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The effects of behavioral history on cocaine self-administration by rhesus monkeys

Michael A. Nader[1,2] David M. Reboussin[3]

[1] Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157–1083, USA

[2] Department of Comparative Medicine, Bowman Gray School of Medicine, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157–1040, USA

[3] Department of Public Health Sciences, Bowman Gray School of Medicine, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157–1063, USA

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Abstract. The purpose of the present study was to examine whether a history of responding under schedules that generate either high or low response rates could modify previously established cocaine self-administration. Eight experimentally naive rhesus monkeys were trained to respond on one of two levers under a fixed-interval (FI) 5-min schedule of intravenous cocaine (0.03 mg/kg per injection) presentation. When responding was stable a cocaine dose-response curve (saline, 0.01–0.3 mg/kg per injection) was determined. Following completion of the dose-response curves, the monkeys were randomly assigned to one of two groups ($n = 4$/group) and trained to respond on the other lever under either a fixed-ratio (FR) 50 or inter-response times (IRT) > 30-s schedule of cocaine (0.03 mg/kg per injection) presentation. After 65 sessions responding was again maintained under the FI5-min schedule of 0.03 mg/kg per injection cocaine for 60 sessions, followed by redetermination of the cocaine dose-response curve. During the initial exposure to the FI schedule, the mean rate of responding was 4.02 ($\pm$ 0.33) responses/min and the cocaine dose-response curve was characterized as an inverted-U shape function of dose, with peak responding at 0.03 mg/kg per injection. The FR50 schedule generated high rates (66.80 $\pm$ 5.6 responses/min), while response rates under the IRT > 30-s schedule were low (2.62 $\pm$ 0.2 responses/min). Following different behavioral histories, response rates under the FI5-min schedule were significantly higher for 60 sessions in FR-history monkeys compared to IRT-history subjects. Compared to the initial FI baselines, cocaine intake (mg/kg per session) was significantly higher following an FR-history and significantly lower following training under an IRT schedule, for 60 consecutive sessions. In addition, there was a significant effect of behavioral history on the cocaine dose-response curve, such that descending limb was shifted farther to the right in FR-history subjects compared to IRT-history monkeys. Results from the present study indicate that previously established "drug-seeking" behavior can be modified by training under different reinforcement schedules. Knowledge of such historical variables may be important in understanding the determinants of drug self-administration.

Key words: Behavioral history – Self-administration – Cocaine – Drug abuse –Schedule-controlled behavior – Fixed-ratio – Inter-response times – Rhesus monkey

Correspondence to: M. A. Nader

There is growing evidence that under certain conditions the behavioral effects of drugs can be profoundly influenced by past experience (see Barrett et al. 1989 and Nader et al. 1992 for recent reviews). For example, Barrett (1977) showed that a history of responding under an avoidance schedule could modify the effects of *d*-amphetamine on punished responding. The significance of this finding was that amphetamine's effects on behavior were modified by exposure to contingencies that were not present during test conditions. In other experiments with human and nonhuman subjects, prior training under certain schedules of reinforcement can produce long-lasting changes in behavior maintained by nondrug reinforcers and in the behavioral effects of drugs (Weiner 1969; Urbain et al. 1978; Nader and Thompson 1987, 1989; Wanchisen et al. 1989). For example, Urbain et al. (1978) found that rats initially trained under a fixed-ratio (FR) schedule had higher rates of responding under a fixed-interval (FI) schedule compared to rats initially trained under an inter-response times (IRT) > t-s schedule; the effects of *d*-amphetamine were different in these two groups. Taken together, these results emphasize the importance of examining the influence of historical variables and how they interact with current contingencies.

