Pharmacology Biochemistry & Behavior, Vol. 17, pp. 223–228, 1982. Printed in the U.S.A.

Acute Tolerance to the Discriminative Stimulus Properties of Morphine

JEFFREY M. WITKIN,[1] LINDA A. DYKSTRA AND RICHARD B. CARTER

Department of Psychology, University of North Carolina, Chapel Hill, NC

Received 14 September 1981

WITKIN, J. M., L. A. DYKSTRA AND R. B. CARTER. *Acute tolerance to the discriminative stimulus properties of morphine*. PHARMAC. BIOCHEM. BEHAV. 17(2) 223–228, 1982.—Two pigeons were trained to discriminate intramuscular injections of 1.0 mg/kg morphine from water by presenting food after keypeck responses on one key when morphine was administered and after responses on a second key when water was administered. Following training, close to 100% of responses occurred on the appropriate key following administration of 1.0 mg/kg morphine or water. Morphine (0.1–5.6 mg/kg) produced dose-dependent increases in the percentage of morphine-appropriate responses (discriminative stimulus properties) and decreases in the rate of responding. A shift to the right of the morphine dose-effect curve for the discriminative stimulus properties of morphine resulted from a single injection of morphine (10.0 mg/kg) 24 hrs prior to testing (i.e., acute tolerance) but not from a single injection of pentobarbital (17.0 mg/kg). Tolerance to the discriminative stimulus properties of morphine was reversible within five days of the single injection. Tolerance did not develop to the effects of morphine on response rate. Naloxone antagonized both the discriminative stimulus properties and the response rate-decreasing effects of morphine. Thus, a single administration of morphine can alter morphine discriminability without affecting other aspects of behavior.

Morphine Naloxone Discriminative stimulus effects Tolerance Antagonism Keypeck Pigeons

THE ability of a variety of opioid analgesics to function as discriminative stimuli has been extensively investigated (cf. [5]). Discriminative stimulus properties of opioids have been studied in a number of species trained to respond differentially in the presence of opioid agonists and their injection vehicles [7, 17, 18, 19, 22, 24, 31, 32, 34]. These studies and others have demonstrated that the ability of opioids to function as discriminative stimuli is the result of a specific interaction of these compounds with central opioid receptors and hence the discriminative stimulus properties of opioids share common functional relationships with other effects of these compounds. Two such relationships are the development of tolerance with repeated administration and antagonism by opioid antagonists.

Tolerance is characterized by a shift to the right of the dose-effect curve such that larger doses are required to produce a given effect (cf. [14,21]). However, the rate and extent of the development of opioid tolerance is not equivalent for all effects or under all conditions. For example, tolerance to the analgesic effects of opioids can occur after a single injection [4,29]; whereas, tolerance to effects of opioids on the gastrointestinal tract and on the pupil do not develop to any appreciable extent, even in subjects made highly tolerant to respiratory depressant and subjective effects by repeated administration [21, 26, 33]. Moreover, whereas tolerance to the discriminative stimulus properties of opioids occurs under some conditions [28, 31, 34], tolerance has not always been reported [8, 9, 20].

Discriminative stimulus properties and other behavioral effects of opioids may likewise be differentially susceptible to tolerance development. For example, tolerance to analgesic effects of morphine occurs at doses that are discriminable from saline [28]. Animals tolerant to the response rate-decreasing effects of opioids still readily discriminate the presence of these drugs [8, 9, 22]. Similarly, animals made tolerant to depressant effects of pentobarbital [23], barbital [41], or marihuana extract [1] are able to discriminate the presence of these compounds. Differential tolerance in these studies and reports that tolerance does not develop at all to the discriminative stimulus effects of drugs has led some writers to imbue the discriminative stimulus properties of drugs with a unique status among the myriad of drug effects (cf. [5, 6, 8, 9, 20]).

The shift to the right of the opioid dose-effect curve, which characterizes tolerance, can also be produced by administration of opioid antagonists. Administration of opioid antagonists has been reported to antagonize the discriminative effects as well as the rate-altering effects of opioid agonists [5, 17, 22, 24, 34, 38, 39].

