THE EFFECTS OF COCAINE ON BEHAVIOR MAINTAINED BY TIMEOUT FROM AVOIDANCE

MARK GALIZIO AND MARGARET O. LIBORIO

UNIVERSITY OF NORTH CAROLINA AT WILMINGTON

Rats were trained on concurrent schedules under which responses on one lever postponed shock (avoidance) and responses on the other lever produced brief (2-min) periods of signaled timeout from avoidance. For 6 rats, timeout from avoidance was programmed on a variable-interval 45-s schedule that generally resulted in rates that were lower than those on the avoidance lever. For another 6 rats, timeout was arranged on a variable-ratio 15 schedule that produced higher baseline rates. Cocaine (3 to 40 mg/kg) produced large, dose-dependent increases in behavior maintained by timeout in both groups of rats. Avoidance responding was also generally increased by cocaine, but the increases were of lesser magnitude. Increases in response rates were seen across a broad range of doses on behavior maintained by either interval or ratio schedules, an outcome that was unexpected on the basis of most studies of cocaine on food-maintained behavior. These results were similar to those of previous studies of the effects of amphetamine on behavior maintained by timeout from avoidance and suggest that stimulant drugs affect behavior maintained under a shock-postponement schedule differently than they affect behavior maintained by timeout from avoidance.

Key words: negative reinforcement, avoidance, timeout from avoidance, amphetamine, cocaine, lever press, rats

A number of nonpharmacological factors are known to determine the behavioral effects of drugs. These include baseline rate and schedule, behavioral history, the extent to which behavior is under stimulus control, the overall environmental context, and the nature of the event maintaining the behavior under study (Barrett, 1987; Branch, 1991). That the effects of some drugs may depend on the event maintaining the behavior is now well established (see Barrett & Katz, 1981), but theoretical understanding of the phenomenon remains elusive.

For example, benzodiazepines generally increase responding maintained by food but decrease behavior maintained by schedules of avoidance or stimulus-shock termination (Ator, 1979; Barrett, Dworkin, & Zuccarelli, 1977). In contrast, opiate drugs such as morphine

have been found to decrease food-maintained responding while increasing avoidance or behavior maintained by stimulus termination (see Dworkin, Pitts, & Galizio, 1993, for a review). However, other drug classes have been found to produce effects that are largely independent of the maintaining event. For example, antipsychotic drugs such as chlorpromazine generally decrease response rates maintained by food, shock, stimulus termination, or avoidance contingencies (Barrett et al., 1977; Kelleher & Morse, 1964). Stimulant drugs such as amphetamine and cocaine also generally show effects that are independent of the maintaining event (Barrett, 1976; Barrett et al., 1977; Kelleher & Morse, 1964; Spealman et al., 1979). One exception is a study by Johanson (1978), who found that amphetamine and cocaine decreased behavior maintained by fixed-ratio (FR) or differential-reinforcement-of-low-rate (DRL) schedules of food presentation at doses that had no effect on (or increased) behavior on FR schedules of stimulus-shock termination in rhesus monkeys.

Most demonstrations of event-dependent effects of drugs have studied squirrel monkeys trained under multiple schedules with food reinforcement in one component and shock presentation or stimulus-shock termination in another. Another approach used in our laboratory involves concurrent schedules of negative reinforcement in rats. In these studies, shock

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postponement (Sidman avoidance) schedules have been programmed on one lever and periods of timeout from avoidance, during which the shock schedule is suspended and the stimuli signaling the avoidance schedule are terminated, are programmed on another lever. Responding on both levers is maintained under these conditions, and schedule control of timeout lever responding can be demonstrated: Low rates of responding on the timeout lever are engendered by variable-interval (VI) 45-s schedules (Perone & Galizio, 1987), and higher rates are produced by variable-ratio (VR) 15 schedules (Galizio & Allen, 1991).

Pharmacological analysis of behavior maintained by timeout from avoidance has led to several findings that may be interpreted as involving event-dependent drug effects. For example, morphine has consistently reduced responding maintained by timeout from avoidance under both VI and VR schedules at doses that increased or did not affect avoidance rates (Galizio & Allen, 1991; Galizio & Perone, 1987). In contrast, alcohol and benzodiazepines increased response rates on the timeout lever at doses that decreased or had no effect on avoidance (Galizio, Hale, Liborio, & Miller, 1993; Galizio & Perone, 1987; Galizio, Perone, & Spencer, 1986). These results parallel those of the studies reviewed above that showed event-dependent effects of opioids and benzodiazepines, but in those studies the contrast was between food reinforcement and some type of shock-related contingency. In the studies of timeout from avoidance, two different types of negative reinforcement (avoidance vs. timeout from avoidance) were compared. Timeout from avoidance has been described as a positive reinforcer by some (e.g., Verhave, 1962), but because it derives its properties by escape from the avoidance schedule, it seems more appropriate to view it as involving contingencies of negative reinforcement. However, in these studies behavior maintained by timeout from avoidance was affected by benzodiazepines and morphine just as these drugs affect food-maintained behavior and not as they typically affect avoidance. These findings suggest that there may be functional similarities between timeout from avoidance and conventional positive reinforcers.

