PHARMACOLOGICAL REVIEWS
Vol. 27, No. 3

Printed in U.S.A.

Pharmacological and Environmental Variables Affecting Drug Preference in Rhesus Monkeys*

CHRIS E. JOHANSON

Department of Psychiatry, Pritzker School of Medicine, University of Chicago, Chicago, Illinois

DURING the past decade many studies have demonstrated that rhesus monkeys repeatedly make responses which have been followed by injections of certain drugs (30). Thus, injections of these drugs can be considered with other events such as food, water, sex, and electric stimulation of the brain as positive reinforcers in that each will increase the subsequent frequency of occurrence of behavior that preceded it (33). Rates of responding maintained by drug injections may be determined not only by the capacity of the drug to reinforce behavior that preceded it but also by the direct effects of the drug on behavior that follows it (30). These direct effects may be so powerful in determining response rate that they override the effects of other variables, particularly when rate of responding is directly related to the rate of drug injection, as is the case when responding is maintained on a ratio schedule of reinforcement.

The effects of a variety of pharmacological and environmental factors have been assessed by measuring changes in the frequency or rate of responding maintained by a drug injection. These factors include the pharmacological class of the drug, drug dose, behavioral requirements for injection, duration of the period of drug availability, concurrent stimulus events, and pretreatment with other drugs (30). Since changes in response rate could result from direct pharmacological effects of a drug, it is important to assess the effects of pharmacological and environmental mainipulations by using schedules of drug injection in which the effect of a drug in maintaining a response can be separated from its direct effects. Attempts to do this have been made in studies by limiting drug intake, with schedules in which increased rates of responding do not lead to increased rates of drug injection, or with dependent variables other than absolute rate of responding.

Balster and Schuster (2) used a 9-min fixed-interval schedule of cocaine injection; thus, rate of responding only minimally affected injection frequency. In addition, they limited drug intake by imposing after each drug injection a 15-min time-out period during which responding had no programmed consequences. Under this schedule, rate of responding increased as the dose was increased from 0.025 to 0.8 mg of cocaine per kg. In contrast, Dougherty and Pickens (6) found in the rat that rate of responding under a 5-min fixed-interval schedule decreased as the dose of cocaine was increased. However, in their study, there was no time-out period after each injection. A comparison of these two studies suggests that the more limited drug intake in the Balster and Schuster study extended the range of cocaine doses over which responding was well maintained.

Goldberg (8) limited cocaine and *d*-amphetamine intake by using a second-order schedule of reinforcement. Under this schedule, every 20th response (20-

* Research supported by National Institute of Mental Health Grant DA-00047 and DA-00250.

response fixed-ratio) during a 5-min time period resulted in the presentation of a brief light; the first 20-response fixed-ratio completed after the end of the 5-min time interval produced the light and an intravenous injection of a drug. Under these conditions, the dose-response curve was relatively flat; that is, rates of responding were well maintained from 0.025 to 0.4 mg/kg. In the same study, the dose-response curve obtained with a 20-response fixed-ratio schedule was sharply peaked; that is, responding was well maintained at only one or two doses. Additional studies with second-order schedules (9, 10) demonstrated that responding on this type of schedule could also be maintained by intramuscular injections of morphine or cocaine and that response rates on the second-order schedule changed little over a wide range of doses. The studies by Balster and Schuster (2) and Goldberg (8, 9) were primarily concerned with limiting drug intake in order to separate the effects of a drug in maintaining behavior from its direct effects. Goldberg *et al.* (10) carried this approach further by allowing only one injection per day at the end of each experimental session and limiting sessions to only three per week. The results of this series of studies showed that response rate either increased or remained about the same as the drug dose was increased over a wide range. This is in striking contrast to the inverse relationship between dose and rate of responding maintained on fixed-ratio schedules where rate of responding directly determines drug intake.

Another approach used in separating the reinforcing and direct effects of drugs is demonstrated in a study by Iglauer and Woods (17), with a concurrent schedule of reinforcement in which responding on each of two levers produced injections of cocaine on independent variable-interval schedules. Rather than comparing absolute rates of responding maintained by different doses of cocaine, they compared relative rates on the two levers and found the rates directly related to the dose of the drug maintaining responding on that lever. Relative rates of responding under these conditions have been used as a measure of preference; thus, in the Iglauer and Woods study preference was directly related to dose. Procedures in which preferences between two drugs can be assessed have been reported in other studies (4, 7, 13, 19–21). In these studies, drug preference was compared by counting the number of times one drug was injected rather than another; in addition, drug intake has been limited by long time-out periods between injections. One of these preference procedures will be described in the present paper and its use in evaluating the effects of various pharmacological and environmental variables will be discussed.

In these studies, rhesus monkeys were given an opportunity to choose between two drug solutions. Initially, each solution was available separately in the presence of an associated stimulus light. Then both drugs were made concurrently available on a trial basis by illuminating both lights. Choice of one solution prevented the delivery of the other solution on each trial. The relative drug dose, type of drug, relative behavioral requirements, relative delay in delivery, and availability of concurrent punishment of the alternatives were varied. Such manipulations were designed to determine the effects of these pharmacological and environmental variables on the ability of different drugs to function as positive reinforcers.

General Procedure

Adult rhesus monkeys weighing between 3 and 10 kg with no prior experimental or drug histories were used. Every animal was anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and prepared with an intravenous polyvinyl chloride, double-lumen catheter. Each monkey was housed in a sound-attenuating wooden cubicle that served as the experimental space. Mounted on the door of the cubicle were two boxes each containing a response lever

and window of Plexiglas which could be transilluminated by stimulus lights.

Each animal wore a stainless steel harness that was connected to a spring arm attached to the back of the cubicle (30). 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 which could deliver solutions at the rate of 6 ml/min.

