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Interaction of Reinforcement History With Methadone on Responding Maintained Under a Fixed-Interval Schedule

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NADER, M. A. AND T. THOMPSON. *Interaction of reinforcement history with methadone on responding maintained under a fixed-interval schedule*. PHARMACOL BIOCHEM BEHAV **32**(3) 643–649, 1989.—Twelve pigeons were initially trained under either a fixed-ratio (FR) 50 or differential-reinforcement-of-low-rate (DRL) 10-sec schedule of food presentation. After 50 sessions of exposure to the foregoing schedules all pigeons key pecked under a fixed-interval (FI) 90-sec schedule. Key-peck rates differed as a function of schedule history, with FR-history subjects responding at significantly higher rates under the FI schedule than DRL-history subjects. To better compare methadone's rate-altering effects on baseline response rates, 8 naive pigeons were trained from the outset to key peck under an FI 90-sec schedule and were subsequently divided into 2 groups based on overall response rates (groups FI-H and FI-L). After at least 40 sessions under the FI schedule methadone dose-response curves were determined at doses of 0.6, 1.2 and 2.4 mg/kg. Low and intermediate methadone doses did not effect key-peck rates by pigeons with an FR history compared to significant rate decreases by pigeons having comparable rates but without a history of responding under an FR schedule (group FI-H). No differential effects following methadone were observed in low-rate subjects (DRL history and FI-L). When methadone (9.0 and 12.0 mg/kg/day) was administered chronically, response rates of all subjects were initially suppressed, with FI control subjects showing more complete recovery of drug-free baselines than either FR- or DRL-history groups. Naloxone (1.0 mg/kg) reversed methadone's rate-decreasing effects, although these actions were significantly less in subjects with prior experience under DRL schedules. Following completion of the chronic phase, and when subjects had been drug free for at least 14 sessions, the methadone dose-response curve was redetermined. The differential effects of methadone associated with reinforcement history were no longer evident, suggesting that a drug history can interact with a schedule history. These experiments add to the growing body of evidence indicating that prior experience can influence the behavioral actions of drugs independent of control rate of responding. Moreover, the data reveal that the influence of reinforcement schedule history depends on whether drugs are administered acutely or chronically.

Methadone Fixed-interval performance Reinforcement schedule history Fixed-ratio Differential-reinforcement-of-low-rate Pigeons

THE behavioral effects of drugs can depend on many factors, such as ongoing rate of responding, the schedule of reinforcement or the context in which responding occurs (2, 3, 6, 7). Under some circumstances, initial exposure to certain reinforcement schedules can influence subsequent behavior maintained by a different schedule; the influence of this variable may not become apparent until drugs are administered [e.g., (1)]. In other cases, prior experience under certain schedules of reinforcement can result in noticeable changes in response rates, thus making interpretations about the significance of reinforcement history on drug action, apart from other subsequent behavioral factors, difficult. For example, Urbain *et al.* (12) found that rats initially trained to lever press under a fixed-ratio 40 (FR 40) schedule responded at higher rates under a fixed-interval (FI) schedule when compared to rats initially trained under a schedule that reinforced interresponse times that were greater than 11 sec (differential-reinforcement-of-low-rates or DRL schedule). They also found that the effects of *d*-amphetamine varied with reinforcement schedule history. However, it is unclear whether *d*-amphetamine decreased FI rates because they were high or because those subjects had a history of responding under FR schedules.

While most studies investigating the role of schedule history on drug action have examined only acute drug administration, a recent report indicated that the influence of reinforcement schedule histories may also depend on whether the drug was administered acutely or chronically (9). In that study, pigeons with a history of responding under either a DRL or FR schedule did not engender different rates of responding under a variable-interval (VI) schedule of food presentation, nor were there differential effects following acute methadone administration. However, pigeons with DRL experience developed more complete and rapid tolerance to the rate-decreasing effects of chronic methadone administration, compared with FR-history subjects or pigeons exposed to the VI schedule throughout the study.

