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The Effects of Chronic Morphine on the Generalization of Buprenorphine Stimulus Control: An Assessment of Kappa Antagonist Activity

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RILEY, A. L. AND S. POURNAGHASH. *The effects of chronic morphine on the generalization of buprenorphine stimulus control: An assessment of kappa antagonist activity.* PHARMACOL BIOCHEM BEHAV **52**(4) 779–787, 1995. – Rats trained to discriminate the mixed mu agonist/kappa antagonist buprenorphine from its vehicle generalize buprenorphine control to morphine. Buprenorphine, however, does not generalize to MR2266. The generalization to morphine suggests that buprenorphine's mu agonist properties mediated in part its discriminative control. The failure to generalize to MR2266, a compound reported to block kappa-mediated effects, however, suggests that its kappa antagonist activity was not involved in its discriminative effects. The ability of buprenorphine's mu (but not kappa) activity to establish stimulus control may be a function of the overshadowing of the kappa properties of buprenorphine by its concurrent mu activity. To test this possibility, in the present experiment rats were chronically exposed to morphine prior to buprenorphine discrimination training. This procedure has been reported to result in tolerance to buprenorphine's mu agonist effects and a more pronounced display of its kappa antagonist properties. The rats were then tested for the generalization of buprenorphine control to morphine, MR2266, and pentobarbital. As expected, buprenorphine failed to generalize to the nonopioid pentobarbital. Although subjects were tolerant to morphine (as evidenced by reductions in morphine-induced behavioral effects and a rightward shift in the doses of morphine substituting for buprenorphine), buprenorphine still failed to generalize to MR2266. The failure of buprenorphine to generalize to MR2266 under conditions that should have allowed for the development of stimulus control by buprenorphine's kappa antagonist activity was discussed in terms of the general inability of kappa antagonist activity to support discrimination learning.

Buprenorphine Drug discrimination learning Conditioned taste aversions Morphine tolerance MR2266

THE MIXED mu agonist/kappa antagonist buprenorphine hydrochloride [see (3,9,23–25,41)] has been reported to substitute for morphine in animals trained to discriminate morphine from its vehicle within the drug discrimination procedure [for reviews, see (19,42,52); for a bibliography, see (44)]. For example, in the initial assessment of the discriminative stimulus properties of buprenorphine Shannon, Cone, and Gorodetzky (46) demonstrated that buprenorphine (0.003–3 mg/kg) substituted for morphine in rats trained to discriminate 3 mg/kg of morphine from saline in a two-choice, shock-avoidance procedure. Other reports of the generalization of morphine stimulus control to buprenorphine have been made for a variety of species under a range of experimental procedures (13, 14,33,39,56,57). Given that both morphine and buprenorphine have mu agonist properties, it is possible that this substitution is based on their common actions at this specific receptor subtype.

Consistent with these reported generalization patterns when morphine is the training drug, Pournaghash and Riley (38) recently demonstrated that animals trained to discriminate buprenorphine (0.56 mg/kg) from its vehicle within the taste aversion baseline of drug discrimination learning [see (26,28,29,42,43)] generalized buprenorphine control to the mu agonist morphine. Buprenorphine, however, did not general-

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ize to MR2266. Although MR2266 binds to mu, delta, and kappa subtypes of the opiate receptor [for relative binding affinities of MR2266 to different opioid receptor subtypes, see (8,27,55)], it has been reported to block the effects of a range of kappa agonists [see (1,6,22,35,40,54)]. Thus, in this preparation, the mu agonist (and not kappa antagonist) activity of buprenorphine appeared to mediate buprenorphine's stimulus effects.

One possible basis for the failure of the kappa antagonist activity of buprenorphine to establish stimulus control is that its mu agonist activity overshadowed or masked its kappa antagonist activity during the acquisition of the drug discrimination. Accordingly, only its mu agonist activity mediated the discrimination, a selectivity reflected in the subsequent generalization to compounds with mu agonist (but not kappa antagonist) effects. Such a possibility has recently been supported by Negus and his colleagues (33) in an assessment of the effects of buprenorphine on morphine- and bremazocine-induced suppression of schedule-controlled responding. Specifically, buprenorphine did not antagonize the suppression of responding produced by the kappa agonist bremazocine. Negus et al. argued that this failure was due to the fact that in opiate-naive subjects, buprenorphine alone suppressed responding (in a manner similar to that produced by morphine and bremazocine). That is, the kappa antagonist effects of buprenorphine on bremazocine's suppression of scheduled-controlled responding would not be evident because of the suppressive effects that buprenorphine itself has on such responding. According to the authors, the buprenorphine-induced suppression of responding was a function of buprenorphine's mu agonist properties, a position supported by the fact that when the animals were given chronic morphine exposure and rendered tolerant to morphine, neither morphine nor buprenorphine suppressed operant responding, although the kappa agonist bremazocine continued to so. In these tolerant subjects, buprenorphine now antagonized bremazocine's effects, i.e., the kappa antagonist properties of buprenorphine were now evident. Negus et al. suggested that because in opiate-naive subjects the mu activity of buprenorphine produced effects similar to that of the kappa agonist bremazocine, it was impossible to see buprenorphine's kappa antagonist properties. Such antagonism was only evident in tolerant subjects [see also (41)].

