ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 54, No. 2, pp. 485–490, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02284-8

Acute and Chronic Effects of Morphine in Pigeons Responding Under a Progressive-Ratio Schedule of Food Delivery

ALAN POLING,[1] MARK LESAGE, DANIEL ROE AND DAVID SCHAEFER

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008 USA

Received 19 June 1995; Revised 6 October 1995; Accepted 19 October 1995

POLING, A., M. LESAGE, D. ROE AND D. SCHAEFER. *Acute and chronic effects of morphine in pigeons responding under a progressive-ratio schedule of food delivery.* PHARMACOL BIOCHEM BEHAV **54**(2) 485–490, 1996.—Although progressive-ratio schedules have often been used by behavioral pharmacologists to index the relative reinforcing effects of drugs of abuse, they have been ignored in the study of tolerance to opioids. The present study examined tolerance to morphine in pigeons responding under a progressive-ratio 5 schedule of food delivery. Acute administrations of morphine produced general dose-dependent reductions in response rates and breaking points. Dose–response curves for both measures shifted rightward substantially (roughly fivefold) following chronic (daily) exposure to morphine, indicating that tolerance developed to the drug's effects.

Tolerance Morphine Progressive-ratio schedule Pigeons

SEVERAL studies have shown that opioid agonists, such as morphine, increase short-term food intake [e.g., (5,6,8,16, 21)]. Given this effect, morphine may increase the reinforcing capacity of food. One assay commonly used to quantify the reinforcing capacity of food, drugs, and other stimuli is the progressive-ratio (PR) schedule [e.g., (1,7,11,13,20)]. The PR schedule, first described by Hodos (10), requires the subject to emit an increasing number of responses to earn each successive reinforcer. For example, under a PR 5 schedule of food delivery, the number of responses required for food delivery in a given session 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. The ratio requirement eventually becomes so long that the subject ceases to respond for a specified period, usually 5 to 15 min [e.g., (11,13,23,24,28)], at which point the session ends. The largest ratio completed before responding ceases is termed the breaking point of the subject's performance. The breaking point under PR schedules is used as a measure of the efficacy of the scheduled reinforcer, or of response strength (10,29).

Given that the PR schedule can be used to index the reinforcing capacity of food, and the widespread interest in the effects of opiate drugs and endorphins on food-related activities [e.g., (2,14)], it is interesting that the schedule has not been used extensively to study the effects of morphine. In one study that did use the PR schedule (24), acute administrations of morphine (0.1 to 5.6 mg/kg) produced general dose-dependent decreases in the response rates and breaking points of rhesus monkeys. Daily exposure to the PR schedule was very brief (10 min), as it was arranged as part of a complex operant test battery. Moreover, only acute data were presented. The purpose of the present study was to extend research concerning the effects of morphine under PR schedules by examining acute and chronic effects of the drug on the response rates and breaking points of pigeons exposed to a PR 5 schedule of food delivery.

Unlike the PR schedule, the fixed-ratio (FR) schedule has been used extensively to study the effects of morphine on food-maintained behavior. Previous studies have revealed that morphine characteristically reduces response rates under FR schedules of food delivery and that some tolerance develops to its rate-decreasing effects [e.g., (3,4,9,17,25,29)]. The PR schedule resembles a conventional FR schedule insofar as the delivery of a reinforcer under both schedules depends on the completion of a specified number of responses. The present study examined the effects of morphine in pigeons responding under a PR 5 schedule of food delivery. The primary purpose

[1] To whom requests for reprints should be addressed.

of the study was to determine whether effects under this schedule are similar to those previously reported under FR schedules. A secondary purpose was to expore the usefulness of the breaking point as a measure of tolerance.

