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Orally Delivered Methadone as a Reinforcer for Rhesus Monkeys: The Relationship Between Drug Concentration and Choice

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MEISCH, R. A., R. B. STEWART AND N.-S. WANG. *Orally delivered methadone as a reinforcer for rhesus monkeys: The relationship between drug concentration and choice.* PHARMACOL BIOCHEM BEHAV **54**(3) 547–554, 1996.—The relative reinforcing effects of orally delivered methadone were studied in five male rhesus monkeys. Drug deliveries were available under either a fixed-ratio (FR) or a fixed-interval (FI) schedule. Three concentrations of methadone, low (0.05 mg/ml), intermediate (0.2 mg/ml), and high (0.8 mg/ml) were delivered in 0.65 ml volumes. In the first experiment, monkeys were presented with a choice paradigm. Under independent FR schedules responding led to a delivery of either a methadone solution or the water vehicle. For each concentration, deliveries of a methadone solution maintained higher response rates than did deliveries of water. In the second experiment, methadone concentrations were tested in pairs in the following sequence: high vs. low, high vs. intermediate, intermediate vs. low, high vs. intermediate (retest), and high vs. low (retest). The retest of the last two pairs was designed to counterbalance the test sequence, so that order effects, if they existed, could be detected. Regardless of the schedule, the higher concentration of the methadone pair maintained a greater response rate than did the lower concentration. The present results are consistent with the generalization based on other studies that over a broad range of concentrations and across pharmacological classes, reinforcement schedules, and routes of administration, reinforcing effects increase with increases in drug concentration.

Drug self-administration Methadone Opioids Drug addiction Reinforcement magnitude
Drug reinforcement Choice Dose Relative reinforcement Fixed-ratio schedules
Choice procedures Oral route Rhesus monkeys

IN DRUG self-administration studies with simple reinforcement schedules response rate is usually an inverted U-shaped (or bitonic) function of dose (26). This response-rate function has been interpreted several ways. The ascending part of the curve often has been ascribed to increases in reinforcing effects with increases in dose, while the descending portion has been attributed to motor impairment, satiation, aversive effects, and/or decreases in reinforcing effects (15). If decreases in response rate do reflect decreases in reinforcing effectiveness, then the dose that maintains the highest rate of responding, that is, the dose at the peak of the inverted U-shaped function should be the most reinforcing dose, and rate of responding would be a universal measure of the magnitude of reinforcing effects. However, this interpretation has not been supported by studies with rhesus monkeys (13,14,17,18, 21,22,37). These studies were conducted with psychomotor stimulants and barbiturates as reinforcers, and indicate that, at least with these drugs, the dose that maintains the highest rate is usually not the most reinforcing dose.

The most reinforcing dose is the dose that consistently maintains higher relative response rates when tested concurrently with other doses. This dose is also the one that maintains the most persistent behavior relative to other doses when schedule size is progressively increased (16–18). The measures of choice and persistence yield the same rank order of doses (23,24).

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Investigations conducted with rhesus monkeys showed that with intravenously delivered cocaine, higher doses maintained more behavior than lower doses. Two related procedures were used. Pairs of doses were compared with either discrete trials (14) or concurrent variable-interval schedules (13). Injections of higher doses occurred in greater numbers than injections of lower doses (14) and response rates maintained by higher doses were greater than response rates maintained by lower doses (13). When other psychomotor stimulants (diethylpropion, methylphenidate) were studied, higher doses also maintained more responding than lower doses (14,37). However, evaluation of high doses was difficult in both investigations due to low response rates and the disruptive effects of the injected cocaine. Nevertheless, the findings are consistent with the generalization that over a broad range of doses, reinforcing effects increase as dose is increased.

The IV cocaine studies were systematically replicated and extended by an oral cocaine study. Under concurrent fixed-ratio schedules rhesus monkeys were given access to pairs of cocaine concentrations (28). A wide range of concentrations was studied: 0, 0.1, 0.2, 0.4, and 0.8 mg/ml, and each concentration was compared with all other concentrations. As in the IV studies, reinforcing effects were directly related to concentration.

