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Naloxone-Induced Modulation of Feline Aggression Elicited From Midbrain Periaqueductal Gray

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SHAIKH, M. B. AND A. SIEGEL. *Naloxone-induced modulation of feline aggression elicited from midbrain periaqueductal gray.* PHARMACOL BIOCHEM BEHAV **31**(4) 791–796, 1988.—In the present study, peripheral administration of naloxone hydrochloride (IP) was employed to identify the role of endogenous opioid peptides in the regulation of two forms of aggressive behavior in the cat—affective defense and quiet biting attack behavior. These forms of aggressive behavior were elicited by electrical stimulation of dorsal and ventral aspects of the midbrain periaqueductal gray, respectively, utilizing monopolar electrodes. Following the establishment of stable baseline thresholds for affective defense and quiet biting attack behavior, naloxone (0.5, 1.0, 4.0 and 7.0 mg/kg) and saline (vehicle control) were administered peripherally (IP). The response thresholds were tested 5–30, 30–60, 60–90, 180–210 and 1440–1470 min following naloxone administration. These results indicated that a dose level of 7.0 mg/kg of naloxone had a profound facilitatory effect on affective defense behavior. Response threshold values returned to prenaloxone baseline levels at 1440–1470 min postinjection. Administration of lower doses of naloxone (1.0 and 4.0 mg/kg) also resulted in a significant facilitation of this response but of shorter durations. Neither the lowest dose of naloxone (0.5 mg/kg) nor saline (vehicle control) were effective in modifying the threshold for affective defense behavior. In contrast, when tested for its effects upon quiet biting attack, the maximum dose utilized in this study (7.0 mg/kg) tended to suppress this response although the overall effect was not significant. The selective dose-dependent facilitatory effects of naloxone upon affective defense behavior in the cat suggests that the opioid peptide system plays a significant (inhibitory) role in the regulation of this response.

Naloxone Cat Affective defense Midbrain periaqueductal gray Quiet biting attack Electrical stimulation of brain

THE periaqueductal gray matter of the midbrain has been shown to play a role in a wide variety of behavioral responses such as flight, affective defense behavior, quiet biting attack (5–7, 9, 14, 19, 34, 47, 51, 53, 54), feeding behavior (4,60), vocalization (36–38) and regulation of pain (42,44).

Typically, in the laboratory, the feline affective defense response is characterized by ear retraction, hissing and growling which are frequently accompanied by a paw-strike often directed towards a second cat or experimenter. The display is associated with autonomic components which include pupillary dilatation, piloerection and urination (12, 27, 29, 34). The quiet biting attack is characterized by an initial stalking and approach to an anesthetized rat and which culminates in the biting of the back of its neck (22,64).

The midbrain periaqueductal gray contains both high affinity opiate binding sites (3) and endogenous opioid peptides which are extensively distributed throughout this region (30,48). Recent studies have implicated opioid peptides in the regulation of processes typically associated with the periaqueductal gray such as nociception, food intake and neuroendocrine regulation (43, 45, 61). In the present study, we sought to determine how the opioid peptide system can modulate affective defense and quiet biting attack behavior elicited from the midbrain periaqueductal gray of the cat. Peripheral injections of naloxone were utilized to test the effects of endogenous opiates in the regulation of these responses.

METHOD

Eight adult cats of either sex that did not exhibit spontaneous aggressive responses when a rat or cat was placed in their home cages were selected for this study. They were maintained on an ad lib feeding and drinking schedule throughout the course of the experiments.

Prior to the experiment, the animals were anesthetized with sodium pentobarbital (45 mg/kg). During aseptic surgery, 12 stainless-steel guide tubes (17 gauge, 10 mm long) were mounted stereotaxically [according to the stereotaxic atlas of Jasper and Ajmone-Marson (35)] over the holes drilled through the skull overlying the midbrain periaqueductal gray. These guide tubes enabled future lowering of elec-

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trodes into brain sites in the periaqueductal gray from which attack responses could be elicited. Three stainless-steel stylets, connected by a silver wire to 8–10 screws embedded in the skull, served as indifferent electrodes. Three plastic bolts were connected to the cranium with dental acrylic to hold a plastic cap that protected the entire assembly.

