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Tolerance to Effects of Cocaine on Schedule-Controlled Behavior: Effects of Fixed-Interval Schedule Parameter[1]

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SCHAMA, K. F. AND M. N. BRANCH. *Tolerance to effects of cocaine on schedule-controlled behavior: Effects of fixed-interval schedule parameter.* PHARMACOL BIOCHEM BEHAV 32(1) 267–274, 1989.—Tolerance to the effects of cocaine on key pecking by pigeons, maintained by differently valued fixed-interval schedules of food presentation, was studied. Key pecking was established on a multiple fixed-interval 5-sec fixed-interval 30-sec fixed-interval 120-sec schedule. Cocaine (1.0–10.0 mg/kg) was administered acutely and then chronically (i.e., before each session) in 5.6 mg/kg doses. Acute cocaine administration produced dose-related decreases in response rates under all three schedules. When cocaine was administered chronically, response rates either recovered fully, or increased to the extent that no reinforcers were missed during the sessions. The development of tolerance was not systematically related to the schedule value. Considered in relation to previous research, these results indicate that different control rates of reinforcement, within the schedules and parameters studied, do not contribute to tolerance to cocaine's behavioral effects.

Fixed-interval Cocaine Tolerance Multiple schedule Behavioral tolerance Keypeck Pigeons

THE occurrence of tolerance to the behavioral effects of cocaine administration when the drug is administered chronically has not been studied fully, but some modulating factors have been implicated. One factor that has been associated with tolerance is the initial degree of disruption in reinforcement rate (6, 15, 21, 24). That is, if the effects of cocaine on behavior initially result in a decrease in reinforcement rate, then tolerance is likely to occur during chronic administration. This assertion, generally known as the "reinforcement loss" hypothesis, was originally put forward by Schuster, Dockens and Woods (17) to explain behavioral tolerance to *d*-amphetamine and has since been extended to other drugs (5, 7, 10, 20).

Others factors have also been implicated as modulators of tolerance to behavioral effects of cocaine. Thompson (21) reinforced completion of a four-response chain by pigeons with presentations of mixed grain on a fixed-ratio (FR) 5 schedule. Under one condition, the sequence changed from session to session (learning condition), and under another the sequence remained the same (performance condition). During chronic administration of cocaine, tolerance to the initial error-increasing effects occurred more slowly, and less completely at larger doses, during the learning condition than during the performance condition. Thompson pointed to the differences in the degree of stimulus control between the conditions as a modulator of tolerance development. Also, during Thompsons's experiment, tolerance did not develop to cocaine's response-rate increasing or decreasing effects during timeouts, where responses had no scheduled consequences, and therefore did not result in disruption of reinforcement frequency. Thus, the development of tolerance to cocaine also was dependent on whether or not responses were explicitly reinforced, and the conditions under which the responses were reinforced.

Hoffman, Branch and Sizemore (11) demonstrated that schedule parameters can also determine whether tolerance to the initial effects of cocaine occurs, or the degree to which it occurs. They reinforced keypecks by pigeons on a multiple FR5 FR25 FR125 schedule of food presentation. Tolerance to the initial response-rate decreasing effects of 5.6 mg/kg cocaine developed for all subjects during the smallest ratio component, and not at all or to a lesser degree during the larger ratio components. Since the initial effect of cocaine was to decrease reinforcement rates under all schedule pa-

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rameters, there were factors other than simple reinforcement loss controlling the occurrence of tolerance. Ratio-value manipulations involve both changes in the response requirement, or number of responses necessary to produce the reinforcer, and baseline reinforcement rates. Since these factors were confounded in the experiment by Hoffman *et al.*, it is unclear what the independent contribution of reinforcement rate and response requirement are with respect to cocaine tolerance.

The present experiment was conducted as a systematic replication of the study by Hoffman *et al.* (11), using fixed-interval (FI) schedules of different parameters. The FI values were chosen so that baseline reinforcement rates obtained in Hoffman *et al.*'s experiment were approximated, enabling the manipulation of baseline reinforcement rates while holding the response requirement constant (at one response per reinforcement). Baseline reinforcement rate has been implicated as a modulator of tolerance to the effects of cocaine (15), but has not been studied directly.

METHOD

Subjects

Three adult, male White Carneau pigeons served. They were housed individually in cages with water and health grit continuously available. Two of the subjects, 636 and 722, were kept at 80% of their free-feeding weights by feeding them grain as necessary in their home cages after the sessions. Subject 563 was kept at 75% of its free-feeding weight due to frequent failure to respond during an FI120-sec schedule component at the beginning of the experiment. All three subjects had been used previously in an undergraduate laboratory class where they were exposed to a variety of reinforcement schedules, but did not receive any drugs.

