EFFECTS OF REPEATED COCAINE ADMINISTRATION ON RESPONDING
UNDER MULTIPLE FIXED-RATIO SCHEDULES OF REINFORCEMENT

By

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During two experiments, key pecking by pigeons was maintained under multiple fixed-ratio schedules of food reinforcement. During Experiment 1, responding by four subjects was reinforced according to either a multiple fixed-ratio 5 fixed-ratio 45 or multiple fixed-ratio 45 fixed-ratio 90 schedule of reinforcement. All subjects in Experiment 1 responded under fixed-ratio 45: two in the context of fixed-ratio 5 and two in the context of fixed-ratio 90. During Experiment 2, responding by four subjects was reinforced under either multiple fixed-ratio 10 fixed-ratio 100 or fixed-ratio 100 fixed-ratio 200. Each of the four subjects in Experiment 2 responded under fixed-ratio 100: two in the context of fixed-ratio 10 and two in the context of fixed-ratio 200. Following determination of the acute effects of a range of doses of cocaine (0.3-10.0 mg/kg in Exp. 1; 1.0-13.0 mg/kg in Exp. 2), doses of cocaine that

produced consistent decreases in response rates were administered to each subject before each daily session. During daily administration, the effects of the acutely administered doses were redetermined by occasionally substituting them for the daily dose. Tolerance was observed more frequently during the smaller ratio schedule in each multiple schedule. During Experiment 1, tolerance was observed during fixed-ratio 45 both when it was the larger schedule and when it was the smaller schedule. During Experiment 2, when the difference between fixed-ratio schedules was larger, tolerance developed in a more schedule-dependent manner. Tolerance was observed more frequently when fixed-ratio 100 was the smaller of the two schedules than when it was the larger schedule. Sensitization was observed more frequently when fixed-ratio 100 was the larger of the two schedules than when it was the smaller schedule. The results lend support to previous findings that response requirement under fixed-ratio schedules may modulate the development of tolerance. The results also point to the context within which a particular fixed-ratio schedule occurs as a possible determinant of whether tolerance or sensitization will be observed.

CHAPTER I

INTRODUCTION

The effect that a drug has on behavior can change following repeated administration of the drug. When the drug produces a greater effect following repeated administration or less of the drug is required to produce the initial effect, then sensitization is said to have developed. On the other hand, tolerance to behavioral effects of a drug refers to a diminished effect of the drug following repeated administrations and the subsequent necessity of using larger doses to recapture the initial effect (Corfield-Sumner & Stolerman, 1978). Tolerance to behavioral effects has been observed with a number of drugs including amphetamines (e.g., Pearl & Seiden, 1976; Campbell & Seiden, 1973), morphine (e.g., France & Woods, 1985; Dworkin & Branch, 1982), barbiturates (e.g., Branch, 1983; Smith & McKearney, 1977), cocaine (e.g., Hoffman, Branch & Sizemore, 1987; Woolverton & Schuster, 1978a, 1978b), ethanol (e.g., Bird, Holloway & Carney, 1985; Chen, 1968), hallucinogens (e.g., Murray, Craigmill & Fischer, 1977), nicotine (e.g., Domino & Lutz, 1973) and delta-9-

tetrahydrocannabinol (e.g., Galbicka, Lee & Branch, 1980; Carder & Olson, 1973).

Tolerance can develop to the effects of some drugs following repeated administration via changes in the metabolism of the drug. For example, drugs such as barbiturates stimulate the liver to secrete enzymes that are instrumental in the metabolism of the drug. The increased level of these enzymes in the blood causes an increase in the rate of metabolism of the drug, thereby increasing the speed at which the drug is eliminated. Since the drug is eliminated more rapidly, the duration of its action is briefer and, therefore, more drug is needed to sustain the initial effect. This process is known as enzyme induction, and tolerance that develops by this mechanism is usually called dispositional tolerance (Dews, 1978). Dispositional tolerance refers to tolerance due to changes in the absorption, distribution and/or metabolism of a drug following repeated administration (Demellweek & Goudie, 1983).

Merely administering a drug repeatedly, however, does not appear sufficient for tolerance to develop to the behavioral effects of that drug in all cases. There are data indicating that for tolerance to develop, the reinforced behavior (i.e., the behavior by which the development of tolerance is to be assessed) must be ongoing while the drug is having its effect.

Chen (1968) examined the effects of ethanol on performance of a circular maze task by two groups of rats. The response to be reinforced by the presentation of a piece of dry spaghetti was two complete turns in the maze. One group, named the behavioral group, received ethanol injections 10 min prior to being placed in the maze before each of four experimental sessions. The other group, called the physiological group, received ethanol injections 1 min following three of the sessions (and then returned to their home cages) and 10 min prior to being placed in the maze before the fourth session. In other words, the two groups received equal exposure to ethanol and equal experience in the maze during the first three sessions but only the behavioral group had experience in the maze while ethanol was having its effects. Performances during the fourth session, when both groups received presession ethanol injections, were compared. It was reasoned that if physiological or pharmacological variables were all that were necessary for tolerance to develop, then the two groups would not differ in tolerance observed. Tolerance to ethanol's effects was observed with the behavioral group but not with the physiological group; that is, subjects in the behavioral group made more correct responses and fewer errors (i.e., any response other than two complete turns in the maze) during the fourth session than did those in the physiological group. Chen (1968) concluded that the

development of tolerance could not be attributed solely to repeated exposure to the drug, since both groups received equal exposure to ethanol, but that some behavioral factor, such as the ability to engage in the behavior while drugged, must have been involved.

Woolverton, Kandel and Schuster (1978a) reported on the effects of pre- and postsession cocaine administration on milk drinking by rats were examined. Experimental sessions consisted of 15-min access to 50 ml of sweetened condensed milk. The initial effect of presession cocaine was to produce dose-related decreases in milk intake. When cocaine (16 mg/kg) was administered before each daily session, tolerance developed to the disruptive effects of cocaine, i.e., milk intake increased toward control levels. However, when an equal amount of cocaine was administered following each daily session, an increase in the disruptive effect (i.e., sensitization) was observed. As in Chen (1968), the subjects in each group received equal exposure to both the drug and the experimental procedure, but tolerance was observed only with those subjects that experienced the effects of cocaine during sessions. These and other data suggest that behavioral and/or environmental variables can influence the extent to which tolerance develops (see Corfield-Sumner & Stolerman, 1978; Wolgin, 1989, for reviews). Tolerance that develops as a function of these types of variables is a form of functional

tolerance (in contrast to dispositional tolerance) and is referred to as behavioral tolerance.

Another example of the influence that behavioral variables can have in the development of tolerance was provided by Schuster, Dockens and Woods (1966). They trained rats to respond under a multiple (Mult) fixed-interval 30-s differential-reinforcement-of-low-rate 30-s (Mult FI 30 DRL 30) schedule of reinforcement. During this procedure, when the house lights were illuminated continuously, the first response that occurred 30-s after the last reinforcer delivery was reinforced (FI 30). When the house lights flashed, responses were reinforced if they were spaced at least 30 s apart (DRL 30). Ten-minute periods of these schedules, separated by 30-s blackouts, alternated during 62.5-min sessions. The initial effects of d-amphetamine on responding under the multiple schedule were varied. For two of the subjects, d-amphetamine produced increases in responding during both of the component schedules. For the third subject, d-amphetamine produced a decrement in responding during the FI schedule and had little effect on DRL responding. Following determination of the acute effects of d-amphetamine, each rat was injected with 1.0 mg/kg d-amphetamine before each daily session for 30 days (chronic administration). Schuster et al. (1966) found that tolerance developed differentially under the two component schedules of the Mult schedule. They found that

tolerance (defined in terms of total responses, interresponse time distributions and total reinforcers earned) developed during DRL components. However, they found that tolerance developed during FI components only when the initial effect of the drug was a decrease in response rate that was accompanied by a decrease in reinforcement frequency. Following analysis of changes in reinforcement rates under the two schedules, Schuster et al. (1966) concluded that when the initial effect of the drug on either schedule was to decrease reinforcement rate, then tolerance was likely to develop.

Schuster, Dockens and Woods' (1966) conclusion was the first statement of what has been termed the "reinforcement-loss" or "reinforcement-density" hypothesis of behavioral tolerance. The hypothesis states that tolerance to a drug's effect is more likely to develop, or will develop more quickly, if the initial effect of the drug results in a reduction in reinforcement frequency. Schuster et al. (1966) went on to state that their hypothesis was not intended to replace physiological theories of tolerance but rather to supplement them by providing an additional variable that may be operating when tolerance is observed in situations not predicted by physiological theories.

As mentioned in the discussion of dispositional tolerance, merely administering a drug repeatedly can result in tolerance. However, even in such cases, the

rate or degree to which tolerance develops may be augmented by behavioral factors. For example, LeBlanc, Gibbins and Kalant (1973) trained three groups of rats on a circular-maze task and then administered ethanol to two of the groups. The task was based on the one used by Chen (1968). Two complete counterclockwise turns in the maze were reinforced by presentation of a food pellet. One group received ethanol injections before treatment sessions ("psychological" group) and the other group received injections after treatment sessions ("physiological" group). The third group (control group) received saline injections before treatment sessions. Every four days test sessions were conducted before which subjects in all groups received ethanol injections. The results indicated that tolerance developed to ethanol's error-producing effects (errors defined as any response other than two complete counterclockwise turns in the maze) for both the psychological and physiological groups but not for the control group. However, tolerance developed more quickly for the psychological group even though the same degree of tolerance eventually developed for the physiological group. LeBlanc et al. (1973) concluded that the opportunity to engage in the task while drugged affected the rate at which tolerance developed. "Behaviorally augmented tolerance" is the phrase that has been coined to describe instances where tolerance develops both for groups receiving the drug

before sessions and those receiving the drug after sessions, but where the rate or degree to which it develops is dependent on behavioral factors such as the opportunity to perform the task while drugged.

Others have argued, however, that in procedures such as the one described by LeBlanc et al. (1973), the group that receives postsession injections and then is tested every four days with pre-session injections (the physiological group), also has the opportunity to perform the task while drugged. Any tolerance observed, it is argued, results as a function of such sessions and the differing rates at which tolerance develops are due to the differing number of opportunities to engage in the behavior while drugged.

To illustrate this point, Wenger, Tiffany, Bombardier, Nicholls and Woods (1981) conducted an experiment similar in design to that of LeBlanc et al. (1973). In their experiment, Wenger et al. (1981) examined the effects of ethanol on performance on a task that required the subjects (rats) to walk on a treadmill. Stepping off the treadmill resulted in electric shocks to the foot. The initial effect of ethanol on performance on this task was to produce dose-related increases in time off the treadmill, and tolerance was measured as reductions in these errors. Ethanol was administered to four groups of rats. Three of the groups were treated identically to those in LeBlanc et al. (1973). One group

received ethanol injections before every experimental session, a second group received injections following sessions for three days but before the session every four days and a third group received saline injections following all sessions. The fourth group received ethanol injections after sessions only. Following 24 days of treatment under these conditions, the degree of tolerance achieved by the group that received ethanol injections before sessions every fourth day matched that of the group that received ethanol before every session; that is, tolerance developed in both groups but more quickly for the group that received ethanol injections before every session (i.e., behaviorally augmented tolerance was observed). On the 24th day, ethanol was administered before the session for the first time to the other two groups. The number of errors produced by the groups that had never received pre-session ethanol injections was not significantly different from each other and both were significantly higher than those produced by either of the two groups that had received pre-session injections. From these data, Wenger et al. (1981) concluded that mere daily exposure to ethanol's effects was not sufficient for tolerance to develop and that some experience with the task while drugged was necessary for tolerance to be observed.

Other more specifically identifiable environmental factors also may modulate the development of behavioral

tolerance. One such factor is the degree to which the behavior is under stimulus control (Thompson, 1977). Another of the variables that has been shown to be an important determinant of a drug's effects is the schedule under which the behavior is reinforced (McKearney & Barrett, 1978). In addition to the type of schedule maintaining behavior, data exist that suggest that the parameters of a particular schedule can influence a drug's effects. McMillan (1969) studied the effects of d-amphetamine on pigeons' responding under a Mult fixed ratio (FR) 30 FI 5-min schedule. High rates of responding maintained under the FR 30 schedule were not affected by small doses of d-amphetamine but were decreased at large doses. Low response rates under the FI 5-min schedule were increased by low doses of d-amphetamine and were decreased by high doses. By varying the parameters of the two component schedules, he found that the values of the schedules influenced the effect of the drug. Specifically, McMillan (1969) raised the response requirement under the FR schedule to 150, and later to 250 responses per reinforcer, which resulted in lower response rates during that component schedule. Likewise, the interval during the FI component was shortened to 60 s, which produced an increase in response rates during that component. The low rates of responding under FR 250 were increased by small doses of d-amphetamine and decreased by large doses while the high response rates

under FI 60 sec were decreased by large doses. Thus, the effects of d-amphetamine on low or high rates of responding, regardless of which schedule maintained those rates, were similar. By manipulating schedule parameters, McMillan (1969) changed control rates of responding under the two types of schedules and observed that drug effects were more dependent on rates of responding than on the type of schedule maintaining those rates.

