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INFLUENCES ON COCAINE TOLERANCE ASSESSED UNDER A MULTIPLE CONJUNCTIVE SCHEDULE OF REINFORCEMENT

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Under multiple schedules of reinforcement, previous research has generally observed tolerance to the rate-decreasing effects of cocaine that has been dependent on schedule-parameter size in the context of fixed-ratio (FR) schedules, but not under the context of fixed-interval (FI) schedules of reinforcement. The current experiment examined the effects of cocaine on key-pecking responses of White Carneau pigeons maintained under a three-component multiple conjunctive FI (10 s, 30 s, & 120 s) FR (5 responses) schedule of food presentation. Dose-effect curves representing the effects of presession cocaine on responding were assessed in the context of (1) acute administration of cocaine (2) chronic administration of cocaine and (3) daily administration of saline. Chronic administration of cocaine generally resulted in tolerance to the response-rate decreasing effects of cocaine, and that tolerance was generally independent of relative FI value, as measured by changes in ED50 values. Daily administration of saline decreased ED50 values to those observed when cocaine was administered acutely. The results show that adding a FR requirement to FI schedules is not sufficient to produce schedule-parameter-specific tolerance. Tolerance to cocaine was generally independent of FI-parameter under the present conjunctive schedules, indicating that a ratio requirement, per se, is not sufficient for tolerance to be dependent on FI parameter.

Key words: cocaine, tolerance, fixed-interval schedule, fixed-ratio schedule, conjunctive schedule, multiple schedule, key peck, pigeons

Tolerance is defined as an attenuation of a drug's effects most often following repeated or prolonged exposure, requiring higher doses to recapture the original drug effect (Corfield-Sumner & Stolerman, 1978; Hardman, Gilman, & Limbird, 1995; Wolgin, 1989). Tolerance is typically reflected in a rightward shift in the drug's dose-effect curve.

Although the definition is silent with regard to mechanisms of tolerance, behavioral factors can mediate tolerance development (Demellweek & Goudie, 1983; Siegel, 1989; Wolgin, 1989). For instance, Hoffman, Branch, and Sizemore (1987) examined the effects of cocaine on rates of responding maintained by fixed-ratio (FR) schedules. Pigeons were exposed to a three-component multiple FR schedule of reinforcement in which the FR values ranged from 5 to 125. Chronic (i.e., once daily) administration of cocaine produced tolerance to the initial decreases in response rates under small- and intermediate FR values, whereas little or no tolerance to the effects of cocaine was observed under large FR values. This effect of relative FR value has been reliably demonstrated in studies examining cocaine's effects in the context of multiple FR schedules with both pigeons (Nickel, Alling, Kleiner, & Poling, 1993; Pinkston & Branch, 2004a; Yoon & Branch, 2004), rats (van Haaren & Anderson, 1994), and squirrel monkeys (e.g., Hughes & Branch, 1991).

In contrast to the findings noted above, Schama and Branch (1989) exposed pigeons to a multiple fixed-interval (FI) schedule of reinforcement in which the three different FI values (i.e., 5 s, 30 s, and 120 s) were chosen to approximate the baseline interreinforcement

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times observed in the Hoffman et al. (1987) study. As in the Hoffman et al. experiment, dose-related decreases in response rates were observed following acute administration of cocaine. Unlike the Hoffman et al. study, however, tolerance to cocaine's rate-decreasing effects was similar across components following chronic administration of cocaine. In other words, tolerance was independent of schedule parameter, as well as the consequent different reinforcement rates.

As differences in baseline reinforcer rates were not sufficient for producing parameter-specific tolerance, an alternative interpretation of the disparate results may lie in the number of responses required to obtain reinforcement. Under an FR schedule, the number of responses required to obtain reinforcement is simply the FR value. Under an FI schedule, however, only one response is required to obtain reinforcement. If rates are very low following drug administration, a single reinforced response may enhance subsequent responding. The added presence of a small FR requirement to the FI schedule eliminates this feature. For example, Pinkston and Branch (2004b) exposed pigeons to a three-component multiple FI schedule of reinforcement in which the FI values were similar to those used in the current study. Additionally, each FI component had a tandem FR 5 requirement. Under tandem schedules, a reinforcer is delivered when two or more schedule requirements, with the same stimulus conditions, are completed in sequence (Catania, 1998; Ferster & Skinner, 1957). In the study by Pinkston and Branch, chronic administration of presession cocaine resulted in comparable tolerance to the rate-decreasing effects across components.