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The present study extends the examination of the interaction of reinforcement history and methadone dosing regimen to pigeons responding under fixed-interval schedules. Responding maintained under FI schedules has been shown to be sensitive to reinforcement schedule histories [e.g., (12–14)], perhaps because responding maintained under FI schedules is less constrained by changes in response rate affecting reinforcement frequency compared with performance maintained under other schedules (15). The experimental design is similar to that of the Urbain *et al.* (12) study in which subjects are initially exposed to either an FR or DRL schedule and then subsequently placed under an FI schedule. In addition, the present study includes a control group trained only under the fixed-interval baseline schedule. The highest response rates in control subjects were similar to those in subjects with an FR history, whereas the lowest control rates were comparable to those in subjects with a DRL history. Although the specific aspects of training that resulted in high or low FI rates by control subjects were not examined, the present study allows for a comparison of methadone's effects in separate groups of subjects with similar control rates but different experimental histories. In this way, it may be possible to determine whether methadone's effects, as a consequence of schedule experience, are a result of baseline response rates. Under FI schedules methadone can produce response rate increases at low doses and rate decreases with higher doses (8) and, under some schedules, these effects appear to be rate-dependent [e.g., (11)].

METHOD

Subjects

Twenty experimentally naive male White Carneau pigeons, maintained at 80% of their free-feeding body weights, served as subjects. The pigeons were individually housed with continuous access to water and grit in a colony room maintained at 24 degrees centigrade with 24-hour illumination. Experiments were conducted 7 days a week.

Apparatus

Eight standard operant test chambers equipped with a three-key pigeon intelligence panel (Model 141-10, BRS/LVE, Beltsville, MD) and solenoid-operated feeder (Model 114-10, BRS/LVE) were used. The feeder was illuminated when operated and mixed grain was presented for 4 sec. All chambers were illuminated by white houselights (1820 bulbs) and white masking noise was continuously presented. The keys were transilluminated with standard 6 color lamps (Dialco 3917 bulb). Programming and data recording were accomplished by two Apple II computers with associated interface and cumulative recorders located in an adjacent room.

Procedure

Differential histories. Twelve pigeons were randomly assigned to an FR 50 or DRL 10-sec group. Pigeons' key-peck responses were autoshaped (4), with a peck to the center white key producing 4-sec access to mixed grain and initiating an FR 1 schedule. For the six pigeons in the FR group training consisted of exposure to progressively increasing ratios until the terminal value of 50 was reached. Under FR schedules, reinforcement is contingent upon the completion of a specific number of responses (5). DRL performance was trained by exposing pigeons to progressively longer interresponse time (IRT) requirements, until 10 sec was reached. Under this schedule, only responses spaced at least 10 seconds were reinforced; responses that occurred less that 10 seconds apart reset the IRT requirement to 10 seconds. All sessions ended after 50 reinforcers were obtained or after 2 hours. All subjects key pecked under either the FR or DRL schedule until at least 2,500 reinforcers were obtained, which required 50 sessions for FR subjects and between 50–68 sessions for pigeons key pecking under the DRL schedule.

Fixed-interval performance. A fixed-interval (FI) 90-sec schedule was introduced after at least 2,500 reinforcers had been obtained under either the FR 50 or DRL 10-sec schedule. Under the FI schedule, the first response after 90 sec was reinforced. FI sessions began with 4-sec access to food. There were no changes in discriminative stimuli (i.e., the center key was white), but sessions ended after 45 minutes, thus decreasing the frequency of reinforcement from 50 to approximately 30 reinforcers per session.

To better determine whether methadone's effects were due to baseline rate of responding, independent of FR or DRL experience, a control group of 8 experimentally naive pigeons, whose key-peck responses were autoshaped as described above, were exposed to increasing FI values until 90 sec was reached. Subjects exposed only to the FI schedule were divided into two groups based on their overall key-pecking rates ($N = 4$ for each group). Control subjects in group FI-H consisted of pigeons with the 4 highest response rates, while pigeons with the 4 lowest rates made up group FI-L. When all subjects ($N = 20$) were exposed to at least 40 sessions under the FI 90-sec contingency and when response rates were stable (see below), a methadone dose-response curve was determined at doses of 0.6, 1.2 and 2.4 mg/kg.

Chronic methadone. Following completion of the methadone dose-response curves, pigeons were reexposed to their FR 50 or DRL 10-sec schedules for 20 sessions. Pigeons in the FI control group continued to respond under the FI 90-sec contingency for the same number of sessions. Following this reexposure, all pigeons were required to key peck under the FI 90-sec schedule for 30 consecutive sessions prior to the beginning of the chronic methadone phase.

