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Diprenorphine as a Stimulus in Drug Discrimination Learning

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SMURTHWAITE, S. T. AND A. L. RILEY. *Diprenorphine as a stimulus in drug discrimination learning.* PHARMACOL BIOCHEM BEHAV **43**(3) 839–846, 1992.—Using the conditioned taste aversion baseline of drug discrimination learning, animals were trained to discriminate diprenorphine from distilled water. In subsequent generalization tests, the opiate antagonists naltrexone and naloxone and the mixed opiate agonist/antagonist nalorphine substituted for the diprenorphine stimulus in a dose-dependent manner, while the opiate agonist morphine and the nonopiate pentobarbital failed to substitute even at the highest doses tested. That a range of opiate antagonists substituted for the diprenorphine stimulus (and an opiate agonist and a nonopiate failed to substitute) suggest that diprenorphine's antagonist properties may mediate the discrimination, presumably by blocking endogenous opiate activity. The ability of these drugs to substitute for the diprenorphine stimulus may also be a function of this receptor activity. The differences in the specific generalization patterns reported in the present assessment and those of earlier reports were discussed.

Drug discrimination learning Conditioned taste aversions Opiate antagonists Generalization

RECENTLY, DeRossett and Holtzman (4) suggested that the often-reported failure of the pure opiate antagonists naloxone and naltrexone to serve as discriminative stimuli in drug discrimination learning [(19,28), but see (16,31,33)] may be a function of their higher affinity for the μ-subtype of the opiate receptor (17,23,34), that is, the relatively selective antagonism of one of the major subtypes of the opiate receptor [i.e., μ, δ, κ; see (9,25)] may not be able to produce a discriminative effect sufficient to support such learning. Accordingly, a broad-based antagonist with comparable binding to these subtypes might provide the best assessment of the ability of opiate antagonists to support drug discrimination learning. Consistent with this position, they were able to train monkeys to discriminate intramuscular injections of low doses of the relatively nonselective opiate antagonist diprenorphine (3,23) from its vehicle in a discrete trial avoidance procedure, indicating that discriminative control can be established by nonselective opiate antagonists. Although diprenorphine did serve as a discriminative stimulus, a number of pure opiate antagonists (naloxone, naltrexone, WIN 44,441) failed to substitute for the diprenorphine stimulus. Further, the μ-receptor agonists morphine and etorphine, the κ-receptor agonists ethylketocyclazocine and normetazocine, and the mixed agonist/antagonist buprenorphine and nalorphine produced *diprenorphine-appropriate* responding. Instead of providing support for opiate antagonist activity mediating diprenorphine's stimulus effects, these patterns are more consistent with opiate agonist activity as the drug stimulus (4,9,18).

These generalization patterns with diprenorphine are not consistent with some recent findings in rats trained to discriminate *naloxone* from its vehicle within the taste aversion baseline of drug discrimination learning [(31); for reviews, see (27,30)]. Specifically, Smurthwaite et al. (31) reported that a number of opiate antagonists, including diprenorphine, substituted for the naloxone stimulus in naloxone-trained subjects. Given that naloxone has no efficacy at the opiate receptor [i.e., it is a pure opiate antagonist; (23)], the substitution of diprenorphine for naloxone is not likely based upon some shared *agonist* property but instead on shared *antagonist* activity at the opiate receptor.

In the DeRossett and Holtzman (4) study, diprenorphine was the training drug, while in the Smurthwaite et al. (31) report naloxone served as the training stimulus. To test whether the training drug is important in the generalization patterns for the opiate antagonists, rats were trained in the present experiment to discriminate diprenorphine from its vehicle within the taste aversion procedure. Specifically, every fourth day rats were injected with 3.2 mg/kg diprenorphine prior to a pairing of saccharin and LiCl. On intervening days, they were injected with the diprenorphine vehicle prior to an exposure to the same saccharin solution but not paired with LiCl. Following establishment of the discrimination, animals were given various doses of diprenorphine, naltrexone, nalorphine, naloxone, morphine, or pentobarbital to assess their ability to substitute for the diprenorphine stimulus.

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METHOD

Subjects and Apparatus

Subjects were 21 experimentally naive, female rats of Long-Evans descent, approximately 120 days of age at the beginning of the experiment. Subjects were housed in individual wire-mesh cages and maintained on a 12 L : 12 D cycle and at an ambient temperature of 23°C for the duration of the experiment.