Results from the oral cocaine study (28) were consistent with earlier oral pentobarbital studies (17,18,23,24). In these pentobarbital experiments reinforcing effects became larger as the concentration was increased (28). Relative reinforcing effects were determined by two procedures. One procedure measured persistence of responding across increases in schedule size. The measure of persistence was the percent of baseline drug deliveries obtained at each concentration when there was an increase in either the size of a ratio schedule (17,18) or length of an interval schedule (19). The second method was a choice procedure that used either concurrent and independent ratio schedules (23,24) or concurrent and mutually exclusive interval schedules (27). Dose was varied either by holding the volume constant and changing the drug concentration or by holding the drug concentration constant and varying the volume. In all studies reinforcing effects were a positive function of drug concentration (26).

The objective of the present study was to determine whether increases in methadone concentration would produce increases in reinforcing effects. Methadone was selected because of its efficacy via the oral route and its importance in human drug abuse treatment programs. To our knowledge, studies with laboratory animals have not used choice procedures to compare doses of opioids.

METHOD

Subjects

The subjects were five adult male rhesus monkeys (*Macaca mulatta*). For four of these monkeys, orally delivered methadone had been established as a reinforcer as described in a prior study (33) and mentioned below. These four monkeys M-NL, M-ED, M-AL, and M-JS had served as subjects in studies of the establishment and maintenance of cocaine (22), etonitazene (21), and methadone reinforced behavior (33). A fifth monkey, M-OP, was experimentally naive. Orally delivered methadone was established as a reinforcer for this monkey in the same manner as it had been established for the other four monkeys. In brief, a fading procedure was used whereby increasing amounts of methadone (0.0063, 0.0125, 0.025, 0.05, 0.1, 0.2, and 0.4 mg/ml) were gradually added to a 2% ethanol solution, and, subsequently, the concentration of ethanol in the solution was gradually decreased in steps until only the methadone solution was present. Responding persisted and was maintained by the contingent delivery of methadone. Animal care was in accordance with the regulations of the Committee on Care and Use of Laboratory Animal Resources, National Research Council (6).

The monkeys' behavior was studied under conditions of food restriction in which the monkeys were maintained at a fixed percentage of their free-feeding weights. Access to food was restricted because such conditions increase drug reinforced behavior (4), and food restriction may also promote health and extend life span (20). The monkeys were fed a measured amount of commercially available chow (Lab Diet high protein monkey diet #5045 PMI™ Feeds, St. Louis, MO) plus fresh fruit and a children's multiple vitamin pill daily. Their weights during the study were: JS, 9.5; ED, 9.1; NL, 8.0; AL, 7.2; and OP, 6.0 kg; these weights represented, 96, 83, 87, 80, and 78% of their free feeding weights. The free-feeding weights were determined over a period of at least 3 months of unlimited access to food, and the values are based on a minimum of one weight determination per month. Free-feeding weights are not necessarily normal weights, because monkeys can become obese after being housed one to a cage with unlimited access to food (24).

Apparatus

Each subject was individually housed 24 h a day in a stainless steel primate cage (Lab Products), which also served as the experimental chamber. Each cage had three solid walls and one barred wall. Cage dimensions (76 × 102 × 81 cm) provided adequate housing space for the rhesus monkeys (6). A liquid-delivery apparatus panel was attached to the outside of one side wall, and spouts and stimulus lights protruded into the cage through holes cut in that wall. Attached to the back of the apparatus panel was a T-shaped bar; on each limb of this bar was fastened a stainless steel reservoir covered with a lid. Liquids contained in each reservoir passed through polyethylene tubing to a solenoid-operated valve at the rear of one of the two brass spouts. These spouts (1.2 cm o.d., 0.2 cm i.d.) protruded 2 cm into the cage, 64 cm above the floor and 15.5 cm either side of the midline. The spouts served as manipulanda for operant responses (mouth contacts with either spout), which were reinforced according to contingencies programmed for the liquid-delivery reinforcement schedules. Mouth contacts on the spout completed a drinkometer circuit and resulted in the illumination of a pair of spout lights for the duration of the contact (see below). The electronic components for the drinkometer circuit were housed in an enclosure at the rear of the spout. With each liquid delivery, a solenoid-operated valve at the rear of a spout was activated for approximately 150 ms, allowing approximately 0.65 ml of liquid to pass through the spout and into the monkey's mouth. To minimize spillage, solenoid activation terminated short of 150 ms if mouth contact with the spout was broken before this interval had elapsed. The liquid-delivery apparatus has been described extensively elsewhere (8,11).