A daily experimental session consisted of two sampling periods followed by choice trials. During a sampling component only one drug solution was available in the presence of a particular discriminative stimulus in order to maximize the opportunity for their association. At the beginning of the first sampling period, the window above the left lever was transilluminated by a stimulus light (S_1) while the right lever remained dark. Five responses on the left lever (five-response fixed-ratio) resulted in the injection of solution A, which lasted 10 sec. S_1 then appeared above the right lever, and five responses on the right lever resulted in the injection of solution A; with each subsequent injection of solution A the position of S_1 alternated. Five injections were permitted during the first sampling period. After the fifth injection, a 30-min time out period occurred; after the time-out, the second sampling period began, in which there were five opportunities to respond under a five-response fixed-ratio schedule of injection of solution B. The stimulus (S_2) associated with availability of solution B was different in color from S_1. In all other aspects, however, the procedures used during this second sampling period were identical with those used during the first sampling period. After the fifth injection of solution B, another 30-min time-out 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 associated with S_1 resulted in the injection of solution A, whereas five responses on the lever illuminated by S_2 resulted in the injection of solution 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. A 15-min time-out period followed each injection. This 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 fixed number of trials were programmed each session; a session lasted until they were completed or until 24 hr had elapsed.

A comparison was continued until the animal chose one solution on at least 75% of the trials for at least three consecutive sessions, or there was no apparent trend in responding after 21 experimental sessions.

Two control procedures were used to insure that preference was based on the nature of the drug injection rather than the color of the stimulus light associated with it. First, the stimulus associated with the preferred solution in a comparison was paired with either the lower dose of drug or saline in the next comparison. Thus, on each new comparison, the higher drug dose was paired with a stimulus previously associated with the nonpreferred drug solution. In some conditions, after 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 solution A and S_1 was now associated with solution B. This was done to further insure that preference was based on the drug injection rather than the color of the stimulus light.

Pharmacological Factors

Comparisons of Drug and Saline

The preference procedure was used to compare choices between different doses of a drug and between different drugs. In the initial experiments, choices were given between different doses of cocaine (ranging from 0.05 mg/kg to 1.5 mg/kg) and saline. All doses of the drug were preferred over

saline for each animal on more than 75% of the choice trials (20). The daily data for the comparison between 0.5 mg/kg cocaine and saline for five animals tested under the original stimulus-drug pairing and the stimulus reversal condition is presented in figure 1. Despite differences among animals in initial preference, number of trials programmed each session, or number of days to reach the 75% criterion, the uniformity of terminal performances is striking. In other words, cocaine ultimately gained preferential control over responding. When the stimulus conditions were reversed, choice changed accordingly. Similar results were obtained with comparisons of methylphenidate (ranging in doses from 0.075 mg/kg to 0.7 mg/kg) and diethylpropion (0.5 mg/kg and 1.0 mg/kg) with saline (20, 21). The preference for these drugs over saline demonstrates that this schedule can maintain reliable responding similar to other schedules of drug injection over a comparable range of doses.

Comparisons of Different Doses of Drug

In the next experiment, different doses of cocaine were compared. In most of these comparisons, the higher of the two doses was chosen (20). Data is presented in figure 2 for three animals, tested in the comparison between 0.1 mg and 0.5 mg of cocaine per kg for both the original stimulus-drug pairing and the stimulus reversal, and shows that the higher dose was preferred. The terminal behavior is similar for all animals despite differences in days required to reach criterion. Data from other comparisons between two doses of cocaine were similar (table 1). Exceptions occurred when relatively high doses were being compared; for example, animals demonstrated no preference between 0.5 and 1.0 mg of cocaine per kg or between 0.5 and 1.5 mg of cocaine per kg. However, during these comparisons most of the animals were markedly hyperactive and irritable, thereby suggesting that the direct effects of cocaine may have been influencing responding relatively more than during comparisons with lower doses. Further studies need to be done with longer time-out periods between injections in an effort to minimize the direct effects produced by

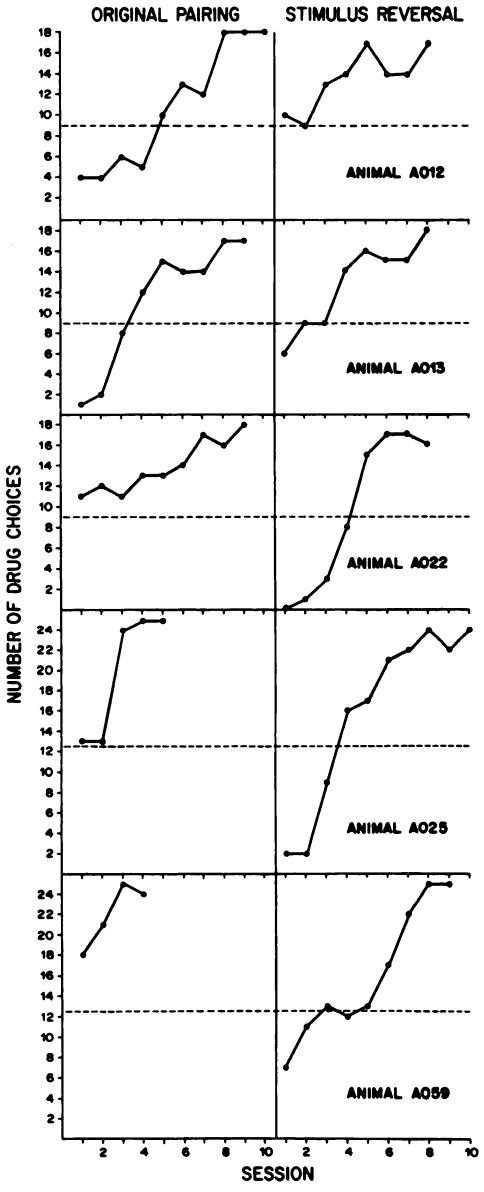

FIG. 1. Number of trials 0.5 mg of cocaine per kg was chosen over saline plotted daily for each animal tested during both the original stimulus-drug solution pairing and the stimulus reversal. The dotted line indicates 50% choice. There was a maximum of 18 choice trials available each session for animals A012, A013 and A022 and 25 were available for animals A025 and A059. [From Johanson and Schuster, J. Pharmacol. Exp. Ther., 193: 676–688, 1975 (20).]

