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Opiate Effects in the Amygdala Central Nucleus on Heart Rate Conditioning in Rabbits[1]

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GALLAGHER, M., B. S. KAPP, C. L. McNALL AND J P. PASCOE *Opiate effects in the amygdala central nucleus on heart rate conditioning in rabbits* PHARMAC. BIOCHEM. BEHAV **14**(4) 497–505, 1981 —Opiate agents were administered into the central nucleus of the amygdala complex of rabbits prior to either classical conditioning or pseudoconditioning of heart rate responding. Compared to control groups, opiate administration into the central nucleus did not significantly alter baseline heart rate, heart rate responding during habituation trials to presentations of the conditioned stimulus alone, or heart rate responding during the pseudoconditioning procedure However, opiate administration altered the acquisition of a conditioned bradycardia response during classical conditioning trials in which the offset of the conditioned stimulus was coincident with the presentation of an aversive unconditioned stimulus The opiate agonist levorphanol (5 0 nmole) significantly impaired the acquisition of the conditioned bradycardia response. This effect was observed to be stereospecific and blocked by concurrent administration of the opiate antagonist naloxone (2.5 nmole) Naloxone (2 5 nmole) administration alone significantly increased the magnitude of the conditioned bradycardia response. These effects produced by opiate administration into the central nucleus were not observed following administration of the same agents into sites 1–2 mm dorsal to the central nucleus

Amygdala central nucleus Heart rate conditioning Opiate receptors Rabbits

RESEARCH from our laboratory has demonstrated that classical conditioning of heart rate responding in rabbits is severely attenuated by lesions of the central nucleus of the amygdala complex [18]. This finding is particularly interesting in light of other recent evidence indicating that the central nucleus of the amygdala complex is anatomically linked to medullary systems which contribute to the expression of the conditioned heart rate response. In the rabbit, classically conditioned bradycardia appears to be mediated primarily by increased cardioinhibitory activity in the vagus nerves [8]. Neuroanatomical studies in the rabbit have demonstrated that central nucleus efferents project to a number of cardiovascular regulatory nuclei in the medulla including the nucleus of the solitary tract and the dorsal motor nucleus of the vagus [31,32]. Therefore, the effects of central nucleus lesions on classical conditioning of heart rate in the rabbit may reflect the effects of interfering with neural circuitry which normally plays an important role in the acquisition of conditioned heart rate.

Our current research is aimed at investigating neural mechanisms within the central nucleus which contribute to the acquisition of conditioned heart rate responding in the rabbit. Our interest in a possible role for opioid peptide function was suggested by our previous research which demonstrated that opiate manipulations within the amygdala complex altered retention of aversive conditioning in rats [9]. Indeed, the results of numerous recent investigations have implicated opioid peptides in learning and memory processes using a variety of conditioning procedures [1, 2, 15, 16, 17, 21, 22]. Since amygdala opioid peptides have been reported to be highly concentrated within the central nucleus region [4, 12, 28, 33], the present investigation was undertaken to assess the effects of opiate manipulations within the central nucleus region on the acquisition of classically conditioned heart rate in rabbits.

METHOD

Animals

One hundred and seventy four experimentally naive New

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Zealand Albino rabbits (Canadian Breeding Farms and Laboratories, Ltd.) weighing from 2.2 to 2.7 kg at the beginning of the experiment were used All animals were maintained on a 12 hr light-dark cycle (lights on from 7:00 a.m. to 7:00 p.m.) and were provided with food and water ad lib.

Surgery and Histology

All animals, with the exception of those in unoperated control groups, were pretreated with chlorpromazine hydrochloride (20 mg in 0.8 cc saline, IV) and anesthetized with Nembutal (30–75 mg, IV). They were mounted in a Kopf stereotaxic instrument fitted with a rabbit headholder, and bregma was adjusted 1 5 mm above the plane of lambda. Bilateral 23 g cannulae were implanted using the following coordinates: 0.1 mm anterior to bregma, 5.7 mm lateral to the midline and 11.8 mm ventral to dura. Animals in one group receiving cannulae positioned dorsal to the amygdala were prepared using the above coordinates with the exception that cannulae were lowered 10.5 mm ventral to dura. Immediately following surgery all animals received intramuscular injections of Crysticillin (30,000 units, Squibb and Sons).

