JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1973, 20, 119-129 NUMBER 1 (JULY)

FIXED-INTERVAL SCHEDULE OF COCAINE REINFORCEMENT: EFFECT OF DOSE AND INFUSION DURATION[1]

ROBERT L. BALSTER[2] AND CHARLES R. SCHUSTER

UNIVERSITY OF CHICAGO

Rhesus monkeys were trained on a fixed-interval 9-min limited-hold 3-min schedule of intravenous cocaine reinforcement. A 15-min timeout followed each reinforcement or limited-hold expiration. An identical schedule of food reinforcement was interspersed in the session to assess rate-modifying effects of the drug infusions not specific to drug reinforcement. In one experiment, response rate for cocaine reinforcement was shown to be a positive function of reinforcement magnitude for a dose range from 0 to 800 ug/kg/inj. At these doses, there was little effect on food reinforced responding except at the highest dose, where responding decreased. Results of the second experiment indicated that increasing the duration of the cocaine infusion produced a change in response rate similar to decreasing unit dose. The response rate change for a given increase in infusion duration was less at a unit dose of 400 ug/kg than at 200 ug/kg.

The intravenous infusion of a number of psychomotor stimulant drugs has been shown to be an effective reinforcer of lever-pressing behavior in experimental animals (Pickens and Thompson, 1971). An inverse relationship between response rate and magnitude of drug reinforcement (dose per infusion) has been found using *d*-amphetamine (Pickens and Harris, 1968), methamphetamine (Pickens, Meisch, and McGuire, 1967), cocaine (Pickens and Thompson, 1968*a*; Woods and Schuster, 1968), and methylphenidate, pipradol, and phenmetrazine (Wilson, Hitomi, and Schuster, 1971). All of the studies utilized a continuous schedule of reinforcement (CRF) where an increase in rate is accompanied by an increase in drug intake. Increased intake of the drug may disrupt a number of ongoing behaviors, including the self-administration response. The duration of this disruption may be dose-dependent and thereby limit total drug intake to a constant level regardless of changes in unit dose.

In the present study, a fixed-interval (FI) schedule of reinforcement was used to assess the effect of unit dose on response rate, independent of frequency of reinforcement. In addition, the use of a short-acting drug, cocaine, as the reinforcer, and a timeout following each reinforcement, minimized the rate-modifying effects of the reinforcer. A fixed-interval schedule of food reinforcement was also interspersed in the session to assess the extent of these rate-modifying effects not specific to drug reinforcement.

EXPERIMENT I

METHOD

Subjects

One female (A019) and two male (A049, A050) rhesus monkeys weighing from 4.2 to 5.6 kg were used. All three monkeys were experimentally naive at the beginning of Experiment I. Although no attempt was made to maintain a specific body weight, the animals were required to work for their entire daily food complement. The animals' earned food, however, was supplemented at least twice a week by fruit, and daily with vitamins placed on a

[1]This research was supported by NIMH Grants MH-18,245 and MH-11,042 to Charles R. Schuster and was carried out while the first author was a post-doctoral fellow in the Departments of Psychiatry and Pharmacology, supported by NIH training grant MH-07,083 to the University of Chicago (Lloyd J. Roth, principal investigator). The authors would like to thank William Bergin, Frederick Clark, Jurate Mazeika, and Gary Reynolds for their valuable technical assistance. The manuscript was improved greatly by the suggestions of Drs. Lewis Seiden and Chris Johanson. Reprints may be obtained from Charles R. Schuster, Department of Psychiatry, The University of Chicago, 950 East 59th Street, Chicago, Illinois, 60637.

[2]Now at the Department of Psychiatry, Duke University, Durham, North Carolina, 27710.

sugar cube. These additional foods were usually given 3 to 4 hr before the daily experimental session.

Apparatus

The animals were individually housed in 4 by 4 by 3 ft (131 by 131 by 92 cm) experimental cubicles. The front of the cubicle contained two levers (LVE 121-07) 50 cm (20 in) apart and 15 cm (6 in.) above the floor of the cage. Above each lever was a stimulus light. A food tray, connected to a pellet dispenser (Gerbrands Model G5210) mounted outside the cubicle, was located to the left of the left lever. In addition, the ceiling contained a 30 by 30 cm (12 by 12 in.) area that could be transilluminated by either a white or red houselight. The cubicles and electromechanical programming equipment were located in separate rooms and masking noise was provided by a fan mounted to each cubicle.

Each subject was fitted with a stainless steel harness (Deneau, Yanagita, and Seevers, 1969) connected to a steel spring restraining arm. The restraining arm was attached to the rear of the experimental cubicle. This arrangement allowed the monkey relatively free movement about the cubicle. After a subject had adapted to this restraint, it was surgically prepared with a chronic venous catheter of siliconized rubber using sterile technique. The catheter was anchored in the sternohyoideus and sternothyroideus muscles with the proximal end passing through the internal jugular vein terminating at the level of the right atrium of the heart. The other end was passed subcutaneously over the shoulder to the back where it exited through a stab wound into the harness and attached to tubing passed from the back of the cubicle through the arm and harness. The distal end of the tubing was connected to a peristaltic infusion pump (Cole-Parmer 7540X) that delivered drug solution at a fixed rate of 6 ml/min.

Drug reinforcement consisted of an injection of cocaine hydrochloride dissolved in 0.9% physiological saline. Fresh solutions were prepared at least weekly, and were made up to allow the appropriate dose to be delivered in 0.2 ml/kg of animal weight. The infusion duration was adjusted for each animal and ranged from 8.4 to 11.2 sec. In the instance of a 0-drug dose, the animal received an injection of the saline vehicle.

