The Influence of Behavioral and Pharmacological History on the Reinforcing Effects of Cocaine in Rhesus Monkeys

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INTRODUCTION

Animal models of drug self-administration have been shown to be valid predictors of human drug abuse (Griffiths et al. 1980; Johanson 1978; Johanson and Schuster 1981; Spealman and Goldberg 1978; Woolverton and Nader 1990). In drug self-administration studies, if responding leading to the presentation of the drug occurs at higher rates than vehicle-maintained responding, then the drug is said to function as a positive reinforcer and have abuse liability. The focus of the research described in this chapter will be to examine the interactions of several environmental and pharmacological variables with the reinforcing effects of cocaine in rhesus monkeys, with emphasis on the long-term effects of these experimental histories. One of the goals of this chapter will be to address technical or methodological issues regarding animal models of drug self-administration. To this end, published data as well as preliminary data will be presented. Although the scientific community urges the presentation of group data, most animal experiments in behavioral pharmacology are conducted on an individual-subject basis. Consequently, to highlight further the methodological issues regarding the influence of environmental and pharmacological variables in modifying cocaine self-administration, most of the data presented will be individual-subject data, rather than group data.

All of the research described in this review will be from studies involving the self-administration of cocaine, intravenously, by rhesus monkeys. Each monkey was surgically prepared with a chronic indwelling intravenous (IV) catheter located in a major vein (internal or external jugular, femoral or brachial vein). Monkeys were individually housed in sound-attenuating cubicles, with visual access to the lab and other monkeys. In all of the experiments, cocaine self-administration was maintained under a fixed-interval (FI) 5-min schedule. Under an FI 5-min schedule, the first response after 5-min results in the presentation of cocaine (IV). This schedule was chosen

because response rates under FI schedules can vary without substantially affecting reinforcement frequency. Zeiler (1977) has suggested that FI responding is sensitive to variables that are imposed without being explicitly prescribed by the schedule (which he called "indirect variables"). Urbain and colleagues (1978) have suggested that because of these indirect variables, responding maintained under FI schedules may be more malleable to operant history or to other determinants of drug effects.

BEHAVIORAL HISTORY AND COCAINE SELF-ADMINISTRATION

Introduction

It has been well established that the behavioral effects of drugs can depend on how behavior is controlled by the environment (Barrett and Katz 1981; Dews and Wenger 1977; Kelleher and Morse 1968). More recently, evidence has accumulated that the individual's behavioral history can have a significant and long-lasting influence on the behavioral effects of drugs. The study of the interactions of behavioral history with drug effects, including drug reinforcement, are important for several reasons. From a clinical perspective, if drugs are abused because of their behavioral effects, and these effects can be modified by prior experience, a better understanding of historical variables will be beneficial to understanding the etiology, maintenance, and treatment of drug abuse (Barrett et al. 1989). From a preclinical perspective, as McKearney (1979) stated:

> [E]xhaustive knowledge of how a particular class of consequent events controls behavior may be valuable information, but its generality is greatly limited if seemingly well-established relationships change completely when the subject's prior experience is different (p. 41).

In treatment settings, drug abusers appear sensitive to contingencies of reinforcement and to changes in schedules of drug availability (Budney et al. 1991; Crowley 1984; Higgins et al. 1993; Stitzer et al. 1979*a*, 1979*b*, 1980) and, consequently, identification in animals of conditions under which drug-seeking behavior could be reduced for extended periods might have direct practical applications. There is evidence with human and nonhuman subjects that prior training under certain schedules of reinforcement can produce long-lasting changes in behavior maintained by nondrug reinforcers (Nader and Thompson

1987, 1989; Urbain et al. 1978; Weiner 1964, 1969). These experiments all assessed the influence of prior experience on behavior maintained under FI schedules, because responding under this schedule is a sensitive baseline from which the effects of historical variables can be assessed (Poling et al. 1980).

Weiner (1964, 1969, 1981) showed that reinforcement schedule history could influence the behavior of human subjects responding under FI schedules of reinforcement. In one study (Weiner 1969), responding by one group of subjects was first maintained under a fixed-ratio (FR) schedule, while subjects in a second group responded under an interresponse-times > t-sec (IRT) schedule. For both groups, the reinforcer was point accumulations. Responding by both groups was subsequently maintained under an FI schedule. Weiner (1969) reported that subjects with an FR history responded at higher rates, compared to subjects with an IRT history; this effect was still evident after 40 sessions. A similar effect of reinforcement schedule history was observed when responding was maintained under a variable-interval (VI) schedule (Weiner 1965). Taken together, these results showed that performance of humans could be systematically changed by a history of responding under certain schedules of reinforcement.

Urbain and colleagues (1978) extended the Weiner results by showing that the rate-altering effects of *d*-amphetamine in rats were influenced by behavioral history. These investigators found that rats initially trained under an FR schedule had higher rates of responding under an FI schedule compared to rats initially trained under an IRT > t-sec schedule. Pretreatment with *d*-amphetamine decreased high rates of responding by FR-history rats and increased low rates of responding by IRT-history subjects. The effects of reinforcement schedule history on FI response rates have been replicated in pigeons (Nader and Thompson 1989), providing the third species to show such orderly effects. In addition, the behavioral effects of methadone were different depending on the reinforcement schedule history of the subjects, suggesting generality of the influence of behavioral history across several drug classes. (See Nader et al. 1992 for more detailed evaluation of these results.)

Effects of Different Cocaine-Reinforcement Histories on Cocaine-Maintained FI Responding

Although it is clear that behavioral history can have long-lasting influences on current behavior, as well as modifying the rate-altering effects of drugs, very little research has been conducted using drug

self-administration (Ator and Griffiths 1993; Schenk et al. 1987; Spealman 1979). Two recent studies have found that FR or IRT reinforcement schedule histories could produce significant and persistent changes in rates of cocaine self-administration in rhesus monkeys (Nader and Bowen 1995; Nader and Reboussin 1994). The primary goal of the first experiment (Nader and Reboussin 1994), was to utilize an A-B-A design to determine whether interpolated training under FR or IRT schedules of cocaine self-administration could modify previously established FI rates of cocaine-maintained responding. It should be pointed out that in all of the studies reviewed previously, the subjects were initially trained under an FR or an IRT schedule, prior to exposure to the FI schedule. An important advantage to using an A-B-A design, in which subjects are initially trained under an FI schedule, is that it allows for the assessment of the effects of behavioral history in each animal (i.e., a within-subjects effect), in addition to the between-groups assessment. This point regarding A-B-A designs can be thought of in two ways: (1) from a preclinical perspective, because of the expense of purchasing and training new animals, it is common to use subjects in several experiments without knowledge of the long-lasting influence of previous reinforcement schedule histories; and (2) from a clinical perspective, the individual comes to the clinic with a self-administration history and the question is: Can behavioral interventions be used to modify the rates of drug-seeking behavior for long periods of time?