Spouts were embedded in Plexiglas disks that covered the 7-cm diameter holes in the cage wall through which the spouts entered. At each spout, two 1.1 W lights, one located 2.5 cm on either side of the spout and visible through the Plexiglas, were aligned diagonally; these spout lights were capped with green translucent lenses. Another two 1.1 W spout lights, one located 2.5 cm on either side of the spout, were aligned on the

opposite diagonal, and were capped with white translucent lenses. Thus, each spout was in the center of a square pattern of four spout lights, two green and two white. The small spout lights provided a stimulus change with each response. A larger, 2.5 cm (diameter), cluster of green light-emitting diodes was located 11.5 cm directly above each brass spout. These stimulus lights served as discriminative stimuli for liquid-delivery reinforcement schedules, as described in the Procedure section below. The programming of experimental events and the recording of behavior were accomplished with a DEC PDP-11 computer and SKED® software. This equipment was located in a room near the rooms containing the experimental chambers.

Procedure

Experimental sessions were 3 h in length (from 1100 to 1400 h) and were conducted 7 days per week. A time-out period was in effect during the hour immediately before the session (1000 to 1100 h). During this period, in which the equipment was not operative, intersession water drinking values were recorded (the number of water deliveries and the volume of water consumed since the last experimental session), and liquids appropriate for the sessions were placed in the monkeys' reservoirs. Some of each solution was drained through the tubing leading from the reservoir to the solenoid-operated spout to displace water remaining in the tubing from the intersession period or to displace solution remaining from the previous day's session. The flushing procedure ensured that the appropriate solution was present on the first delivery of the session. Liquid volumes were measured after flushing to obtain the exact volume in the reservoirs at each session's outset. For 1 h immediately following the session (1400 to 1500 h) another time-out period was in effect. During this period, data from the session were collected (numbers of liquid deliveries and volumes of liquid consumed), and water was placed in one of each monkey's reservoirs and flushed through the tubing to the spout. Water was then available under a Fixed Ratio (FR) 1 schedule from one spout from 1500 h until 1600 h. The spout from which water was available between sessions alternated every 2 days. This double alternation avoided any relationship between intersession water locations and experimental conditions during the 3-h session. A final time-out period was in effect from 1600 until 1700 h, at the beginning of which the monkeys' maintenance feeding was placed in the food hopper attached to the cage. Finally, from 1700 until 1000 h of the next day water was available under an FR 1 schedule from one spout.

When water was available from a spout between sessions, the green stimulus light above the spout was illuminated. Each mouth-contact response on that spout resulted in delivery of water and illumination of the white-lensed pair of spout lights for the duration of the mouth contact. Responses on the spout at which liquid was not available were recorded but had no programmed consequences; the stimulus light over this spout was not illuminated. A 12 L : 12 D cycle was in effect with lights on at 0600 h.

During experimental sessions, the stimulus lights above each spout blinked at a rate of 10 Hz. (Identical discriminative stimuli were used for both spouts to control for differential responding that might otherwise result from the presence of dissimilar exteroceptive visual stimuli.) Each mouth contact with a spout illuminated the green-lensed pair of spout lights for the duration of the response. Deliveries of liquids (approximately 0.65 ml per delivery) were contingent upon a subject making a fixed number of mouth contacts with a drinking spout (FR reinforcement schedule). The schedules for each of the spouts operated independently such that responses on one spout did not alter the number of responses required at the opposite spout. Fixed-ratio values between 8 and 32 were used rather than an FR 1 schedule because moderate-sized FR schedules decrease the effects on drug-maintained behavior of extraneous variables such as those that produce side preferences and nonspecific responding. Moderate size FR schedules can also increase differences in response rates maintained by two events that produce unequal reinforcing effects (23,24).

Changes from one experimental condition to another were made after obtaining six consecutive sessions with no increasing or decreasing trend in the number of deliveries of either available liquid.

Drug. A 0.8 mg/ml stock solution of methadone hydrochloride (National Institute on Drug Abuse, Rockville, MD) was prepared in tap water twice a week and stored at 4°C. Methadone concentrations are expressed in terms of the hydrochloride salt. Monkeys' daily methadone solutions were mixed by adding appropriate amounts of tap water to a measured amount of stock solution approximately 2 h prior to each session. All drug solutions were at room temperature at the start of the sessions.