Data indicating that schedule type and parameter can influence drug effects and that tolerance to a drug's effects can develop differentially according to schedule type led Hoffman, Branch and Sizemore (1987) to investigate the role of schedule parameters in the development of tolerance to behavioral effects of cocaine. They compared the effects of acute and chronic administration of cocaine on responding by pigeons maintained under three-component multiple FR schedules of reinforcement. The component schedules differed in respect to ratio value. The component schedules were FR 5, FR 25 and FR 125 for two of the subjects and FR 5, FR 25 and FR 50 for the third subject.

Once responding had stabilized under these schedules, the acute effects of a range of doses of cocaine were determined. Cocaine produced dose-related decreases in responding with the effects being dependent on ratio size; behavior under the smaller ratios was less sensitive while behavior under the largest ratios was

more sensitive to cocaine's effects. Following chronic administration of 5.6 mg/kg cocaine, tolerance was observed under the two smaller ratios for the subjects whose multiple schedules contained FR 125 and at all three schedules for the third subject (albeit to a lesser degree during FR 50). Thus, for all three subjects, tolerance developed in a schedule-dependent manner, that is, only (or to a greater extent) during shorter ratio schedules.

Hoffman, Branch and Sizemore (1987) concluded that their results were partially consistent with the reinforcement-loss hypothesis. During ratio schedules, there is a direct relationship between response rate and reinforcement rate; reductions in response rates result in reductions in reinforcement rates. Cocaine produced decreases in response rates during acute administration, and Hoffman et al. (1987) concluded that in all cases where tolerance was observed, cocaine produced reductions in reinforcement frequency during acute administration. Response-rate reductions were also observed during FR 125, however, without tolerance developing during that schedule. Hoffman et al. (1987) suggested that their results indicate that there may be conditions under which reinforcement-loss plays less of a role in the development of tolerance. Hoffman et al. (1987) also suggested that the amount of responding (or "effort") necessary for reinforcement may be a factor in the

development of tolerance, a conclusion consistent with that of Branch and Dearing (1981).

Hughes and Branch (1991) performed a systematic replication of the Hoffman, Branch and Sizemore (1987) study using four squirrel monkeys as subjects. In their experiment, lever-pressing was maintained under three-component multiple FR schedules arranged like those used by Hoffman et al. (1987). Hughes and Branch (1991) examined the effects of acute and chronic cocaine administration on responding maintained under the multiple schedules. As in Hoffman et al. (1987), acute administration of cocaine produced dose-related decreases in response rates. Following chronic administration of 1.0 mg/kg cocaine, Hughes and Branch (1991) found that tolerance developed more fully and earlier in sessions during the smaller ratio schedules. Thus, Hughes and Branch's (1991) data support those of Hoffman et al. (1987) in that tolerance developed in a schedule-dependent manner.

Indirect evidence that the ratio of responses per reinforcement may modulate the development of behavioral tolerance was provided by Schama and Branch (1989). In a systematic replication of Hoffman et al. (1987), pigeons responded under three-component multiple FI schedules. Following acute and chronic administration of cocaine, Schama and Branch (1989) found that tolerance to cocaine's rate-decreasing effects developed independently

of FI parameter; that is, some attenuation of cocaine's rate-decreasing effects was observed for all subjects during all FI component schedules. This finding stands in contrast to the results of Hoffman et al. (1987) and Hughes and Branch (1991), who found that schedule parameter was an important factor.

In their experiment, Schama and Branch (1989) chose FI values that approximated the baseline reinforcement rates observed during the FR schedules in Hoffman et al. (1987). Reinforcement rates in Schama and Branch (1989) varied from 12 per minute (FI 5-s) to 0.5 per minute (FI 120-s). Since tolerance developed independently of FI value, Schama and Branch's (1989) data suggest that baseline reinforcement rate may not modulate the development of tolerance to the effects of cocaine.

Fixed-ratio and fixed-interval schedules of reinforcement differ in the relationship between response rate and reinforcement rate. With FR schedules, reinforcement rates change as a direct proportion of changes in response rates. With FI schedules, on the other hand, when response rates are high, reinforcement rates are held relatively constant. When response rates are low, however, the relationship between response rates and reinforcement rates more closely approximates that of FR schedules; that is, if interresponse times exceed the interreinforcement interval specified by the schedule, then the relationship between responses and reinforcement

is the same as under FR 1. This being the case, reinforcement rates under FI schedules are more affected when response rates are low than when response rates are high. Thus, when response rates are low following cocaine administration, responses are seldom reinforced under FR schedules but can be under FI schedules. Schama and Branch (1989) point to this factor as one that may account for their finding that tolerance developed independently of FI parameter.

Fixed-ratio and FI schedules also differ in terms of "effort" required for reinforcement. Under FR schedules, the number of responses required for each reinforcer is specified by the schedule. With FI schedules, on the other hand, only one response is required for reinforcement (the first one after the interval elapses). The fact that FR and FI schedules differ in terms of "effort" points to this factor (i.e., response requirement) as one requiring further study.

Thus, several factors have been identified as important considerations in studies of drug tolerance. Another possibly important variable was pointed out by Hoffman et al. (1987). In their discussion, Hoffman et al. (1987) suggested that it was unlikely that FR 125 was beyond some upper limit above which tolerance to cocaine's effects would not develop. They suggested that the context within which a particular FR schedule exists may determine the functional "largeness" of the schedule

and, therefore, whether tolerance will be observed. For example, in their experiment, FR 125 occurred in the context of a multiple schedule where the next largest FR schedule (FR 25) required one fifth the responses that FR 125 did and tolerance was not observed during FR 125. On the other hand, FR 50 occurred in the context of a multiple schedule where the next largest FR schedule (FR 25) required half the responses as FR 50 and some tolerance was observed during FR 50. These differences in context may have contributed to the differences in tolerance that were observed.

The present experiments were designed to address whether the context within which an FR schedule is found is a determinant of whether or not tolerance will be observed. More specifically, the role of context in the development of tolerance was investigated using two-component multiple schedules. During two experiments, behavior under pairs of multiple schedules with different FR component values was compared to determine whether tolerance to cocaine's effects will develop under a given schedule (e.g., FR 45) when that schedule occurs in the context of a smaller schedule (e.g., FR 5) and/or when it occurs in the context of a larger schedule (e.g., FR 90).

CHAPTER II

EXPERIMENT I

Method

Subjects

Four adult male, experimentally naive White Carneau pigeons served as subjects. Each bird was maintained at 80% of free feeding weight. The subjects were housed individually and had continuous access to water and health grit while in the home cage. The room within which the subjects were housed was maintained on a 16 hr light/8 hr dark cycle.

Apparatus

Experimental sessions were conducted in a two-key operant conditioning chamber. Three sides and the top of the chamber were constructed of plexiglas. Black construction paper was taped to the outside of the plexiglas sides and top. The aluminum front panel contained the two response keys and a rectangular opening (6 cm by 5 cm) through which the pigeons could gain access to mixed grain when the food hopper was elevated. The internal dimensions of the chamber were 31 cm by 31 cm by 30 cm. The response keys were mounted behind 1.8 cm

diameter holes the edges of which were 8 cm from the top of the chamber, 11 cm from the sides of the chamber and 10 cm apart. The left key, which could be transilluminated by red or green lights, was the only key used in the experiment. The right key remained darkened and inoperative throughout the experiment. A force of 0.15 N was required to operate the key. The top of the opening through which food was obtained was centered 13-cm below the response keys, with 6 cm from its bottom edge to the floor of the chamber. The opening was illuminated by a 1.2-W lamp when the food hopper was elevated. A shielded, 1.2-W lamp mounted on the ceiling between the response keys served as a houselight. Both the houselight and the keylight were extinguished when the food hopper was elevated. A relay mounted behind the front wall provided feedback for responses. The chamber was housed in an enclosure constructed of 3/4-inch plywood and whose dimensions were 71 cm by 52 cm by 52 cm. A white-noise generator provided masking noise in the room where the enclosure was located. In an adjacent room, a Digital Equipment Corp. PDP 8/e minicomputer operating under SuperSKED software (Snapper & Inglis, 1978) was used to program and monitor experimental events. A Gerbrands model C-3 cumulative recorder also was used to monitor sessions.

Behavioral Procedure

Pecks on the left key were shaped by the method of successive approximation both when the key was transilluminated red and when it was transilluminated green. Following shaping, two sessions during which each peck resulted in food presentation (Fixed Ratio 1) were conducted. During these sessions the key color alternated between red and green following each of 30 food presentations. Alternating the key light colors following each food presentation defined the procedure as a Multiple (Mult) FR 1 FR 1 schedule of reinforcement. Beginning with the Mult FR 1 FR 1 schedule, and continuing for the remainder of the experiment, experimental sessions began with a 5-min time-out during which lights were not illuminated and keypecks had no consequence. That is, 5 minutes after the subjects were placed in the experimental chamber the houselight and left key light were illuminated and a session began. Throughout the experiment the duration of each food presentation was 4 s. For the remainder of the experiment Mult schedules of reinforcement were in effect. Experimental sessions were conducted seven days a week at approximately the same time each day.

Following the two sessions with Mult FR 1 FR 1, a Mult Random-ratio 2 (Mult RR 2 RR 2) schedule was in effect. During a random ratio schedule of reinforcement, the responses selected to be reinforced are determined on

a probabilistic basis. In the case of an RR 2 schedule, each response has a probability of 0.5 of being reinforced.

From this point to the conclusion of the experiment, Mult schedule components were separated by a 60 s time-out and each experimental session consisted of four components. Specifically, sessions began by the transillumination of the left key by the red light in the presence of which responding was reinforced according to the first of the two ratio schedules. Following five reinforcer deliveries or 20 minutes, whichever occurred first, the 60 sec time-out began. Following the timeout, the key was transilluminated by the green light and the second of the two ratio schedules was in effect. Once again, following five reinforcers or 20 minutes and the 60 s time-out, the key was transilluminated red and the first ratio schedule was in effect for the second time. Finally, following the time out, the second ratio schedule was in effect for a second time. In other words, each of the two ratio-schedule components occurred twice and alternated with one another, thereby comprising a session that contained four components.

Following four sessions of Mult RR 2 RR 2, four sessions of Mult RR 4 RR 4 were conducted. Eleven to thirteen sessions of Mult RR 5 RR 5 were conducted next. Following Mult RR 5 RR 5, a Mult FR 5 FR 5 was put into

effect. The FR requirements were then manipulated and two experimental groups were formed as follows.

For P75, the FR requirement in the presence of the red light remained at FR 5 while the requirement in the presence of the green light was raised to FR 45. Similarly, the response requirement in the presence of the red light for P711 was raised to FR 45 while the requirement in the presence of the green light remained at FR 5. The requirements for both schedules for the remaining two subjects were raised. For P714, the requirement in the presence of the red light was raised to FR 45 and in the presence of the green light to FR 90. Finally, the requirement in the presence of the red light was raised to FR 90 and in the presence of the green light to FR 45 for P449. Thus, the Mult schedules for all four subjects had FR 45 in common. For two of the subjects (P75 and P711) FR 45 occurred in the context of FR 5 and for the two other subjects (P449 and P714) FR 45 occurred in the context of FR 90. For all subjects the response key was transilluminated red during the first and third components of the Mult schedule and green during the second and fourth components.

Assessment of Acute Drug Effects

Once responding under the multiple schedules was deemed stable (following 18 sessions for P75, 18 for P711, 45 for P714 and 18 for P449) the effects of acute

administration of cocaine were determined. Stability was evaluated by visual inspection of the daily data plots of overall response rates for each component schedule.

Cocaine hydrochloride was dissolved in 0.9% sodium chloride solution. Dosages were determined in terms of the salt. Injection volume was 1 ml/kg and each dose was administered at least twice before sessions that were separated by at least three intervening sessions. Saline was also injected at least twice. Injections were made in the pectoral muscle just before the 5-min timeout that preceded a session. The first two administrations of the doses were done in ascending series: 1.0, 3.0, 5.6 and 10.0 mg/kg cocaine for three subjects and 0.3, 1.0, 3.0, 5.6 and 10.0 mg/kg cocaine for P449. Table 1 displays the number of administrations of saline and each dose for each subject.

