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Naltrexone-Induced Aversions: Assessment by Place Conditioning, Taste Reactivity, and Taste Avoidance Paradigms

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PARKER, L. A. AND M. RENNIE *Naltrexone-induced aversions: Assessment by place conditioning, taste reactivity, and taste avoidance paradigms.* PHARMACOL BIOCHEM BEHAV 41(3) 559–565, 1992.—The reinforcing/aversive properties of various doses of naltrexone (0.01, 1, and 10 mg/kg) were assessed in three experiments that employed place conditioning, taste reactivity, and taste avoidance paradigms. Naltrexone produced a place aversion and a taste aversion, but did not produce aversive taste reactivity responses, even at the highest dose (10 mg/kg) tested. This suggests that drugs that produce a place aversion do not necessarily produce a conditional dislike for a flavored solution with which they are paired.

Place conditioning Taste conditioning Conditioned taste aversion Taste reactivity
Palatability Naltrexone Opiates Endorphins Opiate antagonists Drug reinforcement

CONDITIONED taste avoidance (CTA) may be produced by the pairing of a flavored solution with almost any psychoactive drug; in fact, many of these psychoactive drugs are reinforcing to animals in both drug self-administration and place conditioning paradigms [e.g., (11)]. We have argued that the CTA produced by reinforcing drugs may qualitatively differ from that produced by nonreinforcing drugs on the basis of our observation that the pattern of rats' orofacial reactions to flavors paired with reinforcing and nonreinforcing drugs appear to differ (20,22,23,25,33).

Conditioned taste avoidance is generally measured by a consummatory test that provides an indirect measure of the aversiveness of a flavored solution; suppressed consumption of a drug-paired flavor indicates that the flavor is aversive. However, consummatory measures not only measure the rat's response to the tastant, but also the rat's tendency to approach the bottle containing the flavored solution. Motivational factors, as well as the inherent properties of the solution, potentially influence the rat's tendency to approach and drink. An alternative, more direct, measure of the aversiveness of a flavored solution called the Taste Reactivity (TR) test has been devised by Grill and Norgren (9). The TR test measures the rat's orofacial and somatic responses to flavors infused directly into its mouth. Palatable sucrose solutions elicit a characteristic set of responses, called ingestive responses, that include tongue protrusions, mouth movements, and paw-licks. Neutral solutions, such as very dilute concentrations of salt solution, elicit a pattern of responding classified as passive dripping in which the solution is allowed to drip passively from the mouth as it is infused (6). Unpalatable quinine solutions elicit a set of responses, called aversive responses, that include chin rubs, gapes, and paw-treads. These responses are those that facilitate removal of the aversive tasting solution from the rat's mouth (7). After having been paired with lithium, an emetic agent, sucrose solution elicits a pattern of aversive TR responses similar to that elicited by unpalatable quinine solution [e.g., (6,21)]. Although a lithium-paired flavored solution appears to become conditionally unpalatable, an amphetamine-paired flavored solution does not (20,22, 23,25,33). The nature of the TR responses elicited by lithium-paired sucrose and amphetamine-paired sucrose differ, even when the strength of the avoidance response produced by the two drugs is equated [e.g., (20,33)].

Lithium produces not only a CTA and aversive TR responses to drug-paired flavors, but also produces an aversion to drug-paired chambers [e.g., (17,24)]. Even after a single conditioning trial, lithium produces an aversion to a place with which it is paired (24). Since drugs that are reinforcing in the place conditioning paradigm, such as amphetamine [e.g., (26)] and morphine [e.g., (17,18)], do not produce aversive TR responses when paired with a flavored solution, it is conceivable that drugs that are aversive in the place conditioning paradigm do produce aversive TR responses when paired with a flavored solution. That is, the drug agents that produce a conditioned taste aversion by means of producing a palatability shift may also be the drug agents capable of establishing an aversion to a place with which they are paired.