Session 30 under the FI schedule was preceded by a saline injection 15 minutes before testing. All pigeons then received 9.0 mg/kg/day methadone for 8 consecutive sessions, followed by a dose increase to 12.0 mg/kg/day for 15 consecutive sessions. In an effort to maintain a more constant blood level, methadone was administered in half doses (i.e., 4.5 and 6.0 mg/kg) with the first injection 15 minutes before the session and the second injection approximately 12 hours after testing.

Under the 12.0 mg/kg/day schedule, a saline injection immediately preceded the eleventh session, in addition to the 6.0 mg/kg methadone injection 15 minutes before testing. The next session was immediately preceded by a 1.0 mg/kg naloxone injection, in addition to the daily methadone dose administered 15 minutes earlier. Following the naloxone challenge, all pigeons were tested for three more sessions under 12.0 mg/kg/day methadone. The chronic phase ended with saline substituted for methadone 15 minutes before testing and 12 hours later. On the seventh session following discontinuation of chronic dosing, 1.0 mg/kg naloxone was administered immediately before testing.

Redetermination of methadone dose-response curve. When responding was stable and after at least 14 sessions following termination of daily methadone administration, the methadone dose-response curve was redetermined at doses of 0.6, 1.2 and 2.4 mg/kg.

Drug Administration

Methadone hydrochloride (Eli Lilly, Inc., Indianapolis, IN) and naloxone hydrochloride (generously provided by Dupont

Pharmaceuticals, Wilmington, DE) were mixed with isotonic saline (0.9%) to obtain a constant injection volume of 1.0 ml/kg. Doses of all drugs are expressed as the total salt and all injections were given intramuscularly into the breast muscle.

During acute dosing, single doses of methadone were administered 15 minutes before testing when responding was considered stable. Responding was deemed stable when three consecutive sessions occurred in which overall key-pecking rates during individual sessions did not vary by more than ± 10% of the mean for those three days. Saline was administered on at least one of the sessions included in meeting the stability criterion and the order of methadone doses was randomized for each subject. To minimize tolerance development, at least 7 days separated successive methadone administrations.

Data Analysis

Baseline rates of responding are reported in responses per minute (r/min). Dose-response curves are represented as percent control and each point is the mean of 6 (FR or DRL history) or 4 (FI-H or FI-L) subjects. Variability is reported as standard errors of the mean (S.E.). Statistical significance was determined by a two-tailed Student's *t*-test for paired observations using $p<0.05$ as the level of significance. If comparisons were made between groups, Student's *t*-test for unpaired observations was used.

RESULTS

Response Rates

Response rates under the FR and DRL schedules and under the subsequent FI schedule are shown in Fig. 1. The FR 50 schedule generated very high key-pecking rates by all 6 subjects (80.09 ± 8.35 r/min). Responding maintained under the DRL 10-sec schedule was characterized by long pauses and low rates of responding (7.79 ± 1.05 r/min). Upon introduction of the FI schedule, response rates of subjects initially exposed to the FR 50 schedule decreased significantly (Block 1; $p<0.05$), and continued to decrease significantly (Block 2; $p<0.01$) until approximately 30 sessions under the FI schedule, when rates became stable (Fig. 1). Pigeons with experience under the DRL schedule showed significant increases in response rates over the first 10 sessions under the FI schedule ($p<0.05$), although their rates remained much lower than FR-history subjects ($p<0.001$). Responding increased only slightly over the next 30 sessions and, when stable, remained significantly below rates of key pecking by FR-history subjects (Block 4; $p<0.001$).

To obtain stable rates of responding, subjects with FR or DRL histories, in addition to subjects exposed only to the FI 90-sec schedule, were maintained under the fixed-interval schedule for at least 40 sessions before methadone was administered. Figure 2 shows the mean rate of responding over the 5 sessions preceding the first methadone injection. As mentioned earlier, subjects exposed to the FR schedule responded at significantly higher rates under the FI schedule compared to pigeons initially exposed to the DRL schedule (middle two bars). However, FI control subjects with the four highest key-pecking rates (group FI-H) had rates of responding similar to pigeons with an FR history (Fig. 2). The mean rate of responding by the four FI control pigeons with the lowest fixed-interval rates (group FI-L) was similar to that of pigeons with a DRL history, but was significantly different from response rates by pigeons in the FI-H group ($p<0.05$).