Procedure

The terminal schedule of reinforcement consisted of a multiple schedule for food or cocaine reinforcement. The component during which food reinforcement was presented was arranged on the left lever and the component for drug reinforcement was arranged on the right lever. Each daily session, signalled by illumination of the white houselight, consisted of 40 reinforcements, beginning with a food reinforcement followed by three drug reinforcements. This sequence was repeated 10 times for a total of 10 food reinforcements and 30 drug reinforcements. The two components were identical except for lever and reinforcer, and began with a single fixed-interval 9-min limited-hold (LH) 3-min period indicated by turning on the stimulus light over the appropriate lever. The first response between 9 and 12 min after the illumination of the stimulus light was reinforced and initiated a 15-min timeout (S^{Δ}) period during which the stimulus light was off and responses had no scheduled consequence. Failure to respond during the 3-min limited hold was also followed by the 15-min timeout period.

Each food reinforcement consisted of 2 g/kg delivered as a series of 1-g Noyes Formula L Monkey Pellets. Drug reinforcement was accompanied by a change in the houselight color from white to red. In addition, the sound of the infusion pump located on top of the cubicle was readily audible to the animal.

Responses on the FI 9-min LH 3-min S^{Δ} 15-min schedule were rapidly shaped using only food reinforcers by gradually increasing the length of the fixed interval and timeout. Following the acquisition of appropriate schedule performance, the component during which cocaine reinforcement was available was phased in. Due to the marked anorexic effects of cocaine, it was necessary to decrease gradually the proportion of food to drug reinforcements. The unit dose of cocaine used for training was 200 ug/kg.

After several weeks of training, the animals' behavior stabilized and the experimental design was initiated. Drug doses of 0, 25, 50, 100, 200, 400, and 800 ug/kg/inj were each tested for six consecutive daily sessions. The animals were returned to the baseline dose of 200 ug/kg for six sessions between each test dose. The sequence of testing was randomized for each

subject and appears in Table 1. When an animal developed a faulty catheter, it was removed from the experimental cubicle and the catheter was repaired. The animal was returned to baseline conditions before testing resumed. One animal (A049) died before completion of the dose series.

Results

Rate of responding on the last three days of each baseline and test series was used for data analysis. The mean number of responses per fixed interval over these three days during each component was calculated for each baseline and test series (Table 1). Due to a changing baseline, the response rate during each test series was then calculated as the per cent change from the preceding baseline. These derived measures are presented in Figure 1. Response rate for cocaine reinforcement increased as a function of increasing unit dose. The only exception to this was Animal A050 at 800 ug/kg/inj. For Monkeys A019 and A050, response rate for food reinforcement remained stable except at high doses, where it was considerably reduced. At unit doses of 0 and 50 ug/kg, Animal A040, however, had a response rate higher than baseline. This increase was dose-dependent.

The use of a limited hold made it possible for the subjects to earn fewer than the maximum 30 cocaine reinforcements and 10 food reinforcements available per session. The mean number of reinforcers earned over the last three sessions at each dose is shown in Figure 2. At a unit dose of 200 ug/kg and above, the subjects completed all the FI requirements for cocaine reinforcement. There was a general dose-dependent decrease in completed FIs below this dose. These missed reinforcers usually occurred late in the session. In general, the animals completed all the food-reinforced FIs but both animals tested at 800 ug/kg did not. This corresponds to the low response rate for food reinforcement at this dose.

The 9-min FI for cocaine reinforcement was divide into three equal intervals and the index of curvature was calculated for each session (Fry, Kelleher, and Cook, 1960). The mean index of curvature for each subject over the last three sessions at each dose is presented in Figure 3. The result is an inverted U-shaped function with maximum scalloping between 50 and 200 ug/kg. Figure 4 presents cumulative records for a portion of the last day at each test dose for Monkey A019. The loss of scalloping at high doses was accounted for by a steady, paced rate of responding over the fixed inter-

Table 1

Mean number of responses per fixed interval during each component for the last three sessions of baseline and testing for each animal in Experiment 1.

			Baseline		*Test*	
Subject	*Test Dose (ug/kg)*	*Sequence*	*Cocaine Reinforced Responses*	*Food Reinforced Responses*	*Cocaine Reinforced Responses*	*Food Reinforced Responses*
A019	0	5	51.7	22.8	6.0	18.6
	25	3	47.6	32.7	17.8	30.9
	50	6	34.2	16.0	14.4	12.0
	100	1	41.2	46.6	30.8	48.6
	200	7	51.8	16.8	63.8	14.0
	400	4	37.0	27.9	56.7	27.2
	800	2	40.8	46.2	68.0	18.4
A050	0	7	258.0	408.1	27.3	389.8
	25	2	210.0	279.2	47.4	250.5
	50	6	405.8	452.4	105.4	492.6
	100	4	292.2	485.7	250.4	455.6
	200	5	404.2	502.7	405.8	452.4
	400	1	187.7	123.8	257.2	51.7
	800	3	323.5	434.3	191.9	16.8
A049	0	3	172.3	58.9	8.6	95.3
	50	2	130.8	70.0	48.1	93.7
	200	1	141.2	74.3	130.8	70.0

