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Carbamazepine Regulates Feline Aggression Elicited From the Midbrain Periaqueductal Gray

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SHAIKH, M. B., H. M. EDINGER AND A. SIEGEL. *Carbamazepine regulates feline aggression elicited from the midbrain periaqueductal gray.* PHARMACOL BIOCHEM BEHAV 30(2) 409–415, 1988.—Carbamazepine has been utilized both as an anticonvulsant and as a psychotropic drug for the treatment of complex partial seizures and various mood and other emotional disorders such as the episodic dyscontrol syndrome. In the present study, we sought to identify the role of carbamazepine in the regulation of two forms of aggressive behavior—affective defense and quiet biting attack behavior—elicited by electrical stimulation of the midbrain periaqueductal gray matter of the cat in the absence of convulsive activity. The experimental paradigm involved establishment of stable baseline thresholds for affective defense and quiet biting attack responses. Following establishment of a stable baseline, carbamazepine (2.5, 5, or 10 mg/kg) and propylene glycol (vehicle control) were administered peripherally (IP). The response thresholds were tested 5–30, 30–60, 60–90, 120–150, 1440–1470, and 2160–2190 minutes following drug administration. It was observed that carbamazepine administration at 5 and 10 mg/kg dose levels preferentially suppressed affective defense behavior but had no effect upon quiet biting attack, indicating that the selective effects of carbamazepine upon affective attack are not due to any possible sedative effects upon motor responses. The effects of carbamazepine upon affective defense were dose dependent and of long duration when administered at the highest dose level (10 mg/kg).

Carbamazepine Cat Midbrain periaqueductal gray Affective defense Quiet biting attack

CARBAMAZEPINE is known to possess marked anticonvulsant properties in both humans [7,24] and animals [11, 25, 41] and is especially recommended in the treatment of patients with complex partial seizures of temporal lobe origin [7,33].

A positive correlation between temporal lobe epilepsy and violent behavior has often been suggested [3,43], and carbamazepine is considered useful in both controlling seizures and managing the aggressive episodes associated with complex partial epilepsy [33]. Furthermore, it has been suggested that carbamazepine may also be an effective drug for the treatment of affective disorders [1, 8, 9, 28, 38] and in treatment of aggressive schizophrenic patients [16,37]. In order to obtain a better understanding of the action of carbamazepine, we decided to study the effect of this drug on an animal model of aggressive behavior.

Among the aggressive reactions that have been examined in laboratory animals are affective defense behavior and quiet biting (predatory) attack which are known to occur under natural conditions in the cat [22]. These aggressive responses can be elicited by electrical stimulation of wide regions of the preoptico-hypothalamus and the midbrain periaqueductal gray [18, 31, 42]. The affective defense response involves piloerection, retraction of ears, pupillary dilatation, growling, hissing and paw striking [14,36]. Quiet biting attack behavior, in contrast, is characterized by an initial stalking of an anesthetized rat which culminates in a bite to the back of its neck [12,42]. Recent studies conducted in our laboratory and elsewhere have shown that amygdaloid stimulation at seizure or subseizure current levels can modulate the aggressive reactions in the cat [4–6, 10].

A recent report suggested that carbamazepine could block shock-induced fighting in mice [27]. However, interpretation of these results may be difficult since it could not be determined whether carbamazepine specifically suppressed the aggressive reactions in question or had a general inhibiting effect upon all motor responses. We directly sought to investigate the role of carbamazepine in the regulation of two forms of aggressive behavior—affective defense and quiet biting attack behavior, both of which were elicited by electrical stimulation of the midbrain periaqueductal gray in the cat.