Methadone Dose-Response Curves

When methadone was administered to pigeons key pecking under an FI 90-sec schedule (Fig. 3), subjects with an FR history showed a tendency towards rate increases at 0.6 and 1.2 mg/kg doses, while pigeons with similar overall FI rates but no FR history (group FI-H) showed significant rate decreases at all doses tested ($p<0.05$). The difference between FR-history and FI-H groups was significant at the 1.2 mg/kg dose ($p<0.05$) and just below significance at the 0.6 mg/kg dose ($p<0.057$). Responding following 2.4 mg/kg methadone was significantly decreased in both FR-history and FI-H groups ($p<0.05$).

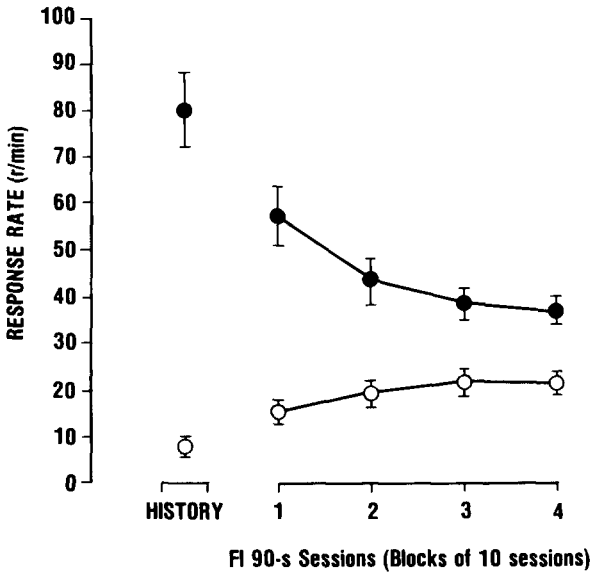

FIG. 1. Rate of responding (r/min) during reinforcement schedule histories and across sessions of fixed-interval performance. Solid circles represent FR-history subjects, open symbols, DRL-history pigeons. The first point is the mean rate of responding for the last 5 sessions under the FR 50 and DRL 10-sec schedules. Points representing FI responding are means for each pigeon across 10 consecutive sessions. Vertical lines indicate standard errors of the mean.

Representative cumulative records of two subjects with similar response rates under the FI 90-sec schedule are shown in Fig. 4. Both subjects had relatively high FI rates and similar patterns of responding, but only one subject had initially been exposed to an FR 50 schedule. The lower records show performance following 1.2 mg/kg methadone. The subject with experience only under the FI schedule showed rate decreases at a dose that increased response rates by the pigeon with an FR history.

Responding by subjects with low baseline FI rates (DRL-history and FI-L groups) was not significantly affected following 0.6 and 1.2 mg/kg methadone. Administration of 2.4 mg/kg methadone significantly decreased response rates by DRL-history subjects ($p<0.05$), while subjects from the FI-L group continued to respond near baseline following the 2.4 mg/kg dose (Fig. 3).

Although baseline rates of FI-H subjects were significantly higher than control rates of FI-L pigeons, low and intermediate methadone doses affected response rates similarly in both groups. However, comparing FR-history subjects to DRL-history subjects revealed significant differences between groups at methadone doses of 0.6 mg/kg ($p<0.005$) and 1.2 mg/kg ($p<0.05$).

Chronic Methadone

Control rates of responding under the FI schedule averaged over the five sessions before the start of daily methadone admin-

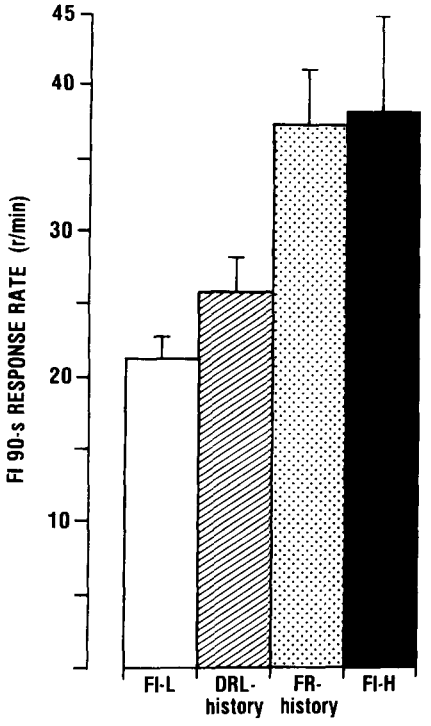

FIG. 2. Fixed-interval 90-sec response rates (r/min) for DRL- and FR-history groups and control subjects. Each point is the mean across the 5 sessions that preceded the first methadone administration (N = 6 for DRL- and FR-history groups; N = 4 for FI-L and FI-H groups). Vertical lines represent standard errors of the mean. Control subjects were divided into 2 groups based on overall rate of responding. (See text for details.)

