Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 3, pp. 635–642, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0007-5

Nalorphine as a Stimulus in Drug Discrimination Learning: Assessment of the Role of μ- and κ-Receptor Subtypes

SCOTT T. SMURTHWAITE[1] AND ANTHONY L. RILEY

Psychopharmacology Laboratory,
Department of Psychology, The American University, Washington, DC 20016

Received 8 June 1993

SMURTHWAITE, S. T. AND A. L. RILEY. *Nalorphine as a stimulus in drug discrimination learning: Assessment of the role of μ- and κ-receptor subtypes.* PHARMACOL BIOCHEM BEHAV **48**(3) 635–642, 1994.—Using the conditioned taste aversion baseline of drug discrimination learning, animals were trained to discriminate nalorphine from distilled water. In subsequent generalization tests, the μ-opiate agonist morphine substituted for the nalorphine stimulus in a dose-dependent manner, while the κ-opiate agonist U50,488H and the μ-opiate antagonists naloxone and naltrexone failed to do so. That the μ-agonist morphine substituted for the nalorphine stimulus while a κ-agonist and μ-antagonists failed to substitute indicate that the discriminative control that was established with nalorphine in the present study was μ-agonist receptor-mediated. The basis for this selective control by the μ-receptor subtype may be related to the relative salience of receptor activity in opiate-naive animals. The present results suggest that discriminative control by compounds with activity at multiple receptor sites is not uniformly mediated by specific activity at all of those sites. The specific site mediating discriminative control appears to be a function of the specific training drug.

Drug discrimination learning Conditioned taste aversions Opiate antagonists Generalization

ANIMALS trained to discriminate opiate agonists with μ-receptor activity typically generalize this control to nalorphine. For example, Colpaert, Niemegeers, and Janssen (2) reported that 83% of the rats trained to discriminate fentanyl (40 mg/kg) from its vehicle displayed fentanyl-appropriate responding when administered various doses of nalorphine. The pure opiate antagonist naloxone failed to generalize at doses as high as 160 mg/kg. Since both nalorphine and fentanyl have agonist activity at the μ-receptor [(14); for discussion see (23)], the generalization between these two compounds is likely due to their shared agonist effects at the μ-receptor subtype [(2); see also (1,11,13,32)].

Nalorphine has also been reported to substitute for other opiates with different receptor activity. For example, monkeys trained to discriminate the κ-agonist ethylketocyclazocine (EKC; 10 mg/kg) from its vehicle displayed EKC-appropriate responding following the administration of nalorphine (10, 28,33,39). Further, nalorphine produced drug-appropriate responding in a subset of rats (5 of 11) trained to discriminate the relatively selective μ-opiate antagonist naloxone from its vehicle [(35); see also (36)]. Thus, it appears from stimulus generalization tests that nalorphine can produce stimulus properties based on its μ-agonist, κ-agonist, and μ-antagonist receptor activity.

If nalorphine's activity at different opiate receptor subtypes can produce stimulus effects sufficient to engender drug-appropriate responding in animals already trained to discriminate an opiate from its vehicle, it might be expected that similar stimulus properties might be revealed in animals trained to discriminate nalorphine from its vehicle (i.e., such animals should generalize nalorphine control to compounds with μ and κ activity). To assess this possibility, in the present experiment rats were trained to discriminate nalorphine from its vehicle within the taste aversion baseline of drug discrimination learning (3,4,9,15–17,19–22,24–27,29–31,34–37,40). Specifically, animals were injected every fourth day with nalorphine prior to a saccharin–LiCl pairing and on intervening days with the nalorphine vehicle prior to a nonpoisoned exposure to the same saccharin solution. Following the acquisition of the discrimination, the subjects were given various doses of

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

morphine (μ-agonist), U50,488H (κ-agonist) and diprenorphine, naloxone, and naltrexone (μ-antagonists) to assess their ability to substitute for nalorphine.

METHOD

Subjects and Apparatus

The subjects were 11 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 maintained on a 12-h light/dark cycle and at an ambient temperature of 23°C for the duration of the experiment. Training and testing were conducted during the light phase of the light/dark cycle.