Apparatus

Sessions were conducted in a 30 by 30 by 33-cm chamber that was enclosed in a sound- and light-attenuating, ventilated box. Three walls and the ceiling of the chamber were made of Plexiglas. The fourth wall was made of stainless steel and contained one translucent Plexiglas key mounted behind a 2-cm diameter hole. A static force of 0.40 N or greater was required to operate the key. A relay click sounded whenever the key was operated while the reinforcement schedules were in effect. The key was transilluminated by red, green, or blue light. Centered 14 cm below the key was a 6-cm by 4.5-cm opening through which access to mixed grain could be arranged by operating a grain feeder. When food was available, the opening was lighted inside by two 1.2-W lamps, and all other chamber lights were turned off. A white houselight, which emitted diffused light from a 1.2-W bulb, was mounted at the center of the ceiling. The chamber was located in a darkened room where white noise was continuously present. Experimental events were arranged and data were recorded in an adjacent room by a Digital Equipment Corporation PDP8-E computer operating under the control of SuperSKED software (18).

Behavioral Procedures

Reinforcers were arranged according to a multiple FI5-sec (blue keylight) FI30-sec (green keylight) FI120-sec (red keylight) schedule. In order to vary the sequence of component presentations while assuring that each component appeared towards the beginning, middle, and end of each session, the sessions were divided into three blocks. Each schedule component was presented once within each block in random order. During each component, the first peck after a fixed amount of time from either the start of the component or the end of the last food presentation resulted in 4-sec access to mixed grain. Each component ended after either five reinforcers were delivered or a specified time limit expired. The time limit was 2 min for the FI5-sec component, 5 min for the FI30-sec component, and 20 min for the FI120-sec component. The components were separated by 60-sec timeouts during which the key was inoperative and all chamber lights were off. Sessions were conducted seven days per week, and began 10 min after the subjects were placed in the chamber.

Determination of Acute Drug Effects

Determination of acute effects began after daily baseline response rates under each of the schedule values was judged to be stable by visual inspection of daily plots. Stability was reached after not more than 88 or less than 62 sessions. Cocaine hydrochloride was dissolved in 0.9% sodium chloride solution. Injections were made into the pectoral muscle 10 minutes before the sessions began. Injections were administered not less than four days apart. The injection volume was 1 ml/kg, and each dose was administered at least twice. Saline was also administered at least twice. Doses were administered in a descending series: saline, 10.0 mg/kg, 5.6 mg/kg, 3.0 mg/kg, and 1.0 mg/kg cocaine. Cocaine concentrations were determined in terms of the salt.

Determination of Chronic Effects

After the acute effects were determined, and after 10 consecutive days of saline injections, 5.6 mg/kg cocaine was administered daily, 10 minutes before the sessions began. This dose was chosen because during acute administrations it reduced overall response rates without completely eliminating responding over the entire session. Response rates stabliized under daily injections of 5.6 mg/kg cocaine in 20 days for all subjects. At this time other doses and saline were occasionally substituted, but not less than four days apart. At least two such substitutions occurred with each dose. Substitutions were made in descending series. No drug was administered on days when saline was injected.

RESULTS

Cumulative Records

Figures 1 and 2 contain cumulative records from Pigeons 636 and 722, respectively, obtained during sessions after saline, 5.6 mg/kg and 10.0 mg/kg cocaine injections under acute and chronic conditions. Acute injections of 5.6 mg/kg and 10.0 mg/kg cocaine decreased all FI response rates of both subjects. The decrease in response rates for Pigeon 722 did not reduce the number of reinforcement deliveries as much as for Pigeon 636. Acute injections of 10.0 mg/kg cocaine eliminated the keypecking of both subjects throughout the session. After response rates stabilized under chronic 5.6 mg/kg cocaine injections, it can be seen that attenuation of the response-rate decreasing effects of cocaine occurred for both subjects. Pigeon 636's response rates after 5.6 mg/kg and 10.0 mg/kg injections of cocaine recovered completely under chronic conditions during all FI values. Recovery was not as complete for Pigeon 722. Response rates increased as a result of chronic injections, but still were below saline