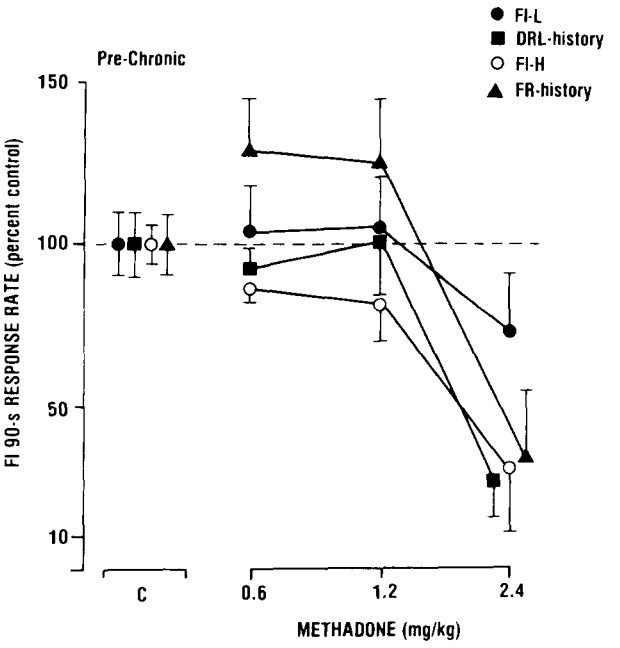

FIG. 3. Fixed-interval 90-sec response rates (percent of control) as a function of methadone dose. Control points are the average of each three-day mean used in the stability criterion, at each dose. Vertical lines indicate standard errors of the mean.

istration are shown in the second column of Table 1. Pigeon P-4 (FR-history group) stopped eating and appeared to be in poor health during the 12.0 mg/kg/day phase and its data were excluded from the analysis of chronic methadone effects.

During the first three sessions of daily methadone administration most pigeons' key-pecking rates were reduced to near 0.0 r/min. By the end of the 9.0 mg/kg/day phase responding occurred at approximately 50 percent of drug-free baselines. Figure 5 shows the relative rate of responding compared to drug-free baseline rates over the last 5 sessions while receiving 9.0 mg/kg/day methadone. At this dose, rates of responding were still significantly below control ($p<0.01$) and the level of recovery of drug-free baselines did not differ between FR- and DRL-history groups (Fig. 5). Responding of control subjects showed more variability with an average decrease about comparable to that obtained in the other groups. Two of four FI-L subjects recovered their drug-free baselines and showed moderate rate increases by the end of the 9.0 mg/kg/day phase, while only one high-rate control subject responded at drug-free baseline rates.

When the daily dose of methadone was increased to 12.0 mg/kg, responding was significantly below drug-free control rates for three groups (FR-, DRL-history: $p<0.01$; FI-H: $p<0.05$). Subjects in the FI-L group showed only modest rate decreases. By the end of the dosing regimen, control subjects, irrespective of their baseline rate of responding, showed more complete recovery of drug-free FI rates than subjects having FR or DRL histories. Responding by subjects with experience under either an FR or DRL schedule remained below control over the last 5 sessions of chronic methadone ($p<0.01$).

When 1.0 mg/kg naloxone was administered, key pecking by all subjects whose rates had been suppressed following daily methadone injections increased to prechronic control levels (Fig. 5). Compared to rates during daily methadone administration the increases in responding following naloxone were significant ($p<0.05$) except for the DRL-history group. Recovery of drug-free baselines occurred when saline was substituted for 6.0 mg/kg methadone (Table 2). Although response rates were elevated in all groups during the first drug-free session, the increases were only significant for FR- and DRL-history groups ($p<0.01$). Table 2 shows that over the first three sessions following discontinuation of daily methadone injections, there were no statistically signifi-

TABLE 1

FIXED-INTERVAL RESPONSE RATES (r/min)*

Group	Prechronic Methadone DRC†	Chronic Methadone‡	Postchronic Methadone DRC†
FR history	37.76	44.70	37.85
	(3.81)	(4.01)	(3.53)
FI-H	38.31	38.63	38.29
	(6.67)	(9.24)	(10.08)
DRL history	25.87	25.28	25.79
	(2.54)	(2.45)	(1.65)
FI-L	21.22	21.95	21.52
	(1.43)	(3.08)	(4.72)

*Numbers in parentheses are standard errors of the mean.

