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Locus Coeruleus Involvement in the Learning of Classically Conditioned Bradycardia

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Opioid agonists are known to inhibit the activity of locus coeruleus (LC) neurons. In this study, microinjections of the μ-opioid agonist [D-Ala², *N*-Me-Phe⁴, Gly⁵-ol]-enkephalin (DAMGO; 1.6 μM) bilaterally into the LC caused a significant impairment in the development of a heart-rate (HR) conditioned response (CR). The adverse effect of DAMGO on the HR CR could be reversed with naltrexone pretreatment. Microinjections of DAMGO into the periaqueductal gray, parabrachial nucleus, or fourth ventricle structures 1–2 mm away from the LC had no effects on the development of an HR CR. We conclude that central noradrenergic activity as mediated by the LC is critically involved in the learning and retention of conditioned cardiovascular responses.

Previously we have shown that rostral fourth ventricle administration of the μ-opioid agonist D-Ala²-Met-enkephalinamide (DALA) blocked the development of a heart-rate (HR) classically conditioned response (CR) in rats without affecting the HR unconditioned response (UR; Harris and Fitzgerald, 1989). Although baseline HR was markedly reduced by DALA during conditioning, raising the possibility that the CR was interfered with by cardiac performance factors, the absence of a CR 48 hr later with no drugs present strongly suggested that DALA prevented the learning of an HR CR. In a subsequent study, we showed that rostral fourth ventricle administration of α_2-adrenergic agonists was as effective as administration of DALA in blocking the conditioning of an HR CR (Harris and Fitzgerald, 1991). Because the locus coeruleus (LC) has one of the highest densities of both μ-opioid and α_2-adrenergic receptors in the rostral fourth ventricle, it seems highly likely that the LC was importantly involved in the CR losses found in both prior studies.

The LC has the largest, most compact collection of noradrenergic cell bodies in the brain and provides the primary source of noradrenergic innervation for most limbic and cortical areas (Moore and Bloom, 1979). It has been proposed that the LC plays a role in attentional (Aston-Jones, 1985) and motivational processes (Redmond, 1979; Gray, 1982), and much controversy has surrounded its possible role in memory formation (Crow, 1973; Amaral and Sinnamon, 1977). The LC responds to a variety of visceral and sensory stimuli (Foote et al., 1980), and in the presence of μ-opioid and α_2-adrenergic agonists, both spontaneous and evoked activity is abolished (Korf et al., 1974; North and Williams, 1985; Aghajanian and Wang, 1987). The present series of experiments was designed to assess more directly the role of the LC in the formation of the HR CR by directly microinjecting a μ-opioid agonist into the LC prior to HR conditioning.

Materials and Methods

Subjects

Male Sprague–Dawley rats (350–400 gm) purchased from Simonsens (Gilroy, CA) and maintained on a 12-hr:12-hr light/dark cycle with food and water available ad libitum were used in all experiments ($n = 39$).

Surgery

The rats were stereotaxically implanted with chronic 24-ga stainless-steel guide cannulas under ketamine anesthesia. Guide cannulas were bilaterally implanted into either the LC [AP, +1.1 mm (anterior to lambda); L, ±1.1 mm (lateral to the midline); V, −4.5 mm (ventral to the dura)], the periaqueductal gray (PAG; AP, +1.1 mm; L, ±1.1 mm; V, −3.2), or the parabrachial nucleus (PBN; AP, +1.1 mm; L, ±1.6 mm; V, −4.5 mm). For one group, a single guide cannula was implanted in the caudal fourth ventricle (AP, −2.5 mm; L, 0.0 mm; V, −5.5 mm). The coordinates were determined from Paxinos and Watson (1986). Lambda was defined by the midpoint curve along the lambdoid suture and was estimated to be 0.3 mm anterior to the interaural line. The skull was angled, to avoid having the cannulas hit the cerebral sinus, by setting the incisor bar at +5 mm. The cannulas were cemented to the skull with dental acrylic. At this same time, cardiac recording electrodes, consisting of three strands of 34-ga stainless-steel wire, were implanted subcutaneously on either side of the rat's thoracic cavity. Each rat was then allowed 4 d to recover from surgery before being tested.