Drugs

Diprenorphine hydrochloride, morphine sulfate, nalorphine hydrochloride, naltrexone hydrochloride, and U50,488H (*trans*-3,4-dichloro-*N*-methyl-*N*-[2-(*l*-pyrrolindinyl)cyclohxyl] benzeactamine methanesulfonate hydrate) were generously supplied by the National Institute on Drug Abuse. Naloxone hydrochloride was generously supplied by DuPont Pharmaceuticals, Inc (Wilmington, DE). All drugs were prepared in distilled water and 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: conditioning. Following 24 h of water deprivation all subjects were given 20-min access to water once a day for 24 consecutive days. On days 25–27 (saccharin habituation) a novel saccharin solution (0.1% w/v Sodium Saccharin; Sigma Chemical Co., St. Louis) replaced water during the daily 20-min fluid-access period. On day 27 all subjects were given an IP injection of distilled water 15 min prior to saccharin access. Subjects were rank-ordered on the amount of saccharin consumed on this day and assigned to one of two groups (group L, $n = 5$; group W, $n = 6$) such that the mean consumption of saccharin on this day was similar for both groups. On the following day (day 28) all subjects were given an IP injection of nalorphine (10 mg/kg) 15 min prior to saccharin access. Immediately following this access, subjects in group L were given an IP injection of 1.8 mEq, 0.15-M LiCl (76.8 mg/kg). Subjects in group W were given an equivolume injection of distilled water (i.e., the LiCl 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 access on recovery days. This alternating procedure of conditioning/recovery was repeated for each individual subject in group L until it consumed less than 50% of the mean amount of saccharin consumed by subjects in group W following administration of nalorphine (10–14 cycles).

Phase II: generalization. The procedure in this phase was identical to that in phase I with the following exception. On the second recovery day following conditioning, one of a range of doses of either diprenorphine (0.18–18 mg/kg), morphine (0.18–18 mg/kg), nalorphine (0.1–18 mg/kg), naloxone (0.18–32 mg/kg), naltrexone (0.18–18 mg/kg), or U50,488H (0.32–18 mg/kg) was administered 15 min prior to saccharin access. All subjects received each of the drugs during this phase with the order of drug administration identical across subjects. For any specific drug the various doses administered were given in a mixed order with the dose order identical across subjects. No injections of LiCl were administered following any of these substitution probes. Individual subjects in group L were tested for generalization only if they had discriminative control by nalorphine immediately prior to a generalization test (i.e., a subject in group L consumed no more than 50% of the mean consumption of the control group 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 for any individual subject was defined as consumption of saccharin by that subject following the probe drug falling either at or below the mean (± SEM) consumption of saccharin by group L following the training drug.

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, 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

All determinations of statistical significance are based on a Mann–Whitney U test and the Wilcoxon matched-pairs signed-ranks test. The Mann–Whitney U test was performed on all between-group comparisons of saccharin consumption. The Wilcoxon matched-pairs signed-ranks test was performed on all within-group comparisons of saccharin consumption. Statements of significance are based on $p < 0.05$, two-tailed.

RESULTS

Phase I: Conditioning

Figure 1 presents the mean amount (± SEM) of saccharin consumed for groups L and W during saccharin habituation and over the repeated conditioning/recovery cycles in this phase. The mean consumption of saccharin averaged over the three days of saccharin habituation (10.5 and 10.4 ml for subjects in groups L and W, respectively) did not differ between the two groups of subjects ($U = 151.5$, 172.5; $p = 0.74$; see Fig. 1). On the first conditioning trial there were no significant differences between groups L and W ($U = 14$, 22; $p = 0.514$) with both groups approximating habituation levels ($z = -1.153$; $p = 0.25$ and -0.943; $p = 0.347$ for groups L and W, respectively). By the fourth conditioning trial significant differences emerged between groups, with subjects in group L drinking significantly less than subjects in group W ($U = 0$, 36; $p = 0.0036$). This difference between groups was maintained for the remainder of conditioning. On the final conditioning trial of this phase subjects in groups L and W drank 2.50 and 9.92 ml, respectively. On recovery sessions following the first six conditioning trials there were no significant differences in saccharin consumption between subjects in groups L and W (all zs < -1.392, $p > 0.164$). On the recovery sessions following the 8th, 10th, and 12th conditioning trials subjects in group L drank significantly more saccharin than subjects in group W (all zs > 2.81, $p < 0.005$). In relation to saccharin habituation, subjects in group L significantly decreased saccharin consumption on recovery sessions following the 1st and 3rd conditioning trials (both zs > 2.308, $p < 0.02$). On recovery sessions following the 7th through 12th conditioning trials these subjects drank significantly more saccharin than during saccharin habituation (all zs > -2.352, $p < 0.018$). There were no consistent changes

