Pharmacology Biochemistry & Behavior, Vol. 30, pp. 977–982. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Differential Tolerance Development to Buprenorphine-, Diprenorphine-, and Heroin-Induced Disruption of Food-Maintained Responding in Macaque Monkeys

SCOTT E. LUKAS, NANCY K. MELLO, MARK P. BREE AND JACK H. MENDELSON

Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School 115 Mill Street, Belmont, MA 02178

Received 9 March 1987

LUKAS, S. E., N. K. MELLO, M. P. BREE AND J. H. MENDELSON. *Differential tolerance development to buprenorphine-, diprenorphine-, and heroin-induced disruption of food-maintained responding in Macaque monkeys.* PHARMACOL BIOCHEM BEHAV **30**(4) 977–982, 1988.—Single daily subcutaneous injections of buprenorphine (1.0 mg/kg), diprenorphine (1.0 mg/kg), or heroin (1.0 mg/kg) were given over 25 consecutive days to examine the degree and the rate of tolerance development to drug-induced suppression of food maintained responding. One gram food pellets were available on a second order schedule (FR 4 VR 16: S) during the 1-hr sessions three times a day. All drug and saline control injections were given at 10:00 a.m., 1 hr before a food session. During the first three days of treatment all three drugs produced marked suppression of food-maintained performance. Recovery from buprenorphine- and diprenorphine-induced suppression of food-maintained responding occurred within four and eight days, respectively. By the 25th day of buprenorphine and diprenorphine treatment, operant responding for food increased significantly above control levels ($p<0.01$). In contrast, the significant heroin-induced disruption of food-maintained responding ($p<0.01$) persisted throughout the 25-day treatment period. Saline substitution for all three drugs resulted in a gradual return to control levels of food pellets earned. Linear regression analysis of the linear portion of the time-effect curve revealed significant differences in both the rate and the degree of tolerance development to these three drugs. These differences in tolerance development may reflect pharmacokinetic differences between the relatively short-acting heroin and the longer-acting diprenorphine and buprenorphine.

Buprenorphine Diprenorphine Heroin Macaque monkeys Food intake Tolerance

BUPRENORPHINE, an oripavine derivative of thebaine and a close analogue of etorphine and diprenorphine, possesses both opiate agonist and antagonist properties in several in vivo preparations [3, 16–18] and is a partial mu receptor agonist in binding studies [32,34]. This opioid mixed agonist/antagonist also has a relatively long duration of action which may contribute to the mild and delayed abstinence syndrome often observed when chronic administration is discontinued [13,20]. The chemical similarities between buprenorphine and diprenorphine, a compound devoid of significant opiate agonist activity, make it the logical opiate antagonist to compare to buprenorphine. Diprenorphine's antagonist potency is equal at mu, kappa and delta opioid receptors [1,23]. Heroin is rapidly hydrolyzed to monoacetyl morphine, then to morphine [30], and it is classified as a pure mu opiate agonist [12,24]. There is an extensive literature showing that opioid agonists disrupt food-maintained responding in several species [10,21].

Previous studies from this and other laboratories have shown that chronic administration of buprenorphine (up to doses of 8.0 mg/kg/day) does not disrupt food-maintained responding in nonhuman primates [19, 27–29]. But acute administration of buprenorphine (0.10 and 0.30 mg/kg/day) significantly suppressed food-maintained responding in rhesus monkeys at doses 3–9 times lower than chronically administered buprenorphine levels [27,29]. Buprenorphine dose-dependent suppression of food-maintained responding has also been reported in squirrel monkeys [4,5]. The discrepancy between acute and chronic buprenorphine effects suggests that tolerance may develop to buprenorphine-induced disruption of food-maintained performance. However, Dykstra [5] did not observe tolerance to the disruptive effects of buprenorphine (0.01 mg/kg) in squirrel monkey over 17 days of observation.