Assessment of Chronic Drug Effects

After the assessment of acute drug effects and after at least 8 days of responding in the absence of cocaine administration, the effects of daily cocaine administration were assessed. The dose chosen as the chronically administered dose was determined for each subject by inspection of the acute dose-effect curves and was the lowest dose that produced consistent decreases in responding during both ratios. The subjects' behavior

Table 1

Total number of administrations of saline and each dose of cocaine under acute- and chronic-administration phases for each subject.

P75

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	5	3	4	3	2
Chronic	2	2	2	8	2

P711

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	6	4	5	5	4
Chronic	2	3	2	2	9

P714

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	6	7	6	5	4
Chronic	6	6	16	2	2

P449

	<u>Saline</u>	<u>0.3</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	6	2	2	5	2	2
Chronic	2	2	2	10	2	2

varied in sensitivity to cocaine's effects and, therefore, different doses were used for different subjects. The dosage used for subjects P714 and P449 was 3.0 mg/kg. The dosages used for subjects P75 and P711 were 5.6 mg/kg and 10.0 mg/kg, respectively. The effects of the other doses of cocaine were redetermined once responding during chronic administration was deemed stable by visual inspection of daily plots of overall response rates. Following 43 days of daily administration for P75, 36 days for P711, 44 days for P714 and 53 days for P449 the other doses and saline were occasionally substituted for the daily dose. The doses that were substituted were administered at least 4 sessions apart. Each dose and saline were substituted at least twice. The chronic administration phase lasted 106 days for P75, 121 days for P711, 217 days for P714 and 155 days for P449. Table 1 displays the number of administrations of saline and each dose for each subject.

Results

Figure one presents cumulative records for Subjects P711 and P714. The first two rows show the effects of saline and 10.0 mg/kg cocaine (the daily dose) on the behavior of subject P711 under acute- and chronic-administration conditions. Responding by P711 was maintained under Mult FR 45 FR 5. The first and third

Figure 1. Cumulative response records for Subjects P711 and P714. The top two rows show records for P711. The first row of records shows the effects of saline and 10.0 mg/kg cocaine on responding during determination of the acute effects of cocaine. The second row shows records following injection of saline and 10.0 mg/kg cocaine during the chronic-administration phase. The third and fourth rows show records for P714. The third row shows records following injection of saline and 3.0 mg/kg cocaine during the acute-administration phase and the fourth row shows records following injection of saline and 3.0 mg/kg cocaine during the chronic-administration phase. Downward deflections of the response pen indicate food deliveries. The response pen reset at the completion of each component. The event pen was up during the first and third components and down during the second and fourth components.

components consisted of FR 45 and the second and fourth components, FR 5. As the upper left-hand panel shows, behavior was well maintained following saline administration during the acute-administration condition. Acute administration of 10.0 mg/kg cocaine, however, disrupted performance. During the session shown, a few responses were emitted during the first component, though not enough to result in reinforcement. No responding occurred during the remainder of the session until the end of the fourth component when responding resulted in four grain deliveries. During the determination of the acute effects of 10.0 mg/kg cocaine, it was not unusual for some responses to be emitted during a session. The second row of records shows the effects of saline and 10.0 cocaine during the chronic-administration phase. Following saline administration, responding resembled that observed during the acute-administration phase. That is, responding was well maintained with relatively short pre-ratio pauses and high rates of responding. A change in the effect of 10.0 mg/kg cocaine was observed following daily administration, however. The record in the right column of the second row is representative of sessions following injection of 10.0 mg/kg cocaine during the chronic-administration phase and shows that responding recovered during the FR-5 components of the Mult schedule but not during FR-45 components.

The third and fourth rows of the figure show the effects of saline and 3.0 mg/kg cocaine (the chronically administered dose) on the behavior of Subject P714 under acute and chronic conditions. Responding by P714 was maintained under a Mult FR 45 FR 90 schedule of reinforcement. The first and third components consisted of FR 45 and the second and fourth of FR 90. As with P711, P714's behavior was well maintained under the Mult schedule following saline injection during the acute-administration phase. Although some relatively long pre-ratio pauses occurred during the final component of this session, all ratios were completed. During the determination of cocaine's acute effects, 3.0 mg/kg cocaine suppressed responding completely during all components of the Mult schedule during the session shown. There were occasions during other sessions when some responses were emitted following the injection of 3.0 mg/kg cocaine, however. The effects of saline and 3.0 mg/kg cocaine during chronic administration are shown in the fourth row of the figure. Following saline injection during the chronic phase, responding occurred at levels similar to those observed prior to the chronic-administration phase. The record in the lower right panel shows that after repeated administration of 3.0 mg/kg cocaine responding recovered to some extent during the FR-45 component schedules, especially in the third component, but not during FR-90 components during this

session. However, there were occasions during other sessions when responding occurred during FR-90 components during the chronic phase, especially early in the phase. As the phase progressed, less responding occurred during FR-90 components following injection of 3.0 mg/kg cocaine.

In summary, for the two subjects whose records are displayed in Figure 1, responding was well maintained following saline injections during the acute-administration phase. During the determination of the acute effects of cocaine, the dose that would later be used as the daily dose either completely or nearly completely suppressed responding during all components of the Mult schedule. Following the chronic administration of that dose, responding recovered to a large extent only during the smaller of the two schedules of the Mult schedule. Finally, when saline was substituted for the daily cocaine dose, rates of responding returned to levels similar to those observed during the acute-administration phase.

Figures 2 and 3 show daily response rates for the last seven sessions of the acute-administration phase (baseline), the first 25 sessions of the chronic-administration phase and the last seven sessions of the chronic-administration phase for all subjects in Experiment 1. For P75, during the initial sessions of the chronic-administration phase, response rates during FR-5

Figure 2. Daily response rates for the last seven sessions of the acute-administration phase, the first 25 sessions of the chronic-administration phase and the last seven sessions of the chronic-administration phase for each component ratio size for P75 and P711.

SESSIONS

RESP/MIN

Figure 3. Daily response rates for the last seven sessions of the acute-administration phase, the first 25 sessions of the chronic-administration phase and the last seven sessions of the chronic-administration phase for each component ratio size for P714 and P449.

SESSIONS

RESP/MIN

components were suppressed to levels similar to those observed following the acute administration of 5.6 mg/kg cocaine. Following thirteen sessions, response rates recovered to an intermediate level with response rates from two of the sessions similar to those observed during baseline. Response rates remained at intermediate levels at the end of the chronic-administration phase. During FR-45 components, response rates were suppressed during the first three sessions of the chronic-administration phase and then recovered to levels somewhat higher than those observed during baseline. Following seventeen sessions of daily administration of 5.6 mg/kg cocaine, response rates decreased to levels that were lower than baseline rates but higher than rates observed following acute administration of 5.6 mg/kg cocaine. Response rates remained at those levels for the remainder of the experiment.

For P711, during FR-5 components, acute administration of 10.0 mg/kg cocaine suppressed response rates nearly completely. Daily administration of 10.0 mg/kg cocaine, on the other hand, reduced response rates to an intermediate level. During FR-45 components, response rates were reduced to low levels at the beginning of the chronic-administration phase and then recovered. Following 14 sessions of chronic administration of 10.0 mg/kg cocaine, response rates decreased again and remained low for the remainder of the

phase. By the end of the experiment, response rates were completely suppressed during FR-45 components.

Response rates were reduced to low levels at the beginning of the chronic-administration phase during FR-45 components for P714. After 3 sessions, response rates returned to approximately 50% of baseline rates where they remained for the rest of the experiment. Response rates at the end of the acute-administration phase were more variable during FR-90 components than they were during the chronic-administration phase. During the chronic-administration phase, after an initial recovery, rates decreased to very low levels where they remained for the rest of the experiment.

For P449, during FR-45 components, response rates during the chronic-administration phase were variable. Response rates during some sessions reached 40% to 50% of those observed during the acute-administration phase while rates during other sessions were suppressed to very low levels. This variability in response rates during FR-45 components persisted for the remainder of the experiment. During FR-90 components, baseline rates were very low and chronic administration of 3.0 mg/kg suppressed responding completely.

To summarize, during smaller-ratio components, response rates at the beginning of the chronic-administration phase were suppressed to levels similar to those observed following the acute administration of the

to-be-chronically-administered dose. Following one to 12 sessions, response rates recovered to varying degrees to levels intermediate to those at the beginning of the chronic-administration phase and the end of baseline. A pattern of initial suppression followed by recovery followed by a second decrease in rates occurred for three of the four subjects during longer-ratio components. For the fourth subject, response rates remained completely suppressed for the entire chronic-administration phase during the longer ratio.

Figure 4 presents complete dose-effect curves for both acute- and chronic-administration phases for each component-schedule size for all four subjects. Points represent means of response rates during both components of each ratio schedule. Open symbols indicate response rates following acute administration of the doses of cocaine and closed symbols indicate response rates during the chronic-administration phase.

Generally speaking, tolerance is said to have developed to the behavioral effects of a drug if response rates following chronic administration of the drug are higher than rates following acute administrations. This is often referred to as the dose effect curve being "shifted to the right" as a consequence of repeated administrations of the drug. The clearest example of tolerance shown in Figure 4 is the change of effect of the two largest doses of cocaine for P75. For this

Figure 4. Dose effects of cocaine on response rates under each FR schedule size for each subject during acute (open symbols) and chronic (closed symbols) administration of cocaine. Dose-effect curves in the left column show the effects of cocaine on responding under the smaller FR schedules. The dose-effect curves in the left column show the effects of cocaine on responding under the larger FR schedules. Subjects and fixed-ratio schedules are identified in the upper right-hand corner of each graph. Points above C are means from sessions that preceded those during which drug effects were examined during the acute-administration phase. Points above V show mean effects of injecting the saline vehicle. Bars indicate 95% confidence intervals.

animal, the effects of 5.6 and 10.0 mg/kg cocaine clearly decreased following repeated administration of 5.6 mg/kg cocaine (i.e., response rates were higher during the chronic-administration phase).

Schedule-dependent tolerance is indicated by the development of tolerance to a dose or to doses of cocaine during one of the component schedules but not during the other. For example, for P711, tolerance developed at 5.6 and 10.0 mg/kg cocaine during FR 5 components but not during FR 45 components. Thus, the development of tolerance was dependent on the schedule of reinforcement. Similarly, context-dependent tolerance would be demonstrated if tolerance was observed during the common FR schedule (i.e., FR 45) in the context of one of the component schedules (e.g., FR 90) but not in the context of the other (e.g., FR 5). Context-dependent tolerance is not clearly evident in Figure 4.

With few exceptions, acute administration of cocaine produced dose-related decreases in response rates for each subject. In most cases, control rates of responding depended on ratio size with higher rates occurring under the smaller of the two ratios (see Table 2). The exception was P75 whose control response rates under FR 45 were somewhat higher than those under FR 5. Interestingly, control rates under FR 45 differed depending on the context in which it was found. Control rates were higher when FR 45 was the smaller of the two

schedules. In general, however, behavior maintained under Mult FR 45 FR 90 (subjects P714 & P449) was more sensitive to cocaine's rate-decreasing effects than was behavior under Mult FR 5 FR 45. For P714 and P449, 3.0 mg/kg cocaine produced significant decreases in response rates during either ratio on a more consistent basis than it did for the other two subjects.

Following chronic administration, a variety of effects was observed. As mentioned above, for P75, tolerance developed to cocaine's rate decreasing effects at doses that had previously produced significant decreases in responding. Tolerance developed during both FR-5 and FR-45 components. Another interesting effect for this subject was a small change in the effects of saline injections following chronic administration of cocaine. For the most part, response rates were higher following saline injection during the chronic-administration phase than they were during the acute-administration phase (see Table 2).

For P711, sensitization to cocaine's effects occurred at the lowest dose during FR 5; that is, 1.0 mg/kg cocaine reliably reduced responding to a greater degree following repeated administration than during the acute phase. At the two largest doses, however, some degree of tolerance developed during FR 5 but not during FR 45.

There was little substantial change in the effects of saline or the doses of cocaine other than the chronically administered dose for P714. Some tolerance was observed at the chronically administered dose during both schedules.

As with P711, several effects were observed with P449. Sensitization occurred at the two lowest doses and some tolerance developed at the chronically administered dose during FR 45. During FR 90, responding was suppressed completely at all but the lowest dose. One noticeable change that did occur was in the effect of saline administrations. Responding following saline injections was lower than that observed during the acute phase.

In summary, following chronic administration, some degree of tolerance developed at the daily dose during the smaller of the ratios for all four subjects while such a change of effect was observed for only two subjects during the larger ratios. No consistent, robust effect was observed across subjects, however. For example, tolerance developed at the two largest doses of cocaine in a manner independent of reinforcement schedule for P75.

To allow for a more complete analysis of the effects of cocaine within experimental sessions, response rates were calculated for each component of the Mult schedule.

