JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1987, 48, 303-315 NUMBER 2 (SEPTEMBER)

INTERACTION OF METHADONE, REINFORCEMENT HISTORY, AND VARIABLE-INTERVAL PERFORMANCE

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In the present study, we examined how a reinforcement schedule history that generated high or low rates of responding influenced the effects of acute (Experiment 1) and chronic (Experiment 2) methadone administration. Initially, key-peck responses of pigeons were maintained under a variable-interval 90-s schedule of food presentation, and a methadone dose–response curve was determined with doses of 0.6, 1.2, and 2.4 mg/kg. The pigeons were then exposed, for at least 40 sessions, to either a fixed-ratio 50 schedule or a differential-reinforcement-of-low-rate 10-s schedule, or were given continued exposure to the variable-interval schedule. The methadone dose–response curve was redetermined after all pigeons again were responding under the variable-interval schedule. The effects of two different daily methadone doses (9.0 and 12.0 mg/kg/day) and withdrawal precipitated by naloxone also were assessed. Experience with a fixed-ratio or differential reinforcement of low rate schedule did not result in significantly different response rates under the variable-interval schedule and, in general, the acute effects of methadone did not have differential effects correlated with schedule history. However, for 2 of 4 subjects the rate-decreasing effects of methadone on rates of key pecking were greater following a history of low-rate responding, suggesting a possible interaction between schedule history and effects of methadone. Daily methadone administration under the variable-interval schedule revealed that pigeons with experience under the differential reinforcement of low rate schedule developed more rapid and complete tolerance to the rate-decreasing effects of methadone. Three of the 4 subjects in this group showed rate increases above drug-free baselines during chronic methadone dosing. Pigeons with a history of fixed-ratio responding also developed tolerance to the rate-decreasing effects of methadone but without the subsequent rate increases seen by subjects with low-rate histories. No subjects with variable-interval histories showed complete recovery of drug-free baselines, suggesting that interpolated training under other schedules may attenuate the rate-altering effects of chronically administered drugs. Naloxone (1.0 mg/kg), administered during the chronic methadone phase, resulted in greater disruption of responding by pigeons with a history of low-rate responding, as compared to subjects in the other two groups. These experiments reveal that although acute doses of methadone did not differentiate performances based on prior reinforcement schedule history, recovery of drug-free baselines during chronic drug administration was more rapid and complete in subjects with low-rate histories. It appears that reinforcement schedule histories can influence the behavioral effects of chronically administered methadone even when no current differences in baseline rates or in the effects of acute administration of methadone are apparent.

Key words: methadone, reinforcement history, variable-interval schedule, key peck, pigeon

The behavioral effects of many drugs can depend upon current environmental contingencies, upon maintaining events, and upon the organism's history (Barrett, 1984, 1985; Barrett & Katz, 1981). In most experiments prior experience is controlled for or minimized instead of studied, possibly overlooking critical factors that may determine behavioral actions of drugs in the natural environment (McKearney, 1979; Weiner, 1981).

Weiner (1964, 1969) showed that performances under various reinforcement schedules can be affected by reinforcement schedule history. In one study using human subjects (Weiner, 1969), participants were initially exposed to either a fixed-ratio (FR) or a differential-reinforcement-of-low-rate (DRL) schedule with points used as reinforcers. Subsequently all subjects were exposed to a fixed-interval (FI) schedule, with new discriminative stimuli. Subjects with an FR history responded at high constant response rates under the FI

This paper was based on the thesis submitted by Michael A. Nader to the graduate school at the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree. The authors wish to thank James E. Barrett for his helpful comments on an earlier version of the manuscript. This research was supported by National Institute of Drug Abuse Grant 1 F31 DA05258, awarded to Michael Nader, and Grants 5 T32 DA07097 and 5 R01 DA02717 awarded to Travis Thompson. Reprint requests should be addressed to Michael A. Nader, Department of Psychiatry, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814.

schedule, whereas subjects previously exposed to the interresponse-time contingency responded at low rates, characterized by long postreinforcement pauses under the FI schedule. This study provided strong evidence for the importance of prior experience with different reinforcement schedules.

In a systematic replication of Weiner's (1969) study Urbain, Poling, Millam, and Thompson (1978) investigated effects of *d*-amphetamine on rats' lever pressing that was reinforced under an FI schedule after exposure to either an FR 40 or a DRL 11-s reinforcement schedule history. After 50 sessions of differential histories, both groups were then exposed to an FI 15-s reinforcement schedule. Animals with the FR history exhibited higher lever-pressing rates than did animals having the DRL history. The effects of *d*-amphetamine on FI performance varied as a result of the organisms' reinforcement history. Rats with DRL experience showed dose-dependent increases in lever-pressing rates whereas rats with the FR history exhibited rate decreases.

To examine the generality of these findings, Poling, Krafft, and Chapman (1980), using rats as subjects, studied the effects of exposure to either FR or DRL schedules on the subsequent response rate–altering effects of *d*-amphetamine on operant performance under a variable-interval (VI) schedule of food presentation. No differences were found in baseline VI response rates as a consequence of prior exposure to the FR or DRL schedules nor were there any differential effects of *d*-amphetamine on percentage of change in response rate by the two groups. Poling et al. concluded that the influences of different schedule histories were less under the VI schedule because responding was more constrained compared to FI performance. Different response rates under FI schedules do not significantly alter reinforcement frequency and thus appear more malleable to variables such as schedule history (Poling et al., 1980).

The present experiments were conducted to examine further the role of reinforcement schedule histories on pigeons' key pecking that was reinforced under a VI schedule of food presentation and to determine whether prior exposure to different schedules altered the effects of methadone upon the VI performance. In an effort to maximize the interactions of schedule history with VI performance, all pigeons were exposed to an FR or DRL schedule after initial training on the VI schedule. Following an extended history of high- or low-rate responding, all subjects were reexposed to the VI schedule. The effects of methadone were assessed only under VI performance, both prior to and following the different reinforcement schedule histories. In addition, we assessed the effects of daily methadone administration on the rate of tolerance development under the VI schedule.