Apparatus

The rats were restrained in an inverted U-shaped plastic holder (Narco Biosystems) with a 3-cm-diameter hole in the top of the holder that provided access to the guide cannulas for infusions. The holder was located in a continuously illuminated, sound-isolated chamber.

Drug infusions

Infusions were made using 32-ga stainless-steel needles precut to extend 0.5 cm beyond the guide cannulas into the LC. The infusions were performed by hand using two mounted, gas-tight, and liquid-tight 5-μl SGE syringes. The syringes were attached to the infusion needles with PE-20 tubing. The volume of the infusions was 0.4 μl/side given over 5 min. The μ-opioid agonist [D-Ala², *N*-Me-Phe⁴, Gly⁵-ol]-enkephalin (DAMGO) was dissolved in an artificial cerebrospinal fluid (CSF) solution. Artificial CSF was also used for all vehicle injections.

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Heart rate conditioning apparatus

Mean beat per minute (bpm) HR values for selected time periods on each trial were measured and recorded with the use of an Apple II microcomputer. The computer also controlled the delivery and timing of the conditioned stimulus (CS) and unconditioned stimulus (US). The US was a 0.5-sec train of 0.5-msec-duration 250-V DC pulses of shock, delivered through the electrocardiogram (EKG) electrodes. A discrimination conditioning paradigm was used in which CS+, a 6-sec electronically generated 3-Hz click, was paired with the US at a 6-sec CS–US interval. The offset of the CS+ coincided with the onset of the US. The CS− was a continuous 6-sec 1-kHz tone that was presented in the absence of the US.

On each trial, bpm HR values were calculated during a 6-sec period just before the CS, during the 6-sec CS–US interval, and during a 6-sec period following the termination of the US. Difference scores were computed on each trial by subtracting pre-CS HR from the CS–US interval HR (the CR) and from the post-US HR (the UR).

Experimental procedure

Experiment 1

This experiment examined the effects of microinjections of the opioid agonist DAMGO into the LC on the development of conditioned bradycardia (LC-DAMGO). The anatomical specificity of the LC microinjections was tested with the use of three specific injection control groups. One group was designed to control for the flow of DAMGO back up the cannula track. In this group (PAG-DAMGO), the bilateral cannulas were placed 1.5-mm above the location used for the LC microinjections, and were located in the vicinity of the periaqueductal gray.

The second group (VENT-DAMGO) was designed to control for the diffusion of DAMGO into the fourth ventricle. In this group, a single cannula was aimed at the roof of the fourth ventricle, slightly caudal to the location of the LC.

The third group (PBN-DAMGO) was designed to control for any lateral flow of DAMGO into neighboring cardiovascular nuclei. In this case, bilateral cannulas were placed in the parabrachial nucleus. Each of these control groups was given the same concentration and volume of DAMGO as that given the LC-DAMGO group. The experiment was carried out over a period of 4 d.

Day 1. On day 1, following a 45-min habituation period in the conditioning chamber, the groups were infused with either DAMGO (1.6 μM; LC-DAMGO, PAG-DAMGO, PBN-DAMGO, VENT-DAMGO groups) or vehicle (LC-Veh group). Infusions were made 5 min prior to the start of testing, while the rats rested in the experimental chamber. Groups then received four CS-alone trials (two trials with each CS), followed by six CS+ and six CS− conditioning trials. All trials were given in a semirandom order at intertrial intervals of either 1.0, 1.5, or 2.0 min (mean = 1.5 min).

Day 2. On day 2, the groups were again infused with the appropriate solution. However, on this day the habituation period was shortened to 15 min, and the CS-alone trials prior to conditioning were eliminated. All groups again received six CS+ and six CS− conditioning trials.

Day 3. Subsequent to the 2 d of conditioning, all groups remained in their home cage to permit full recovery from the effects of the drugs.

Day 4. To assess the presence of conditioning in the absence of drug influences, all groups received six CS+ (no US) and six CS− trials in a semirandom order at the start of day 4. At the end of this nondrug test phase, the LC-DAMGO and LC-Veh groups received further conditioning (10 CS+ and 10 CS− trials) in the absence of any drug. Immediately following this reconditioning phase, both of these groups were infused with the same solution that they had received during the initial conditioning on days 1 and 2. After the drug infusions, both groups received random presentations of four CS+ (no US) and four CS− trials. These trials were used to assess the drug effects on established HR CRs.