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METHOD

Ten adult cats of either sex that did not spontaneously attack rats and weighed between 2.5 and 3.5 kg served as subjects in this study. All the cats had free access to food and water during the entire course of experiment. Prior to the experiment, animals were anesthetized with sodium pentobarbital (45 mg/kg). During aseptic surgery, 12 stainless steel guide tubes (18 gauge, 10 mm in length) were mounted stereotaxically (according to the atlas of Jasper and Ajmone-Marson [21]) over holes drilled through the skull overlying the midbrain periaqueductal gray. After recovery from surgery, these guide tubes enabled the vertical lowering of electrodes into brain sites in the periaqueductal gray from which attack responses could be elicited. Two stainless steel stylets were connected by silver wire to 8 screws embedded within the skull to serve as indifferent electrodes. A plastic cap overlying the electrode assembly was attached to three bolts affixed to the skull in order to protect it from inadvertent damage by the animal in its home cage.

After a recovery period of one week, the animals were placed within a wooden behavioral chamber (61×61×61 cm) in which the subject could be viewed through a one-way mirror. Electrolytically sharpened, stainless steel stylets, 0.6 mm in diameter, insulated with an oil-base paint, calibrated and exposed 0.5 mm from the tip, were used for electrical brain stimulation. The electrodes were lowered vertically through the guide tubes into the midbrain periaqueductal gray in 0.5 mm steps in the freely-moving animal. At each step, stimulation was employed in order to obtain an attack response. The animal was stimulated with biphasic, rectangular pulses (0.1–0.65 mA, 62.5 Hz, 1 msec per half cycle duration) via wires connected to the electrodes. Stimuli were delivered from Grass stimulus isolation units to the cat. A pair of 40 K ohm resistors in series with the cat approximated constant current conditions. The peak-to-peak current was monitored by a Tektronix 502 oscilloscope. Monopolar stimulation of the periaqueductal gray was employed throughout the entire experiment. When a stable affective defense or quiet biting attack response was obtained (in the presence of an anesthetized rat), the electrode was cemented in place with dental acrylic. The sites producing affective defense behavior were located mainly in the rostrodorsal aspect of the periaqueductal gray, while those producing quiet biting attack response were located more ventrally within the periaqueductal gray (Fig. 1). In six cats, one electrode was utilized per animal. In four additional cats, two to four electrodes were employed which included bilateral placements (Table 1).

The experimental paradigm involved establishment of stable baseline thresholds for affective defense and quiet biting attack behavior. Initial current threshold values ranged from 0.1 to 0.65 mA. Interstimulus intervals were maintained at two minutes. Baseline testing (30–45 min per day) for each of these behaviors 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 ascending and descending series of trials were employed. The response threshold was defined as the current intensity at which an attack response occurred on 50% of the trials. A stable baseline threshold was identified as one which remained unchanged over one week of testing. Following the establishment of a stable baseline response threshold for one week, either carbamazepine (2.5, 5.0, and 10.0 mg/kg) dissolved in propylene glycol (1.5 ml), or propylene glycol alone (1.5 ml of vehicle control) was administered peripherally (IP). Then, response thresholds were determined over the following postinjection time periods: 5–30, 30–60, 60–90, 120–150, 1440–1470, and 2160–2190 minutes. Again, a 2-min interstimulus interval was maintained throughout this phase of the experiment. No more than two doses of drug were ever administered to a given animal.

In cases where the effects of different drug doses upon attack behavior were assessed, an interval of one week separated the testing of each drug dose. Similarly, when the effects of carbamazepine upon attack responses were determined where more than one brain site in the same animal was utilized, a period of one week also separated the testing associated with each site. The order of delivery of different doses of drug or vehicle control was randomly determined for all animals. Four animals were prepared with electrodes from which affective defense and quiet biting attack behavior could be elicited from separate sites in the midbrain periaqueductal gray. In three of the cats, drug testing against each of these behaviors was separated in time by a minimum of one week. In the fourth cat, threshold current for elicitation of each of these behaviors was examined concurrently with alternate trials involving affective defense and quiet biting attack responses both prior to and following drug administration. Again, a 2-min interstimulus interval separated trials of quiet biting attack and affective defense behavior.