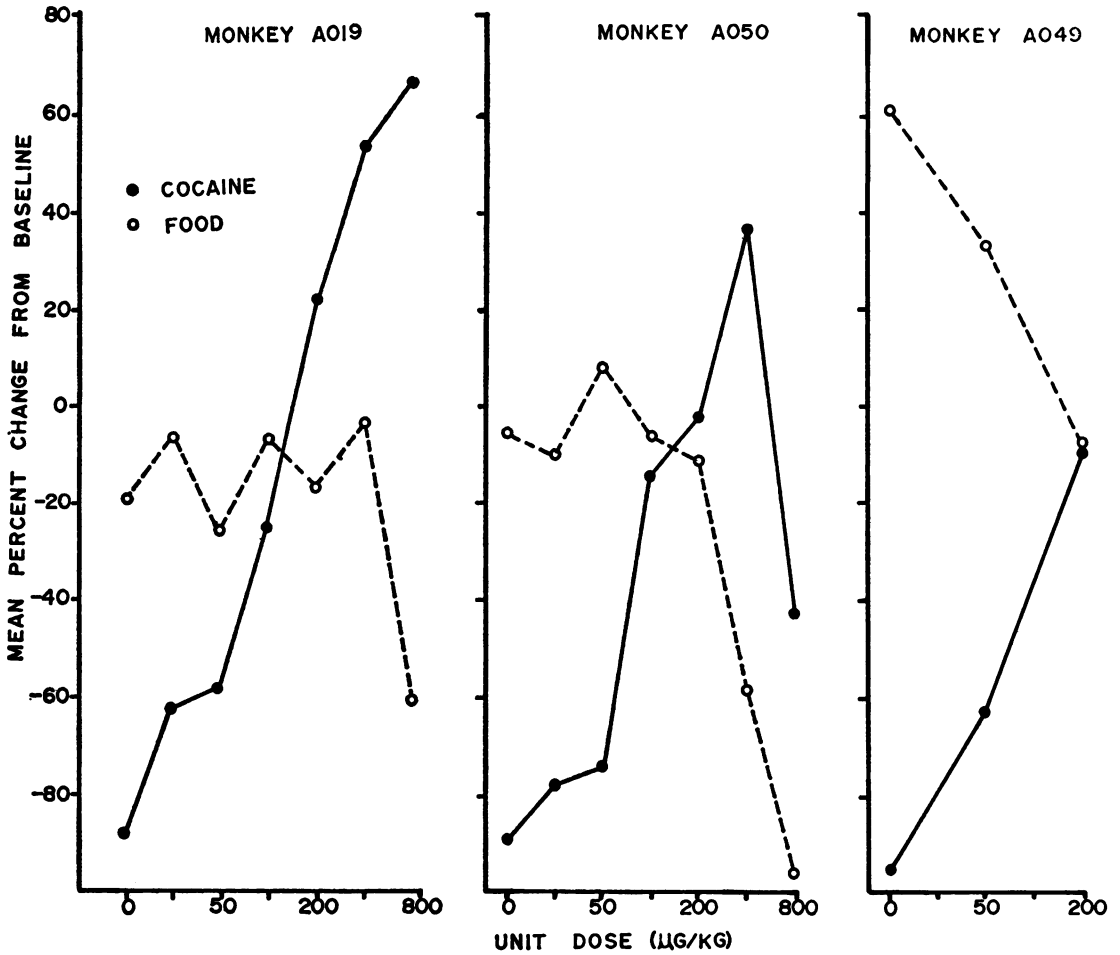

Fig. 1. Change in fixed-interval response rate for food and cocaine reinforcement as a function of dose per reinforcement of cocaine for three animals. Values represent the mean per cent change in response rate for the last three sessions at each unit dose from the three days of baseline dose (200 ug/kg/inj) just preceding it.

val, which at times began during the timeout. The dose-dependent change in response rate during timeout seen in these cumulative records was typical, although there was a great deal of variability in this measure. At the low unit doses, the lack of scalloping is due to sporadic responding at a low rate. For Animals A019 and A049 at 0 ug/kg, the index of curvature was based on fewer than 10 responses per fixed interval and consequently may not be meaningful.

Discussion

Response rate on a fixed-interval schedule of cocaine reinforcement increased with increasing unit dose. Although cocaine given non-contingently does increase overall response rate on a food-reinforced FI 300-sec (Smith, 1964), this mechanism is not likely to account for the increase in response rate for higher doses of cocaine reinforcement seen in this study. If it did, response rate for food also would be expected to increase at higher doses of cocaine. However, in two monkeys (A019, A050) the rate of responding for food was stable across a wide dose range of cocaine reinforcement and decreased at high doses. The other animal (A049) showed an increase in response rate for food reinforcement when the unit dose of cocaine was lowered from 200 to 50 ug/kg or saline. These decreases in rate of responding for food reinforcement may reflect the increasing anorexia at high doses. In any case, the change in response rate for drug seems specific to the reinforcement function of cocaine, and not due to a general tendency for cocaine to in-