Drugs

Diprenorphine HCl, morphine sulfate, nalorphine HCl, naltrexone HCl, and pentobarbital were generously supplied by the National Institute on Drug Abuse (Rockville, MD). Naloxone HCl 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 body weight.

Procedure

Phase 1: Conditioning. Following 24 h of water deprivation, all subjects were given 20-min access to water once a day for 16 consecutive days. On days 17–19 (saccharin habituation), a novel saccharin solution (0.1% w/v sodium saccharin, Sigma Chemical Co., St. Louis, MO) replaced water during the daily 20-min fluid-access period. On day 19, all subjects were given an IP injection of distilled water 15 min prior to saccharin access and were assigned to one of two groups (group L, $n = 9$; or group W, $n = 12$). On day 20, subjects in both groups were given an IP injection of 3.2 mg/kg diprenorphine 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 these recovery days. This alternating procedure of conditioning/recovery was repeated for 13 complete cycles.

Phase 2: Generalization. The procedure in this phase was identical to that in Phase 1 with the following exception. On the second recovery day following conditioning, one of a range of doses of either diprenorphine, naltrexone, naloxone, morphine, nalorphine, or pentobarbital 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.

Statistical Analysis

All determinations of statistical significance for the acquisition of the diprenorphine discrimination are based upon 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 upon $p < 0.05$, two tailed.

RESULTS

Phase 1: Conditioning

Figure 1 presents the mean amount (± SEM) of saccharin consumption 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 3 days of saccharin habituation (11.76 and 12.22 ml for subjects in groups L and W, respectively) did not differ between the two groups of subjects ($U = 455, 517$; see Fig. 1). On the initial conditioning trial, there were no significant differences in saccharin consumption between groups ($U = 47, 61$) with subjects in both groups consuming saccharin significantly below habituation levels ($z = -2.666$ and -2.314 for groups L and W, respectively). By the second conditioning trial, significant differences emerged between groups, with subjects in group L drinking significantly less than subjects in group W ($U = 26$,

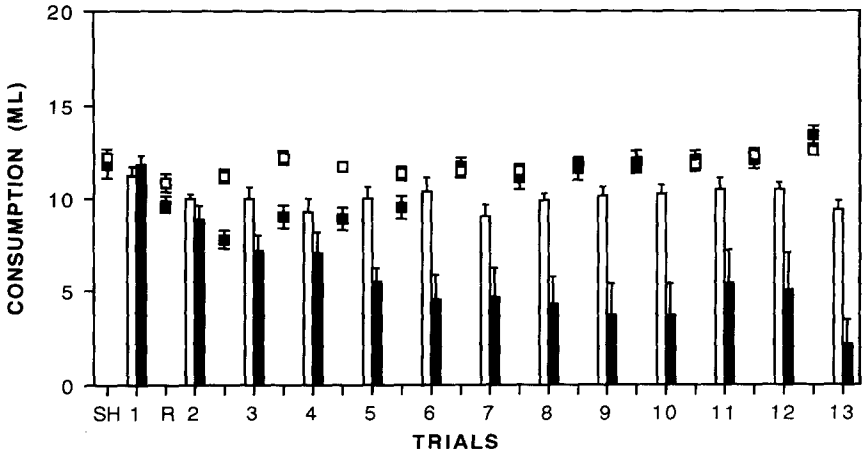

FIG. 1. Mean amount of saccharin consumed (± SEM) for subjects in groups L and W over the repeated conditioning trials (solid and open columns, respectively). The solid and open squares represent a mean of saccharin consumption (± SEM) on the three days of saccharin habituation (H) and on the three recovery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

82). 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 2.22 and 9.44 ml, respectively. On recovery sessions following the first five conditioning trials, subjects in group L drank significantly less saccharin than subjects in group W (all zs < -2.129). After the sixth conditioning trial, saccharin consumption during recovery did not differ between groups ($z = -0.556$), with consumption approximating habituation levels.

Phase 2: Generalization

Diprenorphine. Figure 2 presents the mean amount (± SEM) of saccharin consumption for subjects in groups L and W following various probe doses of diprenorphine (0–10 mg/kg). To be included in the generalization function, individual subjects in group L had to have discriminative control by diprenorphine immediately prior to a generalization test, that is, 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 upon stable discriminative control.

