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Tolerance to response-disruptive effects of cocaine is facilitated by opportunity to respond in the absence of drug

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Abstract

A dose of cocaine that was 1/8 of a logarithmic unit larger than the smallest dose that produced complete suppression of responding of pigeons under a fixed-ratio 20 schedule was administered prior to 50 daily sessions. If responding occurred, then the dose was increased by 1/8 of a logarithmic unit and administered for an additional 50 sessions. The pigeons were divided into either a 'control' or 'saline' group. Control group pigeons received the same dose of cocaine for 100 additional days. Pigeons in the saline group were also exposed to a daily dosing regimen for 100 more sessions except that saline was substituted once every 5 days. Daily dosing then continued and dose–response functions were re-determined by substituting other doses for the daily dose every fifth session. During the first exposure to each dose, tolerance was evident for five of six pigeons in the saline group, whereas sensitization was evident for pigeons in the control group. Tolerance was observed in both groups following subsequent exposures. Tolerance to effects of behaviorally large doses of cocaine was therefore promoted when saline was occasionally substituted for the daily dose. Opportunity to respond during an ongoing regimen of daily cocaine administration enhanced the development of tolerance.

Keywords: Tolerance; Cocaine; Fixed ratio; Key peck; Pigeons

1. Introduction

Daily administration of cocaine may produce either tolerance or sensitization to its behavioral effects (cf. reviews by Corfield-Sumner and Stolerman, 1972; Demellweek and Goudie, 1983; Post et al., 1981; Stewart and Badiani, 1993). Tolerance is characterized by an attenuation of effects after repeated drug administration; that is, a larger dose is necessary to produce an effect that was initially produced by a smaller dose. Sensitization is characterized by the opposite: repeated administration of a drug produces effects at small doses that initially occurred at only the larger doses. Whether tolerance or sensitization occurs appears to depend on many factors, including the dose (Bowen et al., 1993; Branch et al., 2000; Demellweek and Goudie, 1983; Stafford and Branch, 1996), dosing regimen (King et al., 1992; Kleven and Woolverton, 1996; Miller and Branch, 2002; Stafford et al., 1994; Terry, 1992; Thompson et al., 1983), consequent events (Branch, 1979), context (Smith, 1990), reinforcement-schedule parameters (Hughes and Branch, 1991; Hoffman et al., 1987), pre- or postsession administrations (Branch and Sizemore, 1988; Woolverton et al., 1978), and reinforcement loss engendered by the initial effects of a drug (Schuster et al., 1966; Schuster and Zimmerman, 1961).

Repeated exposure to doses of cocaine that completely suppress behavior usually have not resulted in tolerance (Bowen et al., 1993; Branch et al., 2000; Demellweek and Goudie, 1983; Stafford and Branch, 1996). In addition, when a repeatedly administered dose of cocaine has systematically increased, tolerance to effects on performance under relatively small fixed-ratio (FR) schedules has been decreased (Bowen et al., 1993; Branch et al., 2000; Stafford and Branch, 1996). Stafford and Branch (1996), for

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example, showed that when a repeatedly administered dose of cocaine was relatively small tolerance developed to its effects on FR responding of pigeons, but when it was increased by a half of a log unit or more tolerance was eliminated. Similarly, Bowen et al. (1993) found that milk intake of rats showed tolerance when the repeatedly administered dose was small, but no tolerance developed when the chronic dose was large.

There is some evidence that occasional omission of cocaine during a daily dosing regimen may promote recovery from the rate-decreasing effects of relatively large doses of cocaine on schedule-controlled behavior. In a study by Hughes et al. (1996), key pecking by pigeons was maintained under an FR-30 schedule of reinforcement, and the effects of acute and chronic exposure to cocaine were investigated. Occasional exposure to saline and small doses of cocaine during a chronic dosing regimen promoted the development of tolerance. Three of the six pigeons, whose response rates had been zero during a period of daily presession administration of a relatively large dose of cocaine, showed an increase in response rates under the chronically administered dose following interpolated saline administrations.

The current experiment was designed to investigate systematically the effects of periodic omissions of cocaine during a chronic-dosing regimen in order to determine whether, and to what extent, tolerance might be promoted under these conditions. Specifically, pigeons were trained to peck a key under an FR-20 schedule of food presentation and then exposed to daily presession administration of a dose of cocaine that eliminated key pecking. After an extended period of exposure to this regimen, one group of subjects was given periodic exposure (once every fifth session) to a presession injection of saline, which was substituted for the daily cocaine dose. A comparison group continued to receive cocaine before every session. Dose–response functions were then assessed for both groups to determine if exposure to occasional administration of the drug vehicle promoted the development of tolerance.

2. Methods

2.1. Subjects

Twelve male White Carneau pigeons (obtained from Double "T" Farm, Glenwood, IA) served as subjects. Eleven were experimentally naïve. Pigeons were housed individually in a temperature-controlled colony room with a 16:8 h light/dark cycle. All pigeons had continuous access to vitamin-enriched water and grit in their home cages, and were maintained at 80% of their ad libitum weights. These weights ranged from 332 to 445 g. At all times, the "Principles of laboratory animal care" (National Institute of Health publication no. 85-23, revised 1996) were followed.

2.2. Apparatus

Experimental sessions were conducted at approximately the same time 7 days per week in a custom-built operant-conditioning chamber for pigeons. The interior of the chamber measured 30×30×33 cm, and was enclosed in a sound- and light-attenuating wooden box. Three walls and the ceiling were constructed of Plexiglas and the fourth wall was a brushed aluminum work panel. The work panel had one response key, which was a frosted plastic disk that could be transilluminated by a 1.1-W, 28 Vdc lamp and was located 6.5 cm from the ceiling. Located 13.5 cm below the key was a 4.5×5.5 cm hole through which a pigeon could obtain grain when a solenoid-operated hopper was elevated. Whenever the hopper was raised, this aperture was illuminated by a white light and all other lights in the chamber were extinguished. General illumination was provided by two 1.1-W, 28 Vdc lamps (houselights) that were located 7 cm apart from one another on the wall opposite from the work panel, 2 cm below the ceiling. Pecks with a force of 0.1 N or greater to the response key resulted in a 30-ms operation of a relay behind the work panel and were recorded as key pecks. White noise (95 dB) was used to mask extraneous sounds present in the experimental room. Experimental contingencies and data collection were executed under the ECBasic control system (Payla and Walter, 1993) interfaced with an IBM-compatible computer located in an adjacent room. Continuous recordings of responses were obtained using a Gerbrands Model C-3 cumulative-response recorder.