Although the effects of different reinforcement schedule histories on the rate-altering effects of drugs have been systematically examined, there are no data on how sensitive drug self-administration behavior would be to such reinforcement schedule histories. In treatment settings, drug abusers appear sensitive to contingencies of

reinforcement and to changes in schedules of drug availability (e.g., Stitzer et al. 1980; Crowley 1984; Budney et al. 1991; Higgins et al. 1991), and consequently, identifying conditions under which drug-seeking behavior would be reduced for extended periods has practical applicability. The purpose of the present study was to determine if cocaine self-administration by experimentally naive rhesus monkeys could be modified by behavioral history involving different reinforcement schedules. Clearly, a better understanding of the environmental contingencies that result in persistent changes in behavior will be beneficial to understanding the etiology, maintenance and eventual treatment of drug abuse (cf. Barrett et al. 1989).

Materials and methods

Subjects

Eight experimentally naive adult male rhesus monkeys (*Macaca mulatta*) that weighed between 6.0 and 10 kg under free-feeding conditions, served as subjects. Their body weights were decreased to approximately 90% of free-feeding weights, by supplemental feeding of Purina Monkey Chow no sooner than 30 min post-session. Monkeys were weighed approximately once per month and, if necessary, their diet (100–150 g/day) was adjusted to maintain stable weights. In addition, monkeys were given a chewable multiple vitamin tablet 3 days per week and occasionally received fresh fruit.

Apparatus

Monkeys were individually housed in sound attenuating cubicles (91 cm wide × 91 cm deep × 91 cm high; Plas Labs, Lansing, MI); the front wall of each cubicle was Plexiglas to allow the monkey visual access to the laboratory. During experiments, the front wall was covered with a drape. Each cubicle was equipped with two response levers (BRS/LVE, PRL-001, Beltsville, MD) and a peristaltic infusion pump (7531–10, Cole-Parmer Co., Chicago, Ill.) for delivering drug injections at a rate of approximately 1 ml/10 s. Above each lever were four stimulus lights, two covered with white lens caps and two covered with red lens caps. Each monkey was fitted with a stainless-steel restraint harness and spring arm (Restorations Unlimited, Chicago, Ill.) which attached to the rear of the cubicle.

Procedure

Surgery and catheter maintenance. After adaptation to the cubicle and restraint system, each monkey was anesthetized with a combination of ketamine (10 mg/kg, IM) and halothane and a chronic indwelling venous catheter was surgically implanted under sterile conditions. The proximal end of the silicone catheter (0.08 cm inside diameter, Ronsil Rubber Products, Blackstone, VA) was inserted into a major vein (internal or external jugular, femoral or brachial vein), terminating in the vena cava. The distal end of the catheter was threaded subcutaneously and exited through a small incision in the back of the animal. Monkeys were given 1–2 days to recover from surgery, prior to returning to the experiment. Antibiotics (Keflin; cephalothin sodium, Eli Lilly Co., Indianapolis, IN) were administered prophylactically for 7–10 days following surgery. Cocaine HCl (provided by the National Institute on Drug Abuse, Rockville, MD), was dissolved in sterile saline (250–500 ml). During sessions, responding on the lever delivered approximately 1.0 ml of cocaine solution over a 10-s period (0.01–0.3 mg/kg per injection). Prior to the beginning of each session, catheters were flushed for approximately 30 s with the concentration of cocaine available for self-administration. Because each catheter was filled with heparinized saline, the total amount of cocaine solution injected into the animal prior to the start of the session was approximately 1 ml. At the end of each session, catheters were flushed with approximately 3 ml heparinized saline (100 units/ml), to help prevent clotting.

Initial fixed-interval 5-min baseline. On the first day of training, each response on the left lever turned off the white lights above the lever, illuminated the red lever lights and resulted in a 10-s cocaine injection (0.03 mg/kg per injection). Over a 2- to 3-day period the interval between cocaine availability was increased until the final schedule value of 5 min was obtained (fixed-interval 5 min; FI5 min). Under this schedule, the first response after 5 min produced a 10-s cocaine injection; responses during the injection had no scheduled consequence and were not counted. Session length was 2 h for the first 10–15 sessions, after which it was increased to 4 h for the remainder of the experiment.

