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ANALYSIS OF FIXED-RATIO BEHAVIOR MAINTAINED BY DRUG REINFORCERS

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Behavior maintained by intravenously delivered alfentanil, cocaine, or ketamine was assessed using a fixed-ratio schedule of reinforcement. As the dose of each drug was increased, rate of responding also increased up to a maximum. Further increases in dose resulted in decreased response rates (inverted U-shaped curve). An analysis of postreinforcement-pause-time and run-time measures for the ascending limb of the inverted U-shaped functions revealed that behavior was characterized by systematic decreases in both pause time and run time as dose and rate increased. An examination of the descending limb of the dose–response functions revealed that lowered response rates for cocaine and ketamine were correlated with increases in run time and small and inconsistent effects on postreinforcement pause time. Behavior maintained by rate-reducing doses of alfentanil was characterized by lengthened postreinforcement pauses with small increases in run time. These data suggest that at larger doses, drug reinforcers may have unconditioned or direct effects on the behavior that the drug is maintaining, and more important, that the nature of these unconditioned effects depends on the drug that is maintaining behavior.

Key words: fixed-ratio schedule, run time, postreinforcement pause, self-administration, alfentanil, cocaine, ketamine, lever press, rhesus monkeys

The relationship between reinforcer magnitude and overall rate of operant behavior maintained under fixed-ratio (FR) schedules of reinforcement has been described as direct, inverse, or as an inverted U-shaped function. The specific shape of the magnitude-rate function depends on the schedule parameters used during an experimental session. Some of the relevant parameters include the range of reinforcer magnitudes tested (Downs & Woods, 1974; Kliner, Lemaire, & Meisch, 1988; Lemaire & Meisch, 1984, 1985), the fixed-ratio requirement (Kliner et al., 1988; Lemaire & Meisch, 1984, 1985; Moreton, Meisch, Stark, & Thompson, 1977; Pickens, Muchow, & DeNoble, 1981), and the duration of a scheduled postreinforcement timeout (Downs & Woods, 1974; Young & Woods, 1981).

When the FR requirement is held constant and the effects of a relatively large range of reinforcer magnitudes are tested, a consistent finding is that response rates vary inversely with magnitude of reinforcement. For example, response rate was found to vary inversely with magnitude of reinforcement in rats whose behavior was maintained by food, cocaine, or amphetamine under an FR 1 schedule of reinforcement (Pickens & Harris, 1968; Pickens & Thompson, 1968). In addition, an inverse relationship between concentration of a milk reinforcer and response rate was found in rats maintained under FR 30, fixed-interval (FI 60-s) and tandem FR 1 FI 60-s schedules of reinforcement (Lowe, Davey, & Harzem, 1974).

When a wide range of reinforcer magnitudes is assessed, a consistent finding is that response rate is an inverted U-shaped function of reinforcer magnitude. That is, reinforcer magnitude and response rates are directly related until a point at which further increases in magnitude of reinforcement result in progressive decreases in response rates. An inverted U-shaped relationship between response rate and magnitude of reinforcement has been observed under a variety of schedule conditions and with a variety of reinforcers, including food (Kliner et al., 1988), drugs (e.g., Downs & Woods, 1974; Goldberg & Kelleher, 1976; Lemaire & Meisch, 1984; Moreton et al., 1977; Pickens et al., 1981; Winger, Palmer, & Woods, 1989; Woolverton, Goldberg, & Ginos, 1984), and electrical stimulation of the brain (Reynolds, 1958).

The ascending limb of the inverted U-shaped function has been attributed to an increase in reinforcing effect as magnitude of reinforcer increases (Lemaire & Meisch, 1984), whereas the descending limb of the inverted U-shaped function has been attributed to one of two factors: satiation under food reinforcement con-

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ditions (Hodos & Kalman, 1963; Kliner et al., 1988; Sidman & Stebbins, 1954), and direct or unconditioned effects induced by drugs at high doses (Downs & Woods, 1974; Pickens & Thompson, 1968) or high-voltage electrical stimulation of the brain (Reynolds, 1958).

To examine more closely the effects of reinforcer magnitude on operant response rates, some researchers (e.g., Felton & Lyon, 1966; Lowe et al., 1974) have performed a molecular analysis of the behavior whereby overall rate is broken down into temporal components. For example, behavior maintained under an FR schedule of reinforcement has been characterized by a pause that precedes a steady rate of responding until the next reinforcer is obtained. The two temporal components most often analyzed with respect to FR behavior are (a) the time to initiate the response sequence (postreinforcement pause), and (b) the time to complete the FR schedule requirement (run time).

With regard to food-maintained behavior, the relationship between postreinforcement pause and reinforcer magnitude has been described as direct (Lowe et al., 1974; Staddon, 1970), inverse (Meunier & Starratt, 1979; Powell, 1969), or U-shaped (Kliner et al., 1988) depending upon the rate changes produced by variations in reinforcer magnitude. However, unlike postreinforcement pause, run time or running rate has not been found to vary in any systematic manner with overall response rate or manipulations of reinforcer magnitude (Kliner et al., 1988; Lowe et al., 1974; Meunier & Starratt, 1979; Powell, 1969).

When drugs are used to maintain behavior, they may have a greater likelihood of disrupting behavior than does food, and the pattern of this disruptive effect may vary among drugs. An indication that drugs from pharmacologically different classes may differentially affect pause time or run time comes from work by Downs and Woods (1974). Cumulative records of codeine- or cocaine-reinforced responding obtained at doses that lie along the descending limb of the rate–magnitude function suggested that increases in unit dose of codeine resulted in increases in pause time and irregular response patterns as the FR requirement was being completed. An increase in cocaine dose appeared to produced dose-dependent increases in pause time alone (Downs & Woods, 1974). Similarly, data obtained by Pickens and Thompson (1968) suggested that the descending limb of the inverted U-shaped function relating rate to unit dose of cocaine was characterized by systematic changes in postreinforcement pause time with no effect on run time or running rate. When unit doses of cocaine that maintained responding were delivered noncontingently to rats whose behavior was maintained by food, similar dose-dependent increases in postreinforcement pause time were observed, suggesting that the direct or unconditioned effects of cocaine may be characterized by alterations in postreinforcement pause time (Pickens & Thompson, 1968).

Although these findings suggest that drug-specific disruptions in FR performance under high-dose self-administration conditions may be characterized in terms of their effects on the temporal elements of FR responding, a quantitative analysis of these relationships among several self-administered drugs has not been performed. Furthermore, a systematic evaluation of postreinforcement pause and run-time changes for the ascending limb of the inverted U-shaped dose–effect function has not been evaluated under drug reinforcement conditions. To address these issues, we examined changes in overall response rate, postreinforcement pause times, and run times in monkeys whose lever-press responding was currently maintained by alfentanil, cocaine, or ketamine over a range of doses that produced an inverted U-shaped function with response rate.

METHOD

Subjects

Ten rhesus monkeys (*Macaca mulatta*) of both sexes were used as subjects. Monkeys weighed between 5.6 and 9.8 kg and lived in the experimental chambers with unlimited access to water and Purina® Monkey Chow. Monkeys were surgically implanted with intravenous silastic catheters according to the procedure used by Winger et al. (1989). All subjects had moderate to extensive self-administration histories (several months to years) and were exposed to a variety of pharmacological agents prior to the start of this experiment.