Experiment 2

This experiment assessed whether the effects of DAMGO on conditioning in the LC-DAMGO group were due to specific receptor–drug interactions. In this experiment, all procedures were identical to those experienced by the LC-DAMGO and LC-Veh groups in experiment 1, except that both groups of animals were pretreated with the opioid antagonist naltrexone (3 mg/kg, i.p.) prior to the microinjections given at the start of conditioning. The reconditioning and drug-test phases on day 4, however, were not included in experiment 2.

Histology

Cannula placements were verified with dye infusions (1% thionin, 0.4 μl/side). Following dye infusions, rats were deeply anesthetized with Nembutal (50 mg/kg, i.p.) and perfused through the heart with a 10% neutralized buffered formalin solution. The brains were removed and sectioned (100 μm) on a microtome cryostat. The sections were then mounted and stained with thionin to determine cannula location. Histologies were performed prior to data analysis. An animal was included in the data analysis only if the thionin mark terminated in the relevant structure (i.e., LC, PBN, PAG, fourth ventricle).

Data analysis

Groups × CS Type analyses of variance (ANOVAs) were performed during each experimental phase. Follow-up tests of significant interactions involving drug treatment were done using Newman–Keuls tests.

Results

Experiment 1

Histology. The histological sections revealed that the majority of placements were in the intended structures. Figure 1 shows a schematic representation of individual infusion sites for animals in the LC-DAMGO, LC-Veh, PBN-DAMGO, and PAG-DAMGO groups. Also included in Figure 1 are the infusion sites for two animals in the LC-DAMGO group who were excluded from experimental analysis. The symbols denote the most ventral points for the injection sites. Figure 2 shows two representative samples of LC cannula placements. It should be noted that, while some damage to the LC can be seen, in general the tissue damage was small, making dye injections necessary to reveal the injection sites. Histological examination of brain tissue verified correct cannula placement for six animals in the LC-DAMGO group, four in the LC-Veh group, three in the PAG-DAMGO group, three in the VENT-DAMGO group, and six in the PBN-DAMGO group.

Baseline HR. The LC-DAMGO, LC-Veh, PAG-DAMGO, and VENT-DAMGO groups all had similar baseline HRs on all 3 d of testing. Microinjections of neither DAMGO nor the vehicle solution into the LC produced any noticeable changes in baseline HR. The mean HRs of these groups on each day, respectively, were LC-DAMGO: 448, 462, and 448 bpm; LC-Veh: 478, 466, and 442 bpm. In comparison to the other groups, the PBN-DAMGO group showed an immediate and persistent reduction in baseline HR (approximately 100 bpm) following DAMGO administration.

Orienting responses. All groups exhibited bradycardia HR orienting responses (ORs) on the preconditioning CS-alone trials. While the ORs in the LC-DAMGO group were numerically smaller in magnitude than those seen in the LC-Veh group, the differences were not statistically significant. The mean OR of the LC-DAMGO group was −25 bpm compared to −43 bpm in the LC-Veh group. The other control groups did not differ from the LC-Veh group.

Conditioned responses. Figure 3 shows the mean HR response to CS+ during both days of conditioning and during the nondrug test (day 4) for the LC-DAMGO, LC-Veh, and the three injection control groups. Each of the three control groups showed differential responding to CS+ and CS− (CS− data not shown) at a level comparable to that shown by the LC-Veh group. Although the PBN-DAMGO group showed a numerically larger response to CS+ during conditioning than was seen in the other