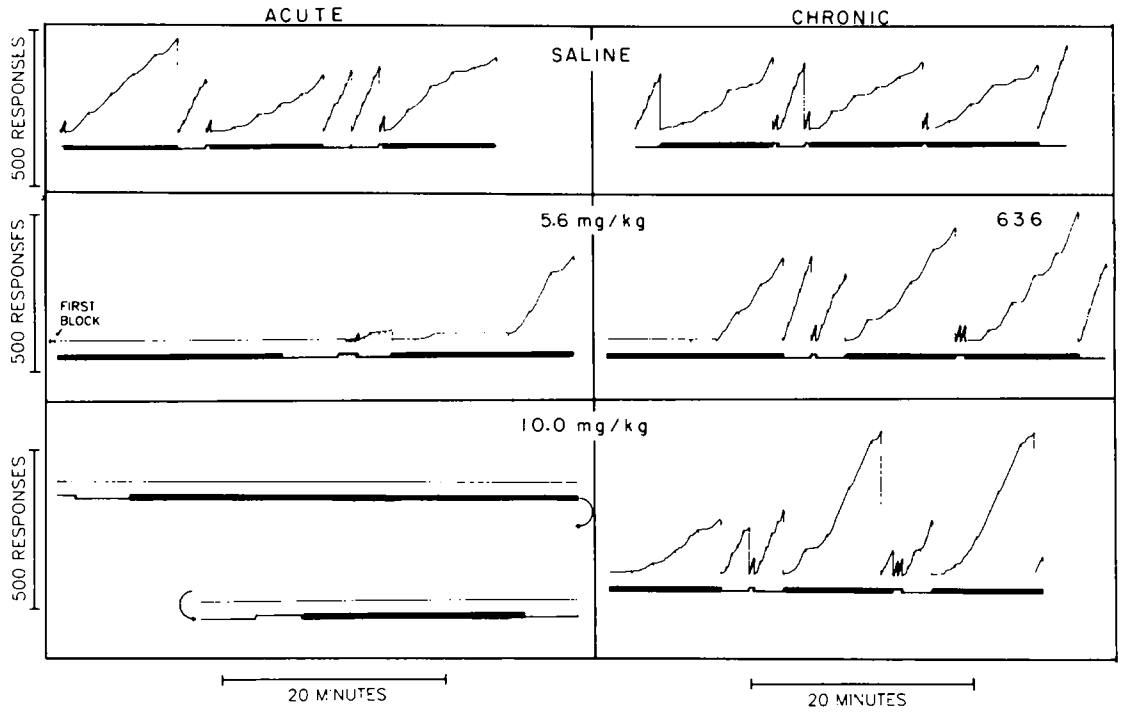

FIG. 1. Cumulative records of keypecking for Pigeon 636. Downward deflections of the response pen indicate food presentations. The response pen was reset after each component. Event pen up indicates the small FI component (FI5-sec), downward deflections indicate the medium FI (FI30-sec), and rapid excursions indicate the long FI (FI120-sec). On the left are records from sessions preceded by injections of saline, 5.6 mg/kg, and 10.0 mg/kg cocaine. On the right are records from sessions preceded by the same type of injections, but during otherwise daily injections of 5.6 mg/kg cocaine. Records were chosen from sessions during which response rates most closely approximated the means reported in Fig. 3.

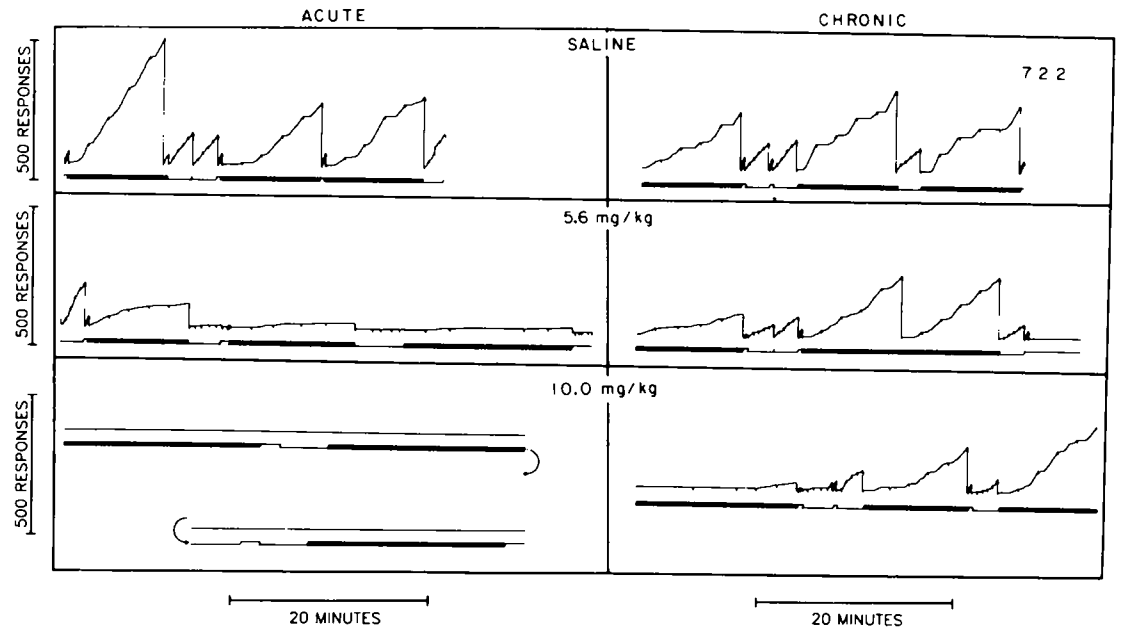

FIG. 2. Cumulative records for Pigeon 722. Conventions are as in Fig. 1.

