Pharmacology Biochemistry and Behavior, Vol. 66, No. 4, pp. 851–856, 2000

0091-3057/00/$–see front matter

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PII S0091-3057(00)00280-X

Morphine Discriminative Control Is Mediated by the Mu Opioid Receptor: Assessment of Delta Opioid Substitution and Antagonism

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Received 8 October 1999; Revised 23 February 2000; Accepted 9 March 2000

STEVENSON, G. W., F. CANADAS, X. ZHANG, K. C. RICE AND A. L. RILEY. *Morphine discriminative control is mediated by the mu opioid receptor: Assessment of delta opioid substitution and antagonism.* PHARMACOL BIOCHEM BEHAV **66**(4) 851–856, 2000.—Morphine is an effective training drug in drug discrimination procedures. In subsequent generalization tests in which other opioids are administered, mu opioid agonists selectively substitute for the training drug. Given the relative selectivity of morphine for the mu receptor, such substitution patterns suggest that the mu opioid receptor is mediating the discriminative control of this compound. The present study assessed this selective mediation by examining the ability of the delta opioid agonist SNC80 to substitute for (and the delta opioid antagonist naltrindole to antagonize) morphine stimulus effects in rats trained to discriminate morphine from its vehicle in the conditioned taste aversion baseline of drug discrimination learning. Although morphine and methadone produced dose-related substitution for morphine (10 mg/kg), there was no evidence of substitution for morphine by SNC80 at any dose tested. Further, although naloxone (3.2 mg/kg) completely blocked the discriminative effects of morphine, naltrindole (3.2–10 mg/kg) did not significantly affect the morphine stimulus. These data suggest that the discriminative control established to morphine is mediated by its activity at the mu, but not the delta, receptor. © 2000 Elsevier Science Inc.

Morphine SNC80 Naltrindole Conditioned taste aversion Rat

AS early as 1971, Hill and his colleagues (11) reported that morphine was an effective cue in drug discrimination learning (5,12,23). Although the initial assessments of morphine discriminative control focused on its acqusition and the conditions under which it occurred, later work focused on its receptor mediation (7,10,25,27,37,39,40,45,47,49). For example, Shannon and Holtzman (37,39) reported that morphine was acting on opiate receptors to effect its discriminative control [see also (5,50)], although the specific opiate receptors involved were not known. Both biochemical and behavioral investigations have implicated three distinct opiate receptors, specifically, mu, delta, and kappa (8,15–17,24). Although morphine is relatively selective for the mu receptor, depending on the dose it binds to it has effects at all three (1,4,16,46). In one of the initial assessments of the receptor mediation of morphine's discriminative effects, Negus and his colleagues (21) reported that rats trained to discriminate morphine from its vehicle selectively generalized morphine control to opioid agonists with relative selectivity for the mu receptor, but not to those selective for the kappa receptor. Thus, similar to a variety of other opioid-induced effects, for example, analgesia, respiratory depression, inhibition of gastrointestinal transit, morphine discriminative control appears to be based on its activity at the mu receptor (20,30,38,45,51).

To date, there have been relatively few reports assessing delta receptor activity in morphine drug discrimination learning. Further, these assessments have been limited to nonselective opioid compounds or selective delta peptides administered ICV (14,48). It is not known if these findings with the centrally administered peptides generalize to systemically active com-

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pounds. For example, in rats trained to discriminate morphine from saline, the delta peptide metkephamid produces morphine-appropriate responding when injected ICV and saline-appropriate responding when injected systemically (14).

Recently, a systemically active delta agonist (+)-4-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC80), the methyl ether of one enantiomer of BW373U86 (3), has been synthesized that demonstrates high selectivity for the delta receptor and at the highest doses tested shows no signs of toxicity (2,22). Such a compound allows for an assessment of the role of the delta receptor in the mediation of morphine drug discrimination. Accordingly, in the present experiment animals were trained to discriminate 10 mg/kg morphine from vehicle using the conditioned taste aversion baseline of drug discrimination learning (9,13,31,32,34,36,45). Once discriminative control was established, a range of doses of SNC80 were administered to assess the ability of this compound to substitute for the morphine discriminative cue. A range of doses of the opioid agonist morphine and the mu agonist methadone (26) were also assessed for their ability to engender morphine-appropriate responding. In a further assessment of the receptor mediation of the discriminative effects of morphine, both the opioid receptor antagonist naloxone (1,16), as well as the delta receptor antagonist naltrindole (29), were administered prior to morphine to determine if the stimulus properties of morphine could be differentially blocked.