Analysis of variance tests were applied to determine both changes in response threshold over time following drug administration relative to pre-drug response threshold values as well as the effects of different dose levels of drug upon response thresholds. In addition, *t*-tests were employed to determine the effects of drug level upon response threshold at each point in time following carbamazepine administration relative to pre-drug values for individual animals as well as for group data. N was defined as the number of animals tested for the following analyses: all F tests as well as *t*-tests which compared the effects to two dose levels at a given time following drug administration. When comparisons were made of the effects of a given dose with 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 were 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. The results of *t*-tests associated with individual attack sites are reported in Table 1.

Blood levels of carbamazepine, drawn from the cephalic vein, were routinely determined by the Fluorescence Immunopolarization Method 30 minutes following carbamazepine administration. This sampling time was selected because it represents the time at which peak plasma and tissue concentrations are reached [26]. In order to avoid potential stress to the animals, additional blood sampling at other times during the testing period was not undertaken.

At the completion of the experiment, the animals were perfused transcardially under deep anesthesia with 0.9% NaCl and 10% formalin. The brains were then removed and blocked. Frozen sections were cut at 50 μm and stained with cresyl violet in order to localize the electrode tips associated with each of the attack responses.

RESULTS

In ten cats, affective defense behavior was obtained by

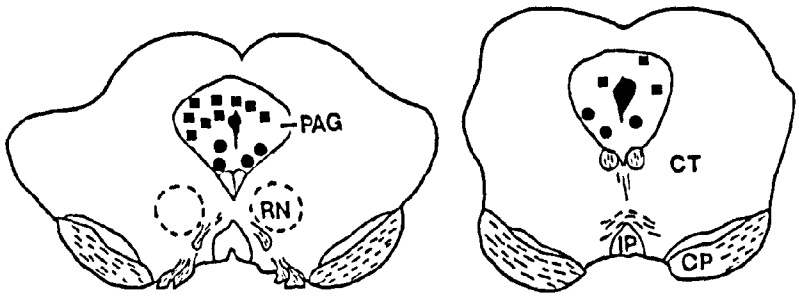

FIG. 1. Maps indicating loci of sites in the midbrain periaqueductal gray from which affective defense behavior and quiet biting attack were elicited in the cat. Squares, affective defense sites; Circles, quiet biting attack sites; CP, cerebral peduncle; CT, central tegmental fields; IP, interpeduncular nucleus; PAG, midbrain periaqueductal gray and RN, red nucleus.