Elicitation of Aggressive Behavior

After a postoperative recovery period of one week, the animals were placed in a wooden behavioral observation chamber (61×61×61 cm) with a one-way mirror. Electrolytically sharpened, stainless-steel stylets insultated with an oil-base paint, calibrated and exposed 0.5 mm from the tip, were used as stimulating electrodes. The electrodes were lowered through the guide tubes in awake, unrestrained animals in 0.5 mm steps. The freely moving animals were stimulated at each of the steps with biphasic, rectangular electrical pulses (0.2 to 0.6 mA, 62.5 Hz, 1 msec half cycle duration) via wires connected to the electrodes. Stimuli were delivered from a Grass S-88 stimulator and led through a pair of Grass stimulus isolation units to the cat. A pair of 40 kΩ resistors in series with the leads to the cat approximated constant current conditions. The peak-to-peak current was monitored by a Tektronix 502 A oscilloscope. Monopolar stimulation of the midbrain periaqueductal gray was employed throughout the entire experiment in the presence of food and an anesthetized rat to determine whether predatory or affective forms of attack could also be elicited from the same site. In four cases, affective defense and quiet biting attack were elicited from opposite sides of the brain of the same animal (Table 1).

Only those sites were chosen for study which produced pure forms of affective defense or quiet biting attack behavior. When an affective defense or quiet biting attack response was consistently observed upon stimulation, the electrode was cemented in place with dental acrylic. In two cats, one electrode was utilized per animal. In six additional cats, as many as three electrodes were employed with bilateral placements (Table 1).

Prenaloxone Response Threshold Baseline Testing

This phase of the experimental paradigm involved the determination of baseline thresholds for affective defense or quiet biting attack behavior over a period of 1–2 weeks. Baseline testing (30–45 min/day with interstimulus intervals of 2 min) was conducted on alternate days for 1–2 weeks. The baseline threshold current for these responses for a given day was determined utilizing the Method of Limits, where 10 ascending and 10 descending series of trials were employed. In these test series, current levels were raised or lowered in 0.05 mA steps in a counterbalanced A-B-B-A design. The response threshold for affective defense or quiet biting attack was defined as the current value at which responses were elicited on 50% of the trials. The latency to hiss or bite was also recorded on each trial of stimulation with the aid of stopwatch. Demonstration of stable baseline thresholds (i.e., a response threshold which remained invariable over a period of at least three test sessions), preceded drug administration.

Peripheral Administration of Naloxone

Following establishment of a stable baseline response threshold (for both affective defense and quiet biting attack behavior), the animals were administered naloxone hydrochloride (Endo Laboratories, Inc., Garden City, NY) peripherally (IV or IP, in 0.5 ml of sterile isotonic saline, pH=7.4). In all 8 animals, a maximum dose of naloxone (7.0 mg/kg) was employed to determine its effects upon affective defense and quiet biting attack. In four of these cats, additional doses (0.5, 1.0 and 4.0 mg/kg) were also tested in order to obtain dose-response curves for the affective defense response. The doses were randomized in order to eliminate any possible order effects. In addition, each animal was used as its own control as it was tested for possible effects of peripheral administration of vehicle alone.

Postnaloxone Threshold Testing

In this phase of the experiment, affective defense and/or quiet biting thresholds were determined over the following postinjection time periods: 5–30, 30–60, 60–90, 180–210 and 1440–1470 min following administration of each dose of naloxone. Here, a paradigm for response threshold testing identical to that employed in the predrug testing phase of this study, was employed. In animals in which dose-response curves were obtained, each drug dose was tested one day per week with a test interval of 6 days.