Apparatus

Monkeys were permanently housed in stainless steel cages (83.3 cm by 76.2 cm by

91.4 cm deep). The front, top, and bottom of the cage were made of barred stainless steel, and a pan was located below the floor to collect animal waste. Located on the wall to the left of the barred front door was a response and stimulus panel 15.4 cm on a side, approximately 10 cm from the front and 19 cm from the bottom of the cage. Near the top of the stimulus panel were three circular openings (2.5 cm), separated by 2.5 cm, that were covered by clear plastic. The center opening could be illuminated from behind by a 5-W green Christmas-tree bulb, the right opening by a red bulb, and the leftmost opening was unlit at all times. Centered below the right and left openings were response levers (Model 121-07, BRS-LVE) capable of being operated by 10 to 15 g (0.10 to 0.15 N) of force. The experimental contingencies were programmed and data were recorded using IBM PCjr® computers located in an adjacent room.

Each monkey wore a stainless steel harness to which a jointed hollow restraining arm was attached. The catheter passed from the monkey through the restraining arm to the outside of the cage, where it attached to a roller infusion pump (Watson and Marlow Co., Model MHRK 55) and necessary filters, valves, and bags of sterile vehicle and drug solutions. The pumps were calibrated to deliver 0.2 mL/s. The restraining- and catheter-protection arm and stainless steel harness have been described in detail elsewhere (see Deneau, Yanagita, & Seevers, 1969; Winger et al., 1989).

Procedure

Monkeys were trained under the experimental contingencies with a method described in detail by Winger et al. (1989). All subjects received two experimental sessions daily, with sessions starting at approximately 10:00 a.m. and 4:00 p.m. Each session was composed of four response periods, during each of which one of four doses of drug was delivered contingent on appropriate responses. Response periods within each session were separated by a 10-min timeout period, and each response period lasted until 25 min elapsed or the subject received 20 injections.

A response period was signaled by illumination of a red light located above the operative (right) response lever; completion of 30 lever-press responses (FR 30) on that lever in the presence of the red light resulted in activation of an infusion pump (signaled by a green light) and was followed immediately by a 45-s timeout, during which both lights were unlit and lever-press responses had no programmed consequence. The doses of drug differed by 0.5 log (base 10) steps and were controlled by varying the duration of pump action from 0.5 to 16.7 s. For example, a 0.01 mg/kg/mL stock solution of cocaine infused with pump durations of 0.5, 1.78, 5.0, or 16.7 s corresponded to cocaine doses of 0.001, 0.003, 0.01, and 0.03 mg/kg/inj, respectively. When response rates were a direct (not inverted U-shaped) function over the baseline dose range, it was necessary to increase the dose range by an increment of 0.5 log (base 10) unit. This was accomplished by increasing the concentration of drug in the stock solution and using identical infusion durations. For example, a 0.03 mg/kg/mL stock solution of cocaine, infused with the same pump durations described above, corresponded to cocaine doses of 0.003, 0.01, 0.03, and 0.1 mg/kg/inj. The drug doses were available in one of four orders (counterbalanced using a Latin square) that were randomly selected across sessions.

Stable FR baseline behavior was maintained for 3 subjects with alfentanil, 5 subjects with cocaine, and 2 subjects with ketamine. After all subjects were exposed to a dose range of the baseline drug that produced an inverted U-shaped function for overall rate (i.e., alfentanil [Janssen Pharmaceuticals], 0.03 to 3.0 μg/kg/inj; cocaine [Mallinckrodt], 0.001 to 0.1 mg/kg/inj; and ketamine [Vetalar, Fort Dodge Laboratories], 0.01 to 1.0 mg/kg/inj), subjects were given the opportunity to self-administer one and then the other of the two remaining compounds on several (no more than 25) consecutive sessions. The same dose ranges as had been used for the previous monkeys were used during crossover substitution sessions. Saline substitutions were also performed during baseline conditions in all subjects to determine whether lever pressing was being maintained by stimuli associated with drug infusions (e.g., the sound of the infusion pump, the stimulus signaling the infusion, subdermal temperature changes, pump vibration, etc.) or the drug stimulus itself. Whereas response rates were generally low during saline conditions, an occasional subject would require two to three consecutive saline sessions before response rates averaged less than 0.5 response per second.

Table 1

The number of response periods at each dose that were used to calculate average overall rate, postreinforcement pause, and run-time values for each monkey.

Monkey	Baseline[a]	Alfentanil dose (μg/kg/inj)				Cocaine dose (mg/kg/inj)				Ketamine dose (mg/kg/inj)			
		0.03	0.1	0.3	1.0	3.0	0.001	0.003	0.01	0.03	0.1	0.01	0.03	0.1	0.3	1.0
R639	COC	3	6	6	6[b]	3	7	14	14	14[a]	7	3	3	3[b]	3	—
80N106	COC	4	5	5[b]	5	1	2	4	4	4[b]	1	3	3[b]	3	3	—
P671	COC	2	7	7[b]	7	5	13	21	21	21[b]	8	2	2	2[b]	2	—
M123[c]	COC	2	4	4	4[b]	1	7	8	8[b]	8	1					
C489[c]	COC	3	5	5	5[b]	2	3	5	5	5[b]	3	2	4	4[b]	4	2
C478	ALF	12	14	14	14[b]	2	5	7	7	7[b]	2	3	5[b]	5	5	2
C1	ALF	9	11	11	11[b]	2	2	5	5[b]	5	3					
82-217[c]	ALF	9	11	11	11[b]	2	4	8	8	8[b]	4					
I11	KET	3	7	7	7[b]	4	3	6	6	6[b]	3	10	12	12[b]	12	2
288	KET	2	4	4	4[b]	2	2	4	4	4[b]	2	10	12	12[b]	12	2

[a] COC, cocaine; ALF, alfentanil; KET, ketamine.
[b] Peak dose.
[c] Monkey did not meet substitution criteria for the ketamine doses.

Overall rate, postreinforcement pause time, and run-time data obtained during several saline sessions were averaged over the four response periods to obtain a single saline value for each dependent variable.

During drug baseline and substitution conditions, criterion self-administration performance required overall response rates to be at least one response per second at at least one dose, and, either a direct, inverse, or inverted U-shaped function of overall rate with dose. During substitution conditions, subjects that did not maintain criterion performance for at least two consecutive sessions over a total of 25 sessions were returned to baseline conditions. If response rates were a direct function of unit dose, subjects that met criterion for two consecutive sessions were provided the opportunity to self-administer a 0.5 log unit higher dose range of the substituted drug over subsequent sessions until a dose was reached that produced a decrease in overall rate of response. Subjects were returned to baseline drug conditions and saline control trials between substitution tests. All 10 subjects met the self-administration criteria on at least two occasions for cocaine and alfentanil, whereas 3 subjects (2 cocaine-baseline and 1 alfentanil-baseline subject) failed to meet criterion self-administration performance under ketamine self-administration conditions.

Three dependent measures were used to describe self-administration behavior for all drugs at each dose: (a) overall rate was the total number of responses divided by the total amount of time available to respond per 25-min response period (i.e., excluding timeout and infusion time), (b) pause time was the amount of time from the onset of a signaled-response period to the first response (postreinforcement pause), and (c) run time was the amount of time from the first response to the completion of 30 responses. Run-time measures were discarded when fewer than 30 responses were emitted. Because the first pause of a response period (the time from the start of the response period to the first response) and the first 30 responses were not preceded by drug injections, these initial data were omitted from the following analyses. The number of observations at each dose for each subject under the various drug and saline substitution conditions that were used to compute average overall rate, pause time, and run time measures are shown in Table 1.

