*DIFFERENTIAL EFFECTS OF COCAINE AND
PENTOBARBITAL ON FIXED-INTERVAL AND
RANDOM-INTERVAL PERFORMANCE*

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Reports have indicated that the behavioral effects of a drug can be related to the nondrug control rate of behavior in the absence of the drug. To investigate the purported relationship between control rate and drug rate, squirrel monkeys were trained under a fixed-interval 300-s schedule of stimulus-shock termination, a procedure that engendered a wide range of response rates. A light illuminated the experimental chamber during the fixed interval, and the first lever press after 300 s had elapsed terminated the light for 30 s and precluded an electrical stimulus to the tail. Following acute intramuscular administration of cocaine (0.03–0.56 mg/kg), overall rate increased and different control rates of responding, during different parts of the fixed interval, converged toward a common rate. Subsequently, the schedule was changed to a multiple fixed-interval 300-s random-interval 300-s schedule; performance during the random-interval component was characterized by steady responding at a uniformly high rate. Analysis of fixed-interval and random-interval performances following acute cocaine administration revealed convergence of response rates toward a common, uniform rate. Pentobarbital (0.3–10.0 mg/kg) only decreased overall rate, and different control rates of responding during the fixed interval did not converge toward a common rate. The results indicate that this type of analysis can be useful in comparing pharmacological agents from different classes and that the rate at which responding becomes uniform can provide a quantitative behavioral end point for characterizing drug effects on behavior.

Key words: fixed-interval schedules, random-interval schedules, stimulus-shock termination schedule, rate constancy, cocaine, pentobarbital, lever press, squirrel monkeys

Studies have indicated that the behavioral effects of a drug can differ depending on a number of variables, including the frequency of occurrence of the behavior in the absence of the drug. A relationship between drug effect (defined as a proportional change in rate) and control rate of responding has been reported, whether one examines overall response rates in the same subjects responding at different rates under different reinforcement schedules or local rates within a given schedule-controlled performance (McKearney & Barrett, 1978; Sanger & Blackman, 1976). In a recent study (Howell, Byrd, & Marr, 1986), the manner in which cocaine altered local response

rates during fixed-interval (FI) performance was used to quantitate the relationship between control response rate and drug rate. Following cocaine (0.03–0.56 mg/kg) administration, overall response rate increased, the pause at the beginning of the interval was shortened, and the pattern of positively accelerated responding engendered by the FI schedule became less curvilinear. A dose of 0.56 mg/kg produced a relatively uniform rate of responding during the interval, and a higher dose (1.0 mg/kg) caused a disruption of performance and a subsequent decrease in response rate. When white noise was presented continuously during a session, local response rates during the FI also converged toward a common rate and, at an appropriate intensity (80 or 90 dB), response rate became uniform. However, an obvious difference between the effects of cocaine and white noise was the rate at which responding became uniform. For all subjects, white noise produced a uniform rate that was greater than that obtained for cocaine. The results indicated that a uniform rate could be produced by drug and nondrug stimuli, and that the rate at which responding became most

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nearly uniform depended upon the type of stimulus being presented.

In the present study we investigated whether contextual effects or the manner in which control rate was engendered could modulate the value of the uniform rate obtained following cocaine administration. Fixed-interval performance was used to study rate-related drug effects because FI schedules typically engender a wide range of local response rates; cocaine, a central nervous system stimulant, was used because of its ability to produce a wide range of changes in FI performance (Byrd, 1979; Howell *et al.*, 1986). Subsequently, a multiple FI 300-s random-interval (RI) 300-s schedule was used to engender different rates and patterns of responding in the presence of different discriminative stimuli. Comparison of the effects of cocaine during the FI 300-s schedule alone and during the FI 300-s schedule when it was a component of the multiple schedule served to determine whether contextual effects could modulate the value of the uniform rate. Moreover, comparison of FI and RI performance during the multiple FI RI schedule served to determine whether the value of the uniform rate depended upon the manner in which control rate was engendered. In addition, two types of behaviorally active substances, cocaine and pentobarbital, were administered to permit comparisons between drugs from two different pharmacological classes.

METHOD

Subjects

Three adult male squirrel monkeys (*Saimiri sciureus*), S-74, S-75, and S-77, were housed individually and provided free access to food and water. All were behaviorally experienced subjects (Howell, Byrd, & Marr, 1983), but none had been used previously in drug experiments.

Apparatus

Daily experimental sessions were conducted within a ventilated, sound-attenuating chamber with each monkey seated in a Plexiglass chair (Byrd, 1979). Illumination could be provided by three pairs of 7-W ac colored lights (red, white, and blue) mounted on the front wall of the chair just above eye level. A response lever (Coulbourn Instrument Co., No.