In the Pinkston and Branch (2004b) study, reinforcement was always delivered contingent on completion of the FR requirement. An alternative method of adding an FR requirement to an interval schedule is to use a conjunctive schedule. Under conjunctive schedules, two or more schedule requirements must all be completed for reinforcement to be delivered, however, their order of completion does not matter (Catania, 1998; Herrnstein & Morse, 1958). Under a conjunctive FI FR schedule, therefore, reinforcement is delivered on completion of the FR, if finished after the lapse of the FI, or on the first response after the lapse of the FI, if the FR has already been completed (cf. Barrett, 1974, 1975, 1976; Herrnstein & Morse, 1958). In the present study, an FR 5 was employed to determine if the presence of a relatively small ratio requirement would interact with the FI to alter the development of tolerance. The current experiment therefore extends the analysis initiated by Pinkston and Branch (2004b) to a procedure that allows the ratio requirement to be completed at any time within the interval.

METHOD

Subjects

Six experimentally naïve White Carneau pigeons, maintained at 80% of their free-feeding weight, served as subjects. They were individually housed in a temperature-controlled colony room with a 16:8 hr light:dark cycle. Pigeons had continuous access to water and health grit in their home cages and were provided supplemental food following sessions as needed to maintain them at 80% of their free-feeding weights. Treatment of the animals was approved by the local Institutional Animal Care and Use Committee.

Apparatus

Sessions were conducted in a BRS/LVE® operant conditioning chamber for pigeons, with interior dimensions 31 cm wide by 35 cm high and 35 cm deep. Except for the front wall, the walls and ceiling were painted white. The chamber floor was composed of steel mesh. The front wall, made of brushed aluminum, was equipped with three response keys, a house-light, and food aperture. The response keys were 2.5 cm in diameter and horizontally aligned 24 cm above the chamber floor. Only the center key was used in the current experiment. The response key could be transilluminated by 1.1-W, 28-VDC lamps and required a static force of approximately 0.18 N, which resulted in a 30-ms tone (2900 Hz) via a Mallory Sonalert™. The house light was a 1.1-W, 28-VDC lamp that was centered 2.5 cm below the top of the panel. An aluminum shield deflected the lamp's light toward the ceiling. The food aperture was 5.8 cm by 6 cm and centered 10 cm from the chamber floor. When mixed grain was available, all other chamber lights were extin-

guished, and the food aperture was illuminated by a 1.1-W, 28-VDC lamp. A MED® Associates Single Channel I/R Source, Detector, and Control generated and sensed an infrared beam across the opening of the food aperture. Entries and exits into and out of the food aperture were detected by breaks in the photo-beam. White masking noise of approximately 95 dB was continuously present in the room where the chamber resided. A ventilation fan on the back chamber wall provided additional masking noise. Programming and recording of experimental events was accomplished via a dedicated computer system (Palya, Walter, & Chu, 1995). A Gerbrands™ Model C-3 cumulative recorder also provided a real-time record of responding.

Procedure

Sessions were conducted 7 days per week at approximately the same time each day. Each session was preceded by a 5-min blackout during which the chamber was dark and no consequences were programmed for responding. Sessions were initiated with illumination of the house and key lights.

Initial training. Subjects reliably ate from the food aperture following one session of training. Subjects 439, 27, and 4970 were subsequently trained to emit key-peck responses on the white key under an FI 120-s schedule of reinforcement. Responding failed to generalize when the other two components were introduced with corresponding other key colors. These subjects were retrained along with the rest of the subjects using the following procedure. Subjects were trained to respond on the transilluminated response key by reinforcing a series of responses that successively approximated pecking (Ferster & Skinner, 1957). Appropriate responses produced 3-s access to grain. The color of the response key alternated among white, green, and red following every reinforcer delivery. Once responding reliably occurred with each key color (one to two sessions) a three-component multiple FI schedule was introduced. The first response occurring after the interval lapsed resulted in 2-s access to food. The timer that controlled food access started when the pigeon inserted its head into the food aperture. If the pigeon did not initiate feeding within 5 s of food presentation, the hopper was lowered and timing of the next FI was initiated. Typically, the FI values began at 1 s and were increased across sessions. Subjects 649, 893, and 612 were exposed to a multiple FI 1-s FI 1-s FI-s (two sessions), multiple FI 10-s FI 10-s FI 10-s (t sessions), multiple FI 10-s FI 30-s FI 30-s, and finally a multiple FI 10-s FI 30-s FI 120-s schedule, with the three FI values correlated with the red, green, and white key lights, respectively. For subjects 439, 27, and 4970, the FI value associated with the white key was introduced at 120 s, rather than 1 s.

