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A CHOICE PROCEDURE FOR DRUG REINFORCERS: COCAINE AND METHYLPHENIDATE IN THE RHESUS MONKEY[1-3]

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ABSTRACT

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A choice procedure was developed to compare the reinforcing efficacy of drug solutions delivered *via* intravenous catheters to rhesus monkeys. Choices were arranged between doses of cocaine or methylphenidate and saline, different doses of the same drug and doses of both drugs. In each session, monkeys were allowed to self-inject one solution five times in the presence of a stimulus. Thirty minutes after the fifth injection, a second solution could be self-injected five times in the presence of a different stimulus. Thirty minutes later, choice trials began in which both stimuli were present and monkeys could choose one of the two solutions. Rate of responding decreased with increases in dose for both cocaine (0.05–1.5 mg/kg) and methylphenidate (0.075–0.7 mg/kg). Response rates maintained by cocaine were 2 to 3 times higher than those maintained by methylphenidate. Drug was always chosen over saline. Higher doses of cocaine were preferred to lower doses except when both were above 0.5 mg/kg, when no preference was shown. Higher doses of methylphenidate were preferred over low doses, but compared to cocaine, a greater absolute difference between dose magnitude was required to demonstrate preference. When equal doses of cocaine and methylphenidate were compared, no preference was shown. On other comparisons between the drugs, the higher dose was generally preferred regardless of the drug. The reinforcing efficacy of drugs must be considered not only in terms of response rate maintained or reinforcement schedule but also with reference to concurrently available drugs.

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[2] This paper is based on a dissertation submitted to the Graduate School of the University of Chicago by C.E.J. in partial fulfillment of the requirements for the degree of Doctor of Philosophy.
[3] Portions of this work have been presented in: SCHUSTER, C. R. AND BALSTER, R. L.: Self-administration of agonists. *In* Agonist and Antagonist Action of Narcotic Analgesic Drugs, ed. by H. W. Kosterlitz, H. O. J. Collier and J. E. Villarreal, pp. 243–254, MacMillan, London, 1973; JOHANSON, C. E.: Choice of cocaine by rhesus monkeys as a function of dosage. Proceedings of the 79th Annual Convention, American Psychological Association 751–752, 1971.

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During the past decade, many studies have demonstrated that a wide variety of drugs are self-injected by rhesus monkeys. Monkeys repeatedly make responses which are followed by

injections of certain psychotropic drugs such as opiates, barbiturates, psychomotor stimulants and alcohol (Schuster and Johanson, 1974). Thus, drugs along with other stimuli such as food, water, sex and electric stimulation of the brain can be considered positive reinforcers in that each will increase the frequency of the behavior it follows (Skinner, 1938).

The efficacy of different reinforcers (or different amounts of the same reinforcer) has been compared by measuring the relative frequency or rate of behavior each maintains or by determining preferences in a choice procedure. With the use of single schedules, the relationship between rate and dose per injection (magnitude of reinforcement) has been investigated with psychomotor stimulant drugs and opiates. When fixed-ratio schedules (every *n*th response followed by drug injection; FR) were used, rate of responding was inversely related to the dose of the drug (Goldberg *et al.*, 1971; Pickens, 1968; Weeks and Collins, 1964; Wilson *et al.*, 1971; Woods and Schuster, 1968). Rates of drug self-injection, however, may be determined not only by the drug's reinforcing efficacy but by any of its other effects. Failure to self-inject a drug could be due, for instance, either to the drug's suppression of ongoing behavior or to its low reinforcing efficacy. For example, cocaine given non-contingently produces a dose-dependent suppression in behavior maintained by food reinforcement (Pickens and Thompson, 1968; Wilson, 1970; Woods and Tessel, 1974). In addition, methylphenidate, as well as the amphetamines, has been shown to either increase or decrease rate of responding depending upon the schedule of reinforcement, dose and species (Kelleher and Morse, 1968; Morse and Kelleher, 1970; Stretch *et al.*, 1966).

The relative efficacy of positive reinforcers has also been assessed using preference procedures where animals are given a choice between two magnitudes of a single reinforcer or between two reinforcers (Findley *et al.*, 1972; Hodos and Valenstein, 1962; Johanson, 1971; Neuringer, 1967). Since a response is required to indicate preference, a failure to respond may not influence the evaluation of either reinforcer's efficacy as it might when absolute rate alone is used as the dependent variable.

In the present experiment, rhesus monkeys were trained to choose between two solutions in order to determine preference between two doses of a compound or between two compounds. Initially, comparisons were made between several doses of cocaine or methylphenidate and saline to determine whether monkeys could differentiate drug and saline. Next, animals were given a choice between a high and a low dose of the same drug (cocaine or methylphenidate) in order to determine the relationship between dose and preference. Finally, cocaine and methylphenidate were compared to each other.