E21-03) mounted on a wall facing the monkey registered a response and operated a feedback relay when depressed downward with a force greater than 0.20 N. The subject's tail was held motionless in a small stock, and two brass electrodes rested on a shaved portion near the end. A 650-V ac source was used to deliver a 6-mA electric shock of 200 ms duration, and electrode paste (EKG Sol) applied to the tail minimized changes in impedance between the tail and the electrodes. A TRS-80 Model I® microcomputer controlled experimental events, and recorded and analyzed data as described previously (Howell *et al.*, 1983; Mapou, Borowiec, Richards, & Byrd, 1984). Sessions were conducted 5 days per week; each session lasted 2 hr during initial training and 1 hr during the experimental procedures. Continuous white noise and an exhaust fan masked extraneous sounds during all sessions.

Drug Administration

Cocaine hydrochloride (National Institute on Drug Abuse, Rockville, Maryland) and pentobarbital sodium (Abbott Laboratories, Chicago, Illinois) were dissolved in sterile distilled water for injection, and doses were determined in terms of the salt. Sterile sodium chloride (saline) solution (0.9%) was used for control injections. All injections were made intramuscularly in the thigh in a volume of 0.4–0.6 mL approximately 5 min before the beginning of each session. Doses of 0.03, 0.1, 0.3, 0.56, and 1.0 mg/kg cocaine and doses of 0.3, 1.0, 3.0, 5.6, and 10.0 mg/kg pentobarbital were studied at least twice in each monkey. All doses of cocaine were administered and studied before initiating experiments with pentobarbital. Drug doses were administered in a mixed sequence with at least 3 days intervening between successive administrations of the drug; saline (control) injections were administered once per week.

Procedure

Subjects were trained under an FI 300-s schedule of stimulus-shock termination (Morse & Kelleher, 1966) with a 3-s limited hold. A red light illuminated the experimental chamber during the interval and, after 300 s elapsed, the animal had 3 s to press the lever and terminate the stimulus that was associated with an impending electric shock. If the animal pressed the lever and avoided the shock, a white

light was illuminated for 2 s followed by a 30-s timeout period during which the chamber was darkened and responses had no consequences. In the absence of a response during the 3-s period, a shock was delivered followed by a 30-s timeout. A session consisted of 10 consecutive FI 300-s components, each followed by a 30-s timeout. Response rates and interresponse times (IRTs) were recorded separately for each of the 10 components. Subsequently, subjects were trained under a multiple FI 300-s RI 300-s schedule of stimulus-shock termination to engender different rates and patterns of responding in the presence of different discriminative stimuli. The chamber was illuminated by red and blue lights during the FI and RI components, respectively. The FI 300-s component of the multiple schedule was the same as that described previously. Interval values during the RI component were determined by a random probability generator that produced values with a constant probability ranging from 1 s to infinity and a mean interval value equal to 300 s. Both components of the multiple schedule had a 3-s limited hold, and a 2-s white light was presented when shock was avoided. Each session began with the FI 300-s component, followed by a 30-s timeout. Subsequently, the RI component was in effect for 300 s, followed by a 30-s timeout. The FI and RI components alternated until each component had been scheduled five times, and a 30-s timeout was scheduled between each component. Response rates and IRTs were recorded separately for each component.

RESULTS

Data Analysis

Characteristic performance before and after drug administration was derived from analysis of individual sessions exclusive of the first two and last two components of each session. Variations in responding during the initial two components of a session (presumably attributable to cocaine absorption and distribution) and during the final two components (presumably due to elimination and clearance) prompted exclusion of these components from data analysis. Warm-up effects were observed consistently in Subject S-77 during exposure to the multiple FI RI schedule and were observed occasionally in Subjects S-75 and S-74 during exposure to the FI schedule. A cu-

mulative record of responding during the FI schedule for Subject S-77 shows the variation due to drug onset and recovery following administration of 1.0 mg/kg cocaine (see Figure 1). A consistent peak drug effect following this high dose was not maintained throughout the entire session. Response rate during the first component and during the end of the session was more typical of performance following administration of 0.1–0.56 mg/kg cocaine. Also, the cumulative record of control performance during the multiple FI RI schedule for Subject S-77 shows that response rate during the first FI was greater than response rate during subsequent FIs (see Figure 5). Although pentobarbital's duration of action was sufficiently prolonged so that the data analysis could include the last eight components, only Components 3 through 8 were used so that direct comparison between the effects of pentobarbital and cocaine could be made without confounding caused by session duration.

Representative cumulative records and IRT distributions were selected by the following criteria. For individual subjects, saline sessions were selected that most closely approximated the mean rate obtained for all administrations of saline. The same criterion applied when a drug dose was administered on three occasions; sessions were selected that most closely approximated the mean rate obtained for all administrations of that dose. When a dose was administered only twice, representative sessions were selected randomly.