Methods

In this experiment, eight experimentally naive rhesus monkeys were initially trained to respond on the left lever under an FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation and cocaine dose-response curves were determined (condition "A"). After approximately 100 sessions under the FI schedule, the monkeys were ranked according to response rates, and pairs of monkeys were randomly assigned to one of two groups (condition "B"). Four subjects were trained to respond on the right lever under an FR 50 schedule, while the other four monkeys were trained under an IRT > 30-sec schedule of 0.03 mg/kg/inj cocaine presentation. Timeouts (TOs) of 2 minutes and 5 minutes were scheduled after each cocaine injection under the FR or IRT schedule, respectively. (See Nader and Reboussin 1994 for more details.) This counterbalanced assignment precluded the possibility that monkeys with the highest FI rates would be assigned to the FR group and that monkeys with the lowest FI rates would be assigned to the IRT group. After 65 sessions under these

conditions, responding on the left lever was again maintained under an FI 5-min schedule of 0.03 mg/kg/inj cocaine (condition "A"). In order to assess whether the effects of behavioral history were transient, the dose of cocaine was not changed for at least 60 consecutive sessions, after which the cocaine dose-response curves were redetermined. In this way, it could be determined whether previously established stable rates of drug-maintained responding under the FI schedule would be increased or decreased by different behavioral histories.

Results

The baseline rate of responding (Å1 SEM) under the FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation, prior to different reinforcement schedule histories, was 4.02 (Å0.33) 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/inj. In condition "B," the mean (Å1 SEM) rate of responding maintained by cocaine 0.03 mg/kg/inj was significantly higher in the four monkeys responding under the FR 50 schedule (66.80Å5.6 responses/min) compared to rates maintained under the IRT > 30-sec schedule (2.62Å0.2 responses/min).

The major finding from this study was that FR-history monkeys had significantly higher rates of responding under the FI 5-min schedule compared to IRT-history subjects (Nader and Reboussin 1994). Within-subjects data comparing the effects of FR- and IRT-histories on FI response rates are shown in figure 1 for two animals. For monkey 9123, the mean rate of cocaine-maintained responding under the FR 50 schedule was 45.12 responses/min, while the mean rate of responding by monkey 9120 under the IRT > 30-sec schedule of 0.03 mg/kg/inj cocaine presentation was 0.76 responses/min (figure 1, filled symbols). After 65 sessions under the FR or IRT schedule, responding was again maintained under the FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation. Following an FR history, FI response rates by 9123 were significantly higher than pre-FR history baseline rates, for 60 consecutive sessions (figure 1; open symbols versus shaded area). In contrast, FI response rates by 9120 were significantly lower than pre-IRT history baseline rates, for 60 consecutive sessions.

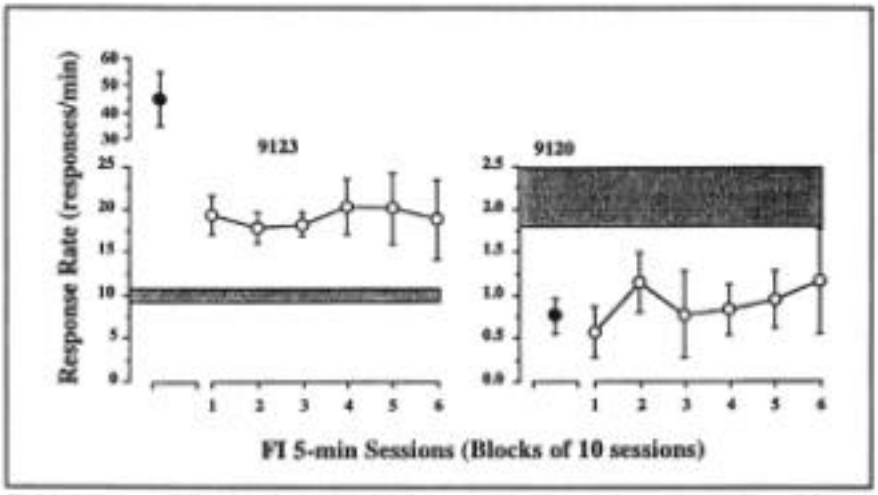

FIGURE 1. *Effects of an FR 50 history (left panel) or an IRT > 30-sec history (right panel) on rates of cocaine-maintained responding under an FI 5-min schedule. For all data, the dose of cocaine was 0.03 mg/kg/inj. Each point represents the mean response rates for 10 sessions; vertical lines represent 1 SD. The filled symbols represent the mean rates under the FR 50 or IRT > 30-sec schedule. The shaded area represents the "prehistory" mean rate under the FI 5-min schedule (±1 SD). Notice that the scales on the ordinate are different for each monkey.*

SOURCE: Data from experiment by Nader and Reboussin (1994).

These results replicate earlier findings in rats, pigeons, and humans and extend those results to drug-maintained responding and a within-subjects analysis. An interesting question that is generated from this study is how the initial FI history influenced rates of cocaine-maintained responding under an FR 50 schedule. In the present study, there was no correlation between baseline FI rates (i.e., pre-FR history) and response rates maintained under the FR 50 schedule. In fact, the highest mean FR 50 rate of responding (125 responses/min) was generated by a monkey with one of the lowest FI baseline rates (approximately 2.0 responses/min).

It should be pointed out that this is the first study in which cocaine self-administration (by any route) was maintained under an unsignaled IRT > t-sec schedule. Cumulative records depicting the changes in response rate and pattern of cocaine self-administration (0.03 mg/kg/inj) that occurred as a function of training sessions under the IRT > 30-sec schedule for monkey 9122 are shown in figure 2.

During the early sessions, responding was characterized by fairly high rates followed by several cocaine injections within a short period of time. As shown in the cumulative record, the majority of cocaine presentations occurred during the last 30 minutes of the session (figure 2, top panel). By session 65, responding by monkey 9122 had come under schedule control and this animal made 93 responses to receive 30 cocaine injections under an IRT > 30-sec schedule (figure 2, bottom panel). In an effort to attenuate the rate-increasing effects of cocaine, a 5-min time out (TO) followed each injection. However, in preliminary examination it appears that TO values as low as 2 minutes do not change rates of cocaine-maintained responding under an IRT > 30-sec schedule. It has not yet been determined what the effects of removing the TO would be on IRT > 30-sec responding, once this schedule is controlling response rates.

Regarding performance under the IRT schedule, the mean rate of responding under the IRT > 30-sec schedule was not significantly lower than the "prehistory" rates maintained under the FI 5-min schedule (4.02Å0.33 versus 2.62Å0.20 responses/min). When these experiments were designed, it was hypothesized that the most important contribution of the IRT history would be the number of reinforced IRTs. To meet this end, 5-min TOs were scheduled after each injection and sessions ended only after the monkeys received 30 injections. Thus, irrespective of whether it took the monkeys 2.5 hours or 8 hours to complete the session, it was certain that at the end of the session each monkey had 30 reinforced IRTs that were greater than 30 seconds. These contin-gencies probably resulted in "higher" rates of responding than would be expected, since response rates did not influence total session cocaine intake. Despite these procedural caveats, the IRT history still resulted in significant reductions in rates of responding under the FI 5-min schedule (Nader and Reboussin 1994).