2.3. Behavioral procedure

At the beginning of each session, there was a 5-min blackout during which the chamber was dark and responding produced no programmed consequences. All sessions lasted for 30 grain deliveries or 30 min, whichever occurred first. Initially, the naïve pigeons were trained to eat from the food aperture (cf. Ferster and Skinner, 1957, p. 31). An autoshaping procedure was then implemented to generate key pecking (cf. Brown and Jenkins, 1968). Once key pecking was established, the number of responses required for food deliveries was systematically increased from 1 to 20. The number of sessions required to achieve an FR-20 schedule of reinforcement ranged from 7 to 12, with a median of 7. Pigeon 82 had previous experience in an undergraduate laboratory class and did not require training to eat or peck in the apparatus; FR-20 performance was established within six sessions for this pigeon.

2.4. Drugs and drug administration procedures

Cocaine hydrochloride (provided by the National Institute on Drug Abuse) was dissolved in 0.9% saline and injected into a pigeon's pectoral muscle immediately before placement in the experimental chamber. Injection volume

was held constant at 1.0 ml/kg, and doses were calculated as the salt. The site of injection alternated between the two sides of the breast when drug deliveries occurred daily. During dose–response assessments, doses were administered in fixed, descending series to facilitate detection of systematic differences with repeated determinations of effects at each dose (cf. Sidman, 1960).

2.5. Acute dosing regimen

Once response rates had stabilized under the FR-20 schedule for each pigeon, as determined by visual inspection of daily response rates and cumulative response records, the acute effects of a range of doses of cocaine (0.1 to 13.0 mg/kg) were tested. The acute dosing regimen consisted of weekly administration of a dose of cocaine or saline immediately prior to the experimental session with no drug injections occurring in intervening sessions. At least two determinations of effects of each dose were obtained for each pigeon, except on two occasions when a dose was delivered only once (Pigeons 28 and 935 with 0.3 and 10.0 mg/kg, respectively). Doses that revealed somewhat variable effects were tested again until we felt that the mean effect was representative. The pigeons were then paired on the basis of similarity of dose–response functions and randomly assigned to one of two groups, either a 'saline' or 'control' condition (i.e., saline and control group). Table 1 displays the range of doses of cocaine and the number of exposures to each dose for all pigeons.

2.6. Chronic dosing regimen

Following the acute dosing regimen, a dose that was 1/8 of a logarithmic unit larger than the smallest dose that produced complete suppression of responding during the acute dosing regimen was administered daily to all pigeons, prior to each session for 50 sessions. An arbitrary criterion of 50 sessions was selected based on the assumption that if responding did not recover in 50 sessions, then it probably would not recover at all. If responding occurred in any session during this time, a dose that was 1/8 of a logarithmic unit larger than the previous dose was then administered daily, beginning with the next session. Increases in dose occurred for two pigeons in the control group and for three in the saline group. This procedure continued until there were 50 consecutive sessions of complete suppression of responding. An exception was Pigeon 300, which received presession injections of cocaine for only 40 sessions. Pigeon 56 completed 47 sessions before it was removed from the experiment due to illness. Table 2 shows the dose and number of administrations for all pigeons during this condition.

2.7. Periodic omission of cocaine

Pigeons in the saline group then received saline every fifth session in substitution for the chronically administered dose of cocaine. This condition was implemented for 100 sessions, resulting in a total of 20 saline and 80 cocaine administrations over that span. Pigeons in the control group continued to receive daily injections of the same dose of cocaine given in the first 50 days of daily dosing for 100 additional consecutive sessions. During this condition, the value of the chronically administered dose of cocaine was held constant for both groups, regardless of whether or not responding occurred.

2.8. Reassessment of drug effects during the chronic dosing regimen

After the 100-day period just described, daily cocaine administration continued and dose effects were obtained by

Table 1
Number of administrations of each dose for acute and chronic dose–effect curves

Subject	Dose (mg/kg)												
	Saline	0.1	0.3	1.0	1.7	2.3	3.0	4.2	5.6	7.4	10.0	13.0	17.0
Control group													
813	2[a] (2)[b]	–	2 (2)	2 (3)	–	–	2 (4)	2 (4)	3 (15)	–	–	–	–
79	3 (3)	–	–	2 (3)	–	–	2 (3)	–	4 (3)	3 (3)	2 (15)	–	–
934	3 (2)	–	3 (2)	3 (2)	–	–	3 (3)	–	4 (3)	2 (2)	3 (14)	–	–
935	2 (3)	–	–	2 (3)	–	–	2 (3)	–	2 (3)	2 (3)	1 (2)	–	0 (17)
912	2 (3)	2 (4)	3 (3)	4 (3)	–	3 (2)	4 (3)	–	2 (18)	–	–	–	–
56	2 (0)	–	2 (0)	2 (0)	–	–	3 (0)	–	3 (0)	2 (0)	2 (0)	2 (0)	–
Saline group													
41	3 (2)	–	2 (2)	2 (3)	–	–	2 (4)	2 (3)	3 (14)	–	–	–	–
82	2 (2)	–	–	3 (2)	–	–	2 (2)	–	3 (2)	2 (2)	3 (10)	–	–
28	3 (2)	–	1 (2)	2 (2)	–	–	2 (2)	–	2 (2)	2 (2)	2 (2)	0 (14)	–
300	2 (3)	–	2 (0)	2 (4)	–	–	2 (2)	–	2 (3)	3 (3)	–	–	0 (15)
4954	2 (2)	–	2 (0)	2 (2)	2 (0)	2 (2)	3 (2)	2 (2)	2 (3)	–	–	–	0 (13)
76	2 (2)	–	2 (2)	4 (2)	–	–	3 (2)	–	4 (2)	2 (2)	2 (2)	–	0 (14)

[a] Values for the acute dosing regimen are to the left of the parentheses.
[b] Values for the chronic dosing regimen are inside the parentheses.