At the completion of behavioral testing, the animals were perfused transcardially with 0.9% NaCl and 10% formalin. The brains were removed, blocked and cut on a freezing microtome at 40 μm. The sections were then stained with cresyl violet and electrode tips from which affective defense or quiet biting attack was elicited were identified.

One-way and 2×3 factorial analyses of variance (ANOVA) were performed to determine the effects of dose and time postinjection upon the changes in threshold for affective defense behavior. In addition, the significance level of drug dose upon behavior at each time point examined was determined by a *t*-test for independent observations, using for comparison, the mean response for animals given vehicle alone at appropriate time points in question. A one-way ANOVA was employed to determine the effects of drug upon the threshold for quiet biting attack. When comparisons were made of the effects of a given dose against baseline values, the data was analyzed in two ways. In one procedure, a *t*-test compared the responses in which the data from all animals was pooled. Here, N was defined as the number of animals tested. A second *t*-test determined the level of significance associated with a given dose for each attack site examined at the times when maximum effects for each dose level were obtained. Here, N was defined as the number of trials administered at each attack site.

RESULTS

The results reported below describe the differential effects of peripheral administration of naloxone upon affective defense behavior and quiet biting attack, respectively. Affective attack sites were situated mainly in the dorsal aspect of the midbrain periaqueductal gray, while quiet attack behavior was generally obtained from stimulation of the ventral half of the periaqueductal gray (Fig. 1).

Effects of Naloxone Upon Affective Defense Behavior

The effects of peripheral administration of naloxone upon affective attack behavior were assessed in 7 cats in which attack responses were elicited from 11 sites in the midbrain periaqueductal gray. The major finding was a marked reduc-

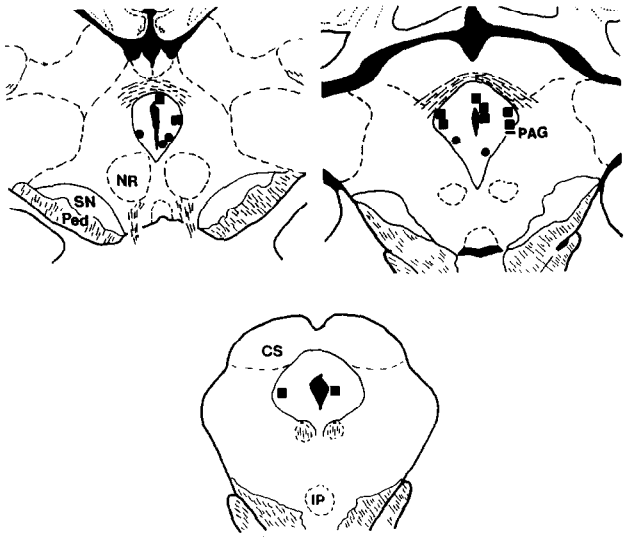

FIG. 1. Sites within the midbrain periaqueductal gray from which affective defense (squares) and quiet biting attack (circles) were elicited. Note that affective defense sites are located mainly in the dorsal half of the midbrain periaqueductal gray while sites from which quiet biting attack were elicited were situated ventrally within this structure. Abbreviations: CS, superior colliculus; IP, interpeduncular nucleus; NR, red nucleus; PAG, midbrain periaqueductal gray; Ped, cerebral peduncle and SN, substantia nigra.