The present study was conducted to determine the time course for development of tolerance to buprenorphine, a

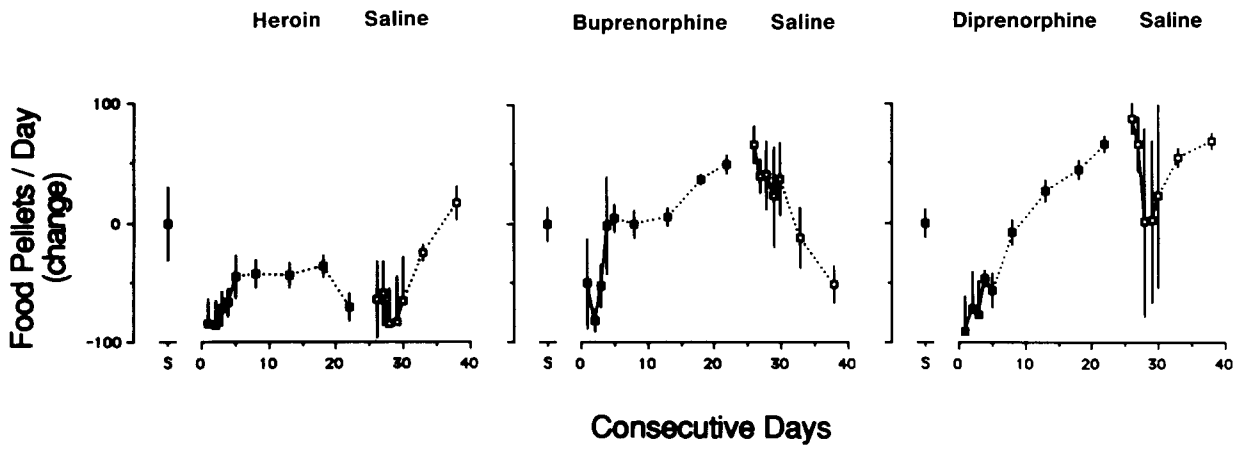

FIG. 1. Changes in total daily food pellets (mean±S.E.M.) earned during chronic daily treatments with 1.0 mg/kg of either heroin, buprenorphine or diprenorphine (filled symbols) followed by abrupt saline substitution (open symbols). Data obtained during the 10 days of predrug saline treatment are indicated by S. During this time monkeys consumed between 125 and 224 pellets per day. Each data point represents the percent change from saline control for three monkeys. Solid lines connect the first five consecutive days in each condition and dotted lines connect subsequent 5-day averages.

mixed agonist/antagonist, and to compare it to pure opioid agonist, heroin, and a pure opioid antagonist, diprenorphine. We previously reported that buprenorphine (0.10–0.30) mg/kg, SC) produced marked disruption of food-maintained performance which returned to control levels within 48 to 72 hours [27]. In the present study, we examined the effects of chronic administration of a higher buprenorphine dose (1.0 mg/kg, SC) and an equivalent dose of heroin and diprenorphine (1.0 mg/kg). This dose of buprenorphine and diprenorphine has been shown to suppress food maintained responding in the squirrel monkey [4], but the effects of chronic diprenorphine administration are unknown.

METHOD

Subjects

Three male Macaque monkeys (*Macaca mulatta* and *Macaca nemistrina*) weighing 4.3 to 8.5 kg were studied. All monkeys had a history of opiate agonist and mixed agonist/antagonist self-administration. Monkeys were maintained at ad lib weight and given multiple vitamins, fresh fruit and vegetables daily to supplement a banana pellet diet. Supplemental food was held constant over the duration of the study. Food pellets obtained during scheduled-controlled performance (see below) constituted 90% of their daily food intake.

Animal maintenance and research was conducted in accordance with the guidelines provided by the Committee on Laboratory Animals' Facility and Care, the National Research Institute of Laboratory Animal Resources. The facility is licensed by the U. S. Department of Agriculture and all protocols are approved by the McLean Hospital Animal Care and Use Committee prior to implementation. The health of the primate colony is periodically monitored by a consultant veterinarian from the New England Regional Primate Center.