Table 2

Overall rate, postreinforcement pause, and run-time data for monkeys self-administering alfentanil. Saline data are shown only for alfentanil baseline subjects. The values are means (*SEM*) based on the number of response periods shown in Table 1.

Monkey	Saline	Alfentanil (μg/kg/inj) 0.03	0.1	0.3	1.0	3.0
Overall rate (r/s)						
R639		0.75 (0.02)	0.79 (0.02)	0.42 (0.09)	0.80[a] (0.28)	0.10 (0.03)
80N106		0.27 (0.10)	0.49 (0.15)	1.53[a] (0.20)	1.12 (0.11)	0.33 —[b]
P671		0.04 (0.02)	0.17 (0.04)	0.88[a] (0.18)	0.85 (0.17)	0.31 (0.04)
M123		0.07 (0.04)	0.11 (0.06)	0.42 (0.08)	0.86[a] (0.13)	0.41 (0.00)
C489		0.03 (0.01)	0.08 (0.02)	0.87 (0.26)	2.26[a] (0.12)	1.59 —[b]
C478	0.24 (0.02)	0.27 (0.05)	0.71 (0.20)	1.75 (0.22)	2.12[a] (0.20)	0.36 (0.02)
C1	0.20 (0.02)	0.36 (0.13)	0.66 (0.20)	1.58 (0.26)	2.22[a] (0.43)	0.56 (0.10)
82-217	0.13 (0.02)	0.15 (0.03)	0.35 (0.13)	1.18 (0.21)	1.43[a] (0.16)	0.40 (0.20)
I11		0.08 (0.03)	0.24 (0.06)	0.31 (0.06)	1.23[a] (0.34)	0.49 (0.09)
288		0.10 (0.01)	0.26 (0.11)	0.45 (0.24)	2.29[a] (0.69)	0.43 (0.03)
Postreinforcement pause (s)						
R639		439.67 (129.62)	385.62 (88.44)	62.45 (35.44)	56.19[a] (21.25)	225.99 (49.41)
80N106		119.73 (53.64)	62.36 (13.04)	8.30[a] (1.84)	8.94 (0.65)	46.31 —[b]
P671		413.22 —[b]	84.85 (32.29)	16.02[a] (4.89)	13.15 (4.84)	36.48 (4.49)
M123		12.85 (6.75)	42.45 (14.27)	17.13 (6.87)	2.90[a] (0.82)	13.35 (5.05)
C489		246.75 (224.85)	444.80 (144.05)	44.60 (31.07)	7.15[a] (0.94)	13.20 —[b]
C478	128.30 (20.87)	136.16 (22.74)	69.76 (18.87)	13.04 (4.37)	8.28[a] (2.15)	76.86 (0.62)
C1	149.45 (20.82)	107.48 (25.90)	91.45 (30.39)	17.17 (7.43)	9.89[a] (3.87)	33.36 (11.83)
82-217	150.87 (28.15)	143.93 (30.96)	182.80 (70.91)	24.38 (9.53)	9.65[a] (1.53)	25.23 (10.96)
I11		90.65 (37.88)	45.31 (18.57)	59.49 (28.34)	20.71[a] (5.38)	47.53 (9.99)
288		83.22 (36.75)	76.66 (29.02)	35.17 (16.04)	7.35[a] (5.47)	49.30 (2.52)
Run time (s)						
R639		71.68 (41.72)	212.85 (144.68)	43.38 (10.91)	34.26[a] (11.78)	163.19 (38.85)
80N106		40.66 (24.80)	15.86 (3.80)	13.13[a] (2.12)	19.39 (2.25)	51.51 —[b]
P671		14.46 —[b]	71.78 (20.75)	31.82[a] (8.11)	30.58 (7.66)	60.70 (10.35)
M123		320.30 —[b]	452.60 (154.70)	225.10 (45.75)	134.60[a] (14.96)	122.00 (24.70)
C489		459.50 —[b]	154.30 (18.95)	90.90 (8.57)	26.30[a] (1.19)	12.61 —[b]
C478	25.19 (4.33)	16.81 (2.88)	33.79 (13.17)	9.91 (1.01)	8.26[a] (0.80)	7.99 (1.23)
C1	32.85 (12.61)	37.97 (20.76)	20.04 (7.64)	15.92 (4.33)	14.55[a] (4.55)	25.67 (5.11)
82-217	85.83 (39.68)	56.19 (22.38)	20.33 (6.87)	24.19 (7.24)	16.21[a] (3.95)	27.46 (5.11)
I11		143.57 (135.33)	137.29 (71.07)	51.85 (13.51)	13.47[a] (3.57)	24.52 (8.41)
288		265.78 (10.33)	205.40 (100.91)	93.23 (80.40)	10.56[a] (2.02)	21.25 (2.81)

[a] Peak dose.

[b] *SEM* not available because only one observation was obtained at this dose.

RESULTS

Averaged overall rate, pause-time, and run-time measures for each subject at each dose of alfentanil, cocaine, or ketamine are presented in Tables 2, 3, and 4 for each drug, respectively. Striking individual differences emerged among subjects in terms of (a) the drug that maintained the highest rate of responding and (b) the response rates maintained at each dose. For example, a cocaine-baseline monkey (80N106) showed an average response rate of 1.12 responses per second when 0.03 mg/kg/inj cocaine was response contingent (the highest rate for this subject) and emitted maximum response rates of 1.53 responses per second and 1.67 responses per second with 0.3 μg/kg/inj alfentanil and 0.03 mg/kg/inj ketamine, respectively. In comparison, an alfentanil-baseline monkey (82-217) maintained maximum average rates of 1.43 and 3.92 responses per second with 1.0 μg/kg/inj alfentanil and 0.03 mg/kg/inj cocaine, respectively, but did not maintain response rates consistently over 1.00 response per second during the ketamine-substitution condition. Furthermore, whereas one dose usually maintained the highest rate of responding for most subjects, at least 2 subjects under each drug condition showed depressed rates at doses that maintained maximal rates in the other monkeys. For example, Subjects

Table 3

Overall rate, postreinforcement pause, and run-time data for monkeys self-administering cocaine. Saline data are shown only for cocaine baseline subjects. The values are means (*SEM*) based on the number of response periods shown in Table 1.