As illustrated, there was an inverse relationship between saccharin consumption and the dose of diprenorphine for subjects in group L. Although there was also a dose-dependent decrease in saccharin consumption for subjects in group W (presumably due to the unconditioned suppressant effects of diprenorphine), 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 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 0.32 mg/kg. At this dose, consumption for subjects in group W was approximately 68% of the amount consumed following distilled water. At a dose of 1.8 mg/kg diprenorphine, subjects in group L displayed complete substitution for the training dose of 3.2 mg/kg (i.e., consumption following this dose was within or below the range of consumption following the training dose of diprenorphine). At this dose, subjects in group W drank approximately 76% of the amount consumed following distilled water. There was individual variability within group L regarding the specific dose at which substitution occurred. For example, two of the nine subjects in this group displayed complete substitution at 0.18 and 0.32 mg/kg, respectively, while a single subject displayed substitution only at the highest dose tested, that is, 10 mg/kg.

Naltrexone. Figure 3 presents the generalization tests with various doses of naltrexone (0–10 mg/kg). As illustrated, there was an inverse relationship between saccharin consumption and the dose of naltrexone for subjects in group L. Consumption did not systematically vary over increasing doses of naltrexone for subjects in group W. The lowest dose at which consumption by subjects in group L was reduced by at least 50% of the amount consumed following distilled water was 0.55 mg/kg. At this dose, consumption for subjects in group W was approximately 74% 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 diprenorphine. At this dose, subjects in group W drank approximately 63% of the amount consumed following distilled water. As with diprenorphine, there was individual variability within group L regarding the dose at which this complete substitution occurred. For example, five of the nine subjects in this group displayed complete substitution at 0.56 mg/kg naltrexone, while a single subject failed to substitute even at the highest dose tested.

Nalorphine. Figure 4 presents the generalization tests with various doses of nalorphine (0–32 mg/kg). As illustrated, there was an inverse relationship between saccharin consumption and the dose of nalorphine for subjects in group L. Control subjects also displayed a dose-dependent decrease in saccharin consumption with increasing doses of nalorphine. This decrease was not as large as that in experimental subjects, especially at the higher doses of nalorphine (see Fig. 4). The lowest dose at which consumption by subjects in group L was reduced by at least 50% of the amount consumed following distilled water was 18 mg/kg. This was also the dose at which complete substitution was evident. At this dose, consumption for subjects in group W was 58% of the amount consumed following distilled water. There was little individual variability within group L regarding the dose at which complete substitution occurred. Spe-

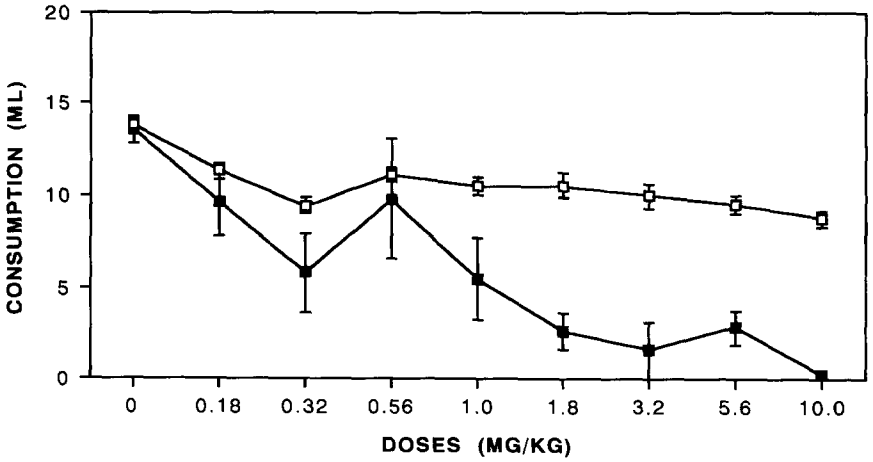

FIG. 2. Mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various 1/4 log doses of diprenorphine during generalization testing. Each point reflects a minimum of seven subjects.