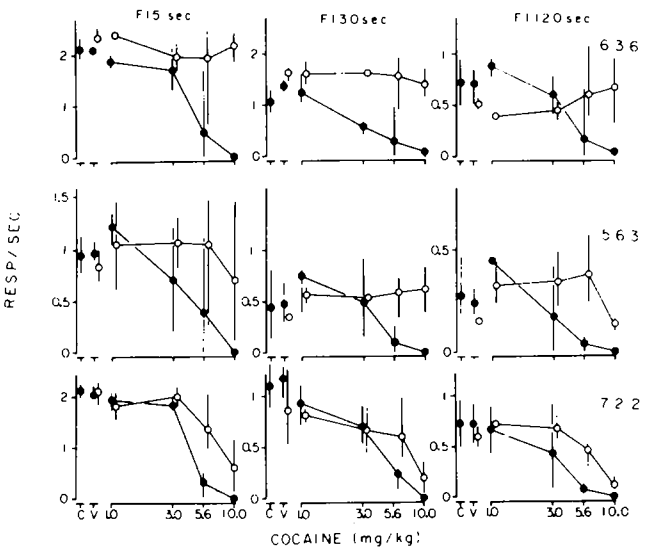

FIG. 3. Response rates for each subject in each component as a function of drug dose or saline injections (V) during both acute (filled circle) or chronic (open circle) phases. Control rates (C) were taken from each day immediately prior to an injection during the acute phase. During the chronic phase response rates during 5.6 mg/kg cocaine are reported from each day immediately prior to an injection of an alternative dose. The data points represent means of all observations under a particular condition, and the vertical bars indicate ranges. Note: ordinate ranges change across components for each subject.

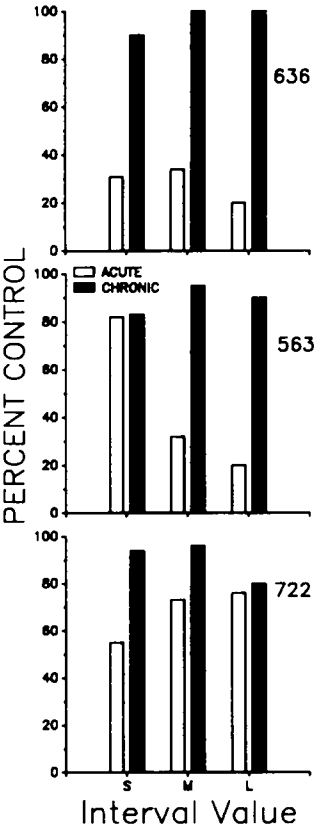

FIG. 4. Mean reinforcement rates after 5.6 mg/kg injections of cocaine as a percentage of mean reinforcement rates after saline for each subject during FI5-sec (S), FI30-sec (M), and FI120-sec (L) components under acute (open bar) and chronic (closed bar) injection regimens.

control values. For both subjects, the degree of recovery observed was not related to the FI value. Cumulative records of Pigeon 563's performance (not shown) were similar to those of Pigeon 636.

Response Rates

In the absence of cocaine, the FI schedules employed maintained stable responding throughout the experiment, with reinforcement rates at or near maximum possible values (Table 1). Figure 3 shows the effects of each dose of cocaine on response rates during each of the FI schedule parameters for each pigeon under acute and chronic injection regimens. For all subjects and schedules during the series of acute injections, there were dose-related decreases in response rates. For Pigeon 563 there were occasional increases after injections of 1.0 mg/kg, and decreases for all larger doses. Overall, acute effects of cocaine were not related to the schedule parameter.

During daily 5.6 mg/kg cocaine injections, the response-rate decreasing effects of the larger doses of cocaine were attenuated for all subjects under all FI schedule parameters, and the degree of attenuation was not systematically related to the schedule value in effect. For Pigeon 636, response rates after 5.6 and 10.0 mg/kg injections were at or near rates after saline injections during all components. This stands in contrast to the large decreases observed during acute injections. During chronic conditions for Pigeon 722, cocaine injections of 5.6 and 10.0 mg/kg continued to decrease response rates to below saline control values. These decreases, however, were not as large as those observed during acute cocaine injections. For instance, 10.0 mg/kg cocaine injections consistently eliminated responding during all schedule parameters before the chronic regimen. After stable response rates were observed during daily 5.6 mg/kg injections, 10.0 mg/kg injections never completely eliminated responding during a session.

Reinforcement Rates

Figure 4 displays the average reinforcement rates per session after 5.6 mg/kg doses of cocaine. Rates are expressed as percentages of saline control values obtained under acute and chronic conditions. Following acute injections, reinforcement rates decreased after injections of 5.6 mg/kg cocaine for all subjects. The effects of this dose of cocaine on reinforcement rates were not systematically related to the schedule parameter across subjects. Subject 722's reinforcement rates did not decrease as much as those of the other two subjects. Inspection of Table 1 shows that absolute decreases in reinforcement rates were larger the shorter the interval.

Decreases in reinforcement rates observed during acute injections of 5.6 mg/kg cocaine were all but eliminated after chronic injections for Subject 636. There was full recovery during the medium- and long-interval components and almost complete recovery during the short-interval compo-