Methods

Animals

Thirteen adult, male, rhesus monkeys between 3.5 and 6.5 kg with no prior experimental or drug history were used. After being adapted for 4 to 9 days to the semirestraint imposed by the harness and arm within the experimental cubicle (see "Apparatus"), each animal was anesthetized with sodium pentobarbital (30 mg/kg i.v.) and prepared with an intravenous polyvinyl chloride, double-lumen catheter (inside diameter = 0.035 inch, no. 1100, U. S. Catheter and Instrument Company, Billerica, Mass.). The proximal end of the catheter was inserted into a major vein for a distance calculated to have it terminate in the superior vena cava; the distal end was threaded subcutaneously and exited the body through an incision in the back of the animal. Since median catheter life was approximately 3 months, it was not always possible to maintain a single catheter for the duration of the experiment. When a catheter became dislodged, the monkey was removed from the experiment for a minimum of 10 days. At this time, a replacement catheter was surgically inserted in one of the internal jugular, external jugular or femoral veins, and the animal was then returned to the experiment.

All animals had continuous access to water and were given 20 Purina Monkey Chow biscuits and a sugar cube saturated with liquid vitamins every morning. In addition, their diet was frequently supplemented with fresh fruit. Occasionally antibiotics were administered intramuscularly to arrest a catheter tract infection.

Apparatus

Each monkey was housed in a sound-attenuated wooden cubicle (1.3 × 1.3 × 1 m) that served as the experimental space. Mounted on the door of the cubicle were two lever boxes, each of which

was 20 cm from the floor and 10 cm from the center line. The front of each box contained a response lever (PRL-001, BRS/LVE, Beltsville, Md.) and a strip of Plexiglas, which was 5 cm above the lever and could be transilluminated by red or green stimulus lights. The door also had a one-way mirror for observing the monkey. The entire ceiling was made of Plexiglas and could be transilluminated by either white or red lights.

Each monkey wore a stainless-steel harness that was connected to a spring arm 46 cm in length and 1.3 cm in diameter (H & M Engineering, Chicago, Ill.) which was attached to the back of the cubicle (Schuster and Johanson, 1974). This arrangement allowed the monkey relatively unrestricted movement within the cubicle and provided protection for the catheter which was threaded through the arm. Outside the cubicle, each lumen of the catheter was connected to a peristaltic infusion pump (7540X, Cole-Parmer Instrument Co., Chicago, Ill.) which delivered solutions at the rate of 6 ml/min.

Cables connected the experimental cubicles to electromechanical programming and recording equipment located in an adjacent room.

Procedure

Training. Initially each lever-press in the presence of a red stimulus light produced cocaine delivery (0.1 or 0.5 mg/kg). Lever responses usually occurred sufficiently often that training was unnecessary; occasionally, however, raisins were taped to the lever to encourage manipulation of it. After acquisition of the lever-press response, the requirement for cocaine delivery was gradually raised to five (FR 5). Next responding on the FR 5 schedule was maintained by cocaine in the presence of a green stimulus light. The stimulus lights randomly appeared above either lever. Total exposure to these conditions never exceeded 2 hours.

Terminal schedule. Each daily session consisted of two sampling periods followed by several choice trials. During the first sampling period, a red or green stimulus light (S_1) was illuminated above the left lever while the stimulus light above the right lever remained dark. At this time, the ceiling was transilluminated by the white light. Five responses on the left lever resulted in the injection of 1 ml of drug A. Responses on the right lever were recorded but had no other programmed consequence. During the injection, which lasted 10 seconds, the lever light and white ceiling light were turned off and a red ceiling light was illuminated. The position of S_1 switched to the right lever box and thereafter alternated with each injection of drug A. Five injections were permitted during the first sampling period. After the fifth injection, a 30-minute timeout occurred during which only the white ceiling light was illuminated and responding was recorded but had no additional programmed consequences. After the timeout, the second sampling period began in which five opportunities were given for self-injection of drug B. The stimulus (S_2) associated with availability of drug B was different in color from S_1. If S_1 were red, S_2 was green, and *vice versa*. In all other respects, however, the procedures used during this second sampling period were identical to those used during the first sampling period. After the fifth injection of drug B, another 30-minute timeout was initiated.

The remainder of the session consisted of choice trials during which S_1 and S_2 were simultaneously presented, one over each lever. Five responses on the lever illuminated by S_1 resulted in the injection of 1 ml of drug A, whereas five responses on the lever illuminated by S_2 resulted in the injection of 1 ml of drug B. The first response on one lever terminated the stimulus over the other lever and made responses on that lever inconsequential for the remainder of the trial. The lever lights and white ceiling light were turned off and a red ceiling light was illuminated during the injection of either drug solution. After each injection, the white ceiling light was illuminated for 15 minutes and responding had no programmed consequences. This time period was the maximum inter-reinforcement time observed by Wilson *et al.* (1971) across the range of doses of cocaine and methylphenidate used in the present experiment and was designed to allow any rate-disruptive drug effects to dissipate. The above procedure was repeated on all choice trials with the restriction that S_1 and S_2 randomly appeared above each lever on 50% of the trials. A session lasted until all choice trials were completed or until 24 hours had passed. The number of choice trials available to individual animals was either 18, 20 or 25. For any comparison, this number remained constant.

Under some conditions, once performance on the choice trials became stable, the stimulus lights associated with the drug solutions were reversed (stimulus reversal); that is, S_2 was now associated with drug A and S_1 was now associated with drug B. This was done to ensure that preference was based on the drug solution rather than the color of the stimulus lights associated with the drug solution.