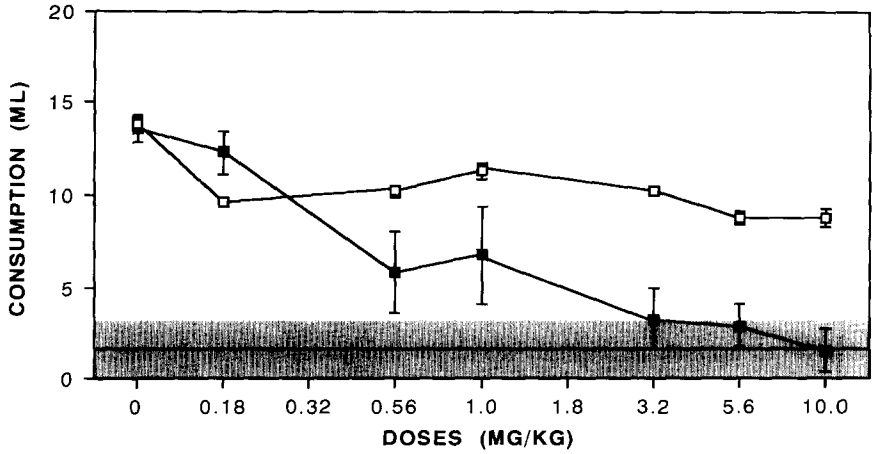

FIG. 3. Mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various 1/4 log doses of naltrexone during generalization testing. The mean amount of saccharin consumed following the training dose of diprenorphine (3.2 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this line illustrates ±SEM. Each point reflects a minimum of six subjects.

cifically, only a single subject displayed substitution for nalorphine at a dose less than 18 mg/kg.

Naloxone. Figure 5 presents the generalization tests with various doses of naloxone (0–32 mg/kg). Although there was an initial inverse relationship between saccharin consumption and the dose of naloxone (0–5.6 mg/kg) for subjects in group L, consumption increased at 10 and 18 mg/kg. Consumption at 32 mg/kg decreased again, but only to the level displayed following the lower doses (e.g., 3.2 and 5.6 mg/kg). Subjects in group W displayed an inverse relationship between consumption and naloxone dose, systematically decreasing saccharin consumption with increases in the dose of naloxone. The lowest dose at which consumption by subjects in group L was reduced by at least 50% of the amount consumed following distilled water was 3.2 mg/kg. At this dose, consumption for subjects in group W was 61% of the amount consumed following distilled water. As noted, for subjects in group L increases in the dose of naloxone above 5.6 mg/kg (to 18 mg/kg) resulted in increases in saccharin consumption to and above the level of control subjects (i.e., group W). At the highest dose of naloxone tested, there was no difference in saccharin consumption between subjects in groups L and W.

Although the overall pattern of consumption for group L appears to indicate a failure of naloxone to substitute completely for the training dose of diprenorphine, six of the nine subjects in group L did display *complete* substitution at some

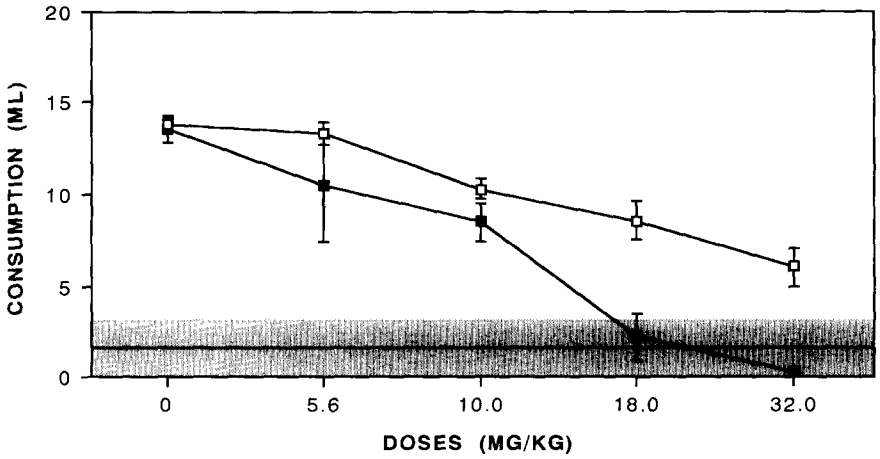

FIG. 4. Mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various 1/4 log doses of nalorphine during generalization testing. The mean amount of saccharin consumed following the training dose of diprenorphine (3.2 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this line illustrates ±SEM. Each point reflects a minimum of six subjects except 5.6 mg/kg, which reflects four subjects.