Methadone was introduced clinically at the end of World War II and is today nearly exclusively used in treating opiate dependence. The pharmacological actions of methadone are similar to those of morphine (Martin, 1983; Tatum, Seevers, & Collins, 1929). Methadone has been shown to produce dose-dependent rate decreases in food-reinforced responding (Leander & McCleary, 1982; Middaugh & Santos, 1978), with some evidence of rate-dependent effects (Thompson, Honor, Verchota, & Cleary, 1984). Other investigators have reported that under both DRL and FR reinforcement schedules, low doses of methadone produce rate increases and higher doses produce dose-dependent rate decreases in operant responding (Ford & Balster, 1976; Goldberg, Morse, & Goldberg, 1976; McMillan, Wolf, & Carchman, 1970). Similar biphasic effects have been reported with morphine (Thompson, Trombley, Luke, & Lott, 1970).

EXPERIMENT 1

In the present study we examined the effects of different reinforcement histories on rates and patterns of key pecking under a VI reinforcement schedule and evaluated whether these different histories altered the effects of methadone. Pigeons' key pecking was initially maintained under a VI 90-s schedule and a methadone dose–response curve was determined. Following subsequent extended exposure to either an FR 50 or a DRL 10-s schedule, the VI schedule was reintroduced and the methadone dose–response curve was redetermined. In this way, the influence of different reinforcement schedule histories on VI responding could be evaluated by comparing prehistory VI response rates with posthistory rates. Also, the effects of different schedule histories on the rate-altering effects of methadone could be assessed by changes in the

methadone dose–response curves. A control group, exposed to the baseline VI schedule throughout, was included to examine the influence of continued exposure to the VI schedule and the effects of subsequent exposure to methadone.

METHOD

Subjects

Twelve experimentally naive male White Carneau pigeons, maintained at 80% of their free-feeding weights, served as subjects. The pigeons were individually housed with continuous access to water and grit in a colony room maintained at 24 °C with 24-hr illumination.

Apparatus

Four standard operant test chambers equipped with a three-key pigeon intelligence panel (Model 141-10, BRS/LVE) and a solenoid-operated feeder (Model 114-10, BRS/LVE) were used. The feeder was illuminated when operated, and mixed grain was presented for 4 s. All chambers were illuminated by white houselights (1820 bulbs) and white masking noise was continuously presented. The keys were transilluminated with standard six-color lamps (Dialco 3917 bulb). Programming and data recording were accomplished by an Apple II® computer with associated interface and cumulative recorders located in an adjacent room.

Procedure

Initial training under VI reinforcement schedule. Each pigeon's pecking was autoshaped (Brown & Jenkins, 1968) with a peck on the center key (white) resulting in 4-s access to mixed grain. The first key peck terminated the autoshaping program and initiated an FR 1 schedule under which reinforcement followed each center-key response. This training was discontinued after at least 100 reinforcers had been delivered. All pigeons were then exposed to a progressively increasing VI schedule until a mean value of 90 s was reached. Under a VI schedule the first response after an interval has elapsed is reinforced, with the interval value varying randomly around a specified mean. The interval values used for the present VI 90-s schedule were determined from the formula described by Catania and Reynolds (1968). Pigeons were exposed to the VI schedule for approximately 100 sessions before methadone was administered.

Differential histories. Following determination of the methadone dose–response curve, each bird was assigned to one of three groups and subsequently exposed to either a differential-reinforcement-of-low-rate 10-s schedule (DRL 10-s), a fixed-ratio 50-responses schedule (FR 50), or to the same VI 90-s schedule as before. To ensure that the groups had similar average VI 90-s key-pecking rates before exposure to the different histories, all pigeons were ranked, from 1 to 12, according to their mean overall VI response rates. Subjects in successive triads were randomly assigned to one of the three groups, so that the pigeons with the three highest rates were each in a different group.

For pigeons in the DRL 10-s and the FR 50 groups the center and left keys were covered while the right key was illuminated green. This change in key color and position was made to facilitate discrimination between the conditions of initial training and those of the new schedule. FR training consisted of initial exposure to an FR 1 schedule and then to progressively increasing ratios until the terminal value of 50 was reached (approximately five sessions). Performance under the DRL schedule was acquired by initially exposing the pigeons to an FR 1 schedule followed by imposition of a schedule with progressively longer interresponse time (IRT) values until 10 s was reached (approximately 10 to 15 sessions).

The VI 90-s sessions ended after 45 min, and FR 50 and DRL 10-s sessions ended after 50 reinforcers were obtained. FR and DRL sessions were terminated after 2 hr if 50 reinforcers had not been earned. Each pigeon was exposed to its differential schedule until at least 2,000 reinforcers were obtained. Most pigeons obtained this number within 50 to 70 experimental sessions. Control subjects (i.e., those exposed to the VI schedule throughout) received 25 to 30 reinforcers per session and their histories were matched with DRL and FR subjects on the basis of number of sessions, not number of reinforcers.

Posthistory VI responding. Following exposures to the different schedules, all pigeons were reexposed to the VI 90-s reinforcement schedule and the methadone dose–response curve was redetermined. For pigeons in the DRL and FR groups the right key was covered and the center key was again illuminated white. At least three sessions under the VI schedule

Table 1

Comparison of response rates (r/min) before, during, and after schedule history.