METHOD

Subjects

Seven experimentally naive White Carneau pigeons, food deprived to 80% of free-feeding body weights, served as subjects. They were individually housed 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 Lehigh Valley Electronics operant conditioning chambers, measuring 32 cm high, 36 cm wide, and 35 cm high, were used. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the front wall, approximately 5.5 cm apart. Only the center key was used in the present study. That key could be illuminated in white. An aperture horizontally centered in the front wall 7.5 cm above the floor allowed access to a hopper filled with Purina Pigeon Grain (Ralston-Purina, St. Louis, MO) when the hopper is raised. The raised hopper was illuminated by a 7-W white bulb. A 7-W white bulb (houselight) located behind a translucent diffusing panel centered on the chamber's ceiling provided ambient illumination and an exhaust fan supplied masking noise and ventilation. Additional masking noise was supplied via speakers mounted in the room where the chambers are located. Control of experimental events and data recording were accomplished through the use of an IBM-compatible computer using MED-PC software (Med Associates, St. Albans, VT).

Behavioral Procedure

The birds initially were autoshaped (18) to peck the center key when lighted in white. After keypeck training, each bird was exposed to a simple FR schedule that was gradually increased over sessions from FR 1 to FR 50. When all birds responded consistently under the FR 50 schedule, they were exposed to a PR 5 schedule. Under the PR 5 schedule, food was delivered for 3 s, dependent upon completing a ratio requirement that began each session at five responses and was incremented progressively by five responses whenever food was earned. Thus, the first 10 ratios in a given session were 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50. Ratio values were incremented by five, rather than by a larger or a progressively increasing value, to facilitate comparison with results of a prior study from our laboratory in which the effects of cocaine on PR 5 responding were evaluated (13). The session continued until responding ceased for 5 consecutive min or until 45 min elapsed, whichever occurred first. Key illumination and general chamber illumination were present from the beginning of the session to its end, when all lights were darkened. Throughout the study, one daily session was conducted for each bird 7 days per week, at about the same time every day. Each session, the largest ratio completed was recorded as the breaking point. Overall response rates also were recorded.

Pharmacological Procedure

After breaking points and overall response rates showed no visually evident trend across 10 consecutive acute control (baseline) sessions, subjects were given intramuscular (IM) injections of isotonic saline solution 30 min prior to four experimental sessions, which were separated from one another by four sessions not preceded by injections. This sequence was intended to acclimate the pigeons to the injection procedure. Following it, actual drug manipulations were begun. The initial drug manipulation was an acute dose–response determination. In this determination, each subject received an ascending sequence of morphine doses. The lowest dose was 0.56 mg/kg. Doses were progressively increased until, for a given bird, a dose was reached at which the overall rate of responding was reduced to below 10% of the control level. Doses were increased in quarter-log units from 0.56 to 5.6 mg/kg (i.e., in the sequence 1, 1.8, 3.2, and 5.6 mg/kg, expressed as the salt), and in eighth-log units above 5.6 mg/kg (i.e., in the sequence 7.5, 10, 13.3, 17.8 mg/kg). Doses were tested in ascending sequence with small incremental increases to examine in each bird doses that produced graded effects, ranging from no behavioral disruption to strong suppression of responding. Given the absence of data concerning the effects of morphine in pigeons responding under PR schedules, the appropriate dose range had to be determined empirically, with due caution (i.e., small dose increases). Drug injections were given according to a BBBBCD design, where B represents baseline sessions (no injection), C vehicle control sessions, and D drug sessions. Each bird received each dose once. Morphine sulfate (Sigma, St. Louis, MO) was dissolved in isotonic saline solution prepared at an injection volume of 1 ml/kg and injected IM 30 min prior to behavioral testing.

In the absence of drug, behavioral measures remained relatively stable throughout the acute phase of the study. After acute dose–response determinations were completed, each bird was exposed to baseline conditions until breaking points and overall response rates showed no visually evident trend across 10 consecutive chronic control sessions. Chronic drug administration immediately followed those sessions. During the chronic phase, the largest dose of morphine that did not completely eliminate responding in an individual bird when given during the initial dose–response determination was administered to that bird prior to every session. With this procedure, one pigeon (bird 3) received 1.8 mg/kg, one (bird 2) received 3.2 mg/kg), four (birds 4, 5, 6, and 7) received 5.6 mg/kg, and one (bird 1) received 10 mg/kg. Chronic dosing continued for each bird for at least 30 consecutive sessions and until responding was stable (i.e., there was no visually evident trend in the breaking point across 10 consecutive sessions). Meeting this criterion required 36, 39, 54, 32, 55, 32, and 32 sessions for birds 1 through 7, respectively.