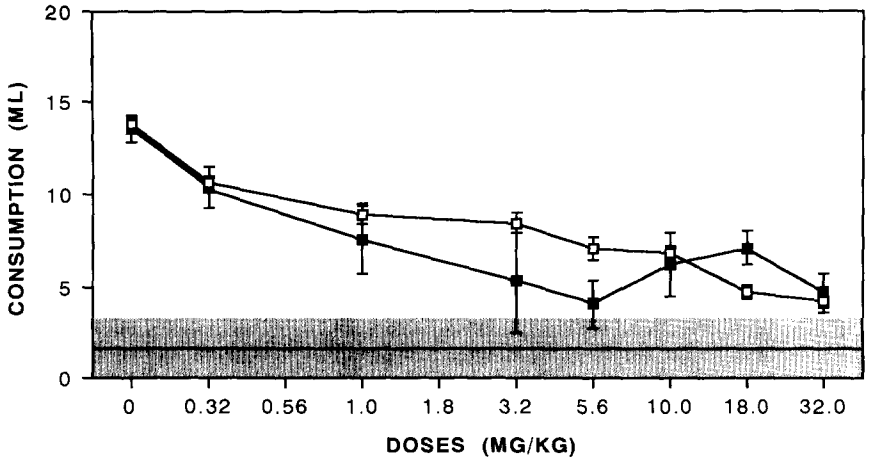

FIG. 5. Mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various 1/4 log doses of naloxone during generalization testing. The mean amount of saccharin consumed following the training dose of diprenorphine (3.2 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this line illustrates ± SEM. Each point reflects a minimum of six subjects except 0.32 mg/kg, which reflects five subjects.

dose of naloxone. (The lowest amount consumed by the remaining three subjects was 4.25, 3.25, and 4.00 ml, respectively.) The failure of the group to substitute in light of the patterns of individual subjects is a result of the U-shaped dose–response function of the individual subjects. Specifically, each subject in group L initially decreased consumption of saccharin as the dose of naloxone increased. For each subject, consumption decreased to (or near) the level of that following the training dose of diprenorphine, that is, complete (or near complete) substitution. With further increases in the dose of naloxone, consumption increased for all subjects. The point at which the curve shifted from a decreasing to an increasing function varied among subjects, with one subject displaying complete substitution at 1 mg/kg, two at 3.2 mg/kg, one at 5.6 mg/kg, and two at 10 mg/kg. The group curve reflects an averaging of different points on the increasing and decreasing arms of the function, yielding partial substitution.

Morphine. Figure 6 presents the generalization tests with various doses of morphine (0–18 mg/kg). As illustrated, subjects in group L decreased saccharin consumption below the distilled water baseline at the two lower doses of morphine (to approximately 53% of the distilled water baseline at 10 mg/kg). At the highest dose tested, that is, 18 mg/kg, consumption increased to approximately 70% of the amount consumed following distilled water. Subjects in group W also slightly decreased saccharin consumption at the two lower doses of morphine. At

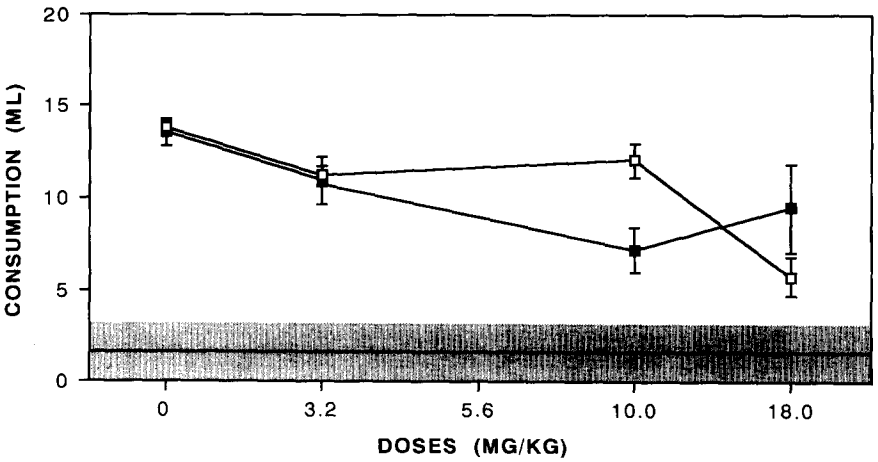

FIG. 6. Mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various 1/4 log doses of morphine during generalization testing. The mean amount of saccharin consumed following the training dose of diprenorphine (3.2 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this line illustrates ± SEM. Each point reflects a minimum of five subjects.