	VI 90-s	History[b]			VI 90-s	
Subjects	Prehistory[a]	Rate	Sessions	S^R	Session 1	Posthistory[c]
VI history						
P-51	77.88 (1.79)	75.37 (2.54)	84	2,343	—	91.82 (5.47)
P-53	31.46 (1.84)	33.04 (1.05)	53	1,456	—	31.71 (0.50)
P-57	49.72 (1.93)	76.20 (1.82)	90	2,505	—	83.75 (3.27)
P-58	42.11 (0.74)	36.30 (2.20)	68	1,855	—	37.22 (2.29)
FR history						
P-54	77.51 (1.71)	109.77 (2.69)	53	2,588	55.22	67.91 (11) (0.85)
P-55	45.99 (1.20)	69.66 (2.96)	78	3,885	63.76	59.67 (4) (0.83)
P-56	30.10 (1.18)	117.76 (2.03)	51	2,478	56.76	33.72 (15) (0.57)
P-60	49.52 (0.95)	53.95 (6.23)	64	3,086	22.89	28.56 (23) (2.09)
DRL history						
P-52	32.26 (1.01)	4.42 (0.26)	51	2,184	4.91	23.62 (14) (0.77)
P-59	86.53 (1.66)	5.62 (0.75)	71	2,656	55.11	60.84 (10) (1.49)
P-61	49.24 (1.65)	17.11 (1.71)	85	1,852	22.67	46.53 (7) (0.75)
P-62	58.70 (1.83)	6.24 (0.21)	52	2,149	53.04	64.32 (10) (1.22)

Numbers in parentheses represent standard errors of the mean unless otherwise specified.

[a] For the FR- and DRL-history groups the numbers represent the average rate of responding from the last five sessions under the VI schedule before training under different schedule histories. For the VI controls the average rates were taken from the five sessions following the final methadone injection.

[b] For the FR- and DRL-history groups these are average rates from the last five sessions under their respective reinforcement schedules. For the VI-history group these are number of sessions between the last methadone administration during determination of the prehistory dose-response curve and the first methadone injection upon redetermination of the dose-response curve.

[c] Control rate of responding before first methadone administration following schedule histories. Numbers in parentheses to the right indicate number of posthistory sessions under the VI schedule before methadone was readministered. Each point is the mean of three sessions.

were required before methadone could be readministered (see Table 1 for number of posthistory VI sessions before methadone was administered for each subject).

Drug preparations and administration. Methadone hydrochloride (Eli Lilly Inc.) was dissolved in isotonic saline (0.9%) to obtain a constant injection volume of 1.0 mL/kg. Doses of methadone (0.6, 1.2, and 2.4 mg/kg) are expressed as the total salt, and all injections were given intramuscularly (i.m.), into the breast muscle, 15 min before the session. Vehicle injections were isotonic saline, and were also injected i.m. 15 min before testing. Single doses of methadone were administered when three consecutive sessions elapsed during which overall rates of key pecking did not differ by more than ±10% of the mean for those 3 days. Saline was administered for at least one of the sessions included in the stability criterion, and the order of methadone doses was randomized for each subject. At least 7 days separated successive methadone administrations. Because baseline rates did change across sessions, 3-day means were calculated to determine a comparison for each methadone dose.