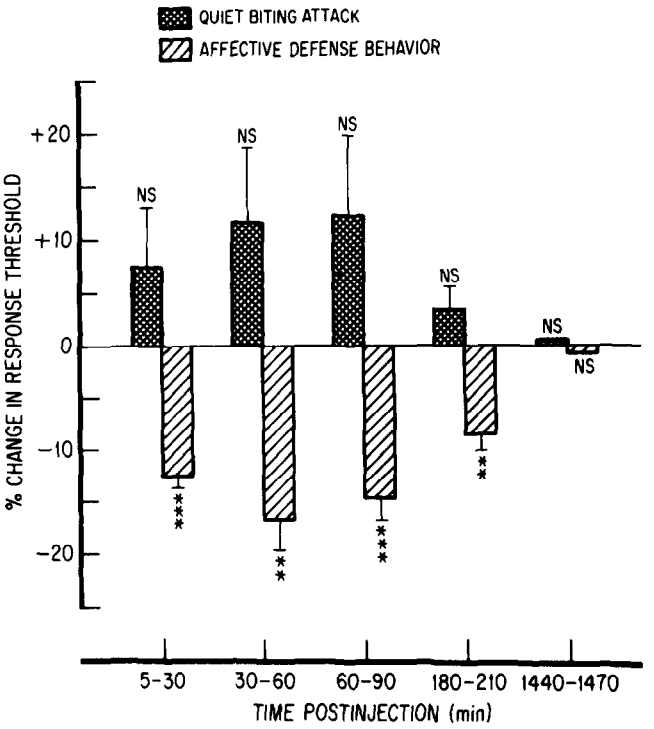

FIG. 2. Bar graphs indicate the time course of the effects of a 7.0 mg/kg dose of naloxone upon affective defense behavior and quiet biting attack. Note that naloxone selectively lowered the threshold for affective defense but not for quiet biting attack. Vertical lines indicate SE values (N=7 for affective defense behavior and N=5 for quiet biting attack). ***$p<0.001$; **$p<0.01$; N.S., not significant.

tion in the affective attack threshold following drug delivery. This effect is shown in Fig. 2, which depicts the effects of a 7.0 mg/kg dose of naloxone upon this response. In 10 of 11 affective sites tested, this dose level of naloxone significantly lowered the threshold for affective defense, $F(4,30)=12.5$, $p<0.001$. Figure 2 also indicates that the effect was observed initially after 5 min with a 12.8% decrease in response threshold, $t(6)=11.03$, $p<0.001$. The duration of this facilitatory effect upon affective defense was rather prolonged, in which response threshold values remained below predrug baseline for at least 210 min postinjection, $t(6)=5.09$, $p<0.01$. Maximal effects were obtained at 30–60 min postinjection where a 16.8% decrease in threshold was observed, $t(6)=5.52$, $p<0.01$. The threshold values for affective defense were shown to have returned to baseline at 24 hours (1440 min) following naloxone administration.

Our observations indicate that when naloxone was administered at 7.0 mg/kg, a profound facilitatory effect upon affective defense was observed. In order to determine the dose response relationships of naloxone, drug doses of 4.0, 1.0 and 0.5 mg/kg were utilized. The corresponding dose-response curve is shown in Fig. 3. ANOVA indicated highly significant differences in the magnitude of the naloxone effect at different dose levels upon affective defense thresholds, $F(2,27)=17.10$, $p<0.0001$. When 4.0 mg/kg naloxone was administered, the reduction in threshold was manifest initially at 5 min, $t(3)=4.2$, $p<0.05$, and this effect extended only for 30–60 min postinjection, $t(3)=6.4$, $p<0.01$. When tested with 1.0 mg/kg of naloxone, significant decreases in attack thresholds were noted only at the 30–60 min postinjection period, $t(3)=11.2$, $p<0.01$. When a minimal dose of 0.5 mg/kg was employed, no change in baseline threshold values was observed for affective defense at any of the time points tested (N=4).

In each animal, 0.5 ml of isotonic saline (pH=7.4) was peripherally injected to determine the effect of administration of vehicle alone. The data indicate that injections of vehicle alone had no effect upon thresholds for either affective defense or quiet biting attack at any of the time points examined.