After the stability criterion was met, chronic dose–response determination was begun. During this determination, every sixth session a substitution dose of morphine was administered in place of the chronic dose. Substitution doses were administered in an ascending series. When substitution doses below the chronic dose were administered, supplemental morphine injections to increase the daily dose to the chronic dose were given immediately after behavioral testing.

RESULTS

One of the seven subjects (bird 2) consistently responded for the entire 45 min during control sessions, and the breaking point for that subject was the largest ratio completed within this period. The other six birds regularly stopped responding for 5 consecutive min before the 45-min session ended, and the breaking point for these birds was defined as the largest ratio completed before responding ceased. As indicated in Fig.

1, the average breaking point during the 10 sessions immediately prior to the acute dose-response determination (acute control breaking point) differed substantially across subjects, ranging from 65 to 266. Chronic control breaking points were similar to acute breaking points, and ranged from 70 to 250 across birds. Figure 1 also shows acute and chronic dose-response curves for the breaking points of individual pigeons. In this figure, breaking points when morphine was administered are presented as percentages of control values. In general, morphine produced dose-dependent decreases in breaking points relative to control values when the drug was administered acutely and chronically. However, the dose-response curves were shifted substantially to the right following chronic exposure.

To quantify the degree of rightward shifting of the dose-response curves, and, therefore, the degree of tolerance, regression lines were fitted by the method of least squares to acute and chronic dose-response curves for individual birds. Acute and chronic ED_{50} values were determined from the equations that described the regression lines. This was accomplished by solving for x (drug dose) when the value of y was set at 50% of the vehicle control value. Table 1 shows for each pigeon acute and chronic ED_{50} doses for breaking points and tolerance ratios calculated by dividing the latter measure by the former. These tolerance ratios ranged from 3.03 to 7.48; the geometric mean tolerance ratio for breaking points was 4.81. The geometric (not arithmetic) mean was determined because the data comprised a set of ratios and the ED_{50} values for individual birds were calculated by a regression on log dose. Comparing mean tolerance ratios for the two dependent variables (breaking points and response rates) allows for a crude overall evaluation of the relative sensitivity of those measures. Mean values must, however, be interpreted carefully, because different birds received different chronic doses.

Like breaking points, mean overall response rates in the absence of drug differed substantially across subjects, and were similar during acute and chronic control determinations. As indicated in Fig. 2, the mean overall acute control rate ranged across birds from 0.43 to 2.84 responses per second. Chronic control rates ranged across birds from 0.57 to 2.50 responses per second. Figure 2 shows drug response rates as percentages of control values. Morphine produced generally dose-dependent decreases in overall response rates when the drug was administered acutely and chronically. Dose-response curves for overall response rates were shifted substantially to the right following chronic exposure.

Acute and chronic ED_{50} doses for overall response rates, and tolerance ratios for response rates, are shown in Table 2. These measures were obtained through the use of procedures comparable to those used to obtain the same measures for breaking points. The geometric mean tolerance ratio for overall response rates was 4.84; the range across birds was from 2.73 to 11.95.

DISCUSSION

Regardless of whether breaking points or overall response rates were used as dependent variables, substantial tolerance developed to the effects of morphine in pigeons responding under a PR 5 schedule of food delivery. The magnitude of the rightward shift in the dose-response curve was similar for the two measures of behavior, with mean tolerance ratios of