However, not all drugs affect behavior maintained by timeout from avoidance just as they affect food-maintained behavior. The first

exception to be reported was amphetamine, which increased behavior maintained by timeout from avoidance at low rates by VI schedules and at higher rates by VR schedules (Galizio & Allen, 1991). Amphetamines generally decrease behavior maintained under ratio schedules and increase lower rates maintained by interval schedules, but Galizio and Allen found that the greatest magnitude of rate-increasing effects were on behavior maintained at the higher baseline rates under VR schedules. Another curious aspect of the findings was that amphetamine's effects were selective: It increased timeout-lever responding more than avoidance. The present study was designed to assess the generality of the Galizio and Allen findings by determining the effects of cocaine, a drug that in many assays produces behavioral effects much like those of amphetamine on behavior maintained by timeout from avoidance.

Like amphetamine, cocaine generally increases low-rate behavior maintained by interval schedules and decreases high-rate behavior maintained by ratio schedules (Barrett, 1976; Shelnett, Hudzik, Lattin, & McMillan, 1992; Spealman et al., 1979; van Haaren, 1992), although increases in behavior maintained by food under interval schedules are not always reported in rats and pigeons (Logan, Carney, Holloway, & Seale, 1989; Schama & Branch, 1989; Smith, 1990). In order to compare the effects of cocaine on low- and high-rate behavior, two groups of rats were evaluated in the present study. Both groups were trained on concurrent schedules with Sidman avoidance schedules arranged on one lever, but the second lever produced timeout from avoidance on a VI 45-s schedule for one group and on a VR 15 schedule in the other.

METHOD

Subjects

Twelve Holtzman mycoplasma-free male albino rats provided data on drug effects. Initial training began when rats were between 90 and 120 days old. Body weights at the onset of cocaine administration ranged from 497 to 750 g. Animals were individually housed with ad lib access to food and water. Eight subjects had been studied with one or more other drugs prior to beginning cocaine testing.

Apparatus

Animals were trained and tested in commercially constructed Gerbrands G7400 series operant conditioning chambers (approximately 28 cm long, 26 cm wide, and 28 cm high). The chambers were equipped with two retractable levers centered 7.5 cm above the floor and 12 cm apart on the front wall. A force of 0.3 N was required on individual levers to register a response. Side walls and ceiling were constructed of Plexiglas, and front and back walls were stainless steel. Illumination was provided by a 28-V houselight located at the top of the chamber. Floors in each chamber consisted of stainless steel rods (0.2 cm diameter) spaced 1.3 cm apart through which a 1-mA 0.5-s shock was delivered by a constant-current shock generator and scrambler (Lafayette 82400-SS and 58020). White noise (78 dB) was supplied through a speaker located behind the front wall. Chamber events were controlled and recorded by a microcomputer.

Procedure

Preliminary training. Rats were first trained on a Sidman avoidance schedule in which each response on the right lever (avoidance lever) produced a brief (0.5-s) termination of white noise (response feedback) and postponed shock for 30 s (response-shock [R-S] interval). In the absence of responding, shocks were presented every 5 s (shock-shock [S-S] interval). White noise accompanied the onset of each session for all animals and was terminated at the end of each 2-hr session. For 10 of the 12 rats, chamber illumination was present throughout the session. However, Rats C1 and C7 were tested under reversed-stimulus conditions in which the chamber light was off for the 2-hr period. The criterion for completion of avoidance training required that the animal avoid 85% of the shocks programmed by the R-S interval for 10 consecutive sessions. This was achieved in 11 to 25 sessions. Next, a discrimination between signaled periods of avoidance and timeout from avoidance was established by programming a multiple schedule of two alternating 10-min components. In one component the avoidance schedule functioned as described above, whereas in the other component (signaled by white noise off and houselight off, except for C1 and C7) no shocks were scheduled. Training on the multiple schedule

continued until virtually no responding occurred during periods of timeout (two to seven sessions).

Concurrent-schedule training. To begin this phase, the left lever was inserted for the first time. Concurrent-schedule training included Sidman avoidance contingencies operational on the right lever and timeout from avoidance (white noise off, houselight off, except for C1 and C7, timeout lever retracted, and the shock schedule suspended) in effect on the left lever. Timeout was available on a schedule of continuous reinforcement such that responses on the timeout lever produced 5-min periods of timeout from avoidance. As timeout responding became established, the 5-min timeout periods were gradually reduced to 2-min periods, and continuous reinforcement was changed to either VI 45 s or VR 15. ^(+ timeout)

Six rats were trained on VR schedules of timeout from avoidance. For these animals continuous reinforcement was gradually changed to an FR 10 schedule in increments of 1. This required from 9 to 33 sessions. After reaching the FR 10 reinforcement value, timeout schedules were changed to VR 5, and response requirements were increased to VR 10 and ultimately VR 15 as responding became established at each level. For 6 rats, schedules of continuous reinforcement were changed to VI schedules in 5-s increments to a terminal parameter of 45 s. Six to 15 sessions were required to reach the VI 45-s contingency. Data were recorded separately for each 20-min period of the 120-min session. Because early-session avoidance performances are often unstable, and in keeping with previous work, only data from the final 100 min were used to determine stability. After stability criteria were met (the difference between the first and last five sessions of a 10-session block had to be less than 15% of the grand mean) on both avoidance and timeout rates (range, 10 to 59 sessions), determination of drug effects began.