Effects of Naloxone on Quiet Biting Attack Behavior

For this phase of this study, five cats were utilized (five sites) and a 7.0 mg/kg dose of naloxone was employed (i.e., the maximum effective dose tested against affective defense used in this study) for its possible effects on quiet biting attack behavior. The results, shown in Fig. 2, indicate that the effects of naloxone upon quiet biting attack were quite different than what was observed for affective defense. Here, it was observed that peripheral administration of naloxone at this dose level suppressed quiet attack in two animals. In three other cats, however, baseline threshold values for quiet attack were not altered at any of the time points tested following naloxone administration. When this data was considered collectively, statistical analysis revealed a weak suppression effect of naloxone upon quiet biting attack which failed to reach statistical significance, $F(4,20)=0.95$, $p>0.50$.

In one animal, separate sites were obtained in the periaqueductal gray from which both affective defense and quiet biting attack were elicited, respectively. Threshold changes for each of these responses were identified on alter-

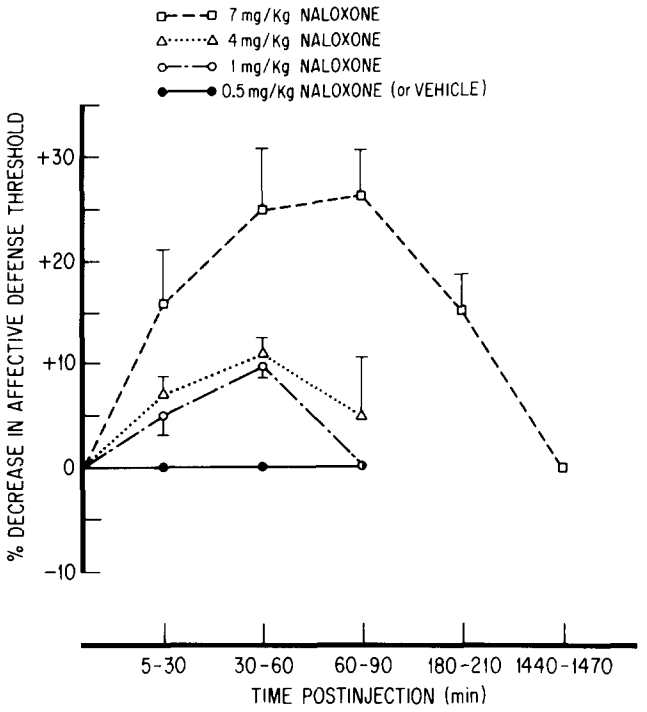

FIG. 3. Time course and dose dependent effects of naloxone (0.5, 1.0, 4.0 and 7.0 mg/kg) upon affective defense behavior. Note that neither the lowest dose of naloxone utilized in this study (0.5 mg/kg) nor vehicle control (0.9% saline) altered the threshold for affective defense behavior (N=4 for each dose level).

nate trials after naloxone administration at 7.0 mg/kg. In this animal naloxone resulted in significantly reduced threshold values for affective defense for at least 3 hours ($p<0.05$), while, in contrast, the threshold of quiet biting attack was significantly elevated during this period ($p<0.01$).

DISCUSSION

Following the discovery of the presence of opiate peptides in the brain, a sizeable number of investigations have been conducted utilizing naloxone as a tool for investigating the role of these peptides in various functions of the nervous system. The overwhelming majority of these studies have implicated endogenous opiates in the regulation of pain and epileptiform activity (1, 10, 16, 17, 23, 24, 41). The present study extends these findings to the process of affective defense behavior in the cat. Here, it was demonstrated that naloxone administered peripherally can significantly facilitate this response elicited from the midbrain periaqueductal gray and that the facilitatory effect of naloxone is dose-dependent. Since naloxone failed to show consistent facilitation of quiet biting attack behavior and, in fact, displayed a tendency to suppress this response, it is reasonable to conclude that opioid peptides selectively suppress the effective defense reaction. Modulation of affective defense behavior by naloxone is not surprising inasmuch as it has been shown that a cat will learn a task to escape brain stimulation from sites where this response can be elicited (2). Such results indicate that this response has aversive properties and may share common features with some of the regulatory mechanisms for nocieption. Moreover, it has been further documented that amygdaloid epileptiform activity can be powerfully enhanced by endogenous opioids and reversed by administration of naloxone (17,41). Since it has also been shown that seizures induced from the amygdala can significantly alter the threshold for elicitation of the affective defense response (13,58), it is plausible to suggest that endogenous opioids may further modulate affective defense behavior by their action upon neurons within the amygdala.