		Cocaine (mg/kg/inj)				
Monkey	Saline	0.001	0.003	0.01	0.03	0.1
Overall rate (r/s)						
R639	0.25 (0.10)	0.35 (0.11)	0.75 (0.17)	1.54 (0.25)	2.12[a] (0.30)	0.82 (0.13)
80N106	0.15 (0.02)	0.30 (0.26)	0.63 (0.36)	0.73 (0.47)	1.12[a] (0.15)	0.73 —[b]
P671	0.17 (0.03)	0.13 (0.02)	0.28 (0.05)	1.03 (0.11)	1.36[a] (0.11)	0.71 (0.07)
M123	0.31 (0.04)	0.20 (0.04)	0.67 (0.14)	1.20[a] (0.14)	1.08 (0.13)	0.19 —[b]
C489	0.11 (0.03)	0.17 (0.08)	0.74 (0.15)	2.23 (0.23)	2.83[a] (0.43)	1.05 (0.51)
C478		0.70 (0.26)	0.51 (0.19)	0.80 (0.30)	2.15[a] (0.40)	0.38 (0.09)
C1		1.16 (0.45)	1.95 (0.71)	2.48[a] (0.60)	2.12 (0.49)	0.97 (0.11)
82-217		2.23 (0.29)	2.46 (0.41)	3.81 (0.41)	3.92[a] (0.54)	2.13 (1.04)
I11		0.25 (0.00)	0.62 (0.38)	0.51 (0.35)	1.57[a] (0.42)	0.82 (0.33)
288		0.36 (0.03)	1.00 (0.44)	1.63 (0.37)	1.68[a] (0.81)	0.54 (0.14)
Postreinforcement pause (s)						
R639	217.14 (36.88)	167.13 (92.90)	68.84 (46.73)	8.26 (2.57)	3.76[a] (1.57)	8.93 (1.69)
80N106	255.20 (18.20)	363.46 (318.80)	121.61 (93.35)	8.89 (0.60)	12.57[a] (2.90)	26.06 —[b]
P671	89.45 (24.01)	106.88 (28.50)	75.78 (17.51)	21.58 (11.71)	1.93[a] (0.19)	1.90 (0.38)
M123	73.79 (20.27)	125.40 (26.85)	46.04 (33.80)	3.19[a] (1.44)	2.15 (0.46)	15.71 —[b]
C489	246.26 (49.43)	223.02 (59.80)	40.81 (7.54)	5.29 (1.28)	4.11[a] (1.23)	3.26 (0.60)
C478		104.15 (68.25)	49.43 (15.68)	129.72 (92.90)	3.97[a] (0.67)	55.67 (42.63)
C1		21.69 (12.41)	11.05 (5.74)	3.75[a] (1.20)	4.44 (1.57)	11.38 (2.79)
82-217		7.85 (3.24)	3.14 (0.63)	1.73 (0.47)	1.42[a] (0.12)	1.39 (0.32)
I11		65.43 (26.68)	88.51 (44.36)	51.78 (16.12)	73.66[a] (61.28)	17.26 (6.13)
288		43.50 (25.36)	55.66 (37.41)	10.49 (4.04)	9.14[a] (5.72)	39.02 (6.97)
Run time (s)						
R639	38.94 (23.62)	54.73 (18.66)	67.41 (29.69)	20.81 (4.37)	18.51[a] (4.06)	32.75 (5.32)
80N106	166.16 (154.08)	17.91 (9.00)	16.31 (3.53)	13.73 (4.60)	15.30[a] (4.11)	16.52 —[b]
P671	32.37 (6.11)	93.67 (33.29)	101.20 (24.72)	29.86 (4.28)	25.60[a] (3.76)	43.69 (3.53)
M123	34.86 (5.87)	72.63 (16.51)	32.23 (2.86)	23.75[a] (2.64)	29.28 (5.24)	164.48 —[b]
C489	139.08 (47.09)	103.97 (49.93)	23.71 (9.76)	11.68 (2.22)	8.61[a] (1.55)	47.21 (9.37)
C478		33.87 (18.50)	32.02 (11.86)	19.63 (3.75)	7.75[a] (0.57)	28.75 (23.66)
C1		8.82 (0.59)	15.51 (4.55)	12.69[a] (3.58)	17.15 (7.10)	21.55 (4.78)
82-217		6.94 (1.31)	12.09 (2.64)	6.99 (1.10)	8.45[a] (2.61)	24.14 (8.51)
I11		39.03 (21.31)	23.85 (7.30)	26.86 (10.05)	13.38[a] (5.39)	15.41 (6.37)
288		16.87 (5.91)	19.01 (8.29)	11.68 (3.52)	12.16[a] (5.26)	22.69 (12.11)

[a] Peak dose.

[b] *SEM* not available because only one observation was obtained at this dose.

80N106 and P671 maintained maximal rates at 0.3 μg/kg/inj alfentanil, whereas all other monkeys showed maximal rates at 1.0 μg/kg/inj alfentanil (see Table 2). Monkeys that emitted highest rates at a dose 0.5 log unit lower than the dose that maintained maximal response rates in the other monkeys were not the same across the drug substitution conditions (e.g., highest response rates at 0.5 log unit lower doses than the other monkeys were 80N106 and P671 for alfentanil, C1 and M123 for cocaine, and C1 and 80N106 for ketamine).

Although the dose–rate functions for individual monkeys were appreciably different, the total amount of self-infused drug under each dose condition was not. All subjects were nearly identical when total drug intake was plotted as a function of dose (data not shown).

To remove the effects of an individual subject's sensitivity to a self-administered drug dose and allow qualitative comparisons to be made among subjects and across drugs, data were "peak aligned" based on the dose that maintained the highest overall response rate. Thus, the peak alignment method involved identifying the dose that produced the highest overall rate of response (peak dose), and obtaining pause-time, run-time, and overall rate values at tested doses in 0.5 log steps above and below the peak dose. Overall rate, pause-

Table 4

Overall rate, postreinforcement pause, and run-time data for monkeys self-administering ketamine. Saline data are shown only for ketamine baseline subjects. The values are means (*SEM*) based on the number of response periods shown in Table 1.

Monkey	Saline	Ketamine (mg/kg/inj) 0.01	0.03	0.1	0.3	1.0
Overall rate (r/s)						
R639		0.11 (0.03)	0.38 (0.31)	0.80[a] (0.27)	0.28 (0.03)	
80N106		0.26 (0.23)	1.67[a] (0.34)	0.57 (0.15)	0.17 (0.01)	
P671		0.06 (0.03)	0.05 (0.05)	1.48[a] (0.26)	0.44 (0.02)	
M123[b]						
C489[b]						
C478		0.25 (0.07)	0.80 (0.21)	0.89[a] (0.17)	0.23 (0.01)	0.11 (0.01)
C1		1.43 (0.86)	2.24[a] (0.70)	0.46 (0.10)	0.15 (0.02)	0.06 (0.00)
82-217[b]						
I11	0.12 (0.03)	0.14 (0.04)	0.47 (0.21)	1.52[a] (0.22)	0.63 (0.04)	0.17 (0.01)
288	0.32 (0.16)	0.31 (0.08)	1.05 (0.21)	1.59[a] (0.16)	0.51 (0.04)	0.10 (0.00)
Postreinforcement pause (s)						
R639		195.16 (48.78)	287.11 (154.15)	27.09[a] (15.24)	20.41 (9.49)	
80N106		227.68 (194.35)	7.65[a] (2.10)	24.69 (12.44)	119.92 (7.58)	
P671		273.06 —[c]	166.01 —[c]	2.53[a] (1.40)	4.33 (0.50)	
M123[b]						
C489[b]						
C478		83.87 (5.16)	27.25 (12.48)	14.10[a] (3.99)	45.38 (10.03)	192.89 (45.87)
C1		53.04 (30.16)	23.23[a] (13.36)	22.45 (5.54)	60.95 (18.17)	477.58 (34.33)
82-217[b]						
I11	127.84 (36.89)	138.18 (44.15)	60.23 (31.69)	7.88[a] (2.37)	6.94 (0.84)	24.84 (7.03)
288	99.69 (19.92)	89.10 (27.21)	78.20 (60.76)	7.53[a] (1.33)	14.61 (5.89)	181.71 (2.91)
Run time (s)						
R639		122.76 (64.79)	16.56 (3.34)	33.22[a] (16.57)	91.95 (17.33)	
80N106		13.33 (5.13)	12.09[a] (2.07)	25.68 (3.84)	69.60 (2.80)	
P671		69.55 —[c]	25.25 —[c]	18.49[a] (2.10)	66.68 (2.84)	
M123[b]						
C489[b]						
C478		55.62 (32.98)	19.88 (3.87)	26.69[a] (7.11)	86.28 (8.41)	99.36 (4.81)
C1		6.82 (2.10)	11.24[a] (3.35)	73.22 (30.31)	204.76 (66.47)	148.41 (50.81)
82-217[b]						
I11	241.34 (85.59)	187.35 (68.44)	144.02 (103.68)	18.45[a] (3.27)	44.92 (4.05)	162.45 (40.59)
288	53.45 (13.69)	71.52 (19.27)	21.07 (8.09)	15.97[a] (3.04)	52.93 (3.57)	197.93 (41.41)

