cocaine injection with previously reported results under second-order fixed-interval schedules of cocaine injection. Goldberg (1971; 1973*a*, *b*) and Goldberg *et al.* (1975) studied responding of squirrel monkeys under a second-order schedule in which every FR 20 or FR 30 component completed during a 5-min fixed interval produced only a brief 2-sec light; the first fixed-ratio component completed after the 5-min interval ended produced both the brief light and an intravenous injection of cocaine. As in the present fixed-interval experiments, each injection was followed by a 1-min timeout and each session ended after 15 injections. Consequently, injection frequency was virtually identical under the two schedules. However, the optimal dose of cocaine for maintaining high response rates was 100 to 200 μg/kg/injection under the second-order schedule studied by Goldberg (1971; 1973*a*, *b*) and Goldberg *et al.* (1975), but was only 50 μg/kg/injection under the present fixed-interval schedule. Thus, both the schedule relating behavior to consequent injections of drug and the dose of drug injected exert powerful control over rates and temporal patterns of drug-maintained behavior.

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