Table 2
Cocaine dose (mg/kg) and number of daily administrations for all pigeons while response-suppression criterion (50 sessions of no key pecking) was in effect during the chronic dosing regimen

Pigeon	Cocaine dose (mg/kg)	No. of administrations
Control group		
813	5.6	50
79	10.0	50
934	10.0	50
935	10.0	5
	13.0	2
	17.0	50
912	5.6	50
56	13.0	14
	17.0	47
Saline group		
41	5.6	50
82	10.0	50
28	10.0	6
	13.0	50
300	17.0	40
4954	7.4	4
	10.0	23
	13.0	1
	17.0	50
76	10.0	10
	13.0	9
	17.0	50

substituting different doses of cocaine (range 0.1 to 13.0 mg/kg) or saline every fifth session, until at least two determinations of each dose and saline were administered for all pigeons. Table 1 displays the number of administrations of each dose for all pigeons during the chronic dosing regimen. The large number of administrations listed for a particular dose for each pigeon, for example, 15 administrations of 5.6 mg/kg for Pigeon 813, indicates the number of sessions that immediately preceded those in which other doses, including saline, were tested during the chronic dosing regimen. The mean effect for that dose was based on all such sessions.

2.9. Additional manipulations

Because responding did not recover for Pigeon 79 of the control group at any dose or even after saline injections, additional manipulations were conducted to determine if responding could be re-established. After reassessment of dose effects during the chronic dosing regimen, Pigeon 79 continued to receive 10.0 mg/kg cocaine prior to each experimental session except that saline was substituted for the chronically administered dose once every five sessions. This condition was implemented for 50 sessions, for a total of 10 saline and 40 cocaine injections. Next, the presession injection was omitted once every five sessions. This was implemented for 20 sessions, for a total of 5 such omissions and 15 cocaine injections. Then, saline was delivered daily for 21 sessions. The presession injection of saline then was eliminated for seven sessions. After that, saline was administered daily for 15 sessions except that 10.0 mg/kg cocaine was delivered on the eighth session. The presession injection of saline again was eliminated for 12 sessions, with a presession injection of 10.0 mg/kg cocaine administered on Session 8. At this point, saline was administered daily for 20 sessions, and dose of cocaine (10.0 mg/kg) was administered on Session 7 during this regimen.

3. Results

Fig. 1 shows acute effects of cocaine (0.1 to 13.0 mg/kg) on response rate for all pigeons. Dose-dependent decreases were observed for all pigeons. Moderate to high doses (4.2 to 10.0 mg/kg) produced complete suppression of key pecking, whereas smaller doses (0.1 to 3.0 mg/kg) and saline produced little or no change in response rates. Average control rates ranged from 66.15 responses per minute (Pigeon 79) to 190.88 responses per minute (Pigeon 934), with a median of 147.54 responses per minute. Effects of each dose were generally consistent from injection to injection, except for Pigeons 934 and 76. The figure is organized with the "matched" pairs in each row. Matching was based on the form of the dose–response function with special emphasis on potency. That is, we tried to match the pigeons on their sensitivity to the rate-decreasing effect of the drug. The subjects whose data are shown in the right column were assigned to the saline group.

Fig. 2 shows response rate across successive sessions for pigeons that received saline once every fifth day in substitution for the chronically administered dose of cocaine (i.e., saline group). Rates of responding under saline increased with successive administrations of saline for all pigeons. The number of saline administrations required before pecking rates approximated baseline levels ranged from 1 (Pigeon 41) to 8 (Pigeon 4954), with a median of three administrations across pigeons. There was a tendency for larger daily doses to be associated with a greater number of administrations before rates under saline increased to baseline levels.

Response rate decrements when cocaine was injected were attenuated after several exposures to saline for Pigeons 41 and 82, although this effect was modest for Pigeon 82. Response rates remained suppressed following each administration of the chronic dose for the other four pigeons. Key pecking remained absent in the control group across the 100 sessions of this phase.

Figs. 3 and 4 show normalized dose–response curves obtained following periodic omission of cocaine (saline group) and daily cocaine administration (control group). The acute dose–response functions from Fig. 1 were normalized and are shown for comparison. We attempted to match pairs on the basis of shape and sensitivity to the effects of cocaine, and the normalized dose–response curves show the attempt was reasonably successful. Fig. 3