The present experiments were conducted to determine whether tolerance develops to the discriminative effects of morphine after pretreatment with a single injection of mor-

[1]To whom correspondence should be addressed: Department of Psychiatry, School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814.

phine (acute tolerance). Of particular interest was whether acute tolerance would occur differentially to the discriminative effects and to the response rate-altering effects of morphine. The pharmacological specificity of the effects of morphine pretreatment was studied by comparison with pentobarbital pretreatment. In order to independently assess the susceptibility of the effects of morphine to perturbation by pharmacological manipulation, effects of the narcotic antagonist naloxone [2], were studied in combination with morphine.

METHOD

Subjects

Two experimentally naive, adult, male, White Carneaux pigeons obtained from the Palmetto Pigeon Plant, Sumter, SC, were maintained at 80% (458 and 495 g) of their free-feeding body weights. Water and oyster shell grit were continuously available in separate home cages housed in a continuously lighted room.

Apparatus

Experiments were conducted in a standard pigeon chamber (36×26×29.5 cm) enclosed in a ventilated, sound- and light-attenuating enclosure supplied with white noise [12]. Three translucent response keys (R. Gerbrands Co.) were mounted behind 2 cm diameter openings in the front panel of the chamber. The keys were 10 cm apart and 22 cm from the floor. The center key could be transilluminated with white light from two GE 1820 lamps. The side keys could be transilluminated with red light by passing light from two GE 1820 lamps through Kodak Wratten gelatin filter (No. 25). An opening 4.5×5.0 cm was positioned in the center of the front panel, 9.5 cm from the floor through which grain could be presented by a solenoid operated feeder. When the feeder operated, the opening was illuminated by a single GE 1820 bulb and the keylights were extinguished. A minimum force of approximately 0.15 N applied to the response keys produced the audible click of a relay mounted behind the front panel and defined a response. Experimental events were scheduled and recorded with electromechanical equipment located in a separate room.

Initial Training

Birds were first trained to approach and eat out of the food hopper. Then they were trained to peck the center response key by the method of reinforcing successive approximations [12]. Initially every response (FR 1) on the center key produced 3.3 sec access to food. The response requirement was raised over several sessions until every 30th response produced food (FR 30). When responding occurred reliably on the center key, sessions began with the center key illuminated for 30 min with the FR 30 requirement in effect. After 30 min, the center key was extinguished and one of the side keys was illuminated for an additional 30 min. The particular side key which was illuminated was varied randomly across sessions with the constraint that the same key was not lit for more than three consecutive sessions. Initially, food presentation occurred after each response on the illuminated side key. The response requirement was gradually increased to a tandem variable-interval 60 sec fixed-ratio 10 schedule (tandem VI 60 sec, FR 10) under which the tenth consecutive response to occur on one key after an average interval of 60 sec elapsed produced 3.3 sec access to mixed grain. This schedule engenders substantial responding in the absence of food presentation during which control of responding by the drug injection can be evaluated [25,40] as described below.

Drug Discrimination Training

Drug discrimination training began when responding had stabilized on all response keys. Immediately prior to experimental sessions, birds were injected with either 1.0 mg/kg morphine or water. The center key was then illuminated for 30 min during which responding produced food under the FR 30 schedule. At the elapse of 30 min, the white center keylight was extinguished and the two red side keylights were illuminated for 30 min. At this time, responding on only one of the side keys produced food according to the tandem VI 60 sec FR 10 schedule. Responding on the other side key reset the FR value of the tandem schedule to 10 but never produced food. The side key upon which responding resulted in food delivery was correlated with the solution administered prior to the session. When morphine was given, responding on the left key produced food for bird P-8026; responding on the right key produced food for P-7918. When water was given, responding on the right key produced food for P-8026; responding on the left key produced food for P-7918. A quasi-random sequence was used to determine which injection solution would be administered each day; the same solution was never given for more than three successive sessions.