The possibility that the mu agonist properties of buprenorphine may mask the display of its kappa antagonist activity has also been supported in work assessing the antagonism by buprenorphine of bremazocine-induced effects in animals pretreated with the highly selective mu antagonist beta-funaltrexamine (b-FNA) (24,25). In these preparations, the antidiuretic and antinociceptive effects of the kappa agonist bremazocine were unaffected by the concurrent administration of buprenorphine, a failure possibly due to the fact that buprenorphine alone produced similar analgesic and antidiuretic effects (via its agonist activity at the mu receptor; see below). Interestingly, when b-FNA was given prior to the concurrent administration of buprenorphine and bremazocine, buprenorphine antagonized bremazocine's behavioral effects. By blocking buprenorphine's mu agonist effects (with b-FNA), the kappa antagonist properties of buprenorphine were displayed.

In relation to the failure of buprenorphine to generalize stimulus control to MR2266, it is possible that the mu activity of buprenorphine was sufficiently salient that it predominantly contributed to the discriminative effects of buprenorphine. That is, the stimulus effects produced by its kappa antagonist activity were overshadowed or masked by its mu agonist properties. In the absence of establishing discriminative control to buprenorphine's kappa antagonist activity, generalization to compounds that block kappa receptors (e.g., MR2266) would not be expected. If this is true, it may be possible to demonstrate such generalization in animals tolerant to morphine and for which the mu agonist properties had been made less salient. This specific prediction was tested in the following experiment in which subjects given chronic exposure to morphine (17 consecutive days) were trained to discriminate buprenorphine from its vehicle. Following the acquisition of discriminative control, subjects were then tested for their ability to generalize this control to morphine, MR 2266 and the nonopioid pentobarbital.

METHOD

Subjects and Apparatus

The subjects were 12 experimentally naive, female rats of Long-Evans descent, approximately 120 days of age at the beginning of the experiment. The subjects were housed in individual wire-mesh cages and were maintained on a 12 L : 12 D cycle and at an ambient temperature of 23°C for the duration of the experiment. Guidelines established by the Institutional Animal Care and Use Committee at The American University were followed at all times.

Drugs

Buprenorphine hydrochloride and morphine sulfate were generously supplied by the National Institute on Drug Abuse. Both drugs were prepared in distilled water. MR2266 [(−)-5,9-diethyl-2-(3-furylmethyl)-2′-hydroxy-6,7-benzomorphan] was generously supplied by Boehringer Ingleheim and was prepared as an emulsion in a vehicle of 4% Tween-80 in distilled water. All drugs were injected in a volume of 1 ml/kg of body weight. Doses for all drugs are expressed in terms of the forms noted above.

Procedure

Phase I: Morphine tolerance. In this phase, all subjects were given an intraperitoneal (IP) injection of morphine (40 mg/kg) at 1700 h each day for 17 consecutive days [see (37)]. To assess the development of tolerance to morphine, all subjects were observed every 15 min for 1 h postmorphine injection. Eye protrusion, rigidity (immobility with stiff body and tail), and reactivity (response to a slight opening of the cage) were recorded over this observation period. During each of these observations, each of these responses was recorded as being present or absent for each subject. Body weight was also monitored. During this phase, subjects were maintained on ad lib access to food and water.

Phase II: Discrimination training. The specific training parameters used in this phase are identical to those used in the prior assessment of buprenorphine discrimination learning with opiate-naive rats [see (38)]. Specifically, on day 1 of this phase, all subjects were deprived of water. At 1200 h on the next day, all subjects were given 20-min access to water. This restricted water access was continued for 14 consecutive days. On days 15–17 (Saccharin Habituation), a novel saccharin solution (0.1% w/v Sodium Saccharin, Fisher Purified) replaced water during the daily 20-min fluid-access period. On day 17, all subjects were matched on saccharin consumption and assigned to one of two groups (groups BL and BW; n = 7 and n = 6 per group, respectively). On day 18, subjects in

groups BL and BW were given an IP injection of 0.56 mg/kg of buprenorphine 30 min prior to saccharin access. Immediately following saccharin consumption, subjects in group BL were given an IP injection of 1.8 mEq, 0.15 M LiCl (76.8 mg/kg). Subjects in group BW were given an equivolume injection of the distilled water vehicle. On the following 3 days, all subjects were injected with distilled water 15 min prior to saccharin access. No injections were given following saccharin on these recovery days. This alternating procedure of conditioning/recovery was repeated for each individual experimental subject until it consumed less than 50% of the mean of the control subjects following administration of the training drug for three consecutive trials. All subjects continued to receive their daily IP injection of morphine (40 mg/kg) at 1700 h each day.