Figure 5. Effects of cocaine on responding during each of the four multiple-schedule components for Subjects P75 (left column) and P711 (right column). The first row of graphs shows effects during the first component of sessions, the second row shows effects during the second component and so on. Effects of cocaine on response rates during acute (open symbols) and chronic (closed symbols) administration are expressed as a percentage of response rates following saline injections. The chronically-administered doses are denoted by asterisks. Bars indicate ranges of saline's effects expressed as a percentage of mean effects.

Figure 6. Effects of cocaine on responding during each of the four multiple-schedule components for Subjects P714 (left column) and P449 (right column). The first row of graphs shows effects during the first component of sessions, the second row shows effects during the second component and so on. Effects of cocaine on response rates during acute (open symbols) and chronic (closed symbols) administration are expressed as a percentage of response rates following saline injections. The chronically-administered doses are denoted by asterisks. Bars indicate ranges of saline's effects expressed as a percentage of mean saline effects.

Table 2

Mean response rates under each component schedule during control sessions and following saline administration for each subject under acute and chronic conditions.

	Acute	Chronic
P75		
Overall Rates		
Control		
FR 5	60.2	30.1 (5.6 COC)
FR 45	71.3	52.5 (5.6 COC)
Saline		
FR 5	60.9	80.4
FR 45	73.0	87.0
Run Rates		
Control		
FR 5	128.0	101.5
FR 45	113.7	97.6
Saline		
FR 5	129.4	167.1
FR 45	108.0	132.1
P711		
Overall Rates		
Control		
FR 5	96.5	15.5 (10.0 COC)
FR 45	57.6	0 (10.0 COC)
Saline		
FR 5	94.9	78.8
FR 45	56.5	44.8
Run Rates		
Control		
FR 5	156.5	39.9
FR 45	80.9	0
Saline		
FR 5	152.6	145.9
FR 45	80.3	70.8
P714		
Overall Rates		
Control		
FR 45	91.6	26.1 (3.0 COC)
FR 90	12.0	10.4 (3.0 COC)
Saline		
FR 45	75.3	83.5
FR 90	20.9	24.5
Run Rates		
Control		
FR 45	146.6	114.6
FR 90	35.2	18.2
Saline		
FR 45	126.8	127.0
FR 90	55.8	37.5

Table 2, Cont.

P449

Overall Rates

Control

FR 45 117.5 14.6 (3.0 COC)

FR 90 20.9 0 (3.0 COC)

Saline

FR 45 117.9 92.2

FR 90 18.0 3.1

Run Rates

Control

FR 45 143.3 68.0

FR 90 51.6 0

Saline

FR 45 147.9 136.1

FR 90 32.9 30.6

Displayed in Figures 5 and 6 are the effects of the different doses of cocaine expressed as a percentage of vehicle (saline) rates for each of the four components for each of the four subjects. Control response rates and response rates following saline injections are presented in Table 2.

Figures 5 and 6 support the observation made with Figure 4 that, in general, behavior maintained by Mult FR 45 FR 90 was more sensitive to cocaine's rate decreasing effects than was behavior maintained under Mult FR 5 FR 45. For P75, acute 1.0 mg/kg cocaine had little effect within experimental sessions. As a session progressed, the effects of acute 3.0 and 5.6 mg/kg cocaine diminished so that by the fourth component, they had little effect. The largest dose consistently suppressed responding completely.

Following repeated administration of 5.6 mg/kg cocaine, tolerance developed during all components of the Mult schedule for P75. The most complete recovery occurred during the third component at the two largest doses and at the largest dose during the final component. As was observed during acute administration, the effects of cocaine diminished as a session progressed.

During the first two components of sessions, acute administration of cocaine produced dose-related decreases in responding for P711. Responding was disrupted less by 3.0 and 5.6 mg/kg but disrupted more by 10.0 mg/kg during

the third and fourth components. That is, as a session progressed, the effects of the lowest three doses diminished whereas the effects of the largest dose increased. The changes in the acute effects of cocaine observed for P75 and P711 seemed to be less related to the size of the component schedule than to the position of the component within the session.

For P711, sensitization occurred as a result of repeated administration of 10.0 mg/kg cocaine at 3.0, 5.6 and 10.0 mg/kg cocaine during the first FR-45 component and at 5.6 mg/kg during the third component. No change in effect was observed at 3.0 mg/kg during the second component or at the three smallest doses during the last component. However, tolerance to cocaine's effects was observed at 5.6 and 10.0 mg/kg during the first FR-5 component (2nd component) and at 10.0 mg/kg during the final FR-5 component. In general, both sensitization and tolerance developed in a schedule dependent fashion for P711 with sensitization developing consistently during the longer ratio components and tolerance developing at some doses during the shorter ratio components.

For P714, acute administration of cocaine produced dose-related decreases in responding. The effect of 3.0 was schedule dependent. That is, following acute administration, the effect of that dose was somewhat less during FR 45 than during FR 90, although the difference

was not very large. The largest dose consistently suppressed responding during all components.

Tolerance developed in a schedule dependent manner at the chronically administered dose for P714. The largest change of effect was observed during the third component which was a shorter ratio component. That is, although some tolerance was observed during the two FR-90 components at 3.0 mg/kg cocaine, responding recovered completely during the third (FR 45) component only. At the smallest dose (1.0 mg/kg), tolerance was observed during the third (FR 45) component.

The acute effects of cocaine were schedule dependent for P449 also. All doses of cocaine suppressed responding significantly during FR-90 components. Following the first administration of 1.0 mg/kg, P449 responded during the third component at a low, but gradually accelerating rate that resulted in four reinforcer presentations. Responding was suppressed during the first FR 90 component during that session, however. The second acute administration of 1.0 mg/kg cocaine resulted in suppression of responding during both FR-90 components.

As can be seen in Table 2, response rates following saline injections were very low during FR 90 for P449 during the chronic phase. Consequently, any responding during FR-90 components resulted in response rates that were high compared to rates following saline injection. During the session following the first substitution of

0.3 mg/kg, P449 responded at approximately four times the rate during the first component than during the first component of sessions following saline injection.

Responding was completely suppressed following the second substitution of 0.3 mg/kg and at all of the other doses during the first component. During the second FR-90 component (3rd component) response rates remained suppressed at all doses. Sensitization to cocaine's effects developed at the two smallest doses during the FR-45 components and tolerance developed at the chronically administered dose during the second FR-45 component (fourth component).

In summary, analyzing the effects of cocaine on a component-by-component basis yielded more information concerning the role played by schedule size in the development of tolerance. Figures 5 and 6 reveal that when tolerance developed it was somewhat more likely to develop during the shorter of the two ratios. This observation is confirmed by an analysis of cumulative records from the chronic-administration phase. As an indication of the number of times that tolerance was observed, Table 3 contains counts of the number of instances where administration of each dose of cocaine during the chronic-administration phase produced a smaller rate-reducing effect than the mean acute effect. These "instances" of tolerance were only counted if every administration of that dose during the chronic-

Table 3

Counts of the number of instances where administration of each dose of cocaine during the chronic-administration phase produced a smaller rate-reducing effect than the mean acute effect. In parentheses are the number of times that acute administration of each dose produced rates lower than the lowest rate during control sessions along with the total number of times that that dose was administered acutely.

P75

	1st (FR 5)	2nd (FR 45)	3rd (FR 5)	4th (FR 45)
1.0	0	0	0	0
3.0	0	0	0	0
5.6	8 (3/3)	0	8 (3/3)	0
10.0	2 (2/2)	2 (2/2)	2 (2/2)	2 (2/2)

P711

	1st (FR 45)	2nd (FR 5)	3rd (FR 45)	4th (FR 5)
1.0	0	0	0	0
3.0	0	0	0	0
5.6	0	0	0	0
10.0	0	0	0	0

P714

	1st (FR 45)	2nd (FR 90)	3rd (FR 45)	4th (FR 90)
1.0	0	0	5 (4/7)	0
3.0	0	0	14 (5/6)	0
5.6	0	0	2 (5/5)	0
10.0	0	0	0	0

P449

	1st (FR 90)	2nd (FR 45)	3rd (FR 90)	4th (FR 45)
0.3	0	0	0	0
1.0	0	0	0	0
3.0	0	0	0	10 (5/5)
5.6	0	0	0	0
10.0	0	0	0	0

administration phase produced a lesser effect than the mean acute effect. This is a conservative measure in that there were many other cases where an administration of a particular dose of cocaine produced a lesser effect during the chronic-administration phase than the mean acute effect, but not following each and every administration. As an indication of the reliability of the acute effect against which the chronic administrations were compared, the number of times that the acute administration of that dose produced rates lower than the lowest rate during control sessions is shown along with the total number of times that it was administered (also shown in Table 1). Table 3 shows that administrations of the doses of cocaine during the chronic-administration phase had less of an effect than during the acute-administration phase in 55 instances and in the smaller of the two FR's in 51 of those instances.

Table 4 presents mean lengths (in seconds) for each component of the Mult schedule during control sessions and following injections of saline and each of the doses of cocaine for each subject during the acute- and chronic-administration phases. From the data presented in Table 4, a measure of recovery from the rate suppressive effects of the chronically-administered dose was derived. This measure indicates the degree to which component lengths changed during the chronic-administration phase compared to component lengths during acute

Table 4

Mean multiple schedule component lengths (in seconds) during control sessions and following injections of saline and each of the doses during acute and chronic administration conditions.

P75	1st (FR 5)	2nd (FR 45)	3rd (FR 5)	4th (FR 45)
Control				
Acute	27.1	216.4	26.1	174.0
Chronic	196.8	430.8	31.2	314.4
Saline				
Acute	32.4	174.0	26.4	204.0
Chronic	24.0	150.0	24.0	159.6
1.0 mg/kg				
Acute	51.6	236.4	24.0	186.0
Chronic	45.6	192.0	24.0	222.0
3.0 mg/kg				
Acute	316.5	310.8	24.0	423.6
Chronic	60.0	324.0	24.0	195.6
5.6 mg/kg				
Acute	1200.0	1200.0	186.0	875.6
10.0 mg/kg				
Acute	1200.0	1200.0	1200.0	1200.0
Chronic	126.0	411.6	24.0	228.0
P711	1st (FR 45)	2nd (FR 5)	3rd (FR 45)	4th (FR 5)
Control				
Acute	277.2	21.6	226.8	20.4
Chronic	1200.0	85.2	1200.0	85.2
Saline				
Acute	249.6	24.6	222.0	24.0
Chronic	372.0	27.6	255.6	24.0
1.0 mg/kg				
Acute	372.0	21.6	219.6	22.5
Chronic	699.6	68.4	291.6	32.4
3.0 mg/kg				
Acute	477.6	79.2	188.4	24.0
Chronic	882.0	39.6	264.0	24.0
5.6 mg/kg				
Acute	696.0	195.6	230.4	39.6
Chronic	1200.0	30.0	696.0	36.0
10.0 mg/kg				
Acute	939.6	331.2	996.0	645.6

Table 4, Cont.

P714 (FR 90)	1st (FR 45)	2nd (FR 90)	3rd (FR 45)	4th
Control				
Acute	168.0	982.8	116.8	968.4
Chronic	967.2	1126.8	121.2	1200.0
Saline				
Acute	246.0	842.4	152.4	831.6
Chronic	225.6	771.6	111.6	1011.6
1.0 mg/kg				
Acute	615.6	1015.2	328.8	670.8
Chronic	684.0	1044.0	111.6	1200.0
3.0 mg/kg				
Acute	1032.0	1200.0	1032.0	1200.0
5.6 mg/kg				
Acute	1039.2	1200.0	1200.0	1200.0
Chronic	1200.0	1200.0	1140.0	1200.0
10.0 mg/kg				
Acute	1200.0	1200.0	1200.0	1200.0
Chronic	1200.0	1200.0	1200.0	1200.0
P449 45)	1st (FR 90)	2nd (FR 45)	3rd (FR 90)	4th (FR
Control				
Acute	838.8	115.2	1124.4	112.8
Chronic	1200.0	922.8	1200.0	576.0
Saline				
Acute	1052.4	129.6	1071.6	120.0
Chronic	1200.0	153.6	1200.0	162.0
0.3 mg/kg				
Acute	1200.0	138.0	1200.0	120.0
Chronic	1200.0	228.0	1200.0	168.0
1.0 mg/kg				
Acute	1200.0	138.0	1200.0	120.0
Chronic	1200.0	276.0	1200.0	180.0
3.0 mg/kg				
Acute	1200.0	986.4	1200.0	1200.0
Chronic	1200.0	922.8	1200.0	576.0
5.6 mg/kg				
Acute	1200.0	1200.0	1200.0	762.0
Chronic	1200.0	1200.0	1200.0	1200.0
10.0 mg/kg				
Acute	1200.0	1200.0	1200.0	1200.0
Chronic	1200.0	1200.0	1200.0	1200.0

administration. The "index of recovery" was calculated by determining the percentage of the total possible component time (20 min) used following acute and chronic administration and subtracting the percentage of time used during the chronic-administration phase from that used during the acute-administration phase. For example, for P75, responding was completely suppressed during the first component following all three acute determinations of 5.6 mg/kg cocaine. This resulted in a mean component duration for the first component of 1200 sec or 100% of total possible time. During chronic administration of 5.6 mg/kg cocaine, on the other hand, the mean component time used during the first component was 196.8 sec or 16.4% of the total possible time. By subtracting 16.4% from 100%, it can be concluded that an average of 83.6% recovery occurred during the first component of the Mult schedule for P75 following daily injections of 5.6 mg/kg cocaine. Table 5 presents the "degree of recovery" for each component for each subject. Inspection of Table 5 reveals that, for the most part, recovery from cocaine's rate suppressive effects was greater during shorter ratios than during longer ratios, the lone exception being responding in the third component (FR 5) for P75. Considering the first and second halves of sessions as separate comparisons, in 7 of 8 possibilities, recovery was more pronounced in the shorter ratio.