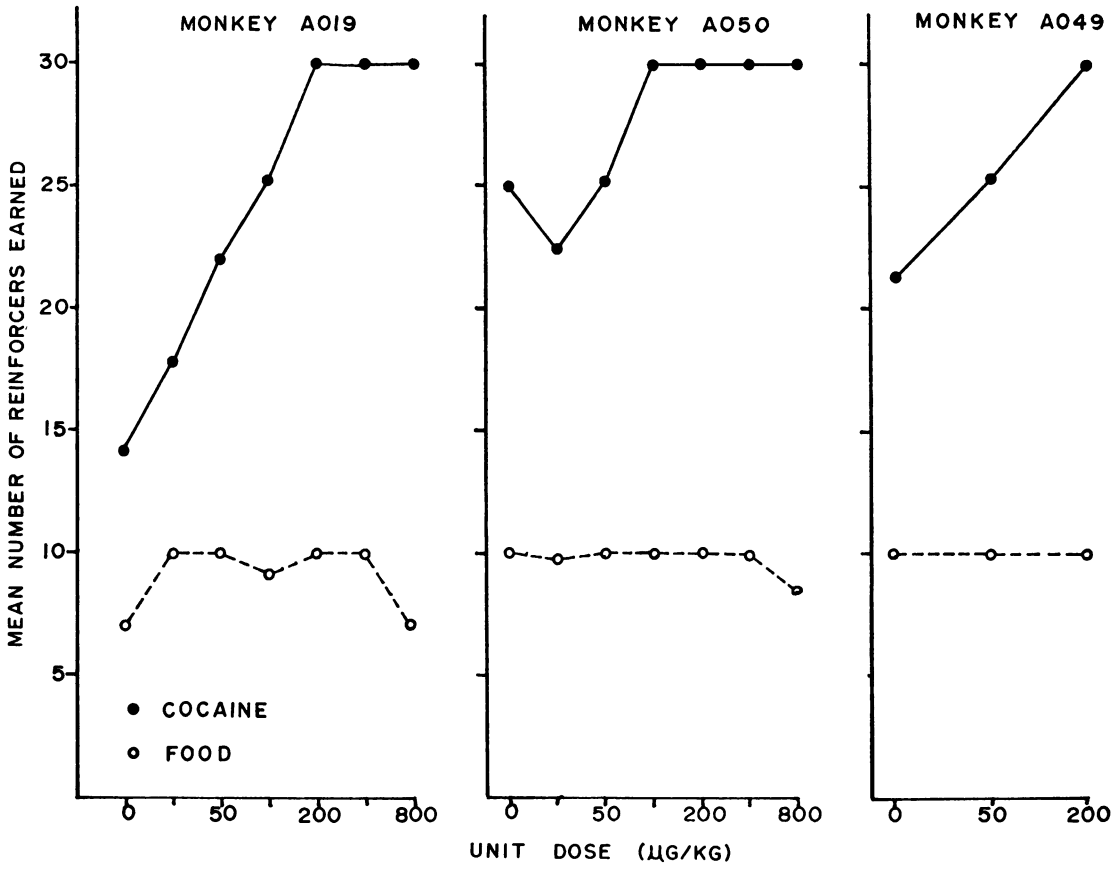

Fig. 2. Mean number of food and cocaine reinforcers earned as a function of dose per reinforcement of cocaine for three animals. Values represent the mean for the last three sessions at each unit dose. The subjects can miss reinforcers by not completing the fixed-interval 9-min limited-hold 3-min schedule of reinforcement. A maximum of 30 cocaine and 10 food reinforcers are possible per session.

crease rate of responding on FI schedules. Since baseline rate has been demonstrated to be an important variable in drug studies (Kelleher and Morse, 1968), it is unfortunate that these rates for food and drug reinforcement could not be equated. In two cases (A019 and A049), the cocaine baseline rate was higher, in the other animal (A050) the food baseline was higher. However, the different baselines did not affect the general nature of the dose response curves, as illustrated in Figure 1. In this regard it should be pointed out that rate of responding for the baseline dose of cocaine (200 ug/kg) did vary over the course of the experiment. By expressing the data in terms of percentage change from the preceding baseline, however, an orderly dose-dependent relationship was found between unit dose and response rate.

The data from Animal A050 responding for 800 ug/kg/inj showed a 40% decrease in response rate from baseline, indicating the beginning of a U-shaped function relating rate to unit dose. The animal appeared hyperactive during test sessions at this unit dose and, in addition, responded at a very low rate for food reinforcement and did not eat all the pellets earned. Due to the likelihood of even higher doses leading to convulsions, no attempt was made to study doses above this range. One would predict a dose-dependent disruption of behavior as dose is increased above 800 ug/kg/inj.

Stebbins, Mead, and Martin (1959), using sucrose concentration, and Meltzer and Brahlek (1968, 1970) using number of food pellets, also found response rate on FI schedules to be positively related to reinforcement magnitude.

