Pharmacology Biochemistry and Behavior, Vol. 66, No. 2, pp. 313–321, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(00)00184-2

Effects of Cocaine and Morphine Under Mixed-Ratio Schedules of Food Delivery: Support for a Behavioral Momentum Analysis

ALAN POLING, TOM BYRNE, LEEANN CHRISTIAN AND MARK G. LESAGE

Western Michigan University, College of Arts and Sciences, Department of Psychology, Kalamazoo, MI 49008-5052

Received 9 July 1999; Revised 27 September 1999; Accepted 20 October 1999

POLING, A., T. BYRNE, L. CHRISTIAN AND M. G. LESAGE. *Effects of cocaine and morphine under mixed-schedules of food delivery: Support for a behavioral momentum analysis.* PHARMACOL BIOCHEM BEHAV **66**(2) 313–321, 2000.—Previous studies have shown that ratio size influenced the development of tolerance under simple and multiple schedules, but not under progressive-ratio (PR) schedules. PR schedules share certain features with mixed-ratio (MR) schedules, and pilot data suggested that ratio size fails to modulate tolerance to cocaine or morphine under MR schedules. The present study examined more comprehensively the pre- and postchronic effects of cocaine and (in separate birds) morphine under MR schedules with fixed-ratio (FR) 5 and FR 95, FR 25 and FR 75, and FR 50 and FR 50 components. Acute doses of cocaine and morphine initially were given in an ascending series (beginning with 0.56 mg/kg) until responding was reduced to near-zero levels. Chronic (daily) dosing with a dose that reduced, but did not eliminate, responding then occurred until response rates stabilized. Finally, postchronic dose–response determinations were conducted. Both cocaine and morphine reduced response rates at all FR values. Tolerance was consistently observed to the effects of morphine, but not to those of cocaine. With both drugs the degree of tolerance observed did not vary as a function of FR value. These findings, like those obtained under PR schedules, indicate that ratio size does not always modulate drug tolerance. A behavioral momentum analysis of drug action appears to account for whether or not ratio size modulates tolerance, and such an analysis is provided. © 2000 Elsevier Science Inc.

Tolerance Morphine Cocaine Mixed schedule Pigeons

TOLERANCE occurs when the dose of a drug required to produce a given effect increases as a result of repeated exposure to that drug (21). That is, the dose–response curve shifts to the right as a result of chronic exposure. The rapidity and extent of tolerance development is influenced by several variables, including the drug and response in question and the manner in which chronic exposure is arranged [e.g., (7)]. When drug effects on operant behavior are considered, the specific conditions under which behavior is maintained can strongly affect the development of tolerance [e.g., (31)]. For example, seven studies, which collectively evaluated five drugs in three species, provide substantial evidence that the amount of responding required for reinforcement, or "effort," influences tolerance (6,9,10,19,20,29,30). In these studies, greater tolerance developed under relatively short fixed-ratio (FR) schedules than under relatively long FR schedules. This effect has been demonstrated, for example, with cocaine under conditions where FRs that differed in length appeared in a multiple schedule arrangement (9,10) and under conditions where FRs that differed in length were arranged for different subjects (19). In both cases, the drug initially reduced response and reinforcement rates, and the greatest tolerance developed at the shortest ratio. Ratio size also has been demonstrated to influence the development of tolerance to the rate-reducing effects of morphine in pigeons responding under a multiple FR 5 FR 25 FR 125 schedule of food delivery, although some tolerance developed at each FR value (20). Under a multiple schedule, component schedules (e.g., FR 5, FR 25, FR 125) alternate, and each one is correlated with a different environmental stimulus (e.g., the key pecked by pigeons might be red during the FR 5, green during the FR 25, and white during the FR 125).

Requests for reprints should be addressed to A. Poling, Western Michigan Univeristy, College of Arts and Sciences, Department of Psychology, Kalamazoo, MI 59008-4500

Ratio size did not, however, appear to influence the development of tolerance to morphine in pigeons responding under progressive-ratio (PR) 5 or 25 schedules (11,25). The PR schedule requires subjects to emit an increasing number of responses to earn each successive reinforcer. For instance, under a PR 5 schedule, the number of responses required for food delivery begins at five, and is incremented by five each time food is earned. Thus, the response requirements for reinforcement across the course of the session are 5, 10, 15, 20, 25, and so on. When pre- and postchronic dose–response curves for morphine at different ratios (e.g., 5, 50, 100) arranged under PR schedules were compared, a similar degree of tolerance was observed at all values. Thus, ratio size did not modulate tolerance.

Under PR schedules, and in contrast to the conditions where ratios size was observed to modulate tolerance, different ratio values were not associated with different discriminative stimuli. It is well known that antecedent stimuli can influence drug effects [e.g., (1,22,24)], and it is possible that tolerance develops most readily in the presence of stimuli with a strong capacity to evoke behavior, such as those correlated with short FR schedules. This analysis suggests that ratio size should not modulate tolerance to morphine or cocaine in animals exposed to mixed schedules similar to the multiple schedules under which ratio size has been shown to modulate tolerance. Mixed schedules are equivalent to multiple schedules, except that in the former no exteroceptive stimuli are correlated with the individual component schedules. The present study examined in pigeons the acute and chronic effects of cocaine and (in separate subjects) morphine under three mixed schedules comprising FR 5 and FR 95, FR 25 and FR 75, and FR 50 and FR 50 components. Based on prior findings with PR schedules and on preliminary results using mixed schedules (2,3), we hypothesized that ratio size would not modulate the development of tolerance to either drug. If ratio size did modulate tolerance, prior findings with multiple schedules suggest that greater tolerance would be observed under the FR 5 schedule than under the longer FRs.

