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Acute Sensitization to Opioid Antagonists

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WHITE-GBADEBO, D. AND S. G. HOLTZMAN. *Acute sensitization to opioid antagonists.* PHARMACOL BIOCHEM BEHAV **47**(3) 559-566, 1994.—Acute morphine pretreatment sensitizes rats to the response rate-decreasing effects of opioid antagonists naloxone and naltrexone. The effect appears to be mu-opioid receptor specific, as pretreatment with non-mu-selective opioid agonists results in less pronounced sensitization. In the present study, food-deprived rats were trained to respond for food reinforcement on a FI 3-min schedule (9.5 min) with multiple trials. Doses of opioid antagonists were administered cumulatively before each trial of a session following 4-h pretreatment with either vehicle or morphine (3.0 mg/kg). Morphine pretreatment sensitized rats to naltrexone, lowering its ED_{50} from 20 to 0.03 mg/kg. It also sensitized rats to naloxone and to diprenorphine, another pure antagonist. Morphine-induced sensitization was stereoselective among the optical isomers of the benzomorphans, cyclazocine, pentazocine, and *N*-allylnormetzocine. In addition, acute morphine pretreatment resulted in sensitization to the mixed agonist/antagonist nalorphine, but not to buprenorphine or nalbuphine. The results extend previous findings concerning the importance of the mu-opioid receptor in the development of sensitization to opioid antagonists.

Morphine Naltrexone Sensitization Operant behavior Opioid antagonists

SPECIFIC opioid antagonists produce relatively few effects in otherwise drug-free subjects at doses that antagonize the acute effects of opioid agonists, but can produce behavioral effects of their own at much higher doses (5,27,38). Chronic morphine treatment increases sensitivity to the actions of opioid antagonists, such as naloxone and naltrexone. Most of the effects resulting from administration of naloxone or naltrexone in a morphine-dependent animal are thought to be related to the precipitation of opioid withdrawal (6,12,39,40). Consequently, sensitivity to naltrexone is a commonly used measure of physical dependence. Animals treated with naloxone following a single dose of morphine also show effects characteristic of opiate withdrawal, for example, jumping in mice (19, 31), wet dog shakes in gerbils (31), loss of body weights, increases in plasma corticosterone and jumping in rats (9,23, 31). The increased potency of antagonists following morphine pretreatment was suggested by Tulunay and Takemori (37) to be a sensitive indicator of the development of tolerance to narcotic analgesics. The enhanced sensitivity to naltrexone following a single dose of morphine has been termed acute sensitization (2) and it is thought to reflect the initial changes occurring in the opioid system in the development of physical dependence.

The opioid antagonists naloxone and naltrexone have a rate-reducing effect on food-reinforced operant responding in naive rats (22,43). Following acute morphine pretreatment, rats are sensitized to the effects of these opioid antagonists as evidenced by a leftward shift in their dose-response curves. Operant responding is considered a sensitive measure for detecting withdrawal changes (4,13,17), and the naltrexone-induced reduction in response rate that occurs following a single dose of morphine provides a reliable and quantitative measure of these changes.

The pharmacological specificity for the appearance of acute sensitization has been examined by comparing the potency of naltrexone in decreasing food-reinforced responding following pretreatment with various opioid agonists (2). All the opioid agonists tested were effective in producing, in varying degrees, acute sensitization to naltrexone. The nonopioids dextrorphan and pentobarbital were ineffective. Pretreatment with kappa-opioid agonists induced substantially less sensitization to naltrexone than did pretreatment with mu-opioid agonists. Although peripheral administration of a single dose of morphine or the mu-opioid agonists levorphanol, fentanyl, or methadone induced a 100–250-fold increase in the sensitization to naltrexone, acute pretreatment with the kappa-opioid agonists U-50,488 or ethylketocyclazocine induced a 10-fold sensitization. Therefore, the elicited sensitization to the rate-decreasing effect of naltrexone is pronounced following pretreatment with opioid drugs that activate mu-opioid receptors.