FI Control Performance

Control performance under the FI 300-s schedule was characterized by little or no responding early in the interval and increasing response rates as the interval elapsed. Figure 1 shows cumulative records for Subject S-77 typical of performance under the FI schedule during control (saline) sessions (top left). Mean response rates during control sessions for Subjects S-74, S-75, and S-77 were 0.61, 0.30, and 0.38 response per second, respectively.

Effect of Cocaine on FI Performance

Response rates increased following drug administration (0.1–0.56 mg/kg), and the pattern of positively accelerated responding engendered by the FI schedule changed to more uniform or steady responding throughout the interval as dose increased. Figure 1 shows cu-

Fig. 1. Cumulative records of lever pressing that display effect of cocaine dose on pattern of responding under an FI 300-s schedule of stimulus-shock termination in a squirrel monkey (Subject S-77). Pen deflection on the time axis (lower horizontal tracing) indicates end of interval. The response pen reset after 500 responses, upon completion of the FI, and upon termination of a 30-s timeout scheduled between intervals. The cumulative record did not advance during timeout.

mulative records for Subject S-77 typical of performance following three doses of cocaine. A dose of 0.56 mg/kg produced a relatively constant rate of responding during each interval, and a higher dose (1.0 mg/kg) caused a disruption of performance and a subsequent decrease in response rate.

A plot of mean response rate versus dose characterized the range of doses having effects (Figure 2, left). For a given dose, the response rate during each FI component was calculated and then combined by averaging across FI components during a session. Mean response rate was plotted on the y axis, and drug dose was plotted on the x axis using a logarithmic scale. The lowest dose of cocaine (0.03 mg/kg) had little effect on mean response rates, and intermediate doses (0.1–0.56 mg/kg) increased rates for all subjects. The maximum rate increase occurred at a dose of 0.56 mg/kg for Subjects S-75 and S-77 and at 0.1 mg/kg for Subject S-74. The highest dose (1.0 mg/kg) decreased responding below maximum

rates for all subjects. However, only Subject S-74 showed a decrease below control rate at a dose of 1.0 mg/kg.

The time between successive responses (IRTs) was recorded in sequence for each experimental session, and then the IRTs were grouped into 41 bins according to duration. The 41st bin included all IRTs that exceeded the upper limit of the 40th bin. Because of the lower response rate of Subject S-75, a larger bin width was chosen to provide comparable spread of the IRT distributions for all subjects. Figure 3 presents IRT distributions for FI components combined during selected sessions. Each distribution was derived from a single session. The top panel shows the shape of the IRT distribution typical of performance during control sessions. The distribution was widespread, corresponding to the wide range of local response rates typical of FI performance. Following administration of 0.1 mg/kg cocaine, there was a shift toward briefer and more uniform IRTs, and the relative fre-

Fig. 2. Effect of cocaine dose on mean response rate during the FI schedule alone (left) and during the multiple FI RI schedule (right) for individual subjects. Mean rate obtained following drug administration was based on two or three observations at each dose. Mean rate obtained following saline (S) administration was based on five or more observations. Bars indicate $\pm$ standard deviation.

Fig. 3. Effect of cocaine dose on interresponse time (IRT) distributions for individual subjects. Each distribution was derived from a representative session. *X* axis values are the upper bounds of the class intervals. *N* = total number of responses emitted for each distribution.

quency of IRTs that exceeded the upper limit of the 40th bin was greatly diminished (center panel). The shift in distribution was greatest after a dose of 0.56 mg/kg (bottom panel), and maximum uniformity in IRTs was observed after this dose.

Figure 4 presents data from Subject S-77

that characterize changes in the relation between drug rate and control rate as dose increased. Response rates during each of 10 successive 30-s segments of each FI were calculated and then combined across the session by averaging FI components. Drug rate for each segment was plotted against control rate for

Fig. 4. Effect of cocaine dose on mean response rate during individual 30-s segments of a 300-s FI schedule for Subject S-77. Response rate during a given 30-s segment when cocaine was administered (drug rate) is plotted as a function of response rate during that segment when saline was administered (control rate). Regression lines were fitted by the method of least squares. The broken diagonal line represents saline (control) data. The upper left panel shows regression lines for all doses. The remaining panels show data points for each segment and the best-fit linear regression line for individual doses.

S-77

Table 1

Effects of cocaine and pentobarbital on fixed-interval performance. Response rate corresponds to the mean rate of responding (response per second) during a session. The slope and the coefficient of variation (r^2) were derived from the linear regression analysis of local response rates during 30-s segments of the FI 300-s schedule.