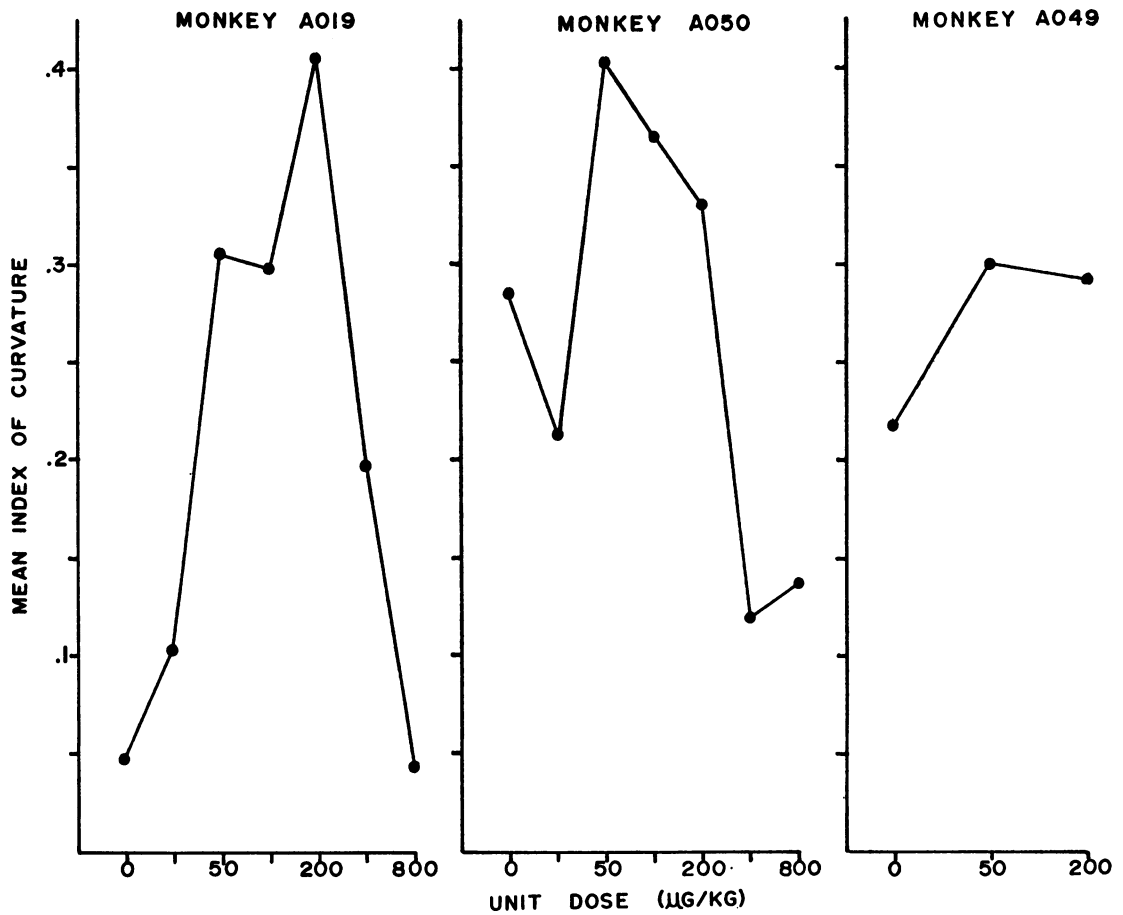

Fig. 3. Mean amount of fixed-interval scalloping as a function of unit dose of cocaine for three animals. Values represent mean index of curvature for the last three sessions at each unit dose. Larger values indicate greater scalloping.

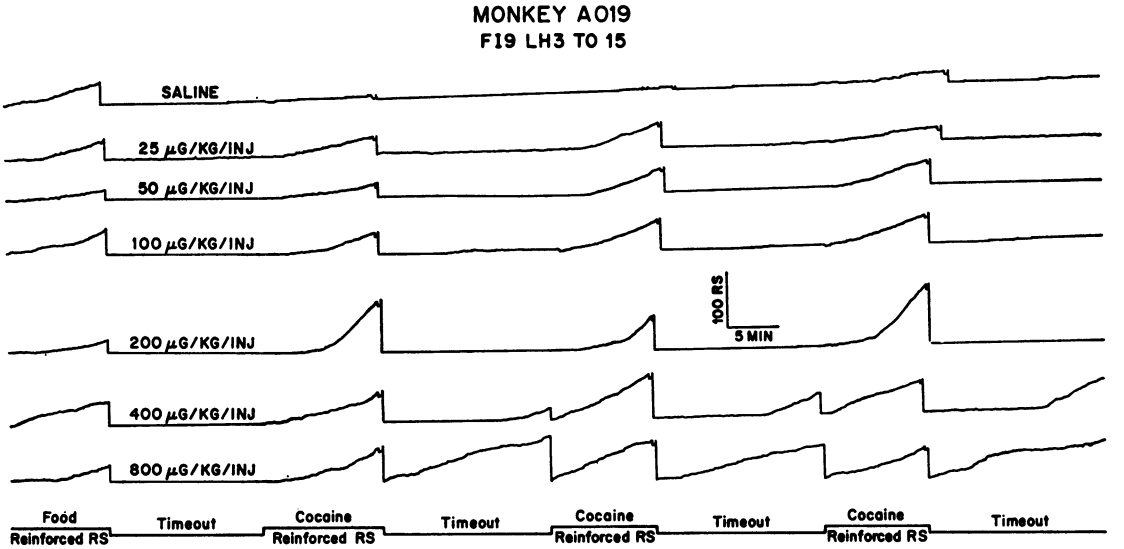

Fig. 4. Portions of the cumulative records for the last day at each test dose for Animal A019. The pen reset at the completion of each fixed interval or limited hold and also after each timeout.

These studies differ, however, in the effect on response distribution. Meltzer and Brahlek found no relationship between the number of pellets and amount of scalloping in the fixed interval when different reinforcement magnitudes were tested in different subjects (1968) and in the same subjects (1970). Stebbins *et al.* (1959), however, found a U-shaped function relating amount of scalloping to sucrose concentration, with maximum scallop at 5% sucrose, minimum at 32%, and intermediate at 50%. The results for cocaine reinforcement were the opposite from Stebbins *et al.* with maximum scalloping at intermediate doses. These differences may be due to the different reinforcers used, differences in schedule contingencies, including the timeout following reinforcement in the present study, return to baseline conditions between successive tests in the present study, satiation at high sucrose concentrations, or more probably the likelihood that different parts of the reinforcement magnitude-response curve were being investigated in the different studies.

The effect of unit dose on rate of cocaine self-administration has also been studied by Pickens and Thompson (1968*a*) with rats and by Wilson, Hitomi, and Schuster (1971) and Goldberg, Hoffmeister, Schlichting, and Wuttke (1971) with monkeys. These studies utilized a CRF schedule of reinforcement. Under these conditions, response rate was an inverse function of unit dose, such that a stable level of drug intake per session was maintained. Goldberg *et al.* also found the same relationship using a fixed-ratio (FR) 10 schedule of cocaine reinforcement. One of the most difficult problems in the investigation of self-administration behavior is that, in addition to their reinforcing properties, drugs possess other dose-dependent behavioral effects that can modify the self-administration response. That problem is clearly evident in the studies cited immediately above, since changes in response rate produce a concomitant change in frequency of reinforcement and, consequently, dose of drug administered. This effect is not unique to drugs as reinforcers. Electrical brain stimulation at high intensities produces side effects that disrupt behavior, consequently producing an inverted U-shaped relationship between rate and reinforcement magnitude (Reynolds, 1958). Even with food reinforcement, the effects of satiation can interfere with rate measures of reinforcement magnitude. Pickens and Thompson (1968*a*) found an inverse relationship between number of food pellets across a range of 1 to 20 45-mg pellets and response rate on a CRF schedule that was in effect 24 hr a day. The animals maintained a stable level of 19 to 22 food pellets per hour independent of the number of pellets per reinforcement. The use of rate measures to assess reinforcement magnitude, particularly as it relates to electrical brain stimulation, is discussed at length by Valenstein (1964).