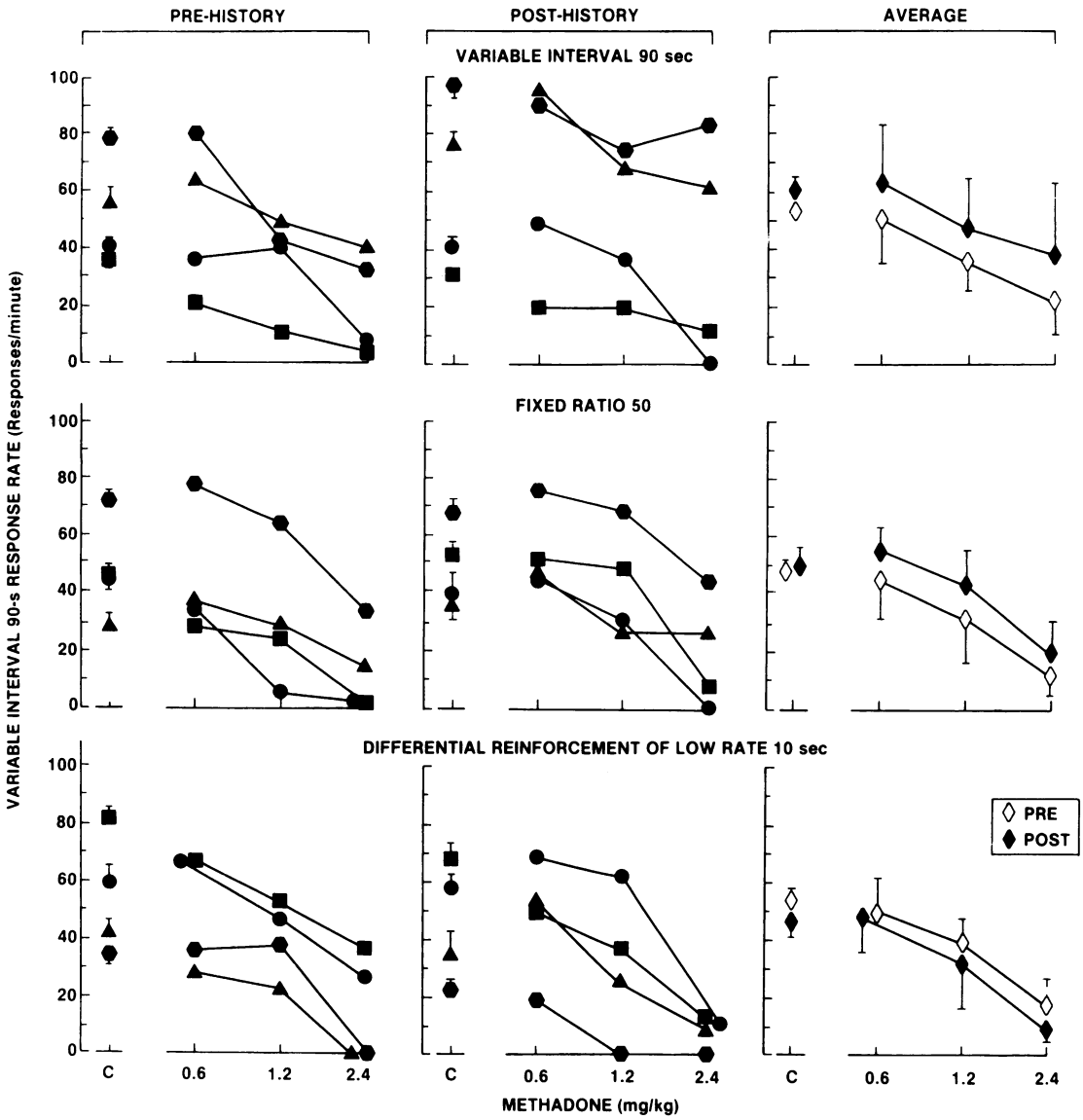

Fig. 1. Response rates (r/min) for each subject under the VI 90-s schedule as a function of methadone dose before (Panel 1) and after (Panel 2) differential histories. For the VI-history group this represents the first and second administration of methadone, respectively, with no intervening schedule changes. Control points (C) are averages computed over the 3-day mean used in the stability criteria, at the three respective doses. Panel 3 represents group means, with each methadone point representing the mean for 4 pigeons. The history group is listed above the middle set of dose-response curves. Subjects are represented as follows: VI history: ● P-51, ■ P-53, ▲ P-57, ● P-58; FR history: ● P-54, ■ P-55, ▲ P-56, ● P-60; DRL history: ● P-52, ■ P-59, ▲ P-61, ● P-62. Vertical lines indicate standard errors of the mean.

Results and Discussion

In general, the VI 90-s schedule generated constant response rates throughout the experimental sessions. The average baseline rates, as shown in Figure 1, ranged from 29.32 to 82.40 responses per minute (r/min). These differences in overall response rate did not affect reinforcement density. The control points in the figure are averages from the three mean response rates used to determine stability. The first panel in Figure 1 shows the methadone dose–response curves for each subject before any interpolated training under the FR 50 or DRL 10-s schedules. Methadone, at the lowest dose tested, produced slight rate increases or

no change in response rates in 7 of the 12 subjects and rate decreases in the remaining 5 pigeons. This wide range of effects at the 0.6 mg/kg dose does not appear to be rate dependent. At the intermediate and high doses, methadone produced dose-dependent rate decreases in all subjects but P-52 and P-58. Response rates for these subjects were slightly increased at the 1.2 mg/kg dose.

Following completion of the methadone dose–response curves, each bird was exposed to either an FR 50 or a DRL 10-s schedule, or remained on the VI 90-s schedule. The mean rate of pecking under the VI schedule, as determined from the five sessions following the last methadone injection, was 56.68 r/min for the 4 pigeons assigned to the DRL group, 50.78 r/min for the 4 FR-history pigeons, and 50.29 r/min for the 4 VI-history pigeons (see Table 1 for individual rates). These mean rates did not differ significantly from one another.

Imposing an FR 50 or a DRL 10-s contingency resulted in large changes in mean response rates compared to the VI baseline. As shown in Table 1, response rates for each subject in the FR- and DRL-history groups changed in the predicted direction during interpolated training. Of the 8 subjects exposed to new schedules, only P-61 earned fewer than 2,000 reinforcers during this history phase. Pigeon P-61 responded the most rapidly under the DRL schedule and consequently received only 1,852 reinforcers; however, this subject was exposed to more sessions under the DRL schedule than any other pigeon in that group. Subjects P-55 and P-60 also differed somewhat from the other 2 subjects in their group in that they were exposed to more FR sessions and earned more reinforcers. This was a result of adjusting the FR value across sessions in an effort to raise response rates. The number of sessions between determinations of the methadone dose–response curve for the VI-history subjects ranged from 53 to 90 sessions, and the number of reinforcers presented varied from 1,456 to 2,505. Although the number of reinforcers is low compared to the other two groups, the number of history sessions is not. Across sessions, 2 VI-history subjects, P-51 and P-57, showed large rate increases. Examination of daily records indicated that the increases were gradual over the entire 90 sessions. The increases in response rates did not appreciably affect reinforcement frequency.

When subjects returned to the VI schedule, response rates increased for all DRL-history subjects, relative to DRL baseline, except for P-52. For this subject, 14 sessions were required before stability in VI rates was obtained, with posthistory rates still lower than prehistory VI rates (Table 1). The first session under the VI schedule, following exposure to FR schedules, resulted in rate decreases for all subjects. Following an FR history, posthistory VI rates were higher compared to prehistory rates in only 1 subject, P-55. Pigeon P-56's rates appeared unaffected by the high-rate history, whereas P-54 and P-60 responded at lower overall rates following training under the FR schedule. Averaging posthistory rates for FR- and DRL-history subjects indicates that following different histories, VI response rates were still very similar (47.47 ± 11.12 r/min vs. 48.83 ± 10.67 r/min for FR- and DRL-history groups, respectively). These data replicate findings of Poling et al. (1980) in that prior exposure to FR or DRL reinforcement schedules did not significantly affect subsequent response rates under VI reinforcement contingencies. In terms of group means, both FR- and DRL-history groups responded at lower VI rates following exposures to the alternative schedules. Control subjects that continued under the VI schedule responded at similar or higher rates across sessions, with the overall group mean showing a substantial increase (50.29 ± 11.46 r/min vs. 61.13 ± 17.92 r/min for VI rates prior to first and second determinations of the methadone dose–response curves; referred to in Table 1 as pre- vs. posthistory rates, respectively). This suggests that interpolated training under different reinforcement schedules may attenuate the rate-increasing effects of continued exposure to the VI contingency.