[a] Peak dose.
[b] Data not available because monkey did not meet substitution criteria (see text).
[c] *SEM* not available because only one observation was obtained at this dose.

time, and run-time values for each subject at relative log doses are presented in Figures 1, 2, and 3, for alfentanil, cocaine, and ketamine self-administration conditions, respectively.

Overall response rate was an inverted U-shaped function of dose for all drugs (Figures 1 through 3, top frames). Response rates under saline conditions were low for all subjects under each drug self-administration condition and were characterized by elevated pause and run times when compared to the dose maintaining the highest response rate.

Pause-time data at relative log doses of alfentanil, cocaine, and ketamine are shown in the middle frames of Figures 1, 2, and 3, respectively. An orderly decrease in pause times as rates increased from the lowest tested dose to peak dose occurred 25 of 28 times for alfentanil, 24 of 28 times for cocaine, and 11 of 12 times for ketamine. Repeated measures analysis of variance (ANOVA) confirmed the dose-dependent decrease in pause time from the peak − 1.5 to peak dose for alfentanil, $F(3, 21) = 7.51$, $p < .01$, and cocaine $F(3, 21) = 5.921$, $p < 0.5$, and from the peak − 1.0 to peak dose for ketamine, $F(2, 8) = 7.63$, $p < .05$. Run-time data for each subject at relative log doses of alfentanil, cocaine, and ket-

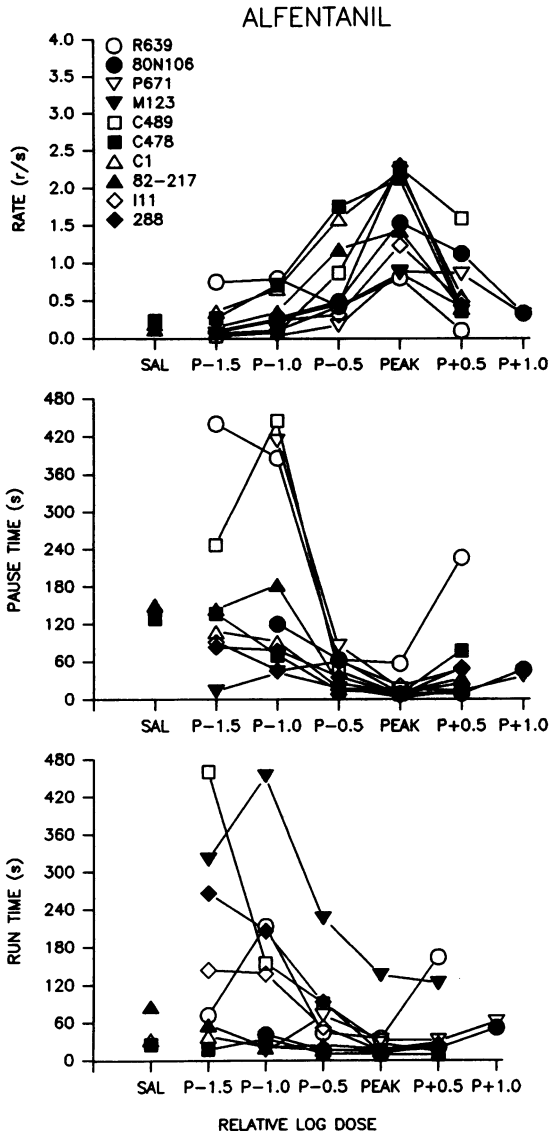

Fig. 1. Peak-aligned overall rate (top panel), pause time (middle panel), and run time (lower panel) plotted as a function of relative log dose for each subject under alfentanil self-administration conditions. Data obtained under saline substitution conditions during baseline response periods are indicated by SAL. Peak dose refers to the dose of drug that maintained the highest rate of responding, whereas peak − 1.5, peak − 1.0, and peak − 0.5 refer to doses 1.5, 1, and 0.5 log units lower than peak, respectively. Peak + 0.5 refers to the relative log dose 0.5 log unit higher than peak dose.

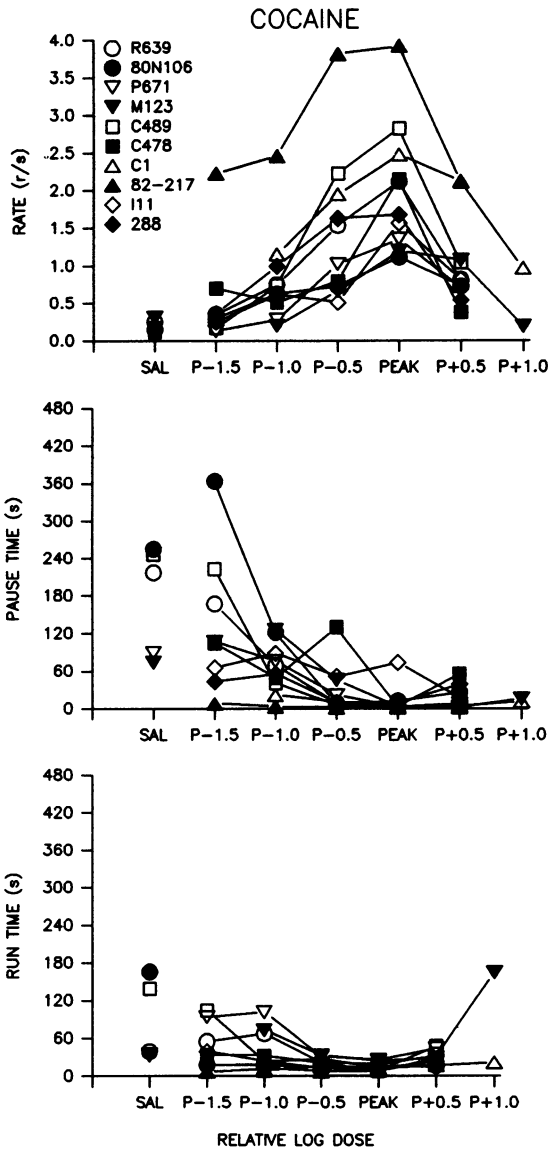

Fig. 2. Peak-aligned overall rate (top panel), pause time (middle panel), and run time (lower panel) plotted as a function of relative log dose for each subject under cocaine self-administration conditions. See Figure 1 for details.

amine are shown in the lower frames of Figures 1, 2, and 3, respectively. Similar to pause times, run times decreased in an orderly manner 24 of 28 times for alfentanil, 19 of 28 times for cocaine, and 9 of 12 times for ketamine. Statistical analyses confirmed that run times were significantly decreased in a dose-related manner from the peak − 1.5 to peak dose for alfentanil, $F(3, 21) = 5.68$, $p < .05$, and cocaine, $F(3, 21) = 4.98$, $p < .01$, and from the peak − 1.0 to peak dose for ketamine, $F(2, 8) = 6.84$, $p < .05$.