The following comparisons were made. Four doses of cocaine (0.05, 0.1, 0.5 and 1.5 mg/kg) and three doses of methylphenidate (0.075, 0.2, and 0.7 mg/kg) were compared to saline. In each case, drug was available during the first sampling period and saline was available during the second sampling period. Cocaine at a dose of 0.05 mg/kg was

compared to 0.1, 0.2 and 0.5 mg/kg of cocaine, 0.1 mg/kg of cocaine was compared to 0.3, 0.5 and 1.5 mg/kg, and 0.5 mg/kg of cocaine was compared to 1.0 and 1.5 mg/kg of cocaine. For each comparison, the lower dose of cocaine was available during the first sampling period and the higher dose was available during the second period. Two animals were given choice trials involving equal doses of cocaine; for one animal this dose was 0.05 mg/kg and for the second animal it was 0.2 mg/kg. Methylphenidate at a dose of 0.075 mg/kg was compared to 0.2, 0.5 and 0.7 mg/kg of methylphenidate. As in the experiments involving cocaine, the lower dose was available during the first sampling period. For comparisons between the two drugs, choices were given first between 0.1 mg/kg of cocaine and three doses of methylphenidate (0.075, 0.2, and 0.7 mg/kg) and finally between 0.5 mg/kg of cocaine and four doses of methylphenidate (0.075, 0.2, 0.5, and 0.7 mg/kg). In each case, methylphenidate was available during the first sampling period and cocaine was available during the second sampling period.

The order of testing was random for each animal except that the first comparison always involved a drug *vs.* saline. Not every animal was tested in each comparison. In order to determine that responding during choice trials was a function of its consequences (*i.e.*, the injection of one drug solution rather than the other drug solution) and not other variables such as color preference or prior drug solution-stimulus pairings, either the lower dose of drug or saline was paired with the stimulus associated with the preferred drug solution in the previous comparison. Thus, on each new comparison, the higher drug dose was paired with the previously nonpreferred stimulus color. A comparison was continued until: 1) the animal chose the drug solution associated with the stimulus not preferred in the last comparison (requiring a switch in stimulus preference) on at least 75% of the trials for at least three consecutive sessions; 2) the animal chose a drug solution between 40 and 60% of the trials for at least seven consecutive sessions indicating no preference; or 3) the animal did not switch its choice of stimulus color for at least seven consecutive sessions. If the monkey did not change its choice of stimulus color, the drug-stimulus pairing was reversed.

All data analyses are based on performance during the last three sessions of each comparison. Performance on choice trials is expressed in terms of the total trials in which cocaine or methylphenidate was selected. Rates of responding during the two daily sampling periods are expressed as responses per minute.

Drug Solutions

Cocaine HCl and methylphenidate HCl were dissolved in 0.9% physiological saline such that all doses were delivered in a 1-ml volume. Doses refer to the salt of each drug. New drug solutions were prepared at least once every 2 weeks.

Results

Performance During Sampling Periods

Figure 1 shows rate of responding during the sampling periods for doses of cocaine and methyl-

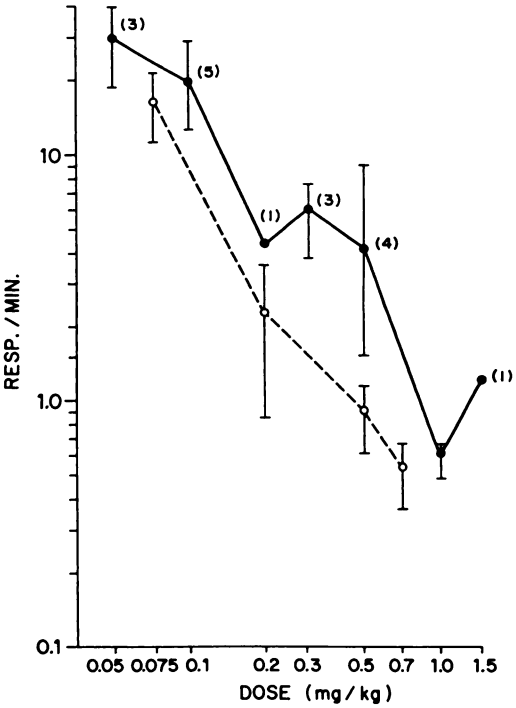

FIG. 1. Mean rates of responding during sampling periods maintained by each dose of cocaine (●——●) and methylphenidate (○- - -○). For every comparison for each animal, response rates during sampling were calculated on each of the last 3 days of the comparison separately for drug A and drug B. These rates were then averaged over the 3 days. If an animal had not self-injected at least 3 different doses of a drug over the course of the experiment, the data from that animal were eliminated from the response rate analysis. It was possible for the data of an animal to be eliminated from the response rate analysis of cocaine but be included for methylphenidate, and *vice versa*. For each animal meeting the criterion of three or more doses, all the response rates from different comparisons for one dose were averaged. The rates for all animals were then averaged. The brackets through the points indicate the range of these means. The number of animals represented by each data point was either two or is indicated by the number in parentheses.

phenidate. Only data from animals that were tested with three or more doses of one drug are presented. Response rate generally decreased as the dose of both drugs increased, although at any dose, responding maintained by cocaine was 2 to 3 times higher than that maintained by an equivalent dose of methylphenidate.