18 mg/kg, these subjects decreased consumption to approximately 41% of the distilled water baseline. Subjects in group L drank less than subjects in group W only at the 10-mg/kg dose. At 18 mg/kg, subjects in group L drank more saccharin than subjects in group W.

Pentobarbital. Figure 7 presents the generalization tests with various doses of pentobarbital (0–18 mg/kg). There was no clear relationship between saccharin consumption and the dose of pentobarbital for subjects in group L. As illustrated, consumption at 3.2 mg/kg was slightly greater than that consumed following distilled water. Consumption increased above the distilled water baseline for three subjects at 10 mg/kg. At the highest dose (18 mg/kg), consumption decreased to approximately 70% of the amount consumed following distilled water. At 3.2 and 10 mg/kg pentobarbital, consumption for subjects in group W did not differ from that consumed following distilled water. At 18 mg/kg, these subjects displayed a marked reduction in saccharin consumption to approximately 41% of the amount consumed following distilled water. Subjects in group L drank more saccharin than subjects in group W at both the 10- and 18-mg/kg doses of pentobarbital.

DISCUSSION

As noted above, monkeys trained to discriminate diprenorphine from its vehicle do not generalize this control to other opiate antagonists (4), whereas rats trained to discriminate naloxone from its vehicle do generalize discriminative control to diprenorphine (31). Because the training drug in these two reports differed, the present experiment was initiated to determine if the training drug was important in the specific generalization patterns obtained for diprenorphine. In the following study, animals injected with diprenorphine prior to a saccharin-LiCl pairing and distilled water prior to saccharin alone rapidly acquired the drug discrimination (within two conditioning trials), avoiding saccharin when it was preceded by an injection of diprenorphine and consuming the same saccharin solution when it was preceded by distilled water. In subsequent tests for substitution, various doses of diprenorphine generalized in a dose-dependent manner, with consumption decreasing as the dose of diprenorphine increased. Similar inverse relationships were displayed for naltrexone and nalorphine. The generalization function for naloxone was U-shaped with consumption initially decreasing as the dose of naloxone increased. With doses greater than 5.6 mg/kg, consumption increased until it was suppressed by the adipsogenic effects of the drug. The opiate agonist morphine and the nonopiate pentobarbital failed to occasion diprenorphine-appropriate responding even at the highest doses tested.

That the generalization patterns observed in the present experiment, that is, opiate antagonist generalization, differed from those previously reported by DeRossett and Holtzman (4) suggests that the training drug may not be a major factor in diprenorphine generalization (12,13). In the present experiment and that of DeRossett and Holtzman, diprenorphine was an effective discriminative stimulus yet very different generalization patterns emerged. Although the basis for the differences in the generalization patterns between the present data and those of DeRossett and Holtzman is not likely due to the training drug, the specific factor(s) responsible for the difference is not known. A number of possibilities do exist, however, for example, the species examined and the specific procedures used in the generalization assessment. The present experiment used rats as subjects, whereas DeRossett and Holtzman used monkeys. Although generalization of opiate control within drug discrimination learning is generally similar for the rat and monkey [as opposed to the pigeon (5,10,11)], the monkey does appear to be relatively more sensitive than the rat to diprenorphine in a number of behavioral procedures (1,20). The degree to which this relative sensitivity affects discrimination learning with diprenorphine or the subsequent generalization of diprenorphine to other antagonists is not known. It is interesting in this context that diprenorphine does *not* substitute for naltrexone in opiate-naive pigeons trained to discriminate naltrexone from its vehicle [(2,33); for a discussion of diprenorphine substitution to antagonists in opiate-experienced animals see (5–8)], suggesting that