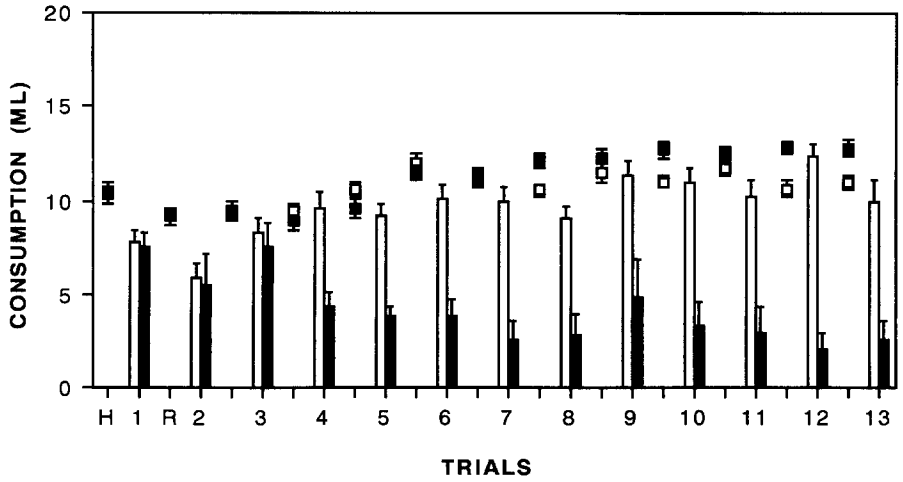

FIG. 1. The mean amount of saccharin consumed (± SEM) for subjects in groups L and W over the repeated conditioning trials (filled and open columns, respectively). ■ and □ represent a mean of saccharin consumption (± SEM) on the three days of saccharin habituation (H) and on the three recovery sessions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

in saccharin consumption during recovery for subjects in group W.

Phase II: Generalization

Nalorphine. Figure 2 presents the mean amount (± SEM) of saccharin consumed for subjects in groups L and W following various probe doses of nalorphine (0–18 mg/kg). As illustrated, there was an inverse relation between saccharin consumption and the dose of nalorphine for subjects in group L. Saccharin consumption for subjects in group W did not vary with increasing doses of nalorphine. The lowest dose at which consumption for subjects in group L was reduced by at least 50% of the amount consumed following the distilled water (vehicle) injection was 5.6 mg/kg. At this dose, subjects in group L displayed complete substitution for the training dose of 10 mg/kg (i.e., consumption following this dose was within or below the range of consumption following the training dose of nalorphine). At 5.6 mg/kg, consumption for subjects in group W was approximately 74% of the amount consumed following distilled water. Subjects in group L drank significantly less saccharin than subjects in group W at 5.6 mg/kg (U = 0.5, 41.5; p = 0.0032), 10 mg/kg (U = 0, 30; p = 0.006), and 18 mg/kg (U = 0, 18; p = 0.018).

Morphine. Figure 3 presents the generalization tests with various doses of morphine (0–10 mg/kg). As illustrated, for group L there were no consistent changes in saccharin consumption over the dose range of 0–3.2 mg/kg morphine. At the two highest doses tested (5.6 and 10 mg/kg), these subjects decreased saccharin consumption. There were no consistent changes in saccharin consumption over the increasing doses of morphine for subjects in group W. The lowest dose at