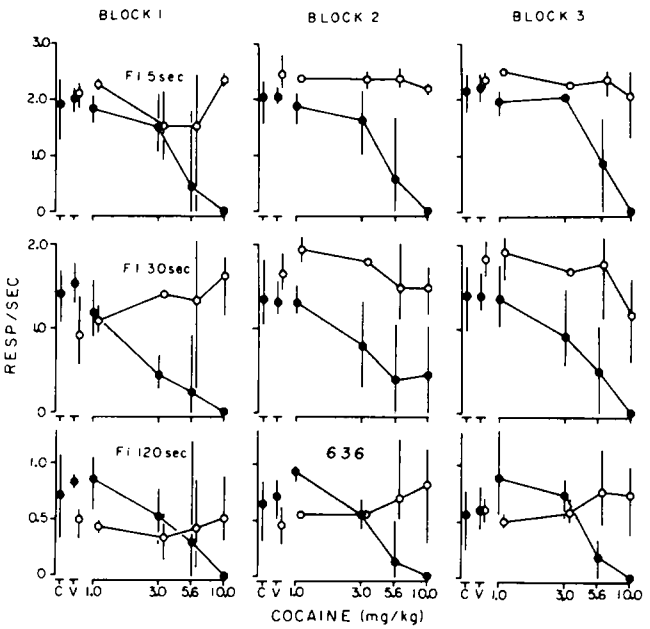

FIG. 5. Mean response rates for Subject 636 under acute and chronic conditions for each schedule value and each block of the session. Each schedule value was presented once within each of three successive blocks during each session. Conventions are as in Fig. 3.

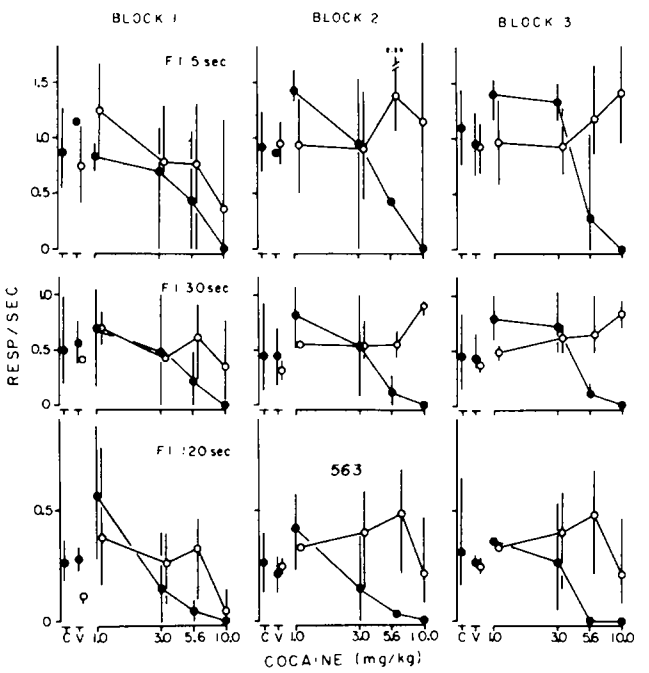

FIG. 6. Mean response rates for Subject 563 under acute and chronic conditions for each schedule value and each session block. Conventions are as in Fig. 3.

nent. For Pigeon 563, substantial attenuation of the reinforcement-rate decreases occurred during the long- and medium-interval components. Very little change occurred during the short-interval component, where the acute effects were not as large. For Pigeon 722, more recovery of reinforcement rates occurred during the short- and medium-interval components. Also, from Table 1 it can be seen that reinforcement rates after injections of 10.0 mg/kg recovered fully under chronic conditions for Pigeon 636, and less so for the other two subjects.

Time Course Effects

In order to assess the time-course effects of cocaine, Figs. 5, 6, and 7 display the effects of each dose of cocaine on response rates under both injection regimens during each successive block of the session. For all subjects, cocaine's acute effects changed very little across the session. There was, however, a slight indication of changes in the amount of tolerance throughout the session. Pigeon 722 (Fig. 7) displayed this most prominently in that the degree of attenuation of acute cocaine effects was larger during the second two blocks. This was also true of Pigeon 563, although to a lesser degree (Fig. 6).

DISCUSSION

During acute administration, cocaine produced dose-dependent decreases in response rates. The degree of response-rate reduction was not systematically related to the FI value across subjects. When cocaine was administered chronically, tolerance developed to its response-rate decreasing effects in all subjects. The degree of tolerance observed was not systematically related to the FI parameters in

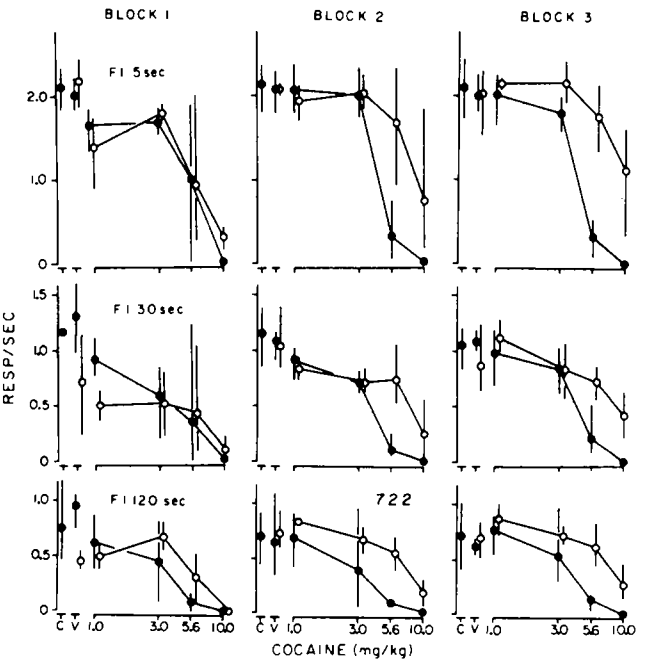

FIG. 7. Mean response rates for Subject 722 under acute and chronic conditions for each schedule value and each session block. Conventions are as in Fig. 3.