METHOD

Subjects

Eight experimentally-naive female White Carneau pigeons, food deprived to 80% of free-feeding body weights, served as subjects. They were retired breeders (mature adults) obtained from Palmetto Pigeon Plant (Sumter, SC) and were individually housed with free access to water and grit in a colony area with controlled lighting (16 h light, 8 h dark each day), temperature (22–24°C), and humidity (60–70%).

Apparatus

Four MED Associates (St. Albans, VT) operant test chambers were used. The chambers were 30 cm long by 25 cm wide by 30 cm high. They were illuminated by a 7-W white bulb on the ceiling. A 7 × 7 cm opening located 2 cm above the floor allowed access to mixed grain when the food hopper was raised. Three response keys spaced 6 cm apart were centered on the front panel 14 cm above the feeder opening. The keys, which required a force of about 0.2 N to operate, could be illuminated white, red, or green. Only the center key was used in the present studies. A speaker supplied white noise to each chamber and an exhaust fan provided ventilation. Programming of experimental events and data recording were controlled by an IBM-compatible computer equipped with MED-PC software.

Procedure

At the beginning of training, birds were randomly assigned to two groups of four. The groups were trained and otherwise treated identically, save that one group (birds 1, 2, 3, and 4) was tested with cocaine, the other (birds 5, 6, 7, and 8) with morphine (see below). For all birds, pecking the center key when lighted in red, white, and green initially was autoshaped [as described by (23)]. After this occurred, the birds were exposed to a multiple FR 1 FR 1 FR 1 schedule. Over several sessions, this schedule was gradually lengthened to FR 100 FR 100 FR 100. After the pigeons responded reliably under this schedule, a multiple schedule with three mixed FR FR components was arranged. Each mixed schedule comprised two FR values and the sum of those values was equal [100] for the three components. At the terminal value, the schedule was a multiple (mixed FR 5 FR 95) (mixed FR 25 FR 75) (mixed FR 50 FR 50). Thus, each of the component schedules was equivalent in terms of the average effort required to produce a reinforcer (50 responses/1 reinforcer), but they differed in terms of the specific FRs arranged. For a given mixed schedule, the FR arranged first was selected at random, with the provision that each FR was arranged first in 6 of the 12 FRs comprised by that mixed schedule in each session. Under each FR, food was delivered immediately following the last response in the specified ratio. For example, food immediately followed every fifth response under the FR 5 and every 95th response under the FR 95.

Each session began with a component that was selected at random from the three possibilities. All components were in effect until four reinforcers (food deliveries) were earned or until 5 min elapsed, whichever occurred first. At that time, all chamber lights were extinguished for 60 s, after which one of the other two components, selected at random, was arranged. When the third component ended, the cycle recurred until each type of mixed schedule occurred three times. All food deliveries were 4 s in duration and a specific key color, selected at random for individual birds, was correlated with each component. Prior to chronic dosing, sessions were conducted 6 days a week, at about the same time each day. After chronic dosing began, sessions were conducted each day.

Subjects were exposed to the multiple schedule until the overall rate of responding under each component appeared stable across 10 consecutive sessions. Stability was assessed by visual inspection of graphed data and was assumed to occur when (a) no trends in rate were evident, and (b) response rates across consecutive sessions varied by no more than 15%. When response rates were stable, dose–response determinations began. During them, each subject received two ascending series of acute drug administrations. Four received morphine, four received cocaine. With both drugs, doses were increased in quarter-log units from 0.56 to 5.6 mg/kg (expressed as the salt), and in eighth-log units above 5.6 mg/kg, until a dose was reached at which the mean overall rate of responding under each of the three mixed schedules fell to below 10% of the rate observed in the most recent control session. Drug injections were given according to a BBBBCD design, where B represents baseline sessions (no injection), C vehicle control sessions, and D drug sessions. Cocaine hydrochloride and morphine sulfate were obtained from the National Institute on Drug Abuse and dissolved in isotonic saline solution. Cocaine and morphine were administered via intramuscular injection (at a volume of 1 ml/kg) 5 and 30 min prior to behavioral testing, respectively.

After dose–response determinations ended, 10 consecutive baseline sessions were arranged. Chronic drug adminis-

tration immediately followed those baseline sessions. During the chronic phase, a drug dose that reduced, but did not completely eliminate responding during the second prechronic exposure was administered prior to every session. All birds tested with cocaine received 3.2 mg/kg during the chronic phase. The dose of morphine administered chronically was 3.2 mg/kg for two birds (5 and 6) and 5.6 mg/kg for two birds (7 and 8). Chronic dosing continued for each bird until responding was stable, as defined above. This required 37, 56, 44, 28, 44, 49, 34, and 42 sessions for subjects 1 through 8, respectively.

After responding stabilized, postchronic dose–response determinations started. During this determination, every seventh session a substitution dose was administered in place of the chronic dose if responding appeared stable over the preceding six sessions. If responding did not appear stable, chronic dosing continued until stability developed. Substitution doses were administered in two ascending series as described for the prechronic dose–response determinations. When substitution doses below the chronic dose were administered, supplemental cocaine or morphine injections to increase the daily dose to the chronic dose were given immediately after behavioral testing. For subjects 1 through 8, respectively, 104, 90, 119, 91, 115, 189, 192, and 170 sessions were required to complete postchronic dose–response testing. Following postchronic dose–response testing, all subjects were given vehicle injections until responding appeared stable across 10 consecutive sessions.