Table 5

Index of recovery from cocaine's acute effects as calculated from changes in component durations for each component of the Mult schedule.

	1	2	3	4
P75 (FR 5 FR 45)	83.6	64.1	12.9	46.8
P711 (FR 45 FR 5)	-21.7	20.5	-10.5	46.7
P714 (FR 45 FR 90)	5.4	6.2	75.9	--
P449 (FR 90 FR 45)	--	5.3	--	52.0

Figure 7 displays dose-effect curves for response rates minus pause time (run rates). The effects of cocaine on run rates are expressed as a percentage of run rates following saline injections. Table 2 presents control run rates and run rates following saline administration.

With only two exceptions, acute administration of cocaine produced orderly dose-related decreases in run rates. The two exceptions are at 10.0 mg/kg during FR 5 for P711 and at 5.6 mg/kg during FR 45 for P449. These findings are essentially in accord with those observed with overall rates. Also consistent with the latter measure is that run rates under Mult FR 45 FR 90 appeared more sensitive to cocaine's effects than those under Mult FR 5 FR 45, especially at the larger doses.

Following chronic administration of 5.6 mg/kg cocaine, no change in effect was observed during FR 5 until the largest dose at which tolerance developed for P75. During FR 45, tolerance was observed at the two largest doses. These effects are similar to those observed with overall rates where tolerance was observed during both FR 5 and FR 45 components.

The effects of daily cocaine administration on run rates were less similar to those observed during acute administration. Sensitization was observed at the largest dose for P711 during FR-5 components, whereas during FR 45, no change occurred at the two smallest doses and

Figure 7. Dose effects of cocaine on run rates under each FR schedule size for each subject during acute (open symbols) and chronic (closed symbols) administration of cocaine. Subjects and fixed-ratio schedules are indentified in the upper right-hand corner of each graph. Dose-effect curves in the left column show the effects of cocaine on run rates under the smaller FR schedules. Dose-effect curves in the left column show the effects of cocaine on run rates under the larger FR schedules. Effects of cocaine on run rates are expressed as a percentage of run rates following saline injections. Asterisks denote the chronically-administered doses. Bars indicate ranges of saline's effects expressed as a percentage of mean saline effects.

sensitization occurred at the two largest doses. With overall rates, on the other hand, tolerance was observed at the largest dose (see Figure 4).

For P714, tolerance was observed at 3.0 mg/kg during FR 45. During FR 90, tolerance also was observed at the chronically administered dose (3.0 mg/kg) while no change in effect was observed at any other dose. Tolerance was observed at 3.0 mg/kg with overall rates also.

For P449, sensitization occurred at the two smallest doses during FR 45. Tolerance was observed at the chronically administered dose (3.0 mg/kg). Run rates were completely suppressed at all but the smallest dose during FR 90 following daily administration of 3.0 mg/kg. This resulted in sensitization at 1.0 mg/kg. Once again, similar results were observed with overall rates. Tolerance was observed at 3.0 mg/kg and sensitization was observed at the two smallest doses during FR 45 with overall rates.

In summary, the effects observed with run rates were less dependent on reinforcement schedule than those observed with overall rates. In general, however, the effects observed with run rates were similar to those observed with overall rates.

Discussion

The results from Experiment 1 suggest that the context within which FR 45 occurred may have been an

important factor determining whether tolerance developed during that schedule. Although Figures 5 and 6 show that tolerance developed during FR 45 both when it was the smaller and the larger of the two schedules, tolerance was observed during FR 45 when it was the larger of the two schedules with only one of the two subjects (P75) responding under Mult FR 5 FR 45. When FR 45 was the smaller of the two schedules (during Mult FR 45 FR 90), tolerance was observed during that schedule for both subjects.

The conservative measure of "instances" of tolerance presented in Table 3 confirms the observation that context played an important role. Table 3 shows that "instances" of tolerance observed during FR 45 tended to depend on the context within which FR 45 was found. Specifically, during Mult FR 5 FR 45, 4 of 24 instances of tolerance were observed during FR 45, whereas during Mult FR 45 FR 90, 31 of 31 instances of tolerance were observed during FR 45. Thus, the results from Experiment 1 provide evidence that the context within which a particular FR schedule is found can play an important role in whether tolerance is observed. Table 3 also shows that tolerance was much more likely to be observed during the second half of sessions.

Absolute ratio size also appeared to be a determinant of whether tolerance was observed. Figures 5 and 6 indicate that within a particular multiple

schedule, tolerance was more likely to develop during the smaller of the two ratio schedules. Some tolerance was observed during the larger of the two schedules also, however, and tolerance during the larger schedules occurred when both FR 45 and FR 90 were the larger schedules. More specifically, Figures 5 and 6 show that the behavior of one of the subjects responding under Mult FR 5 FR 45 and one of those responding under Mult FR 45 FR 90 showed some tolerance during both multiple schedule components. Conversely, the behavior of the other subject responding under each multiple schedule developed tolerance in a schedule-dependent manner, i.e., only during the smaller-ratio component. Table 3 shows no "instances" of tolerance during FR 90, however.

The results from Experiment 1, therefore, indicate that the number of responses required by the various FR schedules used in the present experiment may also have been a variable responsible for whether tolerance was observed. This finding supports the suggestion of Hoffman et al. (1987) and Branch and Dearing (1982) that response requirement may modulate tolerance development. As mentioned above, some degree of tolerance was observed during each of the three component ratios. It may be the case, therefore, that tolerance to cocaine's effects is more likely to develop during ratio schedules similar in size to those used in the present experiment.

Overall, in the present experiment, when tolerance developed to the behavioral effects of cocaine, it was more likely to develop following administration of the chronically-administered dose than following administration of the other doses. Figures 4, 5, 6 and 7, show that tolerance developed most consistently at the chronically-administered dose. This observation is supported by the data in Table 3 showing that more "instances" of tolerance were observed following administration of the chronically-administered dose. Of the other doses, tolerance was more likely to develop following injections of doses larger than the daily dose than following smaller doses. However, for one subject (P711), the chronically-administered dose was the largest dose that that subject received. Whether or not tolerance would have been observed at doses larger than the daily dose for P711 is, therefore, unknown.

During Experiment 1, the rates and patterns of responding under the fixed-ratio schedules were typical of fixed-ratio performance (Ferster and Skinner, 1957). Figure 1 shows that following saline injections during acute administration, high steady rates of responding were maintained. That preratio pauses grew as ratio size increased is also consistent with previous research (Felton and Lyon, 1966). Thus, under baseline conditions, the behavior maintained by the Mult FR schedules was

characteristic of behavior maintained under this type of schedule.

Also in accord with previous research were the effects of acute administrations of cocaine. Acute administration of cocaine produced dose-related decreases in response rates during all three component schedules used in Experiment 1. This finding stands in agreement with previous research (e.g., Hoffman et al., 1987; Bacotti, 1980) and shows that the effects of cocaine prior to chronic administration observed in the present experiment were not atypical.

In conclusion, two variables have been identified as possible determinants of the development of tolerance during the Mult FR schedules employed in Experiment 1: the context within which a particular ratio is found and absolute ratio size. Raising the response requirements of the FR schedules might shed light on the role of these variables in the development of tolerance. By raising the response requirements, larger differences, in terms of number of responses, would exist between the component schedules. The increased difference between the component schedules would then provide new conditions under which to observe whether the context within which a schedule occurs is an important determinant in the development of tolerance. Experiment 2 explored this possibility by employing multiple fixed-ratio schedules with FR 100, rather than FR 45, as the common schedule. Four

experimentally naive subjects were used; two responding under Mult FR 10 FR 100 and two others responding under FR 100 FR 200.

CHAPTER III

EXPERIMENT II

Method

Subjects

Four adult male, experimentally naive White Carneau pigeons served as subjects. They were maintained and housed under the same conditions as in Experiment 1.

Apparatus

The experimental chamber and the programming and monitoring equipment were the same as those used in Experiment 1.

Behavioral Procedure

The details of the procedure were the same as Experiment 1 except in the final FR schedules used in the Mult schedules. Following training on Mult RR 5 RR 5, the response requirements for two of the subjects (P423 and P566) were raised to FR 10 and FR 100 (Mult FR 10 FR 100). For the remaining two subjects (P498 and P522) the requirements were raised to FR 100 and FR 200 (Mult FR 100 FR 200).

Assessment of Acute Drug Effects

Following 16 sessions for P423, 49 for P566, 49 for P498 and 28 for P522, responding was deemed stable via visual inspection of the daily plots of response rates. The effects of acute administration of cocaine were then determined. Each dose of cocaine, prepared as in Experiment 1, was administered at least twice before sessions that were separated by at least three sessions. Saline was also administered at least twice. The first two administrations of the doses of cocaine were done in an ascending order (1.0, 3.0, 5.6 and 10.0 mg/kg for three subjects and 1.0, 3.0, 5.6, 10.0, and 13.0 mg/kg for P522). Injections were made just before the 5 min time-out that preceded sessions. Table 6 displays the number of administrations of saline and each dose for each subject.

Assessment of Chronic Drug Effects

Following the assessment of the acute effects of cocaine and at least 5 days after the last cocaine injection, the effects of daily cocaine administration were determined. The dose chosen as the chronically administered dose was determined for each subject by inspection of the acute dose-effect curves and was the lowest dose that produced consistent decreases in responding during both ratios. The chronically administered dosage used for P423 and P566 was 5.6 mg/kg

Table 6

Total number of administrations of saline and each dose of cocaine under acute- and chronic-administration phases for each subject.

P423

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	5	2	2	2	2
Chronic	3	4	5	14	2

P566

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	6	3	5	5	3
Chronic	4	2	2	11	3

P498

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>
Acute	3	3	3	2	3
Chronic	2	2	3	2	9

P522

	<u>Saline</u>	<u>1.0</u>	<u>3.0</u>	<u>5.6</u>	<u>10.0</u>	<u>13.0</u>
Acute	5	2	2	7	6	2
Chronic	5	2	4	2	15	2

cocaine and the dosage used for P498 and P522 was 10.0 mg/kg cocaine. The effects of the other doses of cocaine were redetermined once responding during chronic administration was deemed stable by visual inspection of daily plots of overall response rates. That is, following 70 days of daily administration for P423, 21 days for P566, 39 days for P498 and 44 days for P522, saline and the other doses of cocaine were occasionally substituted for the chronically administered dose. The substitutions were administered at least 4 sessions apart. Each dose and saline were substituted at least twice. The chronic-administration phase lasted 204 days for P423, 164 days for P566, 101 days for P498 and 167 days for P522. Table 6 displays the number of administrations of saline and each dose for each subject.

Results

Figure 8 presents cumulative records for Subjects P566 and P522. The first two rows show the effects of saline and 5.6 mg/kg cocaine under acute- and chronic-administration conditions for P566. The 5.6-mg/kg dose was administered chronically. The first and third components consisted of FR 100 and the second and fourth components consisted of FR 10. During the acute phase, responding was well maintained following saline injections; high, steady response rates and short pre-ratio pauses were observed. Administration of 5.6 mg/kg

Figure 8. Cumulative response records for Subjects P566 and P522. The top two rows show records for P566. The first row of records shows the effects of saline and 5.6 mg/kg cocaine on responding during determination of the acute effects of cocaine. The second row shows records following injection of saline and 5.6 mg/kg cocaine during the chronic-administration phase. The third and fourth rows show records for P522. The third row shows records following injection of saline and 10.0 mg/kg cocaine during the acute-administration phase and the fourth row shows records following injection of saline and 10.0 mg/kg cocaine during the chronic-administration phase. Downward deflections of the response pen indicate food deliveries. The response pen reset at the completion of each component. The event pen was up during the first and third components and down during the second and fourth components.

cocaine during the acute-administration phase completely suppressed responding for the entire session following each administration.