One of the purposes of this chapter is to describe methodological issues involved in studying the influence of environmental variables on cocaine self-administration. To this end, it would be beneficial to describe the performance of one of the "outlier" IRT-history monkeys. As compared to the pre-IRT baseline, FI response rates by monkey 9127 were significantly higher for 60 consecutive sessions following exposure to an IRT > 30-sec schedule (figure 3, compare shaded area and open symbols), despite the fact that response rates under the IRT contingency (filled symbol) were not different from the prehistory baseline FI rate

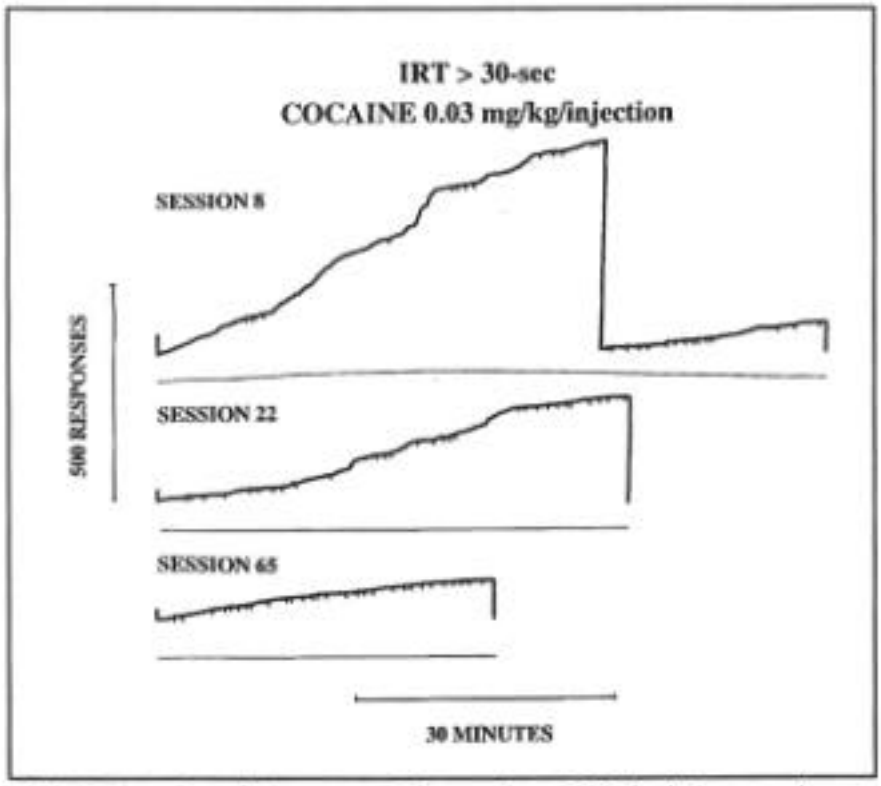

FIGURE 2. *Cumulative records for monkey 9122 depicting cocaine (0.03 mg/kg/inj) self-administration under an IRT > 30-sec schedule during sessions 8 (top panel), 22 (middle panel), and 65 (bottom panel). Deflections of the stepper indicate cocaine injections. During the 5-min TO following each injection, the cumulative recorder was not running.*

(figure 3). Clearly, the IRT-history had a significant effect on response rates under the FI schedule. However, the effects in monkey 9127 were in the opposite direction as was seen in the other three monkeys.

A question that comes up immediately is what aspect of the IRT history resulted in decreases in cocaine self-administration in monkey 9120 but increases in cocaine-maintained response rates in monkey 9127? (See figures 1 and 3.) One possibility is that the pattern of responding under the IRT > 30-sec schedule was different in monkey 9127 and this response pattern subsequently influenced FI response rates. Figure 4 shows the mean IRT distributions for monkeys 9120 and 9127 at three

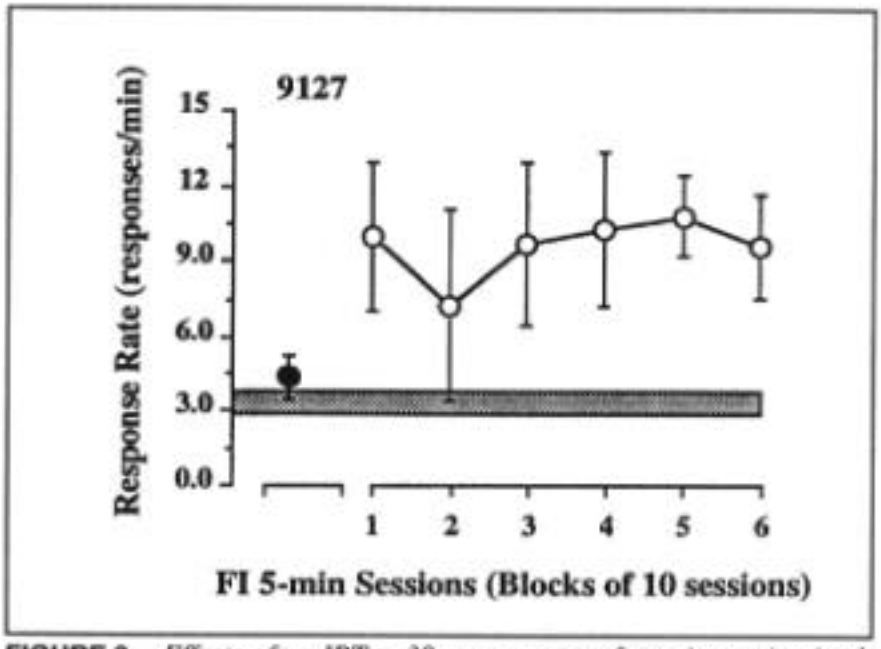

FIGURE 3. *Effects of an IRT > 30-sec on rates of cocaine-maintained responding under an FI 5-min schedule, in monkey 9127. Each point represents the mean response rates for 10 sessions; vertical lines represent 1 SD. The filled symbols represent the mean rates under the IRT > 30-sec schedule. The shaded area represents the "prehistory" mean rate under the FI 5-min schedule (±1 SD).*

SOURCE: Data from experiment by Nader and Reboussin (1994).

different periods during IRT > 30-sec training (sessions 1 through 5, 30 through 35, and 60 through 65). For monkey 9120, changes in the pattern of responding, as represented by the IRT distribution, across the 65 training sessions, indicated that there were substantial decreases in the frequency of short IRTs (< 5 sec) and an increase in the frequency of long IRTs (> 30 sec) with continued exposure to the IRT > 30-sec contingency. In contrast, for monkey 9127 the pattern of responding under the IRT schedule was very different from that observed in the other three monkeys. During the first five sessions under the IRT > 30-sec schedule, the modal IRTs were at 11 to 15 seconds (approximately 18 percent of total responses). By sessions 61 to 65, nearly 55 percent of the responses were spaced between 1 and 5 seconds. Thus, for this monkey, continued training under the IRT > 30-sec schedule resulted in leftward shifts in the IRT distribution (figure 4).