Central administration of morphine and opioid peptides led to results that were consistent with those obtained follow-

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ing systemic administration of opioid alkaloids (3). Therefore, evidence indicates that the acute sensitization to naltrexone is mu-opioid selective and centrally mediated. The pharmacological characteristics of acute agonist-induced sensitization to naltrexone appear to be entirely consistent with the pharmacological characteristics of tolerance and dependence that are produced by chronic administration of mu-opioid agonists (2).

In the aforementioned studies, the agonist used for pretreatment was varied and the antagonist (i.e., naltrexone) was held constant. In an effort to examine further the pharmacological specificity of this effect, in the present study pretreatment with morphine was held constant and various opioid antagonists were tested for changes in sensitivity. We tested representative nonselective pure antagonists (naloxone, diprenorphine), and mixed agonists/antagonists (nalorphine, nalbuphine, and buprenorphine). In addition, we were interested in testing pairs of optical isomers, such as the enantiomers of cyclazocine, where the levorotary member is a mixed agonist/antagonist opioid and the dextrorotary member lacks significant opioid activity. The results will help to define the pharmacological properties of opioid antagonists that are required for demonstrating acute agonist-induced sensitization.

METHOD

Subjects

Male Sprague–Dawley rats weighing 250 to 275 g upon arrival from the breeder (Charles River, Raleigh, NC) were food deprived to approximately 80% of their free-feeding weights. Weights were maintained through restricted feeding of rat chow (Purina Mills, St. Louis, MO) and water was available continuously in the home cage. Rats were housed singly in a temperature-controlled room with a 12 L : 12 D cycle.

Apparatus

Experiments were conducted in standard operant chambers (24 × 30 × 33 cm; Coulbourn Instruments, Lehigh Valley, PA) each housed in a ventilated, sound-attenuating cubicle. Chambers were equipped with a single lever, food receptacle, and house light located on one wall. Session events and data collection were controlled via a computer program (MED Associates, Inc., East Fairfield, VT) run on a desktop microcomputer.

Training

Training and testing were based on procedures used by Adams and Holtzman (2,3). In summary, rats were shaped to press the lever for food reinforcement (45-mg pellet; Bioserv Inc., Frenchtown, NJ) on a fixed-interval 3-min schedule (with a 10-s limited hold). The schedule delivers food reinforcement following the first response after a 3-min time period has elapsed. Once the time period has elapsed, the animal has 10 s to respond or that opportunity for food is lost and the next interval begins. Once animals responded reliably, the multiple trial training was started. Response periods of three fixed-intervals (with 10-s limited hold) were preceded by time-out periods that were increased gradually up to 10 minutes. During the time-out, the house light was off and responses had no programmed consequences. Commencement of the response periods was signalled with the illumination of the house light and a food pellet that was delivered automatically at the start of the trial. Rats were run 6 days per week for two to seven trials, one trial consisting of both a time-out and a response period.

Testing

Animals were tested once a week with the test drug following saline or morphine pretreatment. Although the same rats were used to generate dose–response curves for the test drug following both saline and morphine pretreatment, individual rats did not receive every test drug. Rats were weighed and injected SC with either 3.0 mg/kg of morphine or saline. Four hours later, they were tested with a drug, usually an antagonist, using a cumulative dosing procedure so that an entire dose–effect curve could be generated in a single test session. Saline was administered prior to the first trial with doses of the test drug preceding the following trials. Cumulative dosing continued until response rates decreased to less than 10% of control. Testing was terminated if response rates were below 10% of control for two consecutive trials or after seven trials were completed.

Sensitivity to naltrexone administered in cumulative doses served as the standard for comparison. Rats were retested with naltrexone periodically (following three or four test drug–response determinations) to ensure that their sensitivity was not changing over time.

Drugs

Naltrexone hydrochloride, naloxone hydrochloride (Sigma Chemical Co., St. Louis, MO), morphine sulfate (Penick Co., Newark, NJ), (−)- and (+)-*N*-allynormetazocine hydrochloride [(−)- and (+)-NANM] [National Institute on Drug Abuse, Rockville, MD (NIDA)], and nalbuphine hydrochloride (Dupont-Merck Pharmaceuticals, Wilmington, DE) were dissolved in 0.9% saline. Nalorphine hydrochloride (Merck Sharpe & Dohme, West Point, PA), diprenorphine hydrochloride (NIDA), and (−)- and (+)-pentazocine succinate (NIDA) were dissolved in distilled water. (−)- and (+)-Cyclazocine were dissolved in 3 parts of 8.5% lactic acid and 2 parts of 1.0 N sodium hydroxide. All doses are reported as the free base.