After responding had been maintained under the FI5-min schedule of cocaine presentation (0.03 mg/kg per injection) for approximately 20–30 sessions, saline was substituted for cocaine for at least three consecutive sessions and until responding declined to less than 20% of baseline and was deemed stable. Following stable performance (± 20% of the mean for three consecutive sessions), the conditions were returned to baseline (i.e., 0.03 mg/kg per injection cocaine) for at least five consecutive sessions. A cocaine dose-response function was determined in each monkey (0.01–0.3 mg/kg per injection), with doses tested in a random order. The minimum number of sessions that each dose was available for self-administration was individually determined and based upon the number of sessions that were required for responding to decline to less than 20% of baseline when saline was available (range of three to ten sessions). After a particular dose was evaluated, there was a return to baseline conditions (0.03 mg/kg per injection) for at least five sessions.

After completion of the cocaine dose-response curve, cocaine 0.03 mg/kg per injection was available for 20 consecutive sessions; the mean rate of responding for the last 10 sessions under this condition was considered the "pre-history" FI baseline. Prior to training under different reinforcement schedules, the monkeys were ranked from 1 to 8, based on response rates under the FI5-min schedule. Matched-pairs of monkeys were randomly assigned to one of two groups, so that each group would have similar average FI response rates prior to exposure to different reinforcement schedules. The total number of sessions that responding was maintained under the FI5-min schedule (at all doses), prior to training under the FR or IRT schedules, ranged from 97 to 131 sessions.

Exposure to different reinforcement schedules. Four monkeys were trained under a fixed-ratio (FR) 50 schedule, while the other four monkeys were trained under an inter-response times (IRT) > 30-s schedule of cocaine presentation (0.03 mg/kg per injection) for 65 sessions. Cocaine availability under the FR or IRT schedule was signaled by illumination of the white lights above the right lever (the FI schedule had been programmed on the left lever).

For monkeys trained under the FR50 schedule, the number of responses required for cocaine presentation was increased from 10 to 50 over a 2 to 3-day period, except for monkey 91–19. For this monkey, initial increases in the FR value from 20 to 30 disrupted responding, and consequently, small increases in FR value were made over approximately 15 sessions, until 50 was reached. For all monkeys, each cocaine injection was followed by a 2-min timeout (TO); a 60-min TO followed the 10th and 20th cocaine injections. Under the FR50 schedule, sessions terminated after 30 injections had been received or 5 h had elapsed. After approximately 30 sessions, saline was substituted for cocaine to verify that cocaine was functioning as a reinforcer under these conditions.

Training under the IRT > 30-s schedule occurred over a 3-day period. IRTs greater than 10 s were reinforced for one session (total of 30 injections), with the IRT value being increased by 10 s over the

next two sessions. Under the final schedule conditions, a response occurring less than 30 s after the preceding response reset the IRT timer; a 5-min TO followed each cocaine injection. Session length was 8 h or until 30 injections were obtained. After approximately 30 sessions, saline was substituted for cocaine to verify that cocaine was functioning as a reinforcer under these conditions.

Re-exposure to the fixed-interval 5-min schedule. Following the 65th session under the FR50 or IRT > 30-s schedule, cocaine (0.03 mg/kg per injection) availability was again scheduled on the left lever under an FI5-min schedule. To assess whether changes in response rate as a function of reinforcement schedule history were transient, responding was maintained under the FI5-min schedule of 0.03 mg/kg per injection cocaine presentation for at least 60 consecutive sessions, after which the cocaine dose-response curve was redetermined, as described above. Experiments were conducted daily, 7 days/week, starting at approximately 0900 hours.