At the beginning of every fourth experimental session a 10 min extinction period began after the center keylight was extinguished and the side keys were illuminated; responding during this period had no scheduled consequences. On the rare occasion when no responses occurred during this period, the first response to occur within 30 min initiated another extinction period, which terminated either 10 min later or after 30 min from the illumination of the side keys, whichever came first. Rates of responding and the percentage of responses on each key were measured during the extinction period where they were not influenced by food delivery. Extinction periods with less than 15 responses were excluded from analysis of the percentage of responses on each key.

Tolerance Testing

This phase of the experiment began when a criterion of more than 80% of the responses during the extinction tests occurred on the injection-correlated key for at least four successive extinction tests regardless of the solutions administered the previous session. During this phase of the experiment, dose-effect curves for morphine were determined under three different pretreatment conditions. Development and recovery of tolerance were studied using a five day sequence summarized in Table 1.

On the session designated day 1, either 10.0 mg/kg morphine, 17.0 mg/kg pentobarbital, or water was injected and the birds were placed in the experimental chamber for only 30 min with the FR 30 schedule in operation on the center key. On day 2, they were injected with either water or one dose of morphine (0.1–5.6 mg/kg) and were tested in extinction on the side keys after 30 min of FR 30 on the center key; sessions were terminated after the 10 min extinction period or, if no responses occurred, after 30 min. Experiments were not conducted on days 3 and 4. On day 5, 1.0 mg/kg mor-

TABLE 1
TOLERANCE TESTING SEQUENCE

Day	Pretreatment*	Extinction Test
1	either: (1) water	No
	(2) 10.0 mg/kg morphine	No
	(3) 17.0 mg/kg pentobarbital	No
2	either: (1) water	Yes
	(2) morphine (0.1–5.6 mg/kg)†	Yes
3	no experiments conducted	
4	no experiments conducted	
5‡	1.0 mg/kg morphine	Yes

*Injections given 30 min prior to extinction tests. When no extinction tests were scheduled, subjects were removed from the experimental chamber after 30 min.

†Only one dose of morphine was administered on each test day (0.1, 0.3, 0.56, 1.0, 1.7, 3.0, or 5.6 mg/kg).

‡At least five days of discrimination training intervened between day 5 and day 1 of the tolerance testing sequence.

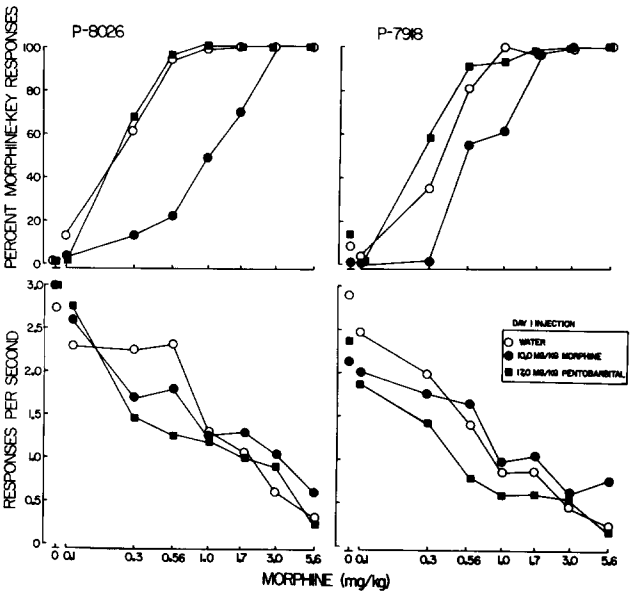

FIG. 1. Effects of morphine on the percentage of responses on the morphine key (upper panels) and on the combined rate of responding on both keys (lower panels). Both birds were trained to discriminate 1.0 mg/kg morphine from water. Data were collected during extinction tests on day 2 when either water, 10.0 mg/kg morphine, or 17.0 mg/kg pentobarbital was administered on day 1. Each point represents the mean of at least 2 determinations. Points above O represent effects of water.

phine, the training dose, was administered and the procedure for day 2 was repeated. If less than 80% of responses occurred on the morphine-key on day 5, experiments were not conducted for two more days, after which 1.0 mg/kg morphine was again tested. This was done to ensure that drug discrimination training was conducted only during times when the pigeons were not tolerant to morphine. The five day sequence was repeated until dose-effect curves for morphine were determined under each of the three pretreatment conditions. At least five sessions of discrimination training intervened between each five day cycle in order to maintain and assess the stability of the drug discrimination. At least 90% injection-correlated responses were required to meet the stability requirement.