The second panel in Figure 1 shows the methadone dose–response curves following exposure to the FR, DRL, and VI histories. By comparing the two sets of dose–response curves for the VI control group the effects of repeated methadone dosing can be assessed. The baseline rates for Subjects P-53 and P-58 did not change substantially across sessions, whereas Pigeons P-51 and P-57 showed progressive increases in rate with continued exposure to the VI contingency. The dose–response curves for P-51 and P-57 shifted to the right, suggesting some degree of tolerance to the effects

of methadone, whereas the first and second determinations of the dose–response curves for P-53 and P-58 appeared similar. The third panel in Figure 1 shows that, in general, the shapes of the curves were not changed following determination of a second methadone dose–response curve, although some degree of tolerance may be evident.

As stated earlier, the effects of an FR history on VI response rates were minimal. The methadone dose–response curves shifted slightly to the right in all subjects from this group, with the largest effect occurring at the 1.2 mg/kg dose in P-60. The dose–response curves for the FR-history group look very similar to those of the VI control group, except at the highest dose where the rate-decreasing effects of methadone were slightly greater for pigeons with FR histories than for pigeons in the VI control group.

The lower set of curves in Figure 1 is for pigeons in the DRL-history group. All 4 subjects showed lower VI control rates following DRL exposure, although the effects were small. Two subjects in this group showed shifts to the left in their methadone dose–response curves, whereas the dose–response curves for the other 2 subjects shifted to the right. Pigeon P-52 had shown slight rate increases at the 1.2 mg/kg dose prior to a DRL history, but responded at a rate less than 0.5 r/min when this dose was administered under the VI schedule following a history of low-rate responding. Pigeon P-59's methadone dose–response curve showed a parallel shift to the left. By examining the effects in terms of percentage of change, the shift to the left does not appear to be a result of a lower baseline rate of responding. Low and intermediate doses of methadone produced slight rate increases for Pigeon P-62. At the 1.2 mg/kg dose, this effect was large compared to the response-rate decreases that occurred when that dose was administered prior to a DRL history. However, administration of 2.4 mg/kg methadone resulted in greater rate decreases following a DRL history. For P-61, the dose-dependent rate decreases under the VI schedule were somewhat attenuated following a history of low-rate responding, with rate increases seen at the lowest dose tested. The average dose–response curve for the DRL-history group showed a small shift to the left, as seen in the third panel of Figure 1.

The fact that the only 2 subjects to exhibit shifts to the left in the methadone dose–response curves were from the DRL-history group suggests that a low-rate history may interact with the rate-decreasing effects of methadone. In Experiment 2 we examined the rate of tolerance development following the daily administration of two high doses of methadone. In addition, the effects of an opiate antagonist, naloxone, were examined.

EXPERIMENT 2

Little attention has been given to possible effects of different reinforcement schedule histories on recovery of drug-free baseline rates during chronic drug administration. In Experiment 1, shifts in the curves of FR- and VI-history groups suggested that development of tolerance to the rate-altering effects of methadone may have occurred, whereas shifts to the left of the methadone dose–response curve were seen in the performance of 2 pigeons with a DRL history. Although those shifts in the methadone dose–response curves were small, they may indicate that reinforcement histories can interact with development of tolerance to the rate-altering effects of methadone. The purpose of Experiment 2 was to examine this interaction. We also examined the magnitude of the disruptive effects of administering naloxone to pigeons receiving daily methadone injections.

METHOD

Subjects and Apparatus

The 12 pigeons used in Experiment 1 served as subjects, and the same apparatus as was used in Experiment 1 was used in the present experiment.

Procedure

All pigeons were reexposed to their respective DRL, FR, or VI schedules for 14 sessions. On Session 15 all pigeons were returned to the VI 90-s schedule. The first seven sessions under this schedule served as the drug-free baseline. Session 7 of VI performance was preceded by a saline injection 15 min before testing. On Session 8 each pigeon received 4.5 mg/kg methadone 15 min before the session and again 12 hr after the session, which initiated the chronic methadone phase. Methadone was administered twice daily in an effort to maintain a more constant blood level. Pigeons continued to receive 9.0 mg/kg/day until visual inspec-

Table 2

VI 90-s key-pecking rates (r/min) for all subjects.[a]

Subject	Day 1 history	Drug-free[b]	9.0/day[c]	12.0/day[c]	Meth + 1.0 nlx	Sal subs.[d]
VI history						
P-51	—	81.58 (3.53)	45.89 (4.89)	22.36 (2.11)	37.58	55.51
P-57	—	73.93 (1.58)	40.64 (1.51)	30.46 (0.47)	58.04	47.69
P-58	—	48.94 (0.93)	46.36 (2.58)	34.03 (3.51)	50.11	44.82
P-53	—	30.53 (1.43)	26.26 (1.94)	22.46 (1.00)	18.96	25.73
FR history						
P-55	82.26	59.40 (1.26)	52.34 (1.65)	47.10 (3.81)	12.69	47.02
P-56	136.24	50.00 (0.92)	40.18 (3.47)	31.89 (5.06)	29.89	35.96
P-54	137.99	47.21 (1.94)	45.23 (2.92)	40.87 (3.04)	42.73	46.07
P-60	67.87	33.77 (1.30)	23.91 (3.62)	30.06 (3.34)	24.36	32.13
DRL history						
P-59	18.32	80.12 (2.20)	36.64 (1.61)	40.65 (3.09)	41.00	53.07
P-62	11.72	66.31 (2.63)	91.70 (2.10)	96.37 (3.35)	56.40	59.02
P-61	13.26	41.53 (2.58)	50.53 (4.26)	35.24 (1.91)	13.49	29.11
P-52	8.98	19.82 (1.89)	21.94 (1.58)	24.89 (0.80)	00.00	6.64

[a] Numbers in parentheses indicate standard errors of the mean.
[b] Average rate of responding for the seven sessions preceding the chronic phase.
[c] Average rate of responding for the last five sessions.
[d] Rate of responding during session in which saline was substituted for 6.0 mg/kg methadone 15 min before testing.

tion of the data indicated no noticeable trends in rates of key pecking across sessions.

