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Assessment of SNC 80 and Naltrindole Within a Conditioned Taste Aversion Design

AURORA C. HUTCHINSON,* GREGORY R. SIMPSON,* JOVITA F. RANDALL,* XIAOYAN ZHANG,† SILVIA N. CALDERON,† KENNER C. RICE† AND ANTHONY L. RILEY*

*Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016 and †Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892

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HUTCHINSON, A. C., G. R. SIMPSON, J. F. RANDALL, X. ZHANG, S. N. CALDERON, K. C. RICE AND A. L. RILEY. *Assessment of SNC 80 and naltrindole within a conditioned taste aversion design.* PHARMACOL BIOCHEM BEHAV **66**(4) 779–787, 2000.—Although compounds with relative selectivity for the mu and kappa opiate receptors subtypes have been reported to condition taste aversions, it is not known whether systemically administered delta compounds have the ability to produce aversions. To that end, female Long-Evans rats were adapted to water deprivation and were given pairings of a novel saccharin solution and various doses of the selective delta agonist SNC 80 (0.32–10.0 mg/kg; Experiment 1) or the selective delta antagonist naltrindole (1.0–18.0 mg/kg; Experiment 2). For comparison, the relatively selective mu agonist morphine (Experiment 1) and mu antagonist naloxone (Experiment 2) were assessed under identical conditions. Both SNC 80 (Experiment 1) and naltrindole (Experiment 2) were effective as unconditioned stimuli within this design, inducing dose-dependent taste aversions with repeated conditioning trials. Although at no dose did animals injected with SNC 80 differ from those injected with morphine, aversions induced by SNC 80 were acquired at a faster rate than those induced by morphine. Subjects injected with naloxone drank significantly less than those injected with naltrindole at the 10 mg/kg dose, and aversions induced by naloxone at 5.6 and 10 mg/kg were acquired at a faster rate than those induced by naltrindole. Although the basis for opioid agonist- and antagonist-induced taste aversions is not known, the differences between aversions induced by SNC 80 and naltrindole and those induced by morphine and naloxone, respectively, may be a function of their relative selectivity for specific opiate receptor subtypes. © 2000 Elsevier Science Inc.

SNC 80 Naltrindole Delta receptor Conditioned taste aversion Rat

IF consumption of a novel solution is followed by illness or poison, the rat will avoid consumption of that solution on a subsequent exposure [see (29,67,73); for a bibliography, see (70)]. This avoidance is typically termed a conditioned taste aversion and presumably reflects an association between the taste and aversive consequences of the drug [though see (21,48)]. Although initially demonstrated in rats poisoned with x-irradiation (30), a wide range of compounds from a variety of drug classes have now been demonstrated to support such learning [see (70,71); see also (3,10,46)].

One specific group of drugs that has received considerable interest in this regard is the opioids. As early as 1972, Berger (7) reported that rats significantly increased the latency to initiate drinking sweetened condensed milk that had previously been paired with morphine (10 mg/kg; administered intraperitoneally). Subsequently, several other laboratories reported that such taste-morphine pairings significantly suppressed consumption as well [see (16,36); see also (4,5,6,47,52,68, 70,79,83)]. Although aversions were induced by morphine, these aversions often took more than a single trial to develop, were highly variable, were often weak and were not dose-related [see (68,79)]. These characteristics are different than those of aversions induced by classical aversion-inducing agents [see (68)], suggesting that opioid-induced aversions

Requests for reprints should be addressed to Aurora C. Hutchinson, Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016. Fax: 202-885-1081. E-mail: ah4984a@american.edu.

and those induced by classical emetics are qualitatively different (2,34,58,68).

Although the initial assessments of opioid-induced aversions focused on the opioid agonist morphine, the ability of the opioid antagonist naloxone to induce aversions has also been assessed. Like morphine, aversions are also induced by naloxone. Such an effect was initially reported by Pilcher and his colleagues who demonstrated that naloxone (10 mg/kg; administered intraperitoneally) resulted in approximately a 40% suppression of saccharin consumption in rats after four conditioning trials [see (62)]. Subsequently, naloxone has been extensively investigated for its ability to induce aversions [see (22,24,35,39,40,51,53,54)]. Interestingly, with few exceptions [see (24,49,51,61,62)] naloxone-induced aversions are weak even at high doses and with repeated conditioning trials.