Opiate blocking agents have been demonstrated to produce a place aversion (2,3,13,16–18), as well as conditioned taste avoidance (13,15,16,30,31). However, the TR responses elicited by flavors paired with opiate antagonists have not been measured. On the other hand, extremely low doses (e.g., 0.01 mg/kg) of naltrexone (IP) have been reported to produce a place preference (2). The authors reasoned that low IP doses

produced selective blockade of peripheral opiate receptors, producing a positive hedonic effect, whereas higher IP doses also produced blockade of central opiate receptors, resulting in a negative hedonic effect. If the reinforcing/aversive properties of drug agents as assessed in the place preference paradigm predicts the ability of doses of drug agents to produce modifications in the palatability of flavored solutions with which they are paired, then only doses of naltrexone that produce a place aversion should produce aversive TR responses. The following experiments assessed the ability of various doses of naltrexone to produce place and taste conditioning at equivalent doses.

EXPERIMENT 1

In Experiment 1, the ability of a range of doses of naltrexone to produce place conditioning was assessed in a three-choice chamber with a central choice area, which provided the animals with the opportunity to select among a naltrexone-paired chamber, a saline-paired chamber, and a novel chamber. The inclusion of a novel chamber among the alternative choices addressed the issue raised by Scoles and Siegel (29), who argued that the demonstration of conditioned place preferences may simply be an artifact of the methodology of place conditioning. When rats are given the opportunity to choose between a novel and a familiar chamber, they spend more time in the novel chamber (1,4,10,24,29). Scoles and Siegel (29) argued that in the place conditioning paradigm pretreatment with the drug may interfere with habituation to the chamber with which it is paired, thereby maintaining the relative novelty of the drug-paired chamber as compared with the saline-paired chamber. When given the choice, rats select the relatively novel drug-paired chamber. Because of this potential artifact, the place conditioning apparatus used in our laboratory consistently includes three chambers and a central choice area; one chamber remains novel. This place conditioning apparatus provides a conservative test of the reinforcing properties of drug agents (24). We recently demonstrated that amphetamine (1.5 mg/kg), apomorphine (1 mg/kg), and morphine (20 mg/kg) produce place preferences greater than those for the novel chamber using the above procedure (24).

METHOD

Subjects

Thirty-six male Sprague-Dawley rats weighing between 262–293 g on the first conditioning trial served as subjects. They were maintained on ad lib food and water except as specified and were housed in individual stainless steel cages. The room was illuminated on a 12 L:12 D schedule.

Apparatus

The place conditioning apparatus employed was a three-arm maze with a central choice point as previously described (24). The arms were arranged in the shape of a T around the central choice point. The wooden walls of the apparatus were painted flat black. The floors of each of the chambers (35 × 25 × 30 cm) differed visually and tactually. The characteristics of each of the floors was as follows: grid (1/2-cm squares), black plastic, and green astroturf. Pretesting indicated that these floors were equally preferred as measured by group means. The floor of the central choice area was painted flat black. Clear plastic lids covered each of the chambers during conditioning trials. On conditioning trials, rats were confined to each chamber with a divider painted flat black. During testing, the divider was removed. The room was illuminated by two fluorescent ceiling lights.

Rats' behavior during testing was recorded by a videocamera located in the ceiling of the testing room. The videocamera transmitted the signal provided by the contrast of the white rat on the black background of the chamber to an activity tracking apparatus, Videomex V, that transmitted a signal to an IBM microcomputer for later analysis. The amount of time that each rat spent in each chamber was later determined.

Procedure

Rats arrived in the laboratory 1 week prior to the experimental manipulations and were handled on each of 5 days prior to the first conditioning trial. They received a total of four conditioning trial cycles separated by 1–2 days, with a cycle consisting of one chamber–naltrexone pairing and one chamber–saline pairing on consecutive days. Half the rats received the naltrexone trial on the first day of the cycle and half received the saline trial on the first day of the cycle. On each conditioning trial, rats were injected IP with one of three doses of naltrexone (0.01, 1, or 10 mg/kg) or with saline 5 min prior to placement into the appropriate chamber for 30 min. The concentration of each drug solution was adjusted to permit equivolume injections (2 ml/kg) of all solutions. Rats in each dosage group (n = 12) were randomly assigned to one of six counterbalancing schemes that varied on the basis of the chamber paired with naltrexone and the chamber paired with saline (naltrexone chamber/saline chamber: grid/plastic, grid/carpet, plastic/grid, plastic/carpet, carpet/plastic, carpet/grid). Immediately after each rat's trial, the apparatus was cleansed with soapy water and dried with a cloth towel.