Concentration-response functions under FR schedules. Initially, a range of methadone concentrations was tested to verify that each was functioning as a reinforcer. The concentrations were tested in the sequence: 0.8 (high), 0.2 (medium), and 0.05 (low), followed by 0.8 mg/ml retest. After completing the series of sessions at 0.05 mg/ml, the methadone concentration was increased for two sessions at 0.2 mg/ml prior to conducting a retest of the 0.8 mg/ml condition. This incremental increase was designed to avoid possible disruptions that can follow a large and abrupt increase in drug concentration. Water was concurrently available from the other spout. Concentrations also can be expressed in terms of dose by multiplying the volume per delivery by the concentration and then by dividing the product by the monkey's weight. Table 1 gives the results of this conversion.

Drug intake per 3-h session was calculated by multiplying the drug concentration by the volume consumed and then dividing the product by the monkey's weight. The FR values were: AL, FR 16; ED, FR 8; JS, FR 8; NL, FR 32; and OP, FR 16. The FR values selected were the lowest size for each monkey that resulted in a clear separation between drug and water deliveries.

TABLE 1

CONVERSION OF CONCENTRATION INTO DOSE IN μg/kg*

	Monkey				
Drug Concen.	JS	OP	AL	ED	NL
0.05 mg/ml	3	5	4	3	4
0.2 mg/ml	13	20	17	13	15
0.8 mg/ml	50	80	66	52	60

*(drug concentration × volume per delivery)/body wt.

Comparisons of different concentrations under FR schedules. In the next set of manipulations, two drug concentrations were made available under concurrently operating, independent FR schedules. The FR values were the same as those used to determine the concentration–response function. The three possible combinations of pairs of concentrations were tested: high vs. low; high vs. medium, and medium vs. low. Two pairs were retested in a counter-balanced sequence, so that any effects due to order of testing could be detected. The concentrations were presented in the following sequence: 0.8 vs. 0.05, 0.8 vs. 0.2, 0.2 vs. 0.05, 0.8 vs. 0.2 (retest), and 0.8 vs. 0.05 mg/ml (retest). The side positions of each solution were reversed each session.

Concentration–response functions and concentration comparisons under FI schedules. Two monkeys, JS and ED, were also tested under fixed-interval (FI) 15-s schedules to determine the generality of the findings with the FR schedules. Under FI schedules, the first response that occurs after a specified time interval has elapsed is reinforced; any responses that occur prior to the expiration of the time interval are recorded but have no programmed consequences. Responding under FI schedules was obtained by starting with a 5-s interval and then over several weeks gradually increasing the interval to 15 s. An important feature was that the FI schedules in effect at the two spouts were synchronized. At the termination of each interval, there was a mutually exclusive choice such that liquid delivery from either spout reset the FI requirement for both spouts. This arrangement eliminates the possibility that a liquid delivery on one spout soon can be followed by a liquid delivery at the other spout because a 15-s interval must elapse between deliveries. The use of mutually exclusive fixed-interval schedules also results in greater separation in the number of liquid deliveries collected at each spout. The same methadone concentrations were tested under the FI schedules as were tested under the FR schedules and in the same order.

RESULTS

Figure 1 shows that for all five monkeys the rates of responding maintained by the three drug concentrations exceeded the rates maintained by the water, the drug vehicle. The drug vs. vehicle comparisons were made under rigorous test conditions in which both the drug and the water were concurrently available and the locations of drug and vehicle were alternated from session to session. Generally, the differences between drug and water values were large, and in 14 of 19 comparisons the range of drug values was above the range of water values (one comparison was inadvertently omitted). These higher response rates maintained by methadone confirm that the drug was serving as a reinforcer. When the concentration of methadone was increased from 0.05 to 0.2 mg/ml, response rate increased. Monkey ED's results were an exception in that the highest rate of responding occurred at the lowest concentration, 0.05 mg/ml. When the concentration was increased from 0.2 to 0.8 mg/ml, response rates of all monkeys declined (Fig. 1). Retest values at 0.8 mg/ml were similar to initial test values. Amount of drug consumed per session (mg/kg) increased directly as a function of concentration (Fig. 2).