The second row of records shows the effects of saline and 5.6 mg/kg cocaine during the chronic-administration phase. When saline was substituted for 5.6 mg/kg cocaine, overall response rates during FR 100 returned to levels somewhat lower than those observed during the acute phase. Although longer preratio pauses were observed, once responding had begun, high, steady rates were observed. During FR 10, following saline administration, response rates were similar to those observed during the acute phase. During the chronic administration of 5.6 mg/kg cocaine, response rates remained suppressed during FR 100 but returned nearly to baseline levels during FR 10.

The third and fourth rows of Figure 8 show the effects of saline and 10.0 mg/kg cocaine on the responding of Subject P522 during the acute- and chronic-administration phases. The dose that was administered chronically was 10.0 mg/kg. Responding was reinforced under FR 200 during the first and third components and under FR 100 during the second and fourth components. During the acute-administration phase, responding was well maintained following saline injections. During FR 200, overall response rates were lower than during FR 100. This can be seen in the first and third components

where longer preratio pauses and pausing after responding had begun occurred. When 10.0 mg/kg cocaine was administered during the acute-administration phase, responding was suppressed completely during all components of the Mult schedule during the session displayed. However, there were occasions during other sessions when some responding occurred during FR-100 components.

During the chronic administration of 10.0 mg/kg cocaine, responding never recovered during FR 200 following saline injection or following the substitution of any of the other doses of cocaine. However, responding did recover to approximately 60% of baseline levels during FR 100 following saline injections. These effects are shown in the bottom left panel.

The lower most right-hand panel shows that responding recovered to varying degrees during the FR 100 components following the daily administration of 10.0 mg/kg cocaine. During the second component, a relatively long pause occurred before the second ratio in this session and the subject stopped responding altogether following the fourth reinforcer delivery. During the fourth component of this session, responding occurred at a level similar to that observed during baseline. This record is representative of those obtained during the chronic-administration phase in that more responding and

higher rates of responding typically occurred during the fourth component compared to the second.

In summary, the cumulative records show that when saline was administered on an acute basis, responding occurred, with few exceptions, at high, steady rates with short preratio pauses. When the to-be-chronically administered dose was administered during the determination of the acute effects of cocaine, responding was suppressed completely during all components of the Mult schedule for both subjects during these sessions. When that dose was administered daily, responding returned to near baseline levels during the shorter of the two ratio schedules but remained suppressed during the longer of the ratios for both subjects. During the repeated-administration phase, responding following saline injection differed to a small extent from that seen during acute administration for P566. For P522, saline administration was followed by a complete absence of pecking during FR 200. During the shorter ratio (FR 100), responding returned to near baseline levels.

Figures 9 and 10 show daily response rates for the last seven sessions of the acute-administration phase, the first 25 sessions of the chronic-administration phase and the last seven sessions of the chronic-administration phase for all subjects in Experiment 2. For P423, during FR 10 components, responding was suppressed completely during the first four sessions of the chronic-

Figure 9. Daily response rates for the last seven sessions of the acute-administration phase, the first 25 sessions of the chronic-administration phase and the last seven sessions of the chronic-administration phase for each component ratio size for P423 and P566.

SESSIONS

RESP/MIN

Figure 10. Daily response rates for the last seven sessions of the acute-administration phase, the first 25 sessions of the chronic-administration phase and the last seven sessions of the chronic-administration phase for each component ratio size for P498 and P522.

RESP/MIN

SESSIONS

administration phase. Following eleven sessions of daily injections of 5.6 mg/kg cocaine, response rates, although variable, did recover to levels higher than those observed following the acute administration of that dose. During FR 100 components, responding was suppressed completely during the first three session of the chronic administration phase. From the fifth to the twenty-fifth sessions, however, responding returned to levels near those observed during baseline. By the end of the experiment response rates again were completely suppressed.

For P566, response rates during FR 10 components were suppressed during four of the first five sessions of daily administration of 5.6 mg/kg cocaine. Following the fifth session, response rates returned to baseline levels where they remained for the rest of the experiment. During FR 100 components, response rates were completely suppressed during all but two sessions during the chronic-administration phase.

Response rates were suppressed completely during FR-100 components following each of the first 39 injections of 10.0 mg/kg cocaine during the chronic-administration phase for P498. Preceding the 40th session, the first substitution of saline for 10.0 mg/kg cocaine took place and responding recovered to approximately 20% of baseline. From that point to the end of the experiment, P498 responded at low rates during FR-100 components.

During FR 200 components, responding was suppressed completely during six of the first seven sessions of the chronic-administration phase and then recovered to a level somewhat lower than those observed during baseline. Response rates decreased further to very low level by the end of the experiment.

Response rates recovered to baseline levels during FR-100 components following the fourth session of the chronic-administration phase for P522. Following the tenth session, however, rates decreased to low levels where they remained for the duration of the experiment. During FR-200 components, response rates were suppressed completely during the chronic-administration phase.

To summarize, the effects of cocaine on response rates during the first 25 days of chronic administration were very inconsistent. The effects observed ranged from complete recovery of response rates to complete suppression. At the end of the chronic-administration phase, however, the effects of cocaine on responding were schedule dependent for all animals. That is, response rates recovered to varying degrees during the smaller FR schedules but remained suppressed during the larger FR schedules for all subjects.

Figure 11 presents complete dose-effect curves for each component-schedule size for both acute and chronic conditions for all subjects. In all but three cases, acute administration of cocaine produced dose-related

Figure 11. Dose effects of cocaine on response rates under each FR schedule size for each subject during acute (open symbols) and chronic (closed symbols) administration of cocaine. Subjects and fixed-ratio schedules are identified in the upper right-hand corner of each graph. Dose-effect curves in the left column show the effects of cocaine on responding under the smaller FR schedules. The dose-effect curves in the right column show the effects of cocaine on responding under the larger FR schedules. Points above C are means from sessions that preceded those during which drug effects were examined during the acute-administration phase. Points above V show mean effects of injecting the saline vehicle. Bars indicate 95% confidence intervals.

decreases in responding. Those exceptions are at 1.0, 3.0 and 5.6 mg/kg cocaine during FR 200 for P498 where increases in response rates were observed.

Control rates of responding depended on ratio size with higher control rates occurring under the smaller ratios in all cases. However, differences in control rates during FR 100 in the context of FR 10 compared to in the context of FR 200 were less consistent. In only one case (P498) were control rates during FR 100 when it was the smaller of the two ratios higher than control rates during FR 100 when it was the larger ratio.

During the chronic administration of 5.6 mg/kg cocaine, tolerance developed at that dose during FR 10 for P423. No change in saline's effect was observed. During FR 100, on the other hand, the effect of saline injections changed drastically. Response rates following saline injections during the chronic-administration phase were approximately four times those observed during the acute phase. In addition, response rates following the various doses of cocaine were considerably lower than those following saline injection. As a result, it is difficult to characterize the changes in the effects of the various doses of cocaine following chronic administration of 5.6 mg/kg. In terms of change as a percentage of rates following saline injection, sensitization occurred at the three smallest doses. However, following chronic administration, response rates following the

administration of the three smallest doses were not reduced to the levels observed following acute administration.

For P566, tolerance and sensitization to cocaine's effects developed in a schedule-dependent manner. That is, tolerance developed at all doses during FR 10 following the daily administration of 5.6 mg/kg cocaine. Sensitization developed at 1.0 mg/kg cocaine and responding was completely suppressed at all other doses during FR 100. Saline's effects did not change during FR 10 following the daily administration of 5.6 mg/kg cocaine but, following saline injection during FR 100, response rates were somewhat lower than they had been during acute administration.

For P498, the effects of saline injections changed to a large extent during both components following the chronic administration of 10.0 mg/kg cocaine. Response rates were much lower following saline injections during the chronic phase under FR 100 but higher under FR 200. Compared to rates following saline injections, the doses of cocaine produced less of an effect on responding under FR 100 during the chronic-administration phase than during the acute-administration phase (i.e., tolerance was observed). On the other hand, whereas response rates were increased at the three smallest doses during acute administration under FR 200, response rates were

increased at 1.0 mg/kg only and decreased at 5.6 mg/kg. That is, sensitization occurred at 5.6 mg/kg cocaine.

Sensitization was observed at 3.0 mg/kg during FR 100 for P522. At the chronically administered dose (10.0 mg/kg) no change in effect was observed whereas tolerance was observed at 13.0 mg/kg. As was mentioned in the description of Fig. 8, responding was suppressed completely during all FR 200 components following the daily administration of 10.0 mg/kg cocaine. Responding did not recover at all following saline injection or the injection of any of the substituted doses.

In summary, tolerance to cocaine's rate-decreasing effects developed consistently during the shorter of the two ratios. On the other hand, sensitization was more likely to develop during longer ratios. That is, tolerance developed in a schedule-dependent manner. Some degree of tolerance was observed at the larger doses for three of the subjects and at all doses for P566 during the shorter ratios.

In order to assess the time course of cocaine's effects within experimental sessions, response rates were calculated for each component of the Mult schedule. The dose effects of cocaine on responding during each component are displayed in Figures 12 and 13 and are expressed as a percentage of response rates following saline injections during that component. Control response

Figure 12. Effects of cocaine on responding during each of the four multiple-schedule components for Subjects P423 (left column) and P566 (right column). The first row of graphs shows effects during the first component of sessions, the second row shows effects during the second component and so on. Effects of cocaine on response rates during acute (open symbols) and chronic (closed symbols) administration are expressed as a percentage of response rates following saline injections. The chronically-administered doses are denoted by asterisks. Bars indicate ranges of saline's effects expressed as a percentage of mean saline effects.

Figure 13. Effects of cocaine on responding during each of the four multiple-schedule components for Subjects P498 (left column) and P522 (right column). The first row of graphs shows effects during the first component of sessions, the second row shows effects during the second component and so on. Effects of cocaine on response rates during acute (open symbols) and chronic (closed symbols) administration are expressed as a percentage of response rates following saline injections. The chronically-administered doses are denoted by asterisks. Bars indicate ranges of saline's effects expressed as a percentage of mean saline effects.

rates and response rates following saline injections are presented in Table 7.

In general, the acute administration of cocaine produced dose-related decreases in responding for P423, although there were two instances where 1.0 mg/kg cocaine produced increases in responding above those observed following saline injections (e.g., during the first and fourth components).

Tolerance and sensitization occurred to some extent at some doses during both schedule components for P423 following daily injections of 5.6 mg/kg cocaine. During FR-10 components, tolerance was observed at the two largest doses during the third component. During FR-100 components, tolerance was observed at 3.0 and 5.6 mg/kg during the fourth component and sensitization was observed at 1.0 mg/kg cocaine during that component.

For P566, the acute administration of cocaine produced consistent dose-related decreases in responding. The effects of the daily administration of 5.6 mg/kg cocaine also produced very consistent effects with P566. Almost complete recovery of responding was observed at all doses during FR-10 components while complete or nearly complete suppression of responding was observed during FR-100 components; that is, tolerance was observed at all doses during the shorter schedule components and sensitization was observed at all doses except the largest one during the longer schedule components.

Table 7

Mean response rates under each component schedule during control sessions and following saline administration for each subject under acute and chronic conditions.

	Acute	Chronic
P423		
Overall Rates		
Control		
FR 10	146.8	47.0 (5.6 COC)
FR 100	27.2	13.3 (5.6 COC)
Saline		
FR 10	138.8	141.4
FR 100	28.5	113.8
Run Rates		
Control		
FR 10	211.4	162.9
FR 100	83.5	22.5
Saline		
FR 10	209.5	231.7
FR 100	84.4	151.6
P566		
Overall Rates		
Control		
FR 10	159.3	116.2 (5.6 COC)
FR 100	96.3	0 (5.6 COC)
Saline		
FR 10	159.0	153.8
FR 100	78.8	60.6
Run Rates		
Control		
FR 10	236.8	190.6
FR 100	129.2	0
Saline		
FR 10	240.3	235.8
FR 100	123.0	101.7
P498		
Overall Rates		
Control		
FR 100	206.8	38.0 (10.0 COC)
FR 200	126.7	21.4 (10.0 COC)
Saline		
FR 100	166.6	94.6
FR 200	160.6	95.3
Run Rates		
Control		
FR 100	225.2	72.0
FR 200	46.0	35.7
Saline		
FR 100	219.4	204.0
FR 200	79.1	126.2

Table 7, Cont.

P552

Overall Rates

Control

FR 100 100.5 18.7 (10.0 COC)

FR 200 33.3 0 (10.0 COC)

Saline

FR 100 109.5 66.7

FR 200 42.2 0

Run Rates

Control

FR 100 133.5 40.7

FR 200 69.0 0

Saline

FR 100 133.5 94.1

FR 200 61.8 3.0

For P498, acute administration of cocaine produced dose-related decreases in response rates. However, during the fourth component (FR 200), cocaine produced increases in response rates compared to those observed following saline injections and compared to control sessions. The increases observed during the fourth component were very large proportionally. Responding was more sensitive to cocaine's rate-decreasing effects during FR-100 components.