When the above criteria were reached the next session was preceded by a 6.0 mg/kg dose of methadone 15 min before the session. The injections 12 hr after the session and all remaining injections during this phase were 6.0 mg/kg. The pigeons continued to receive 12.0 mg/kg/day methadone until their pecking rates appeared stable by visual inspection of the data. When this criterion was met saline was administered immediately before testing. If responding was stable, a single naloxone (1.0 mg/kg) injection was given immediately before the next session, in addition to 6.0 mg/kg methadone 15 min before testing.

All pigeons were tested for five more sessions under 12.0 mg/kg/day methadone after the naloxone challenge. The chronic methadone phase was completed by substituting saline for methadone 15 min prior to testing and 12 hr postsession. All pigeons were tested in this drug-free state for at least seven sessions. When average pecking rates were stable, the effects of 1.0 mg/kg naloxone were again examined.

Drug administration. Methadone HCl and naloxone HCl were dissolved in 0.9% saline to obtain a constant injection volume of 1.0 mL/kg. All injections were administered i.m. in the upper breast muscles—methadone 15 min before testing, naloxone immediately before the session. As in Experiment 1, responding was considered stable when three consecutive sessions elapsed during which overall pecking rates did not differ by more than ±10% of the mean for those 3 days, with saline administered immediately before testing on at least 1 of the days included in the stability criterion.

Results and Discussion

Reexposure to the FR or DRL schedule resulted in immediate schedule-appropriate

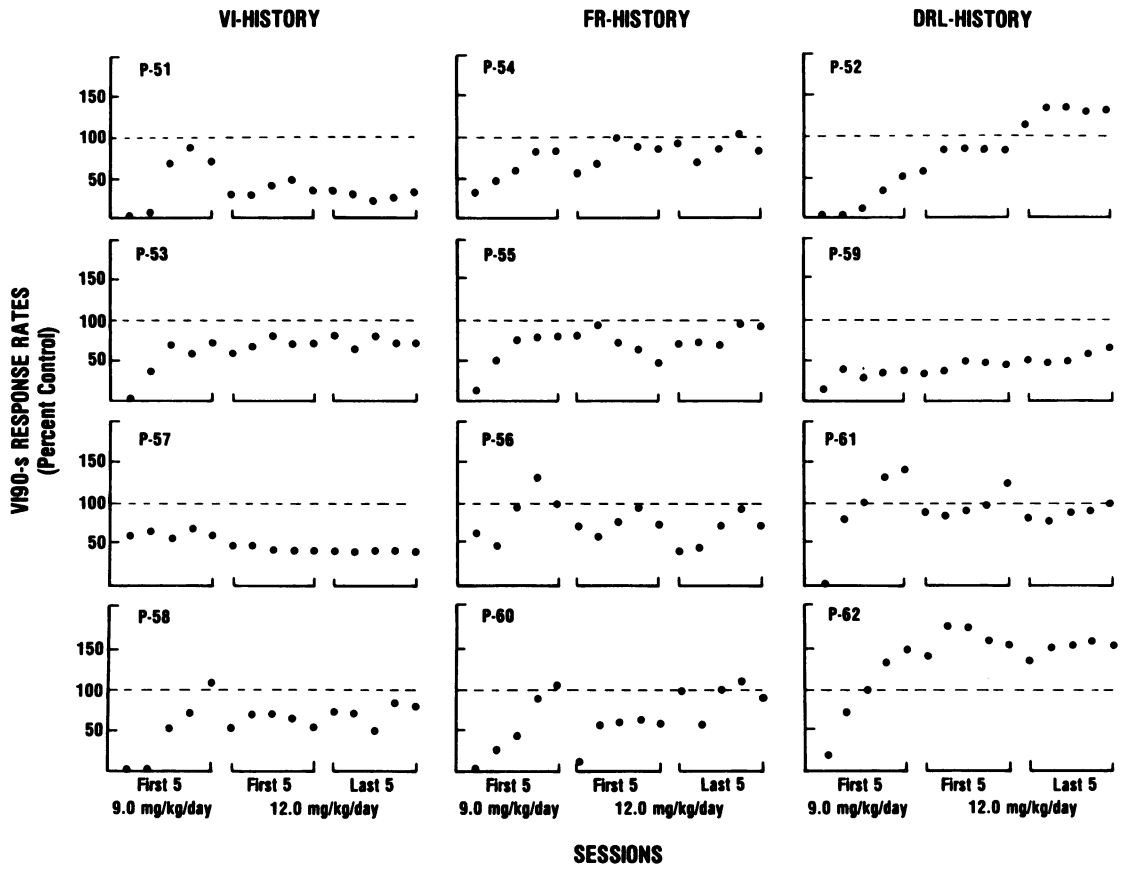

Fig. 2. Response rates, as a percentage of drug-free baselines, for each subject during chronic methadone administration. Subjects are arranged according to their reinforcement history group. Pigeons exposed to the VI schedule throughout the study are in the first panel, FR-history subjects are represented in the middle panel, and pigeons with a DRL history are shown in the last panel. The first five points for each subject represent the effects of 9.0 mg/kg/day across the first five sessions of this dosing regimen. The last 10 data points are for the first five sessions and the last five sessions, respectively, under the 12.0 mg/kg/day methadone dosing regimen. Drug-free baselines were determined from the mean of the last seven sessions under the VI schedule before the start of the chronic methadone phase (see Table 2 for control values).

responding by all subjects (see Table 2). In 14 sessions all FR subjects received the maximum number of reinforcers (700), whereas only 1 DRL subject, P-62, received 50 reinforcers per session. Pigeons P-52, P-59, and P-61 earned 648, 629, and 658 reinforcers, respectively. However, all 3 subjects responded at rates well below their VI baseline rates and their patterns of responding were characteristic of DRL performance.