Naloxone Antagonism

Naloxone antagonism experiments were conducted after the completion of tolerance testing. Extinction tests were conducted on Tuesdays and Fridays. During extinction tests, effects of morphine (0.1–10.0 mg/kg) plus water, naloxone (0.03 and 0.3 mg/kg) plus water, or morphine (0.1–10.0 mg/kg) plus naloxone (0.03 and 0.3 mg/kg) were determined in a non-systematic order. Morphine (1.0 mg/kg) or water was given on every third test in order to assess the stability of the drug discrimination.

Drugs

Morphine sulfate (Merck and Company, Inc., Rahway, NJ), sodium pentobarbital (Sigma Chemical Co., St. Louis, MO), and naloxone hydrochloride (Endo Laboratories, Garden City, NY) were dissolved in distilled water and injected into the pectoral muscle in a volume of 1.0 ml/kg body weight. Water injections were also given in this volume. Drug doses were calculated as the salt. During tolerance testing, effects of 10.0 mg/kg morphine or water pretreatment were generally determined in a mixed order before the effects of 17.0 mg/kg pentobarbital pretreatment were studied. Dose-effect curves for morphine were determined at least twice in each bird for each of the three pretreatment conditions. The 10.0 mg/kg dose of morphine was chosen for study since tolerance to the rate-decreasing effects of morphine occurs in pigeons when this dose is chronically administered [27]. Pentobarbital (17.0 mg/kg) was studied because it produced decreases in response rate that were comparable to those produced by 10.0 mg/kg morphine in the present study.

When double injections were scheduled, during the naloxone antagonism experiments, they were given on opposite sides of the pectoral muscle in a random order within 10 sec of one another. Dose-effect functions for morphine, naloxone, and morphine-naloxone combinations were generally determined once in each bird, in a mixed order.

RESULTS

Acquisition of the 1.0 mg/kg morphine-water discrimination was complete after 32 sessions (8 extinction tests) for P-8026 and 72 sessions (18 extinction tests) for P-7918. Once the discrimination was acquired, close to 100% (range=91–100%) of responses for both birds occurred on the injection-correlated key.

Tolerance Testing

Figure 1 (top panels) shows effects of morphine on the percentage of morphine-key responses on day 2 when birds had been injected with 10.0 mg/kg morphine, 17.0 mg/kg pentobarbital, or water on day 1. In all cases morphine produced dose related increases in responding on the morphine key. Pretreatment with 10.0 mg/kg morphine shifted the dose-effect curve to the right. Effects of the training dose of morphine (1.0 mg/kg) were reduced to 49% for P-8026 and 61%

for P-7918. Higher doses of morphine (3.0 and 5.6 mg/kg) resulted in roughly 100% morphine-key responses in both birds regardless of the pretreatment. When tested on day 5, after 10.0 mg/kg morphine on day 1, effects of 1.0 mg/kg morphine were generally recoverable; mean percent morphine-key responses were 90 and 81 for P-8026 and P-7918, respectively (not shown). In contrast to the effects of 10.0 mg/kg morphine pretreatment, 17.0 mg/kg pentobarbital pretreatment did not alter the dose-effect relationship for morphine.

Overall response rates (left-key plus right-key) during extinction tests are shown in the bottom panels of Fig. 1. Morphine produced dose-dependent decreases in response rate. No tolerance to this effect was evident after pretreatment with 10.0 mg/kg morphine.

Responding on the center response key under the FR 30 schedule was markedly decreased on day 1 by administration of 10.0 mg/kg morphine and 17.0 mg/kg pentobarbital (not shown). Center-key response rates were 28 and 29% of control rates (water injection) when 10.0 mg/kg morphine was given to P-8026 and P-7918 respectively. When 17.0 mg/kg pentobarbital was given, center-key rates were 2 and 4% of control rates for P-8026 and P-7918, respectively. There were no systematic differences in the effects of morphine on center-key responding on day 2 as a function of the solution administered on day 1.