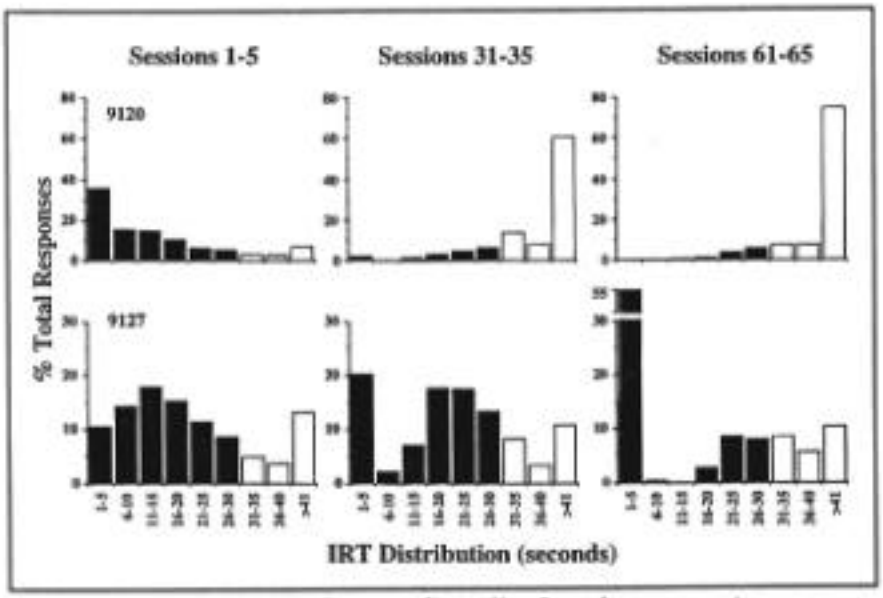

FIGURE 4. *Frequency of responding (% of total responses) as a function of interresponse time (IRT) for monkeys 9121 (top panels) and 9127 (bottom panels), when cocaine (0.03 mg/kg/inj) self-administration was maintained under an IRT > 30-sec schedule. Each histogram represents the mean of five sessions, as determined at three different periods of training. Open bars represent reinforced IRTs.*

SOURCE: Data from experiment by Nader and Reboussin (1994).

Monkey 9127 was retrained under the IRT > t-sec contingency in an effort to decrease FI rates. Initially, the IRT value was 30 seconds for 24 sessions and was increased to 40 seconds for 27 additional sessions. Response rates under the IRT > 40-sec schedule were significantly lower than rates under the FI 5-min schedule (see table 1) and the IRT distribution was shifted to the right relative to the pattern of responding observed under the IRT > 30-sec schedule. By the end of the IRT > 40-sec training, the frequency of short IRTs decreased from 55 percent to 41 percent, while the frequency of IRTs greater than 30 seconds increased to nearly 30 percent. Following exposure to an IRT > 40-sec schedule, response rates under the FI 5-min schedule remained significantly lower than previous FI rates by 41 to 63 percent (table 1). Thus, training under a longer IRT contingency resulted in long-lasting decreases in response rates under an FI 5-min schedule of cocaine presentation.

TABLE 1. *Effects of IRT > 40-sec training on rates of responding (responses/min) for 30 consecutive sessions under an FI 5-min schedule of 0.03 mg/kg/inj cocaine presentation in monkey 9127*.*

Posthistory** FI	IRT > 40	FI Block 1	FI Block 2	FI Block 3
8.16 (1.8)	3.28 (1.0)§	3.58 (0.7)§	7.23 (1.1)	4.66 (0.8)§

KEY: * = Data are expressed as the mean response rate (+1 SD) for 10 sessions; ** = Represents data from the last 10 sessions prior to retraining under IRT > 30- and 40-sec schedules; § = $p < 0.0001$ compared to post-history FI rates.

In summary, results from this experiment indicate that self-administration histories involving FR or IRT schedules can substantially modify rates of cocaine-maintained responding under FI schedules. These differences in FI response rates were still apparent after 60 consecutive sessions. In addition, cocaine dose-response curves were determined prior to FR- or IRT-histories and again after at least 60 sessions under the FI schedule ("post-history"). No pre- versus post-history differences in the cocaine dose-response curve were found in the IRT-history group. In contrast, the FR history resulted in significant rightward shifts in the cocaine dose-response curve, indicating that the effects of a high-rate history generalized across cocaine doses. (See Nader and Reboussin 1994 for more details.)

Effects of Different Food-Reinforcement Histories on Cocaine-Maintained FI Responding

The aspects of an organism's experimental history that accounts for changes in behavior or in the behavioral effects of drugs has not been clearly elucidated. For example, in studies that have found differences in response rates under FI schedules following FR or IRT histories, the behavior was maintained by the same reinforcer under all conditions. An important issue in the present context is whether a history of responding maintained by a nondrug reinforcer, under a particular schedule of reinforcement, can influence the rate of cocaine-maintained responding. In an effort to extend the earlier findings regarding cocaine self-administration and reinforcement schedule

history (Nader and Reboussin 1994), the effects of a behavioral history of low-rate or high-rate responding maintained by food presentation, on the acquisition and maintenance of cocaine-maintained responding under an FI schedule, were examined (Nader and Bowen 1995).

Methods

Eight experimentally naive rhesus monkeys were initially trained to respond on the right lever under either an FR 50 or an IRT > 30-sec schedule of food reinforcement (1 g banana-flavored pellets). After 65 sessions of food-maintained responding, monkeys were surgically prepared with indwelling IV catheters, and 0.03 mg/kg/inj cocaine was contingent on left lever responding under an FI 5-min schedule. As in the earlier study, in an effort to examine whether the influence of behavioral history was transient, the baseline dose of cocaine (0.03 mg/kg/inj) was available under the FI 5-min schedule for at least 60 consecutive sessions, after which a cocaine dose-response curve was determined. The FR 50 schedule generated high rates of food-maintained responding (90.12Å6.2 responses/min), while response rates under the IRT > 30-sec schedule were low (1.87Å0.1 responses/min). These rates were similar to the rates maintained by cocaine presentation in the Nader and Reboussin (1994) study.

Results

The major finding from this study was that across the first 60 sessions, response rates under the FI 5-min schedule were significantly higher for FR-history monkeys compared to IRT-history subjects. In addition, the differences between the groups increased as a function of number of cocaine self-administration sessions, suggesting that the effects of a food-reinforcement history were persistent, not transient (Nader and Bowen 1995). These results demonstrate that behavioral histories involving nondrug reinforcers can significantly influence rates of cocaine-maintained responding under FI schedules.

