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Effect of Naloxone on the Habituation of Novelty-Induced Hypoalgesia: The Collateral Inhibition Hypothesis Revisited

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ROCHFORD, J. AND P. DAWES. *Effect of naloxone on the habituation of novelty-induced hypoalgesia: The collateral inhibition hypothesis revisited.* PHARMACOL BIOCHEM BEHAV **46**(1) 117–123, 1993.—Repeated daily administration of the opiate receptor antagonist naloxone prior to hotplate tests provokes longer paw-lick latencies by attenuating the habituation of novelty-induced hypoalgesia. This hypoalgesia has been found to persist when pain tests are subsequently conducted following saline administration. The present experiments were conducted to determine whether the substrates mediating the hypoalgesia observed during naloxone and saline tests are similar or distinct. Neither the hypoalgesia observed during naloxone nor saline tests were affected by the induction of tolerance to the hypoalgesic effect of morphine, suggesting that both effects are mediated by nonopioid antinociceptive mechanisms. Previous work from our laboratory demonstrated that the hypoalgesia observed during naloxone tests is inhibited by clonidine, enhanced by yohimbine, and unaffected by prazosin and phentolamine. In the present article, we report a similar pattern of results for the hypoalgesia observed during saline tests. It is concluded that the substrates mediating both effects are similar. The results are discussed in relation to the possibility that an opioid substrate involved in habituative learning may be inhibitory on a nonopioid antinociceptive substrate.

Naloxone Novelty-induced hypoalgesia α_2-Receptor Noradrenaline Opioid Nonopioid Habituation Rat

EXPOSURE to novel stimuli, such as the apparatus used to assess pain reactivity, has been shown to provoke hypoalgesia (1,7,20,43). Novelty-induced hypoalgesia habituates with repeated stimulus exposures; animals repeatedly exposed to novel stimuli display lower pain thresholds relative to those exposed to the stimuli for the first time. It has been reported that the habituation of novelty-induced hypoalgesia is attenuated by the opiate receptor antagonist naloxone (18,40). In these studies, one group of animals was pretreated with naloxone prior to being exposed to a hotplate apparatus. Control animals were administered saline prior to hotplate exposures. To control for any nonspecific effects of naloxone administration (42), controls were injected with naloxone 2–4 h after the hotplate exposure. This protocol of injections/exposures was administered once a day for 8 days. Over the first few exposures, the mean paw-lick latencies (PLLs) for both groups of animals were relatively long but did not differ from one another. With progressive testing, the latencies of control animals declined dramatically. The PLLs in naloxone-exposed animals also declined, but the magnitude of this reduction was less than that observed in controls. Thus, by the fourth to sixth hotplate exposure the PLLs exhibited by these animals were significantly longer than those in the controls.

The decline observed in controls has been interpreted as reflecting the habituation of novelty-induced hypoalgesia provoked by repeated exposure to the hotplate apparatus. The more limited decline observed in naloxone-exposed animals was interpreted as arising from an attenuation, provoked by the drug, of the rate of habituation of novelty-induced hypoalgesia. Given that control animals were also administered naloxone, the effect cannot be attributed to naloxone administration alone. Further, it has been shown that the effect develops if animals are repeatedly exposed to a nonfunctional apparatus and then tested once on a functional hotplate (18,40). Consequently, exposure to nociceptive stimulation is also not a necessary condition. These results suggest that the develop-

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ment of the effect is dependent upon animals being exposed to the apparatus while under the influence of naloxone, and are most parsimoniously accommodated by the hypothesis that naloxone retards the rate of habituation of novelty-induced hypoalgesia.

The fact that naloxone does not alter PLLs over the preliminary hotplate tests suggests that the substrate mediating the hypoalgesic response is nonopioid. However, the failure of naloxone to alter a hypoalgesic response does not, in and of itself, constitute sufficient evidence to conclude that it is nonopioid (4,48). A second behavioral criterion that has been used to assess whether a given hypoalgesic effect is opioid or nonopioid in nature is to determine whether the effect displays cross-tolerance with morphine-induced hypoalgesia (8,29,31). Consequently, the first purpose of the present set of experiments was to determine if the longer PLLs observed when animals are tested while under the influence of naloxone can be altered by the induction of tolerance to the hypoalgesic effect of morphine.