†Averages from 3-day means used to determine stability during dose-response curve (DRC) determination.

‡Average rate of responding for 5 sessions preceding daily methadone administration.

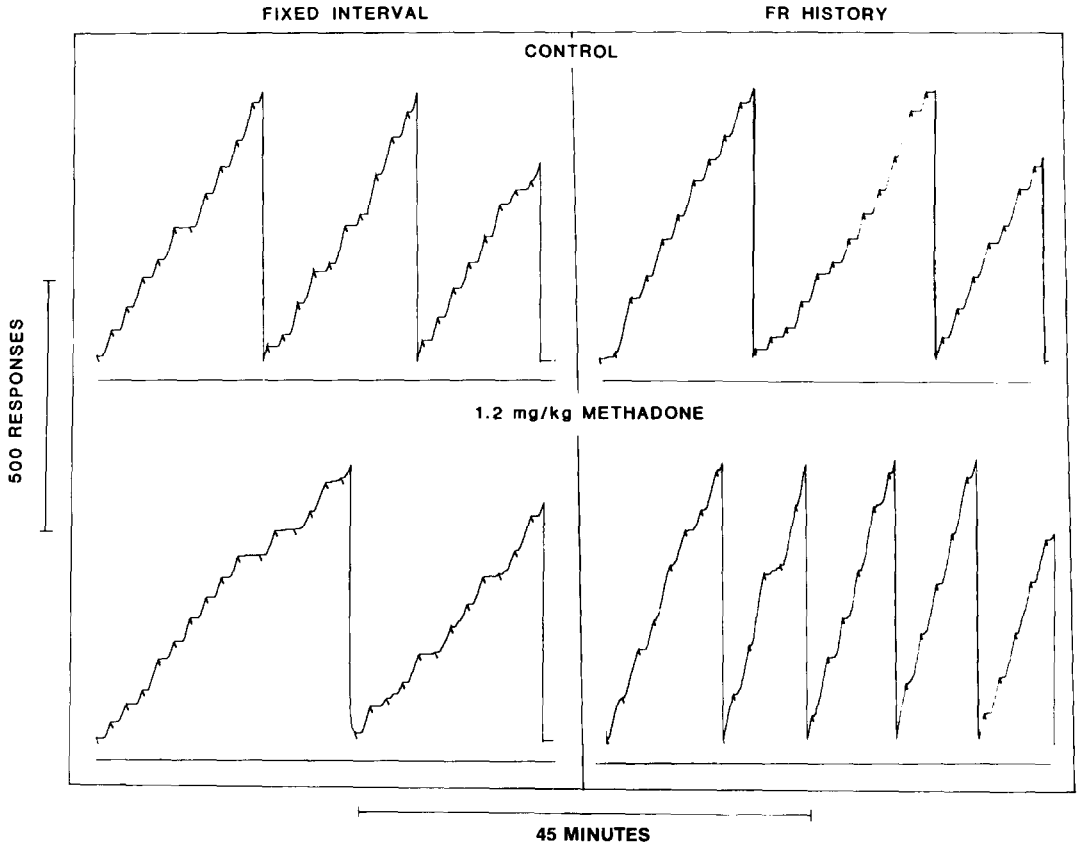

FIG. 4. Cumulative records under a fixed-interval 90-sec schedule. The subject represented on the left is from the FI-H group, while the subject on the right is from the FR-history group. The top records represent control performance, while the bottom panel are records from a session preceded 15 minutes by a 1.2 mg/kg methadone injection.