When response rates were inversely related

to drug dose (the descending limb of the inverted U-shaped function), differences emerged between drugs with regard to their effects on pause time and run time. Under alfentanil self-administration conditions, pause times increased in an orderly manner from the peak to the peak + 1.0 dose 11 of 12 times, whereas run times increased in an orderly manner 9 of 12 times (see Table 2 and Figure 1). Because only 2 subjects had valid data at the peak + 1.0 dose, the statistical analyses were performed over the peak and peak + 0.5 dose range. ANOVAs revealed that the increase in run time from peak to the peak + 0.5 dose was not statistically reliable, whereas the increase in pause time over this dose range approached, but did not attain, statistical significance, $F(1, 9) = 4.62$, $p = .06$.

When response rates decreased from peak to the peak + 1.0 dose for monkeys self-administering cocaine, pause time showed an orderly increase 8 of 12 times, whereas run time increased 12 of 12 times (see Table 3 and Figure 2). As with alfentanil, only 2 subjects had valid data at the peak + 1.0 dose. Therefore, these data were analyzed over the peak to peak + 0.5 dose range. Statistical analyses confirmed the fact that an increase in run time occurred from the peak to the peak + 0.5 cocaine dose, $F(1, 9) = 13.54$, $p < .01$, whereas pause-time increases were not statistically significant over this dose range.

Under the ketamine self-administration condition, an orderly increase in pause time occurred 12 of 15 times, whereas run-time increases were orderly 14 of 15 times over the peak to peak + 1.5 dose range (although only 1 subject was tested at the peak + 1.5 dose). Because 5 of 7 subjects were tested over the peak to peak + 1.0 dose range, data were analyzed first over the peak to peak + 0.5 dose range, and then over the peak to peak + 1.0 dose range. Statistically significant increases in run time, $F(1, 6) = 38.43$, $p < .01$, were found over the peak to peak + 0.5 dose range, whereas pause times were not increased significantly. However, as ketamine dose increased from peak to the peak + 1.0 dose, decreases in response rate were accompanied by increases in both pause time, $F(2, 8) = 9.72$, $p < .01$, and run time, $F(2, 8) = 17.29$, $p < .01$.

To explore more fully the changes in behavior occurring when doses were increased beyond those maintaining maximal rates, we

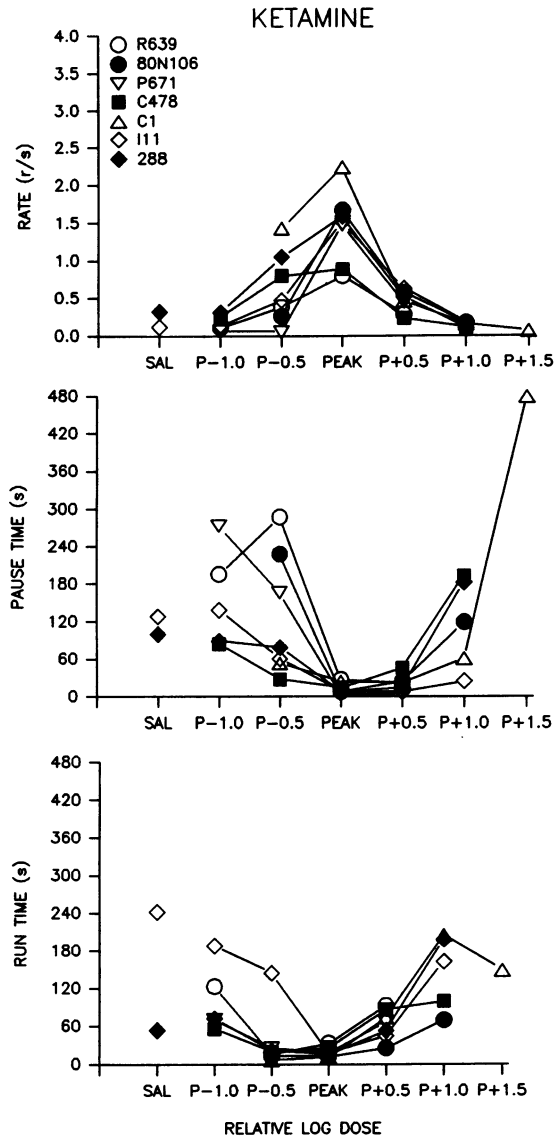

Fig. 3. Peak-aligned overall rate (top panel), pause time (middle panel), and run time (lower panel) plotted as a function of relative log dose for each subject under ketamine self-administration conditions. For details, refer to Figure 1.

examined the relationship between changes in rate, expressed as functions of changes in both run time and pause time. For example, if rate decreases occurring when dose increased from the peak to peak + 0.5 dose were reliably associated with increases in run time for all subjects self-administering cocaine, then one would expect a strong inverse relationship to exist between rate and run time for all subjects.