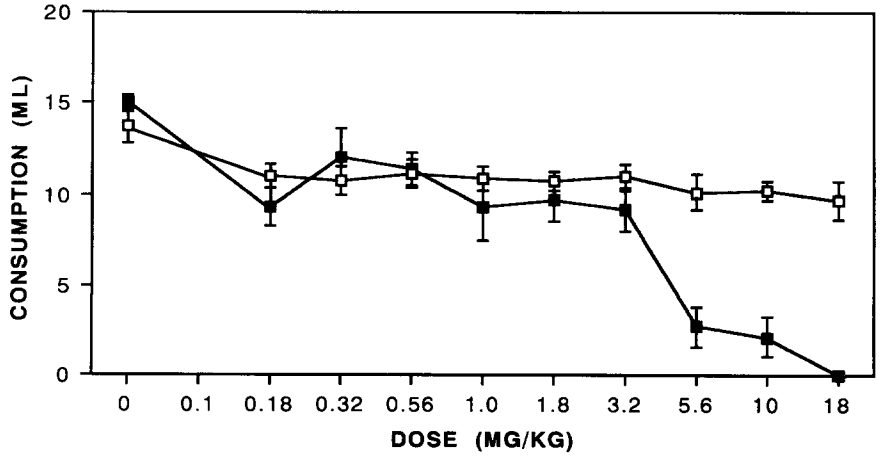

FIG. 2. The mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various doses of nalorphine during generalization testing.

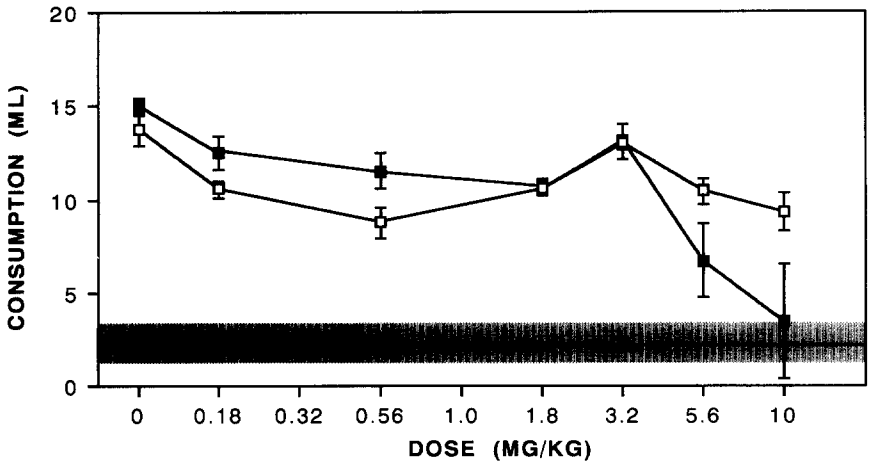

FIG. 3. The mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various doses of morphine during generalization testing. The mean amount of saccharin consumed following the training dose of nalorphine (10 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ±SEM.

which consumption by subjects in group L was reduced by at least 50% of the amount consumed following distilled water was 5.6 mg/kg. At this dose, consumption for subjects in group W was approximately 72% of the amount consumed following distilled water. At a dose of 10 mg/kg, four of the five subjects in group L drank 0 ml, displaying complete substitution for the training dose of nalorphine. Only a single subject did not generalize nalorphine to morphine. This subject drank 17.25 ml at this dose and at control levels at 18 mg/kg (data not shown). At this dose, subjects in group W drank approximately 68% of the amount consumed following distilled water. Statistically, there were no significant differences in saccharin consumption between subjects in groups L and W at any of the doses tested. This failure at 10 mg/kg is likely due to the single subject that failed to generalize.

U50,488H. Figure 4 presents the generalization tests with various doses of U50,488H (0–10 mg/kg). As illustrated, subjects in both groups L and W decreased saccharin consumption as the dose of U50,488H increased. At 1 mg/kg, subjects in group L drank significantly more than subjects in group W (U = 4.5, 25.5; p = 0.049). There were no other significant differences in saccharin consumption between groups L and W. At the highest dose tested (i.e., 10 mg/kg), a single subject in group L displayed complete substitution for the training dose of nalorphine. The remaining subjects in group L were within the control range (i.e., group W).