Phase III: Generalization. The procedure in this phase was identical to that in Phase II, with the following exception. On the second recovery day following conditioning, subjects in groups BL and BW received one of a range of doses of buprenorphine (0–1 mg/kg), morphine (0–42 mg/kg), MR2266 (0–10 mg/kg), and pentobarbital (0–10 mg/kg) 15 min prior to saccharin access. The specific doses assessed in this phase were within the relevant dose range for these specific compounds [see Discussion; also see (38,43)]. For any individual drug, the doses were given in a mixed order with the order identical for all subjects. LiCl was not administered following any of these probes. Individual subjects in group BL were tested for generalization only if they had discriminative control by the training drug immediately prior to a generalization test, i.e., a subject in group BL had consumed no more than 50% of the mean consumption of subjects in the control group (group BW) on the conditioning trial immediately preceding that specific generalization session. Such a criterion ensured that the generalization function was based on stable discriminative control. During this phase, complete generalization was defined as consumption following the probe drug falling either at or below the mean (±SEM) consumption of saccharin following the training drug. Similar to Phase I, all subjects continued to receive their daily IP injection of morphine (40 mg/kg) at 1700 h each day.

If an individual subject displayed weight loss or obvious signs of distress during any phase of the conduct of the experiment, it was removed from training and testing and was given supplemental water and observed for recovery. Only when body weight and consumption were stable was the animal returned to the experimental procedures.

Statistical analysis. Between-group comparisons of saccharin consumption on conditioning and recovery sessions during discrimination training as well as following dose probes during generalization testing were performed using a Mann–Whitney *U*-test. Statements of significance are based on $p < 0.05$. Absolute probabilities are presented for all comparisons.

RESULTS

Phase I: Morphine Tolerance

As described, during the injection regimen prior to discrimination training subjects were observed every 15 min for 1 h following the injection of morphine. Eye protrusion, rigidity, and reactivity were recorded over this observation period. During each of these observations, each of these responses was recorded as being present or absent for each subject and the number of animals displaying these responses for each observation was recorded. Following the first injection day (day 1), 10 of the 13 subjects displayed eye protrusion, rigidity, and reactivity throughout the four observation periods. Over days and within the 1-h sampling period, the number of subjects displaying each of these responses decreased. By day 17, no subject displayed any of the three responses at any of the four observation periods.

Phase II: Discrimination Training

Figure 1 illustrates the mean amount (±SEM) of saccharin consumed for subjects in groups BL and BW during saccharin habituation and over the repeated conditioning/recovery cycles in this phase. As illustrated, there were no significant differences in saccharin consumption between groups during saccharin habituation ($U = 130.5, 139.5$, $p = 0.87$). The mean consumption of saccharin averaged over the 3 days of saccharin habituation was 11.20 and 10.36 ml for subjects in groups BL and BW, respectively. There were also no significant differences between groups on the initial conditioning trial ($U = 17.5, 24.5$, $p = 0.62$), with both groups consuming approximately 13 ml of saccharin. Significant differences in saccharin consumption emerged on the sixth conditioning trial at which point subjects in group BL drank significantly less saccharin than subjects in group BW ($U = 1, 41$, $p = 0.004$). This significant difference in consumption was maintained over the remaining conditioning trials of this phase. On the final conditioning trial, subjects in groups BL and BW drank 3.1 and 14.25 ml of saccharin, respectively.

On the recovery sessions following the second and third conditioning trials, subjects in group BL drank significantly less saccharin than subjects in group BW ($U = 4, 38$, $p = 0.015$; $U = 5.5, 36.5$, $p = 0.027$). There were no consistent differences in saccharin consumption on recovery sessions between groups after this point.

Phase III: Generalization

Buprenorphine. Figure 2 illustrates absolute saccharin consumption for individual subjects in group BL following an injection of distilled water (DW) and various doses of buprenorphine. For comparison, the mean amount (±SEM) of saccharin consumed by group BL following the training dose of buprenorphine (0.56 mg/kg) is also included in the figure. Finally, the mean amount (±SEM) of saccharin consumed by subjects in group BW following distilled water and the various doses of buprenorphine is presented to illustrate the unconditioned effect of buprenorphine on saccharin intake. Two subjects in group BL did not acquire the buprenorphine discrimination, and as such, generalization data were not collected. The data presented in this figure (and all remaining figures) are for the five subjects in this group that acquired and maintained the buprenorphine discrimination.

As illustrated, subjects in group BL displayed a dose-dependent decrease in saccharin consumption. Although the subjects varied in their sensitivity to buprenorphine (in terms of the dose at which buprenorphine affected saccharin consumption), all subjects (with the exception of Subject #2) drank saccharin at or below the training dose level when administered 1 mg/kg buprenorphine. Subject #2 drank approximately 4 ml at this dose (compared to 2.5 ml at the training dose). There were no clear dose-related changes in saccharin consumption for subjects in group BW (see Fig. 2). Although group BL did not differ significantly in saccharin consumption from group BW following distilled water ($U = 11.5, 18.5$, $p = 0.52$) and the two lower doses of buprenorphine ($U = 14, 16$, $p = 0.86$, and $U = 8, 22$, $p = 0.20$, for 0.1 and 0.18 mg/kg, respectively), group BL did consume significantly