Apparatus

Monkeys worked at an operant task for food (1 g banana pellet) and schedules of reinforcement were programmed using custom-designed software and controlled by Apple IIe microcomputers. After completion of the scheduled response requirement, a 1 g banana pellet was automatically dispensed into a food cup located on the operant panel.

Food availability was associated with a colored stimulus light (S+), projected on a translucent Plexiglas® response key in the center of the operant panel. When a food pellet was dispensed, the 3 vertically-oriented colored stimulus lights below the response key flashed for 1 sec. The stimulus light flashes (S+) were also used to signal the completion of each successive component of the second order schedule response requirement. A more detailed description of this apparatus has been published [25].

Procedure

Food self-administration was maintained on a second order schedule of reinforcement. The basic reinforcement schedule was a FR 4 (VR 16:S) which required the monkeys to make an average of 64 responses for each food pellet. Approximately 16 responses on a variable ratio schedule (VR 16) produced a brief colored stimulus light (S+) and a food pellet was delivered only after a fixed ratio of 4 (FR4) of the VR 16 response requirement was completed. Three food sessions were run each day at 11:00 a.m., 3:00 p.m. and 7:00 a.m. Each food session lasted either one hour or until 65 food pellets were delivered. The chamber was dark between 1:00 a.m. and 7:00 a.m. each day. Cleaning and weighing were completed in the morning before the 11:00 am food session.

Once food-maintained performance was stable for a minimum of 30 sessions over 10 days, the effects of single, subcutaneous daily injections (0.5 ml) of either buprenorphine (1.0 mg/kg), heroin (1.0 mg/kg), diprenorphine (1.0 mg/kg), or an equal volume of saline were examined. This dose of buprenorphine previously disrupted food-maintained responding after acute drug administration under comparable conditions [27]. All three monkeys received buprenorphine first and two monkeys received diprenorphine second.

After food self-administration was stable on the final second-order schedule, monkeys were given a single sub-

cutaneous injection of saline (0.5 ml) for 5–10 consecutive days. All injections were given one hour before the 11:00 a.m. food session. Monkeys were then exposed to either buprenorphine, heroin or diprenorphine for 25 consecutive days. Saline was abruptly substituted for each drug and food-maintained performance was studied for an additional 15 days.

Drugs

Buprenorphine HCl, heroin (3,6-diacetyl morphine HCl) and diprenorphine HCl were obtained from the National Institute on Drug Abuse (Rockville, MD). Buprenorphine was dissolved in water and adjusted to a pH 4 with HCl. Heroin and diprenorphine were dissolved in 0.9% saline. Solutions were diluted to the appropriate concentration for individual monkeys and passed through a 44 micron Millipore filter to remove pyrogens. Doses are expressed as the hydrochloride salts. Solutions were checked daily to ensure that no precipitate had formed. Fresh solutions were prepared every 7 to 10 days.

Data Analysis

Analysis of variance (ANOVA) for repeated measures was used to evaluate changes in food self-administration during chronic buprenorphine, heroin or diprenorphine administration. When significant differences between treatment conditions were detected, Dunnett's followup tests were performed to identify specific data points that were significantly different [22]. Statistical analyses were conducted with an Apple IIe microcomputer and software developed by Human Systems Dynamics (Northridge, CA). The linear portions of the time-effect curves were determined by subjecting sequentially more data points to linear regression analyses [35] until the regression coefficient fell. The x-intercept and slope were used to determine the onset and rate of tolerance development.

RESULTS

Effects of chronic daily administration of heroin, buprenorphine and diprenorphine on food-maintained responding are shown in Fig 1. Group data are shown for each of the first 5 days of drug administration and 5-day averages are shown thereafter. Heroin produced a marked decrease in pellets earned per day which persisted for the first 4 days (Fig. 1, left panel). A slight recovery in food-maintained responding was evident by days 5–7, but this plateaued and remained significantly below saline baseline for the duration of treatment ($p<0.01$).