Following behavioral testing all animals were sacrificed and perfused with physiological saline followed by 10% formal-saline. Frozen sections (50M) were taken through the amygdala and stained with Thionin. Cannula tip placement was determined microscopically with the aid of the stereotaxic atlas of Urban and Richard [35]. Cannula tip placements for all groups, except the dorsal placement group, were rated as unacceptable if they were (1) more than 0.5 mm dorsal or ventral to the dorsal surface of the central nucleus; (2) anterior to the central nucleus as represented on plate A 18.5 mm of the Urban and Richard atlas [35]; (3) posterior to the central nucleus as represented on plate A 15.5 mm of the Urban and Richard atlas [35]. Cannula tip placements for the dorsal placement group were rated by the above criteria, with the exception that a placement was rated unacceptable if it was less than 1.0 mm or more than 2.0 mm dorsal to the central nucleus. Only animals with bilaterally acceptable cannula placements were included in the data analysis

Apparatus

The apparatus employed in this experiment was identical to that used previously [10,18]. During conditioning each animal was placed in a Plexiglas rabbit restrainer and positioned in one of four sound attenuating chambers within a shielded, soundproof, IAC room. Shock was delivered through stainless steel dresshooks attached to the upper and lower left eyelids Stainless steel wire loops positioned subcutaneously, one dorsomedial to the left shoulder and one dorsomedial to the right haunch, were inserted shortly before the conditioning session to serve as EKG recording electrodes. The presentation of stimuli and recording of the EKG on a Grass Instruments Model 7 Polygraph were controlled by solid state programming equipment.

Conditioning Procedure

Following 10–14 days of postoperative recovery, animals in the conditioning groups were habituated to the Plexiglas restrainers for four daily one-half hour sessions followed on the fifth day by a one hour habituation session to the experimental chamber. Two days later the animals were placed into one of the four experimental chambers for the Pavlovian conditioning session. Fifteen presentations of the conditioned stimulus (CS), a 5 0 sec, 1000 Hz, 92 dB tone, were first presented using a random, variable, intertrial interval (80, 90, 100 sec; mean=90 sec). The presentation of fifteen CS alone trials, prior to the onset of paired Pavlovian conditioning trials, was used to habituate the decelerative heart rate orienting response Without this habituation, any decelerative heart rate changes to the CS during the initial paired conditioning trials could represent, at least in part, orienting responses to a novel stimulus rather than true conditioned responses Immediately following the 15 CS alone trials 20 paired conditioning trials were presented, again using a random, variable, 90 sec intertrial interval The offset of the CS was coincident with the onset of the unconditioned stimulus (US), a 500 msec, 2 0 mA eyelid shock.

Pseudoconditioning Procedure

Animals in the pseudoconditioning groups received the same procedures as described for the conditioning groups with the exception that the CS and US were presented in an unpaired manner. Following 15 CS alone presentations, animals in these groups received 20 presentations each of the CS and US. A random, variable, intertrial interval (35, 45, 55 sec, mean=45 sec) was used and no more than three presentations of either the CS or US occurred in succession.

Experimental Groups

Seven conditioning and three pseudoconditioning groups were included in this experiment. The seven conditioning groups consisted of two control groups and five drug-injected groups. The control gropus included an unoperated group (UNOP COND) and a vehicle-injected group (VEHICLE). Four drug injected groups, with cannula placements positioned at the dorsal surface of the central nucleus, included separate groups receiving 5.0 nmole injections of the opiate agonist levorphanol (LEV COND), 2.5 nmole injections of the opiate antagonist naloxone (NAL COND), 5.0 nmole injections of the inactive enantiomer of levorphanol, dextrorphan (DEX), and a group receiving combined 5 0 nmole injections of levorphanol and 2.5 nmole injections of naloxone (LEV+NAL). These groups were selected to provide information concerning the effects of manipulating opiate activity within the central nucleus region on heart rate conditioning. It was expected that if opiate agonist administration (group LEV COND) altered the acquisition of conditioned responding via opiate receptor mechanisms, comparable effects would not be observed in groups receiving either the inactive enantiomer of levorphanol (group DEX) or administration of levorphanol in combination with the antagonist naloxone (group LEV+NAL). In addition, it might be expected that if opioid peptides within the central nucleus actively participate in conditioning processes, then opiate antagonist administration (group NAL COND) might alter the acquisition of conditioned responding. Therefore, effects of naloxone administration on conditioning might reflect the effects of blocking endogenous opioid peptide activity.

A final conditioning group included in this experiment was comprised of animals which received 5 nmole injections of levorphanol at cannula placements positioned 1–2 mm dorsal to the central nucleus (LEV DORS) Since high concentrations of opiate receptors and opioid peptides are lo-