TABLE 1

MEAN REINFORCEMENT RATES (FOOD PRESENTATIONS PER MINUTE) AS A FUNCTION OF DOSE OF COCAINE ACROSS THE THREE BLOCKS OF A SESSION, UNDER CONDITIONS OF ACUTE AND CHRONIC ADMINISTRATION

				Acute				Chronic		
	Dose (mg/kg)	N*	FI†	Block 1	Block 2	Block 3		Block 1	Block 2	Block 3
Pigeon 636	C‡	15	5	11.45	11.67	11.68		—	—	—
	V§	3	5	11.65	11.41	11.67	3	11.60	11.66	11.61
	1.0	3	5	11.24	11.66	11.70	2	11.65	11.65	11.69
	3.0	3	5	11.02	11.26	11.64	2	9.54	11.76	11.74
	5.6	4	5	3.29	5.70	7.98	10	8.81	11.71	11.70
	10.0	2	5	0	0	0	3	11.75	11.77	10.61
	C	15	30	1.98	1.98	1.98		—	—	—
	V	3	30	1.98	1.97	1.98	3	1.94	1.99	2.00
	1.0	3	30	1.98	1.97	1.97	2	1.97	1.99	1.99
	3.0	3	30	1.29	1.69	1.96	2	1.99	1.99	1.99
	5.6	4	30	0.92	0.93	1.40	10	1.92	1.99	1.99
	10.0	2	30	0.97	0.10	0	3	1.99	1.99	1.91
	C	15	120	0.50	0.50	0.50		—	—	—
	V	3	120	0.50	0.50	0.50	3	0.49	0.49	0.50
	1.0	3	120	0.50	0.50	0.49	2	0.47	0.49	0.49
	3.0	3	120	0.49	0.49	0.50	2	0.37	0.50	0.50
	5.6	4	120	0.17	0.15	0.13	10	0.43	0.47	0.49
	10.0	2	120	0	0	0	3	0.50	0.47	0.49
Pigeon 563	C	16	5	10.25	10.64	10.75		—	—	—
	V	2	5	10.75	9.85	11.01	2	8.59	10.18	9.98
	1.0	3	5	10.33	10.94	11.24	2	10.50	11.01	10.09
	3.0	4	5	6.76	7.22	11.52	2	10.81	10.87	10.80
	5.6	5	5	5.76	6.54	5.39	10	8.46	11.11	10.29
	10.0	2	5	0	0	0	4	4.30	8.62	10.83
	C	16	30	1.91	1.93	1.92		—	—	—
	V	2	30	1.94	1.83	1.88	2	1.88	1.87	1.84
	1.0	3	30	1.83	1.97	1.96	2	1.92	1.95	1.94
	3.0	4	30	1.03	1.70	1.92	2	1.48	1.95	1.93
	5.6	5	30	0.81	0.85	0.84	10	1.85	1.92	1.96
	10.0	2	30	0	0	0	4	0.91	1.95	1.83
	C	16	120	0.49	0.49	0.49		—	—	—
	V	2	120	0.49	0.49	0.49	2	0.38	0.48	0.48
	1.0	3	120	0.50	0.49	0.49	2	0.45	0.49	0.49
	3.0	4	120	0.27	0.23	0.38	2	0.47	0.49	0.49
	5.6	5	120	0.17	0.09	0	10	0.41	0.50	0.49
	10.0	2	120	0	0	0	4	0.12	0.38	0.41
Pigeon 722	C	16	5	11.68	11.73	11.69		—	—	—
	V	4	5	11.82	11.75	11.72	3	11.70	11.63	11.64
	1.0	3	5	11.63	11.78	11.70	2	11.78	11.56	11.65
	3.0	3	5	11.54	11.82	11.65	2	11.76	11.74	11.81
	5.6	4	5	7.78	5.46	6.66	10	9.65	11.27	11.66
	10.0	2	5	0	0	0	3	8.60	8.14	10.26
	C	16	30	1.97	1.97	1.97		—	—	—
	V	4	30	1.97	1.97	1.97	3	1.90	1.99	1.96
	1.0	3	30	1.97	1.96	1.97	2	1.92	1.98	1.98
	3.0	3	30	1.86	1.91	1.93	2	1.87	1.97	1.98
	5.6	4	30	1.32	1.59	1.47	10	1.80	1.98	1.98
	10.0	2	30	0	0	0	3	1.10	1.58	1.88
	C	16	120	0.50	0.50	0.50		—	—	—
	V	4	120	0.50	0.50	0.50	3	0.48	0.50	0.50
	1.0	3	120	0.49	0.50	0.50	2	0.49	0.50	0.50
	3.0	3	120	0.48	0.45	0.46	2	0.50	0.49	0.49
	5.6	4	120	0.35	0.39	0.40	10	0.48	0.50	0.50
	10.0	2	120	0	0	0	3	0.34	0.45	0.48

*Number of observations; †Seconds; ‡Control; §Vehicle (Saline).

effect. These findings may be contrasted with those reported by Hoffman *et al.* (11), who found, using FR schedules, that the schedule parameter was an important determinant of the occurrence of tolerance in all subjects.