Drug preparation and administration. Cocaine hydrochloride was dissolved in isotonic (0.9%) sodium chloride solution the day of testing and was administered through i.p. injection in a volume of 1 ml/kg immediately prior to the session onset. (Drug doses are expressed in terms of the total salt.) Cocaine or saline injections were administered on Tuesdays and Fridays. Sessions were conducted under baseline conditions on Mondays, Wednesdays, and

Table 1

Responses per minute on the avoidance (AV) and timeout (TO) levers for individual subjects during the initial dose-response determination.

Rat	Response	Baseline ^a	Saline	Cocaine dose (mg/kg)			
				3	10	20	30

Variable-ratio study							
C1	AV	4.89 (0.88)	4.55	4.25	4.98	5.17	4.46
	TO	10.06 (2.92)	22.18	15.08	21.97	78.88	85.48
D10	AV	4.17 (0.85)	4.82	5.30	4.98	10.86	12.05
	TO	33.12 (6.77)	34.73	50.41	100.00	96.24	81.47
D25	AV	6.67 (0.92)	9.59	6.62	7.76	12.45	16.66
	TO	5.64 (1.20)	6.50	26.89	6.15	5.91	1.32
E20	AV	9.44 (1.50)	8.97	10.15	9.23	9.94	10.71
	TO	10.13 (2.44)	14.71	33.59	40.47	58.18	91.62
G31	AV	5.56 (2.20)	6.35	8.90	6.89	8.00	7.22
	TO	7.33 (1.12)	10.00	11.48	10.66	42.92	71.19
G35	AV	4.22 (0.61)	4.43	4.92	5.99	9.01	17.73
	TO	22.65 (4.83)	30.44	27.65	19.65	19.13	13.46
Variable-interval study							
C6	AV	7.68 (1.67)	6.25	7.05	10.31	14.51	27.91
	TO	16.13 (1.90)	17.39	28.44	32.79	26.03	19.53
C7	AV	3.49 (0.16)	3.38	3.12	4.58	3.56	11.67
	TO	0.85 (0.15)	0.86	0.85	1.41	1.40	17.01
D9	AV	3.23 (0.85)	2.88	3.03	5.52	6.72	8.89
	TO	1.25 (0.30)	2.32	2.17	11.87	15.41	18.12
E30	AV	9.11 (1.66)	8.99	9.19	7.36	16.82	14.18
	TO	4.70 (0.85)	3.73	4.86	2.55	5.52	0.53
H38	AV	6.73 (2.27)	5.86	7.46	6.93	7.07	15.98
	TO	4.50 (1.31)	5.37	5.02	6.29	9.38	12.70
J30	AV	9.21 (1.26)	12.20	12.17	14.83	20.18	24.99
	TO	3.13 (0.92)	2.82	4.75	4.88	7.08	13.63

^a Mean of all baseline (Thursday) sessions conducted during the study (5 to 12 sessions). Standard deviation is presented in parentheses.

Thursdays. Only data from baseline sessions conducted on Thursdays during the drug regimen were used in computation of baseline percentages. These data were visually inspected each week to verify that baseline performances remained stable. Stability was maintained throughout the study, with the exception of Rat C1, who became ill and was dropped from the experiment after completing only two determinations of each dose. Otherwise, three to four determinations were made at each dose level, with the exception of the highest dose (40 mg/kg) at which only one determination was made. The order of doses was randomly generated with the constraint that one cycle of dose-response determinations (one exposure to each dose level including saline) be completed before beginning the next cycle. Again, 40 mg/kg was an exception and was administered only after the other cycles had been determined for several animals.

RESULTS

During the course of the drug administration regimen, it became apparent that for many of the animals the effects of cocaine that were obtained during the first cycle of doses were not representative of subsequent determinations. Thus, data from the initial cycle are presented separately (Table 1), and all subsequent analyses present combined data from Cycles 2 through 4. The main results are presented in Figures 1 (VR) and 2 (VI), which show individual-subject response rates.

In rats trained under the VR schedules (Figure 1), cocaine increased timeout responding in a dose-dependent manner for all 6 animals. Generally, minimal increases were seen at the 3 mg/kg dose, but most animals showed clear increases in timeout-lever responding at the 10 or 20 mg/kg dose. In 4 of the 6 animals (D25, E20, D10, and G31), the timeout dose-effect

Fig. 1. Mean response rates on the avoidance lever (black circles) and the timeout lever (white triangles) are plotted as a function of cocaine dose (0 = mean rates after saline injections) for the rats trained with timeout available on a VR 15 schedule (G35, D25, C1, E20, D10, and G31). Vertical lines indicate ranges of two or three determinations (the initial cycle of determinations is omitted) except for the 40 mg/kg dose and all doses for Rat C1, for which results from only a single determination are presented.

Fig. 2. Mean response rates on the avoidance lever (black circles) and the timeout lever (white triangles) are plotted as a function of cocaine dose (0 = mean rates after saline injections) for the rats trained with timeout available on a VI 45-s schedule (C7, E30, D9, J30, C6, H38). Vertical lines indicate ranges of two or three determinations (the initial cycle of determinations is omitted) except for the 40 mg/kg dose, for which results from only a single determination are presented.

curve was nonmonotonic. For E20 and G31, the peak effect was at the 30 mg/kg dose, whereas Rat D10 showed a peak at 20 mg/kg, and D25's timeout rates began to decline at 20 mg/kg. Rats C1 and G35 showed monotonic functions, with peaks of timeout-lever responding at 30 mg/kg. Cocaine also increased avoidance responding in some animals, but the magnitude of increase was much smaller.