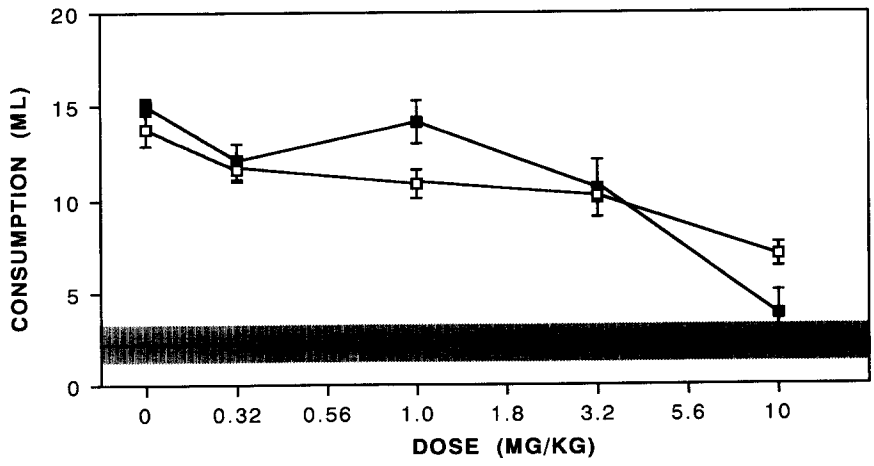

FIG. 4. The mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various doses of U50,488H during generalization testing. The mean amount of saccharin consumed following the training dose of nalorphine (10 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ±SEM.

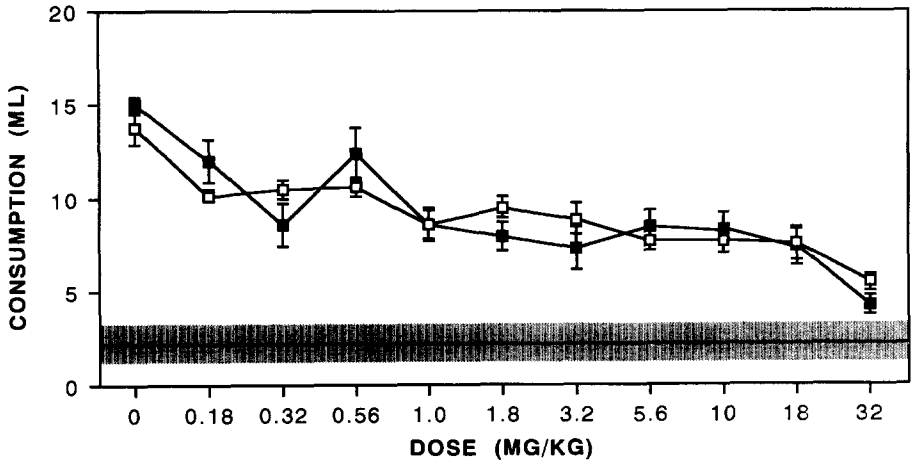

FIG. 5. The mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various doses of naloxone during generalization testing. The mean amount of saccharin consumed following the training dose of nalorphine (10 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

Naloxone and naltrexone. Figures 5 and 6 present the generalization tests with various doses of naloxone (0–32 mg/kg) and naltrexone (0–18 mg/kg), respectively. As illustrated, for both drugs there was an inverse relationship between saccharin consumption and dose for subjects in both groups L and W. Groups L and W did not differ in saccharin consumption at any dose of naloxone or naltrexone.

Diprenorphine. Figure 7 presents the generalization tests with various doses of diprenorphine (0–18 mg/kg). As illustrated, there was an inverse relationship between saccharin consumption and the dose of diprenorphine for subjects in group L. At the lowest dose of diprenorphine (i.e., 0.18 mg/kg), subjects in group W decreased saccharin consumption below that consumed following distilled water. However, there was no further decrease in consumption with increasing doses of diprenorphine. The lowest dose at which consumption for subjects in group L was reduced by at least 50% of the amount consumed following distilled water was 0.56 mg/kg. At this dose, consumption for subjects in group W was 59% of the amount consumed following distilled water. At a dose of 5.6 mg/kg, subjects in group L displayed complete substitution for the training dose of nalorphine. At this dose, subjects in group W drank approximately 54% of the amount consumed following distilled water. At 0.18 mg/kg, subjects in group L drank significantly more saccharin than subjects in group W (U = 1.5, 28.5; p = 0.0132). Subjects in group L

