Pharmacology Biochemistry & Behavior, Vol. 41, pp. 43–47. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/92 $5.00 + .00

Naloxone as a Stimulus in Drug Discrimination Learning: Generalization to Other Opiate Antagonists

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SMURTHWAITE, S. T., M. A. KAUTZ, B. GETER AND A. L. RILEY. *Naloxone as a stimulus in drug discrimination learning: Generalization to other opiate antagonists.* PHARMACOL BIOCHEM BEHAV **41**(1) 43–47, 1992.—Nonopiate dependent animals were trained to discriminate the opiate antagonist naloxone (1 mg/kg) from distilled water within the conditioned taste aversion baseline of drug discrimination learning. Specifically, rats injected with naloxone prior to a saccharin-LiCl pairing, and with its vehicle prior to saccharin alone, rapidly acquired the drug discrimination, avoiding saccharin following the administration of naloxone and consuming saccharin following its vehicle after only three conditioning trials. Once the discrimination was acquired, generalization tests revealed that the opiate antagonists diprenorphine and naltrexone and the mixed opiate agonist/antagonist nalorphine completely generalized to the naloxone cue at doses of 1.8, 5.6 and 18 mg/kg, respectively. That discriminative control was established with a low dose of naloxone (i.e., 1 mg/kg) and other compounds with opiate antagonist activity generalized to the naloxone cue suggest that the stimulus effects of naloxone were likely mediated through the opiate receptor. Because each of these compounds are reported to bind to the mu receptor (with varying affinities and varying degrees of selectivity), the stimulus properties of naloxone are likely mediated at this specific receptor subtype.

Drug discrimination Conditioned taste aversion Opiate antagonists Generalization

AS a result of the relative difficulty in establishing discriminative control with naloxone in opiate-naive animals within a drug discrimination procedure [(11, 23, 24), though see (1)], there is little information on the extent, if any, to which other opiate antagonists generalize to naloxone in animals trained to discriminate naloxone from its vehicle. In one study reporting the acquisition of discriminative control with naloxone, Carter and Leander (1) reported that the opiate antagonists naltrexone and levallorphan and the mixed opiate agonist/antagonists pentazocine and nalorphine substituted for naloxone, while other opiate antagonists (diprenorphine) and mixed agonist/antagonists (cyclazocine and profadol) produced only intermediate degrees of naloxone-appropriate responding. As noted by the authors, because the dose of naloxone (30 mg/kg) used to establish discriminative control in this study was much higher than those needed to antagonize the opiates in other assessments [e.g., see (14, 29, 30)], it is possible that some pharmacological effect of naloxone other than its opiate receptor activity mediated its discriminative control.

Using the conditioned taste aversion baseline of drug discrimination learning in which an animal is injected with a stimulus drug prior to a taste-toxin pairing and the drug vehicle prior to access to the taste alone [see (6, 8, 13, 16, 18, 19, 26, 27, 32)], Kautz et al. (9) have recently reported the rapid acquisition of discriminative control with low doses of naloxone (1 and 3 mg/kg). Although naltrexone generalized to naloxone in subsequent generalization tests, no other antagonists were examined, limiting any conclusions about within-class generalization (i.e., opiate antagonists) to naloxone.

Since little is known about whether opiate antagonists other than naltrexone can generalize to naloxone in subjects trained to discriminate low doses of naloxone from its vehicle, the present experiment examined the substitution profiles of the opiate antagonists diprenorphine and naltrexone and the mixed opiate agonist/antagonist nalorphine in rats trained to discriminate 1 mg/kg naloxone from its vehicle within a taste aversion/drug discrimination procedure. Specifically, following the acquisition of a naloxone/vehicle discrimination, diprenorphine, nalorphine and naltrexone were substituted for the naloxone cue at various doses to assess the ability of these compounds to substitute for the naloxone stimulus.