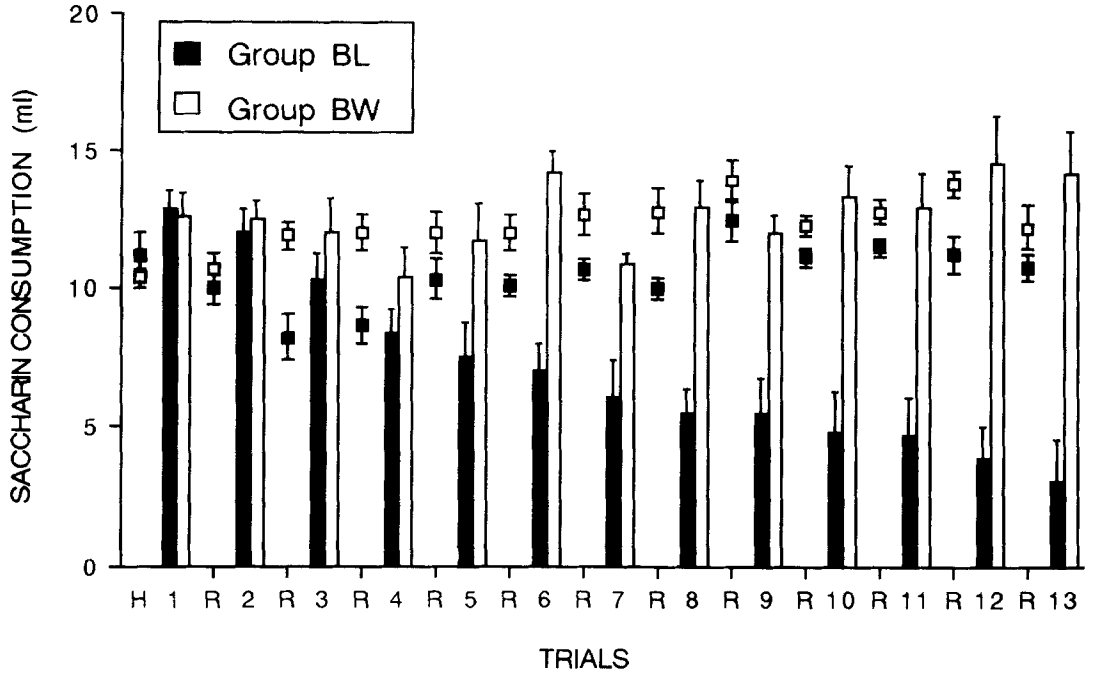

FIG. 1. The mean amount (±SEM) of saccharin consumed for subjects in groups BL and BW over the repeated conditioning trials (filled and open columns, respectively). The filled and open squares represent a mean (±SEM) of saccharin consumption on the three days of Saccharin Habituation (H) and on the three recovery sessions (R) between each conditioning trial.

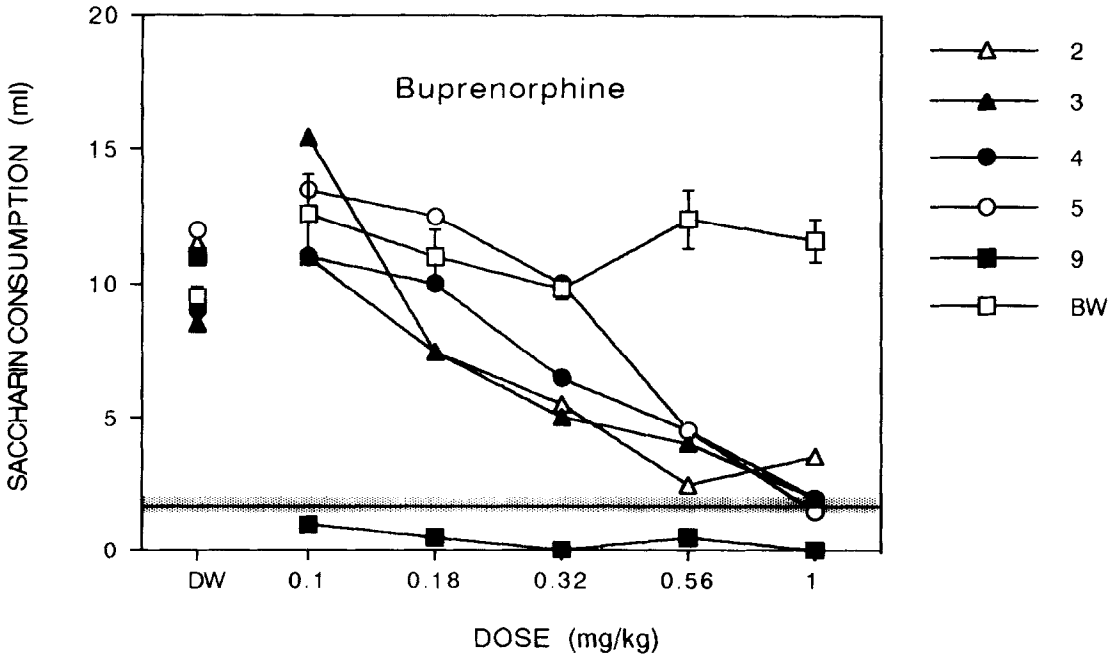

FIG. 2. The amount of saccharin consumed for individual subjects in group BL following distilled water (DW) and various doses of buprenorphine. The mean amount (±SEM) of saccharin consumed by subjects in group BW is indicated by the open squares. The mean amount of saccharin consumed following the training dose of buprenorphine (0.56 mg/kg) for subjects in group BL is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