Rats were tested for their side preference 3 days after the final conditioning trial. Each rat was placed in the central choice area of the apparatus with the chamber dividers removed. The rat was allowed to explore the apparatus for 30 min. The videotracking apparatus recorded the location of the rat during the test period.

RESULTS AND DISCUSSION

Figure 1 presents the mean amount of time spent in each chamber for the groups conditioned with the various doses

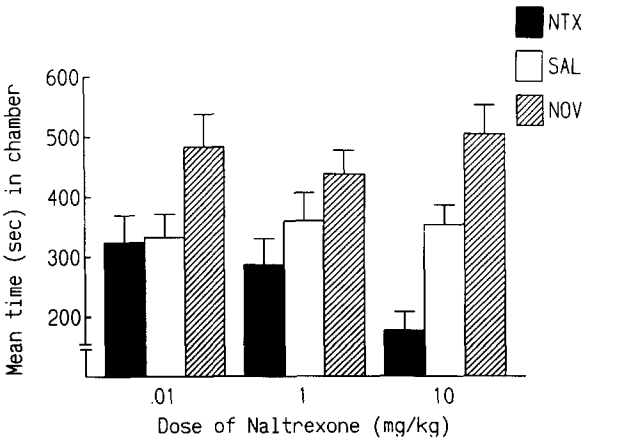

FIG. 1. Mean amount of time (in seconds) spent in each chamber of the place conditioning apparatus after four conditioning cycles in Experiment 1.

of naltrexone. The 3 × 3 mixed-factor analysis of variance (ANOVA) for the factors of dose (0.01, 1, and 10 mg/kg naltrexone) and chamber (naltrexone-paired, saline-paired, and novel) revealed only a significant effect of chamber, $F(2,66) = 14.4$, $p < 0.001$. By subsequent Newman-Keuls analysis across all drug doses, rats spent less time in the naltrexone-paired chamber than either the saline-paired chamber or the novel chamber (p's < 0.05) and they spent less time in the saline-paired chamber than in the novel chamber ($p < 0.025$).

The results of Experiment 1 suggest that IP-administered naltrexone produces an aversive hedonic effect across drug doses as suggested by others (2,3,13,16–18). In addition, the results replicated previous reports that rats prefer novel chambers to familiar chambers (1,4,10,24,29). On the other hand, with the present procedure we failed to replicate the previous report (2) that a low dose of 0.01 mg/kg of naltrexone (IP) produces positive hedonic effects as measured in the place conditioning paradigm; however, the three-chamber apparatus provides a more conservative test of place conditioning (24) than the two-chamber apparatus employed by Bechara and van der Kooy (2).

EXPERIMENT 2

Opiate antagonists not only have aversive effects when measured in the place conditioning paradigm but also have been reported to have aversive effects when measured in a flavor conditioning paradigm. Both naloxone and naltrexone produce a CTA at moderate to high doses [e.g., (13,15,16, 30,31)]; however, the strength of the CTA is relatively weak, with low doses being ineffective in this paradigm [e.g., (12–14,28,32)]. The following experiment assessed the ability of naltrexone to produce flavor–drug associations as measured by both the TR and CTA tests.

METHOD

Subjects

Thirty-seven male Sprague-Dawley rats weighing between 298–360 g on the first conditioning day served as subjects. Rats were maintained on ad lib rat chow and water except as indicated in individual stainless steel cages in a room maintained on a 12 L: 12 D schedule.

Procedure

Surgery. One week after their arrival in the laboratory, rats were implanted with intraoral cannulae as described by Parker (19). After being deprived of water for 24 h, each rat was anesthesized with sodium pentobarbital (50 mg/kg). A 15-ga thin-wall stainless steel needle was inserted through the rat's skin in the midneck region, brought subcutaneously behind its ear along the inside of its cheek, and exited through the soft part of its cheek behind the first molar. The skin around each of the punctured sites was swabbed with iodine. With the needle in place, a 10-cm length of PE 90 tubing was inserted through the barrel. The needle was then removed and the tubing was secured at the neck by a 20-ga intramedic adapter and in the mouth by a 5-mm plastic washer. During recovery from surgery, all rats had 3 days of free access to water and on the final free access day their cannulae were flushed with water to prevent stoppage by food.