Maximal buprenorphine-induced disruption of food-maintained responding was not evident until the second day of treatment (Fig. 1, middle panel). Within 4 days, two of the three monkeys had returned to control levels of food self-administration and remained at control or slightly above control levels for the remaining 20 days of buprenorphine administration. The third monkey achieved similar performance by days 6–8. Diprenorphine, like heroin, produced maximal disruption of food-maintained responding on the first day of exposure (Fig. 1, right panel). Food intake remained suppressed for the first 5 days of diprenorphine treatment but returned to control levels by day 10. From days 15–25 food-maintained responding was significantly above control levels ($p<0.05$).

Although all three drugs initially suppressed food-maintained responding, the rate and absolute level of recovery differed between drugs. To assess this rate of recovery, the linear portion of the time-effect curve was subjected to regression analysis [35] and the results are presented in Fig. 2. The regression line for the heroin data was not significantly different from a slope of 0 ($y = 5.8x - 89.17$, 95% confidence intervals were −5.46 and 17.08, r=.51). Regression lines for buprenorphine and diprenorphine were significantly different from heroin but were not different from one another. The buprenorphine regression line was defined by the equation $y = 16.8x - 98.6$, 95% confidence intervals were 5.35 and 28.28, and r=.897. The diprenorphine curve was defined by the equation $y = 24.3x - 181.8$, 95% confidence intervals were 15.23 and 33.45, r=.951. Regression lines were evaluated for parallelism using the method of Tallarida and Jacobs [35]. Both buprenorphine, $t(10)=5.162$, and diprenorphine, $t(11)=7.93$, were significantly different from zero ($p<0.005$). The buprenorphine and diprenorphine regression lines for recovery of food-maintained performance were parallel, but the diprenorphine curve was shifted to the right, indicating that recovery was delayed by 3 days.

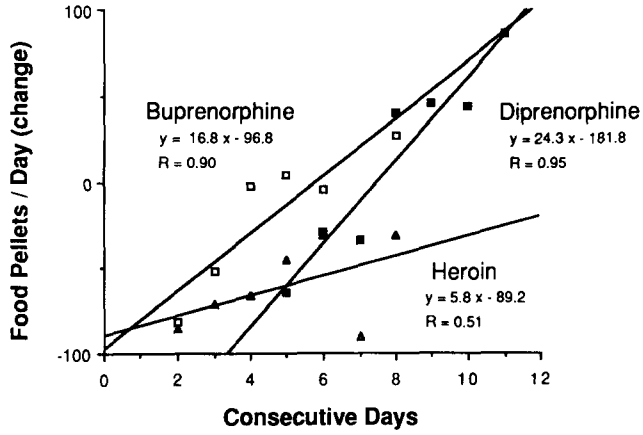

FIG. 2. Regression analysis of the rate of recovery from heroin-, buprenorphine- and diprenorphine-induced suppression of food-maintained behavior. Only the linear portion of the time-effect curve was subjected to analysis which included days 2–8 of heroin and buprenorphine treatment and days 5–11 of diprenorphine treatment.

The effects of abrupt cessation of chronic administration of heroin, buprenorphine and diprenorphine on food-maintained responding are also shown in Fig. 1. Substitution of saline for heroin did not significantly affect the number of pellets earned daily for the first 5 days; pellet intake remained at 60–80 percent below baseline levels. By the 7th day of saline substitution, food intake returned to control levels. Cessation of chronic buprenorphine administration was followed by an initial increase in pellets earned, then a gradual decline during the first 7–10 days of saline treatment. Monkeys remained below control levels of food self-administration for the last 10 days of saline treatment. Substitution of saline for diprenorphine was also followed by increased food self-administration for two days, then a rapid return to control levels. Food-maintained responding then restabilized at a level slightly higher than control levels during the last 10 days of the study.