Naloxone Antagonism

When given in combination with morphine, naloxone produced a dose-dependent antagonism of the percentage of morphine-key responses; naloxone alone produced relatively few morphine-key responses (Fig. 2, top panels). Naloxone also produced a dose-dependent antagonism of the rate-decreasing effects of morphine but produced only small response rate decreases when given alone (Fig. 2, bottom panels).

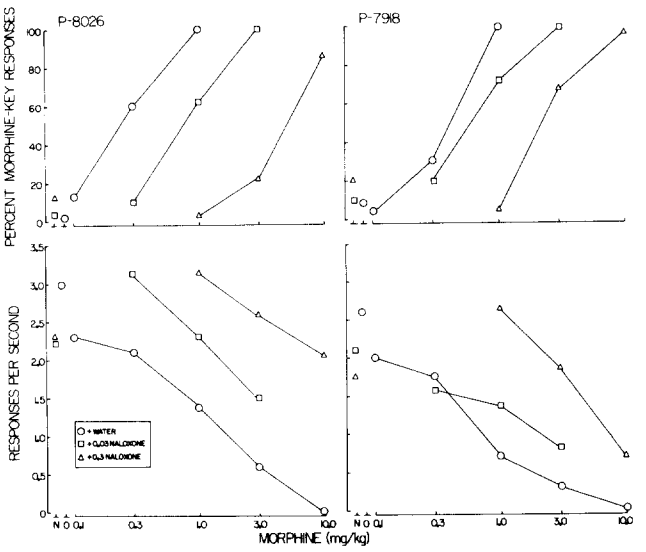

FIG. 2. Effects of morphine given in combination with either water, 0.03 mg/kg naloxone, or 0.3 mg/kg naloxone on the percentage of responses on the morphine key (upper panels) and on the combined rate of responding on both keys (lower panels). Both birds were trained to discriminate 1.0 mg/kg morphine from water. Each point represents the mean of one or more determinations. Data were collected during extinction test sessions. Points above O represent effects of water alone. Points above N represent effects of naloxone alone.

DISCUSSION

Excellent stimulus control of behavior occurred under the 1.0 mg/kg morphine-water discrimination. The 1.0 mg/kg dose of morphine is the lowest dose to be used successfully to establish and maintain a discrimination between morphine and the non-drug condition in any species. With pigeons as subjects, as in the present experiment, Jarbe [22] used 6.0 mg/kg and Herling *et al.* [17] used 10.0 mg/kg morphine. Despite the large difference in training dose, morphine produced dose-dependent increases in the percentage of morphine-key responses as reported by others [5, 17, 22, 24, 32, 34, 35].

Tolerance developed to the discriminative stimulus properties of morphine after pretreatment with a single injection of morphine (acute tolerance) but not after pretreatment with pentobarbital. Tolerance to discriminative effects of morphine has also been shown to occur after repeated administration of high doses of morphine in rats [28, 31, 34]. Thus, as with many effects of opioids [3,14], tolerance can develop to the discriminative effects of morphine after both acute and chronic administration of morphine.

Acute tolerance also develops to effects of opioids on measures of analgesia, swimming, running, and narcosis (e.g. [4, 15, 29, 33]). Development and recovery of acute tolerance seems to depend on a variety of factors such as the response, the dose administered and the interval between doses. It is likely that acute tolerance to the discriminative stimulus properties of morphine would depend on similar factors.

In contrast to the tolerance reported here, Hirschhorn and Rosecrans [20] produced only a marginal degree of tolerance after long term exposure to high doses of morphine. Moreover, Colpaert *et al.* [8,9] did not find any evidence of tolerance to the discriminative stimulus properties of the narcotic analgesic fentanyl. Much of the discrepancy between these findings and those reported here is probably the result of procedural differences. In the Colpaert *et al.* [8,9] and Hirschhorn and Rosecrans [20] studies, drug discrimination training continued during the tolerance regimen. Therefore, discrimination training was probably being carried out in the presence of drug doses functionally lower (due to tolerance) than the dose actually administered. This idea has been suggested previously [20] and gains support from demonstrations that drug discriminations can be maintained at progressively lower doses of drugs [10,30].