less saccharin than group BW following 0.32, 0.56 and 1 mg/kg buprenorphine (U = 3.5, 26.5, p = 0.04; U = 0, 30, p = 0.006; U = 0, 30, p = 0.006, respectively).

Morphine. Figure 3 illustrates the same measures as Fig. 2 for individual subjects in group BL following distilled water (DW) and various doses of morphine. As illustrated, all five subjects in group BL displayed a dose-dependent decrease in saccharin consumption, drinking saccharin at or below the training dose level at 42 mg/kg of morphine. Control subjects also displayed a dose-related decrease in saccharin consumption, although not as large as that displayed by subjects in group BL. Group BL drank significantly less saccharin than group BW following 42 mg/kg morphine (U = 3.5, 26.5, p = 0.04). No other comparisons were significant (all $p >$ 0.12).

MR2266. Figure 4 presents the same measures as Fig. 2 during generalization tests with various doses of MR2266 (0–5.6 mg/kg). As illustrated, at no dose of MR2266 did consumption by subjects in group BL approach the level consumed following the training drug. Following 1.8 mg/kg MR2266, group BL drank significantly more than group BW (U = 4, 26, p = 0.044). No other comparisons were significant (all $p >$ 0.18).

Pentobarbital. Figure 5 shows the same measures as Fig. 2 during generalization tests with various doses of pentobarbital (0–10 mg/kg). At no dose of pentobarbital did consumption by subjects in group BL approach the level consumed following the training drug. Overall, there were no consistent differences between groups in saccharin consumption over the increasing doses of pentobarbital. Group BL drank significantly less saccharin than group BW following 1.8 mg/kg pentobarbital (U = 1.5, 28.5, p = 0.0136) and significantly more saccharin than group BW following 5.6 mg/kg pentobarbital (U = 3.5, 26.5, p = 0.04). No other comparisons were significant (all $p >$ 0.06).

DISCUSSION

As described above, Pournaghash and Riley (38) noted that animals trained to discriminate the mixed mu agonist/kappa antagonist buprenorphine from its vehicle generalized buprenorphine control to morphine but not to MR2266. Given that MR2266 is effective as an antagonist at the kappa receptor (1,6,22,35,40,54), the failure of buprenorphine to generalize to MR2266 suggests that buprenorphine's kappa antagonist activity did not mediate its stimulus properties. Based on the work by Negus and his colleagues [(33); see also (41)], which demonstrated that buprenorphine's ability to antagonize the suppressive effects of the kappa agonist bremazocine on schedule-controlled behavior was only evident following opiate tolerance, the present study examined whether morphine-tolerant subjects trained to discriminate buprenorphine from its vehicle would generalize to MR2266. Specifically, animals were made tolerant to morphine and were then trained to discriminate buprenorphine from the distilled water vehicle. Following the acquisition of the discrimination, the ability of buprenorphine to generalize to MR2266 was tested. As described, buprenorphine did not generalize to MR2266. In fact, the amount consumed following various doses of MR2266 was indistinguishable from that following injections of distilled water or the nonopioid pentobarbital. The fact that in morphine-tolerant animals buprenorphine failed to generalize to MR2266, a compound with antagonist properties at the kappa receptor, suggests that the kappa antagonist properties of bu-