For the FR-history group, response rates were extremely high on the first session of cocaine self-administration and declined rapidly over the next three to five sessions. Cumulative records from the first five sessions under the FI 5-min schedule of cocaine (0.03 mg/kg/inj) presentation, after an FR history of food-maintained responding, are shown in figure 5. It is important to remember that these monkeys were cocaine naive prior to the first session of cocaine availability and that there was no training under the FI 5-min schedule. On the

first session of cocaine availability, responding by monkey 5565 persisted at high rates for the entire 4-hour session. Across the next three sessions responding declined by this monkey, while reinforcement frequency remained near maximum. By session 5, response rates began to increase, relative to session 4; for most FR-history subjects, these increases in FI 5-min response rates continued for the remaining 55 sessions of 0.03 mg/kg/inj cocaine availability. These records demonstrate the rapid change in response rates and patterns when environmental contingencies are modified.

Because there was no explicit training to self-administer cocaine under the FI 5-min schedule, it is possible to compare the rate of acquisition of cocaine reinforcement in monkeys with different histories of food reinforcement (for more detailed discussions of drug acquisition see Carroll, this volume; Carroll and Lac 1993; Carroll et al. 1989; Schenk, this volume). Response rates by FR-history monkeys went from 90.1 responses/min (average food-maintained rate) to 0.6 responses/min in the first four cocaine sessions, and then began to increase across the remaining 56 sessions of cocaine availability (see figure 5). Despite the fact that food and cocaine availability were scheduled on different levers, it is possible that the rapid decline in rate was due to extinction of food-reinforced responding and the gradual increase represented acquisition of cocaine self-administration.

One of the difficulties in interpreting the data in terms of acquisition of cocaine reinforcement is how to differentiate “acquisition” from extinction of food-reinforced responding. In an effort to evaluate the data with regard to acquisition, three assumptions were made (see Nader and Bowen 1995): (1) responding during the first five sessions under the FI 5-min schedule could not be used to measure cocaine acquisition because performance was confounded by extinction of food-reinforced responding and by the direct effects of cocaine on extinction; (2) for each monkey, performance after 60 sessions was an indication of stability under the FI

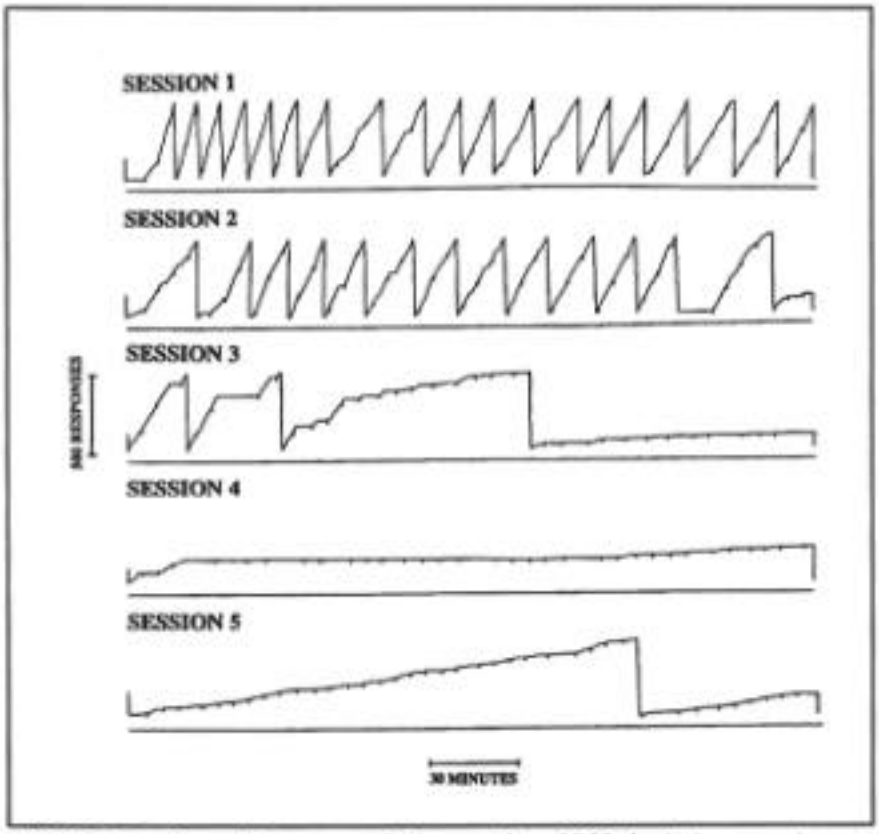

FIGURE 5. *Cumulative records for monkey 5565 depicting cocaine (0.03 mg/kg/inj) self-administration under an FI 5-min schedule during the first five sessions of cocaine availability. Prior to session 1, this monkey was cocaine naive, and responding had been maintained by food presentation under an FR 50 schedule for 65 sessions. There was no training under the FI 5-min schedule. Deflections of the stepper indicate cocaine injections.*

SOURCE: Nader and Bowen (1995).

schedule; and (3) acquisition was complete when performance occurred at > 80 percent of the mean of sessions 56 through 60. Examination of both response rate and cocaine intake data revealed that IRT-history monkeys acquired cocaine self-administration more rapidly than FR-history monkeys. That is, fewer sessions were necessary to achieve performance > 80 percent of stability for IRT-history subjects compared to FR-history monkeys. These results suggest that an FR history disrupted acquisition of cocaine self-administration under an FI schedule, irrespective of how self-administration was defined (i.e., rate or intake). It is important to

note that after several months under the FI schedule, the FR-history group had higher rates of responding compared to response rates observed in IRT-history monkeys. Thus, with continued exposure, a reinforcement schedule history that retards acquisition can result in the maintenance of high rates of cocaine-maintained responding.

As mentioned earlier, this is the first study investigating the effects of reinforcement schedule history on FI response rates that has utilized different reinforcers in the "history" and FI phases of the experiment. Interestingly, when comparisons are made between the two experiments described in this section, experimentally naive monkeys initially trained to self-administer cocaine under an FI 5-min schedule, on average, had higher baseline rates of responding compared to monkeys initially exposed to an FR 50 schedule of food reinforcement; the lowest rates of responding observed in both studies were generated by monkeys with an IRT > 30-sec history of food reinforcement. These results further highlight the profound effects of behavioral history on rates of cocaine-maintained responding. (See Nader and Bowen 1995 for more details.)