In the present experiment, a single injection of morphine induced tolerance to the discriminative stimulus properties of morphine; nevertheless, tolerance to the rate-decreasing effects of morphine did not occur. This differential tolerance is in contrast to reports that rats tolerant to the rate-decreasing or analgesic effects of fentanyl or morphine are not tolerant to the discriminative stimulus properties of these drugs [8, 9, 28]. However, as just discussed, detection of tolerance to the discriminative stimulus properties of morphine and fentanyl was probably precluded by the procedures employed in those studies. Since tolerance to the response rate-decreasing effects of morphine occurs quite readily in pigeons upon repeated administration [16,27] it is possible that tolerance to both the rate-decreasing and discriminative stimulus properties of morphine would have be-

come evident if the pigeons in the present experiment had been pretreated with multiple doses of morphine. Nonetheless, the results of the present study demonstrated that tolerance can develop to the discriminative stimulus properties of morphine without tolerance concurrently developing to the rate-decreasing effects of morphine. This finding raises serious obstacles to the hypothesis that the discriminative stimulus properties of opioids are uniquely resistant to tolerance development (cf. [5, 6, 8, 9]).

The discriminative stimulus properties and the response rate-decreasing effects of morphine were antagonized by administration of naloxone. Naloxone antagonism of the discriminative stimulus properties of morphine provides evidence that the morphine-water discrimination involved the interaction of morphine with opioid receptors. The results of the tolerance experiment support this conclusion. Antagonism by naloxone and other opioid antagonists of the discriminative stimulus and response rate-decreasing effects of morphine and related compounds has been reported by others [5, 17, 22, 24, 34, 38, 39]. Naloxone produced similar effects on the response rate-altering and the discriminative effects of morphine; in contrast morphine pretreatment produced disparate effects on these two measures. Together these results provide additional evidence [7, 8, 9, 22] for the independence of response rate and opioid discriminability. Moreover, antagonism of the rate-decreasing effects of morphine by naloxone demonstrates that the lack of effect of morphine pretreatment on response rate, in the tolerance experiment was not due to a general inability of response rate decreases to be altered.

Tolerance to the discriminative stimulus properties of opioids has parallels with the subjective effects of opioids and with opioid self-administration and abuse. Martin and Fraser [26], in their classic study of ex-narcotic addicts, demonstrated pronounced tolerance to the perceived intensity of drug effect when subjects were given progressively larger doses of heroin or morphine. Tolerance also appears to develop during self-administration of opioids although this has not been well studied. For example, rhesus monkeys increase their total daily intake of morphine over a period of weeks to asymptotic levels [11]. Likewise, opioid abuse in man is often characterized by an escalation in dose with repeated administration [21]. Rats pretreated chronically with various doses of morphine subsequently self-administer morphine in amounts proportional to the pretreatment dose [37]. The discriminative stimulus properties of drugs appear to be related to the subjective effects produced by drugs in man [5, 7, 34]. The present study, therefore, suggests that even a single exposure to opioids may alter their subjective effects on a subsequent occasion. Moreover, since the discriminative stimulus properties of drugs may play a role in their abuse (cf. [5, 13, 36]), then a single exposure may also affect opioid abuse.

ACKNOWLEDGEMENTS

This research was supported by grants MH-14269, GM-22683, and MH-14277 from the U.S. Public Health Service and from the University Research Council of the University of North Carolina at Chapel Hill. We appreciate the helpful comments of Drs. T. U. C. Jarbe, J. D. Leander and R. J. Valentino on an earlier draft of the manuscript. The figures were expertly drafted by Ms. Cedonia Edwards. Ms. Brenda Brown, Angie Hodgin, Delbera Kearney and Cathy Morris provided assistance in the preparation of the manuscript.