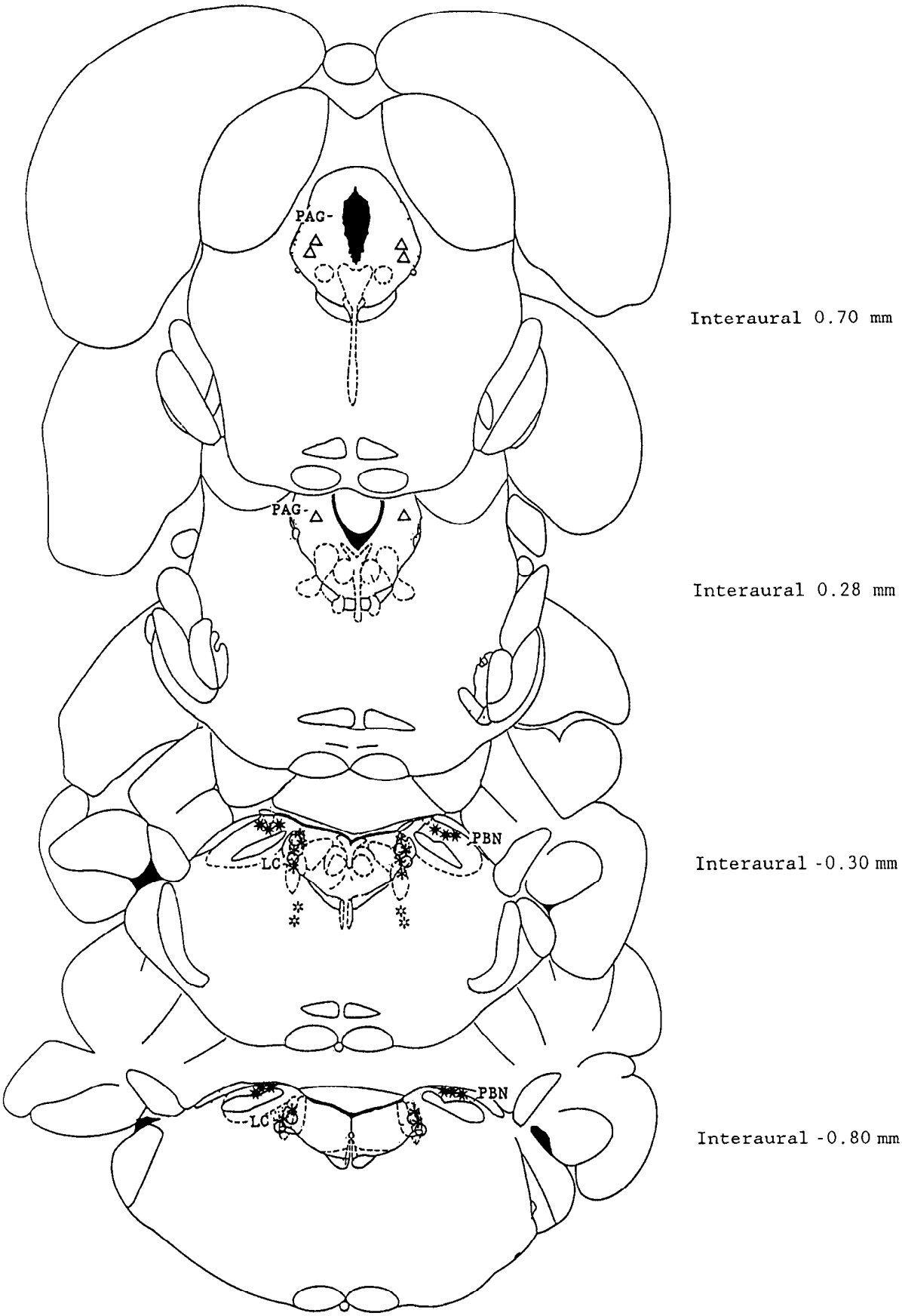

Figure 1. Brain sections modified from Paxinos and Watson (1986) indicating individual rat bilateral injection sites estimated from histological analysis. Infusion sites for the four groups are illustrated as follows: LC-DAMGO (∗), $n = 6$; LC-vehicle (○), $n = 4$; PBN-DAMGO (∗), $n = 6$; PAG-DAMGO (△), $n = 3$. The ∗ symbol represents the location of missed placements from the LC-DAMGO group ($n = 2$).