An additional finding related to this phenomenon is that, once it has developed, the effect is still observed if hotplate tests are administered without the drug (18,40), that is, the longer PLLs observed in naloxone-exposed animals continue to be displayed if saline, rather than naloxone, is administered prior to test. This finding raises the issue of the nature of the relationship between the substrates mediating the hypoalgesia observed when animals are tested following naloxone administration and that observed following saline tests. If naloxone prevented the habituation of novelty-induced hypoalgesia, then it might be expected that an identical substrate mediates both effects. However, it has also been suggested that the substrates underlying these effects may be distinct (40). The basis for this argument rests on the collateral inhibition hypothesis (4,21,28,45). According to this hypothesis, simultaneous activation of both opioid and nonopioid antinociceptive substrates would be maladaptive, or at least superfluous. Accordingly, activation of one substrate will not only induce hypoalgesia but will also inhibit the activation of the other antinociceptive substrate.

Consider the implications of this hypothesis with respect to the nature of the substrates mediating the longer PLLs observed during naloxone and saline tests. It would be expected that the substrate activated during naloxone tests would be nonopioid in that naloxone would block the antinociception provoked by activation of opioid substrates. Of equal importance, naloxone would free nonopioid substrates from opioid inhibition, thereby resulting in a nonopioid form of hypoalgesia. However, when tests are conducted following saline administration, opioid substrates would be activated without blockade, thereby resulting in a hypoalgesic response that could be, at least in part, opioid in nature.

We examined the relationship between the substrates activated during naloxone and saline tests in two ways. First, we assessed whether the hypoalgesia observed during saline tests would display cross-tolerance to morphine. Second, previous work has shown that the hypoalgesia observed during naloxone tests is attenuated by pretreatment with clonidine and augmented by yohimbine (37). These ligands are, respectively, selective agonists and antagonists for the noradrenergic α_2-receptor subtype (41). The effect is resistant, however, to pretreatment with the α_1-receptor antagonist prazosin and the nonspecific α-antagonist phentolamine (38). These results suggest the involvement of noradrenergic mechanisms, in particular the α_2-noradrenergic receptor, in the mediation of the effect. Consequently, in the present experiments we examined whether the hypoalgesia observed during saline tests would be similarly sensitive to α_2 manipulation.

METHODS

Subjects

Experimentally naive, male Wistar rats (275–300 g) were obtained from Charles River Breeding Farms (St. Constant, Quebec). Rats were individually housed with free access to food and water. The colony room was maintained on a 12 L : 12 D cycle (light on 0800–2000 h). All procedures were conducted during the light phase of the cycle.

Apparatus and Drugs

The hotplate apparatus consisted of a 20.3 × 38.1 × 20.3-cm clear Plexiglas chamber mounted on a 0.6-cm thick piece of sheet metal. A hinged, wire-mesh top prevented animals from escaping. Plate temperature was controlled by immersing the sheet metal in a water bath heated by a Haake E2 Immersion/Open Bath Circulator (Berlin, Germany). The apparatus was located in a test room illuminated by two 25-W red light bulbs. During the interval between injection in the test room and analgesic testing, animals were isolated in separate 30 × 20 × 15-cm wooden boxes, which were lined with Beta-Chip and covered by steel grid tops.

Drugs used were naloxone HCl (DuPont de Nemours & Co., Wilmington, DE), morphine SO_4 (Abbott, Mississauga, Ontario), yohimbine HCl, clonidine HCl, prazosin HCl, and phentolamine mesylate (Research Biochemicals Inc., Natick, MA). Naloxone, morphine, and clonidine were dissolved in physiological saline; yohimbine, prazosin, and phentolamine were dissolved in distilled water. The injection volume for each ligand was 1 ml/kg.

Procedure

Experiments 1 and 2: determination of cross-tolerance to morphine.

Naloxone treatment phase. During the 8 days of the naloxone treatment phase, rats in the NAL condition (n = 16 per experiment) were administered 10 mg/kg naloxone in the test room. Rats in the SAL condition (n = 16 per experiment) were administered saline. Test room injections were administered SC in the dorsal neck area. Thirty minutes following injection, each animal was tested for pain sensitivity on the hotplate. The latency to lick a hind paw (PLL) was taken as the measure of pain threshold. The water temperature of the hotplate bath was 48.5 (± 0.2)°C. We found this plate temperature and this dose of naloxone optimal for the expression of novelty-induced hypoalgesia and the effects of naloxone on novelty-induced hypoalgesia (40). If no response was observed within 90 s, the test was terminated and a PLL of 90 s was recorded. Following the hotplate test, animals were returned to the colony room where, 2–4 h later, rats in the NAL condition were administered saline and those in the SAL condition were administered 10 mg/kg naloxone.