REFERENCES

1. Bueno, O. F. A. and E. A. Carlini. Dissociation of learning in marijuana tolerant rats. *Psychopharmacologia* **25:** 49–56, 1972.
2. Blumberg, H., H. B. Dayton, M. George and D. N. Rappaport. N-allylnoroxymorphone: a potent narcotic antagonist. *Fedn Proc.* **20:** 311, 1961.
3. Clouet, D. H. and K. Iwatsubo. Mechanisms of tolerance to and dependence on narcotic analgesic drugs. *A. Rev. Pharmac.* **15:** 49–71, 1975.
4. Cochin, J. and C. Kornetsky. Development and loss of tolerance to morphine in the rat after single and multiple injections. *J. Pharmac. exp. Ther.* **145:** 1–10, 1964.
5. Colpaert, F. C. Discriminative stimulus properties of narcotic analgesic drugs. *Pharmac. Biochem. Behav.* **9:** 863–887, 1978.
6. Colpaert, F. C. Narcotic cue, narcotic analgesia, and the tolerance problem: the regulation of sensitivity to drug cues and to pain by an internal cue processing model. In: *Stimulus Properties of Drugs: Ten Years of Progress,* edited by F. C. Colpaert and J. A. Rosecrans. Amsterdam: Elsevier/North-Holland Biomedical, 1978, pp. 301–321.
7. Colpaert, F. C., H. Lal, C. J. E. Niemegeers and P. A. J. Janssen. Investigations on drug produced and subjectively experienced discriminative stimuli. 1. the fentanyl cue, a tool to investigate subjectively experienced narcotic drug actions. *Life Sci.* **16:** 705–716, 1975.
8. Colpaert, F. C., J. J. M. D. Kuyps, C. J. E. Niemegeers and P. A. J. Janssen. Discriminative stimulus properties of fentanyl and morphine: tolerance and dependence. *Pharmac. Biochem. Behav.* **5:** 401–408, 1976.
9. Colpaert, F. C., C. J. E. Niemegeers and P. A. J. Janssen. Studies on the regulation of sensitivity to the narcotic cue. *Neuropharmacology* **17:** 705–713, 1978.
10. Colpaert, F. C., C. J. E. Niemegeers and P. A. J. Janssen. Factors regulating drug cue sensitivity: limits of discriminability and the role of a progressively decreasing training dose in fentanyl-saline discrimination. *J. Pharmac. exp. Ther.* **212:** 474–480, 1980.
11. Deneau, G., T. Yanagita and M. H. Seevers. Self-administration of psychoactive substances by the monkey: a measure of psychological dependence. *Psychopharmacologia* **16:** 30–48, 1969.
12. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement.* New York: Appleton-Century-Crofts, 1957.
13. Gerber, G. J. and R. Stretch. Drug-induced reinstatement of extinguished self-administration behavior in monkeys. *Pharmac. Biochem. Behav.* **3:** 1055–1061, 1975.
14. Goldstein, A., L. Aronow and S. M. Kalman. *Principles of Drug Action: The Basis of Pharmacology,* 2nd ed., New York: Wiley, 1974, pp. 569–621.
15. Goldstein, A. and P. Sheehan. Tolerance to opioid narcotics. I. Tolerance to the "running fit" caused by levorphanol in the mouse. *J. Pharmac. exp. Ther.* **169:** 175–184, 1969.
16. Heifetz, S. A. and D. E. McMillan. Development of behavioral tolerance to morphine and methadone using the schedule-controlled behavior of the pigeon. *Psychopharmacologia* **19:** 40–52, 1971.
17. Herling, S., E. H. Coale, Jr., R. J. Valentino, D. W. Hein and J. H. Woods. Narcotic discrimination in pigeons. *J. Pharmac. exp. Ther.* **214:** 139–146, 1980.
18. Herling, S. and J. H. Woods. Discriminative stimulus effects of etorphine in the rhesus monkey. *Psychopharmacology* **72:** 265–267, 1981.