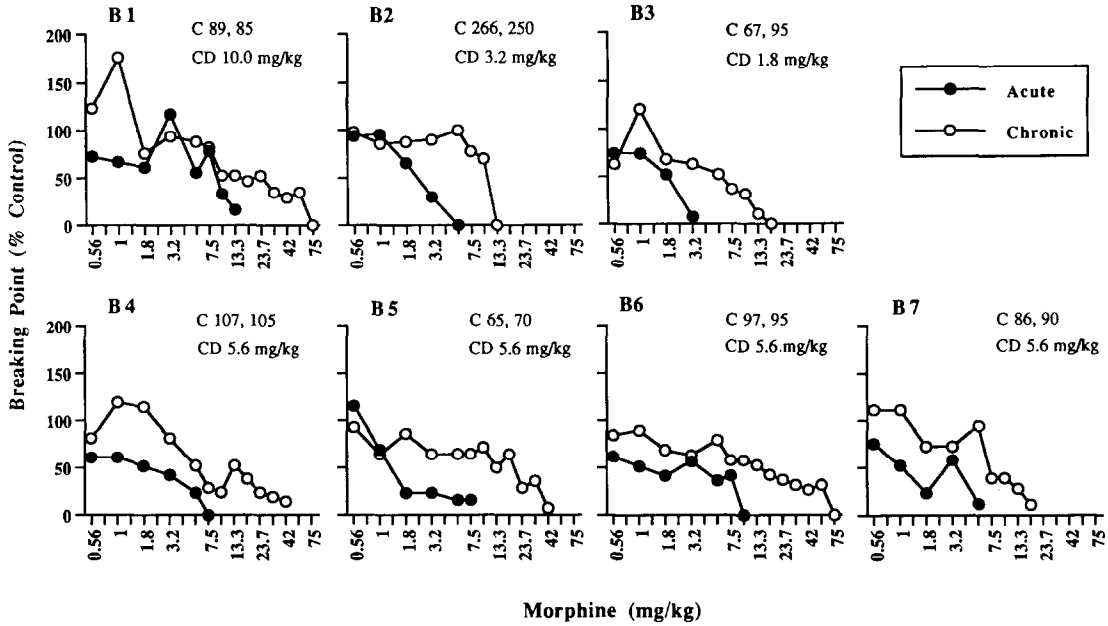

FIG. 1. Acute and chronic effects of morphine on the breaking points of individual pigeons responding under a PR 5 schedule of food delivery. Data are expressed as percentages of mean control breaking points, which are indicated. The first number after C is the acute control breaking point, the second number is the chronic control breaking point. Each data point represents a single drug administration. The acute control breaking point is the mean of all vehicle sessions immediately prior to drug administration (e.g., eight sessions for B1, which received eight drug doses acutely). The chronic control breaking point is the breaking point obtained during a single session when saline was substituted for the chronic dose. The chronic dose received by each bird is indicated as CD.

TABLE 1

THE ED_{50} DOSES FOR THE BREAKING POINTS OF INDIVIDUAL PIGEONS DURING ACUTE AND CHRONIC DOSE-RESPONSE DETERMINATIONS

Subject	Acute ED_{50}	Chronic ED_{50}	Tolerance Ratio
1	6.69 (3.16, 10.22)	27.65 (17.99, 37.31)	4.13
2	2.77 (2.07, 3.47)	8.40 (5.04, 11.75)	3.03
3	1.72 (1.17, 2.27)	6.71 (4.32, 9.10)	3.90
4	2.12 (1.68, 2.55)	14.28 (8.28, 20.29)	6.74
5	2.96 (0.52, 5.40)	17.08 (13.01, 21.14)	5.77
6	2.93 (0.68, 5.18)	21.92 (16.14, 27.71)	7.48
7	2.11 (0.00, 4.57)	8.83 (6.47, 11.18)	4.18

The numbers in parentheses indicate the 95% confidence interval. The tolerance ratios (acute ED_{50} dose/chronic ED_{50} dose) for each bird is also shown.

approximately 5. Across-subject variability in tolerance ratios was, however, somewhat less with breaking points than with overall response rates. These findings suggest that breaking points under PR schedules provide a sensitive measure of tolerance to opioid drugs, although they have not previously been used to index tolerance. It should be noted, however, that breaking points were not more sensitive measures of tolerance than response rates, nor superior measures in other regards.