Data analysis

The primary dependent variable was response rate (responses/min), in which rate was defined as: total responses/(session length − (number of injections × TO). For the FI schedule, TO was 10 (the duration of the pump infusion), while for FR and IRT schedules, TO was 2 and 5 min, respectively. In addition, cocaine intake (mg/kg per session) and quarter-life (QL), which is an index of pattern of responding under FI schedules (Catania and Reynolds 1968), were examined. QL values represent the proportion of the FI elapsed when 25% of the responses in that interval had been emitted. For all analyses, rate and QL values were analyzed without transformation, while intake was replaced by its log value. Group data were analyzed using three mixed model ANOVAs: two comparing the pre- and post-history periods within each group and one comparing the FR and IRT groups during the post-history period. The FR and IRT group comparison in the post-history period included a factor for estimating linear trends over the 60 sessions. For data presentations, pre-history baselines are represented as a mean of eight monkeys, although the statistical analysis of pre- versus post-history effects used the mean from the four monkeys in each group. For analysis of dose-response curves, three mixed model ANOVAs were fitted: one including dose and history during the post period only (i.e., FR versus IRT groups) and two including dose and condition (i.e., pre- versus post-history) separately in the FR and IRT groups. For each dose, data from the last three sessions for a particular dose were included in the analysis, for each monkey. For the baseline dose of cocaine (0.03 mg/kg per injection), the three sessions preceding each change in dose were included in the analysis.

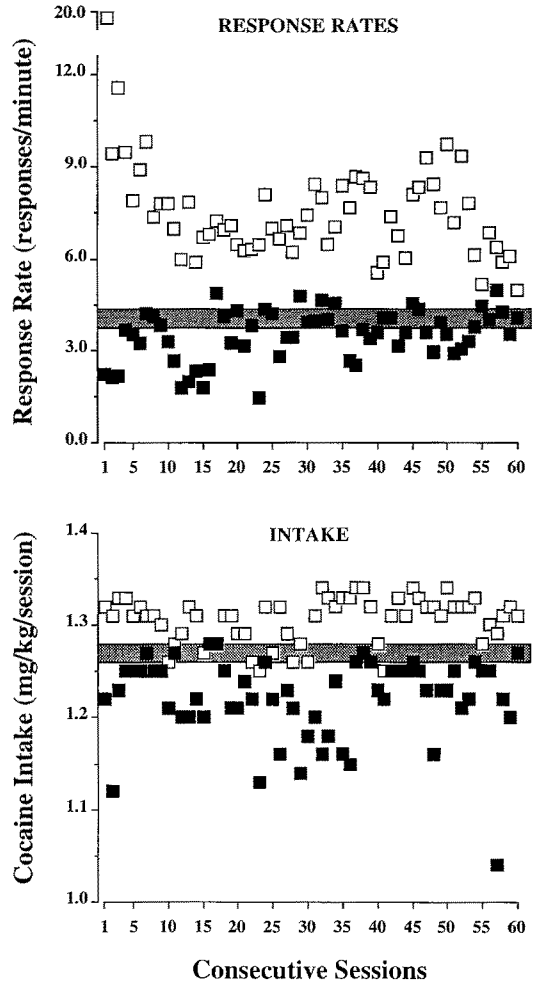

Fig. 1. The effects of training under an FR50 (*open squares*) or an IRT > 30-s (*filled squares*) schedule of cocaine presentation (0.03 mg/kg per injection) on rate of responding (*top panel*) and cocaine intake (*bottom panel*) in monkeys self-administering cocaine under an FI5-min schedule. Each point represents the mean of four monkeys per group. The shaded areas represent the mean (± 1 SEM) for all monkeys (n = 8) prior to different behavioral histories

Results

Effects of reinforcement schedule history on responding maintained under an FI5-min schedule of 0.03 mg/kg per injection cocaine presentation

Responding was initially maintained under an FI5-min schedule of 0.03 mg/kg per injection cocaine presentation and a cocaine dose-response curve was determined (see below). Prior to training under either an FR50 or IRT > 30-s schedule, the baseline rate of responding under the FI5-min schedule was 4.02 (± 0.33) responses/min. Cocaine (0.03 mg/kg per injection) self-administration by four monkeys was subsequently maintained under an FR50 schedule at response rates higher than those maintained by saline, with subjects typically receiving the maximum number of injections each session (30/session). The mean rate of responding for the group across the last ten sessions under the FR50 schedule was 66.80 ± 5.6 responses/min. Low rates of cocaine (0.03 mg/kg per injection) self-administration were maintained under an IRT > 30-s schedule in four monkeys at response rates higher than those maintained by saline, with subjects typically receiving the maximum number of injections each session (30/session). The mean rate of responding for the group across the last ten sessions under the IRT > 30-s contingency was 2.62 ± 0.2 responses/min.