A possible explanation for the observed differences in schedule parameter effects on behavioral tolerance between FR and FI schedules is the amount of "effort," or behavior required by each schedule (6,11). Fixed-ratio schedules specify that a certain number of responses must occur before a reinforcer is delivered, whereas FI schedules specify that only one response need occur, after a fixed amount of time. The parameter manipulation with FR schedules thus involves changing the number of responses required, and with FI schedules it does not. To the extent that the development of tolerance is sensitive to other kinds of "effort" manipulations, such as force requirement or topographical complexity, the generalization may be appropriate. Nevertheless, the number of responses required for reinforcement appears to be an important modulator of cocaine tolerance.

It has been suggested that baseline reinforcement rates can affect an operant's sensitivity to cocaine's rate-decreasing effects, and that the size of the decrease in reinforcement rates after acute injections affects the subsequent development of tolerance (11,15). The fixed-interval values used in the present experiment were chosen to approximate baseline reinforcement rates observed during the experiment by Hoffman *et al.* (11). With baseline reinforcement rates as different as 12 per-minute (FI5-sec) and 0.5 per-minute (FI120-sec) in the present experiment, we found little evidence of differential acute effects or of differential tolerance between the FI schedule values. This implies that differences in baseline reinforcement rates alone were not responsible for the observed importance of schedule parameter effects using FR schedules (11) within the range of parameters and schedules studied.

The present experiment sheds light on previous research where differential drug tolerance was observed under conditions also differing in baseline reinforcement rates. Moerschbaecher *et al.* (15) studied the acute and chronic effects of cocaine and *d*-amphetamine on pigeons' conditional discriminations under performance and repeated-acquisition baselines. They found that tolerance to the drugs' error-increasing effects developed more slowly under the repeated-acquisition condition. They noted that their interpretation that this effect was due to different levels of stimulus control was compromised by the fact that baseline reinforcement rates in the repeated-acquisition component were lower than in the performance component. The differences in reinforcement rates between the components in Moerschbaecher *et al.*'s study were well within the parameters used in the present experiment, where they had little effect on tolerance, providing support for their stimulus-control interpretation.

A way to understand the differences between FR and FI schedules in the occurrence of cocaine tolerance is to consider the different relationships between response rates and reinforcement rates, i.e., feedback functions [cf. (4)] in them. In FR schedules, reinforcement rates are directly proportional to response rates over the whole range of response rates. In contrast, fixed-interval schedules have feedback functions that are steep at response rates that fall below the scheduled reinforcement rate, and flat at response rates above the scheduled reinforcement rate. This means that when response rates are low, reinforcement rates are more closely determined by changes in response rates in FI schedules, but not any more or less in FR schedules. In fact, when interresponse times are longer than the scheduled interreinforcement time under FI schedules, the relation between responses and reinforcement is essentially that of an FR1 schedule. During periods of very low response rates caused by cocaine administration, therefore, reinforcement rates are maximally affected by small changes in response rates during FI schedules. Occasional responses that occur after the programmed interval has timed out produce reinforcement. When rates are low during FR schedules, occasional responses rarely lead to reinforcement, especially during larger FR components. The occasional reinforcement of responses on FI schedules when response rates are low due to cocaine administration may be a factor in the relative insensitivity of tolerance development to FI parameter manipulations. One way to study the effects of this variable may be to employ adjusting ratio schedules that decrease ratio value as a function of increasing interresponse times. One simple way to accomplish this would be to use alternative FR FI schedules where, if the FR is not completed, and the FI has timed out, one response will produce reinforcement.

The acute effects of cocaine and *d*-amphetamine on behavior controlled by FI schedules of positive reinforcement have been studied extensively [e.g., (2, 3, 9, 12, 41, 16, 19, 22)]. Typically, cocaine and *d*-amphetamine produce consistent increases in response rates at lower doses, and decreases at higher doses. In the present experiment, we found expected decreases at the higher doses, but not consistent increases of usual magnitude at lower doses. A possible explanation for this discrepancy is that the FI values used in the present experiment were smaller than those usually studied. Typically, FI values used are 5 min or larger. Support for this view comes from research by Bacotti (1), who studied the acute effects of cocaine on pigeon's keypecking maintained under a concurrent FI FR schedule arrangement, varying the FI values while holding the FR constant. Increases in overall response rates were not observed when the FI value was 1.5 min, but were for two of three subjects when the FI values were 4 and 10 min. Research on the acute effects of *d*-amphetamine on behavior controlled by FI schedules of different values also supports this explanation (8,13).

In the present experiment, the relationship between reinforcement rates after acute 5.6 mg/kg injections of cocaine (Fig. 4) and the subsequent occurrence of tolerance to the response-rate-reducing effects of this dose are interesting with respect to the reinforcement-loss hypothesis (17). Pigeon 722 demonstrated the least disruption of reinforcement rates after injections of 5.6 mg/kg cocaine (although response-rate reductions were comparable to those of other subjects), and developed the least amount of tolerance (Fig. 3). This supports the reinforcement-loss hypothesis in that when the reinforcement rate was less disrupted, less tolerance developed. This relationship was not perfect in this experiment, however, in that after acute injections of 5.6 mg/kg cocaine relatively few reinforcers were lost during the FI5-sec component for Pigeon 563, yet tolerance to the response-rate reducing effects of this dose occurred completely.