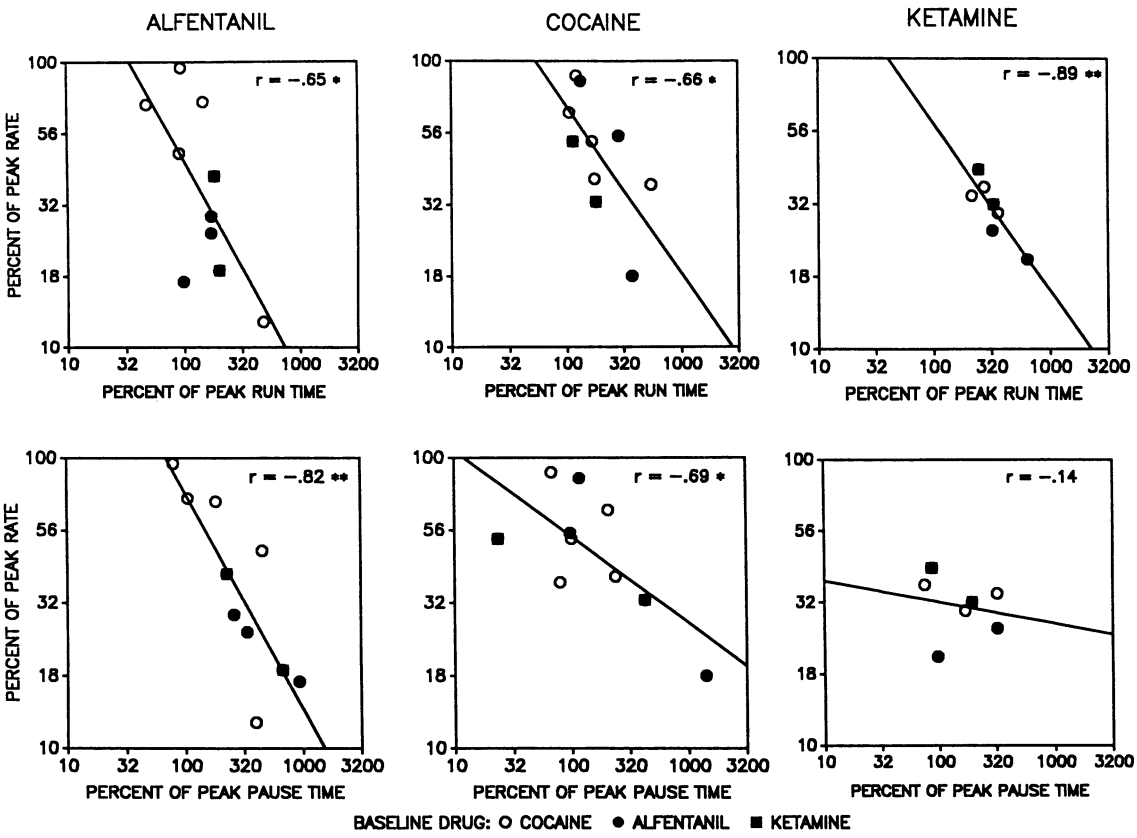

Fig. 4. Percentage decrease in rate from peak to peak + 0.5 dose conditions (y axis) plotted as a function of percentage change in run time (top row) and pause time (bottom row) for each drug. Note that log scales are used for all axes. Symbols represent the data obtained from a single subject and denote the drug used to maintain baseline self-administration behavior. Pearson correlation coefficients are presented in the upper right corners, and asterisks reflect p values: $^{*}p < .05$, $^{**}p < .01$. See text for details.

To investigate these relationships, proportion-change values were computed by dividing rate of responding obtained at the peak + 0.5 dose with rate obtained at the peak dose. Proportion-change values for pause time and run time were similarly computed by dividing values at peak + 0.5 dose with peak dose values. Because visual analysis of the frequency distributions for most variables were positively skewed (data not shown), all values were log (base 10) transformed prior to the computation of Pearson correlations. For purposes of displaying the relationships graphically, data were transformed to percentages by multiplying by 100 and plotted on log–log coordinates.

The relationships between percentage change in rate expressed as a function of percentage change in run time and pause time for alfentanil, cocaine, and ketamine self-administering subjects are shown in Figure 4. The y axis in each frame reflects the percentage of peak rate when dose increased from peak to peak + 0.5 dose. Values near the 100% tick mark on the y axis indicate relatively little change in rate as dose increased from peak to peak + 0.5 dose, whereas more substantial changes (decreases) in rate fall correspondingly lower along the y axis. In a similar manner, run times at the peak + 0.5 dose that did not differ from peak dose run times fall near the 100% value in the x axis, whereas relatively large increases in run time relative to peak dose run times are reflected in data points lying to the right along the x axis in the top row of Figure 4. Regression lines were fit to the data in each frame using the method of least squares, and correlation coefficients (shown in the upper-right corner of each frame in Figure 4)

describe the degree to which data points cluster along the lines of best fit. In addition, the degree to which rate decreases are associated with increases in pause time and/or run time are further described in terms of the slope of the lines of best fit. Thus, differences in slopes reflect the fact that either pause time or run time were more strongly related to decreases in overall rate.

Changes in rate from peak to peak + 0.5 dose were more consistently reflected in changes in pause time than run time for subjects self-administering alfentanil (Figure 4) as evidenced by a larger correlation coefficient for the pause time by rate relationship. Although a tighter relationship emerged between change in rate expressed as a change in pause time, the slopes of the lines of best fit were nearly identical for the run-time (− 0.74) and pause-time (− 0.75) measures.

The degree to which changes in rate were accompanied by changes in run time and pause time for cocaine-maintained subjects is shown in the middle frames of Figure 4. Although the correlation coefficient for pause-time changes was of greater magnitude than for run-time changes, half of the subjects that showed decreases in rates evidenced either no change or a decrease in pause time. In fact, Subject I11 showed a decrease in pause time to 23% of peak accompanied by a decrease in rate to 56% of peak (Figure 4). These data, and the fact that the slopes of the lines of best fit differ markedly among the two measures (rate by run time −0.59, rate by pause time −0.30), suggest that decreases in rate from the peak to peak + 0.5 dose are largely due to increases in run time.

Performance of ketamine-maintained subjects at rate-decreasing doses was clearly associated with consistent increases in run time (slope = −0.55), whereas no relationship emerged between pause time and rate changes (slope = −0.05) for these subjects (Figure 4). These data show that as ketamine dose increased from the peak to peak + 0.5 dose, subjects that showed greater rate reductions were more likely to have lengthened run times.

In addition to assessing the degree to which drugs systematically affect changes in rate as a function of changes in pause and run time, data presented in this form permit comparisons to be made with regard to the drug maintaining baseline self-administration behavior. If, for example, subjects maintained by alfentanil during baseline were more likely to exhibit changes in pause time under cocaine and ketamine substitution conditions, these effects may be found by examining Figure 4. Alfentanil-baseline subjects that showed increases in pause time as rates decreased were no more likely to exhibit reliable increases in pause time as rates decreased under high-dose cocaine and ketamine self-administration conditions (Figure 4). These data, and similar comparisons made for subjects maintained on cocaine and ketamine baselines, indicate that moderate to extensive drug experience under baseline conditions does not predispose subjects to respond in a particular mode when other drug reinforcers are available.

DISCUSSION

Contingent delivery of alfentanil, cocaine, or ketamine following completion of an FR 30 schedule of reinforcement resulted in inverted U-shaped functions of rate as dose (reinforcer magnitude) increased. These findings are similar to those obtained in other self-administration experiments (Carroll & Stotz, 1983; Downs & Woods, 1974; Goldberg & Kelleher, 1976; Moreton et al., 1977; Winger et al., 1989; Woolverton et al., 1984). Moreover, the dose that maintained the highest overall rate of responding differed among the subjects tested, suggesting that some subjects were more sensitive than others to either or both the reinforcing and unconditioned (rate-decreasing) effects of these compounds. When the variability of individual subjects' sensitivity to drug dose was removed by the peak alignment method, overall response rates were qualitatively similar among the drug reinforcers tested.

The analysis of pause-time and run-time measures when rates were a direct function of unit dose indicates that increases in response rates under alfentanil, cocaine, and ketamine reinforcement conditions were accompanied by shortened postreinforcement pauses and run times. In addition, response rates under extinction (i.e., saline substitution) conditions were similar to those obtained under low-dose drug reinforcement conditions in that overall rates were low and pause-time and run-time measures were elevated when compared to behavior maintained by the peak dose. That self-administration behavior maintained by drug

reinforcers from pharmacologically different classes revealed similar patterns with regard to consistent and regular changes in pause-time and run-time measures on the ascending limb of the inverted U-shaped function suggests that a single behavioral process may account for the similarity among drugs observed here. That is, the increase in rate of responding, with concomitant decreases in run and pause times, as doses (reinforcer magnitudes) increased to the peak dose may be attributed to an increase in the reinforcing effect of the self-administered drugs tested here.