Taste reactivity conditioning/testing trials. One week after the rats recovered from surgery, they began their initial adaptation trials on 3 successive days prior to the conditioning trials. On each adaptation trial, each rat was transported into the room that contained the glass test chamber (22.5 × 26 × 20 cm). The room was illuminated by two 25-W light bulbs located 30 cm from either side of the cage. Each rat was placed individually into the test chamber and a 30-cm infusion hose was then connected to the cannula through the ceiling of the chamber. A syringe was connected to the hose and placed into the holder for the Infusion Pump (Harvard Apparatus, Model 22). After a 1-min period of adaptation to the test chamber, the pump delivered water through the tube into the rat's mouth at the rate of 1 ml/min for 2 min. The rat was then returned to its home cage.

On the day following the third adaptation trial, the rats received their first conditioning trial. The procedure of the conditioning trials was identical to that of the adaptation trials except that the rats were intraorally infused with 0.5 M sucrose solution rather than water. Immediately after the TR test, the rats were injected IP with the appropriate solution and then returned to their home cage. There were four groups of rats that differed on the basis of the dose of naltrexone with which they were injected: 0.0 mg/kg (saline; $n = 8$), 0.01 mg/kg ($n = 9$), 1 mg/kg ($n = 8$), and 10 mg/kg ($n = 10$). Each solution was injected in a volume of 2 ml/kg. The TR conditioning/testing trials occurred on each of 5 days with trials on days 1, 3, 6, 8, and 10. Rats received four flavor–drug pairings with the trial on day 10 serving only as a test trial that was not followed by an injection. On each conditioning/testing trial, the orofacial and somatic responses of rats were videorecorded. A videocamera was focused on a mirror located at an angle underneath the test chamber.

The videotaped records of the TR conditioning/testing trials were later scored by a rater blind to the experimental conditions by means of an event recorder package entitled "The Observer" (Noldus, Inc., NL) for an IBM computer. The aversive TR responses included: chin-rubbing (mouth in direct contact with the floor or a wall and projecting the body forward), gaping (rapid large amplitude opening of the mandible with concomitant retraction of the corners of the mouth), and paw-treading (sequential extension of one forelimb forward against the floor while the other forelimb is being retracted). The frequency of each of these behaviors occurring within the 2-min test were combined to produce a total aversive TR response score. The ingestive TR responses included: tongue protrusions (protrusions of the tongue on the midline or on either side of the mouth), paw-licking (licking the forelimb paws while they are held close to the mouth), and mouth movements (low-amplitude, rhythmic openings of the mandible). The duration of these responses were combined to produce a total ingestive TR response score. Finally, the behavior of frequency of passive drips (the solution is allowed to drip passively from the mouth as it is infused) were measured, which constitutes a neutral response [e.g., (5,6)]. Previous research demonstrated that the scoring of these behaviors across raters is reliable [e.g., (20)].

Conditioned taste avoidance test. Rats were tested for a CTA to the 0.5-M sucrose solution on day 11, 1 day after TR Trial 5. Since during conditioning rats had been presented with sucrose by forced infusion via the cannulae and not by free consumption from a bottle, the strength of the CTA was expected to be weaker than one that would be expected after four conditioning trials during which rats actively consumed the sucrose solution over several minutes [e.g., (8,27)]. On the CTA test trial, rats were each presented with two graduated tubes with one containing 0.5 M sucrose solution and the

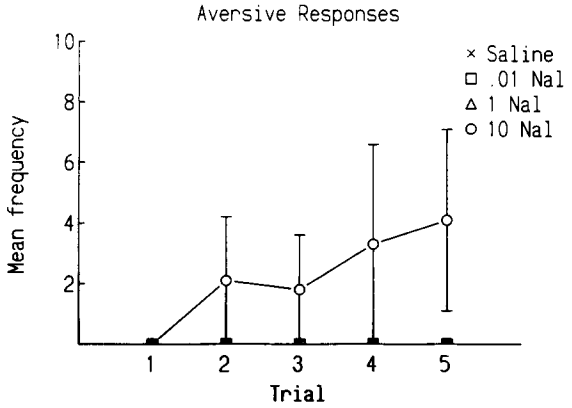

FIG. 2. Mean number of aversive TR responses elicited by sucrose solution during the 2-min taste-drug conditioning/testing trials in Experiment 2.