Response rates of individual animals maintained by saline showed considerable day-to-day variability. For instance, response rates maintained by saline for animal A022 during the sampling period were 34.9, 7.0 and 8.8 responses/min on the last 3 days that 0.5 mg/kg of cocaine was compared to saline.

Performance during Choice Trials

Cocaine or methylphenidate *vs.* saline. As shown in table 1, all doses of cocaine were preferred over saline for each animal in more than 75% of the choice trials. However, preference did not change appreciably with dose. One animal, used in comparing 1.5 mg/kg of cocaine to saline, displayed hyperactivity, irritability and occasional convulsions.

Figure 2 presents the daily data for the comparison between 0.5 mg/kg of cocaine and saline for the five animals tested under the original stimulus-drug pairing and the stimulus reversal condition. Despite differences among animals in number of trials per session, number of days to reach criterion and initial preference, the uniformity of terminal performance is striking. In other words, the stimulus associated with 0.5 mg/kg of cocaine ultimately gained preferential control over responding. When the stimulus conditions were reversed, stimulus preference was also reversed in all cases. The data for comparisons of the other doses of cocaine to saline were similar.

Each of three doses of methylphenidate (0.075, 0.2 and 0.7 mg/kg) was compared to saline. Methylphenidate was preferred over saline (75% criterion) by each animal (table 2). As shown for cocaine, preference did not change

TABLE 1

Mean percent trials cocaine was chosen over saline for each animal calculated from the last three sessions of each comparison

Numbers in parentheses indicate sequence of testing.

Cocaine, 0.05 mg/kg		Cocaine, 0.1 mg/kg		Cocaine, 0.5 mg/kg		Cocaine, 1.5 mg/kg	
Animal no.	Percent	Animal no.	Percent	Animal no.	Percent	Animal no.	Percent
A022 (5)	85.3, 77.3[a]	A012 (2)	92.6, 85.2[a]	A012 (1)	100.0, 83.3[a]	A013 (6)	88.7, 96.3[a]
A061 (3)	90.0	A013 (2)	98.1, 86.9[a]	A013 (1)	88.8, 88.8[a]		
A087 (1)	86.3	A037 (1)	100.0	A022 (1)	94.4, 92.6[a]		
		A069 (1)	96.3	A025 (1)	98.7, 93.3[a]		
		A073 (1)	95.0	A059 (1)	93.3, 96.0[a]		
		A084 (1)	92.5	A061 (1)	90.0		
				A073 (2)	95.0		
				A075 (1)	92.0		
				A084 (2)	92.3		

[a] Stimulus reversal.

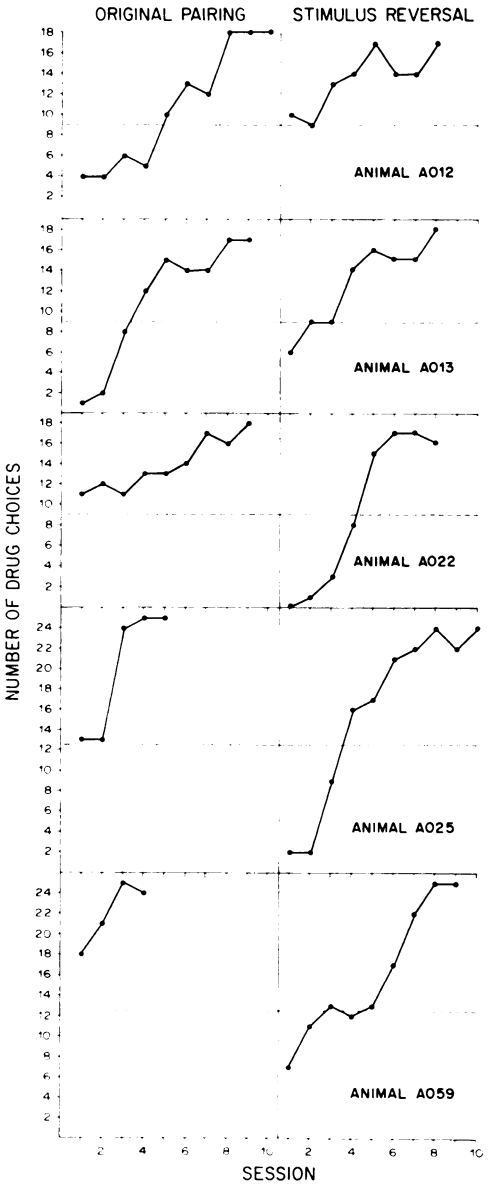

FIG. 2. Number of choice trials 0.5 mg/kg of cocaine was chosen over saline plotted daily for each animal tested during both the original stimulus-drug solution pairing and the stimulus reversal. The dotted line indicates 50% choice.

with dose. Figure 3 presents the performance of A059 on choice trials for the comparison between 0.2 mg/kg of methylphenidate and saline. As can be seen, these data are similar to those shown in figure 2, showing a gradual increase in the number of drug choices under

TABLE 2

Mean percent trials methylphenidate was chosen over saline for each animal calculated from the last three sessions of each comparison

Numbers in parentheses indicate sequence of testing.