Dose	S-74			S-75			S-77		
	Rate	Slope	r^2	Rate	Slope	r^2	Rate	Slope	r^2
FI (only)									
Saline	0.61	1.0	—	0.30	1.0	—	0.38	1.0	—
Cocaine (mg/kg)									
0.03	0.64	0.79	0.94	0.28	0.91	0.95	0.67	0.72	0.98
0.1	0.94	0.67	0.93	0.48	0.46	0.98	0.95	0.51	0.90
0.3	0.87	0.44	0.90	0.53	0.21	0.98	1.42	0.15	0.94
0.56	0.76	0.11	0.85	0.60	0.15	0.77	1.55	0.02	0.25
1.0	0.39	0.06	0.50	0.51	0.04	0.20	0.73	-0.01	0.10
FI (multiple)									
Saline	0.60	1.0	—	0.33	1.0	—	0.41	1.0	—
Cocaine (mg/kg)									
0.03	0.79	0.62	0.84	0.30	0.51	0.85	0.51	1.21	0.94
0.1	0.94	0.47	0.76	0.43	0.42	0.74	0.65	0.66	0.99
0.3	0.94	0.20	0.59	0.56	-0.04	0.04	1.75	-0.02	0.27
0.56	0.81	0.03	0.02	0.51	0.07	0.40	1.58	-0.04	0.69
1.0	0.34	0.17	0.24	0.38	0.06	0.12	1.21	-0.06	0.51
Pentobarbital (mg/kg)									
0.3	0.66	0.73	0.64	0.23	1.07	0.66	—	—	—
1.0	0.59	0.66	0.60	0.20	1.13	0.55	0.32	0.85	0.97
3.0	0.11	—	—	0.03	—	—	0.28	0.33	0.81
5.6	0	—	—	0	—	—	0.27	0.26	0.82
10.0	—	—	—	—	—	—	0	—	—

that segment on logarithmic axes, and a linear regression line was determined using a least-squares estimate. Control rate for each segment was the average of all saline sessions. A diagonal line with a slope equal to one indicated no change from control sessions; a horizontal line with a slope equal to zero indicated that response rate was constant throughout the FI. A regression line was plotted for each dose to quantitate changes in responding due to cocaine administration. In addition, a coefficient of variation (r^2) was computed for each regression line to determine the strength of the relationship between control rate and drug rate.

For all subjects, there was a dose-dependent decrease in the slope of the regression line (i.e., as dose increased, the slope of the regression line decreased; Table 1, top). Doses of 0.56 and 1.0 mg/kg produced slopes near zero, indicating a relatively constant rate of responding and, accordingly, a linear pattern of responding on a cumulative record. There was a corresponding decrease in the coefficient of

variation, indicating that the utility of using control rate to predict drug rate diminished as drug rate became more uniform and the range of values became more restricted. For Subjects S-74 and S-75, the minimal slope occurred following a dose (1.0 mg/kg) on the descending limb of the dose-effect curve that produced less than maximum response rate. For Subject S-77, the slope approximated zero following a dose (0.56 mg/kg) that produced the maximum response rate. A higher dose (1.0 mg/kg) also produced a slope near zero, but response rate was less than half of the maximum rate, and there was evidence in the cumulative records (Figure 1, bottom right) that a dose of 1.0 mg/kg had a disruptive effect on performance characterized by erratic periods of responding and pausing throughout the interval. Hence, once the slope of the regression line approximated zero, a higher dose only suppressed responding while the slope remained near zero. Note that the deviation of data points about the individual regression lines in Figure

Fig. 5. Cumulative response records displaying effects of cocaine dose on pattern of responding under a multiple FI 300-s RI 300-s schedule of stimulus-shock termination for individual subjects. The session began with an FI component, and the FI and RI components alternated during the session. The FI component is indicated by parallel horizontal event lines. The response pen deflected upon presentation of electric shock. Otherwise, as in Figure 1.

4 was comparable for all doses, yet the coefficient of variation decreased markedly as the slope approached zero (Table 1, top).

Multiple FI RI Control Performance

Control performance during the FI component of the multiple schedule was characterized by low to moderate response rates early in the interval and by higher response rates as the interval elapsed (Figure 5, top). The pattern of positively accelerated responding was less curvilinear compared to the pattern observed during the previous FI schedule, but mean response rates were comparable during both conditions (0.60, 0.33, and 0.41 response per second during the FI-multiple condition vs. 0.61, 0.30, and 0.38 response per second during the FI-only condition for Subjects S-74, S-75, and S-77, respectively). In contrast to FI performance, responding during the RI component occurred at a relatively constant rate throughout each component, and mean response rates during the RI were also greater (0.81, 0.41, and 0.99 response per second for Subjects S-74, S-75, and S-77, respectively) than mean rates during the FI.