Conclusions regarding the ability of opioid agonists and antagonists to induce aversions (as well as the nature of aversions induced by such compounds) have generally been based on work with morphine and naloxone. Although limited, assessments of aversion learning with other opioid agonists do exist. For example, methadone (17), fentanyl and sufentanyl (51) and ethylketazocine, U50 488H, tifluadom, bremazocine, (+)-bremazocine, (−)-bremazocine, Mr 2034 and (−)-tifluadom (51) have been reported to condition aversions [though see (87) for a failure with heroin and (26) for a failure with buprenorphine]. Aversions have also been induced by other opioid antagonists, including naltrexone, methylnaltrexone, diallylnormorphinium, Mr 1452 and BC-2860 [see (49,50,59, 62,84,85)].

Although aversions can clearly be induced by opioid agonists and antagonists, it is important to note that such demonstrations are limited to compounds with relative selectivity for the mu or kappa receptor subtypes of the opiate receptor (see above). Accordingly, it is not known if selective delta agonists and antagonists induce aversions and, if so, whether aversions induced by such compounds are similar to those induced by action at the mu and/or kappa receptor subtypes. In the single paper assessing the effects of a delta agonist within the aversion design, Stapleton et al. (82) reported that d-ala^2-methionine enkephalin (10 ug; administered intracerebroventricularly (icv)) failed to induce taste aversions even after four conditioning trials. However, given that icv-administered morphine also failed to condition aversions raised the issue of whether the failure of methionine enkaphalin to induce aversions was due to the ineffectiveness of delta agonists, a general weakness of the induction of aversions when compounds are administered icv [see (12,35,80)], or site specific effects in the brain (2). Further, no specific assessments of delta opioid antagonists have been made within the taste aversion design. Thus, the ability of compounds with selective delta activity to induce aversions remains unknown.

Recently, a number of nonpeptidergic compounds with high delta selectivity have been synthesized which allow for an assessment of the ability of peripherally-administered delta agonists and antagonists to condition taste aversions. For example, SNC 80 ((+)-4-[α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide), a methyl ether of an enantiomer of the selective delta agonist BW373U86, has recently been reported to be a systemically active and highly selective (2000-fold selectivity for delta versus mu) delta agonist (8,14). Naltrindole (17-cyclopropyl-methyl-6,7-dehydro-4,5-epoxy-3,14-dihydroxy-6,7,2′,3′-indolomorphinan) is a nonpeptidergic, delta antagonist that selectively (124-fold selectivity for delta versus mu) antagonizes delta (but not mu and kappa) mediated effects in both in vitro and in vivo assays of opioid activity (18,38,60,63,64,65,72). Given this selectivity (and the ability of these compounds to be administered systemically), the present studies examined the ability of SNC 80 (Experiment 1) and naltrindole (Experiment 2) to induce taste aversions. For comparison, morphine (Experiment 1) and naloxone (Experiment 2) were assessed under identical conditions.

GENERAL METHOD

Subjects

The subjects were experimentally naive, female rats of Long-Evans descent. They were maintained on a 12L:12D cycle (lights on at 0800 h) and at an ambient temperature of 23° C for the duration of the experiments. Food was available ad libitum. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed at all times.

Apparatus

Subjects were individually housed in stainless-steel, wire-mesh cages. Graduated Nalgene 50 ml centrifuge tubes were attached to the front of the cages to provide 20-min access to water or saccharin.

Drugs and Solutions

Morphine sulfate (generously supplied by NIDA), SNC 80 (generously supplied by the Laboratory of Medicinal Chemistry, NIH), naloxone hydrochloride (generously supplied by DuPont Pharmaceuticals) and naltrindole hydrochloride (generously supplied by NIDA) were prepared as 2 mg/ml solutions in distilled water. SNC 80 was prepared as base (solubilized with aqueous HCl). Saccharin (0.1% sodium saccharin, Sigma Chemical Co.) was prepared as a 1 g/l solution in tap water.

Procedure

Phase I: Habituation. Following 23-h water deprivation, all subjects were given 20-min access to water. This procedure was repeated daily until all subjects were approaching and drinking from the tube within 2 sec of its presentation (10 days).

Phase II: Conditioning. On the first day of this phase, all subjects were given 20-min access to a novel saccharin solution during their scheduled 20-min fluid-access period. Immediately following saccharin access, the subjects were ranked according to their saccharin consumption and assigned to an experimental condition using a counterbalanced design. This procedure was used to ensure minimal variation in initial saccharin consumption between experimental groups. Animals were then given a subcutaneous (sc) injection of the appropriate drug and dose, as designated by their experimental grouping. Subjects assigned to the control group (W) were given a sc injection of distilled water (the drug's vehicle), equivolume to the highest dose administered in the experimental groups.

On the following three water-recovery days, all subjects were given 20-min access to water. No injections were given following water access on these days. This alternating procedure of conditioning/water recovery was repeated until all subjects had received four complete cycles. On the day following the final water-recovery session, all subjects were given 20 min access to saccharin in a final one-bottle test of

the aversion to saccharin. No injections were given following this test.