Methylphenidate, 0.075 mg/kg		Methylphenidate, 0.2 mg/kg		Methylphenidate, 0.7 mg/kg	
Animal no.	Percent	Animal no.	Percent	Animal no.	Percent
A022 (13)	98.3	A059 (5)	88.9, 88.9[a]	A022 (15)	88.3
A059 (6)	79.6	A087 (7)	87.0	A073 (6)	83.3
A061 (3)	85.2	A096 (1)	83.3	A087 (10)	91.7

[a] Stimulus reversal.

the original stimulus-drug pairing and stimulus reversal conditions.

Low *vs.* high doses of cocaine. A dose of 0.05 mg/kg of cocaine was compared to three higher doses of cocaine (0.1, 0.2 and 0.5 mg/kg). The higher dose was preferred to 0.05 mg/kg for each animal tested according to the 75% criterion (table 3). In addition, the one animal tested after a stimulus reversal also preferred the high dose to the low dose.

The dose of 0.1 mg/kg of cocaine was compared to three higher doses of cocaine (0.3, 0.5 and 1.5 mg/kg). In every case, the higher dose of cocaine was preferred to 0.1 mg/kg of cocaine

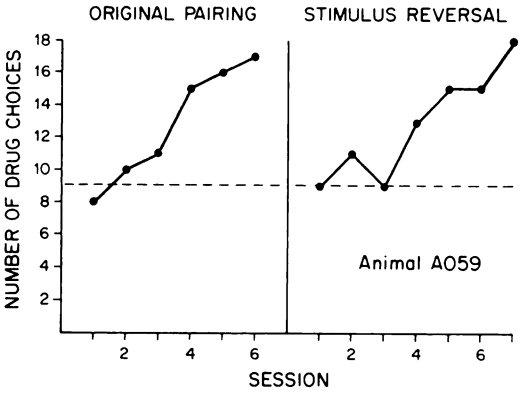

FIG. 3. Number of choice trials 0.2 mg/kg of methylphenidate was chosen over saline plotted daily for A059 during both the original stimulus drug-solution pairing and the stimulus reversal. The dotted line indicates 50% choice.

TABLE 3

Mean percent trials higher dose of cocaine was chosen over lower dose for each animal calculated from the last three sessions of each comparison

Numbers in parentheses indicate sequence of testing.

Cocaine (mg/kg)	Cocaine, 0.05 mg/kg		Cocaine, 0.1 mg/kg		Cocaine, 0.5 mg/kg	
	Animal no.	Percent	Animal no.	Percent	Animal no.	Percent
0.1	A022 (3)	89.0				
	A073 (4)	96.7				
	A087 (2)	86.7				
0.2	A022 (4)	100.0, 90.7[a]				
	A075 (4)	88.0				
0.3			A013 (8)	79.7		
			A073 (5)	88.0		
			A087 (3)	94.4		
0.5	A022 (7)	92.0	A012 (3)	94.4, 85.2[a]		
			A013 (3)	94.4, 83.3[a]		
			A022 (2)	94.4, 88.8[a]		
			A069 (2)	85.0		
			A073 (3)	95.0		
1.0					A012 (4)	50.0
					A013 (4)	71.9
1.5			A013 (7)	96.0	A013 (5)	50.0

[a] Stimulus reversal.

(table 3). No difference in choice behavior occurred when the higher dose of the drug was increased. Only one animal was tested in the comparison between 0.1 and 1.5 mg/kg of cocaine due to the marked toxicity seen at the high dose.

Figure 4 presents the choice data for the three animals tested in the comparison between 0.1 mg/kg of cocaine and 0.5 mg/kg of cocaine for both the original stimulus-drug pairing as well as for the stimulus reversal. Again, as was seen in figure 2, the terminal behavior is similar for all animals despite differences in the number of days required to reach criterion.