METHOD

Subjects and Apparatus

The subjects were 13 experimentally naive, Long–Evans female rats approximately 200–290 g at the beginning of the experiment. They 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. Rat chow (Prolab Rat, Mouse, Hamster 3000) was available ad lib.

Drugs

Morphine sulfate, methadone hydrochloride, naltrexone hydrochloride, naltrindole (all generously supplied by NIDA) and naloxone hydrochloride (generously supplied by DuPont Pharmaceuticals) were dissolved in distilled water. SNC80 (generously supplied by NIDDK) was prepared as a base dissolved in distilled water and 6 M HCl. All drugs were injected intraperitoneally (IP) and prepared at the following concentrations: morphine (10 mg/ml), methadone (10 mg/ml), SNC80 (2 mg/ml), naloxone (1 mg/ml), and naltrindole (2 mg/ml).

Procedure

Phase I: Acquisition. At the outset of training, subjects were given 20-min access to water once a day for 14 consecutive days in their home cages until all subjects consistently drank levels greater than 10 ml. On days 15–17 (saccharin habituation), a novel saccharin solution (0.1 w/v sodium saccharin, Sigma Pharmaceuticals) replaced water during the daily 20-min fluid-access period and was preceded on the last day of saccharin habituation by an IP injection of distilled water (1 ml/kg).

On day 18, conditioning began. All subjects were injected with 10 mg/kg of morphine 30 min prior to 20-min access to saccharin. Immediately following saccharin access, subjects were ranked according to saccharin consumption (i.e., from lowest to highest) and assigned to one of two groups (group ML, i.e., morphine-lithium, $n = 7$, and group MW, i.e., morphine-water, $n = 6$). Subjects in group ML were then injected with 1.8 milliequivalents (mEq), 0.15 M LiCl (76.8 mg/kg), while subjects in group MW were given an equivolume injection of distilled water (i.e., the LiCl vehicle). On the following three recovery days, subjects in both groups were injected with distilled water 30 min prior to 20-min access to the same saccharin solution. No injections followed saccharin on these recovery days. This alternating procedure of conditioning and recovery was repeated until discriminative control had been established for all experimental subjects (i.e., each subject in group ML had consumed at least 50% less than the mean of group MW on two consecutive conditioning trials).

Phase II: Generalization. The procedure during this phase was identical to that of Phase I with the following exception. On the second day following conditioning (the second recovery day within Phase I, but a probe day in this phase), subjects were administered one of a range of doses of morphine (1.8–10 mg/kg), methadone (3.2–7.5 mg/kg) or SNC80 (3.2–24 mg/kg) 30 min prior to saccharin access. On any specific probe day, subjects in group ML were given an injection only if they had consumed at least 50% less than the mean of the control subjects on the two preceding conditioning trials. Doses were administered in a mixed pattern. No injections followed saccharin access on these probe sessions.

Phase III: Naloxone challenge. The procedure for this phase was identical to that of Phase I, with the exception that on the second recovery day following each conditioning trial, animals were given 3.2 mg/kg of naloxone 60 min prior to the training dose of morphine (i.e., 10 mg/kg). This time course of 60 min (for naloxone preexposure) was based on previous research in our laboratory (45) demonstrating complete antagonism of the discriminative effects of morphine when naloxone was administered 60 min prior to morphine. Thirty minutes following the injection of morphine, all subjects were given 20-min access to saccharin. To assess the effects of naloxone alone on saccharin consumption, all subjects were given naloxone 60 min prior to an injection of distilled water and then 30 min later given access to saccharin. No injections followed saccharin access on these test days.

Phase IV: Naltrindole challenge. The procedure for this phase was identical to that of Phase III, with the exception that animals were given one of a range of doses of naltrindole (3.2–10 mg/kg) 60 min prior to the injection of morphine. Thirty minutes following the injection of morphine, all subjects were given 20-min access to saccharin. To assess the effects of naltrindole alone on saccharin consumption, all subjects were given naltrindole 60 min prior to an injection of distilled water and then 30 min later given access to saccharin. No injections followed saccharin access on these test days.