Baseline. Each component lasted for four food presentations or until a time limit had elapsed. The time limits for the 10-s, 30-s, and 120-s FI components were 1.5 min, 4 min, and 10 min, respectively. Components were presented randomly, without repetition within a block. Sessions consisted of three blocks. Maximum session length was therefore 46.5 min.

Once behavior under the terminal FI values was established, all components were changed to a conjunctive FI FR schedule; the FI values remained the same and the FR value was 5 for all components. If five or more responses were made during the FI, then the first response after the lapse of the interval resulted in food presentation. If fewer than five responses were made during the interval, then the fifth response resulted in presentation of food. Baseline was considered stable once response rate, pausing, and cumulative-record response patterns were judged to be so by visual inspection (161 to 201 sessions).

Drug preparation and administration procedures. Cocaine hydrochloride, provided by the National Institute on Drug Abuse, was dissolved in 0.9% saline, which served as the vehicle. Intramuscular injections into the breast muscle occurred immediately prior to a session. When injections occurred daily, the site alternated between the left and right breast in order to minimize potential for tissue trauma. Drug volume was 1.0 ml/kg, and doses are reported as mg of the salt form per kg body weight of the subject.

Acute effects of cocaine. During the Acute Phase, various doses of cocaine were administered immediately before sessions, usually once per week. These probe injections were separated by at least 5 days. Initially, saline, 10.0, 5.6, 3.0, and 1.0 mg/kg of cocaine were administered in that order, and then the sequence was repeated in order to permit

Table 1

Average rates of key-pecking (±SEM) from control and saline sessions from the Acute, Chronic, and Saline Phases.

Subject	FI	Acute Phase Control	Acute Phase Saline	Chronic Phase Saline	Saline Phase Saline
649	10 s	131.4(0.4)	131.4(7.3)	119.7(2.1)	113.3(0.9)
	30 s	71.0(0.8)	87.9(3.0)	80.2(3.6)	80.1(0.8)
	120 s	29.7(0.2)	33.6(0.7)	27.0(3.0)	35.1(0.5)
4970	10 s	100(0.7)	109.5(3.8)	103.7(5.2)	105.6(0.6)
	30 s	79.9(0.5)	77.9(4.0)	67.3(1.2)	81.2(0.4)
	120 s	68.8(0.4)	67.7(1.0)	62.4(2.7)	70.0(0.5)
893	10 s	94.9(0.7)	89.0(5.8)	91.5(6.6)	94.3(1.2)
	30 s	62.2(0.3)	62.7(1.4)	55.1(0.8)	47.5(0.6)
	120 s	68.1(0.5)	59.7(1.8)	57.4(5.5)	57.1(0.3)
612	10 s	126.0(0.4)	134.9(0.9)	79.0(7.8)	120.9(0.4)
	30 s	85.9(0.4)	88.6(1.5)	34.2(2.5)	61.6(0.6)
	120 s	36.4(0.2)	30.0(0.6)	17.9(1.0)	35.7(0.3)
27	10 s	181.6(0.3)	181.9(1.4)	169.3(2.8)	175.9(0.3)
	30 s	89.4(0.6)	89.4(0.6)	94.5(2.8)	83.5(0.7)
	120 s	64.0(0.4)	63.6(4.6)	73.1(3.8)	60.3(0.8)
439	10 s	105.3(0.5)	102.6(2.2)	96.5(6.4)	128.1(1.2)
	30 s	73.3(0.4)	75.5(3.5)	69.2(9.4)	80.0(0.5)
	120 s	38.0(0.3)	36.0(1.6)	36.5(2.5)	38.0(0.4)

assessment of the stability of the dose–response function. Further administrations of these doses or others were investigated on an individual-subject basis in order to provide a complete characterization of the dose–response function and its stability.