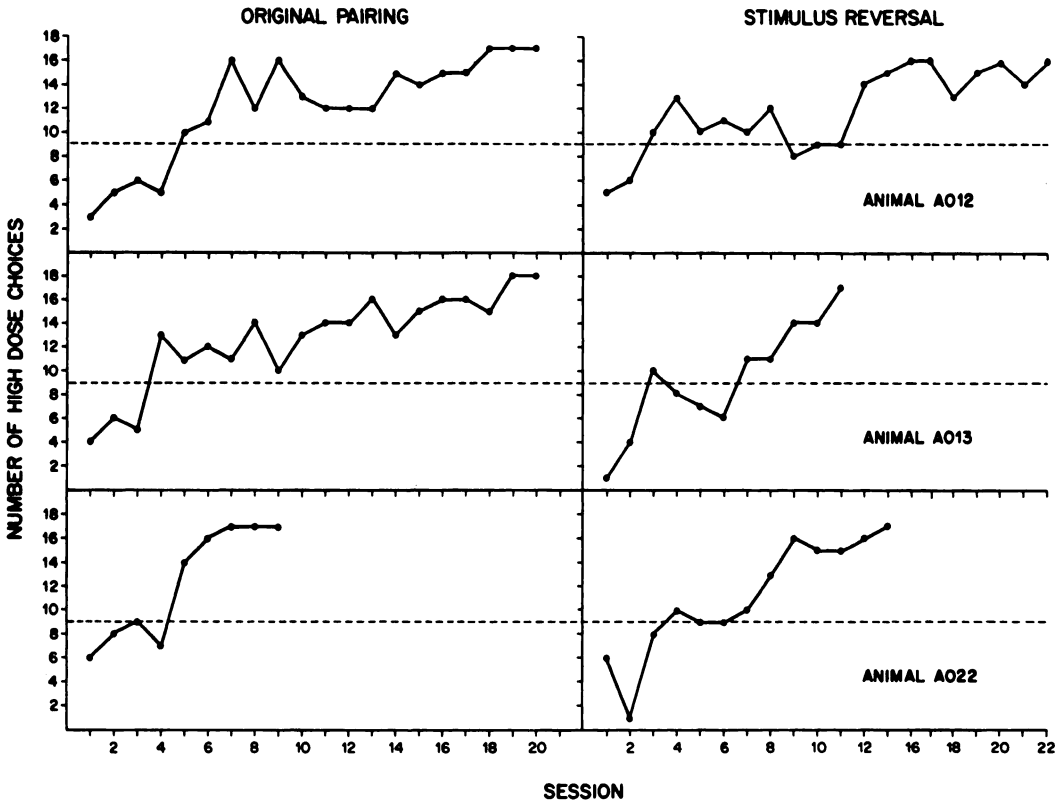

FIG. 2. Number of trials 0.5 mg of cocaine per kg was chosen over 0.1 mg of cocaine per kg for each animal tested during both the original stimulus-drug solution pairing and the stimulus reversal. The dotted line indicates 50% choice. There was a maximum of 18 choice trials available each session. [From Johanson and Schuster, J. Pharmacol. Exp. Ther., **193**: 676–688, 1975 (20).]

TABLE 1

Mean percent trials higher dose of cocaine was chosen over 0.05 mg of cocaine per kg for each animal calculated from the last three sessions of each comparison[a]

0.1 mg/kg		0.2 mg/kg		0.5 mg/kg	
Animal	Percent	Animal	Percent	Animal	Percent
A022	89.0	A022	100,90.7[b]	A022	92.0
A073	96.7	A075	88.0		
A087	86.7				

[a] Based on data from Johanson and Schuster, J. Pharmacol. Exp. Ther. **193**: 676–688, 1975.

[b] Stimulus reversal.

TABLE 2

Mean percent trials higher dose of methylphenidate was chosen over 0.075 mg of methylphenidate per kg for each animal calculated from the last three sessions of each comparison[a]

0.2 mg/kg		0.5 mg/kg		0.7 mg/kg	
Animal	Percent	Animal	Percent	Animal	Percent
A022	64.0	A022	86.7	A073	90.0
A059	50.0	A087	57.4	A087	100.0
A075	50.7			A096	90.7

[a] Based on data from Johanson and Schuster, J. Pharmacol. Exp. Ther., **193**: 676–688, 1975.

the higher doses of cocaine. Nevertheless, in the majority of comparisons the higher dose of cocaine was preferred.

Similar experiments were done comparing a standard dose of methylphenidate, 0.075 mg/kg, to higher doses. As with cocaine, wherever preferences developed, the higher dose was chosen (Table 2). However, unlike cocaine, preference for the higher dose developed only when this dose was 7 to 9 times greater than the standard dose (20). In contrast, a dose of cocaine only twice as high as a standard dose (*e.g.*, 0.1 mg/kg compared to 0.05 mg/kg) was preferred by all animals (table 1). This

suggests that a function relating dose differences and choice might be steeper for cocaine than for methylphenidate. Comparisons of two different doses of diethylpropion (21) also support the conclusion that rhesus monkeys prefer high doses of psychomotor stimulant drugs over low doses. If preference is considered a measure of reinforcing efficacy, higher doses of these drugs are more reinforcing than lower doses.

Reinforcing efficacy has also been assessed with rate of responding maintained by a drug injection. Wilson *et al.* (36) found that rates of responding on a one-response fixed-ratio schedule of injections of various psychomotor stimulant drugs decreased as dose was increased over the range of doses studied. A similar inverse relationship has been found between rate of responding and doses of diethylpropion (21). In the experiments with cocaine and methylphenidate described above, response rates during the sampling periods also decreased as the dose of cocaine and methylphenidate increased (fig. 3). Thus, in the same session, preference was directly related to dose whereas rate of lever-pressing maintained by drug reinforcement was inversely related. This could have resulted when a time-out period was not imposed between injections during a sampling period; thus, the inverse relationship between dose and rate of responding maintained by the drugs probably reflects one or more of the direct effects of the drugs on ongoing behavior. Pickens and Thompson (27), 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 direct function of the dose. A similar dose-dependent decrease in responding maintained by food has also been demonstrated with rhesus monkeys infused with cocaine through intravenous catheters (35). Thus, rate of responding maintained by drug injections may be markedly affected by the effect of the drug on lever-pressing behavior.