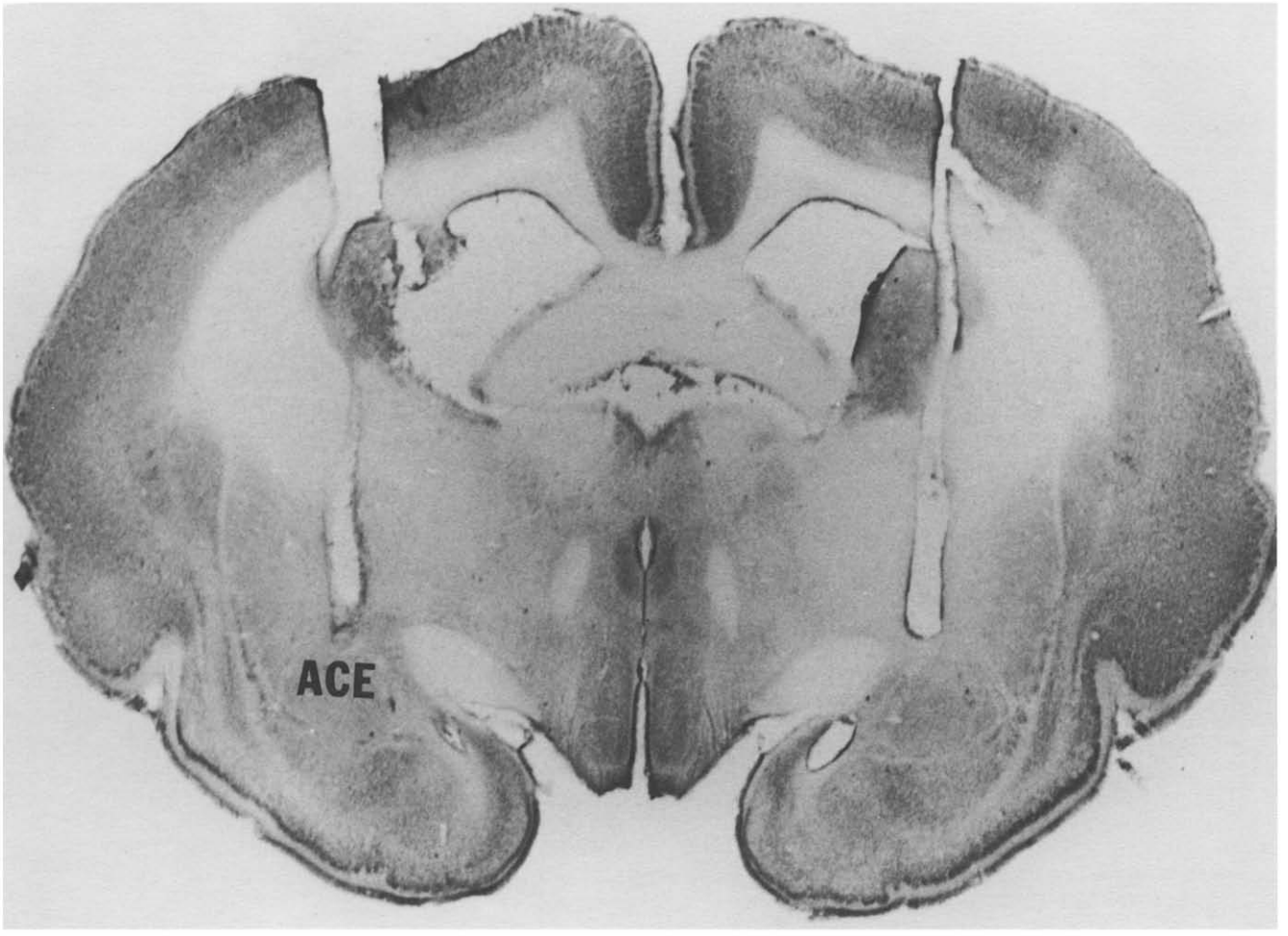

FIG 1 Cannula placements for an animal in the LEV COND group ACE, amygdala central nucleus

cated in basal ganglia structures dorsal to the amygdala [4,28], group LEV DORS was included to provide some information regarding both the localization of drug effects to the central nucleus target region and possible differences in the function of opiate sensitive mechanisms in the amygdala and in adjacent basal ganglia structures. Therefore, if opiate administration into the central nucleus altered conditioning processes by selectively affecting opiate sensitive mechanisms within the central nucleus region, comparable effects might not be observed following opiate administration at placements dorsal to the central nucleus within the basal ganglia.

The three pseudoconditioning groups included in this experiment were an unoperated group (UNOP PSEUD), a group receiving 5.0 nmole injections of levorphanol into the central nucleus (LEV PSEUD), and a group receiving 2.5 nmole injections of naloxone into the central nucleus (NAL PSEUD).

All injections were delivered bilaterally in a 1.0 μl volume approximately 5 min prior to the onset of behavioral testing. The vehicle used for all injections was a Krebs-Ringer phosphate solution [34].

Data Analysis

In order to provide a measure of the heart rate response to the tone CS, heart rate was recorded for 5 sec preceding the presentation of the CS and for the duration of the 5 sec CS. The magnitude of heart rate change to the CS for each trial was computed by comparing the number of beats occurring during the 5 sec CS period with the number of beats occurring during the 5 sec pre-CS baseline period. The difference was expressed as percent change from the pre-CS baseline period.

A measure of baseline heart rate was provided by the number of beats occurring during the 5 sec pre-CS baseline period. Analyses among groups were performed on baseline heart rate during the 15 CS tone alone trials in order to determine whether drug administration altered baseline heart rate.