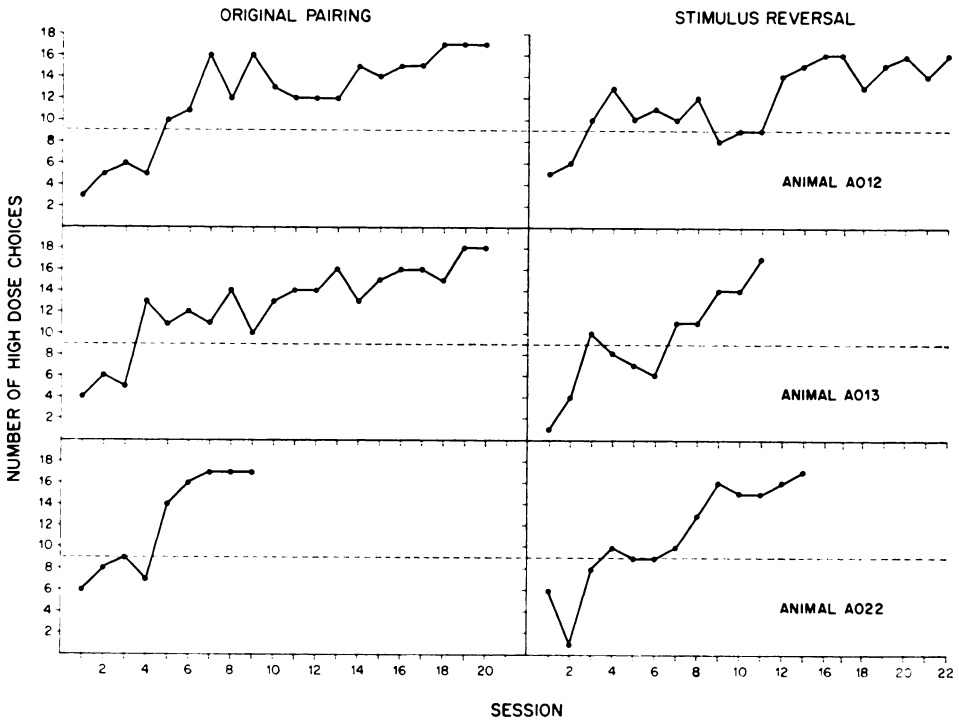

FIG. 4. Number of choice trials 0.5 mg/kg of cocaine was chosen over 0.1 mg/kg of cocaine plotted daily for each animal tested during both the original stimulus-drug solution pairing and the stimulus reversal. The dotted line indicates 50% choice.

The dose of 0.5 mg/kg of cocaine was compared to 1.0 mg/kg of cocaine in two animals and to 1.5 mg/kg in one animal. In no case was either dose clearly preferred, although A013 preferred 1.0 to 0.5 mg/kg of cocaine on 71.9% of the trials. In general, the animals responded almost exclusively on one lever during the choice trials; since each stimulus appeared above each lever on half of the trials, no preference for either drug solution was shown. During the sessions using these high doses of cocaine, all animals were extremely agitated and hyperactive, similar to the animals described by Deneau *et al.* (1969). One animal died during convulsions which occurred after several injections of cocaine.

Two animals were given a choice between two cocaine solutions which were equal in dose. Both solutions were 0.05 mg/kg of cocaine for A022 and 0.2 mg/kg of cocaine for A037. On the last 3 days of the comparison, A022 chose the first-sampled solution a mean of 48.1% of the trials and A037 chose this solution a mean of 57.4% of the trials. Generally, these two animals persisted in responding on only one of the levers during the choice trials.

Low *vs.* high doses of methylphenidate. A low dose of methylphenidate (0.075 mg/kg) was compared to three higher doses of the same drug (0.2, 0.5 and 0.7 mg/kg). Three monkeys given a choice between 0.075 and 0.2 mg/kg of methylphenidate preferred neither of the solutions (table 4). These animals responded exclusively on one lever during the choice trials thereby receiving each solution on half of the trials. When animals were given a choice between 0.075 and 0.5 mg/kg of methylphenidate (table 4), one animal rapidly came to prefer the higher dose, whereas the other animal continued to respond almost exclusively on one lever. All three animals given a choice between 0.075 mg/kg of methylphenidate and 0.7 mg/kg of methylphenidate preferred the higher dose (table 4).

Methylphenidate *vs.* cocaine. Doses of 0.075, 0.2 and 0.7 mg/kg of methylphenidate

TABLE 4

Mean percent trials high doses of methylphenidate were chosen over the low dose of 0.075 mg/kg for each animal calculated from the last three sessions of each comparison

Numbers in parentheses indicate sequence of testing.

Methylphenidate, 0.2 mg/kg		Methylphenidate, 0.5 mg/kg		Methylphenidate, 0.7 mg/kg	
Animal no.	Percent	Animal no.	Percent	Animal no.	Percent
A022 (10)	64.0	A022 (11)	86.7	A073 (7)	90.0
A059 (4)	50.0	A087 (4)	57.4	A087 (5)	100.0
A075 (3)	50.7			A096 (2)	90.7

were compared to 0.1 mg/kg of cocaine in two animals. Methylphenidate was preferred over cocaine in 5 of the 6 comparisons (table 5). Animal A022 showed no preference for 0.075 mg/kg of methylphenidate or 0.1 mg/kg of cocaine but instead responded on only one lever during choice trials.

Four doses of methylphenidate (0.075, 0.2, 0.5 and 0.7 mg/kg) were compared to 0.5 mg/kg of cocaine. Preference for cocaine decreased as the comparison dose of methylphenidate increased (table 5). Regardless of drug, higher doses were generally preferred over lower doses. Two animals given a choice between equivalent doses of methylphenidate and cocaine (0.5 mg/kg) chose each solution on approximately one-half of the trials. Under this condition, both animals generally responded on only one lever.

Figure 5 shows the performance of animal A022 under several comparisons between cocaine and methylphenidate. In the comparisons between 0.1 mg/kg of cocaine and methylphenidate (top row), choice behavior changed from no preference with 0.075 mg/kg of methylphenidate to an exclusive preference for methylphenidate at the two higher doses. In the comparisons between 0.5 mg/kg of cocaine and methylphenidate, figure 5 shows that there was a complete reversal of preference as the dose of methylphenidate was increased.

Discussion

Cocaine in doses ranging from 0.05 to 1.5 mg/kg and methylphenidate in doses ranging from 0.075 to 0.7 mg/kg were reliably preferred to saline. In addition, when animals were given a choice between two solutions of various doses of cocaine or methylphenidate, they preferred the higher dose regardless of the drug. The preference for these drugs over saline complements previous studies with rhesus monkeys (Balster and Schuster, 1973a; Deneau

TABLE 5

Mean percent trials cocaine was chosen over methylphenidate for each animal calculated from the last three sessions of each comparison

Numbers in parentheses indicate sequence of testing.