Effect of Cocaine on Multiple FI RI Performance

Figure 5 shows cumulative records typical of performance under the multiple FI 300-s RI 300-s schedule during control sessions (top) and following two representative doses of cocaine administration (middle and bottom). Response rates increased during the FI and RI components after drug administration, and the pattern of positively accelerated responding during the FI became less curvilinear. At a dose of 0.56 mg/kg, response rates and patterns during the FI and RI were very similar, and performance during both was characterized by steady, high rates of responding.

A plot of mean response rate versus dose characterized the range of doses having effects on FI and RI performance (Figure 2, right column). The lowest dose of cocaine (0.03 mg/kg) increased FI and RI response rates in 2 of 3 subjects (S-74 and S-77), and intermediate doses (0.1–0.56 mg/kg) increased rates in all subjects. Response rates during the FI and RI components converged toward a common rate following a dose of 0.1 mg/kg (S-75) or 0.3

Fig. 6. Effect of cocaine dose on FI (left) and RI (right) interresponse time (IRT) distributions for Subject S-77. Otherwise, as in Figure 3.

mg/kg (S-74 and S-77), and higher doses (0.56–1.0 mg/kg) produced rates that were comparable during both components. The highest dose (1.0 mg/kg) decreased responding below maximum rates for all subjects, but only

S-74 showed a considerable decrease below control rate. Note that the shapes of the dose-effect curves for FI performance were similar during the FI-only condition (Figure 2, left) and the FI-multiple condition (Figure 2, right).

Table 2

Effects of cocaine and pentobarbital on interresponse time (IRT) distributions derived from fixed-interval (FI) and random-interval (RI) performance. Mean IRTs (in seconds) and standard deviations were derived from individual sessions representative of performance under the conditions specified (see Data Analysis).

Dose		S-77		S-75		S-74	
		FI	RI	FI	RI	FI	RI
Saline	Mean	2.34	0.90	3.38	2.27	1.68	1.25
	SD	6.65	0.83	5.66	2.81	1.94	1.24
Cocaine (mg/kg)							
0.1	Mean	1.41	0.81	2.62	2.20	1.21	0.91
	SD	2.99	0.65	4.33	2.54	1.29	0.92
0.3	Mean	0.55	0.67	1.60	1.33	1.01	1.02
	SD	0.47	0.56	1.14	1.26	0.77	1.00
0.56	Mean	0.68	0.73	1.72	1.67	1.25	1.18
	SD	0.55	0.56	1.60	1.42	0.94	0.95
1.0	Mean	0.83	0.79	3.05	3.00	4.17	3.33
	SD	0.69	0.70	2.59	2.68	15.75	18.72
Pentobarbital (mg/kg)							
0.3	Mean	—	—	6.14	3.16	1.25	0.93
	SD	—	—	7.59	3.22	1.84	1.14
1.0	Mean	2.43	1.45	7.14	3.57	1.68	1.23
	SD	10.90	1.44	52.60	6.73	2.30	1.37
3.0	Mean	2.86	1.50	26.80	13.04	6.27	13.24
	SD	7.72	1.42	66.50	35.02	14.50	20.02
5.6	Mean	2.86	1.82	—	—	—	—
	SD	13.04	10.67	—	—	—	—

However, the maximum rate increase occurred at a lower dose (0.3 mg/kg) during the FI-multiple condition for Subjects S-75 and S-77.

Figure 6 shows IRT distributions determined for FI (left) and RI (right) components for Subject S-77. Each distribution was derived from a single session. The top panels illustrate the shape of the IRT distributions during control sessions. The FI distribution (left) was widespread, corresponding to the wide range of local response rates typical of FI performance. In contrast, the RI distribution (right) was less widespread, corresponding to the more constant rate typical of RI performance. Following the administration of cocaine, there was a shift toward briefer and more uniform IRTs for both components, and a dose of 0.56 mg/kg produced distributions that were very similar (Figure 6, bottom). Mean IRTs and standard deviations for IRT distributions as a function of cocaine dose are shown in Table 2 (top) for all subjects. Representative distributions were selected as described in the Data Analysis section, and each mean and standard deviation were derived from

a single session. The dose-dependent decrease in the standard deviation indicates that the IRTs became less variable following cocaine administration. For all subjects, the mean and standard deviation for FI and RI performance were very similar following a dose of 0.56 mg/kg. Note that the standard deviation was greater following a dose of 1.0 mg/kg compared to a dose of 0.56 mg/kg, indicating that the IRTs were more dispersed at the highest dose. However, only Subject S-74 showed an increase above the control value following a dose of 1.0 mg/kg.