Data Analysis

Control data were obtained by averaging response rates over trials conducted on noninjection days preceding the test day. Test drug ED_{50} values were calculated for each subject by linear regression. Potency ratios were calculated by dividing the ED_{50}/ value obtained following saline pretreatment by the ED_{50} value obtained following morphine pretreatment. Paired *t*-tests were used to compare ED_{50} values for each test drug after saline pretreatment and after morphine pretreatment. In cases where assumptions of normality underlying the *t*-test were violated (unequal standard deviations), paired Wilcoxon signed rank tests were used.

RESULTS

Response rates averaged 28.55 responses per minute (range, 9.98–86.5) for the 12 rats used in this study. Rates were not affected when injections of saline, rather than naltrexone, preceded each trial ($p = 0.4015$, one-way ANOVA; data not shown).

Sensitization to Naltrexone

As previously shown, naltrexone produced dose-related decreases in response rates. Following saline pretreatment, doses

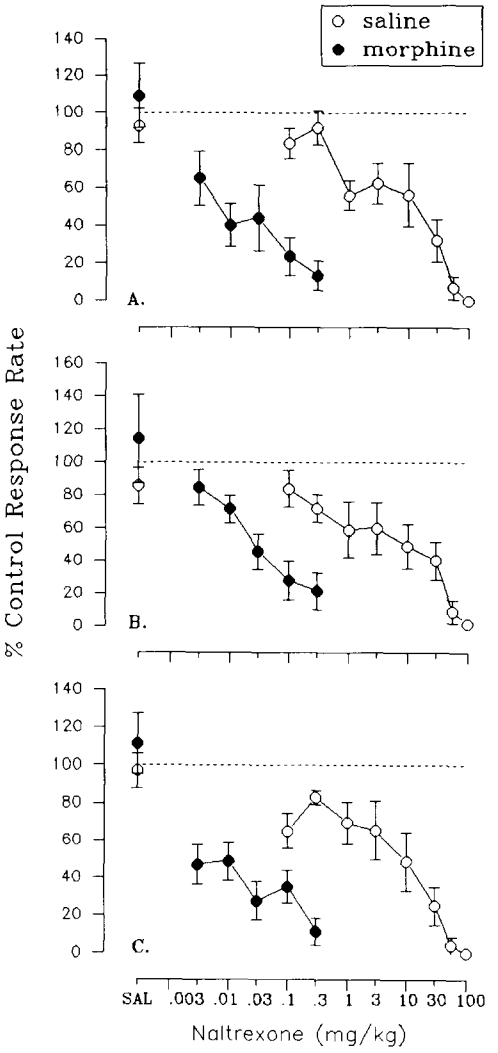

FIG. 1. Reproducibility to the effects of 4-h pretreatment with 3.0 mg/kg morphine on rate-decreasing effects of naltrexone. Doses of naltrexone were administered cumulatively following pretreatment with either saline or morphine. Points represent mean of 11 or 12 animals, vertical bars represent the SE. Points above S (saline) represent percentage of control response rate before the first naltrexone dose was administered. (A) Original determination of dose-response curve, (B) second determination following tests of three to four drugs, (C) third and final determination following tests of three to four more drugs.

of 56 to 100 mg/kg of naltrexone were necessary to reduce responding to 10% of control or less (Fig. 1). Morphine at 3.0 mg/kg did not affect rates after the pretreatment period; however, this dose increased sensitivity to naltrexone and produced a leftward shift in the dose-response curve (Fig. 1). Redeterminations of the naltrexone dose-response curve at intervals of approximately 8–10 weeks revealed consistent sensitivity to naltrexone over the course of the study (Fig. 1A, B, C). Pretreatment with morphine (3.0 mg/kg) consistently produced an approximate 650-fold shift in sensitivity to naltrexone at each determination (Table 1). The first determination resulting in a 687-fold increase in the sensitivity to naltrexone ($W = 45$, $p = 0.0039$), the second determination resulted in a 637-fold increase in sensitivity ($W = 55$, $p = 0.0020$), and the third resulted in a 653-fold increase in sensitivity ($W = 55$, $p = 0.0005$).