METHOD

Subjects and Apparatus

The subjects were 24 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-h light/12-h dark cycle and at an ambient temperature of 23°C for the duration of the experiment.

Drugs

Diprenorphine, nalorphine and naltrexone were generously supplied by the National Institute on Drug Abuse. Naloxone was

generously supplied by DuPont Pharmaceuticals, Inc. All drugs were prepared in distilled water and injected in a volume of 1 ml/kg of body weight.

Procedure

Phase I: Conditioning. Following 24 h of water deprivation, all subjects were given 20-min access to water once a day for 30 consecutive days. On Days 31–33 (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 33, all subjects were given an intraperitoneal (IP) injection of distilled water 15 min prior to saccharin access. Subjects were matched on saccharin consumption on the final day of Saccharin Habituation and assigned to one of two groups (Group L or Group W; n = 12 per group). On Day 34, subjects in both groups were given an IP injection of 1 mg/kg naloxone 15 min prior to saccharin access. Immediately following saccharin 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 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 access on these recovery days. The alternating procedure of conditioning/recovery was repeated for 12 complete 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 diprenorphine (0.1–5.6 mg/kg), nalorphine (0.56–18 mg/kg) or naltrexone (0.032–1.8 mg/kg) was administered 15 min prior to saccharin access. All subjects received each of the three drugs during this phase, with the specific order of drug presentation varying for individual subjects. For any individual drug, the doses were given in a mixed order. No injections of LiCl were administered following any of these substitution probes.

RESULTS

Statistical Analysis

All determinations of statistical significance are based on a Kruskal-Wallis one-way analysis of variance and the Friedman's analysis of variance by rank. The Kruskal-Wallis one-way analysis of variance test was performed on all between-group comparisons of saccharin consumption. If an overall between-group comparison was significant, contrasts were subsequently run and individual group comparisons were based on these contrasts. The Friedman analysis of variance by rank was performed on all within-group comparisons of saccharin consumption over repeated conditioning trials. If an overall within-group comparison was significant, contrasts were subsequently run and individual trial comparisons were based on these contrasts. Statements of significance for both Kruskal-Wallis (H) and for the Friedman (χ_r^2) are based on $p<0.05$, one-tailed.

Phase I: Acquisition. Figure 1 presents the mean absolute saccharin consumption for Groups L and W 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 L and W during Saccharin Habituation [H(1) = 0.02]. The mean consumption of saccharin averaged over the three days of Saccharin Habituation was 12.93 and 13.15 ml for subjects in Groups L and W, respectively (see Fig. 1). On the initial conditioning trial, subjects in both groups significantly decreased saccharin consumption

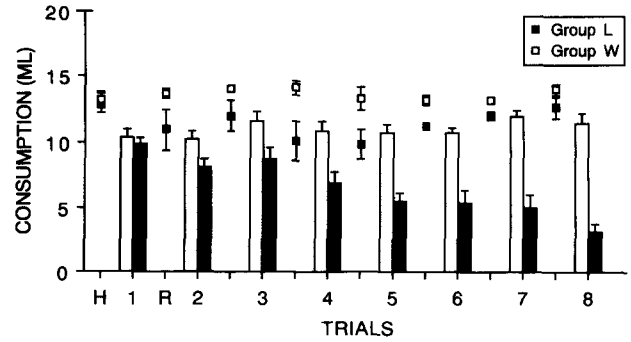

FIG. 1. The mean amount of saccharin consumed (±SEM) for subjects in Groups L and W over the repeated conditioning trials (filled and open columns, respectively). The filled and open squares represent an average of saccharin consumption on the three days of Saccharin Habituation (H) and on the three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

below habituation levels [$\chi_r^2(1) = 12.00$, for both groups]. There were no significant differences between groups on this initial conditioning trial [H(1) = 0.21]. The groups did differ in saccharin consumption on the second conditioning trial, at which point subjects in Group L drank significantly less than subjects in Group W [H(1) = 4.96]. This difference was maintained for the remainder of conditioning. On the final conditioning trial of this phase, subjects in Groups L and W drank 3.13 and 11.42 ml, respectively. During recovery sessions, saccharin consumption for both groups remained high, approximating habituation levels.