In addition to the IRT analysis, drug rate for each of ten 30-s segments of each FI was plotted against control rate on logarithmic axes, and a regression line was plotted for each dose to determine whether data obtained during the RI approximated the regression line determined for FI performance. Control rate for each segment was the average of all saline sessions that occurred during the course of the cocaine experiments. Because the RI schedule engendered a relatively constant rate throughout the interval, a single value (the mean re-

Fig. 7. Effect of cocaine dose on mean response rate during individual 30-s segments of a 300-s FI that was a component of a multiple FI RI schedule for individual subjects. Regression lines were derived from FI performance; data for RI performance were based on overall mean rate during the RI component. Otherwise, as in Figure 4.

sponse rate) for RI components was used in this analysis. Figure 7 shows the results of the regression analysis of drug rate and control rate. For all subjects and all doses, response rate determined for the RI fell very close to, and in several instances, directly on, the regression line derived from FI performance. The results confirmed that cocaine produced a convergence of control rates toward a common rate and that the value of that common rate was independent of how the control rate was engendered.

Comparison of cocaine's effects during the FI schedule alone and when it was a component of the multiple schedule provided a determination of contextual modulation of cocaine's effects on FI performance. During the condition in which the FI was part of a multiple schedule, there was a dose-dependent decrease in the slope of the regression line (Table 1, middle). Doses of 0.3–0.56 mg/kg produced slopes near zero, indicating a relatively constant rate of responding, and there was a corresponding decrease in the coefficient of vari-

ation. For all subjects, the minimal slope occurred at a smaller dose during this condition compared to the FI-only condition. The minimal slope occurred following a dose (0.3 mg/kg) that produced the maximum response rate (Subjects S-75 and S-77) or following a dose (0.56 mg/kg) on the descending limb of the dose-effect curve that produced less than maximum response rate (S-74). The highest dose (1.0 mg/kg) also produced slopes near zero, but response rates were less than the maximum rate for all subjects. Hence, once the slope of the regression line approximated zero, higher doses only suppressed responding below maximum rate while the slope remained near zero. The maximum rates obtained when the slopes first approximated zero were comparable for both conditions (0.81, 0.56, and 1.75 response per second for the multiple-schedule condition and 0.76, 0.60, and 1.55 response per second for the FI-only condition for Subjects S-74, S-75, and S-77, respectively). A dose of 1.0 mg/kg was excluded from consideration because this dose suppressed responding in Subject S-74 and produced less than maximum response rates in Subjects S-75 and S-77. These results demonstrated a dose-dependent convergence of control rates toward a common rate for both conditions (FI-multiple and FI-only), and the value of that common rate was not changed considerably by the context of the multiple schedule.

Effect of Pentobarbital on Multiple FI RI Performance

Because of different sensitivities to the effects of pentobarbital, Subject S-77 was administered doses of 1.0, 3.0, 5.6, and 10.0 mg/kg, and Subjects S-75 and S-74 were administered doses of 0.3, 1.0, 3.0, and 5.6 mg/kg. Figure 8 shows the effect of pentobarbital dose on mean response rate per session for individual subjects during the FI and RI components. The shapes of the dose-effect functions were similar for FI and RI performance, and both could be characterized as monotonically decreasing curves. Mean overall response rates decreased at all doses for Subjects S-77 and S-75, and although Subject S-74 showed less change at the lower doses (0.3–1.0 mg/kg), rate decreased significantly at the higher doses (3.0–5.6 mg/kg). For each subject, the highest dose administered (5.6 or 10.0 mg/kg) suppressed responding well below control values.

Figure 9 shows IRT distributions deter-

Fig. 8. Effect of pentobarbital dose on mean response rate during the multiple FI RI schedule for individual subjects. Otherwise, as in Figure 2.

mined for FI (left) and RI (right) components for Subject S-77. Each distribution was derived from a single session. The top panels illustrate the shape of the distributions during control sessions. Following the administration

Fig. 9. Effect of pentobarbital dose on FI (left) and RI (right) interresponse time distributions for Subject S-77. Otherwise, as in Figure 3.

Fig. 10. Effect of pentobarbital dose on mean response rate during individual 30-s segments of a 300-s FI that was a component of a multiple FI RI schedule for individual subjects. Regression lines were derived from FI performance and plotted as in Figure 7.

of pentobarbital, there was a shift toward longer IRTs and a more dispersed distribution for both components. The highest dose administered that did not completely disrupt responding (5.6 mg/kg) produced IRT distributions that were similar for the two components. Mean IRTs and standard deviations for IRT distributions as a function of pentobarbital dose are shown in Table 2 (bottom) for all subjects. The dose-dependent increase in the standard deviation indicates that the IRTs became more variable following pentobarbital administration.