RESULTS

Table 1 shows mean overall response rates at each FR value during vehicle control sessions. All birds responded at relatively high rates at all ratio values during these sessions, although most birds responded slowest under the FR 5 schedule. Figures 1 and 2 show pre- and postchronic dose–response curves for cocaine at all ratio values. In all figures, the effects of drug are expressed as percentages of the mean overall rate obtained in vehicle control sessions. Data analysis entailed visual inspection of dose–response curves for individual animals. During prechronic administration, sufficiently high doses of cocaine reduced responding, although the dose at which responding dropped to near-zero levels differed across subjects. When individual FRs (5, 25, 50, 75, 95) are examined, prechronic drug effects do not obviously differ as a function of ratio size. That is, for an individual bird, values for percent control responding at a given dose were similar across FR values.

Postchronic effects of cocaine were similar to prechronic effects. That is, at sufficiently high doses, response rates were reduced. Evidence of tolerance was apparent in the data for birds 1 and 3, insofar as there was a rightward shift in their dose–response curves following chronic exposure to cocaine. For these birds, there was no evidence that greater tolerance occurred under the FR 5 than under the longer ratios. That is, the degree of the rightward shift of the dose–response curve was not greater at FR 5 than at longer ratios. Birds 2 and 4 did not appear to develop consistent tolerance; their pre- and postchronic dose–response curves were similar. However, the data for bird 2 at 5.6 mg/kg provide some evidence of tolerance under the FR 5, 25, and 75 schedules and those for bird 4 provide some evidence of tolerance at 3.2 mg/kg under the FR 5 schedule and at 1.8 and 3.2 mg/kg under the FR 50 and 95 schedules.

During prechronic administration, morphine at sufficiently high doses reduced responding to below baseline levels, although different birds were not equally affected by a given dose (Figs. 3 and 4). Effects did not obviously differ as a function of FR value. Postchronic effects of morphine were similar to prechronic effects. That is, at sufficiently high doses, the drug reduced responding under all FRs. Obvious tolerance developed to the rate-reducing effects of morphine in all pigeons under each of the individual FRs. Although the degree of tolerance observed varied across birds, it did not differ consistently as a function of ratio size.

For all birds, response rates during vehicle sessions at the end of the study were very similar to those obtained during vehicle sessions at the beginning of the study (i.e., during prechronic dose–response testing). Therefore, baseline performance apparently did not shift over the course of the study, and it is reasonable to express postchronic drug effects as a percentage of prechronic vehicle rates.

DISCUSSION

The present findings are similar to those of earlier studies (9,10,19) that reported cocaine-induced rate decreases under FR schedules. In those studies, however, tolerance was consistently observed under an FR 5 schedule, but not under substantially longer FR schedules, which differs from the present results. Although tolerance was observed under the FR 5 schedule in some birds in the present study, the effect was not consistent across subjects. Moreover, in the subjects where tolerance was observed under the FR 5, similar tolerance also occurred under longer FRs. This finding differs from results obtained under multiple schedules (9,10), where ratio size consistently influenced tolerance to the rate-reducing effects of cocaine.

It may be that the dose of cocaine administered chronically in the present study (3.2 mg/kg) contributed to the ab-

TABLE 1

MEAN CONTROL RESPONSE RATES (RESPONSES PER SECOND) AT EACH FR VALUE DURING VEHICLE SESSIONS*

Overall Rates											
Birds Tested with Cocaine						Birds Tested with Morphine					
Bird	FR 5	FR 25	FR 50	FR 75	FR 95	Bird	FR 5	FR 25	FR 50	FR 75	FR 95
1	1.73	3.55	2.64	4.12	2.09	5	1.94	2.79	2.05	3.25	2.44
2	2.03	3.43	3.83	4.51	3.03	6	2.23	2.81	3.16	3.48	2.57
3	2.53	4.01	4.21	5.00	3.92	7	1.86	2.53	2.85	3.13	2.18
4	1.83	1.24	1.92	1.96	1.78	8	2.24	2.98	2.69	3.55	2.53

*These values are based on the 10 vehicle control sessions immediately preceding prechronic dose–response determinations.