Sensitization to Pure Antagonists

Morphine induced a 75-fold shift in the naloxone dose-response curve ($W = 21$, $p = 0.0313$) (Fig. 2A), and a 62-fold shift in the diprenorphine dose-response curve ($W = 15$, $p = 0.0313$) (Fig. 2B). The magnitude of sensitization to naloxone and diprenorphine was much lower than naltrexone, and the actual potencies of naloxone and naltrexone postmorphine were similar (ED_{50}s = 0.022 mg/kg and 0.03 mg/kg, respectively).

Sensitization to Mixed Agonists/Antagonists

Rats were not sensitized to either nalbuphine or buprenorphine following morphine pretreatment. Doses up to 10 mg/kg of nalbuphine did not cause a decrease in response rates, and a 4-h pretreatment with 3.0 mg/kg morphine had no effect on this (Fig. 3A). Administration of buprenorphine caused a dose-related decrease in response rates; however, morphine pretreatment was not effective in enhancing sensitivity to its rate-reducing effects (Fig. 3B).

Morphine induced a significant increase in sensitivity to nalorphine ($W = 15$, $p = 0.0313$) (Fig. 3C).

Sensitization to Optical Isomers

Morphine caused a 33-fold increase in the sensitivity to (−)-cyclazocine ($W = 15$, $p = 0.0313$) (Fig. 4A). The ED_{50} values of (+)-cyclazocine were higher than the doses tested and, therefore, no determination of sensitivity to this drug could be made (Fig. 4B). A 2-fold increase in sensitivity to (−)-NANM, $t(3) = 4.14$, $p = 0.0256$, occurred following pretreatment with morphine (Fig. 4C). This represents a significant leftward shift of the dose-response curve for (−)-NANM; however, no significant shift occurred for (+)-NANM (Fig. 4D). Sensitivity to (−)-pentazocine was unaffected by morphine pretreatment (Fig. 4E) as was that to (+)-pentazocine (Fig. 4F).

For each of the drugs, the levorotary isomer was much more potent in decreasing response rates than was its dextrorotary isomer. At a dose two orders of magnitude higher than the ED_{50} of its levorotary isomers, (+)-cyclazocine was ineffective at reducing response rates following saline pretreatment. It was ineffective at reducing response rates following morphine pretreatment only at doses at least three orders of magnitude higher than (−)-cyclazocine. For (+)-NANM, the ED_{50} value for decreasing response rates was higher than the doses tested (>10 mg/kg) and for the (−) isomer, a dose at least three times lower was effective in reducing response rates. (+)-Pentazocine was approximately four times less potent in reducing response rates following saline pretreatment than was its levorotary isomer. (−)-Cyclazocine was much more potent than either (−)-pentazocine or (−)-NANM in reducing response rates following either saline or morphine pretreatment.

Sensitization to Morphine

No significant shift was seen in the rate-reducing effect of morphine following morphine pretreatment, $t(7) = 1.56$, $p = 0.1619$ (Fig. 5).

TABLE 1

ED_{50} VALUES (mg/kg) AND CONFIDENCE INTERVALS FOR DRUGS TESTED 4 h FOLLOWING A SINGLE INJECTIONS OF EITHER SALINE (s) OR 3.0 mg/kg MORPHINE (m)