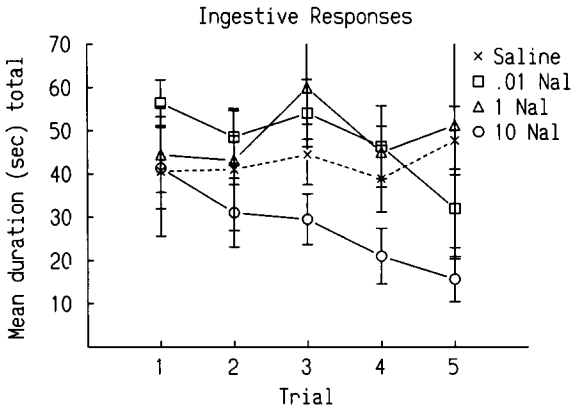

FIG. 4. Mean number of seconds during the 2-min TR taste-drug conditioning/testing trials that rats in the various groups displayed ingestive responding during the sucrose infusion in Experiment 2.

other containing water. The spouts of the bottles were located within 3 cm of one another with the sucrose solution always being presented on the left side. The amounts consumed at 15, 30, 60, 120, and 240 min and 24 h were measured. These scores were converted to sucrose preference ratios on the basis of the following formula: the amount of sucrose solution consumed divided by the total of the amount of sucrose solution and the amount of water consumed. Cumulative measures were tabulated at each interval.

RESULTS AND DISCUSSION

Figures 2, 3, and 4 present the frequency of aversive responses, frequency of neutral passive drips, and total duration of ingestive responses respectively during the 2-min TR trials displayed by the various groups on each of the five trials in Experiment 2. The data for each of these behaviors was analyzed as a 4 × 5 mixed-factor ANOVA for the factors of dose of naltrexone (0, 0.01, 1, and 10 mg/kg) and TR trial.

The analysis of the aversive TR response measure, depicted in Fig. 2, revealed no significant effects; only 2 rats of the 10 in the 10-mg/kg group displayed aversive responding on any trial. On the other hand, the analysis of the neutral response

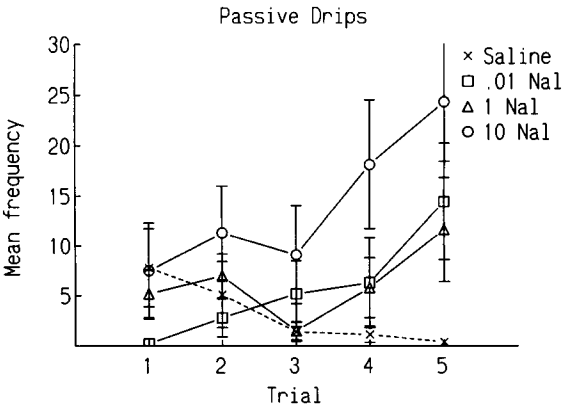

FIG. 3. Mean number of neutral passive drips elicited by sucrose solution during the 2-min taste-drug conditioning/testing trials in Experiment 2.

of passive drips, depicted in Fig. 3, revealed a significant group × conditioning trial interaction, $F(12,132) = 2.4$, $p < 0.01$. Subsequent single-factor ANOVA's among dosage groups were conducted for each trial. Only on Trials 4 and 5 was there a significant group effect, F's$(3,33) > 2.9$, p's < 0.05. Newman-Keuls tests revealed that the group conditioned with 10 mg/kg naltrexone showed more passive drip responding than the group conditioned with saline on Trials 4 and 5 (p's < 0.05). No other effects were significant. Therefore, although groups 0.01 and 1 mg/kg did not differ from group saline, they also did not significantly differ from group 10 mg/kg naltrexone, which suggests that the frequency of passive drips by these two lower doses of naltrexone on Trials 4 and 5 fell intermediate to the frequency of passive drips elicited by sucrose paired with the high dose of naltrexone and sucrose paired with saline.