Experiment 1

On the initial conditioning trial, 63 animals (192-298 g) were assigned to nine groups ($n = 7$ per group) and injected sc with SNC 80 or morphine. Specifically, 15 min following saccharin exposure, subjects in Groups S0.32, S1, S3.2, and S10 were given a sc injection of 0.32, 1, 3.2 and 10 mg/kg SNC 80, respectively. Subjects in Groups M0.32, M1, M3.2 and M10 were given a sc injection of 0.32, 1, 3.2 and 10 mg/kg morphine, respectively. Subjects in the control group (W) were given a sc injection of distilled water at a volume equal to that given to Groups S10 and M10.

Experiment 2

Experiment 2 was run as two separate experiments: Experiment 2a tested doses of naltrindole and naloxone at 1, 3.2 and 10 mg/kg ($n = 6$ per group). A single control group ($n = 8$) received the drug's vehicle. Body weight ranged from 220-336 g within groups. Experiment 2b tested naltrindole and naloxone at 5.6, 10 and 18 mg/kg ($n = 6$ per group). A single control group ($n = 8$) received the drug's vehicle. Body weight ranged from 160-212 g within groups. Collapsed over experiments, 88 animals were injected sc with naltrindole or naloxone on the initial conditioning trial. Specifically, subjects in Groups NT1, NT3.2, NT5.6, NT10 and NT18 ($n = 6$, except Group NT10, $n = 12$) were given a sc injection of 1, 3.2, 5.6, 10 and 18 mg/kg naltrindole, respectively. Subjects in Groups NX1, NX3.2, NX5.6, NX10 and NX18 ($n = 6$, except Group NX10, $n = 12$) were given a sc injection of 1, 3.2, 5.6, 10 and 18 mg/kg naloxone, respectively. Subjects in the control group (W; $n = 16$) were given a sc injection of distilled water at a volume equal to that given to subjects receiving the highest dose of naltrindole and naloxone in Experiments 2a and 2b.

DATA ANALYSIS

Separate analyses were conducted for Experiments 1 and 2. In Experiment 1, differences in saccharin consumption were analyzed using a 9 × 5 Repeated Measures Analysis of Variance (ANOVA) with between-subjects variable of Group [control (W), S0.32, S1, S3.2, S10, M0.32, M1, M3.2 and M10] and within-subjects variable of Trial (Trials 1–4 and Test). As previously mentioned, both Experiments 2a and 2b included a control, NT10 and NX10 group. Three separate 2 × 5 Repeated Measures ANOVAs (Group × Trial), one each for the control, NT10 and NX10 groups, were conducted to compare saccharin consumption over trials between Experiments 2a and 2b. Because there was no significant Group effect nor significant Group × Trial interaction, the data from these two experiments were pooled to form a single control, NT10 and NX10 group. Accordingly, in Experiment 2 differences in saccharin consumption were analyzed using an 11 × 5 Repeated Measures ANOVA with between-subjects variable of Group [control (W), NT1, NT3.2, NT5.6, NT10, NT18, NX1, NX3.2, NX5.6, NX10 and NX18] and within-subjects variable of Trial (Day 1–4 and Test). In both experiments, the repeated measures ANOVAs were followed by one-way ANOVAs for each trial and pair-wise comparisons, using Tukey HSD post-hoc tests. In Figures 1 and 2, W is represented as a dose of 0 mg/kg of the drugs. Alpha was set at 0.05, two-tailed.

RESULTS

Experiment 1

Figure 1 illustrates saccharin consumption (±SEM) for groups injected with varying doses of morphine and SNC 80 over the four conditioning trials and on the final aversion test. The figure compares the dose-response functions for both drugs at 0, 0.32, 1, 3.2 and 10 mg/kg. The 9 × 5 repeated measures ANOVA revealed significant effects of Group, $F(8, 54) = 8.842$, $p < 0.001$, and Trial, $F(4, 216) = 18.546$, $p < 0.001$, and a significant Group × Trial interaction, $F(32, 216) = 2.834$, $p < 0.001$.