The interaction of the direct effects and the reinforcing effects of drugs under ratio schedules of drug injection is further suggested by studies in which the relative potencies of *d*- and *l*-amphetamine and *d*-methylamphetamine are compared. Owen (26) found that in rats these drugs disrupted liquid reinforced fixed-ratio re-

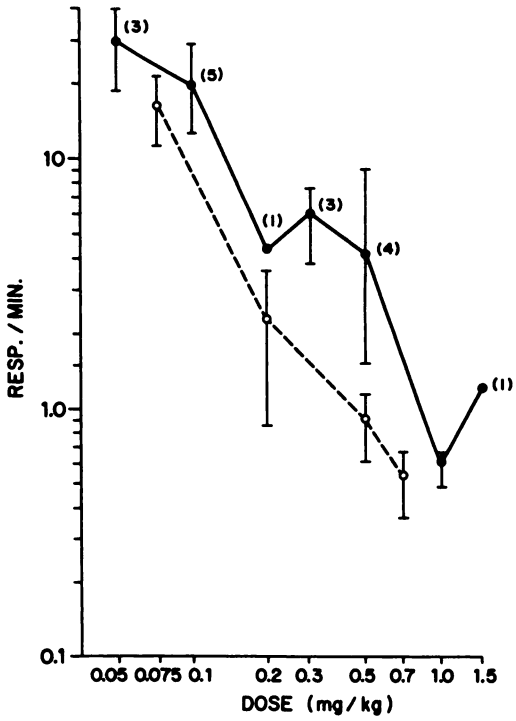

FIG. 3. Mean rates of responding during sampling periods maintained by each dose of cocaine (solid line) and methylphenidate (dotted line). For every comparison for each animal, response rates during sampling were calculated on each of the last 3 days of the comparison separately for drug A and drug B. These rates were then averaged over the 3 days. If an animal had not been studied for at least three 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 of parenthesis. [From Johanson and Schuster, J. Pharmacol. Exp. Ther., **193**: 676–688, 1975 (20).]

sponding in a dose-related manner. Further, Owen's data showed the same potency relationships for these compounds as were found in monkeys when the drugs were compared for their reinforcing effects with a ratio schedule of drug reinforcement (3). This suggests that responding maintained by amphetamine reinforcement is influenced not only by the drug's effects in maintaining behavior but also by its other behavioral effects. The results of the present experiments generate less ambiguous results by using choice rather than rate of responding as the measure of a drug's reinforcing efficacy. With the exception of the comparisons with high doses of cocaine, the results of these experiments were not a function of both variables but instead principally reflected the capacity of the dose of the drug to reinforce responding.

Comparisons of Different Drugs

In the next series of experiments rhesus monkeys were given a choice, first between cocaine and methylphenidate (20) and then between cocaine and diethylpropion (21). Preference in these studies could be viewed as an indication of the relative efficacy of different drugs in maintaining behavior. In order to rank drugs in terms of this property, it is advantageous to use procedures in which response rate is determined by reinforcing efficacy but is not confounded with the direct effects of the drug. In addition, since the previous studies showed that dose is important in determining preference, two drugs should be compared across a wide range of doses of both.

In the comparisons between cocaine and methylphenidate, doses of methylphenidate ranging from 0.075 mg/kg to 0.7 mg/kg were compared to 0.1 or 0.5 mg/kg of cocaine. In general, regardless of drug, higher doses were preferred over loser doses in over 75% of the choice trials. 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.

The data from one animal for the comparisons between cocaine and methylphenidate are shown in figure 4. In the comparisons between 0.1 mg of cocaine and methylphenidate per kg (top row) choice behavior changed from no preference with 0.075 mg of methylphenidate per kg to an exclusive preference for methylphenidate at the higher two doses. In the comparisons between 0.5 mg of cocaine and methylphenidate per kg, a complete reversal of preference was shown as the dose of methylphenidate was increased (fig. 4). Therefore, these two drugs are approximately equal in efficacy and potency in their ability to maintain behavior.

The outcome was different, however, when cocaine and diethylpropion were compared (21). Again, the two drugs were compared over a range of doses in six animals. Two doses of diethylpropion, 0.5 and 1.0 mg/kg, were compared to cocaine in doses ranging from 0.05 to 0.5 mg/kg. The doses of diethylpropion were chosen on the basis of a previous study in which responding was maintained under a 10-response fixed-ratio schedule of diethylpropion injections ranging in dose from 0.01 mg/kg to 3.0 mg/kg. For each of the three animals in that study, responding increased as a function of dose up to the value of 0.2 mg/kg but decreased over the rest of the dose range. The rates of responding maintained by 0.5 mg of diethylpropion per kg were similar to those maintained by 0.2 mg of cocaine per kg in the same animals whereas responding maintained by 1.0 mg/kg was quite low and similar to response levels for saline (21). In the present experiment, cocaine was preferred to diethylpropion regardless of the dose of either drug, although in several of the comparisons neither drug was preferred. Only one animal ever showed a preference for diethylpropion over cocaine. In that case, the dose of diethylpropion was 1.0 mg/kg and the dose of cocaine was 0.1 mg/kg, a 10-fold difference. The data show,