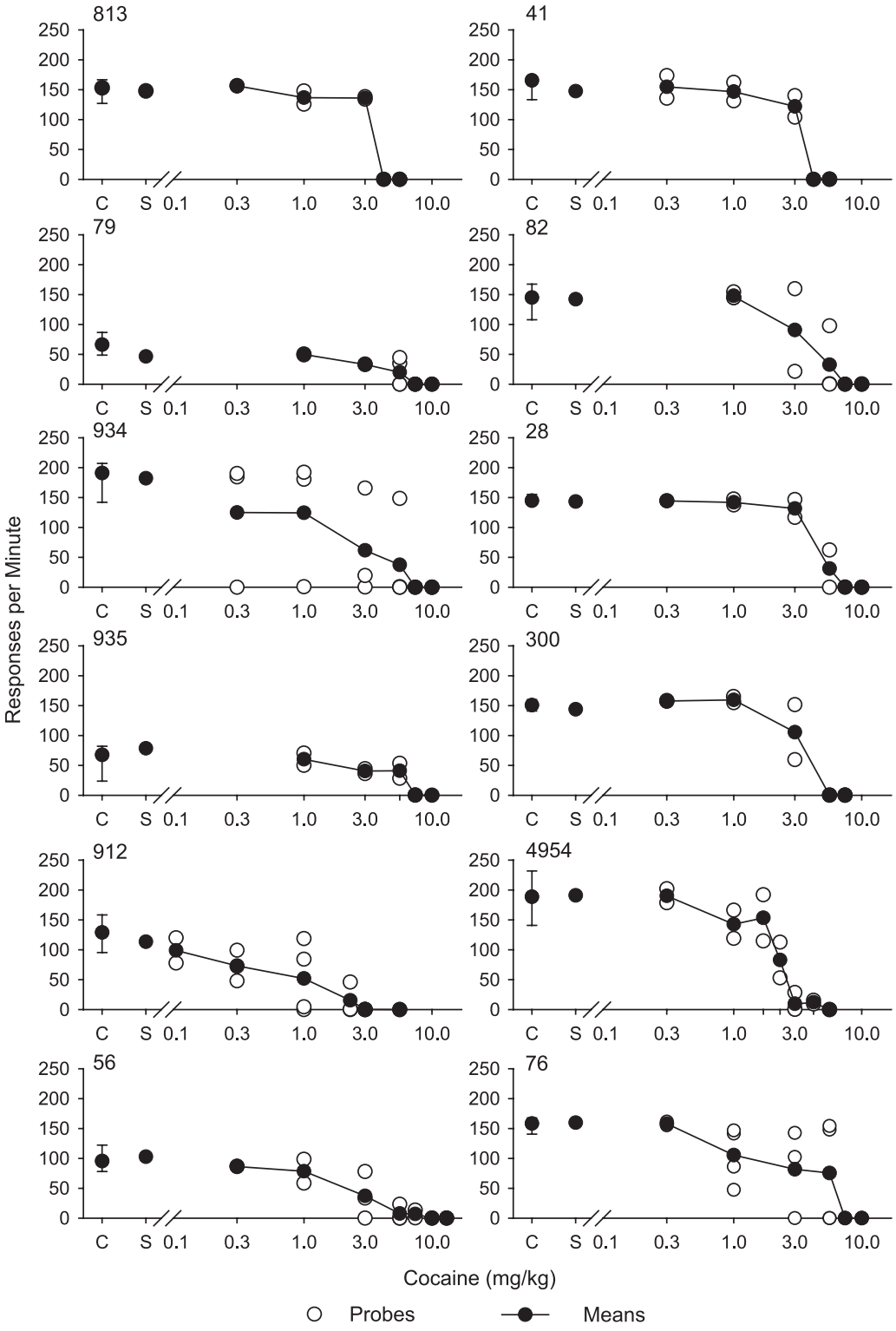

Fig. 1. Responses per minute as a function of dose of cocaine (0.1 to 13.0 mg/kg) for all pigeons during the acute dosing regimen. Open circles show response rates from individual cocaine administrations; filled circles show mean response rates at each dose and saline. Points above "C" are from control (no drug) sessions that immediately preceded those in which cocaine was administered; those above "S" were obtained when saline was administered. The bars indicate the range.

shows the effects of cocaine during the first administration of each dose, whereas Fig. 4 shows effects of subsequent administrations.

Fig. 3 shows that dose–response functions were shifted to the left with respect to the acute dose–response functions for all pigeons in the control group and were shifted to the