Data Analysis

Statements of statistical significance are based on the Mann–Whitney *U*-test ($p < 0.05$) for all between-group comparisons of saccharin consumption, the Wilcoxin Sum Ranks test ($p < 0.05$) for all within-group comparisons of $k = 2$ and the Friedman test ($p < 0.05$) for all within-group comparisons ($k \geq 3$) of saccharin consumption.

RESULTS

Phase I: Acquisition

There were no significant differences in saccharin consumption between groups during saccharin habituation or over the first two conditioning trials (all p values > 0.05). On the third conditioning trial, subjects in group ML drank significantly less saccharin than subjects in group MW ($U = 39$, 3, $p = 0.004$).

This difference was maintained for the remainder of the conditioning. On the final conditioning trial of this phase, subjects in groups ML and MW drank 2.5 and 9.83 ml of saccharin, respectively. During recovery sessions, consumption for both groups remained high, approximating habituation levels.

Phase II: Generalization

Throughout this phase, data are presented for six subjects in group ML (one subject did not maintain discriminative control during this phase; see criterion for generalization testing) and five subjects in group MW (one subject died after the acquisition phase). Figure 1 presents the mean amount (±SEM) of saccharin consumption for subjects in groups ML and MW following various doses of morphine, methadone, and SNC80. As illustrated in Fig. 1 (top panel), for subjects in group ML there was an inverse relationship between the dose of morphine and the amount of saccharin consumed (χ^2 =18; p = 0.001). For subjects in group MW, there were no consistent changes in saccharin consumption over the increasing doses of morphine. Consumption was significantly different between groups ML and MW at 3.2, 5.6, and 10 mg/kg (all p-values $\geqslant$ 0.05). The middle panel of Fig. 1 presents the mean amount (±SEM) of saccharin consumption for subjects in groups ML and MW following various doses of methadone. As illustrated, for subjects in both groups ML and MW there was an inverse relationship between the dose of methadone and the amount of saccharin consumed (χ^2 11.880; p = 0.008 and χ^2 = 14.186; p = 0.003). Consumption was significantly different between groups ML and MW at 5.6 and 6.5 mg/kg (all p-values $\geqslant$ 0.026). The bottom panel of Fig. 1 presents the mean amount (±SEM) of saccharin consumption for subjects in groups ML and MW following various doses of SNC80. As illustrated, there was an inverse dose–response function following injections of SNC80 for both groups (χ^2 = 16.581; p 0.002), with no significant differences between groups ML and MW at any dose tested (all p-values $\geqslant$ 0.05).

Phases III and IV: Naloxone and Naltrindole Challenges

Figure 2 presents the mean amount (±SEM) of saccharin consumption for subjects in groups ML and MW following the naloxone/morphine (top panel) and naltrindole/morphine (bottom panel) combinations. As illustrated in the top panel, for subjects in group ML, consumption following naloxone (10.92 ml) was significantly increased relative to the amount consumed following the distilled water vehicle (0.40 ml), reflective of the blocking of morphine's stimulus effects (T =15, 0, p = 0.031). Conversely, for subjects in group MW, consumption following naloxone (10.95 ml) was significantly decreased relative to the amount consumed following the distilled water vehicle (14.70 ml), indicative of the unconditioned sup-