Tolerance induction phase. Animals within the NAL condition were matched on the basis of their mean PLLs from the last 2 days of the naloxone treatment phase and then randomly assigned to two groups (n = 8). Rats in the SAL condition were also allocated to groups in this manner. One of the groups within each condition was randomly selected for the induction of tolerance to morphine. On days 1–2 of the tolerance induction phase, groups NAL–MOR and SAL–MOR

were administered (IP) 5 mg/kg morphine between 0900 and 1000 h and again between 1600 and 1700 h. The dose was increased to 10 mg/kg on days 3-4, to 15 mg/kg on days 5-6, and finally to 20 mg/kg on days 7-8. Animals in groups NAL-SAL and SAL-SAL were injected with saline throughout this phase. These injections were administered in the colony room. Throughout this phase, animals were not transported to the test room but remained in their home cages.

Test phase. To allow for the dissipation of potential withdrawal effects from morphine administration, animals were allowed to rest in their home cages for the next 4 days. This procedure was adopted to remove any potential confounds of withdrawal-induced changes in motor activity or thermoregulation [cf. (29)]. On the next day, animals were transported to the colony room. In Experiment 1, animals in groups NAL-MOR and NAL-SAL were injected with 10 mg/kg naloxone and then tested 30 min later. In Experiment 2, animals in these groups were administered saline. In both experiments, animals in groups SAL-MOR and SAL-SAL were injected with saline. On the next day, a morphine tolerance test was conducted in which all groups were administered 5 mg/kg morphine prior to the hotplate test.

Experiments 3-6: effects of noradrenergic ligands.

Naloxone treatment phase. The protocol adopted during the naloxone treatment phase of Experiments 3-6 was identical to that described previously. The one difference was that there were eight rats in each of the NAL and SAL conditions in each experiment.

Test phase. The test phase consisted of 2 days. Within each experiment, half the animals in the NAL and SAL conditions were preadministered (IP) drug (2.0 mg/kg yohimbine, 2.0 μg/kg clonidine, 1.0 mg/kg prazosin, and 10.0 mg/kg phentolamine in Experiments 3-6, respectively) on the first test day and vehicle (saline or distilled water) on the second. The dose of each ligand was selected on the basis of previous data (37,38). The other half of the animals received the reverse sequence: Vehicle was administered on the first test day and drug on the second. Thus, the sequence of these injections was counterbalanced within conditions.

These injections were administered in the colony room. Fifteen minutes after injection, animals were transported to the test room, where rats in both conditions were administered saline. Thirty minutes later, hotplate tests were administered. Animals were then returned to the colony room. No post-test colony room injections were administered on the test days.

Statistical Analysis

The data from the naloxone treatment phases of each experiment were analyzed by separate condition × days split-plot analyses of variance (ANOVAs). The data from each test of Experiments 1 and 2 were subjected to condition × morphine treatment ANOVAs. Preliminary analysis of test phase data of Experiments 3-6 failed to reveal a main effect for or interaction including counterbalancing of the colony room injection sequence (i.e., drug-vehicle vs.vehicle-drug). Consequently, the data for each experiment were collapsed over this factor and analyzed by condition × home cage injection ANOVAS. Significant interactions were analyzed by *F*-tests for simple main effects (51). The level of statistical significance adopted was $p < 0.05$.

RESULTS

Experiments 1 and 2

Figure 1 presents the results obtained from Experiments 1 (panel A) and 2 (panel B). The leftmost graph in each panel displays the results from the naloxone treatment phase of each experiment. In both experiments, the mean PLLs displayed by animals within the SAL condition declined substantially over the course of the naloxone treatment phase. The mean PLLs within the NAL condition remained more stable. Animals within the NAL condition displayed significantly longer PLLs than those in the SAL condition beginning on the third or fourth day of the naloxone treatment phase.