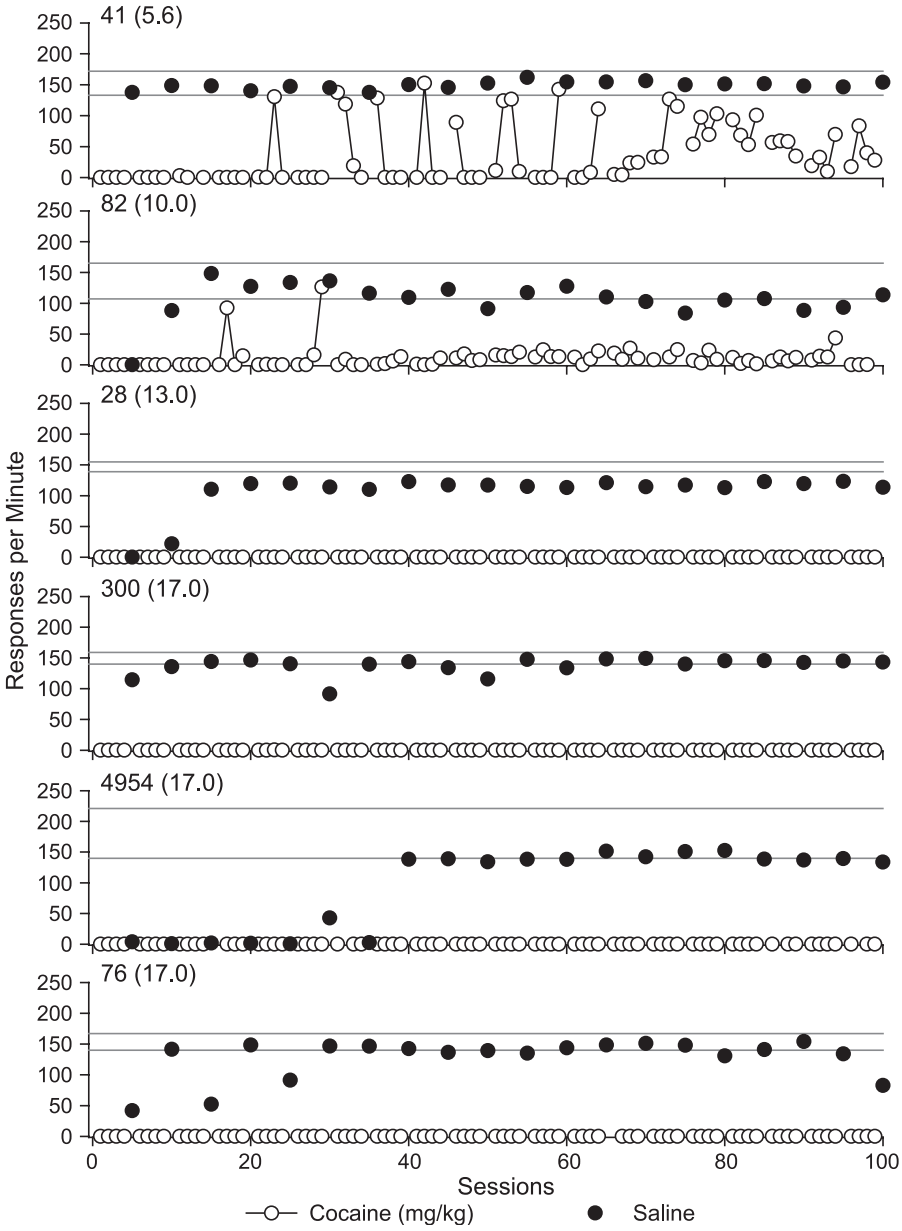

Fig. 2. Responses per minute across successive sessions for pigeons that were exposed to periodic omission of cocaine during chronic cocaine administration (i.e., saline group). Open circles show values obtained during cocaine deliveries, whereas filled circles show values obtained during sessions in which cocaine was omitted (i.e., saline was administered). The chronically administered dose of cocaine is shown in parentheses. Horizontal dotted lines indicate the range of baseline rates of responding (data from control days during acute dosing regimen).

right for the four of the six pigeons in the saline group during the first iteration of the range of doses of cocaine during the chronic dosing regimen. For Pigeon 41 of the saline group, even though the major descending portion of the curve was shifted left, responding was evident at the two largest doses, doses that previously had resulted in no pecking. For Pigeon 76, by contrast, the chronic dose–response curve was shifted to the left with respect to the acute dose–response function, a pattern similar to that found in the dose–response functions of the control group.

Effects of cocaine for the second and subsequent administrations (Fig. 4) revealed greater similarity between the groups. The chronic dose–response curves were shifted to the right with respect to the acute dose–response functions for all pigeons, regardless of whether they were in the saline or control group, except for Pigeon 79 of the control group. The behavior of Pigeon 79 warrants special mention because rates of responding remained completely suppressed for 190 sessions beyond the 100-session criterion despite the numerous manipulations implemented in an attempt to regenerate responding, including periodic and daily administration of saline, that are outlined in the Methods section. Responding finally reoccurred during the third session without a