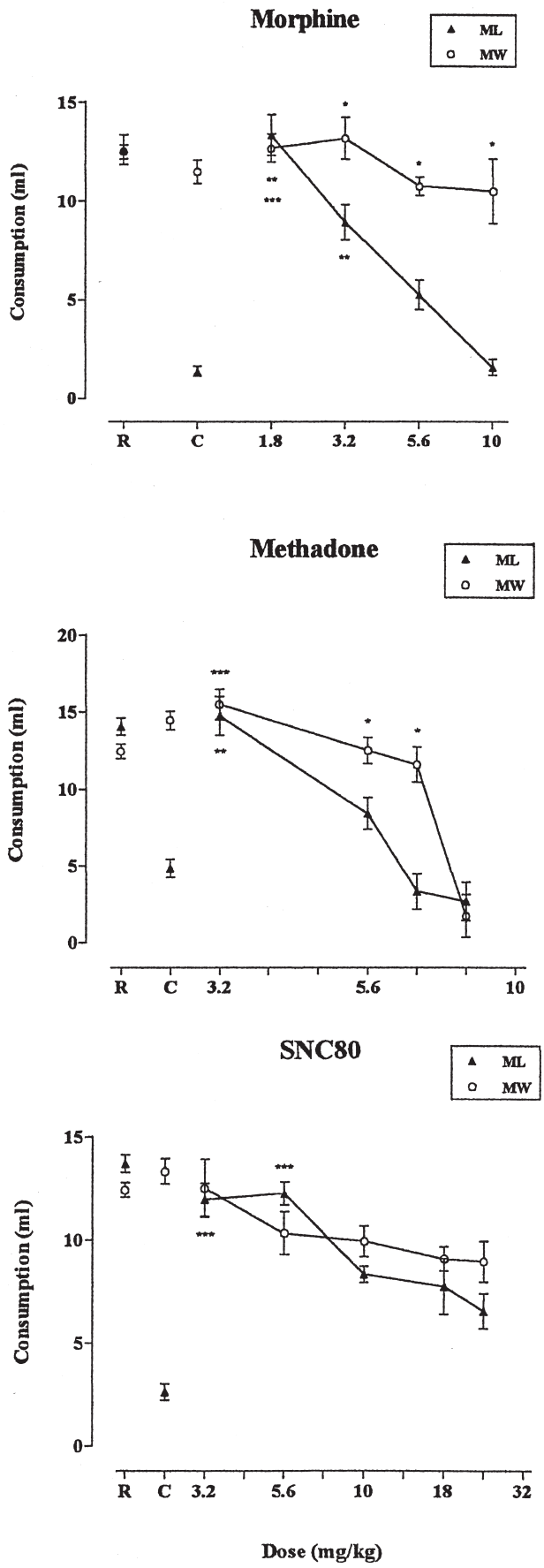

FIG. 1. Mean amounts of saccharin consumption (±SEM) for subjects in groups ML and MW during recovery (R) and conditioning (C) and following various doses of morphine (1.8–10 mg/kg, top panel), methadone (3.2–7.5 mg/kg, middle panel), and SNC80 (3.2–24 mg/kg, bottom panel). Top panel *significantly greater than subjects in Group ML (all p-values $\leqslant$ 0.05). **Significantly greater than consumption at 10 mg/kg for group ML (χ^2 = 18; p = 0.001). ***Significantly greater than consumption at 5.6 mg/kg (χ^2 = 18; p = 0.001). Middle panel *significantly greater than subjects in group ML (all p-values $\leqslant$ 0.026). **Significantly greater than consumption at 6.5 and 7.5 mg/kg for group ML (χ^2 = 11.880; p = 0.008). ***Significantly greater than consumption at 7.5 mg/kg for group MW (χ^2 = 14.186; p = 0.003). Bottom panel ***Significantly greater than consumption at 24 mg/kg for group ML (χ^2 = 16.581; p = 0.002).

pressant effects of naloxone on consumption ($T = 15, 0, p = 0.031$). As illustrated in the bottom panel of Fig. 2, following naltrindole, subjects in group ML did not significantly increase saccharin consumption relative to the amount consumed following the distilled water vehicle ($\chi^2 = 7.364$; $p = 0.061$), indicating that naltrindole did not block the discriminative effects of morphine, although there was a nonsignificant trend toward increased consumption. In addition, following 3.2, 5.6, and 10 mg/kg naltrindole, subjects in group ML continued to drink less saccharin than subjects in group MW (all p-values < 0.05).