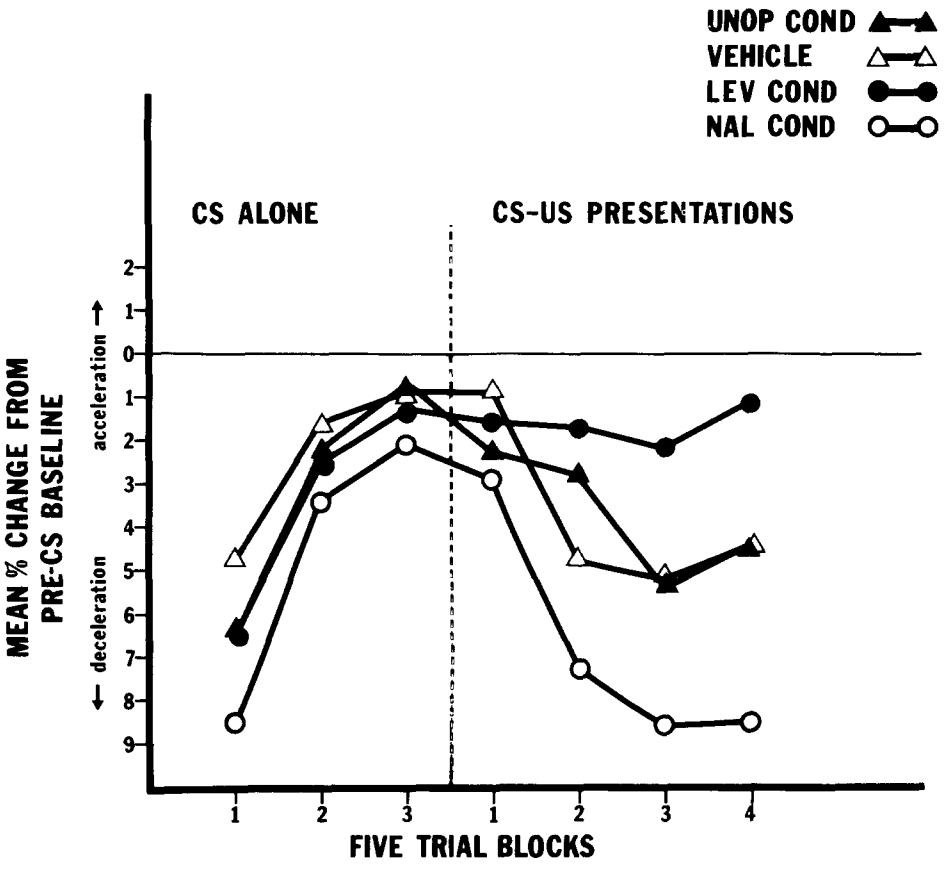

FIG 2 Mean percent change to the CS from pre-CS baseline for groups which received the conditioning procedure Data points represent means for 5 trial blocks

A two factor (Groups×Trials) mixed design analysis of variance was used to analyze the heart rate data.

RESULTS

Histology

Histological inspection of cannula placements yielded bilaterally acceptable placements for eight animals in each group. The data for these animals were included in the data analysis. Representative cannula placements for an animal included in the LEV COND group are presented in Fig. 1.

Heart Rate Responses

The heart rate responses to the CS for the control groups (UNOP COND and VEHICLE) and for the groups receiving levorphanol (LEV COND) or naloxone (NAL COND) injections into the central nucleus prior to the conditioning procedure are presented in Fig. 2. The heart rate responses to the CS for the comparable control and drug-injected groups which were subjected to the pseudoconditioning procedure are presented in Fig. 3. Analyses on baseline heart rate, heart rate responses to the 15 CS alone trials, and heart rate responses to the CS during CS and US presentations, were performed separately on the data for the conditioning groups in Fig. 2 (UNOP COND, VEHICLE, LEV COND, and NAL COND) and on the data for the pseudoconditioning groups in Fig. 3 (UNOP PSEUD, LEV PSEUD, and NAL PSEUD).

Baseline Heart Rate

Baseline heart rate was compared for the groups in Fig. 2. A two factor (Groups×Trials) analysis of variance yielded no significant effects for Groups or for the Groups×Trials interaction. The mean heart rate expressed as beats/min for each group was: UNOP COND, 213; VEHICLE, 229; LEV COND, 236; NAL COND, 225. A comparable analysis performed on the baseline heart rate data for the three pseudoconditioning groups yielded no significant differences among the groups. The mean heart rate for each group was: UNOP PSEUD, 227; LEV PSEUD, 211; and NAL PSEUD, 220. These results indicate that opiate administration into the central nucleus appears to have no significant effect on baseline heart rate.