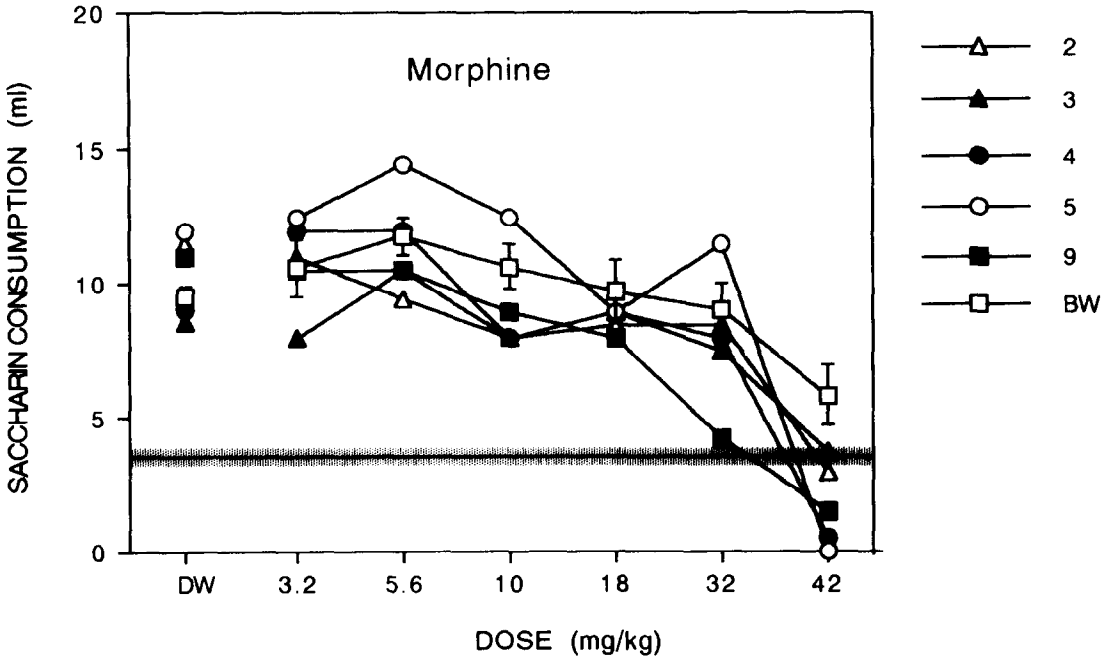

FIG. 3. The amount of saccharin consumed for individual subjects in group BL following distilled water (DW) and various doses of morphine. The mean amount (± SEM) of saccharin consumed by subjects in group BW is indicated by the open squares. The mean amount of saccharin consumed following the training dose of buprenorphine (0.56 mg/kg) for subjects in group BL is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

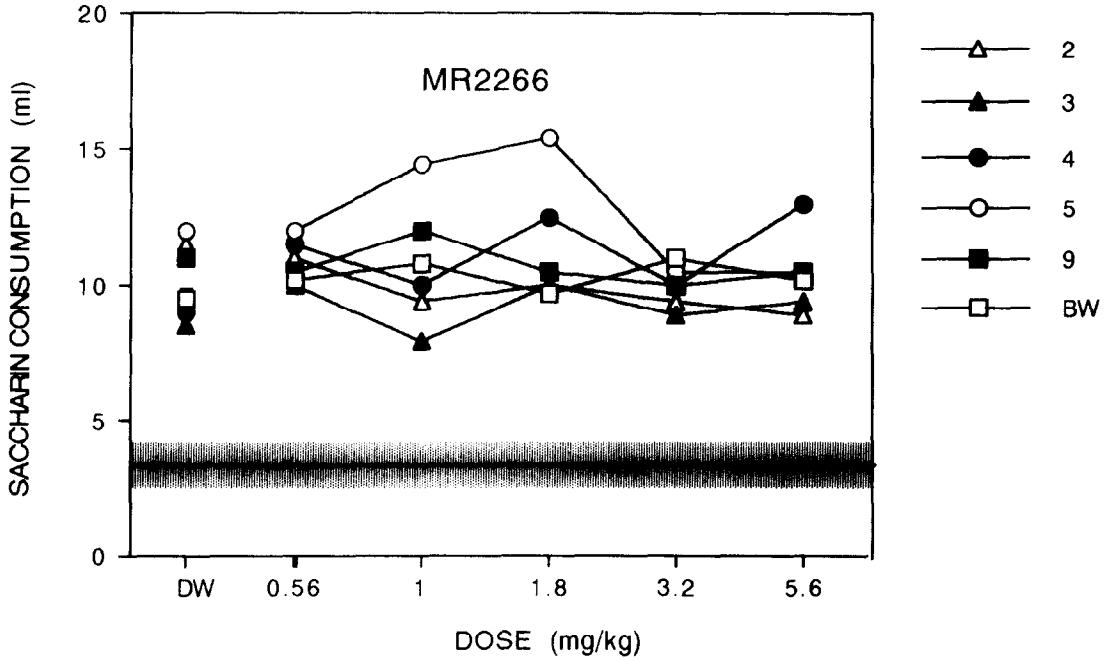

FIG. 4. The amount of saccharin consumed for individual subjects in group BL following distilled water (DW) and various doses of MR2266. The mean amount (±SEM) of saccharin consumed by subjects in group BW is indicated by the open squares. The mean amount of saccharin consumed following the training dose of buprenorphine (0.56 mg/kg) for subjects in group BL is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