All animals were observed for gross signs of withdrawal twice daily during the first 5 days of saline substitution and then once daily thereafter [36]. Termination of diprenorphine resulted in pronounced lethargy, akinesia and apparent

anorexia in one monkey while the other two exhibited only mild lethargy. These signs were not accompanied by diarrhea, profuse salivation, lacrimation or urination. All signs subsided within 2 days of saline substitution. Substitution of saline for heroin and buprenorphine was not associated with any withdrawal signs.

DISCUSSION

Acute Effects of Drugs on Food-Maintained Responding

Results from the present study show that single daily injections of heroin, buprenorphine and diprenorphine (1.0 mg/kg) markedly disrupt food-maintained responding in rhesus monkeys within 1 to 2 days. These data confirm and extend previous studies of the acute effects of diprenorphine and buprenorphine [4, 5, 15, 27] and opiate drugs [4, 10, 21] on food-maintained responding. This effect is not unique to opioids since a number of psychoactive drugs including barbiturates, benzodiazepines, ethanol, *d*-amphetamine and analogues, and hallucinogens also disrupt food-maintained responding [11, 14, 21].

Chronic Effects of Drugs on Food-Maintained Responding

During daily drug administration for 25 days, a different profile of recovery of food-maintained responding was observed for heroin, buprenorphine and diprenorphine. The opioid pure agonist, *heroin*, continued to disrupt food-maintained performance throughout the 25-day treatment period. Although food self-administration returned to about 50 percent of control levels by day 5, this was significantly below baseline. These data are inconsistent with our previous report that heroin self-administration for 20 days did not significantly suppress food-maintained responding when daily intake was 0.18, 1.12 and 1.79 mg/kg at unit doses of 0.01, 0.05 and 0.10 mg/kg/inj. [27]. One explanation for this apparent inconsistency is that during heroin self-administration, drug intake was distributed more evenly throughout the day [27] while in the present study 1.0 mg/kg was given as a single injection. While some tolerance was evident, the lack of complete tolerance to heroin's effects on food-maintained responding is consistent with previous reports that single injections of opiate agonists which are separated by 1–2 days fail to produce tolerance to their subjective effects [7], effects on motor activity [9] or effects on smooth muscle [8].

Diprenorphine, a pure opioid antagonist, disrupted food-maintained behavior for the first six days of treatment, then all three animals quickly returned to control levels of operant responding. Food-maintained responding continued to increase during diprenorphine treatment and pellets earned were 60–70% above control levels by the 25th day of treatment. Thus, it appears that tolerance developed to diprenorphine's rate-suppressant effect on operant responding. These findings are consistent with an earlier report by DeRossett and Holtzman [4] which demonstrated that the duration of diprenorphine-induced suppression of food-maintained responding was shorter after repeated administration. DeRossett and Holtzman [4] concluded that it was not clear if the shortened duration of action represents tolerance due to behavioral, pharmacokinetic or pharmacodynamic variables.

The acute effects of *buprenorphine* on operant behavior are well documented [4, 5, 15, 18, 19, 26, 27], but the effects of chronic administration are more complex. In the present study, animals recovered from buprenorphine's rate suppressant effects within 3–4 days of daily treatment. Food-maintained responding remained stable for about 10 days and then gradually increased—a finding that confirms our previous report [27]. However, Dykstra [5] reported that squirrel monkeys did not develop tolerance to repeated daily injections of 0.01 mg/kg of buprenorphine. The explanation for these discrepant findings is unclear. The most parsimonious explanation is that the dose of buprenorphine used in the present study was 100 fold larger than the dose used by Dykstra [5] and the lower dose may not have produced sustained blood levels of buprenorphine which are conducive to tolerance development. This hypothesis is consistent with previous observations that higher doses of buprenorphine (0.1, 1.0 mg/kg) had a shorter duration of action after repeated administration in squirrel monkey [4].