PUNISHMENT CONTINGENCIES AND COCAINE SELF-ADMINISTRATION

Introduction

When punishment contingencies are utilized, it is assumed that the behavior will remain low even when the contingencies are removed, i.e., the behavioral history will result in long-lasting decreases in behavior. Operationally defined, punishment is the reduction in the probability of a response following either the presentation ("positive" punishment) or the removal ("negative" punishment) of a stimulus (see Azrin and Holz 1966). Johanson and Fischman (1989) have suggested that resistance to the effects of punishment can be used to measure the strength of a reinforcer. If this hypothesis is correct, procedures that can be shown to enhance the effects of punishment on cocaine self-administration may do so by reducing the reinforcing efficacy of cocaine. One of the first studies designed to examine the effects of positive punishment on cocaine self-administration was conducted by Grove and Schuster (1974). In that study, monkeys self-administered cocaine under a multiple FR 1 schedule in which responding was punished in one of the two components. Response-contingent shock decreased cocaine self-administration in the punished component, in an intensity-dependent manner. However, the investigators reported increased rates of cocaine self-

administration during the unpunished component for some monkeys (Grove and Schuster 1974). An interesting possibility proposed by Grove and Schuster (1974), but a hypothesis that has remained untested, is that the increases in response rates and cocaine intake in the unpunished component were related to the phenomena of behavioral contrast (see Reynolds 1961*a*). From a treatment perspective it would be clearly beneficial to identify procedures in which cocaine self-administration remains reduced even when the contingencies that first led to decreased drug use have changed.

Using a discrete-trials choice procedure in which rhesus monkeys were given a choice between two alternatives of IV cocaine, Johanson (1977) reported that if the doses were the same, response-contingent shock would decrease the frequency of choice for that alternative. However, the effects of shock could be attenuated by increasing the cocaine dose administered concurrently with the punishing stimulus. In another study from that laboratory, Bergman and Johanson (1981) reported that intermediate shock intensities only transiently decreased cocaine self-administration; complete recovery from the suppressant effects of the punisher occurred within four sessions. These results suggest that positive punishment may not be an effective method for maintaining decreases in cocaine self-administration.

The effects of negative punishment on cocaine self-administration, by contrast, have not been examined. While both positive and negative punishers can suppress responding equally, they are considered distinct processes (Branch et al. 1977). For example, McMillan (1967) found that response-contingent TO, an example of negative punishment, typically suppressed responding throughout the session, whereas the effects of response-contingent shock dissipated within a session. In addition, negative punishment is more analogous to the drug treatment programs that remove individuals from environments in which drugs are available. There is some preliminary data suggesting that negative punishment can successfully decrease cocaine use in humans (Crowley 1984). The experiments described below are preliminary studies designed to systematically evaluate the effects of negative punishment on cocaine self-administration. These data highlight important methodological considerations involved when studying the effects of punishment contingencies on drug self-administration.

Methods

Rhesus monkeys were trained to respond under a two-component multiple FI 5-min schedule of cocaine presentation. Each component lasted 30 minutes and cycled twice per session. Through all phases of the experiment, the cocaine dose available was the same in each component. Initially, responding was maintained by 0.03 mg/kg/inj cocaine. When responding was stable, a cocaine dose-response curve was determined (saline, 0.01 to 0.3 mg/kg/inj). Each dose was available for at least five sessions and there was a return to baseline (0.03 mg/kg/inj) for at least five sessions between test doses.

After completion of the cocaine dose-response curve, the schedule in the second component was changed to a conjoint FI 5-min cocaine, VI 30-sec TO schedule. In this component, the first response after 5 minutes still resulted in cocaine presentation but, on average, the first response after 30 seconds resulted in a TO. The TO value was initially 10 seconds. During the TO all stimuli within the chamber were extinguished and responding had no consequence (although it was recorded). The FI clock continued to run during the TO. Thus, cocaine was still available following the first response after 5 minutes, irrespective of how many response-contingent TOs were delivered. This is an important methodological consideration because if the FI clock stopped during the TO, it could be argued that reductions in cocaine-maintained responding were due to changes in the FI schedule, not to the negative punishment contingency. When responding in both components was stable, one of two manipulations was made: either the cocaine dose was changed or a different TO value was studied (0, 10, 30, or 60 seconds).

Results

Under the unpunished multiple FI 5-min, FI 5-min schedule, monkeys typically received the maximum number of cocaine injections per session (20) except when the highest cocaine dose (0.3 mg/kg/inj) was available. There were differences in rates of responding in both components, but no systematic differences between subjects. As described earlier, there were several considerations to be made from these studies. First, because there are currently no data on the effects of negative punishment procedures on drug self-administration in animals, the ability of response-contingent TO to suppress cocaine self-administration was examined. A second purpose of these studies was to examine how unpunished cocaine self-administration would be modified under the multiple schedule of reinforcement in which responding in the other component was punished. As previously mentioned, Grove and Schuster (1974) reported that response-

contingent shock presentation suppressed responding in the punished component, but increased self-administration in the unpunished component. These investigators also reported that rates of self-administration increased above prepunishment baselines when the positive punisher was removed. Thus, a third consideration was to examine whether similar phenomena occurred when the negative punishment contingency was removed. In addition, complete cocaine dose-response curves were determined in order to assess whether the effects of negative punishment could be attenuated by higher doses of cocaine, as was reported with positive punishment (Johanson 1977).

Data from one monkey (5514) will be used to describe the effects of negative punishment on cocaine self-administration (figure 6). When the TO value was 0 seconds (i.e., the schedule was a multiple FI 5-min, FI 5-min), cocaine-maintained responding was characterized as an inverted-U shaped function of dose, in both components (figure 6, open symbols). It is important to note that responding was consistently lower in the "punished" components (i.e., components 2 and 4), even when the TO value was 0 seconds (figure 6). This result may suggest that a history of negative punishment contingencies can produce significant and long-lasting reductions in cocaine self-administration.

The effects of response-contingent 10-sec TOs on unpunished and punished responding are also shown in figure 6 (closed symbols). When responding was maintained by 0.03 mg/kg/inj cocaine and the schedule in the second component was changed to a conjoint FI 5-min cocaine, VI 30-sec TO schedule, response rates decreased to approximately 45 percent of unpunished baseline (figure 6, right panel, compare open and closed symbols). It can be seen that the suppressant effects of response-contingent 10-sec TO could not be overcome by increases in cocaine dose. That is, the negative punishment contingency resulted in a downward shift in the cocaine dose-response curve (figure 6). These results demonstrate that negative punishment contingencies can decrease rates of cocaine-maintained responding.