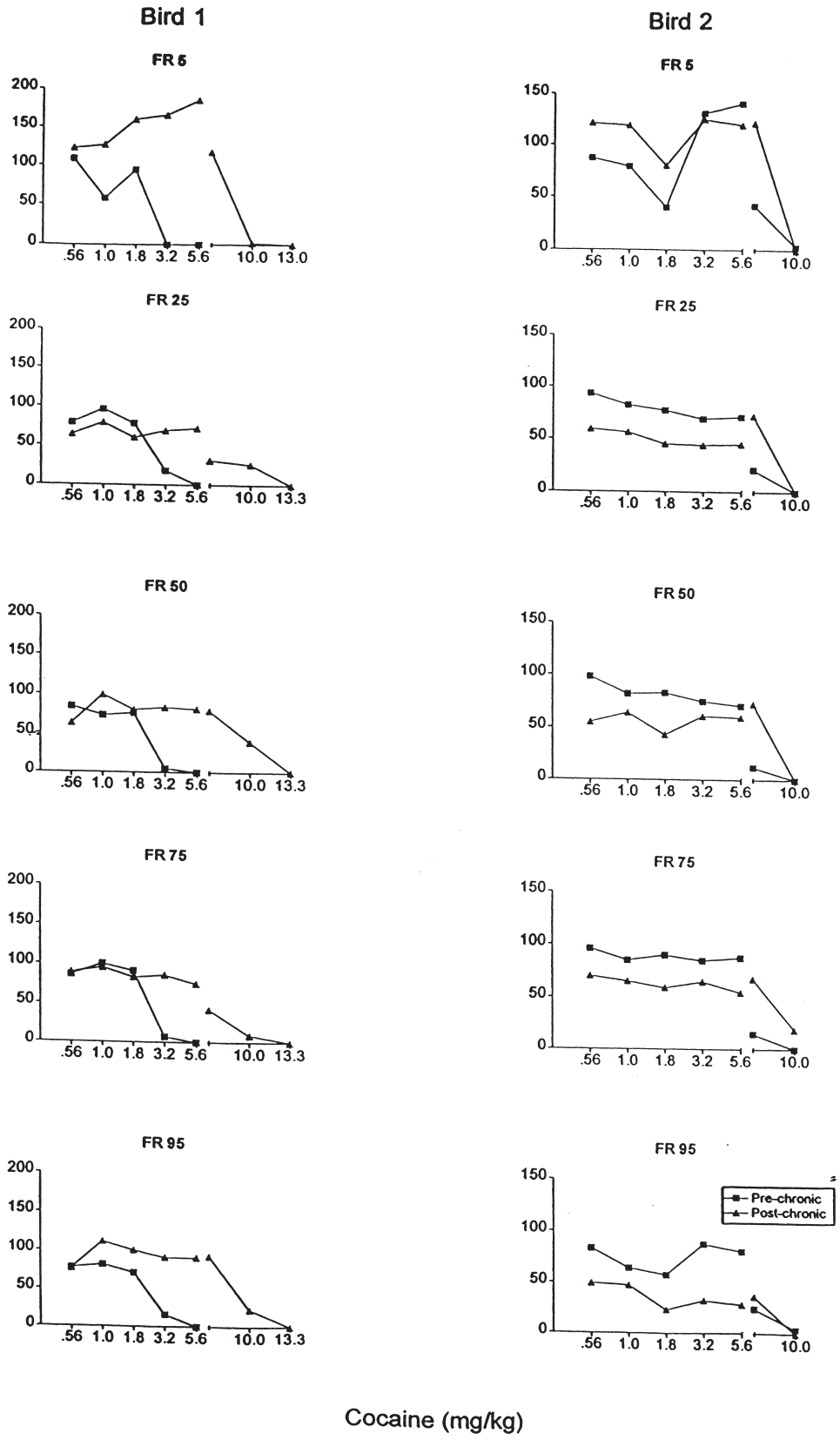

FIG. 1. Pre- and postchronic effects of cocaine on the overall response rates of individual pigeons (bird 1, bird 2) at all FR values. Data are expressed as a percentage of vehicle control rates, which are reported in Table 1. The break in the horizontal axis indicates a shift from a quarter- to an eighth-log scale of doses. Each data point is the mean of two administrations of the indicated dose.