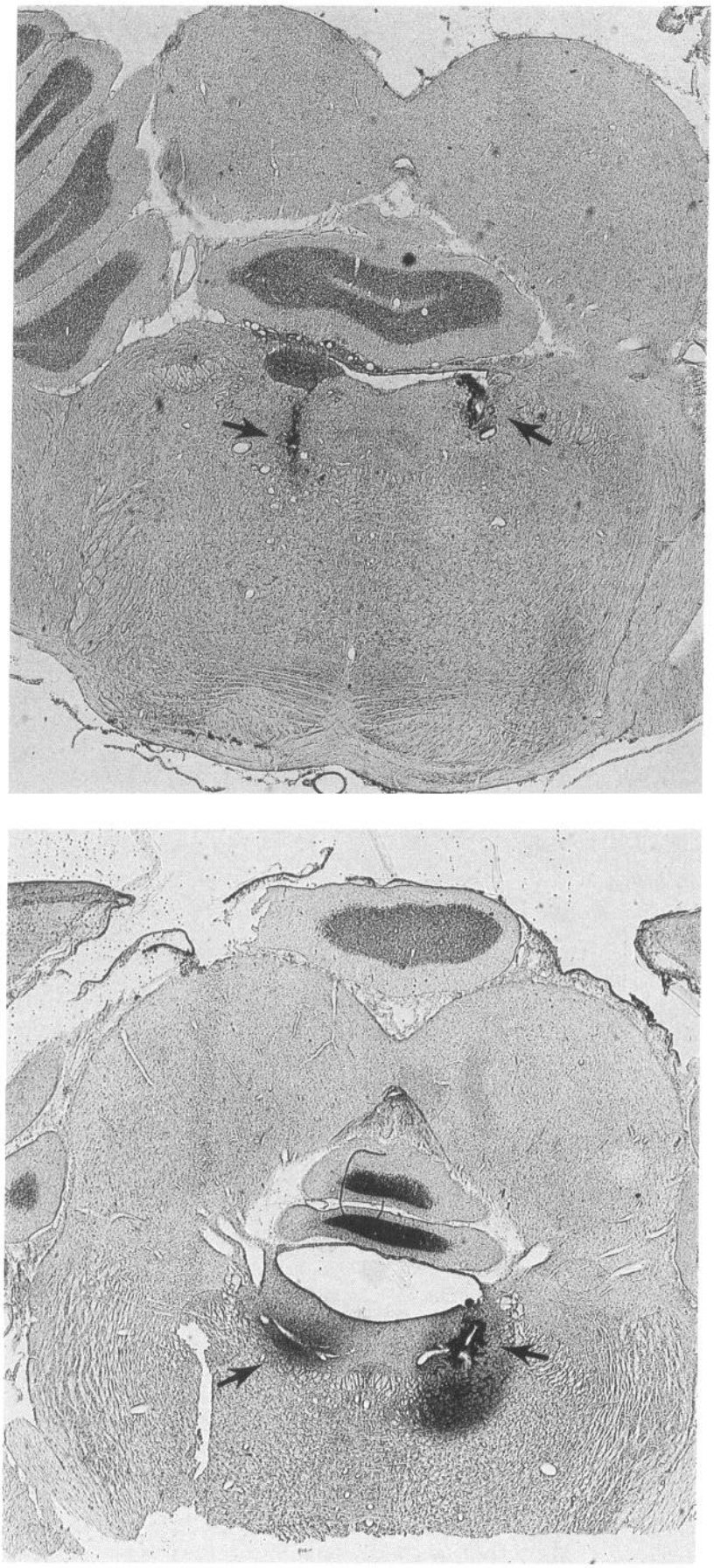

Figure 2. Representative samples of histological sections from two animals, showing microinjection sites (arrows) in the locus coeruleus.