The center graph displays the results from the naloxone test day of Experiment 1 (panel A) and the saline test day of Experiment 2 (panel B). Animals within the NAL condition continued to display significantly longer PLLs than SAL condition rats. Of more importance was the finding that there were no significant differences between the PLLs for groups NAL-MOR and NAL-SAL or between groups SAL-MOR and SAL-SAL. Inspection of the data from these test days suggests that the PLLs observed in NAL condition animals were lower during the saline test of Experiment 2 than during the naloxone test of Experiment 1, particularly in the NAL-MOR groups. However, unpaired *t*-tests contrasting the means of groups NAL-MOR, $t(14) = 1.45$, the means for groups NAL-SAL, $t(14) = 0.16$, as well as the combined means of all animals within the NAL condition in each experiment, $t(30) = 1.14$, indicated that the differences between experiments were not statistically significant ($p > 0.05$, one tailed).

The graphs on the right side of Fig. 1 display the results from the morphine test day. In both experiments, tolerance to the analgesic effect of morphine was induced in groups NAL-MOR and SAL-MOR, as indicated by the finding that these groups displayed significantly lower PLLs following administration of 5 mg/kg morphine than groups NAL-SAL and SAL-SAL.

Experiments 3-6

The results from these experiments are presented in Fig. 2. The left graphs portray the results from the naloxone treatment phase. The pattern of results was similar to those observed in Experiments 1 and 2; the mean PLLs for SAL condition animals fell over the course of this phase whereas those in the NAL condition did not. The mean PLLs for NAL condition rats were significantly longer than those in the SAL condition beginning on days 4-6 of this phase.

The right graphs show the results from the test phase. In each experiment, the PLLs in NAL condition animals were significantly longer than SAL condition rats when saline was administered in the home cage. Of more importance were the results observed when drug was administered. The PLLs in NAL condition animals were significantly enhanced by yohimbine, significantly attenuated by clonidine, and unaffected by either prazosin or phentolamine. These four ligands were without effect in SAL condition animals.

DISCUSSION

The results from the naloxone treatment phase of the present experiments replicate those previously reported (18,40). Over the latter course of this phase, animals administered hotplate tests while under the influence of naloxone displayed significantly longer PLLs than controls. This effect occurred primarily as the result of a decline in latencies in SAL condition animals; the PLLs in NAL condition animals remained relatively constant. The results from the test phase of Experiments 2-6 also replicate those previously reported in that the longer PLLs displayed by NAL condition rats continued to