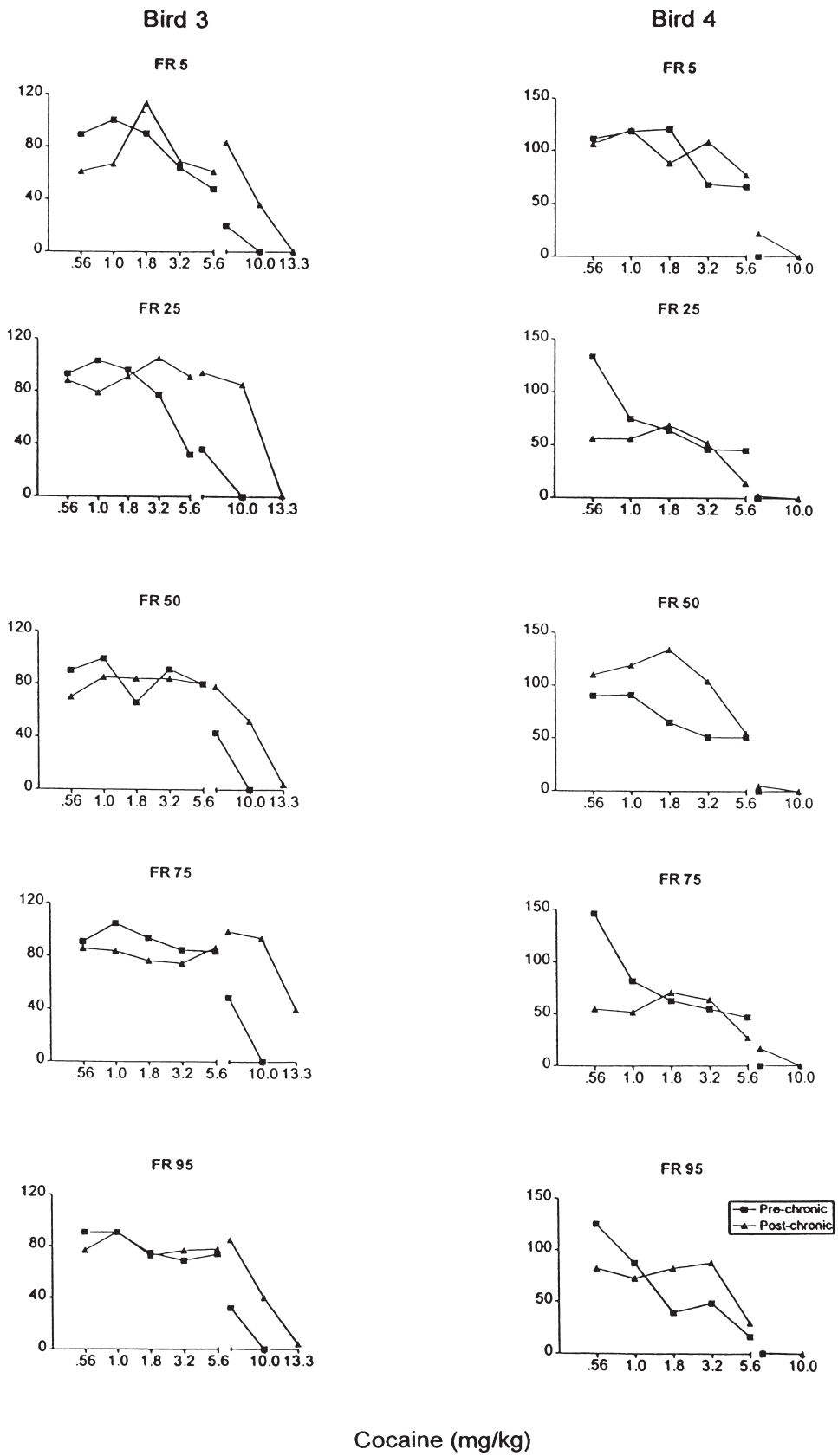

FIG. 2. Pre- and postchronic effects of cocaine in birds 3 and 4. Details are as in Fig. 3.

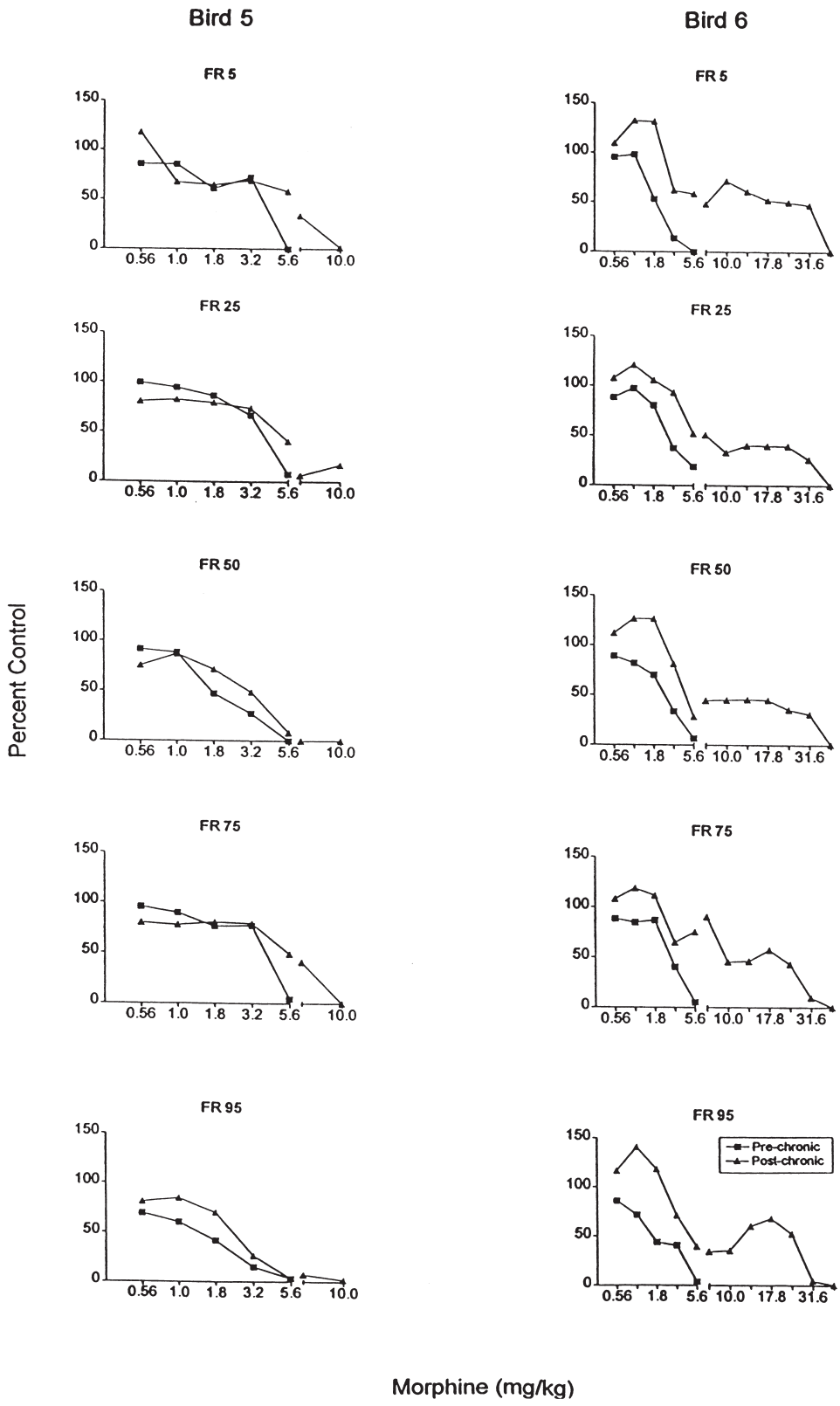

FIG. 3. Pre- and postchronic effects of morphine on the overall response rates of individual pigeons (bird 5, bird 6) at all FR values. Details are as in Fig. 1.