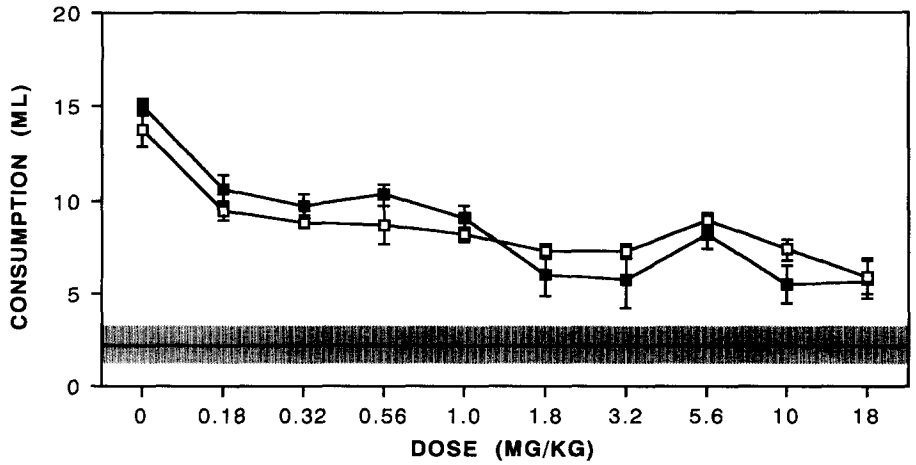

FIG. 6. The mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various doses of naltrexone during generalization testing. The mean amount of saccharin consumed following the training dose of nalorphine (10 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

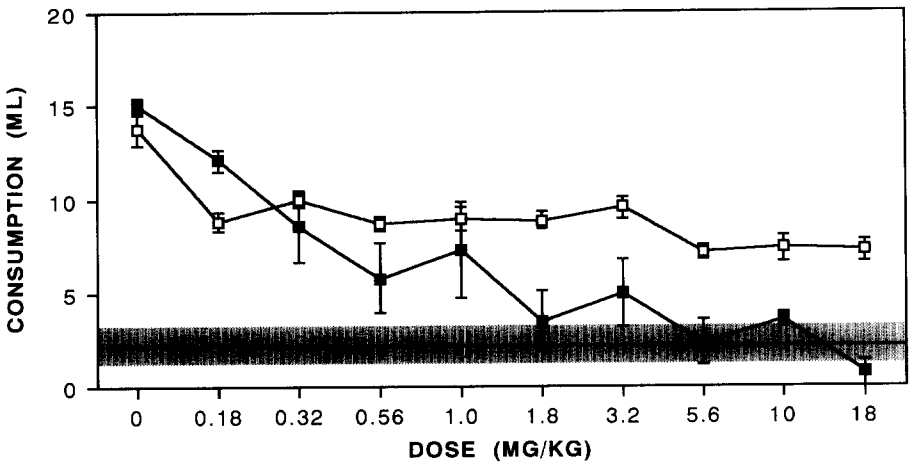

FIG. 7. The mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various doses of diprenorphine during generalization testing. The mean amount of saccharin consumed following the training dose of nalorphine (10 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this horizontal line illustrates ± SEM.

drank significantly less saccharin than subjects in group W at 5.6 mg/kg (U = 2.5, 27.5; p = 0.022) and 10 mg/kg (U = 0.5, 17.5; p = 0.0272).

DISCUSSION

In the present study, animals injected with nalorphine prior to a saccharin–LiCl pairing and the nalorphine vehicle prior to saccharin alone rapidly acquired the drug discrimination, avoiding saccharin when it was preceded by an injection of nalorphine and consuming the same saccharin solution when it was preceded by the drug vehicle. In subsequent tests for generalization, various doses of nalorphine generalized in a dose-dependent manner to the training dose of nalorphine (i.e., 10 mg/kg), with consumption decreasing as the dose of nalorphine increased. Complete nalorphine-appropriate responding was displayed for the μ-agonist morphine. Specifically, morphine completely substituted for the nalorphine stimulus in four of the five animals tested, with each of these subjects completely avoiding saccharin at 10 mg/kg. The remaining animal drank saccharin at levels similar to control animals. On the other hand, nalorphine failed to generalize to the κ-agonist U50,488H or the relatively selective μ-antagonists naloxone and naltrexone. Specifically, U50,488H completely substituted for nalorphine in only one of the five animals tested, with the remaining animals displaying levels of consumption similar to that of control animals. Neither naloxone nor naltrexone occasioned nalorphine-appropriate responding for any subject at any dose tested.