Figure 4 presents the mean total duration of ingestive responding elicited by sucrose paired with the various agents in Experiment 2. The 4 × 5 mixed-factor ANOVA revealed a significant group effect, $F(3,31) = 3.5$, $p < 0.025$. Subsequent Newman-Keuls analysis revealed that overall the group conditioned with 10 mg/kg naltrexone displayed a lower level of ingestive responding than did any other group (p's < 0.05). None of the other groups differed from one another.

Figure 5 presents the mean cumulative sucrose preference ratio for the various groups in Experiment 2 across 240 min of the two-bottle testing. The 4 × 5 mixed-factor ANOVA revealed no significant effects. Since rats were nondeprived during testing, they did not drink a large volume of fluid until later in the testing interval. Therefore, at the 240-min and 24-h intervals of testing, single-factor ANOVA's assessed group differences. These analyses also revealed no significant effects.

With our procedures, after four sucrose-naltrexone pairings, the only TR response changes that occurred were evident in the group conditioned with the highest dose of naltrexone. At the dose of 10 mg/kg, naltrexone conditioned a decrease in the amount of time that rats displayed ingestive responding and an increase in the frequency of neutral passive drips when they were infused with the sucrose solution. No other palatability shifts were evident at any other dose tested. At the low dose (0.01 mg/kg) of naltrexone, there was also no evidence of a reinforcing effect that might be seen as an increase in ingestive responding. The CTA test revealed no evidence of a

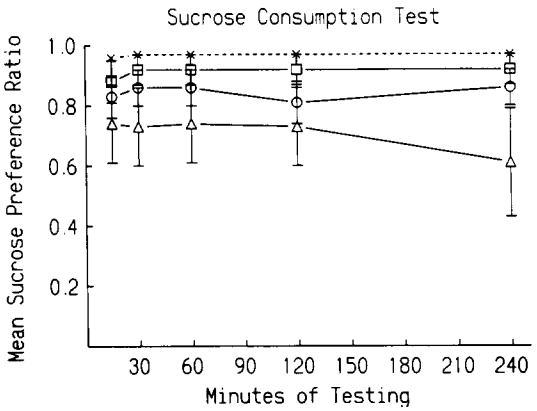

FIG. 5. Mean sucrose preference ratio for the various groups at each interval of testing during the consumption test in Experiment 2.

naltrexone-induced taste aversion, even at the highest dose. The lack of a CTA may be a function of the conditioning procedure in which the solution was passively infused across the rats' tongues prior to the naltrexone pairings rather than being actively consumed by the rats. This latter procedure has been demonstrated to produce a stronger CTA than the procedure we employed [e.g., (8,26)].

EXPERIMENT 3

The failure to demonstrate a naltrexone-induced CTA in Experiment 2 may have been the result of conditioning procedures that differed from those employed by investigators who have demonstrated a naltrexone-induced CTA [e.g., (13,15, 16,30,31)]. During the conditioning trials in Experiment 2, rats were presented with sucrose by forced infusion via intraoral cannulae and not by free consumption from a bottle. This procedure has been demonstrated to produce weaker CTA's than those that would be expected after four conditioning trials during which rats would actively consume the sucrose solution over several minutes [e.g., (8,26)]. Therefore, in Experiment 3 water-deprived rats were allowed to consume sucrose solution from a bottle prior to the injection of the drug agent on each of four conditioning trials. This procedure was designed to produce a maximal CTA. Following the four conditioning trials, rats received a TR test trial and a CTA test trial as in Experiment 2.

METHOD

Thirty-five male Sprague-Dawley rats weighing between 254–281 g on the first conditioning trial served as subjects. Rats were treated in an identical manner as in Experiment 2 except as specified. One week after arriving in the laboratory, rats were implanted with intraoral cannulae.