Chronic effects of cocaine. Based on the dose–response functions generated during the Acute Phase, a dose of cocaine was chosen for each subject that reduced rates of responding without completely suppressing them. This dose was administered daily during the Chronic Phase for at least 50 consecutive sessions and until stability in daily response rates was observed, as judged by visual inspection of daily response rates and cumulative records. Next, probe doses were administered in the context of chronic cocaine administration. Any doses that had been examined during the Acute Phase were administered at least twice, and further doses were administered on an individual-subject basis in order to provide a complete characterization of the dose–response function and its stability. Data from sessions conducted the day before probe sessions were used to represent the effects of the chronic dose. The Chronic Phase was completed within 110 to 206 sessions.

Repeated saline administrations. After the Chronic Phase, administration of daily presession cocaine was replaced by that of saline for at least 50 sessions and until stability in daily response rates was observed, as judged by visual inspection. Next, probe sessions were conducted during the Saline Phase. Each probe dose examined was assessed at least twice, and further determinations were made as needed for each subject. Sessions conducted the day before probe sessions were used to represent the effects of saline.

Data analysis. The curve-fitting program GraphPad Prism© was used to calculate the estimated dose at which responding was decreased to 50% of baseline (ED50; Ross & Kenakin, 2001). First, response rates were normalized as a proportion of rates observed during saline-administration sessions for each component during each phase (Table 1). Second, data points were fitted to a four-parameter sigmoidal model. The four parameters consisted of the ED50 value, the slope of the function, and the bottom and top of the curve. In fitting the model, the bottom and top of the curves were initially constrained to 0% and 100%, respectively. Calculated ED50 values are listed in Table 3. In a small number of cases (3/54), the model would not converge under these conditions. For these cases, the top constraint was removed, and the model converged. As a validity check, all ED50 values were reassessed without constraining the top of the model. By and large, differences in ED50 values were relatively minimal when the top of the model was constrained to 100% and when it was not. In one final case, the model would not converge as the dose–response