Figure 3 shows that when pairs of methadone concentrations were tested, the higher concentration maintained higher response rates than the lower concentration. This phenomenon was observed at 22 of the 25 comparisons (five monkeys × five comparisons each). Usually the differences between concentrations were substantial, and in 19 of the 25 comparisons the range of high concentration values was above the range of low concentration values. Generally, variability was low. No effects due to the order of testing were observed. Monkey AL's results were an exception in that at both comparisons between 0.2 and 0.8 mg/ml, the 0.2 mg/ml concentration maintained higher response rates than the 0.8 mg/ml concentration. In addition, when the 0.8 vs. 0.05 pair was

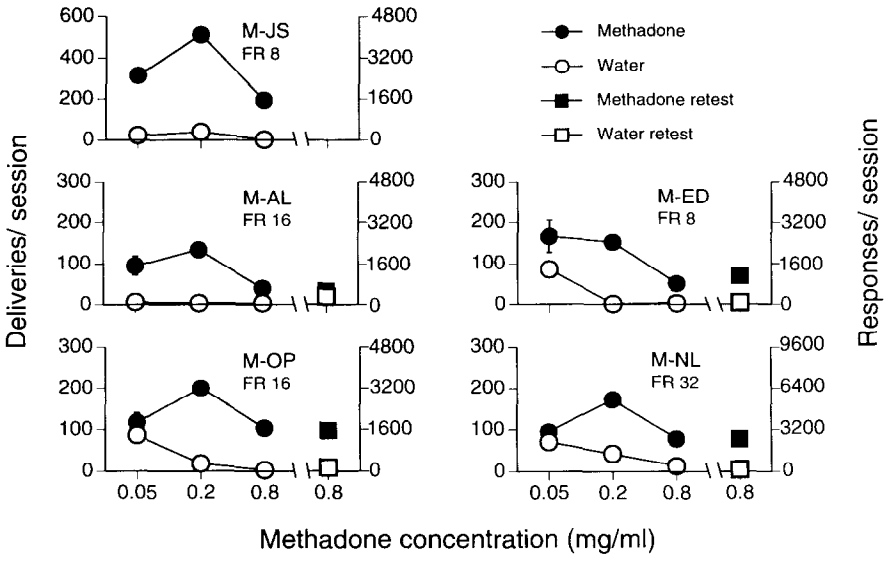

FIG. 1. Responses and deliveries per session as a function of methadone concentration. Concentrations were tested in descending order followed by a retest at 0.8 mg/ml. Each point is the mean from six consecutive sessions of stable behavior. Brackets show the standard error of the mean. Note that in most cases the brackets fell within the area of the plotted point.

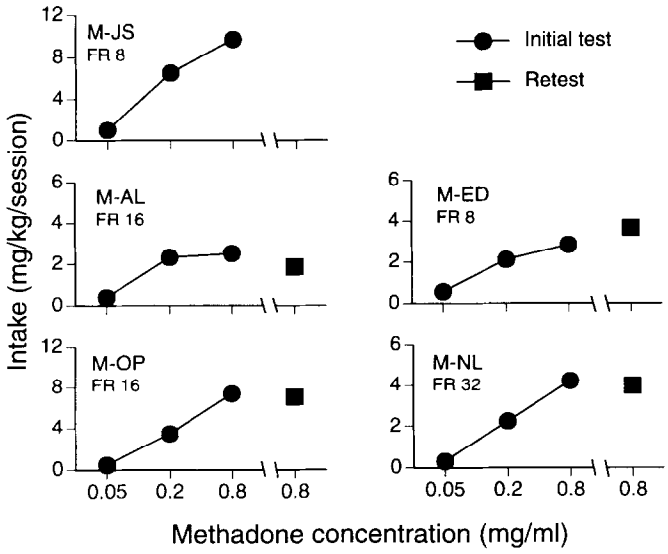

FIG. 2. Methadone intake (mg/kg/session) as a function of concentration. Each point is the mean (±SEM) from six consecutive sessions of stable behavior.

retested, the higher rate of responding was maintained by the lower concentration. To further explore these exceptions with M-AL, additional comparisons were made. Choice between the 0.8 and 0.05 mg/ml concentrations was studied at FR 16, then FR 32, and again at FR 16. Figure 4 shows that at FR 16 the values for the two concentrations overlapped. However, at FR 32 values for the 0.8 mg/ml concentration were far greater than for the 0.05 mg/ml concentration. When FR size was decreased to FR 16, the range of values for the two concentrations again overlapped. Similar results were obtained with the comparisons between 0.8 and 0.2 mg/ml. At FR 16, higher numbers of deliveries were obtained from the spout delivering the 0.2 mg/ml concentration. At FR 32 the preference was reversed. Even larger differences were observed at FR 64. Retest values at FR's 16 and 32 were qualitatively similar to initial test values.