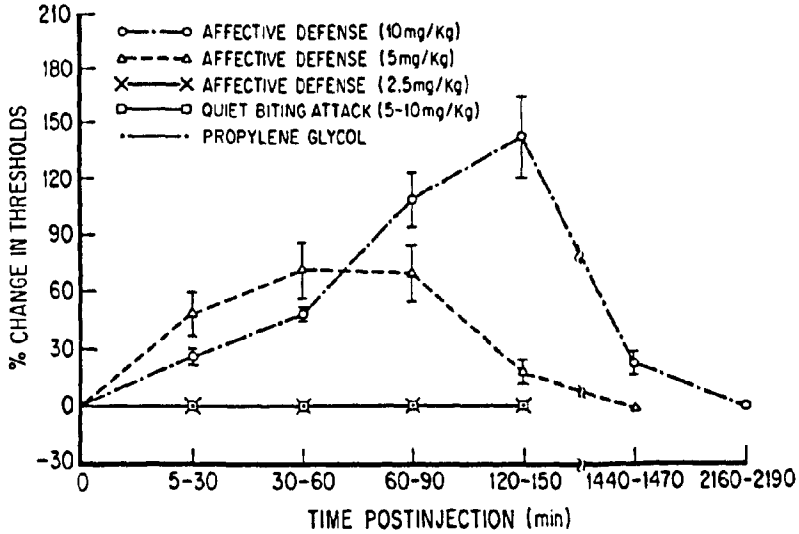

FIG. 2. Summary of the time course of effects of carbamazepine (2.5, 5.0, and 10.0 mg/kg) and vehicle (propylene glycol) administration upon affective defense and quiet biting attack behavior for all cases examined in this study. Note that the minimum dose of carbamazepine had no effect upon the threshold values for affective defense behavior. The threshold for quiet biting attack also remained unaltered following carbamazepine administration and that vehicle administration alone did not produce any changes in thresholds for either response as well. Vertical lines indicate standard errors calculated for each time point examined.

electrical stimulation of 12 sites in the dorsal aspect of midbrain periaqueductal gray (Table 1, Fig. 1). In four of these cats, quiet biting attack behavior was also obtained. Quiet biting attack was generally elicited by electrical stimulation of the ventral part of the periaqueductal gray. Here, seven sites from these animals were examined (Table 1, Fig. 1). For all behavioral sites considered, stimulating electrodes were limited to the rostral half of the periaqueductal gray.

Affective Defense Behavior

In this study, three dose levels of carbamazepine were employed. The maximum dose level—10 mg/kg—was selected because it represents the average dose level given to both humans and other primates [7] and also represents the maximal dose level which did not interfere with ongoing motor responses. Higher doses such as 15 and 30 mg/kg of carbamazepine, when administered to cats, were observed to disrupt such responses and, in fact, resulted in apparent loss of muscle tone and mobility. Pilot data involving the middle dose level—5 mg/kg—indicated an effect of drug upon affective defense which was less pronounced, in which a relatively rapid return to baseline threshold was noted. A minimal dose level—2.5 mg/kg—was also chosen in order to determine whether such a low dose level could result in a modification of the attack response as well.

Changes in affective defense thresholds from five animals (seven sites) were observed after administration of 10 mg/kg of carbamazepine. Such changes were expressed as elevations in attack thresholds, as measured over time, relative to baseline values, and were found to be highly significant, $F(5,24)=5.62$, $p<0.002$. In fact, the mean threshold for affective defense behavior was increased to 50% over its initial baseline threshold levels 30–60 min after drug administration, $t(4)=11.41$, $p<0.001$. This effect appeared to increase over

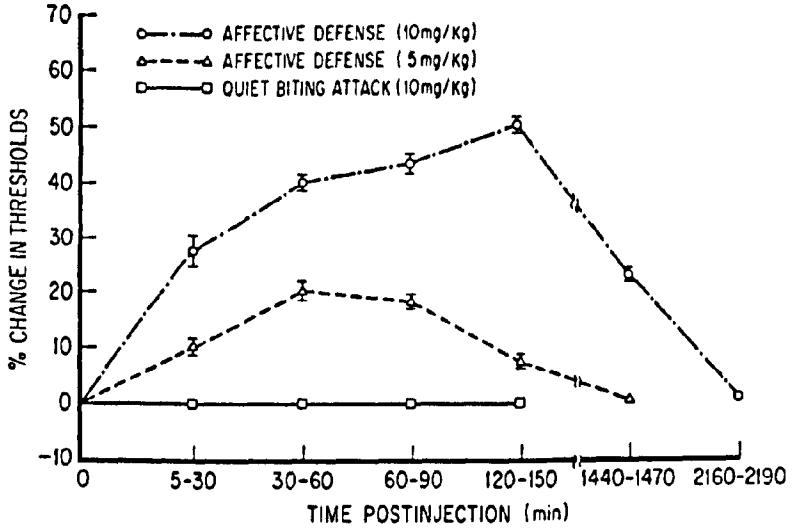

FIG. 3. Threshold curves obtained from a single animal indicating the time course of effects of carbamazepine administered peripherally upon affective defense (5 and 10 mg/kg) and quiet biting attack behavior (10 mg/kg). Note the prolonged effect of a 10 mg/kg dose of carbamazepine upon affective defense behavior and the total lack of effects upon quiet biting attack behavior.