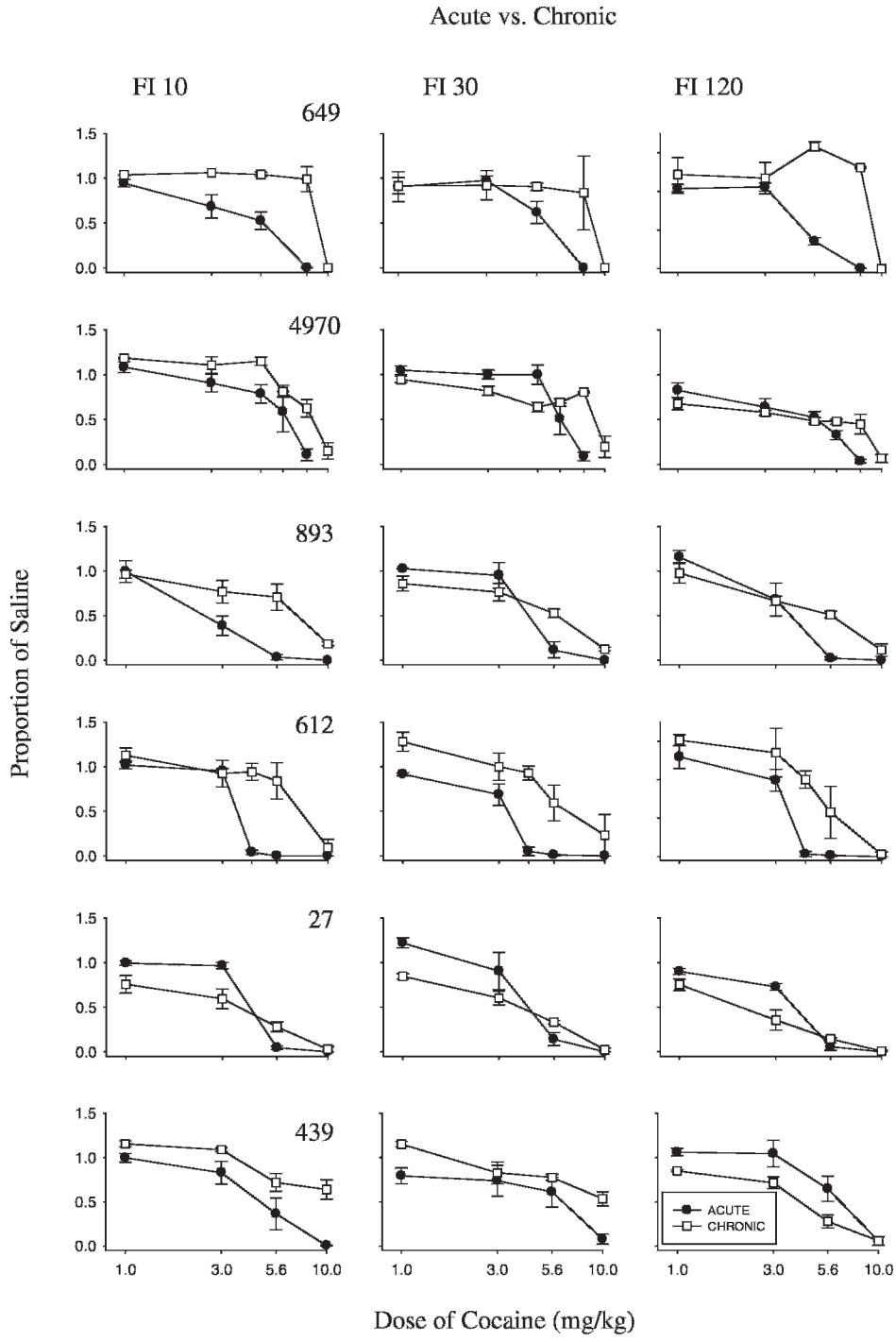

Fig. 1. Key-pecking rates as a function of cocaine dose during the Acute and Chronic Phases. Data for each subject are presented horizontally while components are presented vertically. Circles and squares represent mean rates at each dose during the Acute and Chronic Phases, respectively. Rates as a proportion of those observed during saline sessions are shown on the ordinate. Dose of cocaine is represented on the abscissa on a log scale. Error bars represent ±SEM. Errors bars that are not visible are subsumed by the data point. Note that ordinate extends to 1.5 for each plot except for Subjects 649 and 612 in the FI 120-s component, which extends to 1.75.

Table 2

Obtained ED50 values and comparison of ED50 values from various phases.

		Acute	Chronic	Saline	Acute vs. Chronic p value	Acute vs. Saline p value
649	FI 10 s	5.3	11.1	6.3	**<.0001**	.3400
	FI 30 s	6.0	10.7*	6.7	**<.0001**	.3978
	FI 120 s	5.5**	11.5**	5.4	**<.0001**	>.9999
4970	FI 10 s	7.6	10.3	8.9	**.0020**	.0680
	FI 30 s	7.8	10.6	7.9	**.0006**	.8714
	FI 120 s	5.3	6.7	5.6	**.0209**	.6129
893	FI 10 s	3.0	7.3	4.0	**.0002**	.1655
	FI 30 s	4.5	5.8	5.3	.4144	.5197
	FI 120 s	3.2	5.6	4.1	**.0034**	.1813
612	FI 10 s	3.6	7.4	3.6	**<.0001**	.9635
	FI 30 s	3.3	7.4	3.3	**<.0001**	.6473
	FI 120 s	3.7	5.6	3.5	**<.0001**	.6525
27	FI 10 s	4.4	3.8	2.3	.4829	**.0026**
	FI 30 s	4.5	4.2	3.5	.5943	.0793
	FI 120 s	3.7	2.7	1.7	.0867	**<.0001**
439	FI 10 s	4.5	6.9	5.7	**.0279**	.2764
	FI 30 s	6.1	6.5*	6.4	.9977	.8099
	FI 120 s	5.8	4.2	6.1*	**.0059**	.8345
Average		4.9	7.1	5.0		

Note. Global nonlinear regression was used to compare ED50 values.
* ED50 value obtained with top of the model unbound.
** ED50 value obtained shifting response rate values by the difference from obtained saline values.

function was bimodal (Figure 1, 649, FI 120 s). For this individual instance, data were transformed to fit the model by shifting the curve downwards at doses in which the average rate of responding was higher than that of the average rates observed during saline sessions. First, the average saline rate was subtracted from the average rate for a given dose. This difference was then subtracted from each individual data point for a given dose. This effectively reduced the rate at each dose until it was equivalent with that observed during saline sessions while preserving the variability observed at each dose.