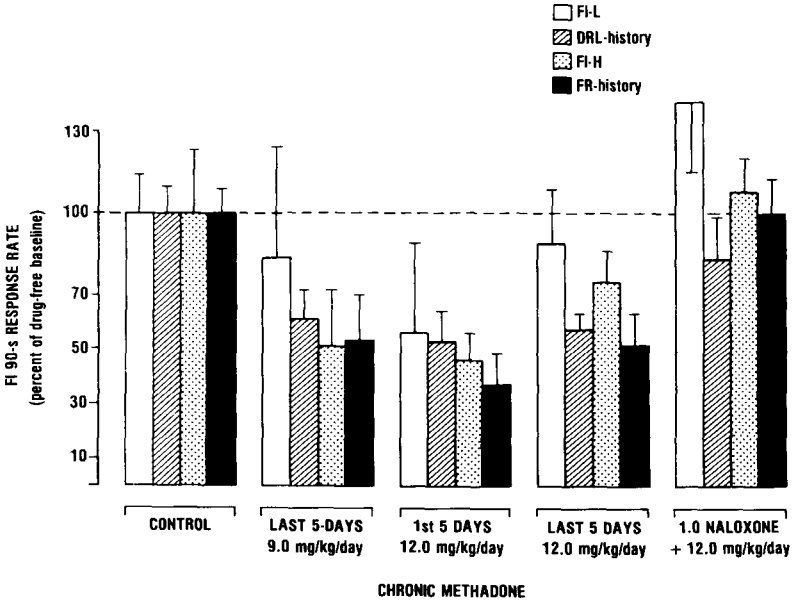

FIG. 5. Fixed-interval 90-sec response rates during daily methadone administration. Data are reported as a percent of drug-free baselines for each group. Each panel represents the mean of 5 sessions. Vertical lines indicate standard errors of the mean.

TABLE 2

EFFECTS OF METHADONE DISCONTINUATION ON RESPONSE RATES (r/min) ACROSS THREE CONSECUTIVE SESSIONS[1]

Group	Last Session 12.0 mg/kg/day	Drug-Free Sessions[2] 1	2	3
FR history	19.89	43.16*	44.29	42.42
	(7.45)	(4.27)	(2.62)	(6.19)
FI-H	33.69	46.05	45.63	43.29
	(6.12)	(12.78)	(13.42)	(13.40)
DRL history	15.15	27.64*	30.08	31.33
	(3.06)	(3.96)	(5.56)	(4.91)
FI-L	20.09	23.64	27.71	24.77
	(3.98)	(2.19)	(3.01)	(2.17)

[1]Numbers in parentheses are standard errors of the mean. *Indicates statistical significance of $p<0.01$.

[2]Saline was administered 15 min before sessions and 12 hours after testing.

cant changes in response rates. Also, 1.0 mg/kg naloxone administered one week after discontinuation of daily methadone injections had no significant effect on response rates (data not shown).

Redetermination of Methadone Dose-Response Curves

After pigeons were drug free for at least two weeks following chronic methadone administration, the methadone dose-response curves were redetermined. Acute methadone administration (0.6–2.4 mg/kg) had no significant effect on fixed-interval response rates following chronic methadone in pigeons with FR or DRL histories and in high-rate control subjects (FI-H group). Subjects from the FI-L group showed large rate increases following methadone administration (Fig. 6), which reached significance at the 1.2 mg/kg dose ($p<0.02$). This effect was not due to baseline rate of responding since subjects with a DRL history responded at nearly identical rates but did not show any significant rate increases following methadone. The significant differences between FR-history and FI-H subjects observed during determination of the first methadone dose-response curve were no longer present following a chronic dosing regimen. In addition, tolerance, as indicated by nonsignificant effects of 2.4 mg/kg methadone, had developed in all groups. At this dose, the difference between the effects observed before and after chronic methadone administration were significant in all groups ($p<0.05$). However, these changes in the methadone dose-response curves were not due to shifts in control response rates, which remained similar in all phases of the study (see Table 1).

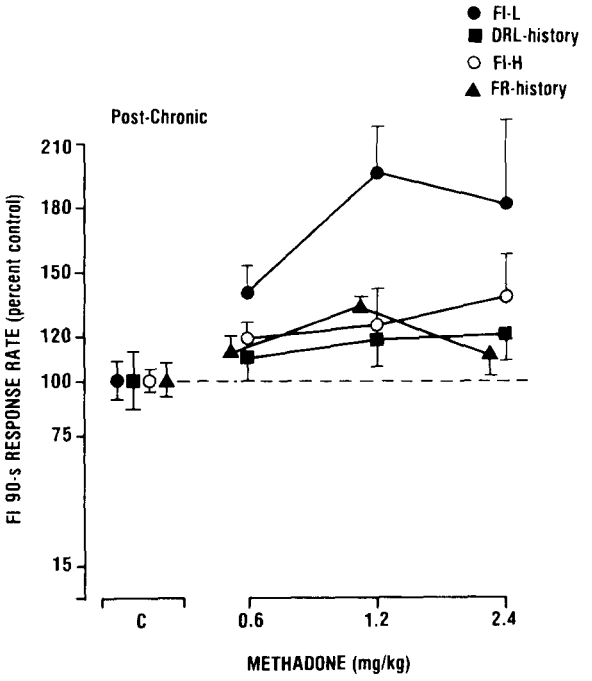

FIG. 6. Fixed-interval 90-sec response rates (percent control) as a function of methadone dose, following chronic methadone administration. Points were determined at least 14 sessions following completion of the chronic methadone phase. Each point is as described in Fig. 3.