After 65 sessions under the FR50 or IRT > 30-s schedule, subjects were re-exposed to the FI5-min schedule of 0.03 mg/kg per injection cocaine presentation for 60 consecutive sessions (Fig. 1, top panel). Following an FR50 history, response rates across all 60 sessions were significantly higher compared to the initial FI baseline rates (Pre- versus Post-FR history; open symbols versus shaded area: $P < 0.0001$). FI response rates were highest

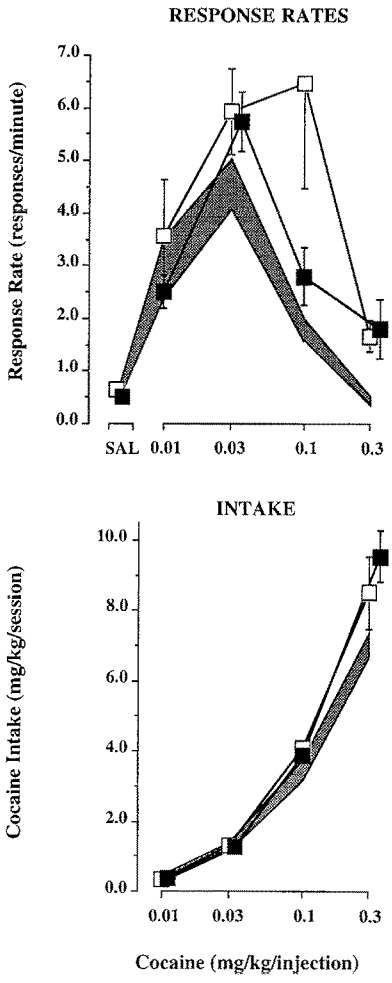

Fig. 2. Effects of different reinforcement schedule histories on response rate (*top panel*) and cocaine intake (*bottom panel*), as a function of cocaine dose (saline, 0.01–0.3 mg/kg per injection) in monkeys self-administering cocaine under an FI5-min schedule. The shaded areas represent the mean (± 1 SEM) dose-response curves obtained before monkeys were trained under either an FR50 (*open squares*) or an IRT > 30-s (*filled squares*) schedule of cocaine (0.03 mg/kg per injection) presentation (n = 8). All other data points were determined after an FR or IRT history. Each point represents the mean of the last three sessions for each monkey (n = 4/group); *vertical lines* represent 1 SEM

on the first session following FR training in all subjects, and declined over the next five to ten sessions before becoming stable. For IRT-history monkeys, although the low-rate history appeared to have substantial effects on FI response rates during the first 25 sessions, overall rates were not significantly lower following training under an IRT > 30-s schedule (Pre- versus Post-IRT history; filled symbols versus shaded area: $P < 0.057$). Between-group comparisons revealed that the trend in responding across the 60 sessions following differential training was significantly different ($P < 0.0001$) for the FR-history group compared to the IRT-history group (open symbols versus filled symbols). However, the mean rate of responding for FR-history monkeys was approaching the mean rate of IRT-history monkeys by the end of the 60 sessions. Thus, the between-group difference in the mean response rates decreased over time ($P < 0.05$), suggesting that the effects of behavioral history were diminishing.