Differences in Tolerance Development

A differential rate and degree of tolerance to heroin, buprenorphine and diprenorphine was observed. The relatively long duration of action of buprenorphine and diprenorphine could account for the development of tolerance to their rate suppressant effects on food-maintained responding. In contrast, chronic administration of heroin, a relatively short acting drug, failed to induce complete tolerance. These data are comparable to previous studies of the relatively short acting opioid agonist, etorphine, where no evidence of tolerance was observed after repeated administration [4]. Although comparative pharmacokinetic data for diprenorphine are not available in the rhesus monkey, its antagonist properties are relatively long-lasting in a number of species [2, 3, 6, 35], but are of shorter duration than buprenorphine [4,5]. While only the 1.0 mg/kg dose of each drug was tested in the present study, this dose produced an equivalent amount of disruption of food-maintained responding after acute administration of all three opioids (compare days 1–2 in Fig. 1).

Differences in drug effects on food-maintained responding were also evident during the saline substitution period. Diprenorphine-induced elevations in food-maintained responding quickly disappeared after saline substitution. However, the number of food pellets earned gradually increased during days 7–15 (Fig. 1). Saline substitution after buprenorphine-induced increases in food-maintained responding resulted in more gradual decreases in food pellets earned than after diprenorphine administration. A completely different pattern of recovery from heroin administration was observed. Food-maintained responding remained depressed during the first 5–6 days of saline substitution and then returned to baseline levels. It is possible that the monkeys became physically dependent on the 1.0 mg/kg dose of heroin and the lack of recovery was due to opiate withdrawal. But, no overt signs of opiate withdrawal were observed and this interpretation would require that dependence had developed in the absence of tolerance to the operant suppressant effects of daily heroin.

The present study employed regression analysis as a statistical tool to assess and compare the rate of tolerance development to buprenorphine, heroin and diprenorphine. Differentiation between tolerance and no tolerance effects was made on the basis of the slope and 95% CI of the linear portion of the time-effect curve. Using this procedure we were able to determine not only that tolerance develops to buprenorphine and diprenorphine, but that the rate of tolerance development was the same (Fig 2). However,

tolerance to diprenorphine developed 3 days after evidence of tolerance to buprenorphine. This delay may have occurred because diprenorphine has a shorter duration of action than buprenorphine and effective drug levels in blood may have taken longer to accumulate. Similar qualitative differences in rates of tolerance development to the direct effects of an opiate mixed agonist/antagonist have not been reported previously.

Finally, it is important to emphasize the differences between the findings of the present study and those reporting that opiate agonists increase food intake and opiate antagonists decrease food intake [31, 33, 37]. These findings strongly suggest that endogenous opiates have an essential role in the central regulation of appetite [31, 33, 37]. However, experimental conditions in the present study are not comparable to those employed to study feeding behavior [31, 33, 37]. It is unlikely that opiate-induced suppression of schedule-controlled behavior reflects alterations in central mechanisms controlling appetite. Instead, nonspecific disruption of operant responding, which was necessary to obtain the food pellets, can account for the present results.

In conclusion, chronic daily injections of heroin, buprenorphine and diprenorphine produced differential degrees and rates of tolerance to the disruption of food-maintained performance. These qualitative differences were quantified using linear regression analysis which revealed that the rates of tolerance development differed. While the exact mechanism of this observed differential rate of tolerance development is unknown, it is likely that the major contributing factor is the pharmacokinetic difference between these drugs.

ACKNOWLEDGEMENTS

We thank A. Baughn, M. Spinelli and S. White for technical assistance, Dr. Prabhat Sehgal for veterinary consultation, E. DeRubeis for editorial assistance and R. Head and L. Wighton for secretarial assistance. We thank the National Institute on Drug Abuse for providing buprenorphine, diprenorphine and heroin used in this study. Supported in part by Grants DA02519 and DA04059, and Research Scientist Awards DA00101, DA00115 and DA00064 from the National Institute on Drug Abuse, ADAMHA.