Figure 2 shows data for the 6 subjects trained under VI schedules of timeout from avoidance. Rates of responding on the timeout lever were increased in a dose-dependent fashion by cocaine, although the absolute magnitude of the increases was considerably less than was the case for the rats responding under VR schedules (note that vertical axes in Figure 2 represent a smaller range of values than those of Figure 1). For 2 of the animals (C6 and E30), an inverted U-shaped dose-timeout response function was observed, but the other 4 rats showed monotonically increasing functions, with peaks at 30 or 40 mg/kg. Increases in avoidance-lever responding were more apparent in Figure 2 than in Figure 1. In all 6 animals trained under the VI schedule, cocaine reliably increased avoidance rates at some doses. The magnitude of effect was as large as that observed for timeout responding in 3 rats (J30, E30, C7), but the other 3 rats showed larger absolute rate increases on the timeout lever than on the avoidance lever.

Table 1 shows the effects of cocaine on performances during the first cycle of cocaine doses. In general, the effects of cocaine were apparent during the first cycle of doses, but in a number of cases the peak effect increased during subsequent administrations. For example, Rats C1, C6, G31, and H38 showed smaller increases in timeout-lever rates in response to every dose of cocaine during the initial cycle (Table 1) than during the later cycles (Figures 1 and 2). Perhaps the most dramatic change was observed in Rat G35, whose initial response to cocaine was a decrease in responding on the timeout lever with corresponding increases in avoidance (Table 1). During subsequent tests, increases in timeout responding were seen at every dose (Figure 1). However, it should be noted that in several rats response to cocaine was changed only slightly or not at all across cycles.

Table 1 also shows control rates of respond-

ing on both levers (means of data collected on Thursday baseline sessions throughout the experiment). In general, rats trained with timeout programmed on the VR 15 schedule showed higher rates of responding on the timeout lever than on the avoidance lever, whereas rats trained with timeout on the VI 45-s schedule had lower rates of responding on the timeout lever than on the avoidance lever. In each group there was one exception (D25, VR; C6, VI).

The tendency for cocaine's rate-increasing effects to be selective to timeout-lever responding in most animals suggested that the effects were not due to an indiscriminate stimulation of responding. Further support for this is derived from analysis of responding on the avoidance lever during the timeout (the timeout lever was retracted during timeouts). This analysis is not presented in detail because virtually no responding on the avoidance lever was seen during control conditions, and, with the exception of Rat G31, cocaine had no effect on the discrimination. For G31, responding occurred during timeouts at higher cocaine doses. However, even in this subject, some discriminative control, as measured by differential responding between periods of avoidance and timeout, was maintained throughout. Avoidance proficiency, defined here as the percentage of the shocks programmed by the R-S interval that were successfully avoided, remained high (above 85%) throughout the study in most cases. Cocaine produced slight improvements in avoidance proficiencies where possible (several animals consistently avoided all shocks under control conditions). In only 1 animal (H38, at the 40 mg/kg dose) was avoidance proficiency somewhat impaired.

Table 2 shows the number of minutes spent in timeout conditions as a function of cocaine dose. Time spent in timeout was comparable under baseline conditions for rats in the VR and VI studies, although there was less variability across subjects for rats studied under the VI schedule. For the rats in the VR study, rate increases produced by cocaine increased the number of timeouts, and thus the number of minutes spent in timeout. As would be expected, time spent in timeout did not increase as much for the rats in the VI study, although small increases were noted at some cocaine doses in most cases.

Because cocaine has a relatively short duration of action, within-session analyses were

Table 2

Mean time spent in timeout (in minutes) across cocaine doses (session duration = 120 min).

Rat	Base- line ^a	Saline	Cocaine dose (mg/kg)				
			3	10	20	30	40
Variable-ratio study							
C1	54.4	65.9	69.4	92.3	93.5	94.2	—
D10	80.5	83.9	86.8	92.0	93.1	91.5	—
D25	41.2	41.5	55.5	73.2	50.6	36.3	—
E20	56.6	65.9	61.8	83.8	90.3	91.7	88.5
G31	48.4	52.5	65.3	70.9	88.6	91.4	91.2
G35	74.1	75.4	81.0	84.8	86.5	87.7	—
Variable-interval study							
C6	70.9	71.5	71.3	71.7	72.5	72.6	—
C7	54.3	57.7	61.2	68.8	70.0	72.2	—
D9	52.6	58.7	68.1	70.9	70.5	71.5	71.5
E30	64.4	63.5	68.4	71.6	70.4	67.4	—
H38	69.0	66.8	69.7	71.6	71.3	71.2	71.4
J30	67.1	69.0	67.4	68.7	67.7	71.7	72.7

^a Mean of all baseline (Thursday) sessions conducted through the study (5 to 12 sessions).

conducted. Table 3 shows response rates for the first 20 min of the 2-hr session. Performances were, in general, fairly consistent with those of the main session (Figures 1 and 2). For rats in both the VI and VR studies, the rate-increasing effects of cocaine were apparent during the first 20 min of the session, but in many cases were somewhat less pronounced than was the case later in the session (but note G31, C6, H38, and J30, for whom larger increases in timeout- or avoidance-lever responding were noted during the initial 20 min).