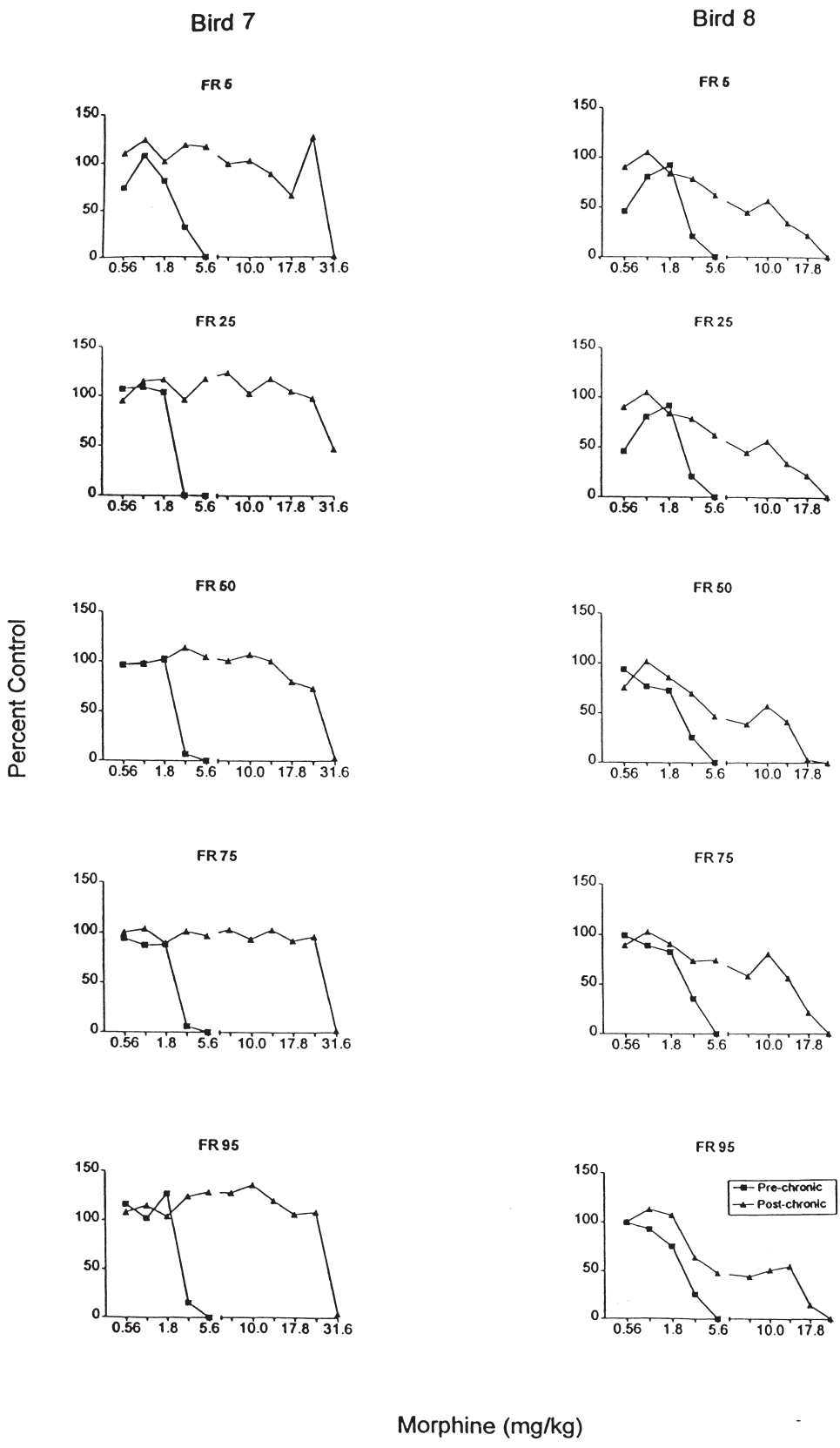

FIG. 4. Pre- and postchronic effects of morphine in birds 7 and 8. Details are as in Fig. 1.

sence of consistent tolerance. Higher doses of cocaine (5.6 mg/kg) characteristically were used in prior studies in which tolerance was observed consistently, including those from our laboratory (19,20), and the 3.2 mg/kg dose used in the present study did not greatly affect responding in some birds (i.e., 2 and 3), especially under the FR 5 schedule. Had a higher chronic dose been used in the present study, more consistent tolerance might have been observed.

In prior studies, morphine reduced response rates under FR schedules of food delivery and tolerance developed to its rate-decreasing effects [e.g., (5,8,14,20,27)]. The present results are in agreement with these findings. A previous study that examined the effects of morphine under a multiple schedule of food delivery found, however, that "tolerance may in general be less likely to occur under relatively long FR schedules than under relatively short ones" [(20), p. 466]. The present findings do not support this conclusion, insofar as similar tolerance was observed under FR schedules ranging from 5 to 95. Comparable tolerance to morphine also was observed across a sizable range of ratio values when they were arranged under PR 5 or PR 25 schedules (11,25). Given those findings and the results of the present study, it becomes apparent that ratio size modulates tolerance development to cocaine and morphine under some, but not all, conditions.