All ED50 comparisons were done using global nonlinear regression analyses (Motulsky & Christopoulous, 2003). The analyses compared whether the data from two dose–response functions were better described by one (shared ED50 value) or two curves (two separate ED50 values). The null hypothesis was that the data would be better described by one curve and the alpha level was set to $p < .05$.

RESULTS

Dose-related decreases in key-pecking were observed during the Acute Phase (Figure 1, filled symbols). Generally, rates of responding were little affected by 1.0 and 3.0 mg/kg of cocaine and were either at 0 or near 0 rates at 10.0 mg/kg of cocaine at all components for all subjects. Rates of responding observed during saline-administration sessions during the Acute Phase closely matched those observed during control sessions. Response rates were generally highest in the FI-10 s component across subjects and tended to decreases as a function of FI value.

Repeated daily administration of cocaine (Chronic Phase) generally resulted in tolerance as shown by rightward shifts in dose–response functions and significant increases in ED50, and that tolerance was generally independent of FI value (Figure 1; Table 2). Significant increases in ED50 values were observed in 5 out 6 subjects in at least one of the components. Overall, significant increases in ED50 values were observed in 66.7% (12/18) of the components and those increases averaged 1.8-fold (SEM ± 0.03; Table 3). Only subject 27's data failed to show tolerance in any of the components. For this subject, ED50 values obtained during the Chronic Phase were lower in all three components relative to the Acute Phase (Table 2), but these decreases were not significant. A significant decrease in the ED50 value (Table 2), mir-

Table 3

Mean percentage of reinforcers (±SEM) delivered on completion of the FR requirement for each component in sessions preceding probe-injection sessions during the Chronic Phase.

Subject	FI 10 s	FI 30 s	FI 120 s
649	0.0(0.0)	0.0(0.0)	2.8(0.3)
4970	3.1(0.5)	7.3(0.4)	3.1(0.3)
893	10.4(1.6)	1.3(0.4)	10.0(1.1)
612	12.5(1.7)	16.4(1.1)	13.5(1.0)
27	1.6(0.3)	8.3(0.6)	16.8(1.4)
439	1.4(0.5)	0.0(0.0)	31.8(1.9)

rored by a leftward shift in the dose–response function (Figure 1), from the Acute to the Chronic Phase was observed for subject 439 in the FI 120-s component. Only subject 439's data showed clear evidence of tolerance related to FI value with significant increases in ED50 values in the FI 10-s and 30-s components and a significant decrease in the ED50 in the FI 120-s component (Table 2).

During the Chronic Phase, the vast majority of reinforcers were delivered on completion of the FI schedule requirement (Table 3). In other words, most of the reinforcers were delivered following more than five responses before completion of the FI schedule requirement. Note, as a point of comparison, only one reinforcer (i.e., Subject 439 in the FI 10-s component) was delivered on completion of the FR requirement in the six sessions preceding the Chronic Phase (data not shown). The percentage of FR-delivered reinforcers (i.e., five or fewer reinforcers) was generally similar across components for any given subject in the Chronic Phase. Two exceptions to this general pattern were Subjects 27 and 439. Subject 27 received an increasing percentage of FR-delivered reinforcers that paralleled increases in the FI interval length. Subject 439 received relatively more FR-delivered reinforcers in the FI 120-s component relative to the other two components. Comparing across subjects, the percentage of FR-delivered reinforcers for 439 was approximately 2 to 11 times greater than any other subject in the FI 120-s component.