Phase II: Generalization.

Naltrexone. Figure 2 presents the mean amount (±SEM) of saccharin consumed for subjects in Groups L and W following injections of naloxone (conditioning), the distilled water vehicle (recovery) and various doses of naltrexone (0.032–1.8 mg/kg). To be included in the generalization function, individual subjects in Group L had to have discriminate control by naloxone immediately prior to the generalization test, i.e., a subject in Group L could consume no more than 50% of the mean consumption of subjects in the control group (i.e., Group W) on the conditioning trial immediately preceding that specific generalization session. Such a criterion ensured that the generalization function was based on stable discriminative control.

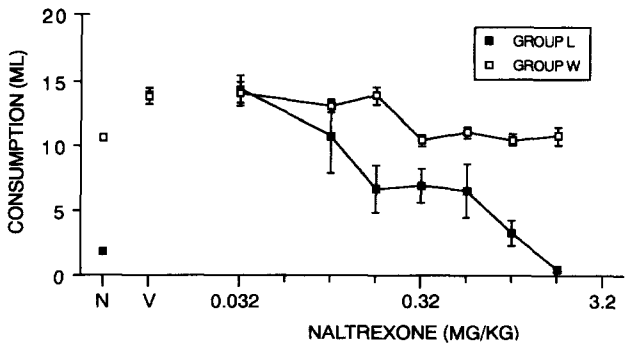

FIG. 2. The mean amount of saccharin consumed (±SEM) for subjects in Groups L and W following naloxone (N), the distilled water vehicle (V) and various doses of naltrexone during generalization testing.

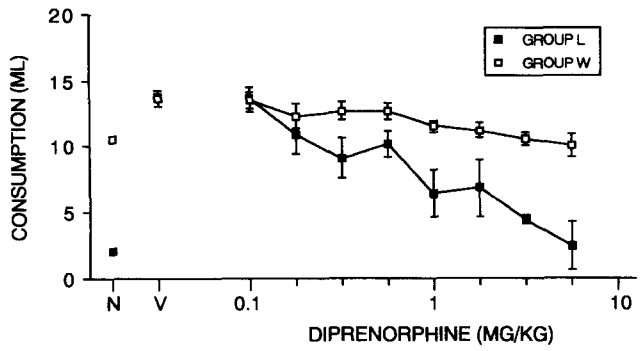

FIG. 3. The mean amount of saccharin consumed (±SEM) for subjects in Groups L and W following naloxone (N), the distilled water vehicle (V) and various doses of diprenorphine during generalization testing.

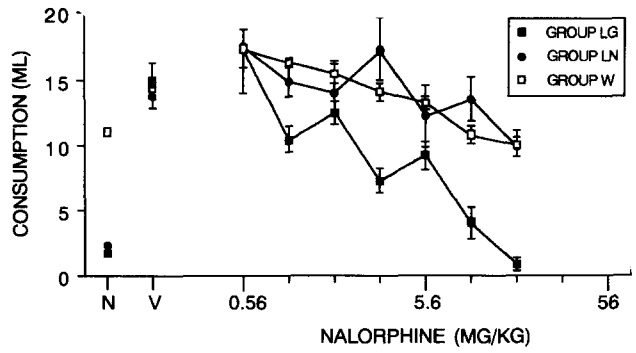

FIG. 4. The mean amount of saccharin consumed (±SEM) for subjects in Groups L and W following naloxone (N), the distilled water vehicle (V) and various doses of nalorphine during generalization testing. Subjects in Group L are grouped according to those for which nalorphine generalized (Group LG) or failed to generalize (Group LN) to naloxone.