Subsequent one-way ANOVAs conducted on individual trials revealed significant between-group effects on Trials 2-5, Fs$(8, 54) > 5.25$, ps < 0.001. The initial conditioning trial showed no significant differences between groups, with all groups drinking approximately 9.5 ml of saccharin. Tukey HSD post-hoc pair-wise comparisons revealed that on Trial 2 Group S10 drank significantly less saccharin than all other groups (ps < 0.01), except Groups M3.2 and M10, neither of which differed from any other group. There were no other significant differences on this trial. On Trial 3, Group S10 drank significantly less than all other groups (ps < 0.01), except Group M10 which differed only from Group M0.32 ($p < 0.05$). Trial 4 revealed significant differences between Group S10 and all other groups ($p < 0.05$), again except Group M10, which on this trial drank less than Groups W, S0.32 and M0.32 ($p < 0.05$). On the final aversion test, Group S10 again drank significantly less saccharin than all other groups except the high dose of morphine ($p < 0.05$). Group M10 drank significantly less saccharin than Groups W, S0.32, M0.32 and M1.0 (ps < 0.05).

All groups drank comparable amounts of water during recovery days, where the average consumption for animals in each group on the recovery days immediately prior to each conditioning day ranged from 11.73 ml to 13.5 ml.

Experiment 2

Figure 2 illustrates saccharin consumption (±SEM) for groups injected with varying doses of naltrindole and naloxone over the four conditioning trials and on the final aversion test. The figure compares the dose-response functions for both drugs at 0, 1, 3.2, 5.6, 10 and 18 mg/kg. The 11 × 5 repeated measures ANOVA revealed significant effects of Group, $F(10, 77) = 16.307$, $p < 0.001$, and Trial, $F(4, 308) = 4.803$, $p < 0.01$, and a significant Group × Trial interaction, $F(40, 308) = 5.617$, $p < 0.001$.

Subsequent one-way ANOVAs conducted on individual trials revealed significant between-group differences on Trials 2-5, Fs$(10, 77) > 4.481$, ps < 0.001. The initial conditioning trial showed no between-group differences, with all groups drinking approximately 9 ml. Tukey HSD post-hoc pair-wise comparisons revealed that on Trial 2 Groups NT18 and NX18 drank significantly less saccharin than all other groups (ps < 0.05), except Groups NX10, NT5.6 and NX5.6, but did not differ from each other. Comparisons on Trial 3 revealed that Group NX18 differed from all groups (ps < 0.01), except Groups NT18 and NX10. Group NT18 also drank less than all other groups (ps < 0.01), except Groups NX10 and NX5.6. Although Group NX10 did not differ from either Groups NX18 or NT18, this group drank significantly less than all other groups (ps < 0.05). No other between-group differences were significant on this trial. Differences noted for Trial 3 were also evident on Trial 4 (ps < 0.05). On the final aversion