The average rate of responding for the first seven sessions under the VI schedule, following FR or DRL reexposure, was used as a drug-free baseline to assess the effects of repeated methadone administrations on VI response rates. On the first day of the chronic dosing regimen, 4.5 mg/kg methadone decreased pecking rates to below 20% of drug-free baselines in 9 of 12 subjects, as shown in Figure 2. Of the subjects whose rates were suppressed the least by this dose of methadone, 2 were from the FR-history group (P-54 and P-56) and 1 was from the VI-history group (P-57). By the third session P-56 and 2 DRL-history subjects (P-61 and P-62) had almost returned to their drug-free baseline rates, and by the fourth session P-61 and P-62 were showing large rate increases. The average rates of responding during the last five sessions under the 9.0 mg/kg/day dosing regimen are shown in Table 2. Only subjects with a history of low-rate responding showed recovery of baselines followed by rate increases during the 9.0 mg/kg/day chronic phase. In fact, P-59, the only DRL-history subject not to show recovery of the drug-free baseline, responded at

Table 3

Number of VI 90-s sessions while receiving 9.0 and 12.0 mg/kg/day methadone.

Subject	9.0/day	12.0/day	Total
VI history			
P-51	29	18	47
P-53	26	12	38
P-57	19	17	36
P-58	10	30	40
FR history			
P-54	14	20	34
P-55	11	26	37
P-56	14	20	34
P-60	11	15	26
DRL history			
P-52	12	33	45
P-59	21	16	37
P-61	8	21	29
P-62	8	24	32

very high rates under the VI schedule prior to chronic dosing.

When the daily dose was increased to 12.0 mg/kg, response rates for 10 of 12 subjects decreased compared to their rates while receiving 9.0 mg/kg/day (Figure 2). Subjects with a DRL history (P-62 and P-52), continued to show rate increases under the chronic phase, whereas P-61's response rates stabilized near the drug-free baseline value. As seen in sessions preceded by 4.5 mg/kg methadone, P-59 was the only DRL subject whose rates were suppressed by daily injections of 12.0 mg/kg methadone. Examination of Table 2 and Figure 2 shows that by the end of the daily 12.0 mg/kg methadone administrations, only DRL-history subjects were responding at rates above their drug-free baseline values. By the end of the chronic testing all 4 subjects in the FR-history group responded at rates near drug-free baseline values. In contrast, response rates by pigeons in the VI control group were suppressed throughout the chronic phase of the experiment. The effects of daily methadone administration on pecking rates of pigeons in the FR-history group were intermediate between the rate increases seen in DRL-history subjects and the overall suppressed rates observed with pigeons in the VI-history group.

The number of sessions under each dosing regimen for each subject is indicated in Table 3. The differential rate of tolerance development was not due to more sessions of daily methadone for the DRL-history pigeons. Under the 9.0 mg/kg daily dosage, performances that returned to drug-free baseline levels did so between 8 and 12 sessions. While receiving 12.0 mg/kg/day, P-52 and P-62 required 33 and 24 sessions, respectively, before ending the chronic phase. However, in both subjects, increases above control levels were obtained early, and the large number of sessions was a result of between-session variability in response rates. Also, subjects with the two highest drug-free VI rates, P-51 and P-59, received the most 9.0 mg/kg/day methadone injections without showing tolerance.

In summary, subjects with a history of low-rate responding showed more complete recovery of response rates and sometimes showed substantial rate increases during chronic methadone administration. Naloxone (1.0 mg/kg) administered immediately before the session also differentially affected pecking rates depending on the pigeon's prior reinforcement history. This dose was chosen on the basis of the dose–response curve determined for P-62. During daily methadone administrations, 10.0 mg/kg naloxone decreased response rates to 37.25% of control. Because such a high dose may "wash out" any influence of history, the effects of lower doses were examined. The effects of 1.0 mg/kg and 3.0 mg/kg naloxone on VI response rates were nearly identical for P-62 (54.35% and 55.90% of chronic methadone baseline), so the lower dose was chosen. During the chronic phase, the largest effects of naloxone were seen in VI- and DRL-history subjects (Table 2). In general, 1.0 mg/kg naloxone produced small decreases in chronic methadone baseline rates or no effect in the 4 FR-history subjects, whereas 3 of 4 DRL-history pigeons showed large decreases in response rates following naloxone administrations. Among subjects exposed to the VI schedule throughout, P-53's rates were unchanged, whereas P-51, P-57, and P-58 all showed rate increases when naloxone was administered prior to testing.

The effects of substituting saline for daily methadone injections 15 min prior to testing are shown in the last column in Table 2. The effects of spontaneous withdrawal with saline were similar to the effects of precipitated withdrawal by naloxone in all subjects except P-55 (FR history) and P-59 (DRL history). Naloxone had no effect on response rates of P-59 when given concurrently with daily methadone administrations; however, when saline was substituted for 6.0 mg/kg methadone, the

methadone-suppressed response rates were increased. For P-55, naloxone decreased rates when administered during the chronic methadone phase, but when saline was given in place of methadone no noticeable effects on VI response rates were apparent. In general, spontaneous withdrawal with saline and precipitated withdrawal with naloxone resulted in rate decreases compared to chronic methadone baselines in subjects whose rates were increased by daily methadone administrations (P-52 and P-62; DRL-history group), while resulting in increases in response rates by subjects whose VI rates were below drug-free baselines during the chronic phase (P-51, P-57, and P-58; VI-history group). Naloxone (1.0 mg/kg) administered to subjects at least 1 week following discontinuation of daily methadone injections had no effect on response rates (numbers not shown in table).