REFERENCES

1. Chang, K. J.; Hazum, E.; Cuatnecasas, P. Novel opiate binding sites selective for benzomorphan drugs. Proc. Natl. Acad. Sci. USA 78:4141–4145; 1981.
2. Cowan, A. Evaluation in nonhuman primates: Evaluation of the physical dependence capacities of oripavine-thebaine partial agonists in patas monkeys. In: Braude, M. C.; Harris, L. S.; May, E. L.; Smith, J. P.; Villarreal, J. E., eds. Narcotic antagonists: Advances in biochemical psychopharmacology. vol. 8. New York: Raven; 1973:427–438.
3. Cowan, A.; Doxey, J.C.; Harry, E. J. R. The animal pharmacology of buprenorphine, an oripavine analgesic agent. Br. J. Pharmacol. 60:547–554; 1977.
4. DeRossett, S. E.; Holtzman, S. G. Effects of naloxone, diprenorphine, buprenorphine and etorphine on unpunished and punished food-reinforced responding in the squirrel monkey. J. Pharmacol. Exp. Ther. 228:669–675; 1984.
5. Dykstra, L.A. Behavioral effects of buprenorphine and diprenorphine under a multiple schedule of food presentation in squirrel monkeys. J. Pharmacol. Exp. Ther. 226:317–323; 1983.
6. Dykstra, L. A.; McMillan, D. E.; Harris, L. S. Antagonism of morphine by long acting narcotic antagonists. Psychopharmacologia 39:151–162; 1974.
7. Goldstein, A.; Aronow, L.; Kalman, S. M. Principles of drug action: The basis of pharmacology. New York: John Wiley & Sons; 1974:602.
8. Goldstein, A.; Schulz, R. Morphine-tolerated longitudinal muscle strip from guinea pig ileum. Br. J. Pharmacol. 48:655–666; 1973.
9. Goldstein, A.; Sheehan, P. Tolerance to opioid narcotics. I. Tolerance to the "running fit" caused by levorphanol in the mouse. J. Pharmacol. Exp. Ther. 169:175–184; 1969.
10. Harris, R.A. Interactions between narcotic agonists, partial agonists, and antagonists evaluated by schedule-controlled behavior. J. Pharmacol. Exp. Ther. 213:497–503; 1980.
11. Harris, R. A.; Snell, D.; Loh, H. H. Effects of *d*-amphetamine, monomethoxy amphetamines and hallucinogens on schedule-controlled behavior. J. Pharmacol. Exp. Ther. 204:103–117; 1978.
12. Jaffe, J. H.; Martin, R. W. Opioid analgesics and antagonists. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. The pharmacological basis of therapeutics. New York: MacMillan Publishing Co.; 1985:491–531.
13. Jasinski, D. R.; Pevnick, J. S.; Griffith, J. D. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch. Gen. Psychiatry 35:601–616; 1978.
14. Katz, J. L.; Barrett, J. E. Ethanol, pentobarbital and chlordiazepoxide effects in squirrel monkeys responding under fixed-ratio food presentation and stimulus-shock termination schedules. Psychopharmacology (Berlin) 56:153–155; 1978.
15. Leander, J. D. Opioid agonist and antagonist behavioral effects of buprenorphine. Br. J. Pharmacol. 78:607–615; 1983.
16. Lewis, J. W. Ring C-bridged derivatives of thebaine and oripavine. In: Braude, M. C.; Harris, L. S.; May, E. L.; Smith, J. P.; Villareal, J. E., eds. Narcotic antagonists: Advances in biochemical psychopharmacology. vol. 8. New York: Raven; 1973:123–136.
17. Lewis, J. W. Buprenorphine. Drug Alcohol Depend. 14:363–372; 1985.
18. Lewis, J. W.; Rance, M. J.; Sanger, D. J. The pharmacology and abuse potential of buprenorphine: A new antagonist analgesic. In: Mello, N. K., ed. Advances in substance abuse: Behavioral and biological research. vol. 3. Greenwich, CT: JAI Press; 1983:103–154.
19. Lukas, S. E.; Brady, J. V.; Griffiths, R. R. Comparison of opioid self-injection and disruption of schedule-controlled performance in the baboon. J. Pharmacol. Exp. Ther. 238:924–931; 1986.
20. Lukas, S. E.; Jasinski, D. R.; Johnson, R. E. Electroencephalographic and behavioral correlates of buprenorphine administration. Clin. Pharmacol. Ther. 36:127–132; 1984.
21. McMillan, D. E.; Leander, J. P. Effects of drugs on schedule-controlled behavior. In: Glick, S. D.; Goldfarb, J., eds. Behavioral pharmacology. St. Louis: C. V. Mosby Co.; 1976:85–139.
22. Madigan S.; Lawrence, J. ANOVA II, Version 1.1: A general Analysis of Variance Program for the Apple II. Northridge, CA; Copyright 1982, 1983 by Human Systems Dynamics.
23. Magnan, J.; Paterson, S. J.; Tavani, A.; Kosterlitz, H. W. The binding spectrum of narcotic analgesic drugs with different agonist and antagonist properties. Naunyn Schmiedebergs Arch. Pharmacol. 319:197–205; 1982.
24. Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, J. A.; Gilbert, P. E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol, Exp. Ther. 197:517–532; 1976.