A fixed-interval schedule, as used in the present study, by making response rate above some minimum level and frequency of reinforcement independent, avoids one of the problems of the previous studies. In addition, the use of a 15-min timeout following each reinforcement to allow the drug to be metabolized decreased the influence of the reinforcer on subsequent behavior. That this was at least partially successful is evidenced by the lack of effect of changes in cocaine dose on responding for food reinforcement except at high doses. These two differences undoubtedly account for the different results obtained in this study.

Finding methods to quantify drug reinforcement magnitude would be extremely useful for laboratory models of drug abuse. In particular, the use of self-administration procedures to evaluate abuse potential of new drugs in man is an attractive alternative to presently available methods (Schuster and Balster, 1973). If measures of reinforcement efficacy using animals can be shown to parallel clinical measures of reinforcing capability in man, then procedures can be developed for studying the elusive concept of drug abuse. This study indicates that response rate measures under the appropriate schedule conditions may prove useful. Alternative methods using preference procedures are also being investigated with encouraging results (Johanson, 1971; Findley, Robinson, and Peregrino, 1972).

EXPERIMENT II

Since cocaine infusions have been shown to be reinforcing, the duration of the infusion might be expected to influence reinforcement magnitude. Pickens and Thompson (1968*b*), however, reported no effect on response rate of changing infusion duration across a range of 25 to 75 sec or volume across a range of 0.2 to

1.0 ml/inj using cocaine reinforcement in rats.

The present study utilized the same procedure as Experiment I to assess the effect of infusion duration of a constant volume of cocaine at two unit doses on FI response rate.

Method

Subjects and Apparatus

Two monkeys from Experiment I (A019, A050) and one native male rhesus monkey weighing 4.2 kg (A053) were used. Monkey A050 was tested with a variable speed peristaltic infusion pump (Cole-Parmer 7545X) and Monkeys A019 and A053 were tested with a variable speed syringe pump (Harvard 940). With these exceptions, the apparatus was identical to Experiment I.

Procedure

The FI 9-min LH 3-min S^{Δ} 15-min schedule of cocaine and food reinforcement was identical to Experiment I. Infusion rates for each animal were adjusted to deliver 0.2 ml/kg of the baseline dose of cocaine hydrochloride in 10 sec. The effect of changes in infusion duration was tested at 200 ug/kg/inj first in all animals, and then repeated at 400 ug/kg/inj in Monkeys A019 and A053. Test infusion durations of 5, 10, 40, 100, and, during the repetition at 400 ug/kg/inj, 200 sec were each substituted for the 10-sec baseline for six consecutive sessions. Between test durations the animals were returned to baseline for six days. The order of testing appears in Table 2. Monkey A050 began consistently to pull his catheter out and did not complete testing.

Results

Rate of responding on the last three days of each baseline and test series was used for data analysis. The mean number of responses per fixed interval over these three days during each component was calculated for each baseline and test series (Table 2). Figure 5 presents the response rate during the food and drug components expressed as the mean per cent change from the preceding baseline. Response rate decreased with increasing infusion duration; however, the slope is much steeper at 200 than at 400 ug/kg/inj. A lawful relationship

Table 2

Mean number of responses per fixed interval during each component for the last three sessions of baseline and testing for each animal in Experiment 2.

				Baseline		*Test*	
Subject	*Test Dose (ug/kg)*	*Infusion Duration (Sec)*	*Sequence*	*Cocaine Reinforced Responses*	*Food Reinforced Responses*	*Cocaine Reinforced Responses*	*Food Reinforced Responses*
A019	200	5	3	88.4	41.8	86.2	41.3
		10	1	62.5	34.6	68.7	32.0
		40	2	68.7	32.0	41.4	28.8
		100	4	82.8	47.6	27.1	25.0
	400	5	6	122.3	36.3	132.1	39.8
		10	8	114.2	32.3	104.5	36.1
		40	5	65.1	36.6	58.5	31.6
		100	7	134.8	29.1	94.8	27.9
		200	9	104.5	36.1	22.0	24.7
A053	200	5	1	43.7	53.2	46.7	46.3
		10	4	65.1	54.0	59.4	63.9
		40	3	90.8	26.3	72.1	34.9
		100	2	79.4	45.6	4.3	82.1
	400	10	6	56.5	54.0	45.0	60.0
		40	7	45.0	60.0	35.0	84.0
		100	8	47.0	77.0	39.3	87.0
		200	5	73.9	66.8	13.1	83.6
A050	200	10	1	414.2	582.7	405.6	519.0
		40	3	265.3	446.3	209.6	424.7
		100	2	274.6	317.0	29.0	343.7

expressing the effect of manipulating unit dose and infusion duration simultaneously would seem to hold; for example at 200 ug/kg/inj an infusion duration of 100 sec produces a response rate decrement comparable to 200 sec at 400 ug/kg/inj. Expressed differently, comparable ratios of infusion duration to unit dose produce comparable changes in response rate.