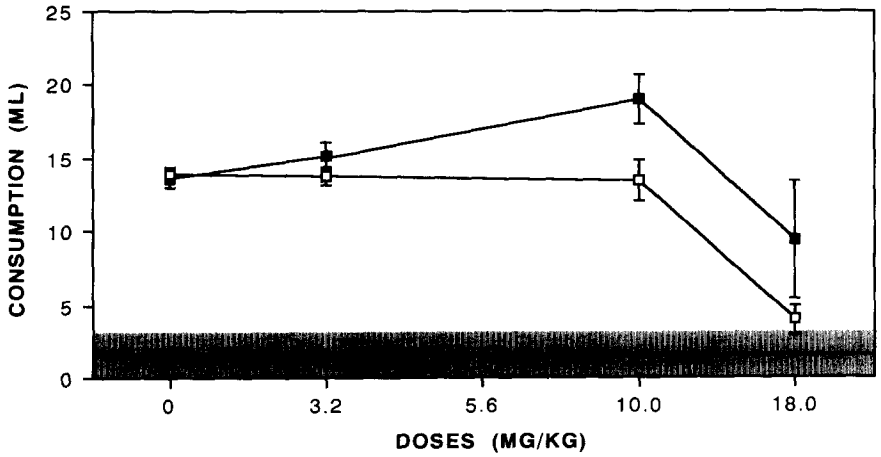

FIG. 7. Mean amount of saccharin consumed (± SEM) for subjects in groups L (■) and W (□) following various 1/4 log doses of pentobarbital during generalization testing. The mean amount of saccharin consumed following the training dose of diprenorphine (3.2 mg/kg) for subjects in group L is indicated by the horizontal line in the center of the shaded area. The shaded area above and below this line illustrates ± SEM. Each point reflects a minimum of five subjects except 3.2 mg/kg, which reflects three subjects.

the pigeon is more like the monkey in the generalization patterns of the opiate antagonists.

An additional difference between the two procedures assessing drug discrimination learning with diprenorphine is the specific assessment of the discrimination. The present experiment utilized the taste aversion baseline of drug discrimination learning, whereas DeRossett and Holtzman (4) utilized a discrete trial avoidance procedure. Different designs are certain to affect the rate of acquisition of the drug discrimination, the probability of demonstrating discriminative control, the types of generalization and the doses at which such generalization occurs (15). Although the limited data that have been generated within the aversion design are in general consistent with those reported from more traditional assessments (14,21,22,26,29,32,35), the aversion procedure does appear more sensitive in establishing opiate antagonist discriminations in opiate-naive animals than other drug discrimination baselines (16,31). This sensitivity may be reflected not only in the dose and the rate at which the discrimination is acquired but also in the resulting generalization patterns.

The present findings of opiate antagonist generalization are consistent with other work assessing the generalization among opiate antagonists within the taste aversion procedure. As noted above, Smurthwaite et al. (31) reported that animals trained to discriminate naloxone from its vehicle within the aversion baseline generalize this control to naltrexone, nalorphine, and diprenorphine. They concluded that the generalization among the opiate antagonists was likely based upon their common affinity for the μ-receptor subtype of the opiate receptor, that is, although the specific binding characteristics of diprenorphine, nalorphine, naloxone, and naltrexone differ (23), they all bind to some degree to the μ-receptor. Although this conclusion is consistent with the substitution of naltrexone and nalorphine for diprenorphine in the present experiment, the generalization pattern at the higher doses of naloxone is not. Specifically, for all individual subjects in group L consumption initially decreased with increasing doses of naloxone, only to increase with higher doses. It might be expected that consumption would continue to decrease with increasing doses if only the μ-receptor mediated the stimulus effects of diprenorphine and naloxone.

Although the discriminative effects of the opiate antagonists may be mediated at the opiate receptor, the mechanism by which such stimulus effects are produced is not known. If the stimulus properties of the antagonist in opiate-naive animals are produced via its antagonist activity at the opiate receptor, presumably these stimulus effects are a result of the antagonism of *endogenous* opiate activity (31). Such a conclusion does not imply that the activity at the receptor is identical for the different antagonists, only that the endogenous opiate levels are sufficiently antagonized. For example, naloxone and naltrexone are pure opiate antagonists (23), compounds with high affinity for, but limited efficacy at, the opiate receptor, that is, while these compounds bind to the opiate receptor they have no intrinsic activity and produce no opiate-like effects. The antagonist activity of nalorphine (and possibly diprenorphine) is somewhat different. Nalorphine is a partial agonist, that is, it has affinity for opiate receptors but an intrinsic activity that is less than that of a full agonist such as morphine [see Table 1 of (24), p. 470]. Accordingly, nalorphine's ability to antagonize effects induced by morphine may be due to its partial agonist activity. Interestingly, diprenorphine has been described as a partial opiate agonist in some preparations as well (18). The important implication in such an analysis is not the specific efficacy of the compound at the receptor but the ability of the compound to antagonize endogenous opiate levels.

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