The mean cocaine intake under the FI5-min schedule of 0.03 mg/kg per injection cocaine, prior to an FR50 or an IRT > 30-s history, was 1.27 (± 0.01) mg/kg per session (Fig. 1, bottom panel, shaded area). Cocaine intake was significantly higher ($P < 0.001$) in FR-history monkeys compared to the pre-FR baseline (open symbols versus shaded area). In contrast, cocaine intake was significantly lower ($P < 0.005$) in IRT-history monkeys compared to the initial FI baseline (filled symbols versus shaded area). Thus, cocaine intake was also modified by different behavioral histories, such that an FR history increased, while an IRT history decreased cocaine self-administration.

The pattern of responding, as measured by quarter-life values, was 0.60 (± 0.02) prior to training under either an FR or an IRT schedule (data not shown). Between-group comparisons revealed that the changes in QL values across the 60 sessions were significantly different between FR- and IRT-history groups ($P < 0.05$). This was primarily due to the fact that QL values were lower in the FR group during the early session and increased across sessions, while the QL values, although variable, remained relatively constant throughout the 60 sessions following an IRT > 30-s history. On session 60, the QL values for the FR- and IRT-history groups were 0.64 (± 0.04) and 0.67 (± 0.06), respectively.

Effects of reinforcement schedule history on the cocaine dose-response curve

During the initial determination of the cocaine dose-response curve, response rates under the FI5-min schedule varied as a function of dose ($P < 0.05$) and were characterized as an inverted-U shape function of dose (Fig. 2, top panel, shaded area), with peak rates occurring at 0.03 mg/kg per injection. When the cocaine dose-response curve was redetermined after an FR or IRT history, the curve was shifted significantly to the right in both groups ($P < 0.01$). In addition, there was a significant interaction ($P < 0.01$) between cocaine dose and behavioral history group (open versus filled symbols, Fig. 2, top panel). This was apparent on the descending limb of the cocaine dose-response curve, where the dose that maintained peak rates was shifted 0.5 log-units to the right, from 0.03 to 0.1 mg/kg per injection, in the FR-history group.

Cocaine intake significantly increased ($P < 0.001$) in a dose-related manner, with peak intakes occurring when 0.3 mg/kg per injection was available (Fig. 2, bottom panel, shaded area). Cocaine intakes were significantly different after FR or IRT histories, compared to the initial dose-response curve (Pre- versus Post-history; $P < 0.05$), due primarily to the increases in intake at the highest cocaine dose (0.3 mg/kg per injection). The fact that differences in Pre- versus Post-history were observed only at the highest cocaine dose was probably due to the fact that most monkeys received the near maximum number of injections per session (46), except at the

highest dose. That is, the maximum intake when 0.3 mg/kg per injection was available is 13.8 mg/kg per session; a session intake never obtained in these monkeys. Thus, unlike the intakes observed when lower unit doses were available, there was not a ceiling effect at the 0.3 mg/kg per injection dose.

Pattern of responding was characteristic of FI performance in that the QL values for all monkeys, at all doses, were greater than 0.25 (data not shown). During the initial dose-response curve, QL values ranged from 0.35 (saline) to 0.50 (0.03 mg/kg per injection). When the cocaine dose-response curve was redetermined after FR or IRT histories, QL values were significantly higher ($P < 0.001$) in both groups, and ranged from 0.40 (0.3 mg/kg per injection) to 0.65 (0.01 mg/kg per injection).

Discussion

Using an A-B-A experimental design, the present study examined whether different reinforcement schedule histories could modify the rates and patterns of cocaine self-administration under an FI5-min schedule. After extended exposure to the FI schedule, one group of monkeys was trained under an FR50 schedule, which generated high rates of responding, while a second group was exposed to an IRT > 30-s schedule, which generated low rates of responding. When responding by all monkeys was again maintained under the FI5-min schedule, FR-history monkeys had significantly higher rates of cocaine-maintained FI responding for 60 consecutive sessions compared to IRT-history subjects. Furthermore, changes in response rates as a function of cocaine dose were significantly different between the groups. These results provide evidence that behavioral history can produce persistent and orderly changes in cocaine self-administration under an FI schedule.