DISCUSSION

Both biochemical and behavioral studies have implicated three distinct opiate receptors: mu, delta, and kappa (8,15–17,24). Although research suggests that the discriminative effects of morphine are mediated at the mu, but not the kappa, receptor (21), there have been relatively few reports assessing delta receptor activity in morphine drug discrimination learning, and they have been limited generally to the peptides (14,48). Because it is not clear to what extent findings with delta peptides generalize to systemically active compounds [interestingly, some delta peptides produce morphine- or vehicle-appropriate responding, depending on the route of administration; see (14)], in the present experiment the systemically active delta selective compound SNC80 was assessed for its ability to substitute for morphine in animals trained to discriminate morphine from distilled water using the conditioned taste aversion baseline of drug discrimination learning (9,13,31,32,34,36,45). A range of doses of the opioid agonist morphine and the mu agonist methadone were also assessed for their ability to engender morphine-appropriate responding. Subsequently, both the opioid receptor antagonist naloxone and the delta opioid receptor antagonist naltrindole were administered prior to morphine to determine if the stimulus properties of morphine could be diiferentially blocked.

As described, animals injected with morphine prior to a saccharin and LiCl pairing acquired the drug discrimination, consuming significantly less saccharin following morphine than following the morphine vehicle. The discrimination was dose-dependent in that as the dose of morphine increased, the amount of saccharin consumed decreased. In subsequent generalization tests, the mu agonist methadone produced morphine-appropriate responding in a dose-dependent manner. That both morphine and methadone substituted for the discriminative effects of the training dose of 10 mg/kg morphine is consistent with other research (6,37), suggesting that morphine's discriminative effects are mediated at the mu opioid receptor. Conversely, the highly selective, systemically active delta agonist SNC80 produced vehicle-appropriate responding. Although data on the ability of systemically active delta agonists to substitute for morphine stimulus control are relatively scarce (see Introduction), the present findings are consistent with previous work reporting that DPLPE fails to substitute for morphine in a discrete trial-avoidance procedure, while the mu selective compounds (DAMGO and FK33824) produce morphine-appropriate responding (48). These selective generalization patterns with methadone and SNC80 suggest that the discriminative effects of morphine are mediated at the mu, but not the delta, receptor. These findings are also similar to those in a recently published report with monkeys (28), demonstrating failure of the discriminative effects of morphine to generalize to SNC80, a similarity that is consistent with the position that rats and monkeys share similar sensitivities for the discriminative effects of opiates (50).