Response rate for food reinforcement for the two monkeys continued from Experiment I (A019 and A050) showed little change from baseline conditions when duration of cocaine reinforcement was changed, although Monkey A019 decreased responding for food at the maximum infusion duration tested at each dosage. This is not due to an early cessation of responding in the session, since this monkey missed only one food reinforcement in the three sessions at 100 sec of 200 ug/kg/inj and none at 200 sec of 400 ug/kg/inj. The experimentally naive monkey (A053), however, increased responding for food reinforcement at longer infusion durations when 200 ug/kg/inj was used as the reinforcer.

The data for the number of reinforcements earned are not presented because they basically follow the data for response rate presented in Figure 5. Decreases in response rate at long infusion durations were accompanied by a decrease in number of cocaine reinforcers earned, whereas the number of food reinforcers earned remained stable at or about the maximum of 10 per session. Animal A053 received as few as six cocaine reinforcements in one session of 100 sec at 200 ug/kg/inj.

The index of curvature for drug reinforced responding showed no consistent relationship to infusion duration, but rather tended to increase over the course of the experiment independent of changes in infusion duration. The range was from 0.39 to 0.58.

Discussion

The results of this experiment indicate that an increase in infusion duration of cocaine reinforcement produces a change in response rate similar to a decrease in unit dose. The magnitude of this response rate decrement with larger infusion durations is dependent upon the unit dose used. Presumably, a family of curves could be drawn representing the reinforcing efficacy of cocaine reinforcement as a

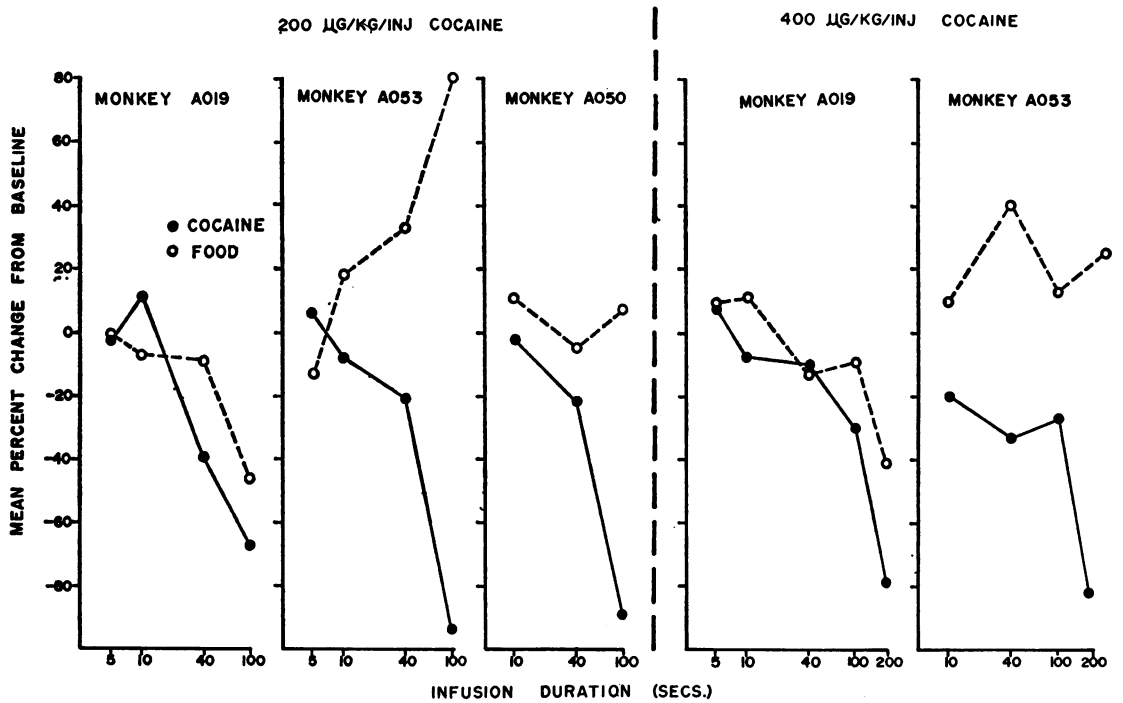

Fig. 5. Change in fixed-interval response rate for food and cocaine reinforcement at two unit doses as a function of infusion duration. Values represent the mean per cent change in response rate for the last three sessions at each infusion duration from the three days of baseline infusion duration (10 sec) preceding it.

joint function of dose and infusion duration as expressed by the following formula:

$$\text{Reinforcement Efficacy} = \frac{\text{Unit Dose}}{\text{Infusion Duration}}$$

This relationship is demonstrated in Figure 6. Change in response rate is expressed as a function of the ratio of unit dose to infusion duration. With the exception of two data points from Monkey A053 at 400 ug/kg/inj, all the curves tend to fit a single line.

The present experiment considered only a very limited range of doses and infusion durations. Whether very small doses would be reinforcing if delivered fast enough, or if long infusion durations of 5 to 10 min could maintain behavior if the dose is high enough, has not been ascertained.

Infusion duration could affect reinforcement magnitude in at least four ways. First, this effect might be due to the "bolus" effect of rapid intravenous administration. Since the drug is being injected directly into the right atrium of the heart, rapid administration would produce an uneven distribution of the drug in the circulatory system (Goldstein, Aronow, and Kalman, 1968) with higher drug concentrations in the heart, lungs, and central nervous system. These higher concentrations in the central nervous system could lead to a higher effective unit dose with more rapid administration, even though identical total amounts of the drug are given. Second, it could be due to the very rapid detoxification of cocaine by the liver; long infusion durations may allow the animal to metabolize the drug sufficiently rapidly so as to prevent the reaching of the same blood levels as at shorter infusion durations. The result again would be a lower effective unit dose. Third, reinforcement by psychoactive drugs may be mediated by *changes* in drug concentration at the receptor site rather than by steady-state blood levels, with more rapid changes reflected in greater reinforcement efficacy. Lastly, long infusions or a long duration of drug action may have some aversive properties that result in lower reinforcement magnitude. Some of these options could be eliminated by measuring blood levels of the drug after varying infusion durations.