The PR schedule comprises an increasing sequence of FR components. Previous studies have revealed that morphine characteristically reduces response rates under FR schedules of food delivery and that some tolerance develops to its rate-decreasing effects [e.g., (3,4,9,17,25,29)]. Given these findings, it is not surprising that morphine reduced response rates in the present study, and that tolerance developed to the drug's rate-reducing effects. The degree of tolerance obtained under a PR 5 schedule in the present study appears to be similar that previously reported in studies of the effects of morphine under FR schedules [e.g., (2-4,9,17,25,29)]. Interestingly, the degree of tolerance observed in the present study appeared to be independent of the size of the chronic dose administered. In many cases, tolerance to morphine is influenced by the size of the dose administered; larger doses lead, in general, to faster and more complete tolerance [e.g., (28)]. Two factors that may have prevented such an effect in the present study are, first, that chronic doses were relatively low and, second, that chronic doses were selected on the basis of observed effects

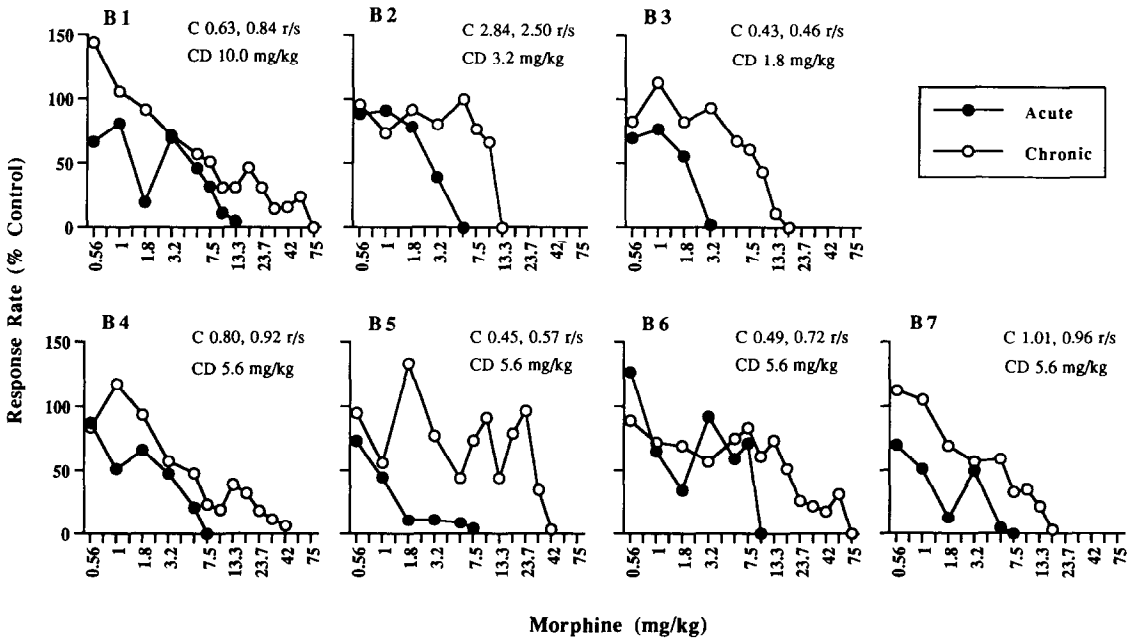

FIG. 2. Acute and chronic effects of morphine on the overall response rates of individual pigeons responding under a PR 5 schedule of food delivery. Data are expressed as percentages of mean control response rates, which are indicated (as responses per second). The acute control response rate is the mean of all vehicle sessions immediately prior to drug administration (e.g., eight sessions for B1, which received eight drug doses acutely). The chronic control response rate is the rate obtained during a single session when saline was substituted for the chronic dose. The chronic dose received by each bird is indicated as CD.

TABLE 2

THE ED_{50} DOSES FOR THE OVERALL RESPONSE RATES OF INDIVIDUAL PIGEONS DURING ACUTE AND CHRONIC DOSE-RESPONSE DETERMINATIONS

Subject	Acute ED_{50}	Chronic ED_{50}	Tolerance Ratio
1	4.29 (1.44, 7.14)	21.11 (11.65, 30.56)	4.92
2	2.92 (2.38, 3.46)	7.96 (4.50, 11.43)	2.73
3	1.68 (0.77, 2.59)	8.52 (7.02, 10.03)	5.07
4	2.91 (1.74, 4.09)	12.07 (6.17, 17.97)	4.15
5	1.48 (0.00, 4.79)	17.68 (9.45, 25.90)	11.95
6	5.03 (1.86, 8.19)	22.25 (15.60, 28.91)	4.42
7	1.81 (0.00, 4.45)	7.55 (5.49, 9.61)	4.17

The numbers in parentheses indicate the 95% confidence interval. The tolerance ratios (acute ED_{50} dose/chronic ED_{50} dose) for each bird is also shown.

in individual birds. Birds in the present study that were less sensitive to morphine received larger chronic doses, and no within-subject comparisons of morphine dose-response curves at different chronic doses were arranged. Had the assignment of birds to chronic doses been at random, or within-subjects comparisons of a range of chronic doses effected, it is probable that the dose administered chronically would have affected tolerance development.