In addition to the IRT analysis, drug rate for each of ten 30-s segments of each FI was plotted against control rate on logarithmic axes, and a regression line was plotted for each dose to characterize further the rate-altering effects of pentobarbital. Control rate for each segment was the average of all saline sessions that occurred during the course of the pentobarbital

experiments. As Figure 10 shows, different control rates during the FI usually did not converge toward a common rate following pentobarbital administration. Regression lines remained parallel to the diagonal (saline) for Subject S-75, and only the intercepts changed (middle panels). For Subject S-74, the shift in the regression lines toward a slope of zero was negligible (right panels). Regression lines for doses greater than 1.0 mg/kg were not included for Subjects S-74 and S-75 because responding was too poorly maintained to provide a meaningful analysis. Although there was a dose-dependent shift in the regression lines for Subject S-77 (left panels), the slope obtained with a high dose (5.6 mg/kg) was greater than +0.26, indicating that response rate did not become constant throughout the interval. At the highest dose (10.0 mg/kg), responding was irregular and too poorly maintained to provide a meaningful analysis for this subject. Table

1 (bottom) shows that no dose of pentobarbital produced a slope or coefficient of variation that approximated zero.

DISCUSSION

The present research was undertaken to identify environmental variables that may influence the value of the uniform rate obtained during FI performance following cocaine administration. The effects of cocaine on FI performance were a direct replication of previous work (Howell *et al.*, 1986), and the results obtained in both studies were in good agreement. Different control response rates converged toward a common rate following the administration of cocaine to monkeys responding under an FI 300-s schedule of stimulus-shock termination. Local response rates during individual 30-s segments of the FI became similar in value, and IRTs became more uniform. The effects of cocaine on FI performance could be described as producing rate constancy (Gonzalez & Byrd, 1977). According to the rate-constancy concept, certain drugs reduce variability in the occurrence of the behavior, and as dose increases, responding approaches a constant and uniform rate (Byrd, 1981). The effects of cocaine on multiple FI RI performance demonstrated that the value of the constant rate did not depend upon the means by which the control rates were engendered. Cocaine administration produced the same constant rate during the FI and RI components even though the FI and RI schedules engendered different control rates and patterns of responding.

The multiple FI RI schedule was used to determine whether the same constant rate was approached during both components even though control rates and patterns of responding differed. The RI schedule engendered a relatively high, constant rate of responding, but the FI schedule engendered a wide range of local response rates. After the administration of cocaine, the pattern of positively accelerated responding engendered by the FI was modified, and response rate increased and became more uniform. Response rate during the RI component also increased and responding was relatively constant. When drug rate was plotted against control rate on logarithmic axes and a linear regression line was determined for FI responding after each dose of cocaine,

mean response rate determined for the RI component fell near the regression line derived from the FI performance. These results confirmed that there was a convergence of control rates toward a common, uniform rate and that the value of the uniform rate was independent of how the control rate was engendered.

A comparison of drug effects during the FI schedule alone and during the FI schedule when it was a component of the multiple schedule provided a determination of contextual modulation of cocaine's effects on FI performance. There was a dose-dependent decrease in the slope of the regression line during both conditions, and once the slope approximated zero, higher doses only suppressed responding below the maximum rate while the slope remained near zero. The maximum rate obtained when the slope first approximated zero was comparable for the FI-multiple and FI-only conditions. The results demonstrated a dose-dependent convergence of control rates toward a common rate for both conditions, and the value of that common rate was not changed considerably by the context of the multiple schedule. However, the minimal slope occurred at a smaller dose during the FI-multiple condition. Evidently, the presence of a constant-rate component made the FI pattern of responding more susceptible to change following cocaine administration.

The IRT distributions quantified further the performance changes resulting from cocaine administration. The distribution during FI was widespread, corresponding to the wide range of local response rates typical of FI performance. In contrast, the distribution during RI was positioned more to the left and was less widespread, corresponding to the high, more uniform rate typical of RI performance. Following the administration of cocaine, there was a shift toward briefer and more uniform IRTs for both components. A dose that produced a uniform rate of responding during the FI produced IRT distributions that were very similar for FI and RI performance. The results indicated that there was a convergence of IRTs toward a common duration and that the value of the duration was independent of the means by which the IRTs were engendered.

Pentobarbital did not produce effects that could be characterized as conforming to the concept of rate constancy. Pentobarbital produced a shift toward longer IRTs and a more dispersed or widespread distribution for FI

and RI performance, and subjects maintained a positively accelerated pattern of responding until the behavior was disrupted at the higher doses. There was a dose-dependent change toward a less curvilinear pattern during the FI for Subject S-77, but responding never became constant throughout the interval. Once the slope of the regression line reached a minimum ($+0.26$), increasing the dose by only one quarter of a log unit disrupted the behavior of S-77 and markedly suppressed response rate. The absence of a shift toward a more uniform rate for S-74 and S-75 suggested that the effect observed in S-77 was probably atypical and that rate-constant effects may not be characteristic of pentobarbital, a central nervous system depressant.