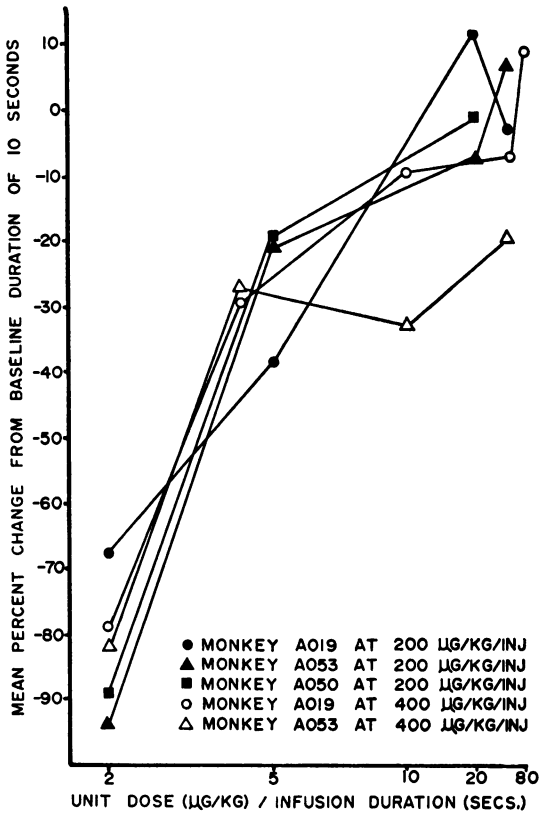

Fig. 6. Change in fixed-interval response rate for two doses of cocaine reinforcement as a function of the ratio of unit dose (ug/kg) to infusion duration (sec). Values represent mean per cent change in response rate for the last three sessions at each infusion duration from the three days of baseline infusion duration (10 sec) just preceding it.

REFERENCES

Deneau, G., Yanagita, T., and Seevers, M. H. Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. *Psychopharmacologia,* 1969, **16,** 30-48.

Findley, J. O., Robinson, W. W., and Peregrino, L. Addiction to secobarbital and chlordiazepoxide in the rhesus monkey by means of a self-infusion preference procedure. *Psychopharmacologia,* 1972, **26,** 93-114.

Fry, W., Kelleher, R. T., and Cook, L. A mathematical index of performance on fixed-interval schedules of reinforcement. *Journal of the Experimental Analysis of Behavior,* 1960, **3,** 193-199.

Goldberg, S. R., Hoffmeister, F., Schlichting, U. U., and Wuttke, W. A comparison of pentobarbital and cocaine self-administration in rhesus monkeys: Effects of dose and fixed ratio parameter. *Journal of Pharmacology and Experimental Therapeutics,* 1971, **179,** 277-283.

Goldstein, A., Aronow, L., and Kalman, S. M. *Principles of drug action: The basis of pharmacology.* New York: Harper & Row, 1968.

Johanson, C. E. *Choice of cocaine by rhesus monkeys as a function of dosage.* Proceedings, 79th Annual

Convention, American Psychological Association, 1971, 751-752.

Kelleher, R. T. and Morse, W. H. Determinants of the specificity of behavioral effects of drugs. *Ergebnesse der Physiologie,* 1968, **60,** 1-56.

Meltzer, D. and Brahlek, J. A. Quantity of reinforcement and fixed-interval performance. *Psychonomic Science,* 1968, **12,** 207-208.

Meltzer, D. and Brahlek, J. A. Quantity of reinforcement and fixed-interval performance: Within-subject effects. *Psychonomic Science,* 1970, **20** 30-31.

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

Pickens, R., Meisch, R. A., and McGuire, L. F. Methamphetamine reinforcement in rats. *Psychonomic Science,* 1967, **8,** 371-372.

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

Pickens, R. and Thompson, T. *Reinforcement by stimulant drugs.* Paper presented at the Seventy-sixth Annual Convention of the American Psychological Association, San Francisco, 1968. (*b*)

Pickens, R. and Thompson, T. Characteristics of stimulant drug reinforcement. In T. Thompson and R. Pickens (Eds.), *Stimulus properties of drugs.* New York: Appleton-Century-Crofts, 1971. Pp. 177-192.

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

Schuster, C. R. and Balster, R. L. Self-administration of agonists. In H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal (Eds.), *Agonist and antagonist actions of narcotic analgesic drugs.* London: Macmillan, 1973. Pp. 243-254.

Smith, C. B. Effects of d-amphetamine upon operant behavior of pigeons: Enhancement by reserpine. *Journal of Pharmacology and Experimental Therapeutics,* 1964, **146,** 167-174.

Stebbins, W. C., Mead, P. B., and Martin, J. M. The relation of amount of reinforcement to performance under a fixed-interval schedule. *Journal of the Experimental Analysis of Behavior,* 1959, **2,** 351-355.

Valenstein, E. S. Problems of measurement and interpretation with reinforcing brain stimulation. *Psychological Review,* 1964, **71,** 415-437.

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,* 1971, **22,** 271-281.

Woods, J. H. and Schuster, C. R. Reinforcement properties of morphine, cocaine, and SPA as a function of unit dose. *International Journal of the Addictions,* 1968, **3,** 231-237.

Received 24 August 1972.
(Final Acceptance 26 February 1973.)