19. Hill, H. E., B. E. Jones and E. C. Bell. State dependent control of discrimination by morphine and pentobarbital. *Psychopharmacologia* **22:** 305–313, 1971.
20. Hirschhorn, I. D. and J. A. Rosecrans. Morphine and Δ^9-tetrahydrocannabinol: tolerance to the stimulus effects. *Psychopharmacologia* **36:** 243–253, 1974.
21. Jaffe, J. H. Drug addiction and drug abuse. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 6th ed., edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: MacMillan, 1980, pp. 535–584.
22. Jarbe, T. U. C. Discriminative effects of morphine in the pigeon. *Pharmac. Biochem. Behav.* **9:** 411–416, 1978.
23. Jarbe, T. U. C. and B. Holmgren. Discriminative properties of pentobarbital after repeated noncontingent exposure in gerbils. *Psychopharmacology* **53:** 39–44, 1977.
24. Jarbe, T. U. C. and C. Rollenhagen. Morphine as a discriminative cue in gerbils: drug generalization and antagonism. *Psychopharmacology* **58:** 271–275, 1978.
25. Kuhn, D. M., J. B. Appel and I. Greenberg. An analysis of some discriminative properties of *d*-amphetamine. *Psychopharmacologia* **39:** 57–66, 1974.
26. Martin, W. R. and H. F. Fraser. A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts. *J. Pharmac. exp. Ther.* **133:** 388–399, 1961.
27. McMillan, D. E. and W. H. Morse. Some effects of morphine and morphine antagonists on schedule-controlled behavior. *J. Pharmac. exp. Ther.* **157:** 175–184, 1967.
28. Miksic, S. and H. Lal. Tolerance to morphine-produced discriminative stimuli and analgesia. *Psychopharmacology* **54:** 217–221, 1977.
29. Mushlin, B. E., R. Grell and J. Cochin. Studies on tolerance. 1. The role of the interval between doses on the development of tolerance to morphine. *J. Pharmac. exp. Ther.* **196:** 280–287, 1976.
30. Overton, D. A. Drug discrimination with progressively lowered doses. *Science* **205:** 720–721, 1979.
31. Overton, D. A. and S. K. Batta. Investigation of narcotics and antitussives using drug discrimination techniques. *J. Pharmac. exp. Ther.* **211:** 401–408, 1979.
32. Schaefer, G. J. and S. G. Holtzman. Discriminative effects of morphine in the squirrel monkey. *J. Pharmac. exp. Ther.* **201:** 67–75, 1977.
33. Schmidt, C. F. and A. E. Livingston. The relation of dosage to the development of tolerance to morphine in dogs. *J. Pharmac. exp. Ther.* **47:** 443–471, 1933.
34. Shannon, H. E. and S. G. Holtzman. Evaluation of the discriminative effects of morphine in the rat. *J. Pharmac. exp. Ther.* **198:** 54–65, 1976.
35. Shannon, H. E. and S. G. Holtzman. Morphine training dose: a determinant of stimulus generalization to narcotic antagonists in the rat. *Psychopharmacology* **61:** 239–244, 1979.
36. Smith, S. G. and W. M. Davis. Behavioral control by stimuli associated with acquisition of morphine self-administration. *Behav. Biol.* **9:** 777–780, 1973.
37. Smith, S. G., T. E. Werner and W. M. Davis. Effects of tolerance on intravenous morphine self-administration behavior. *Physiol. Psychol.* **4:** 97–98, 1976.
38. Teal, J. J. and S. G. Holtzman. Stimulus effects of morphine in the monkey: quantitative analysis of antagonism. *Pharmac. Biochem. Behav.* **12:** 587–593, 1980.
39. Winter, J. C. The stimulus properties of morphine and ethanol. *Psychopharmacologia* **44:** 209–214, 1975.
40. Witkin, J. M., R. B. Carter and L. A. Dykstra. Discriminative stimulus properties of *d*-amphetamine-pentobarbital combinations. *Psychopharmacology* **68:** 269–276, 1980.
41. York, J. L. and J. C. Winter. Assessment of tolerance to barbital by means of drug discrimination procedures. *Psychopharmacologia* **42:** 283–287, 1975.