Young and Thompson (1978) reported that the effects of naloxone in pigeons receiving daily morphine injections were not due to naloxone's blockage of morphine's rate-decreasing effects. In that study pigeons received up to 90 mg/kg morphine daily while performing under a conjunctive response-initiated fixed-interval 2 min interresponse times greater than x seconds (FI 2-min IRT > x s) schedule. Low doses of naloxone (0.01 to 1.0 mg/kg) increased overall response rates in 3 subjects whose responding had not recovered to drug-free baseline levels during the chronic phase, but also in a fourth subject whose response rates were not appreciably different from predrug rates. In the present study, chronic methadone administration resulted in both rate increases (DRL-history subjects) and rate decreases (especially in VI-history subjects). In agreement with results reported by Young and Thompson (1978), naloxone did not increase response rates suppressed during daily methadone treatment in Subjects P-56 (FR history) and P-59 (DRL history) and further decreased the response rates of Subjects P-53 (VI history) and P-55 (FR history). However, naloxone did significantly disrupt response rates that were increased by methadone in 3 of 4 DRL-history subjects. These effects do not appear rate dependent (see below) and suggest an interaction between schedule history and the rate-altering effects of naloxone in subjects chronically exposed to methadone.

There is some evidence in the literature that tolerance to the rate-decreasing effects of opiates develops more completely in subjects performing at lower response rates (e.g., Heifetz & McMillan, 1971). In the present study, initial key-pecking rates may have influenced the rate of development of tolerance to the rate-decreasing effects of methadone, irrespective of the organism's history. Table 2 presents subjects, within each group, in the order of their drug-free VI rates (i.e., the first subject in each group had the highest rates, and the last subject responded at the lowest rates). The data presented in the table are organized by groups, although correlations were calculated using all subjects, irrespective of history. The drug-free baseline rates were not highly correlated with the rate of responding during daily methadone administrations, as determined from the mean rate of responding over the last five sessions of chronic methadone ($r^2 = .07$), suggesting the development of tolerance in DRL-history subjects was not a consequence of drug-free VI 90-s key-pecking rates. The penultimate column in Table 2 shows the rate of responding during precipitated withdrawal with 1.0 mg/kg naloxone. The disruptive effects of administering an opiate antagonist concurrently with daily methadone administrations also were not rate dependent ($r^2 = .25$).

In summary, VI responding of pigeons with a DRL history returned to their predrug baseline values more rapidly and more completely than did subjects with an FR history and subjects exposed to the VI schedule throughout the study. Also, the administration of an opiate antagonist concurrently with daily methadone injections resulted in disruption of responding in 3 DRL-history subjects and in increases in key-pecking rates by pigeons exposed to the VI schedule throughout the experiment.

GENERAL DISCUSSION

Experimental evidence is accumulating to show that organisms' past experiences are important determinants of drug action, even when current performance does not appear to be different in the absence of the drug (Barrett, 1985; Barrett & Witkin, 1986). The experiments reported here provide further support for the importance that an organism's history can have on the behavioral effects of drugs.

A history of responding under an FR 50 or DRL 10-s schedule did not significantly affect response rates under the VI 90-s schedule. One possible reason that the VI response rates for

these two groups did not differ may have been a consequence of scheduling the histories on different keys with differing colors. Pigeons in both the FR and DRL groups showed strong stimulus control. Changing the key position and color (right green vs. center white) resulted in immediate schedule-appropriate responding (see Table 2). The probability of influencing VI key-pecking rates by exposure to FR or DRL contingencies may have been decreased by making such a strong distinction between the schedules.

When doses of methadone were readministered following DRL or FR schedule histories only 2 subjects' (P-52 and P-59) methadone dose–response curves shifted to the left. Both subjects had received interpolated training under a DRL schedule. The shift in the methadone dose–response curve was not large, but considering that tolerance may have developed following single determinations (cf. Figure 1, VI controls), the influence of the DRL history may be even more significant.

The results from Experiment 2, examining the effects of daily methadone administration on VI key-pecking rates, showed that reinforcement history can influence the rate of tolerance development. The DRL-history group showed more complete and rapid recovery to drug-free baseline levels, compared to FR- and VI-history subjects. Two different daily doses of methadone resulted in rate increases compared with drug-free baselines for 3 of 4 pigeons with DRL histories. These effects occurred under identical (VI) schedule conditions and when response rates were comparable, thereby controlling for the otherwise important influence of these factors (Dews & Wenger, 1977; Kelleher & Morse, 1968). It is also interesting to note that subjects exposed to the VI schedule throughout showed the largest disruptive effects when receiving methadone daily. As a group, VI-history subjects responded at slightly higher drug-free rates compared to FR- and DRL-history pigeons, although, in the present study, development of tolerance did not appear to be rate dependent. It may be that exposure to certain schedule histories can attenuate the rate-decreasing effects of chronically administered drugs (some schedules more effectively than others) possibly through mechanisms such as response topography.

Results from other studies suggest that tolerance to the rate-altering effects of opiates may be schedule dependent. Heifetz and McMillan (1971) found that tolerance to the rate-decreasing effects of morphine in pigeons developed more rapidly and more completely in the FI component of a multiple FI FR schedule. Babbini, Gaiardi, and Bartoletti (1976) reported rats' complete recovery of lever-press responding to drug-free baseline levels under an FI 2-min schedule of food presentations with daily morphine injections. However, these effects do not appear to be rate dependent (i.e., it may be easier to show recovery of low rates compared to high rates), because Ford and Balster (1976) were unable to demonstrate tolerance development in rats chronically treated with morphine while responding under a DRL 15-s schedule.

Schedules of reinforcement have been shown to exert a substantial influence on the effects of drugs on behavior (Kelleher & Morse, 1968). Studies that have demonstrated schedule-dependent drug effects have emphasized the importance of the prevailing contingencies, even though performances under a schedule reflect the influence of past as well as current consequences. More recently, reinforcement schedule histories have been shown to alter the behavioral effects of drugs when current contingencies are identical (Barrett, 1977). The present experiments provide further support for the importance of examining the role of historical variables on schedule-controlled behavior. In addition to providing additional evidence for historical influences on drug action, this is the first systematic demonstration of the important role of schedule history on the rate of tolerance development. A better understanding of behavioral processes and of the factors that influence drug effects on behavior will be obtained through the systematic use and examination of historical variables.

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Received March 21, 1986
Final acceptance June 15, 1987