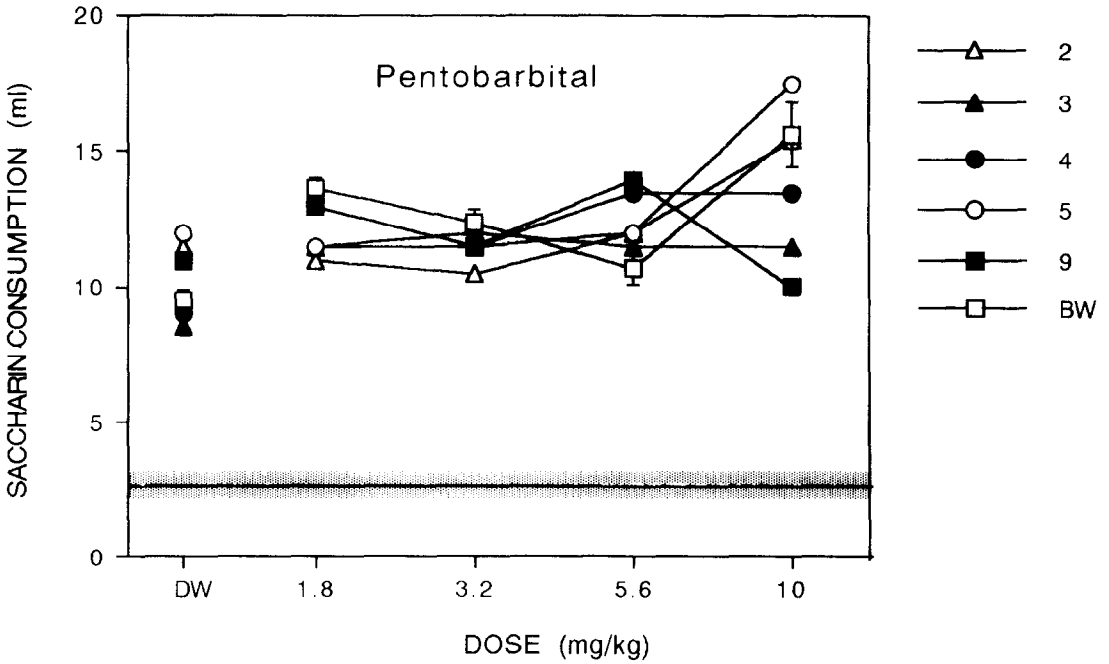

FIG. 5. The amount of saccharin consumed for individual subjects in group BL following distilled water (DW) and various doses of pentobarbital. The mean amount (±SEM) of saccharin consumed by subjects in group BW is indicated by the open squares. The mean amount of saccharin consumed following the training dose of buprenorphine (0.56 mg/kg) for subjects in group BL is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

prenorphine had not established stimulus control even in animals for which the mu agonist properties of buprenorphine were attenuated.

Although the basis for the failure of the kappa antagonist properties of buprenorphine to establish discriminative control remains unknown, a number of possibilities exist. First, it is possible that in the present experiment animals did not develop tolerance to morphine, a condition necessary to unmask buprenorphine's kappa properties (33,41). As described, however, immediately prior to discrimination training morphine was no longer effective in producing rigidity, eye protrusion, or reactivity, suggesting that all subjects had clearly developed tolerance. Further, the dose of morphine required to produce buprenorphine stimulus control in the present experiment was 2.5 times greater than that in opiate-naive rats [see (38)], a shift in the dose-response curve to the right indicating tolerance to morphine (56,57). Although tolerance may have developed to morphine, it is certainly possible that this tolerance was not complete. The fact that buprenorphine control did generalize to morphine (albeit at higher doses than in opiate-naive animals) does suggest that mu activity was still discriminable. If tolerance of mu activity was not complete, it, nonetheless, would have been expected that chronic morphine exposure would have modulated the ability of the mu activity of buprenorphine to mask its kappa antagonist effects. The generalization patterns with MR2266 in the opiate-exposed subjects in the present experiment, however, were identical to those previously reported in opiate-naive animals (38), suggesting that the failure of buprenorphine's kappa antagonist activity to establish discriminative control was not a function of this activity being masked by its mu agonist effects.

The kappa antagonist activity of buprenorphine, however, may have been masked in a manner different than that suggested by Negus et al. (33). Specifically, buprenorphine may have precipitated some degree of withdrawal in the opiate-tolerant subjects, and this withdrawal may have been the stimulus supporting the drug discrimination. Opioid compounds with weak or partial mu agonist effects do precipitate withdrawal, and precipitated withdrawal can support such learning [(15–17,30); see (11) for a general review of this issue]. Interestingly, buprenorphine has been reported to precipitate withdrawal in opiate-exposed subjects under some conditions. The reports of buprenorphine-precipitated withdrawal, however, are quite mixed. Although Dum and Herz (10) reported that buprenorphine precipitated withdrawal in morphine-pelleted rats, this effect was only evident at doses 3 mg/kg and greater, doses considerably higher than the training dose used in the present experiment (0.56 mg/kg). Further, Cowan, Lewis, and MacFarlane (9) failed to see any signs of precipitated withdrawal by buprenorphine in opiate-dependent rats (although such effects were noted in mice and monkeys). In unpublished work from this laboratory, rats exposed to the same opiate dosing regimen as reported here (i.e., 40 mg/kg each day for 17 consecutive days) were injected with 0.56 mg/kg buprenorphine and several indices of precipitated withdrawal were assessed (changes in body weight and the acquisition of aversions to a novel saccharin taste presented immediately prior to the injection of buprenorphine). Under these conditions, body weight was unaffected and no aversions were acquired to the solution given prior to the buprenorphine injection. If the opiate antagonist naloxone is given (instead of buprenorphine), large decreases in body weight occur and strong aversions develop to the saccharin solution given prior to the naloxone injection (37). Further, in the present experiment there were no decreases in saccharin consumption from baseline when the opiate-tolerant control subjects (i.e., group BW) were administered buprenorphine (either during training or during probe sessions). Thus, although under some conditions higher doses of buprenorphine can precipitate withdrawal, it appears unlikely that withdrawal occurred under the present procedure.