Test Drug		ED_{50} values		Potency Ratio
Naltrexone (1)	(s)	19.23	(2.65 -139.42)	687
	(m)	0.028*	(0.009- 0.082)	
Naltrexone (2)	(s)	21.67	(3.60 -130.45)	637
	(m)	0.034*	(0.01 - 0.85)	
Naltrexone (3)	(s)	21.55	(3.14 -148.06)	653
	(m)	0.033*	(0.01 - 0.10)	
Naloxone	(s)	1.64	(0.54 - 5.0)	75
	(m)	0.022*	(0.0 - 0.07)	
Diprenorphine	(s)	15.15	(7.90 - 29.02)	62
	(m)	0.243*	(0.10 - 0.62)	
Nalorphine	(s)	5.26	(1.22 - 22.69)	12
	(m)	0.42†	(0.05 - 3.26)	
Buprenorphine	(s)	0.072	(0.01 - 0.43)	1.09
	(m)	0.066	(0.01 - 0.29)	
Nalbuphine	higher than doses tested			
(−)-Cyclazocine	(s)	0.068	(0.02 - 0.27)	34
	(m)	0.002†	(0.0 - 0.02)	
(+)-Cyclazocine	higher than doses tested			
(−)-Pentazocine	(s)	4.35	(2.85 - 6.65)	1.23
	(m)	3.55	(2.29 - 5.49)	
(+)-Pentazocine	(s)	15.88	(6.25 - 40.38)	2.10
	(m)	7.57	(4.48 - 12.79)	
(−)-NANM	(s)	2.94	(2.51 - 3.44)	2.23
	(m)	1.32†	(0.14 - 12.80)	
(+)-NANM	(s)	higher than doses tested		
	(m)	9.20	(2.49 - 34.0)	
Morphine	(s)	4.34	(3.32 - 5.68)	1.63
	(m)	2.63	(1.77 - 3.89)	

(1), first determination; (2), second determination; (3), third determination.
*$p < 0.01$ compared to corresponding saline pretreatment.
†$p < 0.05$ compared to corresponding saline pretreatment.

DISCUSSION

The ratios of corresponding ED_{50} values for antagonists following saline and morphine pretreatment replicate several reports showing that pronounced sensitization is induced to pure antagonists following acute as well as chronic morphine pretreatment (2,10,20,25,26). The determinations of sensitivity to naltrexone after saline and morphine pretreatment were done at intervals of approximately 2–2.5 months. The degree of sensitization to naltrexone remained stable throughout the course of the present study (approximately 5 months), allowing for a reliable comparison of the drugs tested.

Morphine appeared to sensitize rats to the rate-decreasing effects of naltrexone to a much greater degree than to any of the other pure antagonists studied. Although morphine consistently induced an approximately 650-fold sensitization to naltrexone, sensitization to the rate-decreasing effects of both naloxone and diprenorphine were less than 100-fold. This result may in part be due to the unusually low ED_{50} value obtained for naloxone following saline pretreatment (1.64 mg/kg). As mentioned previously, the absolute ED_{50} values were similar for both naltrexone and naloxone following morphine pretreatment. Naloxone and naltrexone have a higher affinity for the mu-opioid receptor than they do for other opioid receptor subtypes (21,41), consistent with the conclusion that the appearance of acute sensitization is a mu receptor-mediated effect.

A significant degree of sensitization occurred to the levorotary, but not dextrorotary, optical isomers of the mixed agonists/antagonists, cyclazocine and NANM, which also occurs following chronic morphine treatment (8). (−)-Cyclazocine and (−)-NANM have agonist activity at kappa and phencyclidine receptors, and have been shown to have partial mu agonist activity (16,29). In the present study, a significant but relatively small degree of sensitization occurred to (−)-NANM following morphine pretreatment, providing further evidence that (−)-NANM has more moderate antagonist activity at the mu-opioid receptors than does (−)-cyclazocine. Although no sensitization occurred to (−)-pentazocine, the rats were 33-fold more sensitive to (−)-cyclazocine following acute morphine pretreatment. The lack of sensitization to (−)-pentazocine may be due to the relatively greater agonist