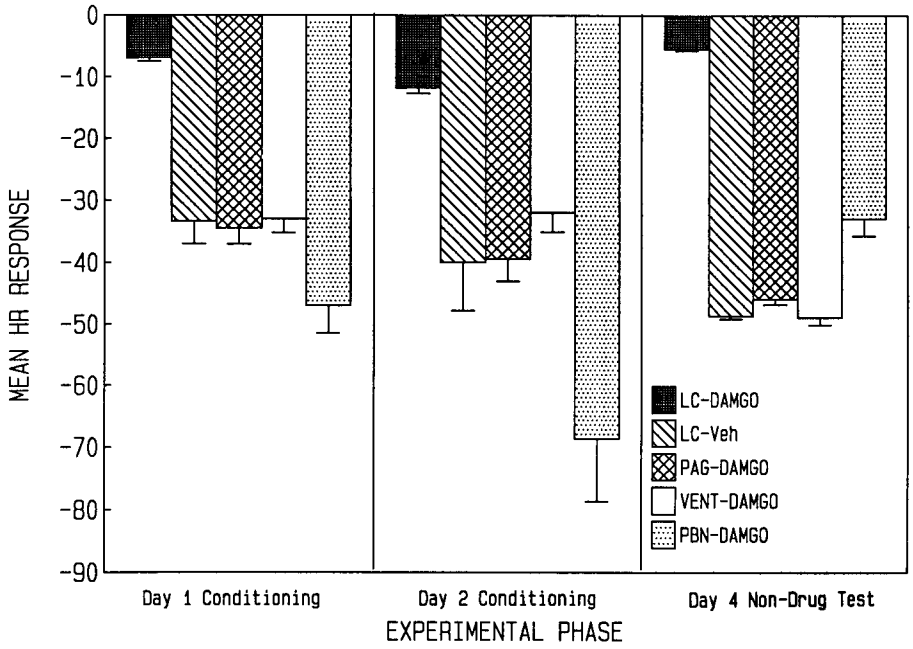

Figure 3. Mean change in HR from pre-CS baseline HR to CS+ for the LC (LC-DAMGO, LC-Veh), PAG (PAG-DAMGO), fourth ventricle (VENT-DAMGO), and PBN (PBN-DAMGO) microinjected groups (DAMGO, 1.6 μM; Veh, artificial CSF). Responses were averaged over the 6-sec CS period and over trials for days 1 and 2 and for the nondrug test that occurred on day 4. *Error bars* reflect SEMs.

groups (especially on day 2), their responses were not statistically different from the LC-Veh group.

It may be seen that on both days of conditioning the responses of the LC-DAMGO group to CS+ were considerably smaller than those in the LC-Veh group and the other control groups. When tested on day 4, the LC-DAMGO group showed little retention of an HR CR during the nondrug test, whereas the LC-Veh group and the other control groups showed sizable HR CRs.

A significant Groups × CS Type interaction on both days of conditioning [day 1: $F(1,8) = 18$, $p < 0.01$; day 2: $F(1,8) = 6.5$, $p < 0.05$] led to follow-up comparisons confirming that the CS+ response was significantly reduced in the LC-DAMGO group on both days ($p < 0.01$). A significant suppression in the CS+ response was also found in the LC-DAMGO group relative to the LC-Veh group during the nondrug test [$F(1,8) = 50.5$; $p < 0.001$].

Figure 4 depicts HR responses of the LC-DAMGO and LC-Veh groups to CS+ and CS− during the drug-free reconditioning and drug-test phases on day 4. In the absence of drug, the LC-DAMGO group showed the development of a CR during the second trial block [CS+ response was significantly greater than the CS− response; $F(1,10) = 11.4$; $p < 0.01$]. The magnitude of the CR in the LC-DAMGO group, however, was less than that shown by the LC-Veh group. During the drug test, the newly formed CR in the LC-DAMGO group was abolished when DAMGO was readministered. A follow-up test on a significant Groups × CS Type × Trial Block interaction in the reconditioning phase [$F(1,8) = 9.8$; $p < 0.01$] indicated that relative to the LC-Veh group the CST response in the LC-DAMGO group was significantly suppressed during both trial blocks ($p < 0.05$). Similarly, the follow-up on a significant Groups × CS Type interaction during the drug-test phase [$F(1,8) = 8$; $p < 0.05$] again confirmed that the CR to CS+ in the LC-DAMGO group was significantly suppressed.

Unconditioned responses. All groups exhibited similar tachycardia HR URs to the US. A one-way ANOVA showed that there were no significant drug-treatment effects.

Experiment 2

Histological examination of brain tissue verified the correct placement of cannulas in four animals in each of the naltrexone-pretreated groups. Figure 5 shows the HR responses of each group during the three phases of experiment 2. It can be observed that both groups showed a differential response to CS+ and CS−, indicating successful conditioning. Pretreatment of the LC-DAMGO group with naltrexone completely blocked the decremental effects of DAMGO administration on the HR CR found in experiment 1. These data suggest that the suppression of CR formation found in experiment 1 was due to the activation of opioid receptors and not to any nonspecific effects of the drug. No significant group differences were found during any phase of experiment 2.