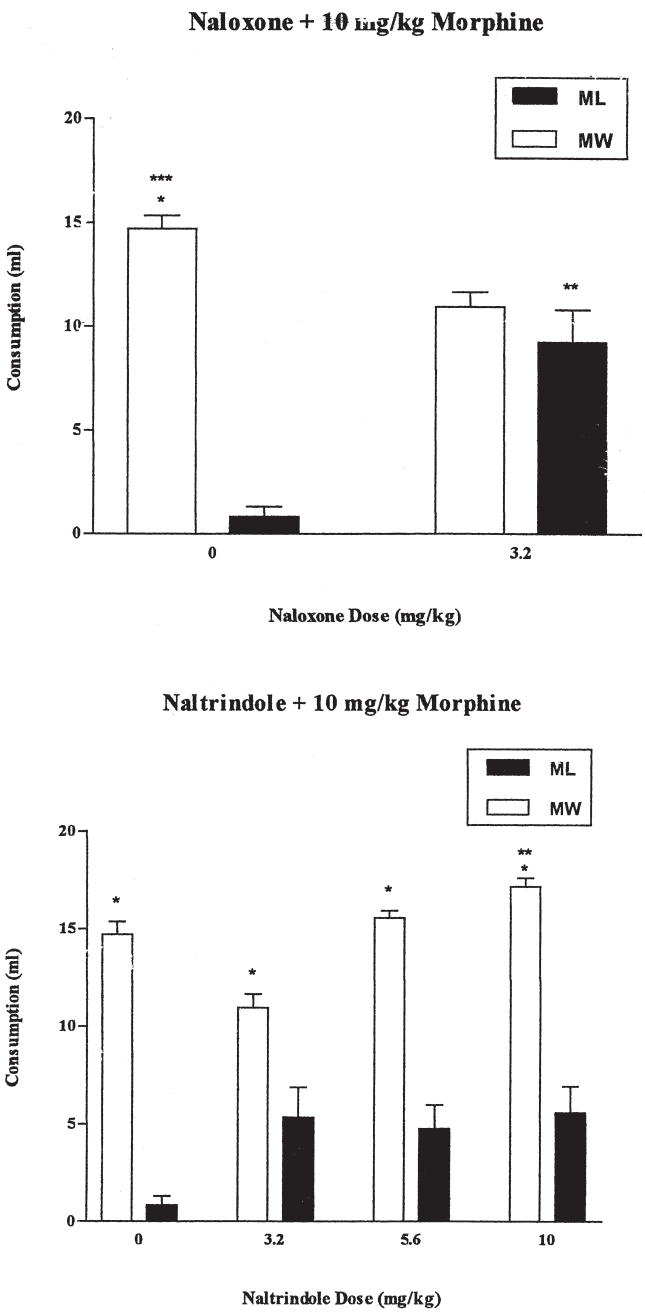

FIG. 2. Mean amounts of saccharin consumption (±SEM) for subjects in groups ML and MW following the naloxone/morphine (top panel) and naltrindole/morphine (bottom panel) combinations. Top panel *significantly greater than subjects in group ML at 0 mg/kg ($U = 30$, $p = 0.002$). **Significantly greater than consumption at 0 mg/kg for group ML ($t = 15, 0$, $p = 0.031$). ***Significantly greater than consumption at 3.2 mg/kg for group MW ($t = 15,0$, $p = 0.031$). Bottom panel *significantly greater than subjects in group ML (all p-values ≤ 0.05). **Significantly greater than consumption at 0, 3.2, and 5.6 mg/kg for group MW ($\chi^2 = 13.280$; $p = 0.010$).

The conclusion that morphine's stimulus effects are mediated at the mu receptor is further supported by the fact that morphine's discriminative control was completely blocked by the opioid antagonist naloxone, but not by the delta antago-

nist naltrindole. That naloxone completely antagonized morphine's discriminative effects is in agreement with a variety of other reports (5,37,38,45) demonstrating complete antagonism of morphine stimulus control by naloxone. Although naltrindole failed to block the discriminative effects of morphine, it should be noted that there was a slight increase in saccharin consumption in subjects given naltrindole prior to morphine, suggesting a partial antagonism of the morphine cue. However, this increase in consumption was not significant (relative to consumption when the vehicle was given prior to morphine). Given that the delta agonist SNC80 did not substitute at any dose for morphine, the slight increase in saccharin consumption following the naltrindole/morphine combination unlikely reflects a partial antagonism of the morphine cue or any delta mediation of morphine's discriminative effects. The fact that control subjects drank significantly more saccharin following the highest dose of naltrindole than following vehicle suggests that naltrindole alone may have an unconditioned stimulant effect on drinking.

The results of the present experiment suggest that the discriminative effects of morphine are not mediated at the delta receptor. This conclusion, however, is based on the specific parameters within the present experiment. For example, it is not clear if the ability of SNC80 to substitute for, or naltrindole to antagonize, the discriminative effects of morphine vary according to (a) dose range, (b) route of administration, (c) time course, (d) training dose, (e) gender, or (f) testing condition. A more complete analysis of these parameters may further characterize the selective receptor mediation of the prototypical opioid agonist morphine. Although each of these factors may influence to some degree the occurrence of delta receptor mediation of morphine discriminative control, one of these factors, i.e., the testing condition, deserves discussion. Specifically, the assessment in the present experiment utilized the conditioned taste aversion baseline of drug discrimination learning. As reviewed elsewhere (33,35), this baseline appears especially sensitive in terms of the speed of acquisition of discriminative control and the varieties of drugs to which discriminative control can be established [for discussions of limitations within this baseline, see (33,35)]. Given the relative newness of this preparation, the range of drugs that have been examined and the conditions under which control can be established and blocked are relatively limited (34). As such, it is not known how data generated within this design compare to those produced in more traditional assessments. In the limited comparisons that have been made, discriminative control within the aversion design appears to be affected by similar parametric conditions as those reported in other procedures (18,19,45). Further, pharmacological classifications established within the aversion baseline (41–43) parallel those established under other drug discrimination designs (and general pharmacological assessments). Interestingly, the manner by which the drug stimulus is processed in drug discrimination learning appears to be quantal under both the aversion and traditional designs (44). The degree to which data from the aversion design generalize to other preparations will necessitate further use of this procedure in the general assessment of the stimulus properties of a variety of drugs, including the opioids.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Mellon Foundation to A.L.R.

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