Cocaine (mg/kg)	Methylphenidate, 0.075 mg/kg		Methylphenidate, 0.2 mg/kg		Methylphenidate, 0.5 mg/kg		Methylphenidate, 0.7 mg/kg	
	Animal no.	Percent	Animal no.	Percent	Animal no.	Percent	Animal no.	Percent
0.1	A022 (18)	51.7	A022 (16)	21.7			A022 (14)	6.7
	A087 (6)	13.0	A087 (9)	16.7			A087 (8)	10.0
0.5	A022 (9)	80.0	A022 (8)	76.0	A022 (12)	45.0	A022 (17)	10.0
	A025 (2)	97.3	A059 (3)	50.0	A061 (4)	53.7	A087 (11)	15.2
	A059 (2)	92.0	A075 (2)	74.7				

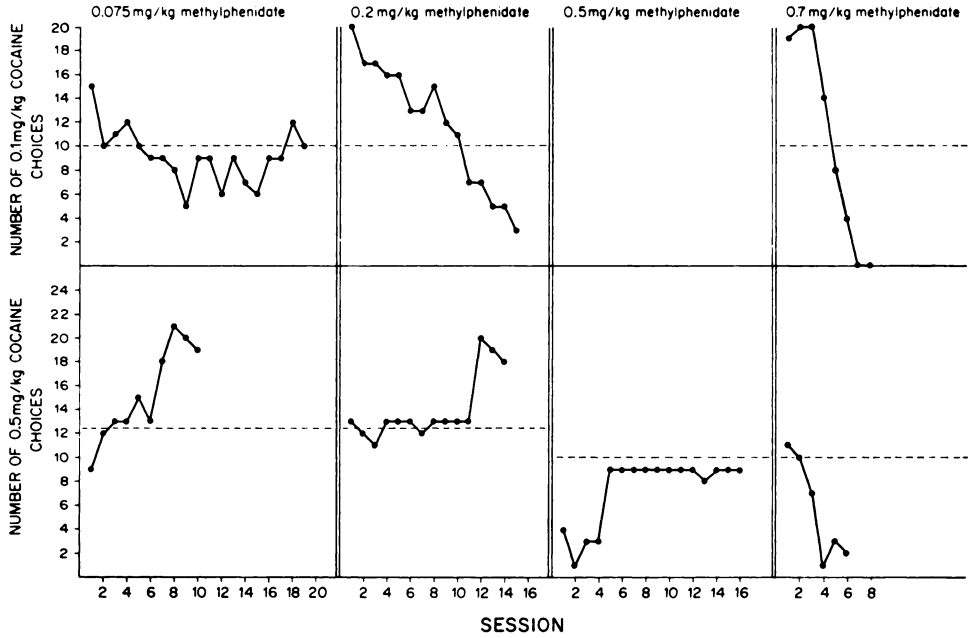

FIG. 5. Number of choice trials 0.1 mg/kg of cocaine (top row) or 0.5 mg/kg of cocaine (bottom row) was chosen over different doses of methylphenidate plotted daily for each comparison for A022. The dotted lines indicate 50% choice. The comparisons shown here were made in the following order although other comparisons were interspersed as indicated by an asterisk (*): 1) 0.2 mg/kg of methylphenidate *vs.* 0.5 mg/kg of cocaine; 2) 0.075 mg/kg of methylphenidate *vs.* 0.5 mg/kg of cocaine*; 3) 0.5 mg/kg of methylphenidate *vs.* 0.5 mg/kg of cocaine*; 4) 0.7 mg/kg of methylphenidate *vs.* 0.1 mg/kg of cocaine*; 5) 0.2 mg/kg of methylphenidate *vs.* 0.1 mg/kg of cocaine*; 6) 0.7 mg/kg of methylphenidate *vs.* 0.5 mg/kg of cocaine; and 7) 0.075 mg/kg of methylphenidate *vs.* 0.1 mg/kg of cocaine.

et al., 1969; Goldberg, 1973; Goldberg *et al.*, 1971; Hoffmeister *et al.*, 1970; Iglauer and Woods, 1974; Schlichting *et al.*, 1971; Wilson *et al.*, 1971; Woods and Schuster, 1968; Yanagita *et al.*, 1965) which have demonstrated that the same range of doses can serve as positive reinforcers for lever-pressing behavior, although in the case of methylphenidate, only doses as high as 0.4 mg/kg have been used (Wilson *et al.*, 1971). In most comparisons between two doses of cocaine, the higher of the two doses was chosen over the lower. In the comparisons between 0.5 and 1.0 mg/kg of cocaine and between 0.5 and 1.5 mg/kg of cocaine, the animals demonstrated no preference and responded almost exclusively on one lever during the choice trials. When a standard dose of 0.075 mg/kg of methylphenidate was compared to higher doses of the same drug, preference for the higher dose developed only when this dose was 7 to 9 times greater than the standard. In contrast, a dose of cocaine only twice as high as a standard dose (*e.g.*, 0.1 compared to 0.05 mg/kg) was reliably preferred by all animals. This would indicate that the function relating dose and choice is steeper for cocaine than for methylphenidate. A general conclusion is that rhesus monkeys preferred the higher dose of the pair both for intra-drug and for cross-drug comparisons.