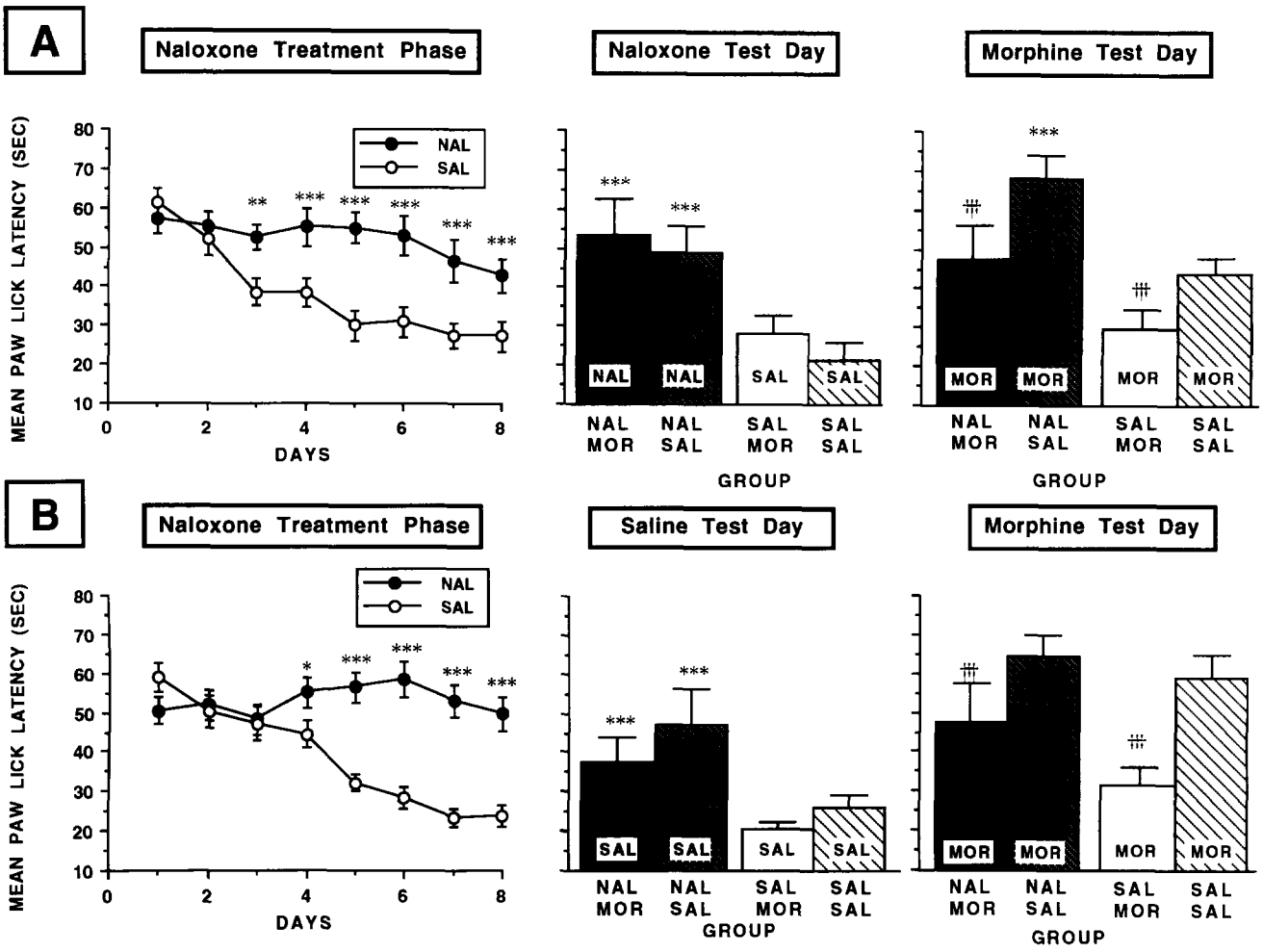

FIG. 1. Mean paw-lick latencies (±SEM) during each phase of Experiments 1 (A) and 2 (B). The graphs on the left present the results from the naloxone treatment phase of each experiment. The middle figure in (A) shows the results from the naloxone test day; the respective panel in (B) displays the results from the saline test day. The graphs on the right portray the results from the morphine test day in each experiment. The trigrams within each bar represent the ligand administered to each group for each test day. Asterisks denote significant comparisons contrasting the mean for the groups in the NAL condition with the mean for the respective SAL control groups: $*p < 0.05$, $**p < 0.025$; $***p < 0.01$. Daggers indicate significant contrasts within each condition (i.e., NAL-MOR vs.NAL-SAL and SAL-MOR vs. SAL-SAL): $\dagger\dagger\dagger p < 0.01$.

persist when these animals were administered saline, rather than naloxone, prior to test.

During the naloxone test day of Experiment 1 and the saline test day of Experiment 2, animals in the NAL-MOR group displayed latencies of similar magnitude to those in group NAL-SAL. This was equally true of the SAL-SAL and SAL-MOR groups. However, on the morphine test day in both experiments the mean PLLs for the NAL-MOR and SAL-MOR groups were, respectively, lower than those for the NAL-SAL and SAL-SAL groups. These latter results demonstrate that the administration regimen adopted to induce tolerance to the hypoalgesic effect of morphine was successful. Thus, the longer PLLs observed during both the naloxone and saline tests were not cross-tolerant with morphine-induced hypoalgesia, suggesting that both effects are mediated by nonopioid substrates (8,29,31).

Pretreatment with prazosin, a selective α_1-noradrenergic receptor antagonist, did not influence pain sensitivity in either NAL or SAL condition animals during the saline hotplate test. However, the PLLs exhibited by animals within the NAL condition were augmented by pretreatment with the α_2-noradrenergic receptor antagonist yohimbine and inhibited by clonidine, an α_2-receptor agonist. These ligands were without effect in control animals. This specificity supports the conclusion that yohimbine and clonidine acted directly upon the substrate mediating the hypoalgesia observed in NAL condition animals and adds further to the evidence implicating noradrenaline as at least one of the transmitters mediating the effect (36-38).

Previous work has implicated noradrenaline in the mediation of a variety of nonopioid forms of stress-induced hypoalgesia, and it appears that these effects are more profoundly affected by α_2-specific ligands in contrast to ligands that are less selective for this receptor subtype (10,12,13,27,30,32,39).