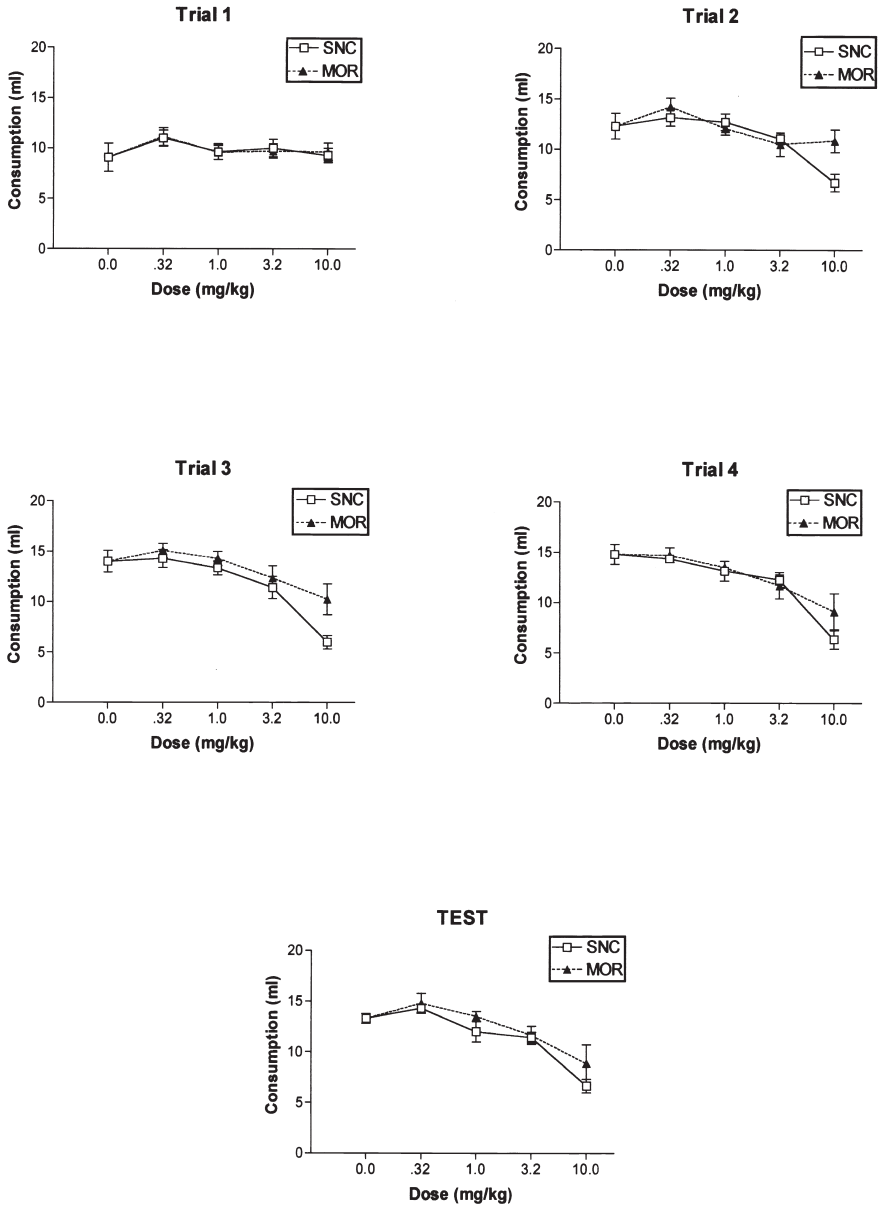

FIG. 1. The mean (±SEM) amount of saccharin consumed following taste-drug pairings with various doses of SNC 80 and morphine on each of four conditioning trials and on the final one-bottle aversion test.

test, Group NX18 still differed from all other groups ($ps < 0.01$), except Groups NT18 and NX10. Group NT18 differed from all groups ($ps < 0.01$) except the three highest naloxone dose groups (NX5.6, NX10, NX18). Group NX10 differed from all but the high dose groups of both naloxone and naltrindole ($ps < 0.01$), and Group NX5.6 drank significantly less saccharin than Groups NX1, NT1 and NT3.2 ($ps < 0.05$). There were no other significant between-groups differences on this test.

All groups drank comparable amounts of water during recovery days, where the average consumption for animals in each group on the recovery days immediately prior to each conditioning day ranged from 11.2 ml to 13.14 ml.

DISCUSSION

Assessments of opioid-induced conditioned taste aversions have focused primarily on compounds relatively selective for the mu and kappa opiate receptor subtypes (34,51,83). To date, the present experiments are the first assessments of systemically administered delta-selective compounds within the conditioned taste aversion design. As demonstrated, both the selective delta receptor agonist SNC 80 (8,14) and the selective delta receptor antagonist naltrindole (63,64,65,72) were effective as unconditioned stimuli within this design, inducing taste aversions over repeated conditioning trials. Specifically, in Experiment 1 aversions were induced by 10 mg/kg SNC 80. These aversions were significant in comparison to