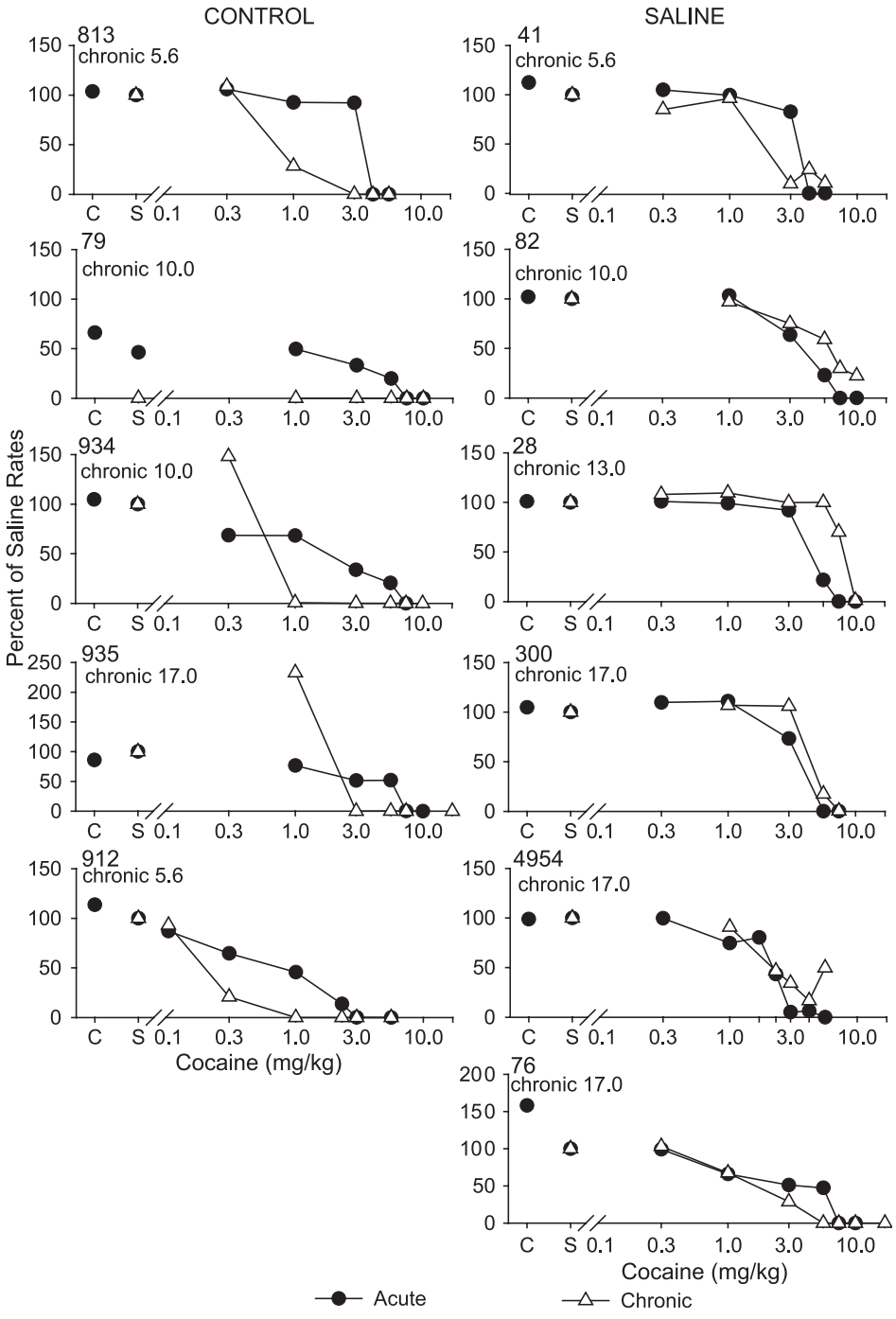

Fig. 3. Response rate, expressed as percent of rates following saline administration, across doses of cocaine (0.1 to 13.0 mg/kg) during acute (shown by filled circles) and chronic (shown by open triangles) dosing regimens. Data from the first exposure to a range of doses of cocaine and saline during the chronic dosing regimen are shown by the open triangles. The filled circles are the functions from Fig. 1 expressed as percent of saline response rates. Data for pigeons in the control group are shown in the left column and those for pigeons in the saline group are shown in the right column. Note the different *y*-axis scales for Pigeons 935 and 76.

presession injection, and increased to near baseline rates by the fifth session.

To permit a quantitative analysis of the data presented in Figs. 3 and 4, ED_{50} values were computed for the normalized dose–response functions for all pigeons during acute and chronic cocaine administration. These values are presented in Table 3 and were obtained in the following manner. Linear regression was used to fit a line to the descending portion of the dose–response function, and this equation was then used to estimate the point along the range of doses of cocaine that would produce a 50% reduction in response rates relative to control rates for each pigeon (Tallarida and Murray, 1981). The descending part of the dose–response function was defined as extending

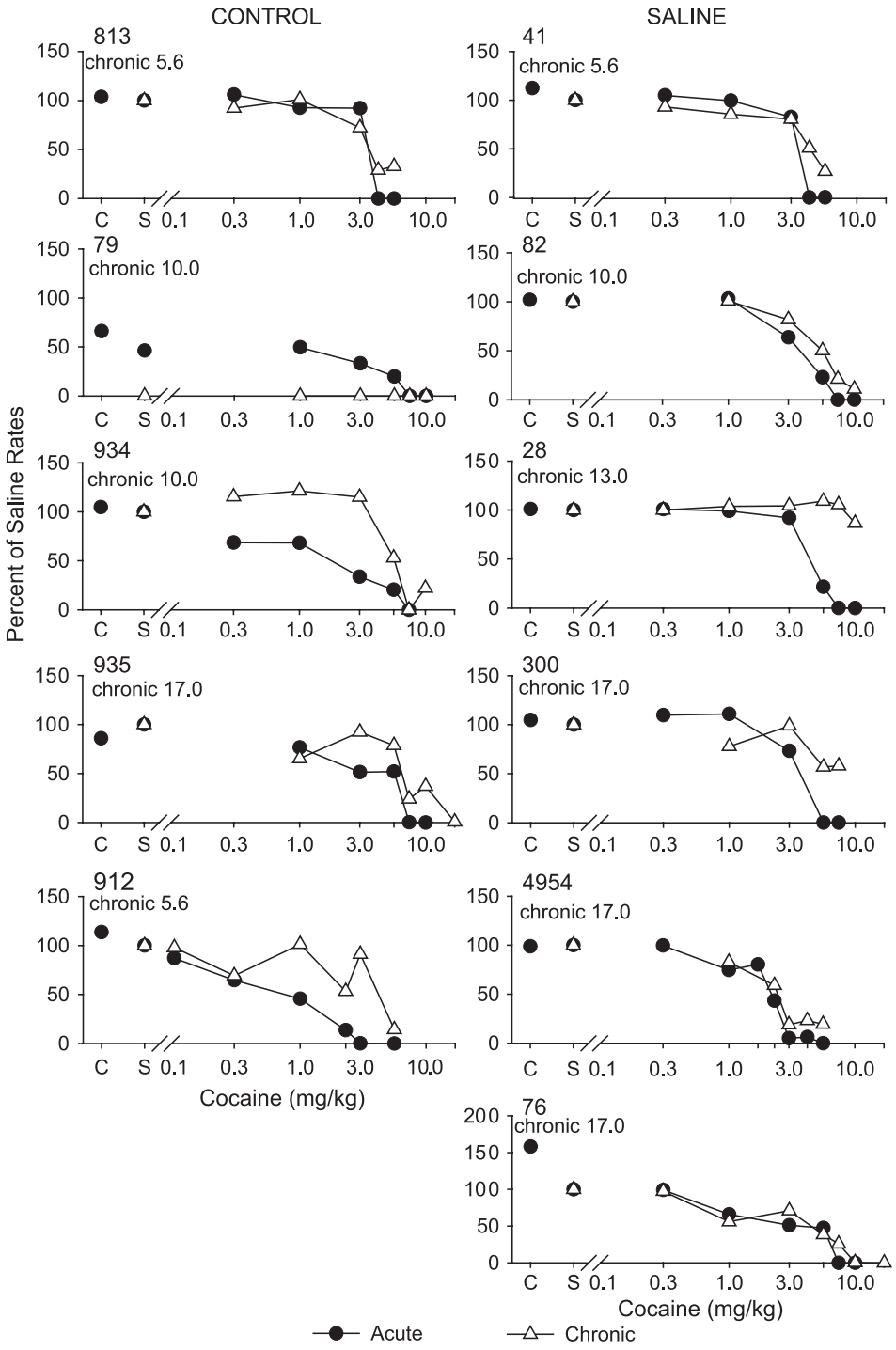

Fig. 4. Response rate, expressed as percent of saline rates as a function of dose of cocaine during the chronic dosing regimen. Open triangles show the mean response rates during the second and subsequent exposures to a range of doses of cocaine and saline. Filled circles show acute dose response functions.

from the largest dose that produced response rates within the control range to the smallest dose that produced complete suppression of responding. If these criteria were not met, values from the entire dose–response function were used. As an example, consider dose–response functions for Pigeon 813. The descending portion of the acute dose–response function was between 3.0 and 4.2 mg/kg, and log-linear regression was computed with respect to these doses. Based on this analysis, the ED_{50} was 3.47 mg/kg cocaine. Additionally, we used the linear regression feature in SigmaPlot 8.0 to compute r^2 values for fit functions across pigeons, and these ranged from .79 to 1, with a mean value of .93.