While our findings strongly suggest that the opioid peptide system could powerfully modulate affective defense behavior, the present study does not address the issue of the possible sites of action where the effects of opioid peptides may become manifest. Possible regions where this system may be acting are suggested from recent immunocytochemical studies. Likely candidates include forebrain structures such as amygdala, bed nucleus of stria terminalis and hippocampal formation (8, 21, 28, 31–33, 39, 40, 46, 50, 62, 63, 66), all of which have been shown to modulate aggressive behavior in the cat (11, 13, 15, 20, 26, 55, 65). Two other

TABLE 1

EFFECTS OF PERIPHERAL ADMINISTRATION OF NALOXONE UPON AFFECTIVE DEFENSE AND QUIET BITING ATTACK BEHAVIOR

	Dose of Naloxone (mg/kg)					
Animal	0.5	1.0	4.0	7.0	Response	Effect
1′				X	AD	F†
1″	X				AD	N.S.
1″			X		AD	F*
1″		X			AD	F*
1″				X	AD	F*
2				X	AD	F*
2″				X	AD	F‡
3′				X	AD	F†
4				X	AD	F*
4′		X			AD	F‡
4′				X	AD	F†
4′			X		AD	F*
4′	X				AD	N.S.
5		X			AD	F*
5				X	AD	F*
5	X				AD	N.S.
5			X		AD	F*
5′				X	AD	N.S.
7′			X		AD	F†
7′	X				AD	N.S.
7′		X			AD	F†
7′				X	AD	F*
8				X	AD	F†
1				X	QBA	S*
2′				X	QBA	N.S.
3				X	QBA	S*
6				X	QBA	N.S.
7				X	QBA	N.S.

AD, affective defense; QBA, quiet biting attack; F, response facilitation; S, response suppression; *$p<0.001$; †$p<0.01$; ‡$p<0.05$; NS, not significant; '–", a second and third attack site tested from the same animal.

regions of the brain include the medial preoptico-hypothalamus and midbrain periaqueductal gray. Both have been shown to be central for the expression of affective attack behavior (6, 25, 59) and are rich in enkephalins (3, 30, 39, 48, 52, 63, 66). In fact, recent studies in our laboratory have indicated that local microinjections of DAME ([D-Ala^2, Met^5]-enkephalinamide) placed into the bed nucleus of the stria terminalis (15) or midbrain periaqueductal gray (49, 56, 57) suppress affective defense behavior in the cat. Thus, it is likely that the facilitation of affective defense observed in the present study with naloxone resulted from the collective blocking of the effects of endogenous opioid peptides in both forebrain and brainstem structures associated with the regulation and elicitation of this behavior.

Although the present findings favor the view that endogenous opioid peptides powerfully modulate affective defense behavior, the possibility also exists that the facilitatory effects of naloxone upon this response may have been mediated via a GABAergic mechanism. This notion is based upon evidence that naloxone can antagonize the effects of GABA, especially when administered at a high dose (i.e., 90 mg/kg) where it can produce seizures in mice and potentiate the convulsant activity bicuculline (18). In the present study, however, a much lower dose of naloxone (i.e., 1 mg/kg) was found to be effective in modulating thresholds for affective defense behavior. Thus, it would appear that the relatively low doses of naloxone utilized in the present study would be insufficient to directly involve the GABAergic system. Nevertheless, the existence of such a mechanism is one that remains logically possible and is, in fact, currently being investigated in our laboratory.

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