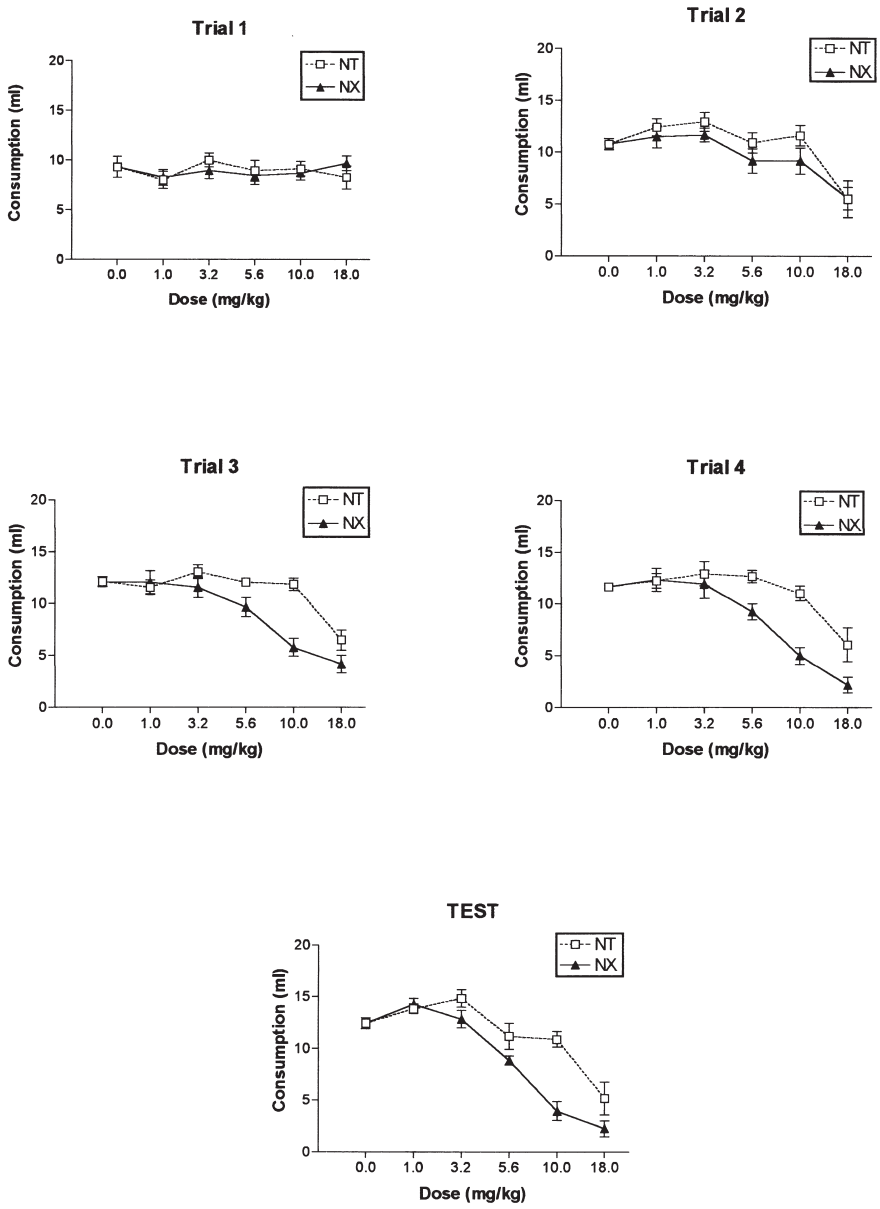

FIG. 2. The mean (±SEM) amount of saccharin consumed following taste-drug pairings with various doses of naltrindole and naloxone on each of the four conditioning trials and on the final one-bottle aversion test.

those induced by the vehicle and to the other doses of SNC 80 tested (i.e., 0.32, 1 and 3.2 mg/kg, sc). Furthermore, aversions induced by 10 mg/kg SNC 80 occurred after a single conditioning trial. Aversions were also induced by naltrindole in Experiment 2 and, similar to SNC 80, were evident only at the highest dose tested (i.e., 18 mg/kg, sc). These aversions were significant in comparison to those induced by the vehicle and the other doses of naltrindole tested (i.e., 1, 3.2, 5.6 and 10 mg/kg, sc) and were evident after two conditioning trials. The present demonstration that SNC 80 and naltrindole have aversive properties adds to the growing list of biochemical, physiological and behavioral effects of systemically administered delta compounds [see (8,11,19,23,33,42,45,55)]. Furthermore, the paradoxical ability of SNC 80 to act as both an aversive (taste aversion) and reinforcing (place preference) stimulus (41) is consistent with the effects demonstrated with a range of psychoactive drugs, particularly drugs of abuse including morphine (4,6,15,16,27,28,34,52,68,69).

Comparisons of aversions induced by SNC 80 and naltrindole to those induced by morphine and naloxone, respectively, revealed differences between their aversive effects. For example, although in Experiment 1 there were no significant differences in saccharin consumption between groups of subjects exposed to comparable doses of SNC 80 and morphine, there were differences in the rate of acquisition of the aversions. For example, whereas SNC 80-induced aversions at 10

mg/kg were evident after a single conditioning trial relative to vehicle and the other doses of SNC 80 tested, aversions induced by morphine were not evident until the third and fourth conditioning trials (relative to the 0.32 on Trial 3 and to the 0.32 mg/kg morphine and vehicle-injected groups on Trial 4). The fact that the rate of acquisition of the aversion induced by morphine was slower than that by SNC 80 suggests that SNC 80 may be slightly more aversive than morphine in this preparation. Such a conclusion should be made cautiously, however, given that the rate of acquisition of the aversion to SNC 80 in comparison to morphine was faster by only two trials (relative to controls) and at a single dose (10 mg/kg) and that there were no significant differences between the SNC 80 and morphine groups at comparable doses. Assessments with higher doses of SNC 80 and morphine might have revealed larger, more consistent differences; however, it should be noted that aversions to other opioids (e.g., morphine) are typically weak and dose-independent (16,34,36,68,79,88) and administration of higher doses may reduce the selectivity of these compounds for their respective receptors, resulting in non-specific behavioral effects (74).