The present finding that nalorphine generalizes to morphine is consistent with earlier findings that animals trained to discriminate a μ-agonist (e.g., fentanyl) from its vehicle generalized this control to nalorphine (2), a generalization presumably based on their shared agonist activity at the μ-receptor. The failure of nalorphine to generalize to either the κ-agonist U50,488H or the μ-antagonists naloxone and naltrexone, however, is not consistent with earlier work [(10,14, 28,33,39); though see (38)]. As described above (see the introductory section), monkeys trained to discriminate the relatively selective κ-agonist EKC from its vehicle generalized EKC control to nalorphine (10). Further, 5 of 11 animals trained to discriminate naloxone from its vehicle under conditions identical to those of the present experiment [i.e., similar drugs and dose range and within the taste aversion baseline of drug discrimination learning (35)] generalized this control to nalorphine.

The basis for the differences in the generalization patterns across studies is not known, although it is possible that the pattern reported in the present experiment may be a function of the specific training dose of nalorphine—that is, different patterns may have emerged with different doses. Although possible, similar generalization functions have been obtained under conditions identical to those of the present experiment when 3.2 mg/kg nalorphine was the training stimulus (data not presented). Specifically, 3.2 mg/kg nalorphine generalized to morphine and not naloxone, naltrexone, or U50,488. Thus, it is unlikely that the training dose influenced the specific drugs to which generalization was reported.

The differences in generalization patterns across studies may be more a function of the specific training drug than the training dose. For example, the μ-agonist properties of nalorphine may be more salient than its κ-agonist or μ-antagonist properties such that during the acquisition of stimulus control its μ-agonist properties masked or overshadowed its other receptor activity. Stimulus control by nalorphine thus would be mediated by its agonist activity at the μ-receptor only. That receptor activity of compounds acting at multiple receptors may have differential salience in establishing discriminative control is supported in recent work by Pournaghash and Riley (29), who have reported that while the μ-agonist/κ-antagonist opioid buprenorphine can be used as a discriminative stimulus in drug discrimination learning, its stimulus properties appear to be based totally on its μ-agonist activity. Specifically, following the acquisition of discriminative control with buprenorphine, animals generalize this control selectively to μ-agonists and not κ-antagonists.

As described above, however, animals trained to discriminate the κ-agonist EKC (10,28,33,39) or the μ-antagonist naloxone [(35); see also 36)] from its vehicle generalize this control to nalorphine, suggesting that, although weak, the μ-antagonist and κ-agonist properties of nalorphine in opiate-naive animals are sufficiently salient in animals for which μ-antagonist or κ-agonist activity presumably mediates the discrimination. Thus, when a compound with activity at other receptors is the training drug and stimulus control is mediated by this receptor activity, this control will generalize to any compound with activity at these receptors (e.g., nalorphine). The training drug would clearly impact generalization patterns according to this analysis.

That diprenorphine substituted for the nalorphine training stimulus appears inconsistent with the failure of naloxone and naltrexone to substitute. Diprenorphine is typically reported as being an opiate antagonist (6,7,35,36); however, there is considerable evidence in other preparations to suggest that diprenorphine may possess agonist activity as well (5). For example, like morphine, diprenorphine inhibits contractions of the electrically stimulated guinea pig ileum (18) and partially suppresses the flexor reflex in the chronic spinal dog preparation (8). Further, a number of μ-opiate agonists, including morphine and etorphine, substitute for diprenorphine in animals trained to discriminate diprenorphine from its vehicle (5). Thus, the ability of diprenorphine to substitute for nalorphine in the present study may be based on their shared partial μ-agonist activity.

Independent of the specific basis for the differences in the generalization patterns reported in the present experiment in which nalorphine served as the training drug and in other reports in which subjects were trained on other opiate agonists and antagonists, it is clear that differences in generalization do exist between nalorphine and several other opiate agonist and antagonist compounds. Interestingly, such differences have also been reported with nalorphine in generalization assessments with the opiates pentazocine and cyclazocine (12). The present data do suggest that the basis for discriminative control by compounds with activity at multiple receptor sites is not uniformly mediated by specific activity at all those sites. One factor influencing which of the receptor subtypes mediates discriminative control appears to be the specific training drug.

ACKNOWLEDGEMENTS

The research on which this article is based was supported by a grant from the Mellon Foundation to Anthony L. Riley.

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