In order to permit a more detailed analysis of the time course of cocaine's action, data are presented with the session divided into 20-min periods in Figure 3. For each rat, mean response rates were computed for each 20-min period of sessions conducted following the 30 mg/kg dose. These values were converted to percentage of baseline for each animal, and group means determined for the VI and VR studies are presented in Figure 3. The top panel shows VI performances and reveals that the effects of cocaine on timeout-lever responding peaked during the second 20-min period and declined somewhat thereafter. However, mean response rates on the timeout lever were still well above baseline even during the final 20-min bin. Effects of cocaine on avoidance rates were most pronounced during the first 80 min, but remained above baseline through-

Table 3

Mean responses per minute for the initial 20 min of each session.

Rat	Re- sponse	Saline	Cocaine dose (mg/kg)				
			3	10	20	30	40
Variable-ratio study							
C1	AV	10.3	9.0	11.4	10.2	9.4	—
	TO	7.3	15.6	42.5	58.0	102.5	—
D10	AV	4.8	5.5	11.6	13.7	11.6	—
	TO	37.2	61.8	89.1	79.2	50.0	—
D25	AV	7.9	11.7	17.4	17.3	19.6	—
	TO	5.4	7.7	4.2	0.0	0.1	—
E20	AV	9.2	14.2	16.7	18.5	21.0	10.7
	TO	22.4	19.4	28.4	49.5	62.5	62.2
G31	AV	7.0	8.7	11.1	7.6	14.6	6.3
	TO	6.3	15.2	76.0	121.7	101.3	135.8
G35	AV	6.0	11.0	11.1	17.9	18.4	—
	TO	7.5	35.2	32.1	17.6	221.6	—
Variable-interval study							
C6	AV	12.4	19.1	22.3	25.3	34.2	—
	TO	18.5	32.7	32.5	34.6	12.1	—
C7	AV	4.1	6.1	9.0	8.7	7.8	—
	TO	1.3	2.7	7.5	7.6	10.4	—
D9	AV	3.2	3.3	8.0	6.2	6.9	3.8
	TO	0.6	3.1	15.6	12.3	11.3	3.9
E30	AV	10.6	7.8	18.1	14.9	15.4	—
	TO	6.7	3.2	12.0	6.9	4.9	—
H38	AV	5.7	11.7	8.9	18.0	18.7	13.6
	TO	7.6	11.8	12.5	25.6	31.1	14.0
J30	AV	11.8	15.0	12.7	25.2	36.1	36.5
	TO	3.5	3.3	3.7	9.0	17.3	32.3

out the session. The bottom panel of Figure 3 shows performances of rats in the VR study. The 30 mg/kg dose of cocaine produced peak increases in responding on the timeout lever between 20 and 60 min into the session, and the effects were still quite apparent at the session's end. In contrast, the increases in avoidance responding were apparent only during the first 40 min. These findings may be of more than passing interest, because they show that the duration of action, often considered to be an invariant property of a drug, in this case depended on the schedule conditions in effect.

Figure 4 presents representative cumulative records for Rat H38 of the VI study and Rat G31 of the VR study. The top records show 30-min segments of a representative baseline session, and the lower records show the effects of 30 mg/kg cocaine. During baseline conditions, H38 showed regular patterns of responding that alternated between the timeout and avoidance levers. The VR timeout schedule produced a somewhat different pattern that was apparent in Rat G31's record, with bursts

of responding on the timeout lever alternating with avoidance responses. The postreinforcement pause was generally brief, but noteworthy in the baseline record for G31 was that, on some of the higher ratios, runs of responding on the timeout lever were broken by long pauses. The effects of cocaine are seen simply as rate increases on both levers in the cumulative record of Rat H38 on the VI timeout schedule (lower left). For Rat G31 (lower right), cocaine resulted in a change to a pattern of responding that was more typical of VR schedules. Response bursts on the timeout lever commenced immediately after timeout offset and were maintained until the next timeout was produced. Although avoidance responses occurred intermittently, the alternation was generally accomplished without disruption of the steady high rates on the timeout lever.

In summary, full-session analysis of the absolute response-rate data above (e.g., Figures 1 and 2) revealed that behavior maintained by timeout from avoidance was generally increased more than avoidance by cocaine, and that behavior maintained under VR 15 schedules was increased more than behavior maintained under VI 45-s schedules of timeout. However, these conclusions are complicated by the widely differing baseline rates across the three schedules studied, which necessitated different scales on the vertical axes of Figures 1 and 2. Figure 5 shows data averaged for all rats studied in each group presented as a percentage of baseline performance. The finding that timeout responding was increased more than avoidance is quite evident in Figure 5, but the differences between the VI 45-s and VR 15 groups were eliminated by the percentage-of-baseline analysis. For comparison, data from the Galizio and Allen (1991) study of amphetamine were also replotted using percentage of baseline and are shown in Figure 6. The functions were strikingly similar to those obtained with cocaine, with timeout responding increasing with amphetamine dose about equally for VI 45-s and VR 15 baselines, but with avoidance increasing only slightly.