As Table 3 confirms, ED_{50} values obtained during the acute dosing regimen show no systematic differences between groups, as one would expect given the matching

Table 3
ED_{50} values for acute and chronic dose–response curves for all pigeons

	Acute	Chronic	
		1st[a]	2nd, 3rd, 4th[b]
Control group			
813	3.47	2.39	3.55
79	3.72	0.00	0.00
934	1.17	0.66	5.24
935	2.69	2.37	8.32
912	0.55	0.22	4.17
56	2.04	–	–
Mean	2.27	1.13	4.26
Standard deviation	1.26	1.17	3.00
Saline group			
41	2.81	2.14	4.57
82	3.24	5.12	5.13
28	3.55	7.40	17.78
300	3.09	4.57	7.59
4954	2.14	10.20	6.76
76	2.29	1.48	2.45
Mean	2.85	5.15	7.38
Standard deviation	0.55	3.27	5.40

[a] Values are from the first exposure to the range of doses of cocaine (0.3 to 13.0 mg/kg) and saline following prolonged exposure to the drug.
[b] Values were obtained from the second and subsequent exposures to cocaine and saline.

of subjects across groups. The mean ED_{50} values for the control and saline groups were similar, with values of 2.27 and 2.85 mg/kg, respectively. A t test for independent means shows that the mean difference in ED_{50} values was not statistically significant (t=−1.01, df=10, P=.33).

A comparison of ED_{50} values across groups during the first iteration of a range of doses of cocaine during the chronic dosing regimen shows that the mean ED_{50} value was substantially greater for the saline group than for the control group at 5.15 mg/kg compared to 1.13 mg/kg, respectively (t=2.60, df=9, P=.03).

The mean ED_{50} value of 1.13 mg/kg for subjects in the control group during the first dosing cycle of the chronic dosing regimen was less than the mean value of 2.27 mg/kg generated under acute dosing and all five pigeons in the control group showed a shift to smaller ED_{50} values. The mean ED_{50} value for pigeons in the saline group during the first cycle of doses under the chronic dosing regimen was 5.15 mg/kg compared to the mean ED_{50} of 2.85 mg/kg obtained during acute administrations, with four of the six pigeons showing an increase in ED_{50} values from the acute to chronic dosing regimen.

Dose effects assessed after exposure to either 100 consecutive days of daily drug administration (control group) or periodic administration of saline during the 100-session period (saline group) changed after the first round of doses. The changes were most pronounced in the control group. Four of the five pigeons in this group showed tolerance when doses were tested subsequently, with the group mean ED_{50} increasing from 1.13 to 4.26 mg/kg (t=−2.83, df=4, P=.05). Curves also tended to be shifted a bit more to the right in the saline group during subsequent administrations, with the group-mean ED_{50} increasing from 5.15 to 7.38.

4. Discussion

The main findings of this study were that (a) tolerance to the effects of cocaine was immediately evident after a condition in which a chronically administered dose was omitted once every fifth session across a 100-session period that followed a 50-day period of complete suppression; (b) sensitization was evident initially after a rate-suppressing dose had been administered daily, for 150 sessions, without periodic omissions of cocaine; (c) tolerance was evident when dose effects were assessed again in this group; and (d) recovery of responding at the chronically administered dose occurred for two of six pigeons during the 100-session period when vehicle administrations were interspersed. The comparison between the saline group and control group showed that periodic omission of cocaine during a daily dosing regimen promoted the development of tolerance to behavioral effects of cocaine. The findings therefore bolster the report of Hughes et al. (1996) in showing that once responding is re-established by providing occasional interruptions in a series of administrations of cocaine, tolerance may well be evident.

Tolerance was present (for most pigeons) in the saline group yet no tolerance was evident (at least initially) in the control group after a relatively lengthy period of exposure to a large dose of cocaine. The difference between these two groups is that the control group received cocaine daily, whereas the saline group had occasional sessions without the drug. This finding suggests that the failure to see tolerance to behavioral effects might involve behavioral processes. The occasional sessions without drug in the saline group may have served as “reminders” about the operant contingencies in effect during sessions. That is, occasional sessions with saline allowed the animal to come into contact with positive reinforcement contingencies upon completion of the FR requirement. Increased responding at doses that initially eliminated or suppressed responding may have been due to opportunity to complete ratio requirements under saline. Studies of forgetting have shown that re-exposure to the training conditions (or contingencies of reinforcement) promote reinstatement of the originally trained response. This effect has been demonstrated with rats (Campbell and Jaynes, 1966; Campbell and Spear, 1972; Spear and Parsons, 1976), human infants (Hartshorn, 2003; Hayne et al., 2000; Rovee-Collier et al., 1980), and children (Priestley et al., 1999). An important feature of these findings is that occasional re-exposure to some elements of the original training condition promotes responding after a prolonged delay between training and testing. It stands to reason that some of these elements include the contingencies of reinforcement. In the current experiment, periodic omissions of cocaine were sufficient to

reinstate responding and this effect may have generalized to moderate and large doses of cocaine.