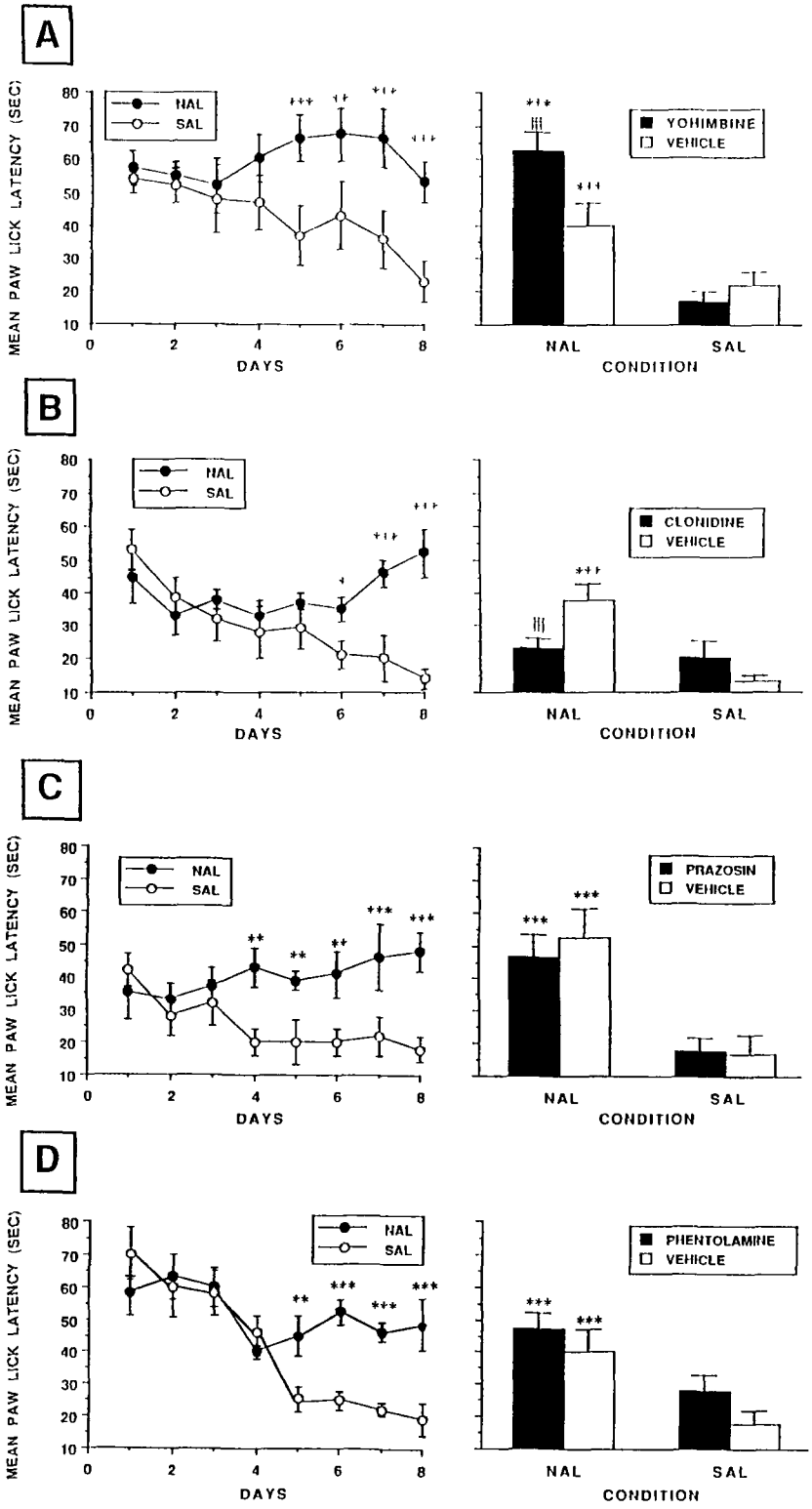

FIG. 2. Mean paw-lick latencies (±SEM) from the naloxone treatment phase (left) and the test phase (right) of Experiments 3–6. Panels (A)–(D) portray, respectively, the results from the experiments examining the effects of yohimbine, clonidine, prazosin, and phentolamine. Asterisks represent significant between-group contrasts between the means for NAL condition animals and those in the SAL condition: $^{*}p < 0.05$, $^{**}p < 0.025$, $^{***}p < 0.00$. Daggers reflect significant within-condition contrasts between the means observed following drug administration and those observed following vehicle administration: $\dagger\dagger\dagger p < 0.01$.