Wilson *et al.* (1971) found that rate of responding maintained by cocaine as well as methylphenidate decreased as the dose was increased. In the present experiments, response rate during the sampling periods also decreased as the dose of cocaine and methylphenidate increased. Thus, in the same session, preference was directly related to dose while rate of lever-pressing maintained by drug reinforcement was inversely related. This inverse relationship between rate of responding maintained by drugs and dose probably reflects one or more of the drug's other effects on ongoing behavior. Pickens and Thompson (1968), for example, found

that an intravenous injection of cocaine disrupted food-reinforced lever pressing in a rat and that the duration of this disruption was a function of the dose. In single schedules of reinforcement, therefore, rate of responding maintained by drug reinforcement may be markedly affected by the drug's overall suppressant effect on behavior. The interaction of the disrupting and reinforcing effects of drugs is further suggested by studies comparing the relative potencies of *d*- and *l*-amphetamine and *d*-methamphetamine. Owen (1960) found that these compounds disrupted the liquid reinforced fixed-ratio responding of rats in a dose-related manner. Further, Owen's data showed the same potency relationships for these compounds as were found in monkeys when the compounds were compared for their reinforcing effects (Balster and Schuster, 1973b). This suggests that responding maintained by amphetamine reinforcement is influenced not only by the drug's reinforcing actions but also by its other behavioral effects. These data draw attention to the inherent difficulty of utilizing rate of self-injections under single schedules for comparing the relative reinforcing efficacy of drugs in general.

In the present experiments, differences in rate of responding maintained by cocaine and methylphenidate during the sampling periods probably reflect a greater duration of methylphenidate's disrupting action on behavior rather than its having less reinforcing efficacy than cocaine. This contention is supported by the choice data showing that equivalent doses of cocaine and methylphenidate were equipotent as reinforcers. The differences in the rate and preference measures are most likely attributable to the fact that in the choice trials failure to respond *per se* did not influence the evaluation of the reinforcing efficacy of each drug. Further, a timeout period followed choice trials so that the immediate general suppressant actions of the injected drug had some time to dissipate. Balster and Schuster (1973a) utilized a 15-minute timeout after each cocaine injection maintaining fixed-interval responding in order to separate the behavioral suppressant effects from the reinforcing effects of cocaine. Under these conditions, rate of responding was a direct function of dose. That the schedule alone cannot account for this result is suggested by the fact that Dougherty and Pickens (1973) found an inverse function relating dose and rate of responding using an FI schedule of cocaine reinforcement in rats with no timeout after reinforcement. Iglauer and Woods (1974) used monkeys trained under a concurrent variable-interval variable-interval schedule of cocaine reinforcement where the dose in each independent variable-interval schedule differed in magnitude and found that the relative rates of responding maintained by these different doses was a direct function of their magnitude. An important feature of the schedule in that study was a 5-minute timeout period after each injection to minimize the interactions of the drug's disrupting and reinforcing effects. Further, the authors conclude that the measure of relative rate was not greatly influenced by the drug's rate-decreasing effects. Goldberg (1973), using monkeys trained under a second-order fixed-interval schedule of fixed-ratio components maintained by cocaine injections, found that response rate did not decrease with increments in dose as it did using a single fixed-ratio schedule. One of the common features of these studies is the use of schedules minimizing rate of reinforcement to avoid, at least in part, the interaction of the reinforcing and other behavioral actions of drugs. In addition, in the present study, the use of preference procedures provided measures of reinforcement which were minimally effected by failure to respond *per se*.

Discrepancies between different measures of reinforcement efficacy are not unique to drug self-injection studies. In studies using single schedules of food reinforcement, response rate has been shown to both increase (Guttman, 1953; Stebbins *et al.*, 1959) or decrease (Goldberg, 1973; Pickens and Thompson, 1968) with increases in magnitude of reinforcement. Still other studies have found rate to be relatively insensitive to changes in reinforcement magnitude (Jenkins and Clayton, 1949; Keesey and Kling, 1961). Such inconsistencies have also been reported using schedules of electric brain stimulation in rats. For example, Olds and Milner (1954) and Sidman *et al.* (1955) found that rate increased with increases in stimulation voltage. On the other hand, Reynolds (1958) found an inverted U-shaped function relating

response rate and voltage. In contrast, compound schedules of reinforcement such as concurrent and chain schedules have shown response rate to be directly related to reinforcement magnitude (Catania, 1963; Pliskoff and Hawkins, 1967). It would thus appear that compound schedules show a positive relation to reinforcement magnitude whether the reinforcer is food, electric brain stimulation or a drug. Further, choice procedures such as that employed in the present study have shown performance to have a positive relation to magnitude of food (Neuringer, 1967) or electric brain stimulation (Hodos and Valenstein, 1962) reinforcement. The present study extends the generality of these findings relating reinforcement magnitude and preference to behavior maintained by drug reinforcement.

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