Heart Rate Orienting Response

The orienting responses to the initial 15 CS alone presentations for the conditioning groups in Fig. 2 did not differ significantly. A two factor (Groups×Trials) analysis of variance revealed no significant effects for either Groups or for the Groups×Trials interaction. All groups exhibited a

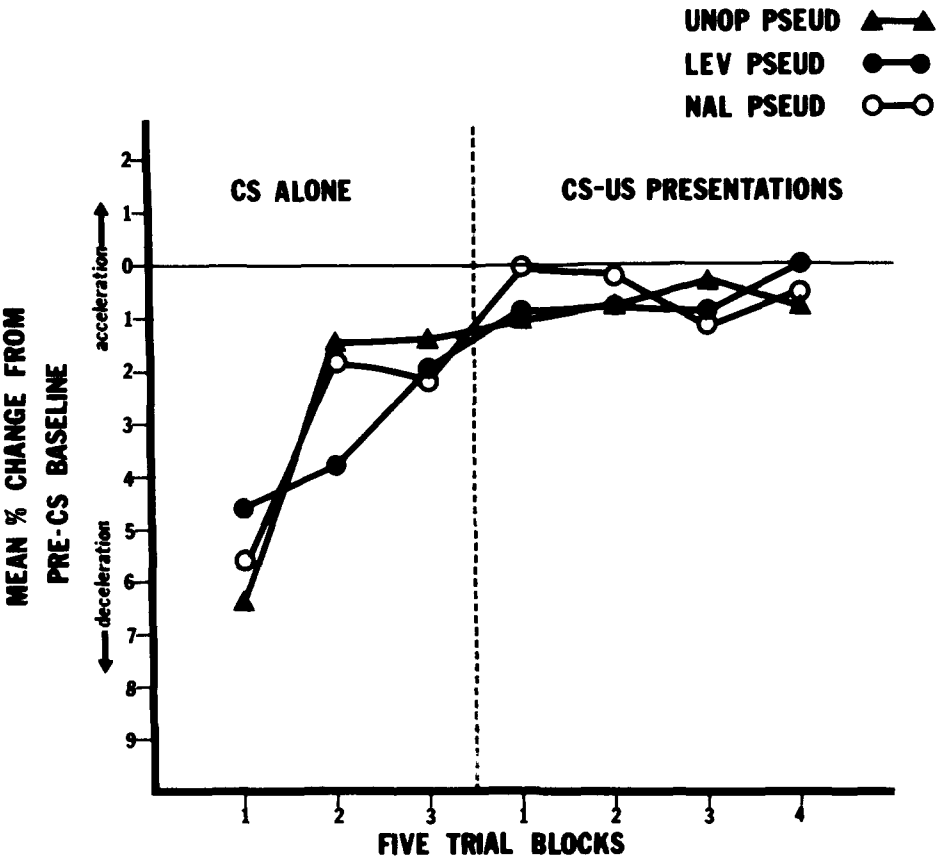

FIG 3. Mean percent change to the CS from pre-CS baseline in groups which received the pseudoconditioning procedure. Data points represent means for 5 trial blocks

bradycardia response to initial presentations of the CS which habituated over trials as reflected in a significant Trials effect $F(14,385)=17.72$, $p<0.001$. Analysis of the heart rate responses to the initial CS alone presentations for the pseudoconditioning groups in Fig. 3 yielded similar results. While no significant effects for Groups or for the Groups $\times$Trials interaction were obtained, the analysis yielded a significant Trials effect $F(14,294)=6.83$, $p<0.001$.

Conditioned Heart Rate Response

An analysis of variance performed on the heart rate responses to the CS during the 20 paired trials for the conditioning groups in Fig. 2 revealed significant effects for Groups $F(3,28)=8.23$, $p<0.001$ for Trials $F(19,514)=4.94$, $p<0.001$ and for the Groups$\times$Trials interaction $F(57,514)=1.63$, $p<0.005$. Since analysis for simple effects comparing the two control groups (UNOP COND and VEHICLE) revealed no significant effects for either Groups or Groups$\times$Trials interaction, the surgical and drug injection procedures did not appear to significantly alter the acquisition of conditioned responding. In the absence of any significant group differences, the significant Trials effect $F(19,269)$ $.3.26, p<0.001$ obtained in the comparison of the two control groups reflects the emergence of heart rate responses to the CS for both groups over trials.

Subsequent analyses were performed between the vehicle-injected group and each drug-injected group in Fig. 2. An analysis of variance, performed on the VEHICLE and LEV COND groups, yielded a significant Groups effect $F(1,14)=4.71$, $p<0.05$, while the Groups$\times$Trials interaction failed to reach significance $F(19,262)=1.55$, $p<0.07$. An analysis performed on the data for the VEHICLE and NAL COND groups revealed a significant Groups effect $F(1,14)$ $=7.62$, $p<0.02$, while the Groups$\times$Trials interaction approached significance $F(19,514)=1.85$, $p<0.06$. The results of these analyses reveal that opiate administration into the central nucleus significantly alters the acquisition of conditioned heart rate responding. Whereas opiate agonist administration decreases the magnitude of conditioned responses to the CS, opiate antagonist administration increases the magnitude of conditioned responses.