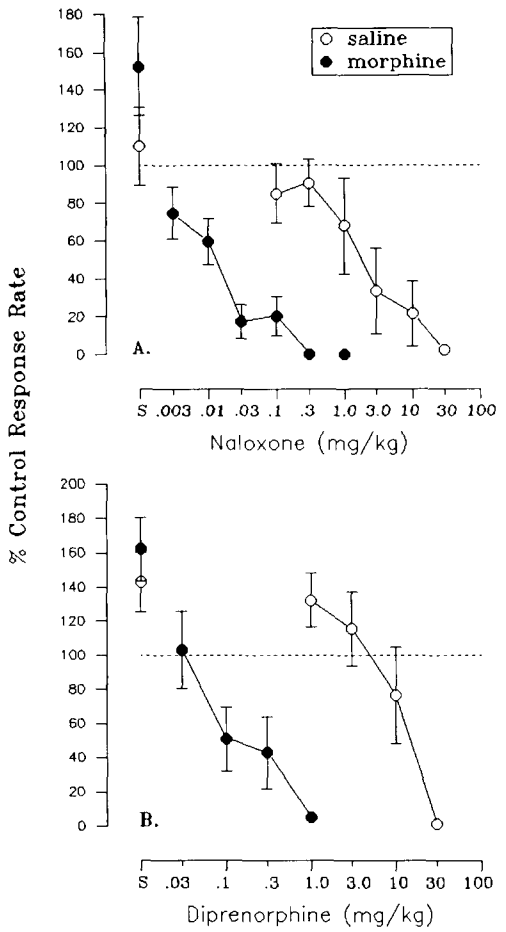

FIG. 2. Four-hour pretreatment with 3.0 mg/kg of morphine sensitizes rats to the response rate-decreasing effects of naloxone (A) and diprenorphine (B). Each point is a mean ± SEM; n = 6. Other details as in Fig. 1.

efficacy of pentazocine, or the rate-decreasing effects of pentazocine are due to actions at other receptor types (29).

The lack of sensitization to the dextrorotary isomers of benzomorphan opioids indicates that sensitization induced by acute morphine pretreatment is stereospecific, consistent with mu-opioid receptor mediation. Naloxone and naltrexone are ineffective in attenuating changes in schedule-controlled behavior induced by the (+)-isomers of the benzomorphans (14,18). The dextrorotary isomers of cyclazocine, pentazocine, and NANM fail to generalize to morphine in drug discrimination procedures (29) and, except for pentazocine, generalize to phencyclidine (15,34,36). The lack of increased sensitivity to these compounds following acute morphine pretreatment indicates the pharmacological specificity of this procedure for stereoisomers on the basis of their relative affinities for the mu-opioid receptor.

The (−)-isomers of benzomorphan derivatives were more potent in decreasing response rates than were their (+)-isomers, a finding in accord with results of previous studies (18,30,33). (−)-Cyclazocine was at least 150 times more potent than (+)-cyclazocine in reducing response rates. Both (−)-NANM and (−)-pentazocine were roughly four times as potent as their respective dextrorotary isomers in reducing response rates to 50% of control values. The levorotary isomers of the benzomorphans are generally more potent than the dextrorotary isomers in other assays of opioid activity in numerous species (1,28,30).

Nalbuphine, a partial mu/kappa agonist that reportedly has fewer behavioral or psychomimetic-like effects in rats than does nalorphine or pentazocine (32), did not reduce response rates in doses up to 10 mg/kg, either with or without morphine pretreatment. Therefore, it is difficult to draw conclusions on the basis of the current data. Sensitivity to nalbuphine was found to be unaffected by either acute or chronic morphine