Although the PR schedule has been used rather often to index the effectiveness of scheduled events (e.g., abused drugs, food) as reinforcers, the assay does not provide a simple indication of how drugs influence the reinforcing effectiveness of those events. Previous studies have shown that morphine and related opioid agonists increase food intake when given acutely [e.g., (5,6,8,16,21)]. This finding suggests that opioid agonists may increase, and certainly should not decrease, the reinforcing capacity of food. If breaking points under the PR schedule are assumed to provide an index of the reinforcing effectiveness of the scheduled event (i.e., food delivery), as they are suggested to be (10,11,29), the present data and those reported by Schulze and Paule (24) suggest that acute administrations of morphine reduced, not increased, the reinforcing effectiveness of food. Moreover, data from a previous study (13) indicate that acute administrations of cocaine, which produces anorectic effects (27), increased the reinforcing effectiveness of food, insofar as the drug increased breaking points under a PR 5 schedule. Clearly, caution is justified in interpreting such findings. As Jones et al. (13) indicated, "Drugs may influence schedule-controlled responding through many behavioral mechanisms (15,19), and it should not be automatically assumed that drug-induced changes in PR breaking points provide an uncontaminated index of the relative effectiveness of the scheduled reinforcer" (p. 330). For example, morphine produces substantial sedation (12), and may reduce PR response rates and breaking points through this mechanism, regardless of its effects on ingestive behavior.

Finally, as studies of the effects of lesions of the ventromedial hypothalamus (VMH) clearly demonstrate, the effects of a given perturbation on food-related behavior may depend critically on the specific behavior being indexed, and the assays used to index that behavior. Rats with bilateral VMH lesions become very obese when given access to palatable food, but expend less energy than nonlesioned rats to procure food (22). For instance, Teitelbaum (26) reported that rats with VMH lesions lever-pressed more than nonlesioned rats to produce food under an FR 1 schedule, but pressed less than nonlesioned controls when the ratio requirement increased. At FR 256, the lesioned animals failed to produce a single pellet during a 12-h experimental session, whereas controls responded frequently and produced many pellets. The effects of opioids on feeding, although less striking, are apt to be similarly complex, as is generally recognized (2,14). Multidisciplinary research, using a range of behavioral and neuropharmacological techniques, will undoubtedly be required to tease out and clarify those effects.

ACKNOWLEDGEMENTS

The reported research was supported by Grant DA07869 from the National Institute on Drug Abuse.

REFERENCES

1. Bedford, J. A.; Bailey, L. P.; Wilson, M. C. Cocaine reinforced progressive ratio performance in the rhesus monkey. Pharmacol. Biochem. Behav. 9:631-638; 1978.
2. Cooper, S. J.; Jackson, A.; Birkham, T. C.; Turkish, S. Endorphins, opiates and food intake. In: Rogers, R. J.; Cooper, S. J., eds. Endorphins, opiates, and behavioural processes. London: Wiley; 1988:143-196.
3. 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. 249:386-393; 1989.
4. Gilbert, R. M. Microanalysis of fixed-ratio responding in the rat: Behavioral tolerance to morphine. Bull. Psychon. Soc. 3:229-231; 1974.
5. Gosnell, B. A.; Levine, A. S.; Morley, J. E. The stimulation of food intake by selective agonists of mu, kappa, and delta opioid receptors. Life Sci. 38:1081-1088; 1986.
6. Gosnell, B. A. Central structures involved in opioid-induced feeding. Fed. Proc. 46:163-167; 1987.
7. Griffiths, R. R.; Bradford, L. D.; Brady, J. V. Progressive ratio and fixed ratio schedules of cocaine-maintained responding in baboons. Psychopharmacology (Berlin) 65:125-136; 1979.
8. Gulati, K.; Ray, A.; Sharma, K. K. Effects of acute and chronic