Two monkeys were also tested under FI schedules to determine the generality of the results obtained under the FR schedules. Similar manipulations were performed in that the three methadone concentrations used in the FR studies were also employed with a FI 15-s schedule. A concentration-response function was initially obtained with water concurrently available with each methadone concentration. Figure 5 shows that at all three concentrations methadone reinforced responding markedly exceeded water values, and the highest rate of re-

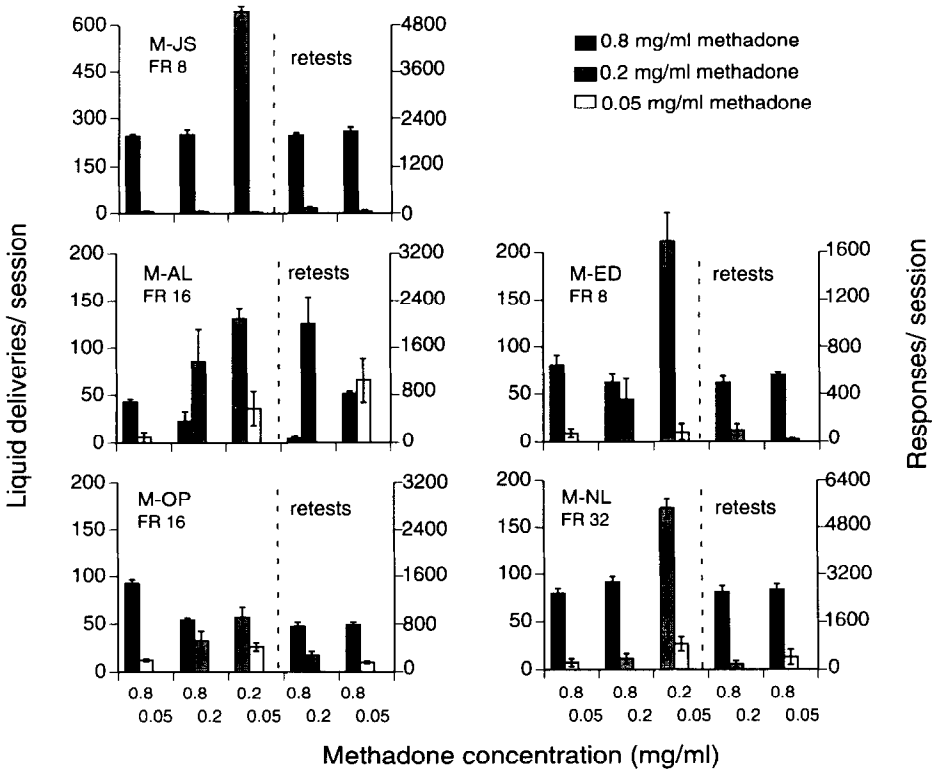

FIG. 3. Methadone responses and deliveries as a function of concentration pairs. The pairs including retests are listed from left to right in the sequence in which they were tested. Each bar is the mean (±SEM) from six consecutive sessions of stable behavior.

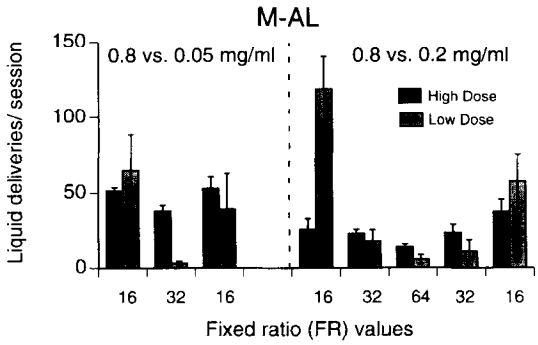

FIG. 4. M-AL's methadone deliveries for each concentration pair as a function of FR size. The pairs including retests are listed from left to right in the sequence in which the fixed-ratio values were tested. Each bar represents the mean from six consecutive sessions of stable behavior. Brackets show the standard error of the mean.

sponding occurred at the intermediate concentration of 0.2 mg/ml. Drug intake increased directly with drug concentration. At all concentration comparisons, substantially greater numbers of responses occurred at the spout delivering the higher concentration (Fig. 6, upper panel). At all of the FI test points variability was low and at adjacent concentrations, the ranges of drug values did not overlap. With interval schedules, unlike ratio schedules, the number of responses per drug delivery can vary. Figure 6 (lower panel) shows that within pairs of methadone concentrations, consistently more deliveries were obtained at the higher concentration.