With regard to unpunished responding (i.e., components 1 and 3), there were no changes in the cocaine dose-response curve as a consequence of

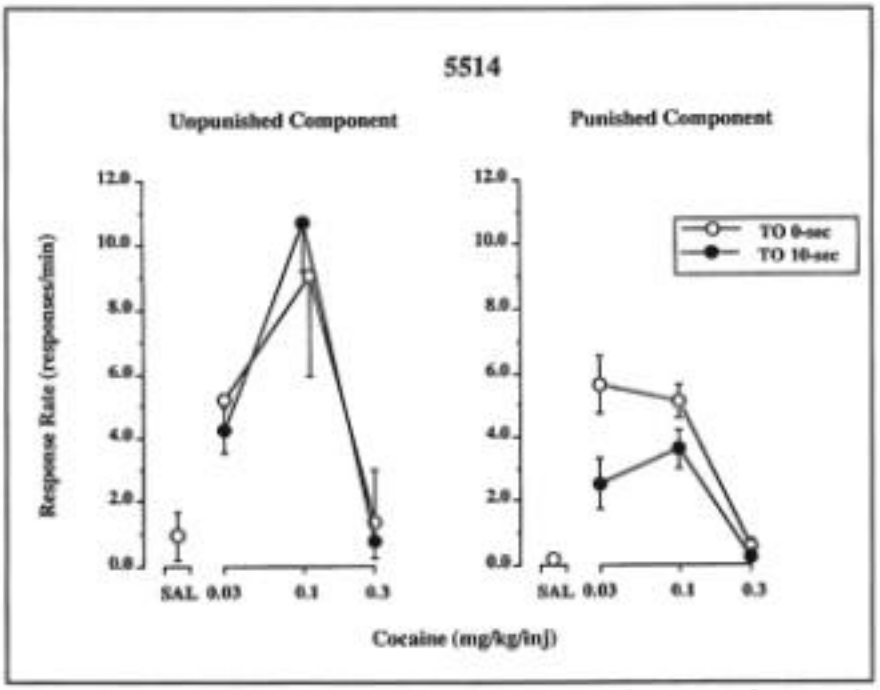

FIGURE 6. *The effects of negative punishment and cocaine dose on the rate of responding in monkey 5514 self-administering cocaine under a multiple FI 5-min, conjoint FI 5-min, VI 30-sec schedule. Data represent the mean of the last 3 sessions of a dose and condition.*

punishing responding in the other components (figure 6, left panel, compare open and closed symbols). Thus, unlike what was observed with positive punishment, no behavioral contrast was evident when responding was suppressed by negative punishment contingencies. Of course there are several differences between this experiment and the Grove and Schuster (1974) study that may account for the qualitative differences in the unpunished component. For example, the schedule of reinforcement was FR 1 in the latter study and FI 5-min in the present study. Such schedule differences, as well as baseline rates of responding, may have accounted for the different results. In addition, it should be pointed out that there was also no evidence that response rates increased above prepunishment baselines when the schedule was changed from conjoint FI 5-min, VI 30-sec to a simple FI 5-min schedule. Although these data are preliminary, the results suggest that negative punishment contingencies significantly decrease rates of cocaine self-administration. Clearly, more research is necessary to systematically compare the effects of positive and negative punishment on drug self-administration.

Another characteristic of positive punishment contingencies, described earlier, is the observation by Bergman and Johanson (1981) of between-session tolerance to the rate-suppressing effects of electric shock presentation. At this point, no evidence of attenuation in the suppressant effects of the negative punishment contingencies on cocaine-maintained responding has been observed. In addition, in preliminary data collected, there is an orderly decrease in response rates as a function of TO length. These results parallel the results from Grove and Schuster (1974) in which they reported an intensity-dependent decrease in rates of cocaine self-administration. In one monkey tested at a TO value of 60 seconds, punished responding was decreased by approximately 70 percent of baseline. Interestingly, there was a reduction in unpunished response rates of approximately 50 percent. No such "response induction" (see Reynolds 1961*b*) was observed with positive punishment contingencies and cocaine self-administration (Grove and Schuster 1974). Again, this may be due to different experimental protocols. For example, it is well known that at high enough shock intensities responding will be completely suppressed and no between-session tolerance will develop (Bergman and Johanson 1981). However, when those shock intensities are studied in the context of discrete-trials choice (Johanson 1977), monkeys will still self-administer the dose available as the unpunished alternative. Thus, response induction was not seen with positive punishment when studied under a discrete-trials choice procedure.

As can be seen, there is still a great deal to be learned about the efficacy of punishment contingencies in decreasing drug self-administration. From a basic science viewpoint, direct comparisons of positive and negative punishment procedures on drug self-administration have not been conducted. From a clinical viewpoint, negative punishment contingencies are already operating in the drug abuser's environment and a better understanding of how these contingencies mediate drug use would be of obvious value.

PHARMACOLOGICAL HISTORY

Introduction

This chapter has attempted to highlight some important methodological issues regarding environmental modulation of the reinforcing effects of cocaine in monkeys, with emphasis on the long-term effects of these behavioral histories. Before closing, the role of pharmacological history in mediating the reinforcing effects of drugs will be briefly discussed. This issue is especially important in primate research because it is common to use the same animals in several experiments. For the most part, this is an advantage of using primates: within-subject comparisons of the effects of several independent variables, across years of study, can be made. However, it is important to keep in mind that experimental (including pharmacological) history can have long-lasting effects on behavior, and important information can be gained from studying history, rather than simply controlling for it.

One of the most frequently used protocols in drug self-administration research is the substitution procedure. In this procedure, animals are first trained to self-administer a drug with known abuse liability and then test compounds are substituted for that drug. If response-contingent presentation of the test drug maintains rates that are higher than rates maintained by drug vehicle, then the test drug is functioning as a reinforcer and has abuse liability. When cocaine is the baseline drug, experiments utilizing a substitution procedure have shown that compounds that bind to dopamine D_1 (Self and Stein 1992; Weed et al. 1993), D_2 (Woolverton et al. 1984; Yokel and Wise 1978), and D_3 receptors (Caine and Koob 1993; Nader and Mach, in press) can function as reinforcers, maintaining rates higher than those maintained by vehicle presentation. It is important to remember that when the presentation of an agonist maintains high rates of responding, the results only suggest the possibility that a receptor subtype is involved in the reinforcing effects of the baseline drug (in this case, cocaine). However, by comparing the reinforcing effects of a test compound in substitution procedures versus acquisition in drug-naive animals, an indication of the importance of pharmacological history, as well as the neuropharmacological changes that occur as a consequence of long-term drug exposure, can be assessed (Nader and Mach, in press).

Methods

Substitution Procedure. Three cocaine-experienced monkeys had been self-administering cocaine for 2 to 3 years prior to the start of this study. Responding was maintained under an FI 5-min schedule of IV cocaine (0.03 mg/kg/inj) presentation, during daily 4-hour sessions. When responding was stable, a cocaine dose-response curve was determined, as described earlier. After completion of the cocaine dose-response curve, various doses of the dopamine D_3/D_2 agonist 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT) were substituted for the baseline dose of cocaine. Each dose of 7-OH-DPAT was available for at least three consecutive sessions; there was a return to cocaine (0.03 mg/kg/inj) between 7-OH-DPAT doses.