The results of the present study and earlier investigations with PR schedules are "negative," insofar as they failed to demonstrate an effect of a variable (ratio size) shown to influence tolerance under other conditions. They are consistent, however, with a substantial body of literature showing that tolerance to the behavioral effects of drugs are influenced by a wide range of variables, and that chronic drug effects under a particular schedule may depend on the context in which that schedule is arranged [e.g., (7)]. For example, in one study prior exposure to other schedules influenced the development of tolerance to methadone's rate-reducing effects under a variable-interval schedule of food delivery (13). In another study, whether or not tolerance developed to the rate-increasing (and reinforcement-decreasing) effects of *d*-amphetamine under an interresponse-time-greater-than-*t* schedule depended on whether that schedule was arranged alone, or as one component of a multiple schedule with a random-ratio schedule as the other component (28). In both cases, chronic drug effects under a given schedule depended on how that schedule was arranged relative to other schedules.

Comparing results across studies suggests that the chronic effects of morphine and cocaine at particular ratio values and, therefore, whether ratio size modulated tolerance, depended on how different ratio values were arranged. Specifically, a discriminative stimulus was uniquely correlated with each FR value in experiments in which ratio size influenced tolerance to cocaine or morphine (9,10,19,20), but not in the present experiment or in the prior studies that used PR schedules (11,25). Thus, antecedent stimulus control may be necessary for FR size to modulate tolerance. Such an outcome is consistent with a behavioral momentum analysis of drug effects. Nevin and his associates have shown repeatedly that behavior has more "momentum," in the sense of being more resistant to change and recovering more rapidly from changes that are induced, in the presence of a stimulus correlated with relatively frequent reinforcement than it has in the presence of a stimulus correlated with relatively infrequent reinforcement [e.g., (15–18)]. In the arrangements under which FR size has modulated tolerance, short FRs have been accompanied by stimuli correlated with frequent reinforcement, whereas long FRs have been accompanied by stimuli correlated with less frequent reinforcement. In those studies, as predicted by a behavioral momentum analysis, the acute effects of cocaine (9,10) and of morphine (20) were greater in the presence of stimuli correlated with less frequent reinforcement. That is, relative rate reductions increased with ratio size. In addition, recovery from drug-induced rate reductions (i.e., tolerance) occurred more rapidly and more completely under relatively short ratio schedules than under longer ones. In the present study, and in prior studies that used PR schedules (11,25), acute drug effects did not differ in magnitude as a function of ratio size. This outcome is consistent with a behavioral momentum analysis because the frequency of reinforcement was approximately equal under all stimulus conditions.

In two studies involving other drugs, however, acute effects were not largest under conditions where behavior momentum should have been least (4,12). In addition, Schama and Branch (26) reported that tolerance to cocaine developed similarly under fixed-interval (FI) 5-s, FI 30-s, and FI 120-s components of a multiple schedule. The momentum of behavior under those schedules should differ, but tolerance did not differ as a function of FI length. These findings call into question the general utility of a behavioral momentum analysis of drug action. In this context, it is noteworthy that all of the studies that failed to support a behavioral momentum analysis had time components, whereas purely response-based schedules were used in the studies consistent with a behavioral momentum analysis. It may well be that behavioral momentum analyses of drug effects are appropriate only when certain kinds of schedules are used to maintain behavior.

In any case, in view of the paucity of proposed instrumental mechanisms of drug tolerance—only the reinforcement-loss hypothesis has garnered serious attention, and support for it is equivocal, at best (7)—further attempts to apply a behavioral momentum analysis to drug effects on operant behavior may be warranted. Such attempts will, at minimum, help to reveal the limits of Nevin's theoretical model and to clarify how the effects of drugs differ from those of other disrupters of behavior (e.g., extinction, satiation) that have been more extensively studied in the context of that model. Although rarely used in this context in recent years, drugs can be a useful tool in the study of operant behavior and its controlling variables.

ACKNOWLEDGEMENTS

The reported research was supported by grant DA07869 from the National Institute on Drug Abuse, which also supplied cocaine and morphine. Currently, Tom Byrne is at Massachusetts College of Liberal Arts in North Adams, Mark LeSage is currently at the Louisiana State University Medical Center in Shreveport, and LeeAnn Christian is at the Institute for Applied Behavior Analysis in Los Angeles.

REFERENCES

1. Branch, M. N.: Behavioral pharmacology. In: Iversen, I. H.; Lattal, K. A., eds. Experimental analysis of behavior, part 2. New York: Elsevier; 1991:21–77.
2. Byrne, T.; LeSage, M. G.; Poling, A.: Tolerance development to morphine under mixed-ratio schedules. In: Leslie, J., ed. Proceedings of the third European meeting for the experimental analysis of behavior. Cleraine, Northern Ireland: University of Ulster; 1997:2.