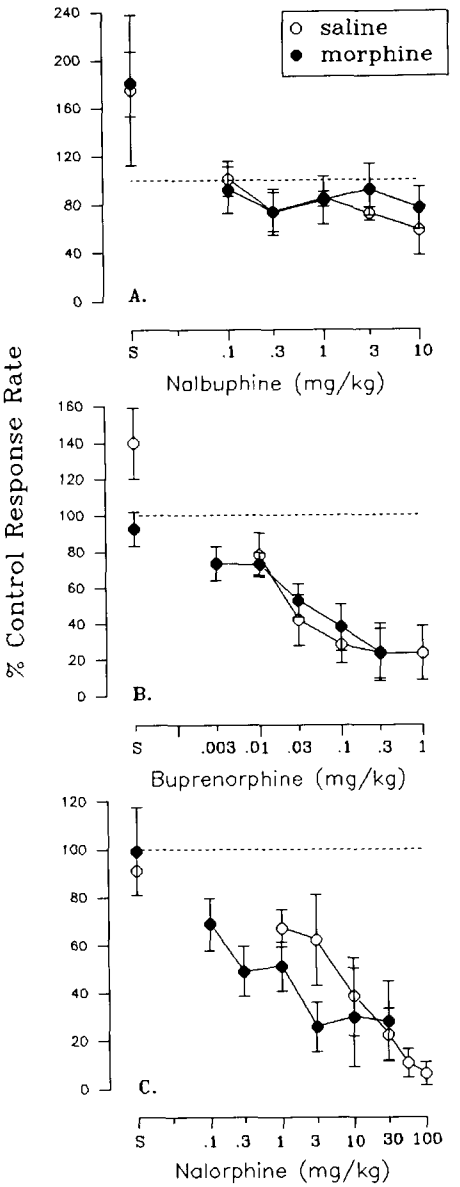

FIG. 3. Effects of 4-h pretreatment with 3.0 mg/kg of morphine on the rate-decreasing effects of the mixed agonist/antagonist opioids nalbuphine (A), buprenorphine (B), and nalorphine (C). Each point is a mean ± SEM; n = 5-6.

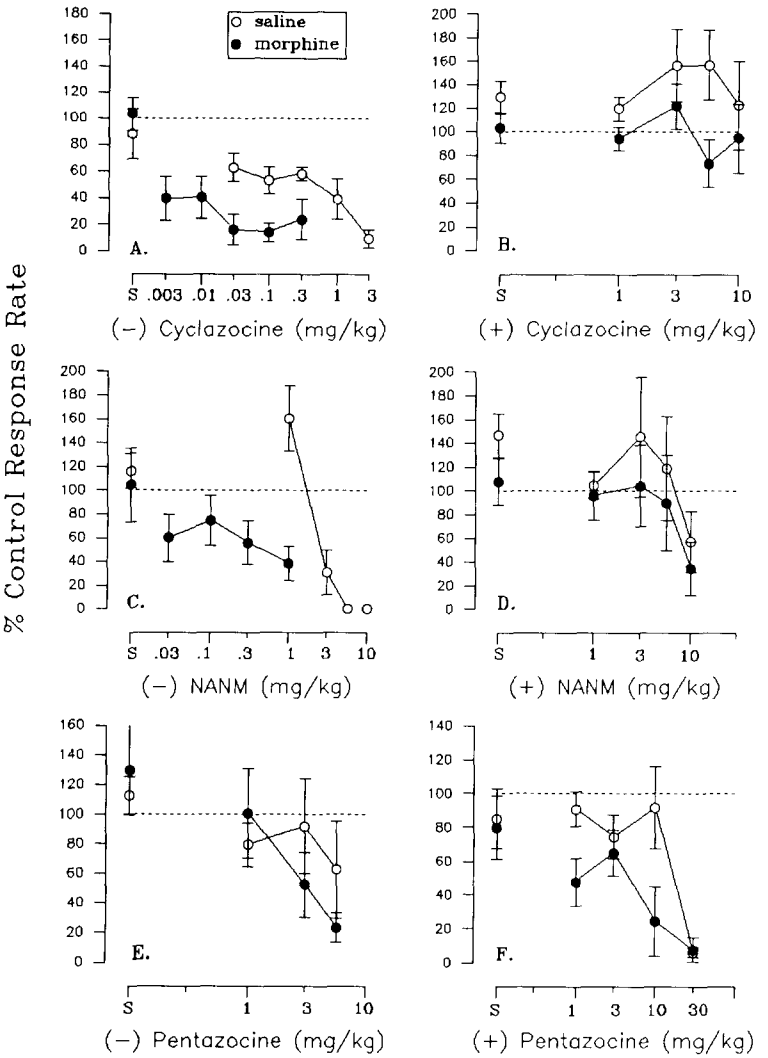

FIG. 4. Effects of 4-h pretreatment with morphine on the response rate-decreasing effects of the optical isomers of the benzomorphan derivatives cyclazocine (A, B), NANM (C, D) and pentazocine (E, F). Each point is a mean ± SEM; $n = 6$.

pretreatment in a study by Oliveto et al. (26). Nalbuphine also failed to occasion naltrexone-appropriate responding in morphine-treated rhesus monkeys discriminating between injections of saline and naltrexone (11). Additional evidence indicates that nalbuphine has moderate mu-opioid agonist activity. Drug discrimination studies show that nalbuphine fully generalizes to a low training dose of morphine while antagonizing generalization to a higher training dose (42). Taken together, these results indicate that nalbuphine has moderate intrinsic efficacy at the mu-opioid receptor.