Acquisition in Cocaine-Naive Monkeys. After the reinforcing dose range of 7-OH-DPAT was established in three cocaine-experienced animals, 7-OH-DPAT self-administration was evaluated in six cocaine-naive monkeys under two different protocols. For three cocaine-naive monkeys, various doses of 7-OH-DPAT were available under a low FI schedule (initially an FI 15-sec schedule), during daily 4-hour sessions. The lever was frequently baited with sucrose pellets to facilitate the association between a response, the illumination of the lever lights, and the delivery of an IV injection of 7-OH-DPAT. After approximately 14 sessions, 0.03 mg/kg/inj cocaine was made available for self-administration. Three additional cocaine-naive monkeys were first trained to respond under an FI 5-min schedule of food presentation and then 7-OH-DPAT (0.003 to 0.03 mg/kg/inj) was substituted for food. After completion of the 7-OH-DPAT dose-response curve, cocaine was studied.

Results

In cocaine-experienced monkeys, when substituted for cocaine, 7-OH-DPAT functioned as a reinforcer in all three monkeys. Response rates varied as a function of dose and were characterized as inverted U-shaped; intake increased in a dose-dependent manner (Nader and Mach, in press). These results are in agreement with previously published results using rats (Caine and Koob 1993) and provide a direct comparison of the reinforcing potency of the two compounds. 7-OH-DPAT was 0.5 to 1.0 log units more potent than cocaine, with peak rates maintained at 0.003 or 0.01 mg/kg/inj 7-OH-DPAT.

In all six cocaine-naive monkeys, 7-OH-DPAT-maintained responding occurred at very low rates; an effect that was opposite to

results observed in the substitution study. For monkeys in which 7-OH-DPAT was available under low FI schedules, little or no responding could be maintained in any of the monkeys. After 10 to 13 sessions of 7-OH-DPAT availability, cocaine was made available to these animals and response rates increased within one to four sessions, indicating that the catheters were patent and that cocaine functioned as a reinforcer in these animals. After these monkeys were allowed to self-administer cocaine, 7-OH-DPAT was again made available and functioned as a reinforcer. Response rates maintained by 7-OH-DPAT were still substantially lower than rates maintained by monkeys with an extensive cocaine history. These results suggest that prior cocaine exposure modified the reinforcing effects of 7-OH-DPAT (Nader and Mach, in press).

Others have reported on the importance of pharmacological history in the reinforcing effects of opiates, dissociative anesthetics, benzodiazepines, and NMDA antagonists (Beardsley et al. 1990; Bergman and Johanson 1985; Schlichting et al. 1970; Young and Woods 1981; Young et al. 1981). When pharmacological history has been shown to be important, one mechanism that is frequently discussed is that the test compound shares discriminative stimulus effects with the baseline drug. According to that hypothesis, 7-OH-DPAT functioned as a reinforcer in cocaine-experienced animals, but not in cocaine-naive animals, because 7-OH-DPAT shares discriminative stimulus effects with cocaine. Consistent with this hypothesis is recent data demonstrating that 7-OH-DPAT can substitute for cocaine in monkeys trained to discriminate cocaine from saline (Lamas et al. in press; Spealman 1994).

Results from the first three cocaine-naive monkeys suggest that a cocaine history was an important determinant of the reinforcing effects of 7-OH-DPAT. However, it is possible that 7-OH-DPAT functioned as a reinforcer because of the monkeys' exposure to the FI schedule (i.e., behavioral history), not because of their pharmacological history involving cocaine. However, this apparently was not the case, since monkeys that were first trained to respond under an FI 5-min schedule of food presentation responded at very low rates when 7-OH-DPAT was made available (Nader and Mach, in press). Thus, training the animal to respond under the FI schedule did not enhance the reinforcing effects of 7-OH-DPAT.

Results from the present study suggest that behavioral mechanisms (i.e., discriminative stimulus effects and FI histories) may not be involved in the low rates of 7-OH-DPAT self-administration in

previously cocaine-naive monkeys. A second possibility is that neuropharmacological changes as a consequence of prior cocaine exposure modified the reinforcing effects of 7-OH-DPAT. For example, it is possible that long-term cocaine exposure resulted in an upregulation of dopamine D_3 and/or D_2 receptors. However, studies utilizing the noninvasive imaging technique positron emission tomography (PET), have shown that D_2 receptor densities are lower in cocaine abusers (Volkow et al. 1990, 1993), suggesting a downregulation of D_2 receptors with chronic cocaine exposure. In preliminary PET studies, a similar reduction in D_2 binding in cocaine-experienced monkeys compared to cocaine-naive controls has been observed (R.H. Mach, M.A. Nader, and R. Ehrenkaufer, unpublished observations). A more probable explanation for the present results is that chronic cocaine exposure resulted in reductions in basal dopamine levels that enhanced 7-OH-DPAT binding to D_3 receptors, although this latter hypothesis will have to be tested further.

The most important point of this study is that the combination of a substitution procedure in animals self-administering cocaine and acquisition in cocaine-naive animals revealed possible behavioral (i.e., discriminative control) and/or neuropharmacological changes that are a consequence of long-term cocaine exposure. These data suggest that it is possible to track the timecourse of these behavioral and neuropharmacological changes by having "probe" sessions in which 7-OH-DPAT is frequently substituted for cocaine. From a treatment perspective, these results suggest that 7-OH-DPAT would have low abuse liability in cocaine-naive individuals. With regard to treating cocaine abusers, the fact that 7-OH-DPAT functions as a reinforcer after chronic cocaine exposure suggests that compliance would be high.

CONCLUSIONS

This chapter has reviewed the influence of several environmental and pharmacological variables on rates of cocaine self-administration. To this end, the experiments had the same primary goal: to study the effects of current environmental contingencies and the long-term consequences of these experimental histories on rates of cocaine self-administration. Behavioral histories could increase (i.e., FR histories) or decrease (i.e., IRT > 30-sec histories) rates of cocaine-maintained responding. Importantly, behavioral histories involving nondrug reinforcers could also significantly influence cocaine self-administration. Negative punishment contingencies were extremely

effective in reducing cocaine-maintained response rates. Also, the fact that response rates were lower in the punished component, even when the punishment contingency was removed, suggests that behavioral histories involving negative punishment can produce long-lasting reductions in cocaine self-administration. Although the focus of this chapter was on environmental variables, the effects of pharmacological history were also discussed. The inclusion of pharmacological history in this chapter was by no means arbitrary. There is a growing database on drug-behavior interactions modifying the behavioral effects of drugs. (See Barrett et al. 1989 for reviews.) Perhaps future research will show that a combination of behavioral and pharmacological treatments will be the most clinically effective strategy. For example, while it has been shown that administration of dopamine D_3 agonists decrease cocaine-maintained response rates (Caine and Koob 1993), it may be that these pretreatments will be significantly more effective when combined with certain behavioral histories, environmental contingencies, or environmental contexts. That is, the identification of potential pharmacotherapies for cocaine abuse will be enhanced by a better understanding of the behavioral variables that modify the reinforcing effects of cocaine.

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