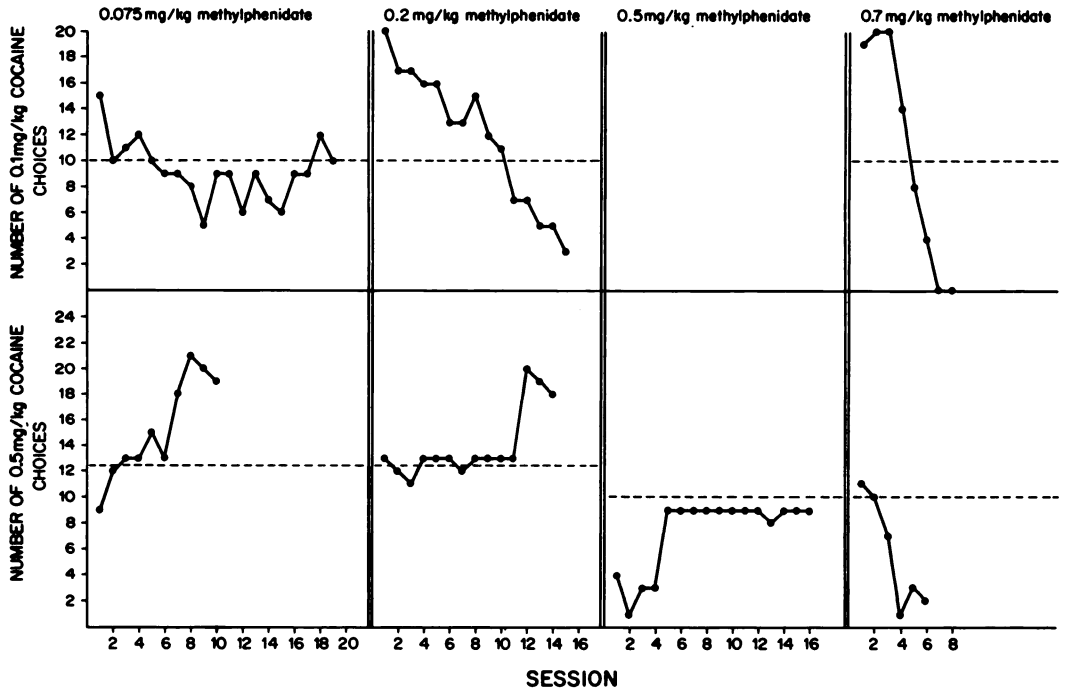

FIG. 4. Number of trials in which 0.1 mg of cocaine per kg (top row) or 0.5 mg of cocaine per kg (bottom row) was chosen over different doses of methylphenidate plotted daily for each comparison for one animal. The dotted lines indicated 50% choice. There were a maximum of 20 trials available during each session except in the comparisons of 0.075 and 0.2 mg of methylphenidate per kg with 0.5 mg of cocaine per kg when 25 trials were the maximum. [From Johanson and Schuster, J. Pharmacol. Exp. Ther., **193**: 676–688, 1975 (20).]

therefore, that these two drugs clearly differ in potency, and suggest a difference in reinforcing efficacy independent of dose.

The general conclusion which can be drawn from these experiments is that in single schedules, differences in rate of responding maintained by any of the drugs probably reflect a difference in the direct effects of the drug on behavior as well as its reinforcing efficacy. The preference procedure avoids this interaction in two ways. First a time-out period followed choice trials, so that the immediate general suppressant actions of the drug injected had some time to dissipate. Second, suppression of responding *per se* did not influence the evaluation of the reinforcing efficacy of each drug since, as long as some responding was maintained, preference could be assessed.

The effects of changes in amount of food or intensity of intracranial stimulation of the brain have also been shown to vary as a function of schedule parameters. In studies with single schedules of food presentation, response rate has been shown both to increase (15. 34) or decrease (8, 27) with increases in amount of food presented. Still other studies have found rate to be relatively insensitive to such changes in reinforcer magnitude (18, 23). Such differences have also been reported with single schedules of electric brain stimulation in rats. For example, Olds and Milner (25) and Sidman *et al.* (32) found that rate increased with increases in stimulation voltage. On the other hand, Reynolds (29) found an inverted U-shaped function relating response rate and voltage. In contrast, schedules of reinforcement such as concurrent, multiple, and chain schedules have shown response rate to be directly related to reinforcer magnitude (5, 28). Further procedures such as that employed in the present study, have shown choice to be directly related to amount of food (24) or

intensity of electric brain stimulation (16). The present study extends the generality of these findings relating reinforcement magnitude and preference to behavior maintained by drug injection.

Environmental Factors

Changes in Response Requirements

In the next series of investigations, the effects of environmental variables including size of the fixed-ratio, delay of injection, and punishment were assessed. In the first experiment, the same preference procedure was used except that the fixed-ratio requirement necessary to produce the preferred dose of cocaine was systematically increased while the behavioral requirements for the alternative, but less preferred dose of cocaine, remained the same. In the original studies, the fixed-ratio value was five for both solution A and solution B. In this study, however, the procedure was modified so that the fixed-ratio requirement necessary to produce the injection of solution B was increased by five responses each session until a change in preference occurred. It was reasoned that although animals prefer higher doses of cocaine over lower doses, if the behavioral requirements for the preferred dose were great enough, the animals would choose the alternative. In addition, the greater the difference between the size of the doses of the two alternatives, the greater the increase in ratio value necessary to alter preference. However, the results of this experiment are only preliminary and it is unclear whether these hypotheses will be verified. Four animals were tested with this modified procedure but their results failed to replicate each other. The first animal was tested in three different comparisons: 1) solution A was 0.05 mg of cocaine per kg and B was 0.5 mg of cocaine per kg; 2) solution A was 0.05 mg of cocaine per kg and B was 0.1 mg of cocaine per kg; and 3) solution A and B were both 0.05 mg of cocaine per kg. In each comparison, the response requirement to produce solution B was increased by five responses each session while the requirement for solution A remained at five. Solution B was always the higher dose except in the last comparison in which one of the two solutions, both being equal, was arbitrarily designated as B. Before the increases in response cost, the higher dose was preferred on over 75% of the choice trials. The results of all three comparisons are shown in figure 5. Both initial preference and maximum fixed-ratio value were directly related to the size of the dose of solution B, as would be predicted. The maximum fixed-ratio value when solution B was 10 times as high as A (0.5 *vs.* 0.05 mg/kg) was only five responses greater than when solution B was only twice as high as A (0.1 *vs.* 0.05 mg/kg). Similar results were obtained for a second animal although only two comparisons could be completed before the animal accidently died from a cocaine overdose. In the comparison between 1.0 mg and 0.2 mg of cocaine per kg, the animal initially preferred the high dose. However, when the requirement for this high dose was increased to fixed-ratio 125, he chose the lower dose exclusively. When equal doses