25. Mello, N. K.; Mendelson, J. H. Self-administration of an enkephalin analog by rhesus monkey. Pharmacol. Biochem. Behav. 9:579–586; 1978.
26. Mello, N. K.; Mendelson, J. H. Behavioral pharmacology of buprenorphine. Drug Alcohol Depend. Monogr. 14:283–303; 1985.
27. Mello, N. K.; Bree, M. P.; Lukas, S. E.; Mendelson, J. H. Buprenorphine effects on food-maintained responding in macaque monkeys. Pharmacol. Biochem. Behav. 23:1037–1044; 1985.
28. Mello, N. K.; Bree, M. P.; Mendelson, J. H. Buprenorphine self-administration by rhesus monkey. Pharmacol. Biochem. Behav. 15:215–225; 1981.
29. Mello, N. K.; Bree, M. P.; Mendelson, J. H. Comparison of buprenorphine and methadone effects on opiate self-administration in primates. J. Pharmacol. Exp. Ther. 225:378–386; 1983.
30. Misra, A. L. Metabolism of opiates. In: Adler, M. L.; Manara, L.; Samanin, R., eds. Factors affecting the action of narcotics. New York: Raven; 1978:297–343.
31. Morley, J. E.; Levine, A. S.; Kneip, J.; Grace, M.; Billington, D. J. The effect of peripherally administered satiety substances on feeding induced by butorphanol tartrate. Pharmacol. Biochem. Behav. 19:557–582; 1983.
32. Rance, M. J. Animal and molecular pharmacology of mixed agonist-antagonist analgesic drugs. Br. J. Clin. Pharmacol. 7:281S–286S; 1979.
33. Sanger, D. J.; McCarthy, P. S.; Metcalf, G. The effects of opiate antagonists on food intake are stereospecific. Neuropharmacology 20:45–47; 1981.
34. Schulz, R.; Herz, A. The guina pig ileum as an in vitro model to analyze dependence liability of narcotic drugs. In: Kosterlitz, H. W., ed. Endogenous opioid peptides. Amsterdam: North Holland; 1976:319–326.
35. Tallarida, R. J.; Jacob, L. S. The dose-response relation in pharmacology. New York: Springer-Verlag; 1979.
36. Villarreal, J. E.; Karbowski, M. G. The actions of narcotic antagonists in morphine-dependent rhesus monkeys. In: Braude, M. C.; Harris, L. S.; May, E. L.; Smith, J. P.; Villarreal, J. E., eds. Narcotic antagonists: Advances in biochemical psychopharmacology. vol. 8. New York: Raven; 1973: 273–289.
37. Yim, G. K. W.; Lowry, M. T. Opioids, feeding and anorexias. Fed. Proc. 43:2893–2897; 1984.