It should be pointed out that the FI response rates of monkeys with FR or IRT histories began to converge by the end of the 60 sessions, suggesting that the influence of reinforcement schedule history was diminishing with continued exposure to the FI contingency. Weiner (1969) was the first to study the effects of FR or IRT histories on FI responding and reported that the effects of behavioral history were not transient in human subjects, tested over ten sessions. In animal studies using food-maintained responding, response rates for FR- and IRT-history groups began to converge with continued exposure to the FI contingency, although their rates remained different at the end of the experiment (Urbain et al. 1978; Nader and Thompson 1989). In the present study, response rates were not substantially different in the two groups by session 60, perhaps due to the fact that all of the monkeys were initially trained under the FI schedule, unlike the subjects in the earlier studies (Urbain et al. 1978; Nader and Thompson 1989), which were initially trained under the FR or IRT contingencies. However, it should be pointed out that there were still significant differences between FR- and IRT-history monkeys when the cocaine dose-response curve was redetermined after baseline rates had been maintained for at least 60 sessions. Thus, several months after the exposure to different reinforcement schedules, FR and IRT histories continued to modify previously established rates of cocaine self-administration under an FI schedule. From a treatment perspective, such an effect suggests that behavioral interventions may produce long-lasting changes in well-established drug-seeking behaviors.

In addition to response rate changes, cocaine intake (mg/kg per session) was significantly modified by FR and IRT histories. An FR history resulted in significant increases in daily cocaine intake, while the IRT history resulted in significant decreases in cocaine intake. This result was somewhat unexpected considering that others have reported no effect of behavioral history on reinforcement frequency (Urbain et al. 1978; Nader and Thompson 1989; Wanchisen et al. 1989). In fact, it has been speculated that because changes in response rates typically do not influence reinforcement frequency, behavior maintained under FI schedules is sensitive to historical variables (cf. Poling et al. 1980). Nevertheless, the fact that training under an IRT > 30-s schedule resulted in decreases in cocaine intake suggests that reductions in self-administration may be obtained through nonpharmacological interventions.

In the present study, four monkeys self-administered cocaine under an IRT > 30-s schedule at rates higher than those maintained by saline injections. This is the first study reporting drug self-administration under an *unsignaled* IRT > t schedule, and suggests that cocaine self-administration can be maintained under schedules in which long pauses between responses are reinforced. Meisch and colleagues (Lemaire and Meisch 1991; Meisch et al. 1992), using rhesus monkeys, have reported oral pentobarbital self-administration under signaled IRT schedules. In those studies, availability of pentobarbital or water were signaled by illumination of lights in the cubicle; responses occurring before illumination of the lights reset the IRT clock. Responding was under excellent stimulus control and subjects emitted few responses prior to illumination of the cubicle lights (cf. Lemaire and Meisch 1991). Herling (1981) studied codeine self-administration under a chain differential-reinforcement of other behavior (DRO) 30-s schedule, FR30 schedule in rhesus monkeys, and reported low rates of responding (approximately 0.6 responses/min) in the DRO link of that schedule. Taken together, these results provide unequivocal evidence that rates of drug self-administration can be reduced to low levels by environmental contingencies. The present results further show that such experience may produce long-lasting decreases in total drug intake when the schedule of drug availability is changed.

Under some circumstances, a particular reinforcement schedule history is necessary for the establishment of a drug as a reinforcer (cf. Nader et al. 1992). For example, the intermittent presentation of food can induce large volumes of oral drug intake that are necessary to establish the drug as a reinforcer (e.g. Falk and Tang 1989). In other cases, the availability of a nondrug reinforcer (Carroll et al. 1989) or individual differences in exploratory behavior (Piazza et al. 1989) have influenced the acquisition of drug self-administration. Results from the present

study indicate that the *maintenance* of cocaine self-administration can be influenced by prior experience. Importantly, the effects of behavioral history were apparent across a range of cocaine doses being self-administered. Future work will address the issue of whether certain histories can influence the effectiveness of treatment interventions to decrease the reinforcing potency and efficacy of cocaine.

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