DISCUSSION

Cocaine produced increases in responding maintained by timeout from avoidance in all animals. In most cases, rate increases were noted at low to moderate doses (3 to 10 mg/

Fig. 3. Mean response rates on the avoidance lever (black circles) and the timeout lever (white triangles) are expressed as a percentage of baseline and are presented in 20-min periods for sessions conducted following a 30 mg/kg dose of cocaine. Mean response rates were determined for each rat for baseline and 30 mg/kg cocaine sessions. Group means for the rats of the VI study are presented in the top panel, and group means for the VR study are presented in the bottom panel. Vertical lines indicate standard errors. Mean absolute response rates (responses per minute) across periods for the rats of the VI study were as follows: 7.8, 6.9, 6.7, 6.5, 6.5, and 6.4 on the avoidance lever and 4.4, 5.0, 5.1, 5.0, 5.0, and 5.8 on the timeout lever. For the rats of the VR study, response rates were 7.2, 6.5, 5.8, 6.1, 5.8, and 5.8 on the avoidance lever and 12.5, 13.1, 12.4, 16.8, 15.8, and 16.0 on the timeout lever.

Fig. 4. Representative cumulative records for Rat H38 of the VI study (left) and Rat G31 of the VR study (right) showing 30-min segments of a baseline session (top) and a 30 mg/kg cocaine session (bottom). The stepping pen is incremented by responses on the timeout lever, and avoidance responses deflected the event pen. The stepping pen deflected briefly when a shock was delivered and deflected and remained down for the duration of each timeout.

kg) and persisted through very high doses (30 to 40 mg/kg in some subjects). At the same doses, avoidance response rates were also increased, but the effects were often of lesser magnitude. All 6 of the rats trained under VR timeout schedules showed larger rate increases on the timeout lever than on the avoidance lever at some doses of cocaine. Increases in avoidance-lever responding were more apparent in the rats trained under VI schedules, but even here there was some tendency for rate increases on the timeout lever to be greater than on the avoidance lever in 4 of the 6 rats.

These results were quite similar to those noted earlier with amphetamine (Galizio & Allen, 1991) and suggest that the pattern may be general for stimulant drugs. Galizio and Allen reported timeout response rates as high as 40 to 70 responses per minute at some amphetamine doses. Cocaine produced even higher timeout response rates, some in excess of 130 responses per minute. Rates this high are extraordinary with negatively reinforced behavior in rats.

The stimulation of avoidance behavior and responding maintained at relatively low rates by VI schedules of timeout from avoidance

may be seen as largely consistent with the literature on the effects of cocaine on schedule-controlled behavior. However, the large increases in rates maintained by VR schedules of timeout from avoidance were inconsistent with previous studies of the effects of cocaine on food-reinforced behavior maintained by ratio schedules that found only decreases in rate (Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Shelnett et al., 1992; Smith, 1990; Spealman et al., 1979). In the present study, cocaine not only increased behavior maintained under ratio contingencies, but in many cases increased it as much or more than lower rate behavior maintained under Sidman avoidance or VI schedules.

One account that might be developed to explain these results is that behavior maintained by contingencies of negative reinforcement is less sensitive to rate-decreasing effects of cocaine (and amphetamine) than is food-maintained behavior. Some studies have found that amphetamine and cocaine differentially affect behavior maintained by negative reinforcement contingencies (Johanson, 1978; Smith, 1990). However, when baseline schedules and rates are matched, the more general finding is

Fig. 5. Mean percentages of baseline response rates for rats in the VR 15 conditions (left) and VI 45-s conditions (right) are plotted as a function of cocaine dose. Mean baseline rates were determined for each rat and were used to express drug effects as a percentage of baseline for individual subjects. The mean baseline responses per minute were 5.8 (avoidance) and 14.8 (timeout) for the VR study and 6.6 (avoidance) and 5.1 (timeout) for the VI study. Points plotted here are group means for the two schedule conditions. Vertical lines indicate standard errors.

that the effects of amphetamine and cocaine do not depend on the maintaining event (e.g., Barrett, 1976; Barrett et al., 1977; Kelleher & Morse, 1964; Speelman et al., 1979). Thus, other explanations of the present findings seem to be more parsimonious.

For example, one possibility is that although there was a differentiation of baseline rates across VI, Sidman avoidance, and VR schedules, the rates engendered by the VR schedule were not sufficiently high to observe cocaine-induced decreases in response rate. Although the VR baselines were generally higher than those generated by the Sidman avoidance or the VI schedules (VR rates ranged from 8 to 42 responses per minute; see Table 1), they were not as high as would be expected under schedules of positive reinforcement. Thus, baseline rates in many of the studies available for comparison in rats with positive reinforcement or in monkeys with stimulus-shock termination were substantially higher than in the VR baselines of the present study. As McKearney (1981) has pointed out, detection of

rate-dependent drug effects may be obscured when the range of control rates is limited.

Another account of the present results might emphasize the role of schedule interactions, not present in comparison studies, due to the concurrent Sidman avoidance and timeout schedules. The effects of drugs on concurrent performances maintained by food reinforcement may differ from those obtained in single-schedule experiments (cf. Bacotti, 1979, 1980; Todorov, Gorayeb, Correa, & Graeff, 1972; Ziriax, Snyder, Newland, & Weiss, 1993). Of particular relevance here, baseline rates have been less useful in accounting for the effects of amphetamine on behavior under the control of concurrent schedules (Bacotti, 1979; Todorov et al., 1972).