Pseudoconditioned Heart Rate Response

An analysis of variance performed on the heart rate responses to the CS during the 20 unpaired trials for the pseudoconditioning groups in Fig. 3 (UNOP PSEUD, LEV PSEUD, and NAL PSEUD), revealed no significant effects.

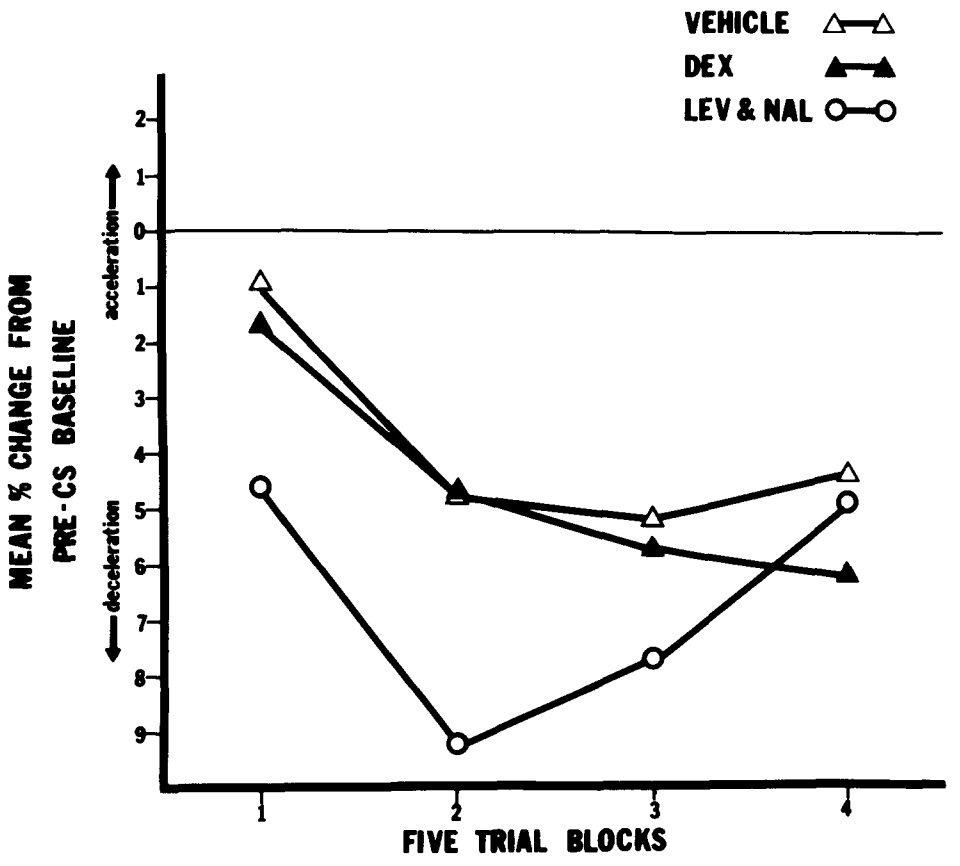

FIG. 4. Mean percent change to the CS from pre-CS baseline for groups VEHICLE, DEX, and LEV+NAL All of these groups received the conditioning procedure. Data points represent means for 5 trial blocks

Additional analyses, comparing each pseudoconditioning group with its respective conditioning group, revealed significant differences between the two unoperated groups $F(1,14)=70.02$, $p<0.001$ and between the two naloxone injected groups $F(1,14)=70.02$, $p<0.001$. However, an analysis comparing the LEV COND and LEV PSEUD groups did not yield any significant effects. Therefore, while the UNOP COND and NAL COND groups exhibited decelerative heart rate responses to the CS which are clearly distinguishable from those of the UNOP PSEUD and NAL PSEUD groups, the responses of the LEV COND were not significantly different from those of the LEV PSEUD group

Pharmacological Specificity

In order to determine whether the effects of opiate administration on heart rate conditioning exhibit stereospecificity, an analysis was performed on the data from the VEHICLE group and the group receiving injections of the inactive enantiomer of levorphanol, dextrorphan (group DEX). As illustrated in Fig. 4 dextrorphan administration did not significantly alter the acquisition of conditioned responding. While no significant effects for Gruops or for the Groups× Trials interaction were observed in the analysis comparing groups DEX and VEHICLE, a significant Trials effect $F(19,264)=3.73$, $p<0.001$ reflects the emergence of conditioned responding for both groups over trials. These results demonstrate that the effects produced by levorphanol administration are not produced by an equivalent dose of dextrorphan, which is a relatively inactive opiate receptor agonist.