With regard to the descending limb of the magnitude–rate functions, the analysis of pause-time and run-time measures revealed differences among the self-administered drugs. Overall, these data suggest that a self-administered compound may affect specific measures of drug-taking behavior and, further, that the effects may be specific to the drug that is self-administered. Delayed initiation of an FR response sequence (i.e., increase in postreinforcement pause) characterized the direct effects of alfentanil, whereas a slowing of responding during completion of the FR requirement (i.e., increase in run time) characterized the direct effects of cocaine and ketamine on self-administration behavior. Because the drugs differentially affected molecular aspects of self-administration behavior, a single behavioral process (self-titration, satiation) does not account completely for rate declines at relatively large self-administered doses.

With regard to cocaine-maintained behavior in rats (Pickens & Thompson, 1968) and monkeys (Downs & Woods, 1974), postreinforcement-pause time increased directly as a function of cocaine dose for the descending limb of the magnitude–rate function. Our results showing that run times reliably increased as dose of cocaine increased beyond peak dose levels, and, further, that 5 of the 10 subjects had shorter postreinforcement pauses at a rate-decreasing dose than at a peak-cocaine dose (see Table 3), suggest that a direct relationship between dose and pause time may not always develop, despite the findings of such a relationship by Downs and Woods (1974) and Pickens and Thompson (1968). It seems likely, at least for half of the subjects, that the rate-dependency hypothesis may account for the direct or unconditioned effects of relatively large cocaine doses on cocaine self-administration behavior (Dews, 1958). That is, the pause-and-run pattern characteristic of FR responding may have been affected by cocaine such that under conditions in which response rates are low (as during the postreinforcement pause), cocaine served to increase the probability of responding, whereas under conditions that typically engender high response rates (as when the FR requirement is being completed), cocaine reduces responding. This interpretation is consistent with the findings reported by McAuley and Leslie (1986) on the effects of amphetamine in rats responding under FI schedules of food reinforcement.

Self-administered drugs have dual effects in the sense that they serve as reinforcers at the same time and at the same doses that they act as unconditioned stimuli that disrupt ongoing response patterns. On the ascending limb of the unit-dose–response-rate function, there is a direct relation between dose and the reinforcing effect of the drug, although this limb of the curve is almost certainly modified by the direct effects of the drug on rates of responding. As unit dose increases further and rates of responding decrease (descending limb of the function), the reinforcing effects of the drug probably continue to increase but are masked by the rate-reducing effect of the drug. Initially, the overall pattern of rate reduction may differ somewhat among drugs in that some drugs may modify aspects of the pattern of drug-maintained responding that are less affected by other drugs. However, as dose and total drug intake continue to increase, the net effect is further suppression of responding, reflected in a general lengthening of pause time and run time.

REFERENCES

Carroll, M. E., & Stotz, D. C. (1983). Oral *d*-amphetamine and ketamine self-administration by rhesus monkeys: Effects of food deprivation. *Journal of Pharmacology and Experimental Therapeutics*, **227**, 28–34.

Deneau, G., Yanagita, T., & Seevers, M. H. (1969). Self-administration of psychoactive substances by the monkey. *Psychopharmacologia*, **16**, 30–48.

Dews, P. B. (1958). Studies on behavior: IV. Stimulant actions of methamphetamine. *Journal of Pharmacology and Experimental Therapeutics*, **122**, 137–147.

Downs, D. A., & Woods, J. H. (1974). Codeine- and cocaine-reinforced responding in rhesus monkeys: Effects of dose on response rates under a fixed-ratio schedule. *Journal of Pharmacology and Experimental Therapeutics*, **191**, 179–188.

Felton, M., & Lyon, D. O. (1966). The post-reinforcement pause. *Journal of the Experimental Analysis of Behavior,* **9,** 131–134.

Goldberg, S. R., & Kelleher, R. T. (1976). Behavior controlled by scheduled injections of cocaine in squirrel and rhesus monkeys. *Journal of the Experimental Analysis of Behavior,* **25,** 93–104.

Hodos, W., & Kalman, G. (1963). Effects of increment size and reinforcer volume on progressive ratio performance. *Journal of the Experimental Analysis of Behavior,* **6,** 387–392.

Kliner, D. J., Lemaire, G. A., & Meisch, R. A. (1988). Interactive effects of fixed-ratio size and number of food pellets per fixed ratio on rats' food-reinforced behavior. *Psychological Record,* **38,** 121–143.

Lemaire, G. A., & Meisch, R. A. (1984). Pentobarbital self-administration in rhesus monkeys: Drug concentration and fixed-ratio size interactions. *Journal of the Experimental Analysis of Behavior,* **42,** 37–49.

Lemaire, G. A., & Meisch, R. A. (1985). Oral drug self-administration in rhesus monkeys: Interactions between drug amount and fixed-ratio size. *Journal of the Experimental Analysis of Behavior,* **44,** 377–389.

Lowe, C. F., Davey, G. C. L., & Harzem, P. (1974). Effects of reinforcement magnitude on interval and ratio schedules. *Journal of the Experimental Analysis of Behavior,* **22,** 553–560.

McAuley, F., & Leslie, J. C. (1986). Molecular analyses of the effects of *d*-amphetamine on fixed-interval schedule performance of rats. *Journal of the Experimental Analysis of Behavior,* **45,** 207–219.

Meunier, G. F., & Starratt, C. (1979). On the magnitude of reinforcement and fixed-ratio behavior. *Bulletin of the Psychonomic Society,* **13,** 355–356.

Moreton, J. E., Meisch, R. A., Stark, L., & Thompson, T. (1977). Ketamine self-administration by the rhesus monkey. *Journal of Pharmacology and Experimental Therapeutics,* **203,** 303–309.

Pickens, R., & Harris, W. C. (1968). Self-administration of *d*-amphetamine by rats. *Psychopharmacologia,* **12,** 158–163.

Pickens, R., Muchow, D., & DeNoble, V. (1981). Methohexital-reinforced responding in rats: Effects of fixed ratio size and injection dose. *Journal of Pharmacology and Experimental Therapeutics,* **216,** 205–209.

Pickens, R., & Thompson, T. (1968). Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. *Journal of Pharmacology and Experimental Therapeutics,* **161,** 122–129.

Powell, R. W. (1969). The effect of reinforcement magnitude upon responding under fixed-ratio schedules. *Journal of the Experimental Analysis of Behavior,* **12,** 605–608.

Reynolds, R. W. (1958). The relationship between stimulation voltage and rate of hypothalamic self-stimulation in the rat. *Journal of Comparative and Physiological Psychology,* **51,** 193–198.

Sidman, M., & Stebbins, W. C. (1954). Satiation effects under fixed-ratio schedules of reinforcement. *Journal of Comparative and Physiological Psychology,* **47,** 114–116.

Staddon, J. E. R. (1970). Effect of reinforcement duration on fixed-interval responding. *Journal of the Experimental Analysis of Behavior,* **13,** 9–11.

Winger, G., Palmer, R. K., & Woods, J. H. (1989). Drug-reinforced responding: Rapid determination of dose–response functions. *Drug and Alcohol Dependence,* **24,** 135–142.

Woolverton, W. L., Goldberg, L. I., & Ginos, J. Z. (1984). Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics,* **230,** 678–683.

Young, A. M., & Woods, J. H. (1981). Maintenance of behavior by ketamine and related compounds in rhesus monkeys with different self-administration histories. *Journal of Pharmacology and Experimental Therapeutics,* **218,** 720–727.

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