3. Christian, L.; LeSage, M. G.; Poling, A.: Tolerance development to cocaine under mixed-ratio schedules. In: Leslie, J., ed. Proceedings of the third European meeting for the experimental analysis of behavior. Cleraine, Northern Ireland: University of Ulster; 1997:23.
4. Cohen, S. L.: A pharmacological examination of the resistance-to-change hypothesis of response strength. J. Exp. Anal. Behav. 46:363–379; 1986.
5. Craft, R. M.; Picker, M. J.; Dykstra, L. A.: Differential cross-tolerance to opioid agonists in morphine-tolerant pigeons responding under a schedule of food presentation. J. Pharmacol. Exp. Ther. 249:389–393; 1989.
6. Genovese, R. F.; Elsmore, T. F.; Witkin, J. M.: Environmental influences on the development of tolerance to the effects of physostigmine on schedule-controlled behavior. Psychopharmacology (Berlin) 96:462–467; 1988.
7. Goudie, A. J.; Emmett-Oglesby, M. W.: Psychoactive drugs: Tolerance and sensitization. Clifton, NJ: Humana Press; 1989.
8. Heifetz, S. A.; McMillan, D. E.: Development of behavioral tolerance to morphine and methadone using the schedule-controlled behavior of pigeons. Psychopharmacologia 19:40–52; 1971.
9. Hoffman, S. H.; Branch, M. N.; Sizemore, G. M.: Cocaine tolerance: Acute versus chronic effects as dependent upon fixed-ratio size. J. Exp. Anal. Behav. 47:363–376; 1987.
10. Hughes, C. E.; Branch, M. N.: Tolerance to and residual effects of cocaine in squirrel monkeys depend on reinforcement-schedule parameter. J. Exp. Anal. Behav. 56:345–360; 1991.
11. Jarema, K.; Macomber, C.; LeSage, M.; Poling, A.: Acute and chronic effects of morphine under a progressive-ratio 25 schedule of food delivery. Pharmacol. Biochem. Behav. 62:209–214; 1999.
12. Lucki, I.; DeLong, R. E.: Control rate of response or reinforcement and amphetamine's effect on behavior. J. Exp. Anal. Behav. 54:163–172; 1983.
13. Nader, M. A.; Thompson, T.: Interaction of methadone, reinforcement history and variable-interval performance. J. Exp. Anal. Behav. 48:303–315; 1987.
14. Negus, S. S.; Picker, M. J.; Dykstra, L. A.: Kappa antagonist properties of buprenorphine in non-tolerant and morphine-tolerant rats. Psychopharmacology (Berlin) 98:141–143; 1989.
15. Nevin, J. A.: Behavioral momentum and the partial reinforcement effect. Psychol. Bull. 103:44–56; 1988.
16. Nevin, J. A.: An integrative model for the study of behavioral momentum. J. Exp. Anal. Behav. 57:301–316; 1992.
17. Nevin, J. A.; Smith, L. D.; Roberts, J.: Does contingent reinforcement strengthen operant behavior? J. Exp. Anal. Behav. 48:17–33; 1987.
18. Nevin, J. A.; Tota, M. E.; Torquato, R. D.; Shull, R. L.: Alternative reinforcement increases resistance to change: Pavlovian or operant contingencies? J. Exp. Anal. Behav. 53:359–379; 1990.
19. Nickel, M.; Alling, K.; Kleiner, M.; Poling, A.: Fixed-ratio size as a determinant of tolerance to cocaine: Is relative or absolute size important? Behav. Pharmaol. 4:471–478; 1993.
20. Nickel, M.; Poling, A.: Fixed-ratio size as a determinant of the development of tolerance to morphine. Behav. Pharmacol. 1:463–467; 1990.
21. O'Brien, C. P.: Drug addiction and drug abuse. In: Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G., eds. The pharmacological basis of therapeutics. New York: McGraw-Hill; 1996:557–577.
22. Picker, M.; Negus, S. S.: Drugs and stimulus control: Generalization, discrimination and threshold procedures. In: van Haaren, F., ed. Methods of behavioral pharmacology. New York: Elsevier; 1993:117–145.
23. Picker, M.; Poling, A.: Effects of anticonvulsants on learning: Performance of pigeons under a repeated acquisition procedure when exposed to phenobarbital, clonazepam, valproic acid, ethosuximide, and phenytoin. J. Pharmacol. Exp. Ther. 130:307–316; 1984.
24. Poling, A.: A primer of human behavioral pharmacology. New York: Plenum Press; 1986.
25. Poling, A.; LeSage, M.; Roe, D.; Schaefer, D.: Acute and chronic effects of morphine in pigeons responding under a progressive-ratio schedule of food delivery. Pharmacol. Biochem. Behav. 54:485–490; 1996.
26. Schama, K. F.; Branch, M. N.: Tolerance to effects of cocaine on schedule-controlled behavior: Effects of fixed-interval schedule parameter. Pharmacol. Biochem. Behav. 32:267–274; 1989.
27. Smith, J. B.: Prevention by naltrexone of tolerance to the rate-decreasing effects of morphine in the pigeon. Psychopharmacology (Berlin) 63:49–54; 1979.
28. Smith, J. B.: Effects of chronically administered *d*-amphetamine on spaced responding maintained under multiple and single-component schedules. Psychopharmacology (Berlin) 88:296–300; 1986.
29. Smith, J. B.: Effects of fixed-ratio length on the development of tolerance to decreased responding by l-nantradol. Psychopharmacology (Berlin) 90:259–262; 1986.
30. Smith, J. B.: Effects of fixed-ratio requirement on observed tolerance to decreased responding by clonidine. Pharmacol. Biochem. Behav. 36:993–996; 1990.
31. Wolgin, D. L.: The role of instrumental learning in behavioral tolerance to drugs. In: Goudie, A. J.; Emmett-Oglesby, M. W., eds. Psychoactive drugs: Tolerance and sensitization. Clifton, NJ: Humana Press; 1989:17–114.