Sensitization and tolerance developed in a schedule-dependent manner for P498. Tolerance was observed at the two largest doses during the third (FR 100) component. Sensitization developed at the two largest doses of cocaine during the fourth component (FR 200).

For P522, the smaller doses of cocaine produced increases in response rates compared to those observed following saline injections during the second and third components. In general, however, behavior was more sensitive to cocaine's effects during FR-200 components.

Tolerance developed in a schedule-specific manner for P522. Tolerance was observed at the largest dose during both FR-100 components, although it developed more fully during the final component. Sensitization was observed at the three smallest doses during the FR-200.

In summary, Figures 12 and 13 show that tolerance was more likely to develop during the shorter ratio components. In addition, an analysis of the cumulative

records from the chronic-administration phase revealed that, at doses that produced reliable decreases in response rates following acute administrations, 61 "instances" occurred where response rates following all administrations during the chronic-administration phase were higher than the mean effect observed during the acute-administration phase (see Table 8). Of those 61 instances, 56 occurred during the smaller of the two ratios. Figures 12 and 13 also reveal that, in most cases, when tolerance developed during the shorter ratio components, it developed more fully during the second of the two shorter ratio components, i.e., during the second half of sessions.

Component-schedule lengths during control sessions and following injection of saline and the doses of cocaine are given in Table 9. From the data in Table 9, an "index of recovery" was derived. This measure indicates the degree to which component lengths changed during the chronic-administration phase compared to component lengths during acute administration. The "index of recovery" was calculated, as in Experiment 1, by determining the percentage of the total possible component time used following acute and chronic administration and subtracting the percentage of time used during the chronic-administration phase from that used during the acute-administration phase. Table 10 presents the degree of recovery for each component of the

Table 8

Counts of the number of instances where administration of each dose of cocaine during the chronic-administration phase produced a smaller rate-reducing effect than the mean acute effect. In parentheses are the number of times that acute administration of each dose produced rates lower than the lowest rate during control sessions along with the total number of times that that dose was administered acutely.

P423

	1st (FR 10)	2nd (FR 100)	3rd (FR 10)	4th (FR 100)
1.0	0	0	0	0
3.0	0	0	0	5 (2/2)
5.6	0	0	14 (2/2)	0
10.0	2 (2/2)	0	2 (2/2)	0

P566

	1st (FR 100)	2nd (FR 10)	3rd (FR 100)	4th (FR 10)
1.0	0	0	0	0
3.0	0	2 (4/5)	0	2 (4/5)
5.6	0	12 (5/5)	0	12 (4/5)
10.0	0	3 (3/3)	0	3 (3/3)

P498

	1st (FR 100)	2nd (FR 200)	3rd (FR 100)	4th (FR 200)
1.0	0	0	0	0
3.0	0	0	0	0
5.6	0	0	2 (2/2)	0
10.0	0	0	0	0

P522

	1st (FR 200)	2nd (FR 100)	3rd (FR 200)	4th (FR 100)
1.0	0	0	0	0
3.0	0	0	0	0
5.6	0	0	0	0
10.0	0	0	0	0
13.0	0	0	0	2 (2/2)

Table 9

Mean multiple schedule component lengths (in seconds) during control sessions and following injections of saline and each of the doses during acute and chronic administration conditions.

P423 1st (FR 10)	2nd (FR 100)	3rd (FR 10)	4th (FR 100)
Control			
Acute 25.2	933.6	21.6	1057.2
Chronic 268.8	1194.0	24.0	1105.2
Saline			
Acute 28.8	892.8	25.2	981.6
Chronic 24.0	345.6	21.6	296.4
1.0 mg/kg			
Acute 24.0	1146.0	24.0	792.0
Chronic 27.6	502.8	22.8	913.2
3.0 mg/kg			
Acute 36.0	1200.0	24.0	1200.0
Chronic 50.4	1008.0	22.8	1058.4
5.6 mg/kg			
Acute 618.0	1200.0	1200.0	1200.0
10.0 mg/kg			
Acute 1200.0	1200.0	1200.0	1200.0
Chronic 726.0	1200.0	72.0	1200.0
P566 1st (FR 100)	2nd (FR 10)	3rd (FR 100)	4th (FR 10)
Control			
Acute 351.6	22.8	387.6	22.8
Chronic 1200.0	24.0	1200.0	24.0
Saline			
Acute 416.4	21.6	336.0	19.2
Chronic 720.0	24.0	307.2	21.6
1.0 mg/kg			
Acute 795.6	414.0	752.4	416.4
Chronic 1200.0	24.0	1200.0	24.0
3.0 mg/kg			
Acute 1046.4	964.8	1113.6	963.6
Chronic 1200.0	24.0	1200.0	24.0
5.6 mg/kg			
Acute 1034.4	964.8	1065.6	964.8
10.0 mg/kg			
Acute 1200.0	1200.0	1200.0	1200.0
Chronic 1200.0	32.4	1200.0	24.0

Table 9, Cont.

P498 1st (FR 100)	2nd (FR 200)	3rd (FR 100)	4th (FR 200)
Control			
Acute 168.0	1138.8	153.6	1150.8
Chronic 1200.0	1200.0	900.0	1006.8
Saline			
Acute 192.2	699.6	156.0	1068.0
Chronic 714.0	768.0	156.0	540.0
1.0 mg/kg			
Acute 380.4	452.4	180.0	468.0
Chronic 492.0	510.0	174.0	444.0
3.0 mg/kg			
Acute 260.4	524.4	200.4	512.4
Chronic 860.4	720.0	168.0	576.0
5.6 mg/kg			
Acute 1200.0	852.0	1200.0	594.0
Chronic 1200.0	1200.0	234.0	1026.0
10.0 mg/kg			
Acute 1200.0	1200.0	1200.0	1200.0
P522 1st (FR 200)	2nd (FR 100)	3rd (FR 200)	4th (FR 100)
Control			
Acute 1144.8	352.8	1146.0	301.2
Chronic 1200.0	1200.0	1200.0	816.0
Saline			
Acute 1200.0	290.4	1164.0	300.0
Chronic 1200.0	640.8	1200.0	667.2
1.0 mg/kg			
Acute 1200.0	234.0	1200.0	258.0
Chronic 1200.0	780.0	1200.0	444.0
3.0 mg/kg			
Acute 1200.0	324.0	1182.0	246.0
Chronic 1200.0	684.0	1200.0	546.0
5.6 mg/kg			
Acute 1200.0	559.2	1200.0	475.2
Chronic 1200.0	1038.0	1200.0	384.0
10.0 mg/kg			
Acute 1200.0	1046.4	1200.0	909.6
Chronic 1200.0	1200.0	1200.0	816.0
13.0 mg/kg			
Acute 1200.0	1200.0	1200.0	1200.0
Chronic 1200.0	1200.0	1200.0	504.0

Mult schedule for each subject and reveals that in all cases recovery from cocaine's rate suppressive effects was greater during the shorter ratio components than during longer ratio components.

Figure 14 displays dose-effect curves for run rates during each of the component schedule sizes for each of the subjects. The effects of acute and chronic cocaine administration are expressed as a percentage of response rates following vehicle injections. Table 6 presents control run rates and run rates following saline injections.

In most cases, acute administration of cocaine produced dose-related decreases in run rates. The two smallest doses had little or no effect on run rates during the shorter ratio components for P423 and P522.

The effects of the chronic administration of cocaine on run rates were very similar to those observed with overall rates in Figures 11, 12 and 13. In general, tolerance developed during the shorter ratio components and sensitization developed during longer ratio components. For P423, a variety of effects was observed. Tolerance was observed at the two largest doses during FR-10 components. During FR-100 components, tolerance occurred 5.6 mg/kg cocaine. As with overall rates, tolerance was observed at all doses during FR 10 for P566. Tolerance was observed at the two largest doses of cocaine during FR-100 components for P498. For P522,

Table 10

Index of recovery from cocaine's acute effects as calculated from changes in component durations for each component of the Mult schedule.

	1	2	3	4
P423 (FR 10 FR 100)	29.1	0.5	98.0	7.9
P566 (FR 100 FR 10)	-14.6	78.4	-11.2	78.4
P498 (FR 100 FR 200)	--	--	25.0	16.1
P449 (FR 200 FR 100)	--	-12.8	--	7.8

Figure 14. Dose effects of cocaine on run rates under each FR schedule size for each subject during acute (open symbols) and chronic (closed symbols) administration of cocaine. Subjects and fixed-ratio schedules are identified in the upper right-hand corner of each graph. Dose-effect curves in the left column show the effects of cocaine on run rates under the smaller FR schedules. Dose-effect curves in the right column show the effects of cocaine on run rates under the larger FR schedules. Effects of cocaine on run rates are expressed as a percentage of run rates following saline injections. Asterisks denote the chronically-administered doses. Bars indicate ranges of saline's effects expressed as a percentage of mean saline effects.

during FR 100, tolerance was observed following 13.0 mg/kg cocaine. During FR 200, run rates were suppressed completely following saline injections and all doses of cocaine.

In summary, the effects of cocaine on run rates were very similar to those observed with overall rates. Tolerance was more likely to develop during the shorter ratio components, especially at the higher doses. In fact, tolerance was observed at the largest dose during the shorter ratio components for all four subjects, whereas no change in the effect of the largest dose was observed during the longer ratio components for any subject.

DISCUSSION

The results from Experiment 2 provide strong evidence that the context within which FR 100 occurred was correlated with whether tolerance was observed during that schedule. Tolerance was observed more often during FR 100 components when it was the smaller of the two FR schedules than when it was the larger of the two FR schedules. That is, tolerance developed in a context-dependent manner during Experiment 2. The only tolerance observed during FR 100 when it was the larger of the two FR schedules occurred with one subject (P423) during the final component. When FR 100 was the smaller schedule, however, tolerance was observed during that schedule for

both subjects. Thus, the data from Experiment 2 support the suggestion made by Hoffman, et al. (1987) that the context within which a particular FR schedule is found may modulate the development of tolerance to the behavioral effects of cocaine during that schedule. Further support for this contention comes from the analysis of the cumulative records. Table 8 shows that of the instances of tolerance observed during Mult FR 10 FR 100, only 5 of 52 occurred during FR 100 while during Mult FR 100 FR 200 4 of 4 instances of tolerance were observed during FR 100. Although very few instances of tolerance were observed during Mult FR 100 FR 200, Figure 13 shows that there were changes in the effects of cocaine that suggested tolerance; particularly during the second half of sessions (i.e., the third component for P498 and the fourth component for P522).

Ratio size was also a determinant of whether tolerance was observed. Figures 12 and 13 show that when tolerance developed, it was more likely to develop during the smaller of the two ratios within a particular multiple schedule. The data in Table 8 confirm this observation. Tolerance was observed more often during FR 10 components than during any other. No tolerance was observed during FR 200 components. Thus, overall, tolerance developed in a schedule-dependent manner. These results are consistent with those of Hoffman, et al. (1987) and Branch and Dearing (1982) in that response

requirement under FR schedules was implicated as a factor in tolerance development.

As in Experiment 1, rates and patterns of responding in the absence of cocaine were typical of performance under fixed-ratio schedules. Some of the effects of acutely administered cocaine, however, were somewhat different from those observed by other researchers. At some doses and for some subjects, cocaine produced increases in response rates. Other researchers have found cocaine to produce dose-related decreases consistently in response rates (Hoffman et al. 1987; Schama and Branch, 1989; Bacotti, 1980).

The results of Experiment 2 indicate that tolerance was somewhat more likely to develop following administration of the daily dose than following injection of the other doses. Figures 11, 12, 13 and 14 and Table 8 show that, at doses where tolerance was observed, most occurred at the chronically administered dose. Of the other doses, tolerance developed nearly equally often following administration of doses larger and smaller than the daily dose.

CHAPTER IV

GENERAL DISCUSSION

The context within which an FR schedule exists can influence the development of tolerance to the behavioral effects of cocaine during that FR schedule. Experiments 1 and 2 showed that whether or not tolerance developed during a particular FR schedule (i.e., FR 45 in Experiment 1, FR 100 in Experiment 2) generally was dependent on whether it was the larger or smaller schedule in a two-component Mult FR schedule. Figures 5, 6, 12 and 13 show that tolerance was more likely to be observed during FR 45 in Experiment 1 and during FR 100 in Experiment 2 if those schedules occurred in the context of a larger FR schedule. Tables 3 and 8 confirm this observation by showing that "instances" of tolerance were much more likely to occur during the common FR schedule of the Mult FR schedules if that schedule was the smaller of the two schedules. Furthermore, Tables 5 and 10 show that, for the most part, recovery from cocaine's initial effects was greater during smaller ratio components. Thus, whether tolerance was observed during a particular schedule depended on whether it occurred in the context of a smaller or larger schedule.