One week after surgery, rats were deprived of water and on each of the following 3 days received 20 min of water from a graduated tube at the same time each day. Twenty-four hours later, rats received their first conditioning trial. On the conditioning trials, the rats were presented 0.5 M sucrose solution in a graduated tube for 20 min. Immediately after the sucrose solution was removed, rats were injected, intraperitoneally, with the appropriate drug solution. There were four groups that differed on the basis of the dose of naltrexone that was administered: 0.0 mg/kg naltrexone (saline; n = 9), 0.01 mg/kg naltrexone (n = 8), 1 mg/kg naltrexone (n = 9), and 10 mg/kg naltrexone (n = 9). Rats received four identical conditioning trials with Trials 1 and 2 and Trials 3 and 4 on consecutive days; 5 days intervened between Trials 2 and 3. If a rat failed to consume 2 ml, it was given a forced exposure to 2 ml sucrose solution. During the intervening 5 days, rats received free access to water for 2 days and were then administered 20 min/day of water for the remaining 3 days. They were maintained on the schedule of 20 min/day of water throughout the remainder of the experiment.

Three days after the fourth conditioning trial, rats were given adaptation training to the TR test chambers as in Experiment 2. Rats received two adaptation trials during which they were infused intraorally with 2 ml water at the rate of 1 ml/min. On the following day, they were given the TR test trial. On the test trial, rats were infused with 0.5 M sucrose solution in a manner identical to that of Experiment 2. Their orofacial reactions were videorecorded and later scored for TR responses.

On the day following the TR test trial,while 24 h water deprived, rats received the CTA test trial. As in Experiment 2, rats were presented with a graduated tube containing 0.5 M sucrose solution and a graduated tube containing tapwater

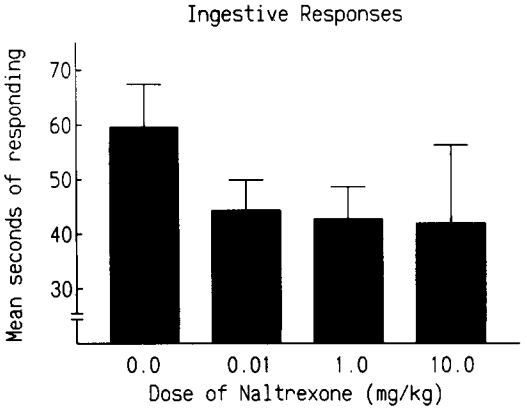

FIG. 6. Mean number of seconds during the 2-min TR test that rats in the various groups displayed ingestive responding during the sucrose infusion of Experiment 3.

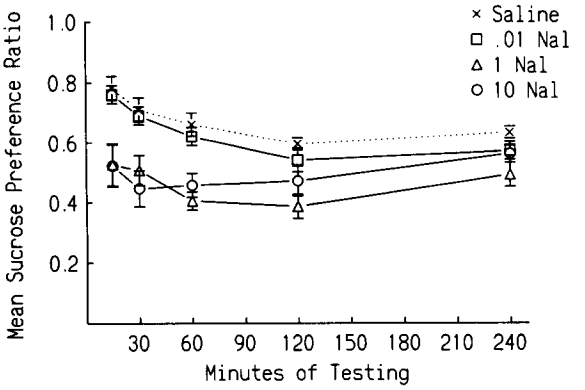

FIG. 7. Mean cumulative sucrose preference ratios for the various groups during each interval of testing during the consumption test of Experiment 3.

and the amount consumed at 15, 30, 60, 120, and 240 min and 24 h were measured. Cumulative preference ratios were calculated for each interval of testing.

RESULTS

During the single TR test trial of Experiment 3, there was only one display of any aversive response by any of the rats. Furthermore, no rat displayed the neutral response of passive dripping. Figure 6 presents the mean number of seconds that rats conditioned with the various doses of naltrexone spent displaying ingestive responses during the TR test trial. A single-factor ANOVA indicated that groups did not significantly differ in the mean duration of ingestive responding.