Additional support for the interpretation that opiate agents injected into the central nucleus alter conditioning via opiate receptor mechanisms is provided by the data from group LEV+NAL (Fig. 4). When administered independently, levorphanol and naloxone were observed to produce opposing effects on conditioned responding. Although group LEV+NAL exhibited relatively large conditioned responses, an analysis performed on the data from the VEHICLE group, and from the group receiving combined administration of levorphanol and naloxone (LEV+NAL), revealed no significant effects for Groups or for the Groups× Trials interaction. A significant Trials effect was obtained $F(19,264)=2.84$, $p<0.001$. These findings are in agreement with the interpretation that the effects of levorphanol and naloxone on conditioning may be mediated by the competitive effects of these agents on opiate receptor mechanisms.

Anatomical Specificity

Finally, a comparison between the VEHICLE and LEV DORS groups was performed to determine if the effects of levorphanol administration were produced by diffusion of

TABLE 1
CONDITIONED RESPONSES DURING 20 PAIRED CS-US TRIALS

Group	N	Mean % Change to CS
VEHICLE	8	4.2
LEV COND	8	1 6
LEV DORS	8	6.5
LEV ANT	4	6 0
LEV LAT	4	6 2
LEV POST	3	4 6

The VEHICLE, LEV COND, and LEV DORS groups are those described in the text The LEV ANT, LEV LAT, and LEV POST groups received bilateral levorphanol (5.0 nmole) injections prior to the conditioning session LEV ANT animals had histologically confirmed bilateral cannula placements at the dorsal surface of the anterior amygdala area at least 0.5 mm anterior to the emergence of the central nucleus. LEV LAT animals had bilateral placements at the dorsal surface of the lateral nucleus approximately 0 5 mm lateral to the central nucleus LEV POST animals had bilateral placements at the dorsal surface of the lateral posterior nucleus at least 0 5 mm posterior to the central nucleus.

the drug from the injection site to opiate sensitive sites dorsal to the amygdala complex. Analysis of variance comparing the VEHICLE and LEV DORS groups did not reveal any significant differences between these groups. A significant Trials effect was obtained $F(19,266)=6.80$, $p<0.001$. In addition, an analysis comparing the data from group LEV DORS with that from the group which received levorphanol administration into the central nucleus (LEV COND), revealed significant effects for groups $F(1,14)=14.55$, $p<0.002$ and for the Groups×Trials interaction $F(19,266)=3.27$, $p<0.001$. These results support the interpretation that levorphanol does not impair conditioning by exerting its effects on regions dorsal to the central nucleus injection site.

The additional possibility that opiates injected into the central nucleus exert some or all of their effects on amygdala nuclei adjacent to the central nucleus is addressed by the data presented in Table 1. Histological analysis of the LEV COND animals included in this experiment revealed a number of bilaterally symmetrical placements at the dorsal surface of the amygdala either anterior, lateral, or posterior to the central nucleus. While these animals were excluded from the LEV COND group, their data may provide some preliminary information regarding the effects of opiate administration into amygdala nuclei adjacent to the central nucleus. The conditioned responses exhibited by animals which received levorphanol injections into these sites surrounding the central nucleus appear similar to those of the VEHICLE group, providing limited support for the possibility that opiate agonist administration impairs conditioning by affecting opiate sensitive systems within the region of the central nucleus.

DISCUSSION

The heart rate data obtained from the unoperated control groups in this experiment are similar to those reported in other studies using similar classical conditioning procedures [10, 18, 19, 29]. The heart rate orienting response to initial presentations fo the CS alone consisted of a bradycardia which habituated rapidly with repeated CS presentations. During paired presentations of the CS and US, conditioned bradycardia responses developed rapidly in the UNOP COND group, whereas the UNOP PSEUD group did not exhibit comparable responses to the CS during unpaired stimulus presentations. These findings demonstrate that the procedures used in this experiment result in significant associative conditioned responding in the UNOP COND group. In addition, the acquisition of conditioned responses of animals subjected to the surgical and injection procedures used in this experiment (group VEHICLE), did not differ from those of the unoperated control group (UNOP COND).

Opiate administration into the central nucleus in this experiment appeared to selectively alter the acquisition of conditioned heart rate responses. No significant effects of opiate administration were observed on either baseline heart rate or on the heart rate orienting response. Furthermore, injections of opiates into the central nucleus did not alter heart rate responding to the CS in groups subjected to the pseudoconditioning procedure. However, opiate agonist and opiate antagonist administration into the central nucleus produced opposing effects on the acquisition of conditioned responses during paired CS-US presentations. Whereas levorphanol decreased conditioned responding compared to the vehicle-injected group, naloxone increased the magnitude of conditioned responding. Indeed, the observation that responding to the CS in the conditioning and pseudoconditioning groups which received levorphanol did not significantly differ, suggests that opiate agonist administration into the central nucleus blocked the acquisition of conditioned responses.