The failure of the kappa antagonist properties of buprenorphine to establish discriminative control may be less an issue of the masking of its kappa antagonist activity than with the general inability of kappa antagonists to establish discriminative control. This possibility does not assume anything unique about buprenorphine, but simply notes that for some as yet undetermined reason kappa antagonist activity does not produce a stimulus effect detectable by the rat. Although it has been very difficult to establish discriminative control with opioid antagonists in more traditional assessments of drug discrimination learning unless extremely high doses are used or extensive training is given (7,21,36), such learning has been reported within the taste aversion baseline for naloxone (20,48), diprenorphine (49), and nalorphine (50). Using this design in our laboratory, however, we have been unable to establish discriminative control with MR2266 (1 to 10 mg/kg, IP). Specifically, every fourth day various doses of MR2266 were administered prior to a saccharin–LiCl pairing. On the intervening days, subjects were given an injection of the distilled water vehicle prior to a nonpoisoned exposure to saccharin. After 20 conditioning trials, there was no evidence of discriminative control. Thus, under conditions that readily establish control to a variety of mu antagonists [see (20,48–50)], at least one compound effective as a kappa antagonist (i.e., MR2266) was unable to support discrimination learning.

Accordingly, the inability of the kappa antagonist properties of buprenorphine to support discrimination learning may be a result of the general inability of kappa antagonist activity to do so. The question now becomes why such activity is ineffective in the discrimination design. Interestingly, kappa antagonists (in the same dose range used in the assessment of MR2266's discriminative control) are effective in a variety of behavioral and physiological preparations. For example, Fanselow, Calcagnetti, and Helmstetter (12) have reported that 0.3–3 mg/kg of MR2266 reduced saccharin/glucose intake in naive female rats [see also (53)]. Also, Bhargava, Kremer, Gibbons, Philips, Driver, and Chou (5) demonstrated that MR2266 (0.3–3 mg/kg) antagonized morphine-induced analgesia and hyperthermia. Further, Bechara and van der Kooy (2) have reported that MR2266 produced both conditioned place aversions (1 and 10 mg/kg) and preferences [0.01–0.1 mg/kg; see also (18) for similar conditioning with 1-WIN 44,441-3, another compound with kappa antagonist activity].

A possible explanation for the failure to establish discriminative control with kappa antagonist activity may come from recent work by Bertalmio, France, and Woods (4) assessing the basis of agonist/antagonist activity of various opioids. To account for how a specific compound might have agonist activity in one preparation but antagonist activity in another, they note that different behavioral preparations may differ in the level or degree of a biological signal necessary to initiate a response (with the level of the biological signal being determined by the intrinsic activity of the drug at a specific receptor). Accordingly, compounds with weak intrinsic activity might function as antagonists in designs necessitating large biological signals (e.g., analgesia), whereas the same compounds might function as agonists in designs for which a small or weak biological signal is required (e.g., self-administra-

tion). Although the discussion by Bertalmio, France, and Woods focused on the agonist activity of various compounds and how such activity might function differently in different designs, the discussion may still be relevant to work on opioid compounds with no reported agonist effects. Specifically, in accounting for the ability of naloxone and naltrexone to support drug discrimination learning, Smurthwaite and Riley (49,50) argued that such effects were based on the blocking of endogenous opioid activity. Such an argument has been presented to account for the ability of naloxone to condition place aversions (31,32) and MR2266 to condition place preferences (45). That is, the blockade of central opioid activity may mediate many of the motivational effects of opioid antagonists [see 45,47,51)]. In relation to the fact that kappa antagonists produce a conditioned place preference but do not support drug discrimination learning, it is possible that the conditioned place preference preparation requires only a weak biological signal (i.e., blocking endogenous opioid activity) to effect a change. On the other hand, the drug discrimination learning preparation may require a stronger biological signal, one which a kappa antagonist is incapable of producing. The ability of a drug to effect responses in different behavioral preparations, thus, may depend on the differences in the strength of the biological signals these preparations require.

In conclusion, buprenorphine's discriminative effects appear to be based on its mu agonist properties. The failure of the kappa antagonist properties of buprenorphine to establish discriminative control in opiate-tolerant rats (i.e., under conditions in which the kappa antagonist properties of buprenorphine should have been maximally displayed) suggests that such receptor activity produces stimulus effects insufficient to establish discriminative control, a conclusion supported by the failure of MR2266 to establish control at high doses and with repeated training. These data are consistent with the position that the different receptor activity of compounds acting at multiple receptors may not be equally salient in their discriminative effects. The basis for this differential salience remains unknown.

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