Figure 7 presents the mean cumulative sucrose preference ratios for minutes 15-240 of the CTA test. A 4 × 5 mixed factor ANOVA revealed a significant group effect, $F(3,31) = 8.0$, $p < 0.01$, intervals effect, $F(4,124) = 20.5$, $p < 0.01$, and group × intervals effect, $F(4,124) = 3.74$, $p < 0.01$. Single-factor ANOVA's for each interval of testing (15-240 min) revealed significant group effects, F's$(3,31) > 3.7$, p's < 0.025. At 15, 30, and 60 min of testing, groups 0.0 and 0.01 mg/kg had significantly higher sucrose preference ratios than groups 1 and 10 mg/kg (p's < 0.05). At 120 and 240 min of testing, group saline had higher sucrose preference ratios than group 1 mg/kg (p's < 0.05), but not group 10 mg/kg naltrexone. At 24 h of testing, groups did not significantly differ from one another.

DISCUSSION

Using a procedure designed to produce a maximal-strength CTA, the results of Experiment 3 demonstrated that 1 and 10 mg/kg naltrexone were effective in establishing a CTA when paired on four occasions with sucrose solution. Although these doses produced a CTA, they were ineffective in modifying the palatability of the sucrose solution as measured by the TR test. The naltrexone-paired sucrose solution neither elicited aversive TR responding nor neutral passive drip responding, even in the group conditioned with the highest dose (10 mg/kg). In fact, no group displayed suppressed ingestion responding when exposed to the naltrexone-paired sucrose solution. Although rats consumed less naltrexone-paired sucrose solution in the 1- and 10-mg/kg groups, it does not appear that their avoidance of the solution was motivated by a palatability shift.

On the other hand, in Experiment 2 a sucrose palatability shift from highly ingestive to neutral was evident in the group conditioned with 10 mg/kg naltrexone; rats displayed suppressed ingestive TR responding and enhanced neutral passive drip responding, but not aversive TR responding, when intraorally infused with sucrose solution previously paired with 10 mg/kg naltrexone. Surprisingly, in Experiment 2 the subsequent test for a CTA to the naltrexone-paired sucrose solution revealed no evidence of the development of a CTA. It is conceivable that the context of the conditioning in Experiments 2 and 3 influenced the form of conditioned responding. In Experiment 2, the conditioning context included the TR infusion procedure and conditioning chamber; consequently, the taste-naltrexone association in the 10-mg/kg group was evident in this context but not in the CTA context. On the other hand, in Experiment 3 the conditioning context included consumption from a bottle in the home cage; therefore, the taste-naltrexone association was apparent in the CTA context but not in the TR context.

GENERAL DISCUSSION

Doses of naltrexone (IP) were assessed for their ability to produce place and taste conditioning after four place-drug or taste-drug pairings. The place conditioning paradigm produced clear evidence of aversion conditioning with naltrexone across the doses tested. The demonstration of a naltrexone-induced place aversion replicates the findings of other investigators (2,3,13,16-18). We originally conceived that doses of drugs that produce a place aversion may also be effective in producing aversive TR responding. This conception was based upon the finding that lithium chloride, which produces a place aversion [e.g., (24)], also produces aversive TR responses when paired with a flavored solution [e.g., (9,16,20-23,25, 33)]. On the other hand, drugs that produce a place preference, such as amphetamine [e.g., (26)] and morphine [e.g., (17,18)], are ineffective at producing aversive TR responses at reinforcing doses [e.g., (22,23)]. Since naltrexone produced a clear place aversion, but did not produce aversive TR responses, even at the highest dose of 10 mg/kg, our results do not support the suggestion that doses of drugs that are aversive in the place conditioning paradigm are also capable of establishing aversive responses when paired with a taste in the TR paradigm.

Contrary to previous reports (2,3), we found no evidence of reinforcing properties of a very low dose of naltrexone (0.01 mg/kg). This dose produced neither a place nor a taste preference. However, the method of place conditioning used in Experiment 1 differed from that of the earlier studies, which could account for the difference in the pattern of results at the low-dose range. Our place conditioning apparatus included three chambers and a central choice point. Rats were not forced to choose between a familiar saline-paired chamber and the drug-paired chamber, but also had the option of entering the novel chamber. Such a method of assessing the ability of a drug to produce a place preference is more conservative than the standard two-choice procedure (24).

ACKNOWLEDGEMENT

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