These results are consistent with those of Hoffman et al. (1987) in that, during Mult FR schedules, tolerance developed differentially during the different-sized-ratio schedules. The present data support the notion that the amount of responding, or "effort", required by a particular FR schedule may be an important factor in the development of tolerance. That is, in the context of the multiple schedules studied, tolerance was more likely to develop during the schedules that required fewer responses per reinforcer. Figures 5, 6, 12 and 13 show that tolerance occurred at more doses during the smallest of the FR schedules (i.e., FR 5 and FR 10) than during any other. The present results are also consistent with those of Hughes and Branch (1991) in that when tolerance developed during both large and small FR's (Subjects P75, P714 & P423), it developed more fully during the smaller ratio schedules.

The results of the study by Hoffman et al. (1987) showed that tolerance did not develop during FR 125 when that schedule occurred in the context of smaller FR schedules. Similarly, during Experiment 2, tolerance was never observed during the largest schedule (FR 200) which occurred only in the context of an FR schedule half its size. Perhaps if FR 200 occurred in the context of larger schedules tolerance might be observed during FR 200 as well.

Unfortunately, little has been done to date exploring schedule parameter as the main independent variable in studies of cocaine tolerance. Smith (1986), however, did an experiment studying the effects of daily injections of 1-nantradol on responding by pigeons under FR 100 or FR 300. 1-Nantradol is a synthetic cannabinoid that resembles morphine in its analgesic effects. Smith (1986) found that tolerance developed to 1-nantradol's rate-decreasing effects for the subjects responding under FR 100 but not for the subjects responding under FR 300. When the response requirement was changed for those subjects responding under FR 300 to FR 100, tolerance was then observed. When the response requirement was changed for the subjects responding under FR 100 to FR 300, tolerance diminished. Along with the results of the present experiments and those of Hoffman et al. (1987), Smith's (1986) data support the suggestion that fixed-ratio size may be a factor in the development of tolerance, not only to cocaine but to other drugs as well.

Previous research has shown that pigeons will respond differentially on the basis of fixed-ratio size (Rilling & McDiarmid, 1965; Pliskoff & Goldiamond, 1966; Hobson, 1975). In a discrete trial procedure, Hobson (1975) trained pigeons to respond under fixed-ratio schedules on the center key of a three-key operant chamber. The ratios on the center key alternated on a

quasi-random basis between "large" and "small" ratios. When the ratio was completed on the center key, it was darkened and the two side keys were illuminated. Responding on one side key resulted in reinforcement if the ratio on the center key was the large one. Responding on the other key resulted in a 3-s timeout. The contingencies were reversed if the ratio on the center key was the small one. Each large ratio (FR 10, FR 20 or FR 30) was tested against a range of smaller ratios. Hobson (1975) found that as the difference between ratios decreased, fewer responses on the "correct" key were emitted. She also found that discriminability between ratios improved with absolute ratio size. Although Hobson (1975) used ratio schedules smaller than those used in the present experiments (FR 2-FR 30), her data show that differences between fixed-ratios can control behavior. The present results indicate that differences in ratio size may control whether tolerance will be observed as well.

A confound exists between absolute differences between ratios and proportional differences between ratios in the present experiments, however. For example, during Experiment 1, the differences in number of responses required between FR 5 and FR 45 and between FR 45 and FR 90 were similar (40 responses and 45 responses respectively). The proportional differences between the ratios in each multiple schedule were much less similar.

Fixed-ratio 45 requires 9 times the responses that FR 5 does whereas FR 90 requires only twice the responses as FR 45. Similar proportional differences between ratios in each multiple schedule existed in Experiment 2 also. The design of the present experiments arraigned for the differences between the ratios across the multiple schedules in each experiment to be approximately equal. Future research should examine whether or not tolerance will develop differentially if proportional differences between ratios are equated across multiple schedules. Thus, the results of the present experiments provide some evidence that the differences in size between fixed-ratio schedules in multiple fixed-ratio schedules may be one aspect of the context within which a particular FR schedule is found that modulates the development of tolerance during that schedule.

The results of the present experiments add to others that suggest that the reinforcement-loss hypothesis accounts for only some conditions under which tolerance to the behavioral effects of drugs occurs. During Experiments 1 and 2, acute administration of cocaine consistently produced dose-related decreases in response rates. Under FR schedules, reductions in response rates result in reductions in reinforcement rates. In all cases where tolerance was observed, response rates (and, therefore, reinforcement rates) were suppressed following acute administration of cocaine. There were, however,

many instances where response rates were reduced following acute administration of cocaine and tolerance was not observed. In those cases, either sensitization or no change of effect was observed. Therefore, it does not appear that reinforcement loss is a sufficient condition for tolerance to develop in all cases. It may be the case that reinforcement loss only plays a role in the development of tolerance when the initial effect of the drug produces a reduction in relatively high rates of reinforcement, i.e., during small FR schedules, but not when rate of reinforcement is low. This conclusion is supported by the present data as well as those of Hoffman et al. (1986), and, to some degree, Hughes and Branch (1991), and Smith (1986), where tolerance was observed more often and/or to a greater degree during smaller FR schedules. Further research should attempt to specify the conditions that define whether or not the reduction of a particular reinforcement rate by the repeated administration of a drug will result in the development of tolerance to that effect.

Another difference between the results of the two experiments is that sensitization developed in different ways during the two experiments. During Experiment 1, some sensitization was observed during both the smaller and larger of the ratio schedules. Also, sensitization to the effects of some doses was observed during FR 45 when it was both the smaller and the larger schedule. During

Experiment 2, on the other hand, sensitization developed in a more schedule-dependent manner; that is, it was observed at more doses during larger ratios than during smaller ratios.

The fact that sensitization was observed at all stands in contrast with the results of Hoffman et al. (1987) and Schama and Branch (1989) where sensitization was not observed during three-component Mult FR or three-component Mult FI schedules. Hughes and Branch (1991), however, did observe changes in baseline response rates following chronic administration of cocaine in some cases. Those changes resulted in lower response rates following substitution of the various doses compared to those observed during acute administration. In general, however, tolerance, not sensitization, is the typical effect observed with operant behavior following chronic pre-session administration of cocaine (Branch & Sizemore, 1988; Branch & Dearing, 1982; Moore & Thompson, 1978; Woolverton, Kandel & Schuster, 1978a, 1978b; Thompson 1977). In fact, a review of the literature describing sensitization to "stimulant" drugs led Kilbey and Sannerud (1985) to conclude that no clear examples of sensitization during operant procedures had yet been published.

The conditions under which sensitization develops are not well understood. Other researchers, however, have reported sensitization to cocaine's effects on dependent

variables other than operant behavior; such as hyperactivity, stereotypy, startle response, and seizure (Downs & Eddy, 1932a, 1932b; Post, 1980; Post et al., 1981). As pointed out by Hoffman et al. (1987), however, the doses of cocaine used in those studies are typically larger than those used in research on operant behavior. The range of doses used in the present experiments was similar to those used by Hoffman et al. (1987) and Schama and Branch (1989) and yet sensitization occasionally was observed.

The present experiments were not designed explicitly to explore the conditions under which sensitization to cocaine's behavioral effects develops. However, the fact that both tolerance and sensitization were observed implies that the factors responsible for tolerance development also may be factors in whether sensitization will develop. The "effort" required by a particular FR schedule and the context within which a schedule occurs are implicated in the present experiments as modulators of both tolerance and sensitization. Further research should concentrate on identifying the conditions under which sensitization develops during experiments using operant procedures.

One such condition observed in the present experiments that might account for the observation of sensitization was the degree of maintenance of responding during the larger ratios for some subjects. During the

course of the experiments, it was observed that some subjects would occasionally stop responding during larger ratio components before all ratios had been completed. Since sensitization was observed most often during larger ratios, this relatively weak maintenance of responding might have been a factor in whether or not sensitization was observed during those ratios. A systematic examination of the effects of repeated cocaine administration on behavior under weak behavioral control would shed light on whether this variable is important in whether sensitization will be observed.

Another variable that may have contributed to the observation of sensitization in the present experiments is the dose of cocaine used as the daily dose. In most experiments examining the effects of repeated cocaine administration, the same dose was used as the daily dose for each subject (Hughes & Branch, 1991; Hoffman, Branch & Sizemore, 1987; Branch & Dearing, 1982; Woolverton, Kandel & Schuster, 1978a, 1978b). In the present experiments, however, different doses were administered chronically to different subjects within experiment. It is worth noting that sensitization consistently developed for those subjects who received 10.0 mg/kg cocaine as the daily dose (P714, P498 & P522) but less consistently for those subjects who received smaller doses.

Typically, acute administration of cocaine produces dose-related decreases in response rates during FR

schedules (e.g., Bacotti, 1980; Branch & Dearing, 1981; Hoffman et al, 1987; Hughes & Branch, 1991; McPhail & Seiden, 1975). For the most part that effect was observed during the present experiments, indicating that proper control of responding was maintained by the FR schedules and that the effects of cocaine on the subjects' behavior was similar to what has been observed by other researchers. Another difference between the results of Experiments 1 and 2, however, is the extent of sensitivity to cocaine's initial rate-decreasing effects observed during the two experiments. During Experiment 1, responding under Mult FR 45 FR 90 was somewhat more sensitive to the acute effects of cocaine. Inspection of Figures 5 and 6 reveals that responding was suppressed to a greater degree following the administration of 3.0 and 5.6 mg/kg cocaine for those subjects responding under Mult FR 45 FR 90 than for those responding under Mult FR 5 FR 45. Across the four subjects in Experiment 1, however, cocaine's acute effects did not appear to be schedule dependent; that is, the doses of cocaine produced similar effects regardless of ratio schedule. The only exception was at the two smallest doses for P449 where response rates during FR 90 were suppressed to a greater degree following acute administration than were rates during FR 45.

In contrast, during Experiment 2, responding under the multiple schedules with smaller ratios (Mult FR 10 FR

100) was more sensitive to the acute effects of cocaine than responding under the multiple schedule containing the larger FR schedules (FR 100 FR 200). Responding following injections of 1.0, 3.0 and 5.6 mg/kg was suppressed to a greater degree during Mult FR 10 FR 100 than during Mult FR 100 FR 200.

These differences in acute effects are reflected in the doses of cocaine used as the chronically-administered doses. In general, larger daily doses were needed to suppress responding consistently during Experiment 2 than during Experiment 1. During Experiment 1, 3.0 mg/kg cocaine was used as the chronically-administered dose for those subjects that responded under the largest schedules (FR 45 FR 90). During Experiment 2, on the other hand, 10.0 mg/kg served as the daily dose for the subjects responding under the largest schedules (FR 100 FR 200). The chronically-administered doses in both experiments were functionally similar, however, in that they were the doses that produced consistent decreases in response rates during both ratio schedules for each subject.

Further research designed to examine the development of tolerance and sensitization using two-component Mult FR schedules should address some of the shortcomings of the present experiments. For example, during the two experiments, the order in which component schedules occurred was counterbalanced across subjects responding under the same multiple schedules. In some cases

different effects were observed between subjects responding under the same multiple schedule. For example, in Experiment 1, tolerance was observed during all components for P75 but only during FR 5 components for P711. It is not suggested that component order was necessarily responsible for the differences, but including more subjects responding under each component-schedule order might reveal which was the more reliable effect. Another variable that might have been responsible for the different effects observed between P75 and P711 is the dose used as the daily dose. Subject P75 received a smaller daily dose (5.6 mg/kg) than did P711 (10.0 mg/kg). Future research should address whether dosage and schedule parameter interact in such a way as to account for some of the differences in effect observed in the present experiments.

In summary, the results of the two experiments show that in two-component Mult FR schedules the context within which a schedule occurs is correlated with the likelihood that tolerance to the behavioral effects of cocaine will be observed during that schedule. In addition, the present experiments show that tolerance is more likely to develop during the smaller ratio schedule in two-component Mult FR schedules. It was also demonstrated that sensitization can occur in a schedule-dependent fashion in that in the present experiments it was observed more frequently during larger ratio

schedules than during smaller ratio schedules. The fact that sensitization was observed at all in the present experiments is unusual compared to previous studies of the effects of repeated cocaine administration on operant behavior and deserves further investigation.

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BIOGRAPHICAL SKETCH

Forrest John Files was born on March 6, 1955, in Oil City, PA. He received his B.A. in psychology from Lycoming College, Williamsport, PA, in 1978. After receiving his M.S. in psychology from Northeast Louisiana University in 1982, he attended the University of Florida where he received his Ph.D. in psychology in May, 1992.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Marc N. Branch, Chairman
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

E. F. Malagodi
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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