morphine on food intake in rats: Modulation by oxytocin and vasopressin. Pharmacol. Biochem. Behav. 40:27-32; 1991.
9. Heifetz, S. A.; McMillan, D. E. Development of behavioral tolerance to morphine and methadone using the schedule-controlled behavior of the pigeon. Psychopharmacologia 19:40-52; 1971.
10. Hodos, W. Progressive ratio as a measure of reward strength. Science 134:943-944; 1961.
11. Hodos, W.; Kalman, G. Effects of increment size and reinforcer volume on progressive ratio performance. J. Exp. Anal. Behav. 6:387-392; 1963.
12. Jaffee, J. H.; Martin, W. R. Opioid analgesics and antagonists. In: Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., eds. The pharmacological basis of therapeutics. New York: Pergamon Press; 1990:485-521.
13. Jones, C.; LeSage, M.; Sundby, S.; Poling, A. Effects of cocaine in pigeons responding under a progressive-ratio schedule of food delivery. Pharmacol. Biochem. Behav. 50:527-531; 1995.
14. Levine, A. S.; Billington, C. J. Opioids: Are they regulators of feeding? Ann. NY Acad. Sci. 575:209-219; 1989.
15. McKearney, J. W.; Barrett, J. E. Schedule-controlled behavior and the effects of drugs. In: Blackman, D. E.; Sanger, D. J., eds. Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978:1-68.
16. Morley, J. E.; Levine, A. S.; Grace, K. M.; Zengner, H.; Shearman, G. T. The κ-opioid receptor and food intake. Eur. J. Pharmacol. 112:17-25; 1985.
17. Negus, S. S.; Picker, M. J.; Dykstra, L. A. Kappa antagonist properties of buprenorphine in nontolerant and morphine-tolerant rats. Psychopharmacology (Berlin) 98:141-143; 1989.
18. 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. 230:307-316; 1984.
19. Poling, A. A primer of human behavioral pharmacology. New York: Plenum Press; 1986.
20. Roberts, D. C. S.; Loh, E. A.; Vickers, G. Self-administration of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. Psychopharmacology (Berlin) 97:535-538; 1989.
21. Sanger, D. J.; McCarthy, P. S. Differential effects of morphine on food and water intake in food deprived and freely feeding rats. Psychopharmacology (Berlin) 72:103-106; 1980.
22. Schacter, S. Some extraordinary facts about obese humans and rats. Am. Psychol. 26:129-144; 1971.
23. Schulze, G. E.; Paule, M. G. Acute effects of *d*-qamphetamine in a monkey operant test battery. Pharmacol. Biochem. Behav. 35: 759-765; 1990.
24. Schulze, G. E.; Paule, M. G. Effects of morphine sulfate on operant behavior in rhesus monkeys. Pharmacol. Biochem. Behav. 38:77-83; 1991.
25. Smith, J. B. Prevention by naltrexone of tolerance to the rate-decreasing effects of morphine on schedule-controlled responding in the pigeon. Psychopharmacology (Berlin) 63:49-54; 1979.
26. Teitelbaum, P. Random and food-directed activity in hyperphagic and normal rats. J. Comp. Physiol. Psychol. 51:486-490; 1958.
27. Thompson, D. M. Enhancement of progressive-ratio performance by chlordiazepoxide and phenobarbital. J. Exp. Anal. Behav. 17:287-292; 1972.
27. Vee, G. L.; Fink, G. B.; Constantine, G. W. Anorexic activity of cocaine and coca extract in naive and cocaine tolerant rats. Pharmacol. Biochem. Behav. 18:515-517;1983.
28. Woods, J. H.; Carney, J. Narcotic tolerance and operant behavior. In: Krasnegor, N. A., ed. Behavioral tolerance: Research and treatment implications. Rockville, MD: Department of Health, Education, and Welfare; 1978:54-66.
29. Young, A. M.; Herling, S. Drugs as reinforcers: Studies in laboratory animals. In: Goldberg, S. R.; Stolerman, I. P., eds. Behavioral analysis of drug dependence. New York: Academic Press; 1986:9-67.