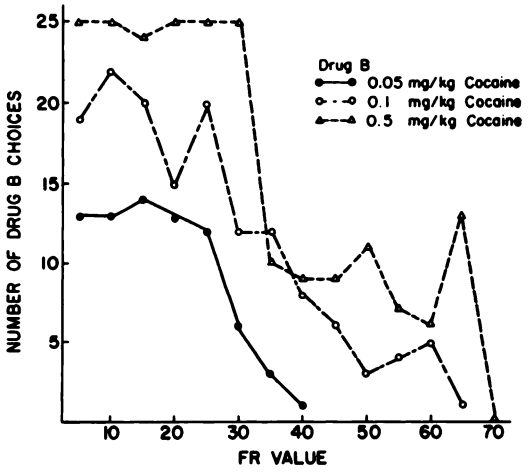

FIG. 5. Number of choice trials different doses of cocaine (drug B) were chosen over 0.05 mg of cocaine per kg as a function of fixed-ratio (FR) requirements for the delivery of drug B. The fixed-ratio requirement for the delivery of 0.05 mg of cocaine per kg was 5. The maximum number of choice trials programmed each session was 25.

of cocaine were compared this same animal chose solution A when the response requirement for B was 60. Unfortunately changes in fixed-ratio size did not alter preference in the other two animals. One animal, given a choice between 0.1 mg of cocaine per kg (solution A) and 0.5 mg of cocaine per kg (solution B), consistently preferred the higher dose despite increases in the response requirements necessary for its delivery up to a value of 95; at this point, the animal ceased responding entirely. The results of the second animal on the same comparison were erratic; even at a response requirement of 300 the animal was not choosing the lower dose. Clearly, the results from this study are ambiguous and seem to indicate that the manipulation of fixed-ratio values does not produce consistent results, since preference was altered in only two of the four animals. In addition, in one animal (fig. 5) tested under three conditions which varied in terms of the dose of solution B, the response requirement necessary to alter preference changed only minimally with dose. Brady *et al.* (4) by using a progressive ratio schedule within the context of a preference procedure, found that manipulations in dose of a drug did not affect the maximum fixed-ratio size which could maintain responding. However, this value differed considerably for different drugs. Yanagita *et al.* (37), however, with a progressive ratio schedule in which responding was maintained by injections of psychomotor stimulant drugs, found that the maximum fixed-ratio value maintaining responding was directly related to the dose of the drug. The effects of manipulating the value of the behavioral requirements necessary to produce a drug injection seem to differ depending upon the specific procedure being used. Since the three studies discussed differ in so many parameters, it remains to future investigations to delineate the relevant differences. Nevertheless, the present study demonstrates that changes in behavioral requirements can affect preference between two doses of cocaine for some animals.

Delay of Reinforcement

One of the problems with fixed-ratio studies is that as the value of the fixed-ratio increases, there can be a comparable increase in delay between the first response and the onset of the reinforcement. That is, one cannot differentiate between temporal and response variables.

There have been no published investigations of the acquisition and maintenance of responding which is followed by an injection of a drug when a delay is introduced between responding and the delivery of the drug reinforcement. However, investigations of other reinforcers have shown that delay of reinforcement is a significant variable; both acquisition and maintenance of behavior are weakened as a function of time delay (33). In order to determine the effect of delay on responding maintained by an injection of a drug, the original choice procedure was modified to include a 15-sec time delay between the completion of the ratio requirement and the onset of the injection. This delay was imposed after one of the two alternatives was chosen but not after the other. During the delay, the red ceiling light, which normally was on only during an injection, was illuminated. The peristaltic infusion pump, on the other hand, was not on during the 15-sec delay, eliminating the undoubtedly powerful auditory stimulus cues of this sound. The animals tested under these conditions were originally offered a choice between two equal doses of cocaine (0.1 mg/kg). Before introduction of the 15-sec delay, both animals were choosing the stimuli associated with each of these solutions an equal number of times. When the 15-sec delay occurred between the completion of the fixed-ratio for solution B and the onset of its injection, the animals chose B on over 70% of the trials. The same results were found after a stimulus reversal. Thus with these parameters, monkeys

showed a preference for drug injections which were delayed by 15 sec to immediate injections of the drug. Although these results can only be considered preliminary, they are puzzling. A possible explanation for these data is that the stimulus present during the delay, by virtue of its being paired with the drug injection was maintaining the choice behavior. It is certainly known that the stimuli associated with drug reinforcement can exert powerful effects on responding (8–12, 31). In addition, the delay did not decrease the overall frequency of reinforcement. Clearly, additional studies are necessary to delineate the mechanism involved in producing these results.

Concurrent Punishment

Punishment is defined as a reduction in the probability of a response as a consequence of the presentation of a stimulus contingent on the response (1). Many studies have shown that an intense electric shock delivered immediately after a response is capable of suppressing responding maintained by reinforcers such as food and water. In addition, Grove and Schuster (14) showed that electric shock delivered after each response decreased rate of responding on a one-response fixed-ratio schedule of cocaine injection. The degree of suppression was a direct function of the intensity of the electric shock. However, increasing the dose of the cocaine injection did not influence the degree of response suppression. If the function relating response suppression to shock intensity is related to the capacity of the drug to serve as a reinforcer, it is surprising that Grove and Schuster (14) did not find the responding maintained by the higher dose of cocaine more difficult to suppress. The problem may have been that the measure of suppression used was change in response rate, which itself was a function of both reinforcing efficacy and the direct effects of the drug; indeed, rate of responding maintained by the higher dose was lower than response rate maintained by the lower dose so that degree of suppression was difficult to compare. In addition, the direct actions of cocaine may alter the effect of electric shock on any ongoing responding.