Discussion

The major finding of this study was that the administration of DAMGO into the LC produced a naltrexone-reversible decrement in the development of the bradycardia CR without producing any changes in baseline HR. In addition, the administration of DAMGO also severely attenuated a recently learned HR CR. By contrast, the infusion of DAMGO into a region of the PAG directly above the LC, into the neighboring PBN, or into the fourth ventricle caudal to the LC did not interfere with the acquisition of the HR CR. The fourth ventricle finding is in contrast to those we found previously when the opioid injections into the fourth ventricle were made more rostrally in the vicinity of the LC (Harris and Fitzgerald, 1989). Taken together, these findings strongly suggest that any diffusion of DAMGO outside the area of the LC was not significantly involved in the learning deficits. Therefore, the decremental effects of LC DAMGO administration were most probably due to the activation of opioid receptors within the vicinity of the LC.

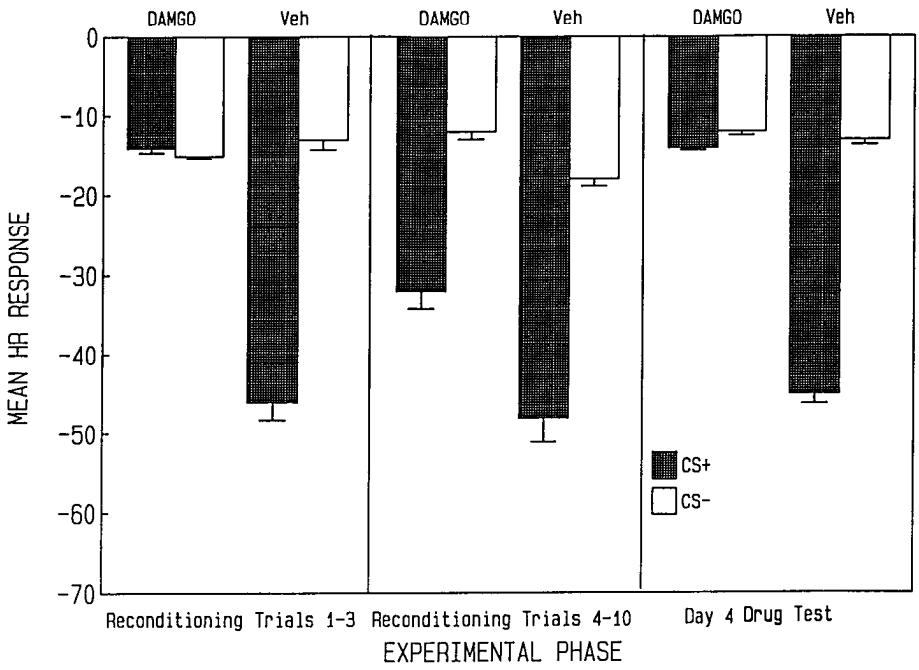

Figure 4. Mean change in HR from pre-CS baseline HR to CS+ and CS− for the LC microinjected groups (DAMGO, 1.6 μM; Veh, artificial CSF). Responses are averaged over the 6-sec CS period, over trials *1–3* and *4–10* during the reconditioning phase on day 4, and over the *drug test* trials that occurred after reconditioning on day 4. *Error bars* reflect SEMs.

The LC-DAMGO group in experiment 1 failed to show any consistent differential responding to CS+ on day 1 of conditioning, and though it showed slightly greater responses to CS+ on day 2, this level of responding was not maintained 48 hr later on the nondrug test. When the LC-DAMGO group was retrained, with no drugs present, it showed the acquisition of a CR to CS+. The rate of acquisition of the CR seen in this group during reconditioning was comparable to that shown by naïve rats, suggesting that any learning that may have occurred during the initial training was not retained or carried over into the retraining phase. The reconditioning data also indicate that the animals in the LC-DAMGO group were capable of learning and that damage to neural tissue from either the cannula placements or the microinjections was not responsible for deficits in CR acquisition.