DISCUSSION

Concentrations of orally delivered methadone maintained response rates that substantially exceeded rates maintained by

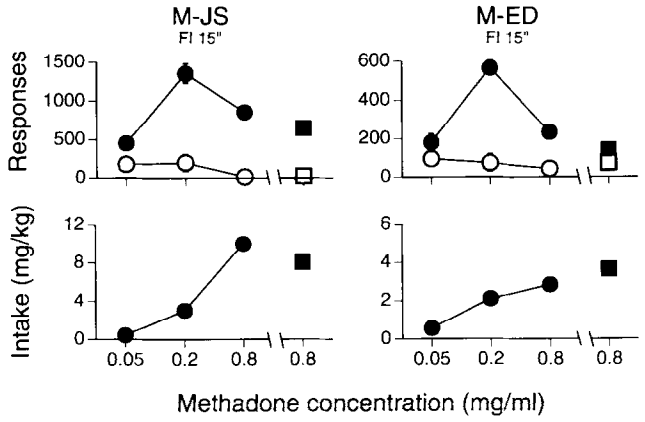

FIG. 5. Responses and methadone intake (mg/kg/session) as a function of drug concentration. Methadone (filled symbols) and the water vehicle (open symbols) were tested under FI-15 s reinforcement schedules. Concentrations were tested in descending order followed by a retest at 0.8 mg/ml. Upper panels show responses and lower panels show drug intake for the same sessions. Each point is the mean from six consecutive sessions of stable behavior. Brackets show the standard error of the mean for responses. Note that in most cases the brackets fall within the area of the plotted point. Disconnected points on the right are retest values.

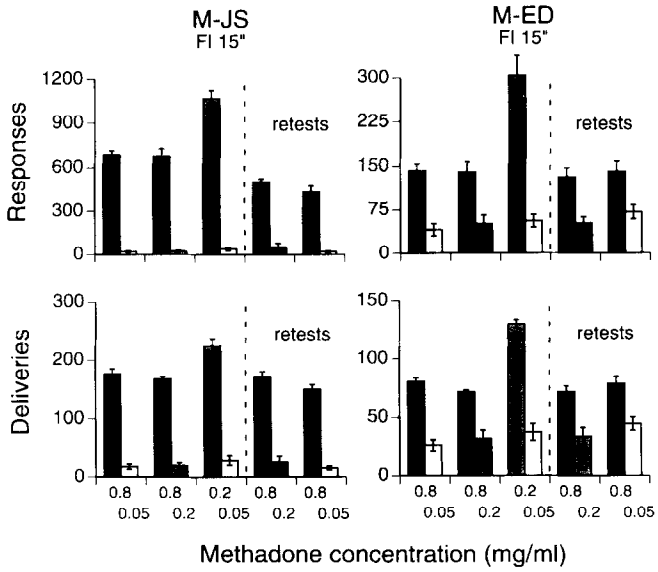

FIG. 6. Responses per session (upper panel) and deliveries per session (lower panel) as a function of concentration pairs under 15-s FI schedules. The pairs including retests are listed from left to right in the sequence in which they were tested. The height of each bar is the mean from six consecutive sessions of stable behavior. Brackets show the standard error of the mean.

the water vehicle. The differences in rates occurred under rigorous test conditions: both liquids were available under independent FR schedules and the side positions of drug and vehicle were alternated each session. Exteroceptive stimulus conditions were identical for both liquids, and a broad range of concentrations was tested. Methadone intake (mg/kg/session) increased with increases in concentration; this relationship between dose and intake is frequently observed in drug reinforcement studies (26). These results corroborate an earlier report in which orally delivered methadone functioned as a reinforcer (33) and also show that methadone deliveries can maintain responding under FI schedules. All monkey subjects in the earlier study had self-administration experience with the potent opioid, etonitazene. In the present study, methadone came to serve as a reinforcer for M-OP, an animal with no prior opioid experience. Thus, experience with etonitazene is not a prerequisite for establishing methadone reinforced behavior. The results with the oral route are consonant with the reports that intravenously delivered methadone can reinforce responding in rhesus monkeys (9,29) and rats (5,30).