Evidence provided in this experiment supports the interpretation that the effects of opiates on conditioning are due to changes in opiate receptor activity. First, the effect obtained with administration of the agonist levorphanol exhibited stereospecificity because dextrorphan administration did not alter conditioning. Second, animals which received combined administration of levorphanol and naloxone exhibited conditioning which did not differ significantly from that of the VEHICLE control group. These findings are consistent with the pharmacological characterization of opiate receptors within the central nervous system as exhibiting stereoselectivity and competitive occupation by agonist and antagonist agents [13,23]. Furthermore, the finding that naloxone administration into the central nucleus facilitates conditioning, suggests that endogenous opioid activity within this region may actively inhibit conditioning processes. According to this interpretation, the enhanced conditioning observed following naloxone administration may reflect the effects of blocking endogenous opioid peptides.

The data obtained in this experiment provides some support for the interpretation that the effects of opiates on conditioning are due to the effects of these agents within the target region. Injections of levorphanol at sites dorsal to the central nucleus were ineffective in altering the acquisition of conditioned responding. This result is consistent with a previous study, which reported that extensive lesions of the striatum failed to alter a classically conditioned heart rate response in rats [25]. In addition, somewhat more restricted lesions of the caudate have been reported to have no significant effect on the acquisition of classically conditioned bradycardia in rabbits [24]. Furthermore, our preliminary observations indicate that injections of levorphanol into the amygdala, at sites surrounding the central nucleus, did not

produce comparable effects on conditioning. Indeed, given the size of the rabbit brain, and in particular the dimensions of the central nucleus in this species, the injection volume used in this experiment would not be expected to result in significant diffusion of the opiate agonist beyond the central nucleus [20]. This expectation is supported by the finding that in the LEV DORS group levorphanol administration 1–2 mm from the effective injection site, did not significantly alter conditioning.

The precise role which opiate activity within the amygdala plays in conditioning processes has not been established in the present investigation. However, several lines of evidence suggest that alterations in sensory processing are probably not responsible for the observed results. Animals injected with opiates into the central nucleus exhibited normal heart rate orienting responses to the tone CS. Although we have not investigated possible analgesic effects of opiate administration into the central nucleus on sensitivity to the shock US, other investigators have reported that activity at opiate receptors within the central nucleus in rats does not alter shock sensitivity [27] In addition, a number of studies have demonstrated that systemic opiate antagonist administration does not appear to significantly alter threshold sensitivity when electric shock is used as a noxious stimulus [5,11]. Therefore, it is unlikely that the enhanced acquisition of conditioned responding observed in animals injected with the antagonist naloxone is due to increased shock sensitivity.

Other evidence has implicated opioid peptides within this brain region in the regulation of functions which may be relevant to the results of this investigation. Several lines of evidence suggest that the central nucleus, and opioid sensitive mechanisms within this region, contribute to the regulation of emotional states. Animals with central nucleus lesions have been reported to display decreased emotional reactivity and, in particular, an attenuation of fear-like behaviors [37]. Conversely, a pattern of behavioral and autonomic changes similar to those elicited by fear-evoking stimuli, can be produced by electrical stimulation at sites within the central nucleus [6,36]. In support of the possibility that opiate sensitive mechanisms within the central nucleus regulate emotional responses, it has been recently reported that opiate administration into the central nucleus decreases emotional reactivity in rats [7]. In light of these observations, the results of the present investigation are consistent with the notion that opiate manipulation within the central nucleus in rabbits may affect the acquisition of conditioned heart rate responses by altering the arousal of fear

At the same time, a number of investigations have now provided evidence that opioid peptides may be involved in memory processes. Specifically, post-conditioning administration of opiates, both agonist and antagonist, as well as opioid peptides have been reported to alter retention of training experiences [1, 2, 15, 16, 17, 21, 22]. While most of these investigations have used aversive conditioning procedures, opiate effects on memory processes have also been reported in studies which have used non-noxious stimuli in the training procedure [15, 16, 17] Previous research conducted in our laboratory demonstrated that in rats at least a component of the opiate sensitive system involved in memory processes appears to be located within the amygdala complex [9]. Post-training administration of the agonist levorphanol into the amygdala produced stereospecific, and naloxone reversible, decreases in retention of passive avoidance conditioning. Naloxone administration alone produced a dose-dependent increase in retention. Whether an opiate-sensitive substrate within the central nucleus serves a common function, underlying the effects of opiate manipulation on the acquisition of conditioned responses and the retention of conditioning, remains an important question for future research.

Finally, the results of this investigation may have important implications for understanding the contribution of specific neural mechanisms within the amygdala to autonomic function and, in particular, to the regulation of cardiovascular function Recent interest has focused on the influence of forebrain structures on medullary systems which regulate cardiovascular function [3]. Interconnections between the amygdala central nucleus and the nucleus of the solitary tract, as well as the dorsal motor nucleus of the vagus in the medulla have been described in a number of species including the rabbit [14, 26, 31, 32]. A role for opioid peptides in the regulation of these projection systems has been suggested by the presence of opioid peptides within both the central nucleus and these medullary regions [4, 28, 33]. Our results, therefore, provide evidence supporting a role for an opiate sensitive system within the central nucleus region of the amygdala in the regulation of conditioned cardiovascular responses.

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