Given the well-documented role of opioid compounds in inhibiting LC activity (Korf et al., 1974; Duggan and North, 1984), the results of the present experiments suggest that LC activity may be important for learning the significance of an environmental stimulus signaling an aversive event. Electrophysiological evidence has suggested that noradrenaline (NA) release in LC target areas enhances neuronal responding to strong stimuli

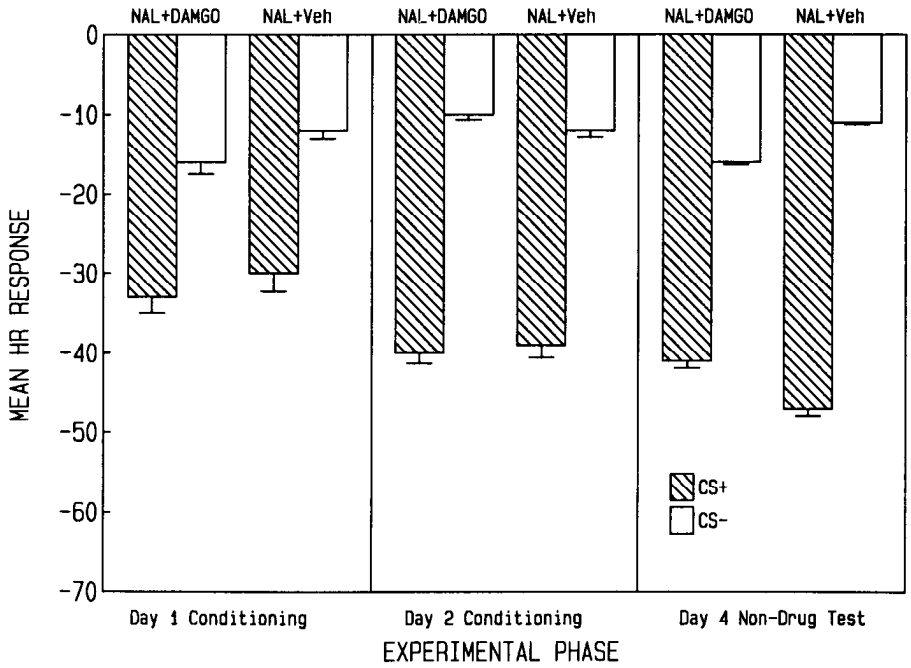

Figure 5. Mean change in HR from pre-CS baseline HR to CS+ and CS− for LC microinjected groups from experiment 3 (DAMGO, 1.6 μM; Veh, artificial CSF). Both groups were pretreated with the opioid antagonist naltrexone (*NAL*; 3 mg/kg, i.p.). Responses are averaged over the 6-sec CS period and over trials for days 1 and 2 and for the nondrug test that occurred on day 4. *Error bars* reflect SEMs.

(Madison and Nicoll, 1982; Segal, 1985; Waterhouse et al., 1988) and in particular to behaviorally salient stimuli (Segal and Bloom, 1976). While these data might suggest a role for NA transmission in promoting attention and or memory formation, there is a well-documented lack of effect of NA depletion on the learning and performance of a wide variety of behavioral tasks (Mason and Iversen, 1975; Amaral and Sinnamon, 1977; Roberts, 1981; Robbins and Everitt, 1982; Robbins et al., 1985).

There is, however, evidence indicating that LC target areas can show significant levels of recovery following LC or dorsal noradrenergic bundle lesions (Acheson et al., 1980; U'Prichard et al., 1980; Harik et al., 1981; Abercrombie and Zigmond, 1989). These data suggest that lesions may not be the best way to assess the role of LC activity in learning. The present experiments demonstrate that pharmacological agents that temporarily inhibit LC activity during a learning task can be used successfully to uncover learning deficits involving the LC.

It is possible that the learning deficits found in this study were due to the inability of the LC to respond to the CS or US following opioid administration, thereby blocking NA release in LC target areas critical for the learning of an HR CR. While there is evidence that the LC projects to brainstem areas important for central cardiovascular regulation (Lindvall and Bjorklund, 1974), the fact that the LC-DAMGO group showed no changes in either baseline or evoked HR responses (i.e., OR and UR) suggests that the animals in this group had impairments neither in cardiovascular functioning nor in the processing of sensory events. There is considerable evidence that the amygdala, which receives a major LC input, is important in the autonomic aspects of aversive CS conditioning (Kapp et al., 1984; Davis et al., 1987). A previous study has shown that blockade of NA activity within the amygdala central nucleus severely impaired the learning of an HR CR (Gallagher et al., 1980). The loss of NA release in LC target areas during conditioning could impair attention, arousal, or the development of fear that may be necessary for the learning of an HR CR. The emotional impact of the US or the ability to associate it with the CS may have been what was lost following DAMGO administration into the LC.

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