One of the few studies of drug effects on concurrent schedules of negative reinforcement (Dalrymple & Stretch, 1971) found that amphetamine increased responding maintained by an FR 75 schedule of timeout from avoidance in 1 squirrel monkey with a relatively low baseline FR-lever response rate. They

Fig. 6. Mean percentages of baseline response rates for rats in the VR 15 conditions (left) and VI 45-s conditions (right) of the Galizio and Allen (1991) study are plotted as a function of amphetamine dose. Mean baseline rates (data collected on nondrug sessions throughout the study) were determined for each rat and were used to express drug effects as a percentage of baseline for individual subjects. The mean responses per minute were 6.2 (avoidance) and 16.9 (timeout) for the VR study ($N = 6$) and 6.2 (avoidance) and 3.3 (timeout) for the VI study ($N = 7$). Points plotted here are group means for the two schedule conditions. Vertical lines indicate standard errors.

noted further that the baseline pattern involved frequent pauses in FR-lever responding, during which avoidance responses occurred. The rate-increasing effects of amphetamine appeared to be related to a reduction in these pauses. In contrast, amphetamine decreased response rates in another monkey with a high and steady baseline rate. Figure 4 suggests a related account of the rate increases produced by cocaine in the present study. Baseline response patterns under the VR 15 schedule showed frequent pauses (upper right panel) that were greatly reduced by cocaine (lower right panel).

This result may be of significance because Dews (1958) and Morse and Herrnstein (1956) in single-schedule experiments found that methamphetamine increased behavior maintained by demanding FR schedules of food presentation in pigeons when the baseline performances were characterized by ratio strain. Although not all animals studied in the VR conditions of the present study showed inter-

ruptions of ratio responding to the extent revealed by Rat G31 (Figure 4), a pattern in which ratio runs (on the timeout lever) were at least briefly interrupted by avoidance responses was characteristic of each rat studied under the VR 15 schedule. Thus, increased timeout-lever response rates produced by cocaine (in the present study) or amphetamine (Galizio & Allen, 1991) are consistent with outcomes of studies of food-maintained behavior in which ratio response rates are low or show ratio strain.

Another aspect of the present results that warrants consideration is a comparison of the absolute and percentage-of-baseline data. In terms of absolute response-rate change, it was noted that cocaine increased timeout responding much more when it was maintained under the VR schedule (Figures 1 and 2). However, because baseline timeout responding was maintained at very low rates under the VI 45-s schedule in several of the rats, small absolute rate increases represented large percentage in-

creases. Thus, if the measure of drug effect is viewed in terms of percentage change, then VR and VI response rates were increased about equivalently (Figure 5). The same observations can be made for the effects of amphetamine (see Galizio & Allen, 1991, for absolute rates, and Figure 6 for percentage-of-baseline data).

Finally, a significant feature of the present findings is that behavior maintained by timeout from avoidance on either schedule was increased more than behavior maintained under the avoidance schedule by cocaine (and amphetamine). This differential effect was evident whether the data were considered in absolute or percentage change units. These differences might be explained by differential resistance to change of avoidance versus timeout, by some reduced sensitivity to rate acceleration of postponement schedules, by an antipunishment account (if behavior allocated to the timeout lever is viewed as suppressed by occasional exposure to shock), or as an increase in the reinforcement efficacy of timeout from avoidance by the drug (see Galizio & Allen, 1991, for further elaboration of these hypotheses). More direct experimental analysis of the various possible accounts of these findings is indicated.