As illustrated, for subjects in Group L there was an inverse relationship between the dose of naltrexone and the amount of saccharin consumed. Following a dose of 0.18 mg/kg naltrexone, consumption was reduced to 50% of the amount consumed following the distilled water (vehicle) injection. At this dose, consumption for subjects in Group W remained high (100% of the amount consumed following its vehicle injection). Naltrexone completely generalized to naloxone at 1.8 mg/kg, i.e., consumption following naltrexone was within or below the range of consumption following naloxone. Although there was a dose dependent decrease in saccharin consumption for subjects in Group W due to the unconditioned suppressant effects of naltrexone, this decrease was not as large as that for subjects in Group L, indicating that the dose dependent decreases in saccharin consumption for subjects in Group L were due to the discriminative function of naltrexone.

Diprenorphine. Figure 3 presents the same measures as Fig. 2 during generalization tests with various doses of diprenorphine (0.1–5.6 mg/kg). As illustrated, there was an inverse relationship between the dose of diprenorphine and the amount of saccharin consumed. Following a dose of 1 mg/kg diprenorphine, consumption was reduced to 50% of the amount consumed following the distilled water (vehicle) injection. At this dose, consumption for subjects in Group W remained high (82% of the amount consumed following its vehicle injection). Diprenorphine completely generalized to naloxone at 5.6 mg/kg. Although control subjects also displayed a dose-dependent decrease in saccharin consumption with increasing doses of diprenorphine, this decrease was not as large as that in experimental subjects.

Nalorphine. Unlike naltrexone and diprenorphine for which every subject displayed generalization to naloxone, there were two distinct subgroups of subjects in the nalorphine condition. Each of these subgroups is illustrated in Fig. 4. For five subjects (Group LG), there was an inverse relationship between the dose of nalorphine and the amount of saccharin consumed. Following a dose of 3.2 mg/kg nalorphine, consumption was reduced to 50% of the amount consumed following the distilled water (vehicle) injection. At this dose, consumption for subjects in Group W remained high (100% of the amount consumed following its vehicle injection). For Group LG, nalorphine completely generalized to naloxone at 18 mg/kg. For the remaining subjects (Group LN), consumption paralleled that of the control group, i.e., there was no evidence of generalization. There was a dose-dependent decrease in saccharin consumption for the control subjects as the dose of nalorphine increased. This decrease, however, was not as large as that in Group LG.

DISCUSSION

Rats trained to discriminate 1 mg/kg of naloxone from its vehicle rapidly acquired the naloxone discrimination, avoiding saccharin consumption when naloxone was administered prior to a saccharin-LiCl pairing and consuming saccharin when the vehicle was given prior to a nonpoisoned exposure to the same saccharin solution [see also (9)]. During subsequent generalization tests, naltrexone and diprenorphine generalized to the naloxone stimulus for all subjects. Nalorphine generalized to naloxone for five of the subjects tested. The dose at which complete generalization was evident was 1.8, 5.6 and 18 mg/kg for naltrexone, diprenorphine and nalorphine, respectively.

It has been reported that in opiate-naive animals, the discriminative stimulus effects of naloxone most likely result from actions on nonopioid systems, because the dose of naloxone used to establish discriminative control is considerably larger than those that produce antagonism in nondrug discrimination designs, and a number of other compounds with opiate antagonist activity do not generalize to the naloxone stimulus [for a discussion, see (1); see also (5,33)]. That in the present experiment, discriminative control was established with a low dose of naloxone (i.e., 1 mg/kg), and the opiate antagonists diprenorphine and naltrexone and the mixed opiate agonist/antagonist nalorphine generalized to the naloxone cue, suggest that the stimulus effects of naloxone within the taste aversion design may be mediated through the opiate receptor.