The evidence to date does not allow us to specify the precise manner in which this transmitter mediates the hypoalgesia observed in NAL condition animals; however, evidence from both electrophysiological and biochemical studies does suggest a potential mechanism. Specifically, naloxone has been shown to enhance stress-induced firing rate and release in noradrenergic neurons, suggesting that noradrenergic neurotransmission is under inhibitory opioid control (2,25,33,35,47). This finding raises the possibility that repeated exposure to the hotplate apparatus may provoke a progressively larger, opioid-mediated, inhibition of noradrenergic neurotransmission, thereby accounting for the decline in PLLs observed in SAL condition animals. Naloxone administration would block this inhibition, thereby maintaining noradrenergic neurotransmission close to its original level. Further, noradrenergic firing rate and release have been shown to be augmented by the pharmacological blockade of presynaptic α_2-receptors (3,14, 25,35) and inhibited by presynaptic α_2-receptor stimulation (6,26,44,46). Consequently, yohimbine would be expected to augment the hypoalgesia by enhancing noradrenergic release whereas clonidine would reverse this effect through its inhibitory action on noradrenergic neurotransmission.

The one problem with this hypothesis stems from the failure of phentolamine to influence the paw-lick latencies in NAL condition animals. Although this ligand displays a slightly higher affinity for the α_1-receptor, it also possesses significant affinity for the α_2-receptor subtype (41). Accordingly, phentolamine, like yohimbine, should have enhanced the paw-lick latencies observed in NAL condition animals. The reason this effect was not observed is unclear at the present time. One possibility could be that the enhancement of noradrenergic release provoked by phentolamine's actions at presynaptic sites may be countered by the concomitant blockade of postsynaptic α_1-receptors. However, we recently reported that the enhancement of paw-lick latencies provoked by yohimbine is not reversed by pretreatment with either phentolamine or with the specific α_1-antagonist prazosin (38). Alternatively, it is possible that yohimbine and phentolamine differentially influence different α_2-receptor subtypes (41) or that these ligands may exert differential effects on other neurotransmitter systems [e.g., serotonin; cf. (17)]. Further research will be required to assess the validity of these hypotheses.

The primary purpose of the present experiments was to determine the relationship between the mechanisms mediating the long paw-lick latencies observed in NAL condition animals when they are tested with and without naloxone. The results from the test days of Experiments 1 and 2 demonstrate that both effects do not exhibit cross-tolerance with morphine-induced hypoalgesia. Further, the results from the test days of Experiments 3–6 have shown that the hypoalgesia observed during saline tests, like that observed during naloxone tests (37,38), is sensitive to clonidine and yohimbine administration but unaffected by prazosin and phentolamine. The hypoalgesic responses observed during naloxone and saline tests, therefore, appear to be nonopioid in nature and are similarly sensitive to a specific subset of noradrenergic ligands. The present data do not rule out the possibility that other transmitter systems may be differentially involved in these two effects. This proviso notwithstanding, current evidence does not favor the hypothesis (40) that the substrates mediating each effect are distinct; it suggests, on the contrary, that there is a high degree of isomorphism.

It is important to delineate the implications of the present data for the collateral inhibition hypothesis. The data suggest that, within the experimental protocol followed in the present experiments, opioid and nonopioid antinociceptive substrates do not interact. This does not rule out the possibility that an interaction may exist under other experimental conditions, and there is a growing body of evidence that attests to such an interaction (5,9,21,28,45).

Moreover, our results are consistent with a modified version of the collateral inhibition hypothesis. The original hypothesis assumed an inhibitory interaction between opioid and nonopioid antinociceptive substrates. However, because opioid mechanisms have been implicated in a variety of learning phenomena (19), and because mechanisms involved in learning have been shown to influence antinociceptive substrates (11,15,16,34,49), it is not unreasonable to advance the argument that opioid substrates involved in learning may be inhibitory upon nonopioid antinociceptive substrates. Naloxone has been shown to enhance the Pavlovian conditioning of a nonopioid hypoalgesic response, suggesting that the acquisition of nonopioid conditioned hypoalgesia is under inhibitory opioid control (22–24,50). The present data can be accounted for by assuming a similar interaction during habituative learning. Naloxone maintains relatively long PLLs by blocking an opioid substrate involved in the habituation of nonopioid novelty-induced hypoalgesia.

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