Direct behavioral comparisons of SNC 80 and morphine are limited, and as such, it is difficult to draw conclusions concerning the relative effects of these two compounds in other preparations. Furthermore, the comparisons that have been made are limited to mice. In one of these assessments that examined writhing responses induced by intraperitoneal injections of acetic acid in mu-knockout and wild-type mice, a 10 mg/kg, sc dose of morphine produced a significantly greater reduction in writhing responses in wild-type mice compared to a comparable dose of SNC 80 (81). Similarly, in an assessment of the antagonism of antinociception induced by SNC 80 and morphine in the hot-plate and tail-flick tests (8), a dose of 100 mg/kg SNC 80 produced comparable levels of antinociception to that induced by morphine at a 10 mg/kg dose. As noted, there are no direct behavioral comparisons between SNC 80 and morphine in rats. Comparisons, however, can be made across studies in which the effects of SNC 80 and morphine have been examined. For example, SNC 80 [i.e., 1.25 and 5 mg/kg, sc, (41)] and morphine [i.e., 1 and 3 mg/kg, sc, (51); 1 and 5 mg/kg, sc, (66)] have been shown to produce comparable dose-dependent conditioned place preferences in rats. That SNC 80 is less analgesic than morphine in analgesia assessments, comparable in the conditioned place preferences design and marginally more aversive than morphine in the conditioned taste aversion procedure suggests that differential effects of these two compounds are design-and/or possibly species-specific.

With respect to the antagonists, comparisons between the naltrindole and naloxone dose-response curves revealed the opposite pattern than the comparisons between SNC 80 and morphine. Specifically, in Experiment 2 there were significant differences in saccharin consumption between groups of subjects exposed to 10 mg/kg naltrindole and naloxone. This difference was evident on the third conditioning trial in which the naloxone group exposed to 10 mg/kg drank significantly less saccharin than the naltrindole group at the same dose and was maintained on the subsequent conditioning trial as well as on the test day. Furthermore, consumption was significantly less following 10 mg/kg naloxone relative to the control group after repeated conditioning trials and on the final test. Such differences were not evident for naltrindole, suggesting minimally that the rate of acquisition of aversions at this dose was faster for naloxone than naltrindole. Finally, although there were no between-group differences for comparable doses of naltrindole and naloxone (other than at 10 mg/kg), consumption of saccharin following 5.6 mg/kg naloxone was significantly less relative to 1 and 3.2 mg/kg naltrindole and 1 mg/kg naloxone. Thus, aversions induced by naloxone were stronger relative to aversions induced by naltrindole. Interestingly, the fact that aversions induced by the highest dose of naltrindole (18 mg/kg) did not differ from those induced by naloxone at this dose suggests that as the dose of naltrindole increased it may no longer have been selective for the delta receptor subtype, i.e., naltrindole at such a dose may have interacted with the mu opiate receptor subtype to produce aversions comparable to naloxone. Such an explanation has been suggested by several researchers trying to account for naltrindole antagonism of effects presumably mediated by mu receptor activity (25,56; though see 86). In support of this possibility, Kitchen and Kennedy (37) reported that 2 mg/kg naltrindole antagonized the effects of the selective mu receptor agonist fentanyl on corticosterone release. On the other hand, Drower et al. (20) reported that naltrindole at 10 and 30 mg/kg, sc did not antagonize the analgesic effects of the mu receptor agonist, DAMGO (although it partially antagonized the effects of the delta agonist, DADLE). Further, Bilsky et al. (8) has reported that 20 mg/kg naltrindole fully blocked SNC 80-induced analgesia but had no effect on morphine-induced analgesia. Thus, there is no agreement as to the effects of increases in the dose of naltrindole on naltrindole's selectivity for the delta receptor. Such a possibility remains, however, and conclusions regarding the selectivity of naltrindole at high doses must be cautiously made.

The differential induction of taste aversions by naloxone and naltrindole are consistent with a recent assessment of the role of delta opioid receptors in mediating conditioned place aversions induced by precipitated withdrawal in opioid-dependent rats (25). In this study, morphine-pelleted rats received place conditioning with either naloxone (0.001-1 mg/kg, sc) or naltrindole (0.01-3 mg/kg, sc). Following one conditioning trial, place aversions were induced by both naloxone and naltrindole; however, significant place aversions for naloxone were evident at a dose of 0.01 mg/kg versus 0.1 mg/kg for naltrindole. Place aversions induced by both naloxone and naltrindole at the 0.1 mg/kg dose did not differ in magnitude. Thus, the acquisition of place aversions occurred at lower doses of naloxone than naltrindole. It is interesting that the relative effects of naltrindole and naloxone in the place aversion preparation were similar to those of the present experiment given that the aversive effects of naltrindole and naloxone were assessed in opioid-exposed and opioid-naïve animals, respectively. Although comparisons between naltrindole and naloxone within the place and taste conditioning procedures have demonstrated naltrindole to be weaker relative to naloxone, other studies have shown these compounds to be comparable in their effects. For example, two recent studies in rats examining the role of opiate receptors in ethanol-induced place preferences following exposure to stress manipulations (43,44) have shown that naltrindole and naloxone at doses of 1 and 3 mg/kg, sc significantly attenuated place preferences in a dose-dependent manner and to a similar degree. Thus, the differential effects of naltrindole and naloxone (like SNC 80 and morphine) appear to be, in part, task-dependent.