Although diprenorphine, nalorphine and naltrexone generalized to naloxone, presumably via their antagonist activity at opiate receptors, the mechanism underlying this generalization is less clear. Specifically, opiates are known to act at a number of receptor subtypes (12,16), and diprenorphine, nalorphine and naltrexone differ in their activity at these locations [see (36)]. For example, naltrexone (like naloxone) is a broad-based opiate antagonist with higher affinity for the mu receptor (10, 15, 34). Diprenorphine has almost equal affinity for mu, delta and kappa receptors (2, 15, 28). Finally, nalorphine binds to both mu and kappa receptors with higher affinity for the mu subtype (2, 15, 34). From these receptor profiles, the common characteristic that might underlie the cross generalization among these compounds is their activity at the mu receptor. Such a suggestion is consis-

tent with the complete generalization of naltrexone and diprenorphine to naloxone. However, if this generalization is a function of their common mu activity, it might be expected that nalorphine would also generalize to naloxone. As noted, such generalization was evident only in five subjects. The remaining subjects displayed vehicle-appropriate responding. Although the basis for this failure to generalize to naloxone is not known, it may be a function of the kappa agonist activity of nalorphine. The differential receptor activity of mixed agonist/antagonists may not be equally salient in the drug discrimination procedure. For example, buprenorphine, an opiate with mu agonist/kappa antagonist properties, generalizes to morphine in animals trained to discriminate morphine from its vehicle (4, 21, 22, 31), a generalization apparently based on their shared mu activity [see (21,35)]. Similarly, morphine generalizes to buprenorphine in animals trained to discriminate buprenorphine from its vehicle, a generalization also likely based on mu activity (25). Interestingly, neither diprenorphine nor MR 2266, compounds with kappa antagonist activity, generalizes to buprenorphine (25). That the kappa antagonist properties of buprenorphine do not seem to be revealed in the drug discrimination design suggests that its mu properties tend to override its kappa properties [see also (20)], at least within the procedures testing for such stimulus control. Although it is possible that in the present experiment nalorphine's kappa properties overshadowed its mu properties in subjects that failed to generalize nalorphine to naloxone, it would still be unclear why such overshadowing was evident in only these specific subjects.

The specific generalization patterns demonstrated in the present assessment within the taste aversion baseline are not entirely consistent with those previously reported using pure opiate antagonists as the training drug. As noted above, although Carter and Leander (1) reported that pigeons displayed naloxone-appropriate responding when given naltrexone, only one of two subjects displayed generalization when given diprenorphine (Carter, personal communication, 1991), and even with this subject the generalization was complete only at the highest dose of diprenorphine (30 mg/kg). Further, all subjects tested with nalorphine displayed complete generalization to naloxone. Similarly, Valentino, Herling and Woods (33) reported that although naloxone generalized to naltrexone in pigeons trained to discriminate naltrexone from its vehicle in a two-key, avoidance task, other opiates with antagonist activity, e.g., diprenorphine, nalorphine, MR 2266 and WIN 44,441 did not generalize to the naltrexone stimulus, even at doses that markedly suppressed response rates. Finally, DeRossett and Holtzman (3) have reported that in monkeys trained to discriminate diprenorphine from its vehicle in a two-lever, food reinforcement task, neither naloxone, naltrexone nor WIN 44,441 produced diprenorphine-appropriate responding while a number of opiate agonists (e.g., buprenorphine, etorphine and morphine) generalized to the diprenorphine cue. The basis for these differences is not known, although a number of parameters, including training dose, training drug and species, varied across the studies assessing drug discrimination with pure opiate antagonists. Any one of these factors (or some combination) may be important to the specific patterns obtained (7). Further, the contribution of the specific procedure used in the assessments may also be important. The taste aversion procedure used in the present experiment [see also (9)] is different from more traditional assessments of drug discrimination learning in terms of the rapidity with which discriminations are acquired [see (13, 18, 19)]. Because assessments of drug discrimination learning with taste aversions have been limited to basic demonstrations of stimulus control and generalization of that control to other compounds, it is not known to what extent findings from more traditional assessments of drug discrimination learning will compare to those eventually produced in the aversion design (27).

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