Once daily administration of presession cocaine was replaced with that of saline vehicle (Saline Phase), dose–response functions generally shifted to the left and often mirrored those observed during the Acute Phase (Figure 2). Likewise, ED50 values almost universally decreased (17/18) from those observed during the Chronic Phase and in most cases recaptured those observed during the Acute Phase (Table 2). The only increased ED50 value was observed in the FI 120 s component for subject 439. Note that this subject was the only one to show a significant decrease in ED50 value for that component during the Chronic Phase. Comparison of normalized dose–response functions from the Acute Phase and Saline Phase showed only significant decreases in ED50 values for subject 27 in the FI 10-s and 120-s components (Table 2).

DISCUSSION

The purpose of the current experiment was to examine the effects of cocaine on responding under conjunctive FI FR schedules of reinforcement. The major findings were that (1) almost all subjects exhibited some degree of tolerance to the response-rate-decreasing effects of cocaine following repeated administration of presession cocaine, (2) the degree of tolerance observed was generally independent of FI parameter size, and (3) when repeated administration of cocaine was replaced by that of saline, dose–response functions from the Acute Phases were generally recaptured.

The overall pattern of tolerance observed in the current experiment is comparable to that observed in studies utilizing comparable schedule parameters from our laboratory (Hoffman et al., 1987; Pinkston & Branch, 2004a; Pinkston & Branch, 2004b; Schama & Branch, 1989; Weaver & Branch, 2008; Yoon & Branch 2004) and other laboratories as well (Nickel et al., 1993; van Haaren & Anderson, 1994). Thus, the current experiment adds to the increasing body of work showing tolerance to the disruptive effects of cocaine on responding by pigeons under multiple schedules of reinforcement.

The effects of daily cocaine administration were generally similar across components and therefore congruent with other studies using similar multiple FI schedules of reinforcement (Schama & Branch, 1989; Pinkston & Branch, 2004b). The combined results of the current experiment and those of Pinkston and Branch (2004b) suggest that the mere presence of an FR requirement is not sufficient for consistently developing schedule-parameter-specific tolerance. In contrast to the above studies, Weaver and Branch (2008) observed parame-