A series of experiments were conducted with the choice procedure to determine how effects of electric shock might alter preference for a high dose of cocaine over a low dose. The procedure was modified such that a 5 mA electric shock 300 msec in duration was delivered at the onset of the injection of solution B, which was either equal to or higher in dose than solution A. The shock electrodes were two round gold-plated silver discs, 0.234 inches in diameter, surgically implanted within the lumbar muscles to the right of the spinal cord, approximately 1 to 2 inches apart. Each electrode was soldered to 28 gauge stranded silver-coated wire coated with Teflon which traveled with the catheter through the arm and then was connected to a BRS/LVE constant current generator. Impedence values varied between 15 and 50 k ohm but were stable for any one animal. Representative data from one animal are shown in figure 6. This animal was initially given a choice between two equal doses of cocaine, both 0.1 mg/kg. However, as explained above, a 5 mA electric shock was paired with the solution associated with S_2 (solution B). After only 5 days the animal was choosing the solution that was not paired with shock, *i.e.*, associated with S_1. The dose of solution B was then increased to 0.2 mg/kg and A remained at 0.1 mg/kg. In addition, the stimuli were reversed so that S_1 was associated with 0.2 mg of cocaine per kg and shock. The animal quickly reversed his choice, preferring an injection of the lower dose of cocaine rather than the injection of the higher dose which also resulted in the delivery of electric shock. As shown in figure 6 the same pattern was repeated with 0.5 mg/kg as solution B. However, when 0.75 mg/kg was the higher dose, this animal chose it despite the shock. In addi-

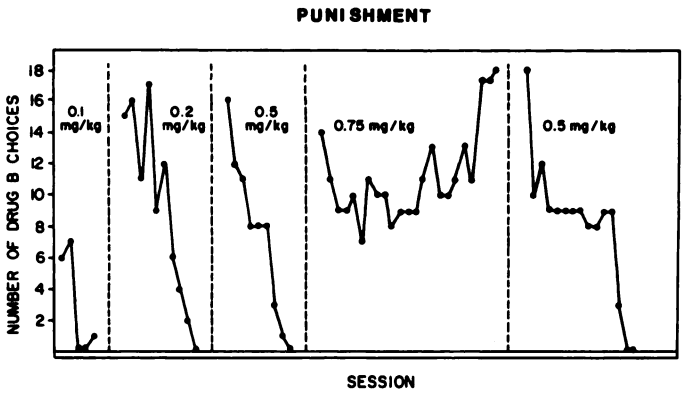

FIG. 6. Number of choice trials different doses of cocaine (drug B) were chosen over 0.1 mg of cocaine per kg when the injection of drug B was associated with a 5 mA electric shock 300 msec in duration. A maximum of 18 trials were available each session.

tion, lowering the dose of the drug injection paired with shock to 0.5 mg/kg resulted in a switch in preference to the lower but unshocked alternative. The results are similar to studies in which responding was maintained by food (1, 22) which showed that electric shock was more effective in eliminating responding if an alternative response was available. However, the present study went further by showing that responding can be eliminated by electric shock even if the unpunished alternative is of a lower magnitude, *i.e.*, a lower dose. In previous experiments with this choice procedure without punishment, 0.5 mg of cocaine per kg was preferred to 0.1 mg of cocaine per kg by all animals tested (fig. 2). However, when responding maintained by 0.5 mg of cocaine per kg also produced electric shock, as in the present experiment, the alternative 0.1 mg/kg was preferred. The results indicate that the capacity of electric shock to suppress responding maintained by cocaine can be influenced by the dose. A low dose of cocaine (0.1 mg/kg) was preferred to both 0.2 mg and 0.5 mg of cocaine per kg when an electric shock was delivered in conjunction with the injection of these higher doses. However, when the alternatives were 0.75 mg and 0.1 mg of cocaine per kg, the higher dose was preferred despite the delivery of electric shock. It seems, then, that if the difference in dose is great enough, the ability of electric shock to suppress responding is eliminated.

General Conclusions

The present series of experiments showed the effects of several pharmacological and environmental variables on drug preference in rhesus monkeys self-injecting psychomotor stimulant drugs. Preference was determined in a choice procedure which limited drug intake and a rate-free measure of preference was used. Hopefully, such an approach has several advantages over procedures with absolute rate of responding to indicate preference, since rate in these procedures is influenced not only by the reinforcing effects of drug but their direct effects as well. The results indicate that with cocaine, methylphenidate, or diethylpropion, higher doses are preferred over lower doses of the same drug. In addition, cocaine and methylphenidate are equally potent in terms of preference despite differences in potency in maintaining responding on a five-response fixed-ratio schedule of reinforcement. Diethylpropion on the other hand, is at least only 1/10 as potent as cocaine in terms of preference and there are some indications that it is generally less efficacious in this capacity. These studies also showed that preference can be modified by changes in response requirements, by a time delay preceding an injection, as well as by pun-

ishment with electric shock. In general, the results of these studies in which responding is maintained by an injection of a psychomotor stimulant drug are consistent with the results of studies in which responding is maintained by other events such as food, water, and electric stimulation of the brain.