Although taste aversions were induced by each of the compounds tested in the present experiment, the basis for these aversions is not known. The fact that both opioid agonists and antagonists induced aversions seems somewhat paradoxical if the assumption is made that a common mechanism

underlies aversions to all drugs. Although considerable attention has been devoted to determining this common mechanism, there is little evidence to suggest that one exists (2,13). Further, when commonalities are presented (e.g., parabrachial nucleus, nucleus tractus solitarius and periacqueductal gray mediation or c-fos and c-jun activity) they are often reported for select compounds, and as such the generality of these commonalities has not been established (9,13,89). For other compounds, not only do the behavioral characteristics of the aversions differ, but also their biochemical and physiological substrates (4,9,34). As such, it is assumed that the basis for aversions induced by these compounds differ, although the specific basis has not been determined. Such is the case with the opioid agonists. Specifically, although the issue of what specific opioid agonists induce aversions has been addressed, there is no consensus as to what it is about these compounds that results in the acquisition of taste aversions. Such possibilities include disruptions in homeostasis, drug novelty, nausea, incentive contrast, stress reactivity (ACTH) and catecholamine activation (3,10,31,58,68). The fact that aversions are induced by opioid agonists has been used to suggest that the drugs are aversive, and interestingly each of the aforementioned possibilities assumes to some degree an aversive characteristic of such drugs. Given that the basis for such aversions has not been determined, however, it is difficult to speculate on why the strength of aversions to compounds with varying selectivity at specific receptor subtypes might differ.

The basis for aversions to the opioid antagonists has received similar attention, although the majority of the explanations for such aversions have focused on their ability to block endogenous opiate activity (77,83). In such explanations, it is assumed that there is some receptor tone of the endogenous opiates that act at the various receptor subtypes and that antagonism of this endogenous tone by compounds such as naloxone and naltrexone is aversive, an assumption based on the fact that a variety of opioid agonists are rewarding (see 77,83). Given that the delta opiate receptor subtype has been implicated in the rewarding properties of exogenously-administered opioids (41,55,78), it is an extension of this position to suggest that the antagonism of activity at this subtype is aversive as well. The fact that in the present experiment aversions induced by naloxone appear stronger than those induced by naltrindole would suggest that antagonism of opiate activity by naloxone is more aversive than that by naltrindole. This may be a function of the lack of selectivity of naloxone for various opiate receptor subtypes (i.e., naloxone may be blocking mu and delta endogenous tone), whereas naltrindole's antagonism is limited to the delta subtype (especially at intermediate doses; see above). Although the explanations for aversions induced by opioid antagonists generally assume that the blocking of endogenous tone mediates the aversive effects of the compound, in the present experiment aversions to naloxone and naltrindole were evident only at high doses, doses that exceed the levels required to block other opioid-mediated effects (see 56). Thus, in this case it is not clear if the aversions were, in fact, based on opioid antagonism or a non-specific effect of such high doses. Although possible, it should be noted that 15 mg/kg, sc naltrindole does not affect alcohol consumption (86) and 17 mg/kg, sc naltrindole increases schedule controlled responding for heroin (56), suggesting that within these preparations these doses do not produce nonspecific behavioral suppression. Further, because naloxone- and naltrindole-induced aversions were different at 10 mg/kg (and displayed faster acquisition at 5.6 mg/kg), it would have to be assumed that the nonspecific effects produced by these compounds were different. In the absence of knowing what such nonspecific effects might be, it remains unknown to what extent such effects contribute to aversions induced by these compounds.

Regardless of the mechanisms underlying the differential effects of SNC 80 and naltrindole in relation to morphine and naloxone, the present experiments demonstrate that agonists and antagonists at the delta opiate receptor subtype have aversive properties. It should be noted, however, that SNC 80 and naltrindole represent only two nonpeptide delta selective compounds. Thus, it is unknown whether the effects produced by these drugs represent the full spectrum of delta-mediated activity (1,32,75,78). If generalizable, these findings may have potential clinical implications given that both SNC 80 and naltrindole have been suggested as, or are currently being examined for, possible pharmacotherapeutic uses (8,33,42,57,76). Thus, the motivational properties of SNC 80, naltrindole and other novel nonpeptide selective delta compounds warrant further investigation.

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