Pentobarbital has been reported both to increase and to decrease FI response rates depending on the dose and schedule being studied. At low doses, pentobarbital produced modest increases in food-maintained responding in pigeons (McMillan, 1973) and in squirrel monkeys (Spealman, 1979) during the FI (food) component of a multiple FI (food) FI (food + punishment) schedule, and higher doses decreased response rates. When responding in pigeons was maintained under a multiple FR FI schedule of food presentation without punishment, pentobarbital only decreased response rates during the FI component (Leander & McMillan, 1974). It appears, therefore, that the increase in FI responding reported by McMillan (1973) and Spealman (1979) may have been due, in part, to the interaction between the FI (food + punishment) component and the FI (food) component of the multiple schedule. Responding maintained in squirrel monkeys under shock-postponement schedules typically shows a monotonic decrease with increasing doses of pentobarbital, and the decline in response rate takes place at doses less than those sufficient to reduce responding under FI schedules of food presentation (Dews & DeWeese, 1977). In the present study, responding was maintained by the termination of stimuli associated with shock. Although the FI schedule of stimulus-shock termination is not technically a shock-postponement schedule, the finding that pentobarbital only decreased rate suggests that the behavioral processes involved in the two types of procedures may be similar.

The rate-increasing effects of cocaine on FI responding were in agreement with previous

results obtained with several behavioral stimulants. Responding in squirrel monkeys during the FI (food) component of a multiple FI (food) FI (food + punishment) schedule (Spealman, 1979) and during the FI component of a multiple FR FI schedule of food presentation (Gonzalez & Goldberg, 1977) was increased by cocaine and *d*-amphetamine. Response rates during the FI component of a multiple FI FR schedule of either food or stimulus-shock termination were also increased by cocaine (Spealman, Kelleher, & Goldberg, 1983) and its phenyltropane derivatives, WIN 35,065-2 and WIN 35,428 (Spealman, Goldberg, Kelleher, Goldberg, & Charlton, 1977). Cumulative records and local response rates during the FIs in these studies indicated that each of these behavioral stimulants produced a dose-dependent shift toward a constant rate. In the present study, cocaine increased overall rate, and different control rates of responding converged toward uniform rate. However, pentobarbital, which only decreased overall rate, did not produce a shift in local response rates toward a uniform rate. These results indicate that rate-constant effects may be more characteristic of drugs that increase overall rates of FI responding.

At present, there are several quantitative indices for measuring changes in FI performance. Mean rate of responding during the entire FI schedule indicates whether the total number of responses per total time is increased or decreased, but it provides no information about the pattern of FI responding. Quarter-life, the percentage of the FI taken to complete the first quarter of responses, provides an index of the temporal patterns of FI responding that is largely independent of mean FI rate (Gollub, 1964; Herrnstein & Morse, 1957). Index of curvature is another quantitative measure of the magnitude and direction of curvature in patterns of FI responding, and this index is also mainly independent of mean FI rate (Fry, Kelleher, & Cook, 1960). The analysis of local rates of responding during individual segments of the FI became popular following the development of the rate-dependency hypothesis (Dews, 1958). Typically, data are displayed so that drug-induced, proportional changes in response rate are plotted on logarithmic axes as a function of control or non-drug response rates. Data are interpreted as demonstrating rate dependency if a distribution of points approximates a straight line hav-

ing a slope other than zero. The slope of the regression line for rate-dependent plots has provided a useful quantitative index for assessing the behavioral effects of drugs. For example, McMillan (1973) used the slope of the regression line to demonstrate that rate-dependent effects of drugs on punished responding are not always the same as they are for nonpunished responding.

The present study shows that rate constancy can provide a useful quantitative framework for characterizing the manner in which drugs influence and modulate behavior. It provides end points for describing and comparing the effects of drugs on schedule-controlled behavior. The slope of the regression line is a direct numerical measure of change in pattern of responding, and the mean value of the data points comprising the regression line is equal to the mean response rate. For drugs that produce a constant rate of responding, the slope of the regression line will decrease in numerical value from one to zero as dose increases, and at a certain dose, the slope will approximate zero. When responding is constant and uniform, the value of the y intercept will be the constant rate. The constant rate has been used previously to differentiate between the effects of cocaine and white noise on fixed-interval performance even though both stimuli produced qualitatively similar effects (Howell et al., 1986). It is apparent, therefore, that this type of analysis can be useful in comparing pharmacological agents from different classes.

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