Nalorphine is a partial mu agonist/kappa agonist (7,16). Morphine pretreatment resulted in a significant sensitization to nalorphine, providing further evidence that nalorphine acts as a mixed agonist/antagonist with weak activity at the mu-opioid receptor. In a drug discrimination study (42), nalorphine generalized to a low training dose of morphine and antagonized the stimulus effects of a higher training dose, indicating that nalorphine has low efficacy at the mu-opioid receptor compared to that of morphine and nalbuphine (42). Sensitization occurred to the rate-reducing effects of nalorphine in rats following chronic but not acute morphine pretreatment (26), suggesting that the antagonist effects of mixed-agonist/antagonist compounds are not reliably demonstrated by acute morphine pretreatment.

Although we examined many of the same mixed-action compounds that were studied by Oliveto et al. (26), there appear to be several divergent results. In our study, rats were sensitized to nalorphine following acute morphine pretreatment whereas a trend towards *tolerance* was seen in the study by Oliveto et al. (26). The absolute ED_{50} values for naltrexone after saline pretreatment were similar in both studies. However, acute morphine pretreatment resulted in naltrexone ED_{50} values of at least an order of magnitude lower in our study than in the one by Oliveto et al. (26). In addition, morphine pretreatment induced a greater degree of sensitivity to diprenorphine than to either naltrexone or naloxone in the study by

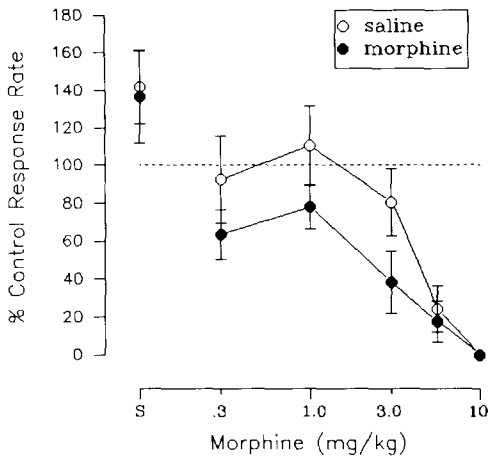

FIG. 5. Four-hour pretreatment with morphine does not affect the response rate-decreasing effects of morphine. Each point is a mean ± SEM; $n = 8$.

Oliveto et al. (26), but resulted in less sensitization to diprenorphine than to naloxone and naltrexone in the current study. It is not clear what factor or factors may account for these differences between the studies. However, there were several procedural differences between the two studies that may have contributed to the differences observed: schedule of reinforcement (FR30 vs. FI 3-min), morphine pretreatment dose (5.6 vs. 3.0 mg/kg), pretreatment interval (5–6 h vs. 4 h), and strain of rat (Long-Evans hooded vs. Sprague-Dawley). Similar to the study by Oliveto et al. (26), acute morphine pretreatment produced neither sensitization nor tolerance to morphine. The similarities and apparent discrepancies between the studies indicate the importance of comparing a full series of drugs within the same study.

Sensitivity to buprenorphine, a mu/kappa antagonist with a higher intrinsic efficacy for the mu-opioid receptor than either (−)-pentazocine, (−)-NANM, or (−)-cyclazocine (24), was unaffected by morphine pretreatment under the current conditions. Rats develop a large degree of cross-tolerance to buprenorphine's rate-decreasing effects following chronic morphine administration, and buprenorphine substitutes for high training doses of morphine, indicating that it has low to moderate mu-opioid agonist activity (24,35). Conditions under which the antagonist activity of buprenorphine can be elicited are therefore limited by the relative efficacy requirements of the task.

We have shown that among the antagonists currently tested, sensitization induced by acute morphine administration is greatest for those antagonists with high affinity and no intrinsic activity at the mu-opioid receptor, such as naloxone and naltrexone. In addition, acute sensitization appears to be stereoselective and greatest for those compounds whose rate-reducing effects are mediated by mu-opioid receptors. The present results give additional evidence of the importance of the mu-opioid receptor in acute agonist-induced sensitization (2,3) and extend observations to additional opioid antagonists.

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