The design of the current study might have been strengthened by the addition of a second control group that was matched to the saline group for total exposure to cocaine during the repeated administration phase. Such a group would have had every fifth session omitted in a manner linked to the saline group, which received the saline vehicle every fifth session. Consequently, the group would have received the same number of injections of cocaine during the 100-day period as did the saline group, but would not have had a chance to contact the contingencies of reinforcement while not drugged. Omission of such a group, however, is consistent with results reported by Wolgin and Hughes (2001), who found that effects produced by repeated administration of amphetamine on milk drinking were unaffected by suspending drug administrations and the opportunity to respond for a period of as long as 31 weeks. We presumed, therefore, that occasional suspensions from a regimen of presession drug administration that lasted only one day would be unlikely to alter the effects of cocaine. Additionally, the outcome of the repeated saline injections in the present study was tolerance. Thus, if total exposure to cocaine was the driving factor in its development, one might well have expected the control group to reveal more tolerance because animals in that group had experienced 20 more cocaine administrations at the end of the 100-day phase than had those in the saline group.

Sensitization observed in the control group was transient in that it was present only during the first exposure to a range of doses during chronic dosing. Tolerance was observed for four of the five pigeons in this group once doses were tested again and it was maintained across subsequent cycles of doses. The transient nature of sensitization may be considered a validation of the effectiveness of occasional vehicle exposures in enhancing tolerance. Recall that the test doses were given in a descending order. That is, large doses were tested first, with exposure to smaller, perhaps ineffective, doses and the vehicle (a dose of zero) occurring last. Once pigeons in the control group had experienced sessions with the vehicle or small doses that resulted in responding, subsequent assessments revealed tolerance. Interestingly, four of the five pigeons in the control group responded on the key upon initial exposure to the saline vehicle at the end of the 100-day regimen, and all four subsequently showed tolerance. In contrast, only three of the six subjects in the saline group pecked upon the first exposure to saline at the beginning of the 100-day series and for none of those three was tolerance to effects of the repeated dose evident at that time. The results from the control group, therefore, may be interpreted as indicating that only one or two exposures to conditions that permitted the subject to contact the operant contingencies were sufficient to permit the observation of tolerance that was presumably generated by exposure to the repeated-dosing regimen. That is, the many exposures to the vehicle in the saline group after responding had recovered during sessions preceded by its administration were probably unnecessary to permit the observation of tolerance.

Attenuation of response rate decrements occurred at the chronically administered dose for only two of six pigeons in the saline group during the period of occasional saline administration. Recovery of responding was most pronounced in the pigeon given the smallest dose (5.6 mg/kg) chronically; modest in the pigeon at the second smallest dose (10.0 mg/kg); and not observed with larger doses (13.0 and 17.0 mg/kg). Five of the six pigeons in the saline group, however, revealed tolerance when other doses were tested. Thus, even though no change in performance was evident at the repeated dose, the experience with the vehicle sessions had produced a change in the dose–response curve. In contrast, subjects in the control group showed no tolerance. In fact, all of the subjects in that group showed sensitization at the end of the 100-day period.

The repeatedly administered doses can be viewed as initially behaviorally equivalent across subjects because they were selected to be slightly larger than the smallest dose that would eliminate pecking in the session. The across-subject correlation between dose and recovery or its absence, however, suggests that absolute value of the dose was important. Prior research with large doses has generally shown that tolerance is not evident when those doses are given repeatedly (Bowen et al., 1993; Branch et al., 2000; Demellweek and Goudie, 1981; Stafford and Branch, 1996; Woolverton et al., 1978).

Key pecking was sometimes absent on the initial exposure to the drug vehicle after extended exposure (more than 50 consecutive days) to a dose that eliminated it. This effect may be due to conditioning of the rate-decreasing effects of cocaine to the experimental context. For example, if key pecking is absent when the vehicle is given, it is reasonable to assume that it would remain so if a dose of the drug were given. That is, one would observe a generalized suppression of responding that is independent of dose. That was evident in the control group during the initial dose–response assessment after the 100-day drug regimen. If the effect is relatively independent of dose, it suggests that the result does not reflect a pharmacological sensitization, but instead indicates a change that is of behavioral origin. That view is supported by the result showing that the generalized suppression of responding can be eliminated by arranging conditions in which the animal occasionally makes contact with the operant contingencies. What was revealed, once the generalized suppression was eliminated, was tolerance. One interpretation, therefore, is that repeated drug exposure had produced tolerance but its presence was masked by a generalized behaviorally based suppression of pecking.

One possible account of the origin of the apparent generalized suppression is that a startle reaction to the feeder operation gets enhanced by cocaine. Normal pigeon feeders like that used in the present experiment make a substantial

sound and also produce seismic effects when operated. If a startle reaction to those stimuli is enhanced by cocaine to the degree that approach to or eating from the feeder is compromised, the food reinforcer would lose effectiveness, thus resulting in response rate decrements. Acoustic startle in rats has been shown to increase in a bitonic fashion as a function of cocaine dose (Borowski and Kokkinidis, 1994; Davis, 1985; Willick and Kokkinidis, 1995). In the current study, perhaps a startle reaction interfered with the reinforcing efficacy of grain delivery and diminished its effectiveness as a reinforcer. Periodic omission of cocaine may have lessened this aversion and promoted responding by providing Pavlovian counter conditioning that weakened the eliciting effects of the feeder operation. In other words, periodic omission of cocaine may have counter-conditioned startle reactions enhanced by cocaine. Future research could examine these speculations by varying the "magnitude" or features of the reminders or by explicit manipulations to make the presentation of food less likely to have aversive characteristics.

In sum, the present study showed that interpolating exposure to the drug vehicle in a series of exposures to a relatively large dose of cocaine may reveal tolerance to effects of the drug that might otherwise not be evident. Repeated exposure to a large, key-peck-eliminating dose appears to have produced a generalized suppression that prevented tolerance from being observed. Once that suppression was removed, tolerance was generally evident. These data show that long-term exposure to large doses of cocaine can result in tolerance to its effects on operant performance of pigeons.

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