DISCUSSION

The present study provides further evidence that historical variables can influence the behavioral effects of drugs independent of changes in baseline rate of responding (1,9). Pigeons initially exposed to an FR schedule responded at higher rates under a subsequent fixed-interval schedule than subjects with a history of responding under DRL schedules, replicating results from earlier reports using rats (12) and humans (13,14). The inclusion of a control group exposed only to the FI schedule and then divided according to their overall rate of responding allowed for an assessment of methadone's effects in groups of subjects with similar response rates but different experimental histories.

Acute administration of methadone resulted in significant differences in performance between FR-history pigeons and FI-H subjects. At doses that decreased high rate performance in control subjects, methadone had no effect on key-pecking rates of FR-history pigeons. Others have shown that under FI schedules methadone can decrease high rates of responding to a greater extent than low rates [e.g., (11)]; an effect that is consistent with what was observed in control pigeons from the present study. The fact that FR-history pigeons responded at similar control rates, but were not significantly affected by comparable methadone doses, may suggest that a history of responding under FR schedules can attenuate the rate decreasing effects typically observed following intermediate doses of methadone.

In an earlier study, pigeons exposed to an FR or DRL schedule prior to reexposure under a variable-interval schedule, did not differ in baseline VI rates nor were differences observed following acute methadone administration (9). Thus it appears that reinforcement schedule history can influence response rates following acute methadone administration when these effects are assessed under an FI baseline rather than a VI baseline. Similar FI sensitivity compared with VI schedule performance has been reported for *d*-amphetamine (10,12). Although response rates under interval schedules are more sensitive to indirect variables (15), or variables not directly prescribed by the schedule (of which reinforcement history is an example [cf. (10)]), it is at present not clear what aspects of FI schedules make responding more malleable to reinforcement schedule histories compared to VI performance.

No differential effects between FR- and DRL-history groups were observed during chronic methadone administration. This is in contrast to a previous study using VI schedule performance as baseline for assessing the interaction of schedule history with methadone's rate-altering effects. In that study, subjects with experience under a DRL schedule developed rapid and complete tolerance to the rate-decreasing effects of methadone compared to subjects with an FR history and subjects exposed to the VI schedule throughout the study (9). In addition, pigeons with prior

experience under DRL schedules were the only subjects to show rate increases compared with drug-free baselines during chronic methadone administration.

Interestingly, in the present study subjects exposed only to the FI schedule recovered their drug-free baseline rates during daily methadone, while response rates by subjects with a history of responding under FR or DRL schedules remained significantly below control rates throughout the chronic phase. Thus, it appears that a history of responding under other schedules may attenuate the rate of tolerance development under FI schedules, as determined by recovery of drug-free control rates. Although both history groups did not recover their drug-free baseline rates during chronic methadone, tolerance did develop to methadone's acute effects as indicated by the relatively flat dose-response curve following chronic drug administration. The fact that reinforcement frequency did not change during the latter stages of daily methadone administration cannot account for the lack of recovery of FI baselines, since reinforcement frequency was not significantly decreased in FI-H and FI-L groups during chronic methadone administration.

At present it is not clear why, after chronic methadone dosing, subjects in the FI-L group showed large response rate increases following acute methadone. Also, these pigeons showed the least disruption in responding following a high dose of methadone (cf. Fig. 3). The large differences between pigeons with an FR history and FI-H subjects were no longer evident following daily methadone administration suggesting that chronic dosing interacts with the effects of prior schedule experience. The results from the present study, along with those from an earlier report (9), argue strongly that the influence of reinforcement schedule history can depend on both the baseline schedule (FI or VI) and the dosing regimen (acute or chronic). Exactly what aspects of a reinforcement schedule history influence the behavioral effects of drugs remains to be determined.

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