In summary, the response-rate reducing effects of higher doses of cocaine were attenuated after chronic administration. The degree of attenuation was not systematically related to the FI value, suggesting that baseline reinforcement rate alone, within the parameters studied, is not a potent modulator of cocaine tolerance.

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REFERENCES

1. Bacotti, A. V. Effects of cocaine and morphine on concurrent schedule-controlled performances. J. Pharmacol. Exp. Ther. 212:280–286; 1985.
2. Barrett, J. E. Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. J. Pharmacol. Exp. Ther. 196:605–615; 1976.
3. Barrett, J. E.; Dworkin, S. I.; Zuccarelli, R. R. Effects of *d*-amphetamine, chlordiazepoxide and promazine on responding of squirrel monkeys maintained under fixed-interval schedules of food presentation and stimulus-shock termination. Pharmacol. Biochem. Behav. 7:529–535; 1977.
4. Baum, W. M. The correlation-based law of effect. J. Exp. Anal. Behav. 20:137–153; 1973.
5. Branch, M. N. Behavioral tolerance to stimulating effects of pentobarbital: A within subject determination. Pharmacol. Biochem. Behav. 18:25–30; 1983.
6. Branch, M. N.; Dearing, M. E. Effects of acute and daily cocaine administration on performance under a delayed-matching-to-sample procedure. Pharmacol. Biochem. Behav. 16:713–718; 1982.
7. Branch, M. N.; Dearing, M. E.; Lee, D. M. Acute and chronic effects of delta-9-tetrahydrocannabinol on complex behavior of squirrel monkeys. Psychopharmacology (Berlin) 71:247–256; 1980.
8. Branch, M. N.; Gollub, L. R. A detailed analysis of *d*-amphetamine on behavior under fixed-interval schedules. J. Exp. Anal. Behav. 21:519–539; 1974.
9. Byrd, L. D. Magnitude and duration of the effects of cocaine on conditioned and adjunctive behaviors in the chimpanzee. J. Exp. Anal. Behav. 33:131–140: 1980.
10. Corfield-Sumner, P. K.; Stolerman, I. P. Behavioral tolerance. In: Blackman, D.E.; Sanger, D. J., eds. Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978:391–448.
11. Hoffman, S. H.; Branch, M. N.; Sizemore, G. M. Cocaine tolerance: Acute versus chronic effects as dependent on fixed-ratio size. J. Exp. Anal. Behav. 47:363–376; 1987.
12. McKearney, J. W. Effects of *d*-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. J. Pharmacol. Exp. Ther. 190:141–153; 1974.
13. McMillan, D. E. Effects of *d*-amphetamine on performance under several parameters of multiple fixed-ratio, fixed-interval schedules. J. Pharmacol. Exp. Ther. 167:26–33; 1969.
14. McMillan, D. E.; Healey, M. L. Some effects of *d*-amphetamine and pentobarbital on performance under a long fixed-interval schedule. J. Exp. Anal. Behav. 25:389–399; 1976.
15. Moerschbaecher, J. M.; Boren, J. J.; Schrot, J.; Simoes-Fontes, J. C. Effects of cocaine and *d*-amphetamine on the repeated acquisition and performance of conditional discriminations. J. Exp. Anal. Behav. 31:127–140; 1979.
16. Richelle, M. Combined action of diazepam and *d*-amphetamine on fixed-interval performance in cats. J. Exp. Anal. Behav. 12:989–998; 1969.
17. Schuster, C. R.; Dockens, W. S.; Woods, J. H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia 9:170–182; 1966.
18. Snapper, A.; Inglis, G. SKED software system: Time shared superSKED. Kalamazoo, MI: State System; 1978.
19. Spealman, R. D.; Goldberg, S. R.; Kelleher, R. T.; Goldberg, D. M.; Charlton, J. P. Some effects of cocaine and two cocaine analogs on schedule-controlled behavior of squirrel monkeys. J. Pharmacol. Exp. Ther. 202:500–509; 1977.
20. Thompson, D. M. Repeated acquisition of behavioral chains under chronic drug conditions. J. Pharmacol. Exp. Ther. 188:700–713; 1974.
21. Thompson, D. M. Development of tolerance to the disruptive effects of cocaine on repeated acquisition and performance of response sequences. J. Pharmacol. Exp. Ther. 203:294–302; 1977.
22. Urbain, C.; Poling, A.; Millam, J.; Thompson, T. *d*-Amphetamine and fixed-interval performance: effects of operant history. J. Exp. Anal. Behav. 29:385–392; 1978.
23. Woolverton, W. L.; Kandel, D.; Schuster, C. R. Effects of repeated administration of cocaine on schedule-controlled behavior of rats. Pharmacol. Biochem. Behav. 9:327–337; 1978.