Comparisons of pairs of concentrations were also conducted under rigorous test conditions identical to those used initially to identify reinforcing effects, except that a second methadone concentration was present instead of water. Additionally, the pairs of concentrations were tested in a counterbalanced order to permit detection of possible sequence effects. The outcome of these comparisons is that the relative reinforcing effects of orally delivered methadone can be assigned the following ordinal ranking: 0.8 > 0.2 > 0.05 mg/ml. Because all three concentrations maintained higher response rates than water, the ranking can be extended to 0 mg (water vehicle) such that 0.8 > 0.2 > 0.05 > 0 mg/ml. The finding of increases in reinforcing effects with increases in the concentration of methadone, a member of the opioid lass, extends results of earlier studies with cocaine and pento-

barbital. In this study, as in earlier examinations of choice between concentrations there was no direct relationship between the rate of responding maintained by different drug concentrations and relative reinforcing effects associated with those concentrations. That is, the response rates measured when each concentration was tested alone (but with the water vehicle concurrently available), were not predictive of response rates measured when each concentration was paired with another concentration. For example, with M-ED the 0.05 mg/ml concentration maintained the highest rate when tested alone but the lowest rate when tested with the other two concentrations, 0.2 and 0.8 mg/ml.

For one monkey, M-AL, at three comparisons (0.8 vs. 0.2 mg/ml at test and retest, and at 0.8 vs. 0.5 retest), higher rates were maintained by the lower concentration. However, when the FR size was increased, responding changed and the higher concentration was selected. When FR size was decreased, the original pattern of behavior returned. The reversal of preference with increases in FR size was also observed with two out of four monkeys in a study (25) of choices between drug combinations (pentobarbital plus ethanol) and their components (pentobarbital alone or ethanol alone). These reversals in preference were orderly in that at higher ratios, the larger magnitude reinforcer maintained greater response rates, whereas at lower FR values the smaller reinforcer maintained higher response rates. These results suggest that one determinant of choice is the schedule size. This finding can be described with terminology from behavioral economics [e.g., (2)]: the increases in schedule requirements result in an increase in price (defined as the ratio of reinforcer size to schedule value), and one effect of price increases may be changes in preference (10).

To our knowledge there have been no laboratory animal studies with choice procedures that have compared different opioids or doses of an opioid. However, there have been studies with progressive ratio procedures that used the intravenous route of administration. Two studies used rhesus monkeys (12,29), and two other studies used rats (32,36). Four agonists were examined: heroin, codeine, methadone, and morphine. In two studies the "breaking point" (the ratio size at which responding drops below a criterion) increased with increases in drug dose (12,36) and in two other studies the breaking point increased with dose except for the highest dose tested (29,32). The results presented here are consistent with those of progressive ratio studies.

Methadone serves as a reinforcer for human methadone maintenance patients. In one laboratory study with human subjects the reinforcer was a small dose of methadone taken by mouth. Responding was maintained under FR, FI, variable interval (VI), and differential reinforcement of low rate (DRL) schedules (1). In clinical studies, contingent access to methadone has also been used to reinforce: a) abstinence from abused drugs (16), b) attendance at counseling sessions (35), and c) compliance with clinic rules (34).

With methadone maintenance patients, there may be an increase in reinforcing effects that is directly related to dose size: methadone treatment subjects were given a choice between 50 mg of methadone vs. either 60, 75, or 100 mg (3). Choice between doses was conducted under conditions blind to the subject. The percentage of choices for the higher dose increased directly with the size of that dose. Our present results concur with those of the human study (3). The results of the present study with rhesus monkeys suggest the feasibility of conducting parallel studies of methadone reinforcement with both human and nonhuman subjects. In such studies the same reinforcer (i.e., methadone), the same vehicle, and the same route of administration can be employed, as well as the same experimental design.

An emerging generalization is that over a broad range of doses, increases in dose produce increases in reinforcing effects. The present findings and results of prior studies with other drugs support this generalization. The generalization holds across routes, paradigms, schedules of reinforcement, and drug classes. For example, in studies with cocaine, dose increases produced similar results with both the oral and intravenous routes (13,14,28). The relative persistence of drug reinforced behavior across increases in schedule size is directly related to dose (17,18), and these results are consistent with findings from choice procedures (17,18,23,24). A direct relationship of dose to reinforcing effects has been obtained with both interval and ratio reinforcement schedules (13,14,19). Results from studies where food and cocaine compete as reinforcers also find an increase in reinforcing effects with increases in dose (31). All of these investigations with drug reinforcers are consistent with findings with more conventional reinforcers such as food, namely, that increased reinforcing actions accompany increases in reinforcer size (7).

SUMMARY

The findings demonstrate that the relative reinforcing effects of methadone deliveries are a direct function of concentration. These results are consistent with earlier findings obtained with psychomotor stimulants and barbiturates, and extend the generality of earlier findings to the opioid drug class.

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