REFERENCES

1. Azrin, N. H. and Holz, W. C.: Punishment. *In* ed. by W. K. Honig, Operant Behavior: Areas of Research and Application, pp. 380–447, Appleton-Century-Crofts, New York, 1966.
2. Balster, R. L. and Schuster, C. R.: Fixed-interval schedule of cocaine reinforcement: Effect of dose and infusion duration. J. Exp. Anal. Behav. **20:** 119–129, 1973.
3. Balster, R. L. and Schuster, C. R.: A comparison of d-amphetamine, l-amphetamine, and methamphetamine self-administration in rhesus monkeys. Pharmacol. Biochem. Behav. **1:** 67–71, 1973.
4. Brady, J. V., Griffiths, R. and Winger, G.: Drug-maintained performance in the evaluation of sedative-hypnotic dependency potential. Proc. of the Upjohn Conference on Hypnotics, Kalamazoo, Michigan, 1974, in press.
5. Catania, A. C.: Concurrent performances: A baseline for the study of reinforcement magnitude. J. Exp. Anal. Behav. **6:** 299, 1963.
6. Dougherty, J. and Pickens, R.: Fixed-interval schedules of intravenous cocaine presentation in rats. J. Exp. Anal. Behav. **20:** 111–118, 1973.
7. Findley, J. P., Robinson, W. W. and Peregrino, L.: Addiction to secobarbital and chlordiazepoxide in the rhesus monkey by means of a self-infusion preference procedure. Psychopharmacologia **26:** 93–114, 1972.
8. Goldberg, S. R.: Comparable behavior maintained under fixed-ratio and second-order schedules of food presentation, cocaine injection or d-amphetamine injection in the squirrel monkey. J. Pharmacol. Exp. Ther. **186:** 18–30, 1973.
9. Goldberg, S. R.: Control of behavior by stimuli associated with drug injections. In Psychic Dependence, ed. by L. Goldberg and F. Hoffmeister, pp. 106–109, Springer-Verlag, Berlin, 1973.
10. Goldberg, S. R., Morse, W. H. and Goldberg, D. M.: Behavior maintained under a second-order schedule of intramuscular morphine or cocaine injection in the rhesus monkey. Personal communication, NAS-NRC, 1974.
11. Goldberg, S. R. and Schuster, C. R.: Conditioned suppression by a stimulus associated with nalorphine in morphine-dependent monkeys. J. Exp. Anal. Behav. **10:** 235–242, 1967.
12. Goldberg, S. R. and Schuster, C. R.; Conditioned nalorphine-induced abstinence changes: persistence in post morphine-dependent monkeys. J. Exp. Anal. Behav. **14:** 33–46, 1970.
13. Griffiths, R., Findley, J., Brady, J. V., Dolan-Gutcher, K. and Robinson, W.: Comparison of progressive ratio performance maintained by cocaine, methylphenidate and secobarbital. Personal communication, 1975.
14. Grove, R. N. and Schuster, C. R.: Suppression of cocaine self-administration by extinction and punishment. Pharmacol. Biochem. Behav. **2:** 199–208, 1974.
15. Guttman, N.: Operant conditioning, extinction and periodic reinforcement in relation to concentration of sucrose used as a reinforcing agent. J. Exp. Psychol **46:** 213–224, 1953.
16. Hodos, W. and Valenstein, E. S.: An evaluation of response rate as a measure of rewarding intracranial stimulation. J. Comp. Physiol. Psychol. **55:** 80–84, 1962.
17. Iglauer, C. and Woods, J. H.: Concurrent performances: Reinforcement by different doses of intravenous cocaine in rhesus monkeys. J. Exp. Anal. Behav. **22:** 179–196, 1974.
18. Jenkins, W. O. and Clayton, F. L.: Rate of responding and amount of reinforcement. J. Comp. Physiol. Psychol. **42:** 174–181, 1949.
19. 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.
20. Johanson, C. E. and Schuster, C. R.: A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. J. Pharmacol. Exp. Ther. **193:** 676–688, 1975.
21. Johanson, C. E. and Schuster, C. R.: A comparison of cocaine and diethylproprion under two different schedules of drug presentation. Presented at *Contemporary Issues in Research*, Durham, N.C., Nov. 10, 1975.
22. Johnston, J. M.: Punishment of human behavior. Amer. Psychol. **27:** 1033–1054, 1972.
23. Keesey, R. F. and Kling, J. W.: Amount of reinforcement and free-operant responding. J. Exp. Anal. Behav. **4:** 125–132, 1961.
24. Neuringer, A. J.: Effects of reinforcement magnitude on choice and rate of responding. J. Exp. Anal. Behav. **10:** 417–423, 1967.
25. Olds, J. and Milner, P.: Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J. Comp Physiol. Psychol. **47:** 419–427, 1954.
26. Owen, J. E.: The influence of *dl*-, *l*-amphetamine and *d*-methamphetamine on a fixed-ratio schedule. J. Exp. Anal. Behav. **3:** 293–310, 1960.
27. Pickens, R. and Thompson, T.: Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. J. Pharmacol. Exp. Ther. **161:** 122–129, 1968.
28. Pliskoff, S. S. and Hawkins, T. D.: A method for increasing the reinforcement magnitude of intracranial stimulation. J. Exp. Anal Behav. **10:** 281–289, 1967.
29. Reynolds, R. W.: The relationship between stimulation voltage and rate of hypothalmic self-stimulation in the rat. J. Comp. Physiol. Psychol. **51:** 193–198, 1968.
30. Schuster, C. R. and Johanson, C. E.: The use of animal models for the study of drug abuse. *In* Research Advances in Alcohol and Drug Problems, vol. I, ed. by R. J. Gibbins, Y. Israel, H. Kalant, R. E. Popham, W. Schmidt, and R. G. Smart, pp. 1–31, John Wiley and Sons, Inc., New York, 1974.
31. Schuster, C. R. and Woods, J. H.: The conditioned reinforcing effects of stimuli associated with morphine reinforcement. Int. J. Addict. **3:** 223–230, 1968.
32. Sidman, M., Brady, J. V., Boren, J. J. and Conrad, D. C.; Reward schedules and behavior maintained by intracranial self-stimulation. Science **122:** 830–831, 1955.
33. Skinner, B. F.: The Behavior of Organisms, Appleton-Century-Crofts, New York, 1938.
34. Stebbins, W. C., Mead, P. B. and Martin, J. M.: The relation of amount of reinforcement to performance under a fixed-interval schedule. J. Exp. Anal. Behav. **2:** 351–355, 1959.
35. Wilson, M. C.: Variables which influence the reinforcing properties of cocaine in the rhesus monkey. Unpublished doctoral dissertation, University of Michigan, 1970.
36. Wilson, M. C., Hitomi, M. and Schuster, C. R.: Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. Psychopharmacologia **22:** 271–281, 1971.
37. Yanagita, T., Takahashi, S. and Oinuma, N.: Progressive-ratio performance with CNS-stimulant reinforcers in rhesus monkeys. Personal communication, 1972.