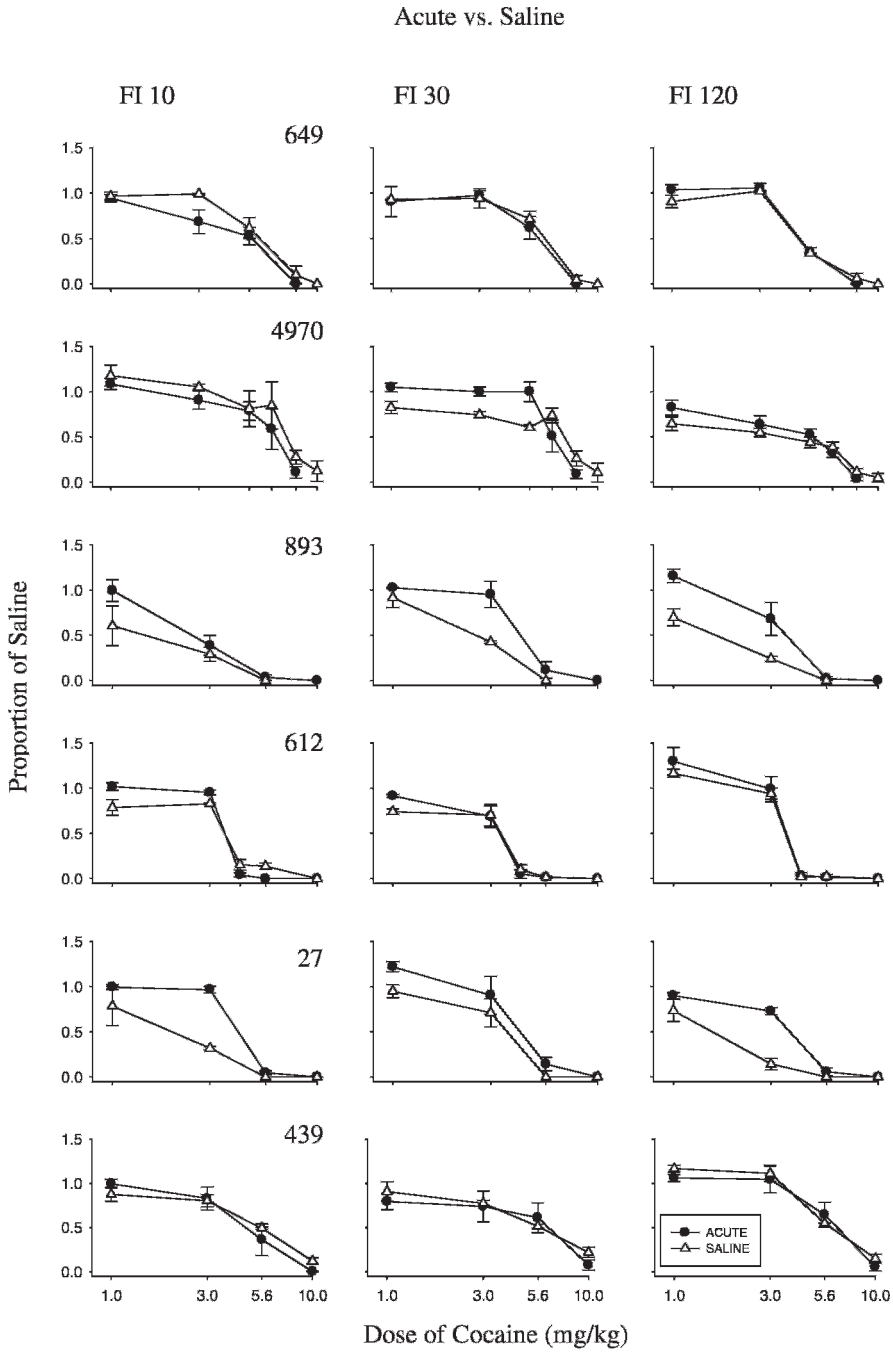

Fig. 2. Key-pecking rates as a function of cocaine dose during the Acute and Saline Phases. Triangles represent mean rates at each dose during the Saline Phase. All other details are as in Figure 1.

ter-specific tolerance using a response-initiated, multiple-FI (FI 5 s, FI 15 s, & FI 60 s) schedule of reinforcement, or a multiple FI schedule with an initial tandem FR1 requirement. The results of that study suggested that delay to reinforcement from the initial response may play a role in the manifestation of parameter-specific tolerance.

Related to the above discussion, Subject 439 was the one exception that showed parameter-specific tolerance in the current experiment (Figure 1). One way in which Subject 439's experience differed from the other pigeons was the relatively high percentage of FR-delivered reinforcers in the FI 120-s component (Table 3). Despite the findings noted in the Weaver and Branch (2008) study noted above, we find it unlikely that the delay between the first response in an interval and food delivery was responsible for the development of parameter-specific tolerance in Pigeon 439. In fact, it is likely that in interfood intervals terminated by the FR 5 the delay between the peck that ended the pause and food presentation was likely relatively short, rather than long. Also, as noted earlier, Pinkston & Branch (2004b) had a tandem requirement that arranged that every food presentation was delivered upon completion of an FR 5, and they did not observe parameter-related tolerance. One possibility is that there are individual differences in the interaction between required extra responses and the FI parameter size. For example, Subject 27 also experienced a relatively higher percentage of FR-delivered reinforcers in the FI 120-s component, although this number was only half of that which Subject 439 experienced (Table 3). One logical follow-up experiment would therefore be to manipulate either the conjunctive FR or FI requirement across a broader range than previously reported in an attempt to increase the relative percentage of FR-delivered reinforcers or to see if the interaction might be related to interfood-interval value.

When daily administration of presession cocaine was replaced with that of saline, dose–response curves were shifted to the left and in most cases recaptured the effects observed during the Acute Phase (Figure 2). These results are congruent with those from studies using rats as subjects investigating the effects of psychomotor stimulants, mainly amphetamine, which have generally shown attenuation of tolerance when sessions were experienced in the absence of drug (Hughes, Popi, & Wolgin, 1999; Poulous, Wilkinson, & Cappell, 1981; Wolgin & Hughes, 1997, 2001). The study conducted with pigeons and cocaine most similar to the current one has shown similar findings (Pinkston & Branch, 2004b; although see Stafford, Branch, & Hughes, 1994 for an exception).

Overall, the current study showed that tolerance to cocaine was generally independent of FI parameter even when a small ratio requirement was added. The presence of a ratio requirement per se, therefore, was not reliably sufficient to make tolerance dependent on the FI parameter.

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