REFERENCES

- Ator, N. A. (1979). Effects of chlordiazepoxide on comparable rates of responding maintained under food and shock avoidance schedules. *Psychopharmacology*, 66, 227-231.
- Bacotti, A. V. (1979). Pentobarbital and *d*-amphetamine effects on concurrent performances. *Journal of the Experimental Analysis of Behavior*, 31, 141-158.
- Bacotti, A. V. (1980). Effects of cocaine and morphine on concurrent schedule-controlled performances. *Journal of Pharmacology and Experimental Therapeutics*, 212, 280-286.
- Barrett, J. E. (1976). Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. *Journal of Pharmacology and Experimental Therapeutics*, 196, 605-615.
- Barrett, J. E. (1987). Nonpharmacological factors determining the behavioral effects of drugs. In H. Y. Meltzer (Ed.), *Psychopharmacology: The third generation of progress* (pp. 1493-1501). New York: Raven Press.
- Barrett, J. E., Dworkin, S. I., & Zuccarelli, R. R. (1977). Effects of *d*-amphetamine, chlordiazepoxide, and promazine on responding of squirrel monkeys maintained under fixed-interval schedules of food presentation and stimulus-shock termination. *Pharmacology Biochemistry and Behavior*, 7, 529-535.
- Barrett, J. E., & Katz, J. L. (1981). Drug effects on behaviors maintained by different events. In T. Thompson, P. B. Dews, & W. A. McKim (Eds.), *Advances in behavioral pharmacology* (Vol. 3, pp. 119-165). New York: Academic Press.
- Branch, M. N. (1991). Behavioral pharmacology. In I. H. Iversen & K. A. Lattal (Eds.), *Experimental analysis of behavior* (Part 2, pp. 21-78). Amsterdam: Elsevier.
- Dalrymple, S. D., & Stretch, R. (1971). Effects of amphetamine and chlorpromazine on second-order escape behavior in squirrel monkeys. *Psychopharmacology*, 21, 268-282.
- Dews, P. B. (1958). Studies on behavior. IV. Stimulant actions of methamphetamine. *Journal of Pharmacology and Experimental Therapeutics*, 122, 137-147.
- Dworkin, S. I., Pitts, R., & Galizio, M. (1993). Schedule-controlled behavior: Negative reinforcement. In F. van Haaren (Ed.), *Methods in behavioral pharmacology* (pp. 101-116). Amsterdam: Elsevier.
- Galizio, M., & Allen, A. R. (1991). Variable-ratio schedules of timeout from avoidance: Effects of *d*-amphetamine and morphine. *Journal of the Experimental Analysis of Behavior*, 56, 193-203.
- Galizio, M., Hale, K. L., Liborio, M. O., & Miller, M. (1993). Variable-ratio schedules of timeout from avoidance: Effects of anxiolytic drugs. *Behavioural Pharmacology*, 4, 487-493.
- Galizio, M., & Perone, M. (1987). Variable-interval schedules of timeout from avoidance: effects of chlordiazepoxide, CGS 8216, morphine, and naltrexone. *Journal of the Experimental Analysis of Behavior*, 47, 115-126.
- Galizio, M., Perone, M., & Spencer, B. A. (1986). Variable-interval schedules of timeout from avoidance: Effects of ethanol, naltrexone, and CGS 8216. *Pharmacology Biochemistry and Behavior*, 25, 439-448.
- Hoffman, S. H., Branch, M. N., & Sizemore, G. M. (1987). Cocaine tolerance: Acute versus chronic effects as dependent upon fixed-ratio size. *Journal of the Experimental Analysis of Behavior*, 47, 363-376.
- Hughes, C. E., & Branch, M. N. (1991). Tolerance to and residual effects of cocaine in squirrel monkeys depend on reinforcement-schedule parameter. *Journal of the Experimental Analysis of Behavior*, 56, 345-360.
- Johanson, C. E. (1978). Effects of intravenous cocaine, diethylpropion, *d*-amphetamine and perphenazine on responding maintained by food delivery and shock avoidance in rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics*, 204, 118-129.
- Kelleher, R. T., & Morse, W. H. (1964). Escape behavior and punished behavior. *Federation Proceedings*, 23, 808-817.
- Logan, L., Carney, J. M., Holloway, F. A., & Seale, T. W. (1989). Effects of caffeine, cocaine and their combination on fixed-interval behavior in rats. *Pharmacology Biochemistry and Behavior*, 33, 99-104.
- McKearney, J. W. (1981). Rate-dependency: Scope and limitations in the explanation and analysis of the behavioral effects of drugs. In T. Thompson, P. B. Dews, & W. A. McKim (Eds.), *Advances in behavioral pharmacology* (Vol. 3, pp. 91-110). New York: Academic Press.
- Morse, W. H., & Herrnstein, R. J. (1956). Effects of drugs on characteristics of behavior maintained by

- complex schedules of intermittent positive reinforcement. *Annals of the New York Academy of Sciences*, 65, 303-317.
- Perone, M., & Galizio, M. (1987). Variable-interval schedules of timeout from avoidance. *Journal of the Experimental Analysis of Behavior*, 47, 97-113.
- Schama, K. F., & Branch, M. N. (1989). Tolerance to effects of cocaine on schedule-controlled behavior: Effects of fixed-interval schedule parameter. *Pharmacology Biochemistry and Behavior*, 32, 267-274.
- Shelnutt, S., Hudzik, T. J., Lattin, D. L., & McMillan, D. E. (1992). Effects of cocaine and ethylcocaine on schedule-controlled responding in rats. *Pharmacology Biochemistry and Behavior*, 43, 509-511.
- Smith, J. B. (1990). Situational specificity of tolerance to decreased operant responding by cocaine. *Pharmacology Biochemistry and Behavior*, 36, 473-477.
- Spealman, R. D., Goldberg, S. R., Kelleher, R. T., Morse, W. H., Goldberg, D. M., Hakansson, C. G., Nieforth, K. A., & Lazer, E. S. (1979). Effects of norcocaine and some norcocaine derivatives on schedule-controlled behavior of pigeons and squirrel monkeys. *Journal of Pharmacology and Experimental Therapeutics*, 210, 196-205.
- Todorov, J. C., Gorayeb, S. R. P., Correa, D. L., & Graeff, F. G. (1972). Effects of amphetamine on choice behavior in pigeons. *Psychopharmacologia*, 26, 395-400.
- van Haaren, F. (1992). Differential effects of cocaine on high and low response rates maintained with and without rate requirements. *Behavioural Pharmacology*, 3, 435-441.
- Verhave, T. (1962). The functional properties of a timeout from an avoidance schedule. *Journal of the Experimental Analysis of Behavior*, 5, 391-422.
- Zirix, J. M., Snyder, J. R., Newland, M. C., & Weiss, B. (1993). Amphetamine modifies the microstructure of concurrent behavior. *Experimental and Clinical Psychopharmacology*, 1, 121-132.

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