the next 60 min to 143% over initial baseline value. However, at this point, an increase in variability was also observed which reduced the level of significance, $t(4)=2.92$, $p<0.05$. At 24 hours (1440 min), the suppressive effects of carbamazepine were also shown to be significant, $t(4)=3.46$, $p<0.05$. Response threshold returned to baseline values when tested at 36 hours (2160 min) (Fig. 2). Blood levels of carbamazepine were determined 30 min after the delivery of 10 mg/kg and ranged between 3.01 and 10.70 μg/ml, mean value of 6.9 μg/ml (see Table 1).

The effects of a lower dose (5 mg/kg) of carbamazepine upon affective defense behavior elicited from five animals (five sites) in the periaqueductal gray were examined. Again, at each of these sites, the affective defense response was suppressed with a maximal increase from baseline threshold of 72% which occurred 30–90 min following drug injection, $t(4)=2.41$, $p<0.05$. However, when tested at 120–150 min period, response threshold values began to approach baseline levels, $t(4)=2.15$, $p>0.05$. A return to baseline levels was clearly observed when animals were tested 24 hr postinjection (Figs. 2,3). Blood levels of carbamazepine sampled 30 min postinjection ranged between 1.81 and 3.90 μg/ml, mean values of 2.76 μg/ml (Table 1).

The minimal dose of carbamazepine employed in this study—2.5 mg/kg—was assessed in five animals (five sites). Drug administration at this dose level did not result in any changes in response threshold for affective defense at any of the time points measured ($p>0.50$). Blood levels of carbamazepine sampled at 30 min postinjection ranged from 1.0 to 1.4 μg/ml, mean value at 1.25 μg/ml (Table 1).

Control Injections

The results of vehicle injection alone (propylene glycol, 1.5 ml, IP) upon affective defense behavior were assessed in 4 animals. The data indicate that injections of vehicle alone had no effect upon the thresholds for affective defense at any of the time periods tested postinjection ($p>0.50$) (Fig. 2).

Quiet Biting Attack Behavior

The effects of carbamazepine administration upon quiet biting attack behavior elicited from the midbrain periaqueductal gray were assessed in four animals (seven sites). In all of these animals, carbamazepine was injected at dose levels of 5 mg/kg (four sites) and 10 mg/kg (seven sites). At each of these dose levels and for all time periods tested postinjection, there were no changes in response thresholds that could be detected ($p>0.50$) (Table 1, Figs, 2 and 3). It should be noted that four animals were specifically implanted with multiple electrodes at sites in the periaqueductal gray from which affective defense and quiet biting attack could be elicited. In such instances, carbamazepine administration resulted in an elevation of response threshold for affective defense but not for quiet biting attack behavior, thus indicating the apparent specificity of the effect of this drug. Blood levels of carbamazepine for the cases in which the drug was administered at 10 mg/kg, ranged from 4.23–10.0 μg/ml mean value of 8.0 μg/ml, while the range for the drug administered at 5 mg/kg was between 2.81 and 2.96 μg/ml, mean value of 2.83 μg/ml. It should be noted that there were no systematic differences in blood levels of carbamazepine following injections of 10 mg/kg between animals from which affective defense was elicited and those from which quiet biting attack behavior was produced, $t(10)=-0.72$, $p>0.50$. At both drug dose levels, blood samples were taken at 30 min postinjection. As noted for affective defense, animals administered carbamazepine at each dose level showed no observable changes in either ongoing motor or behavioral responses.

DISCUSSION

In the present study, the effects of carbamazepine upon

TABLE 1

SUMMARY OF DOSE AND BLOOD LEVELS OF CARBAMAZEPINE AND ITS EFFECTS UPON AGGRESSIVE BEHAVIOR

Animal	Carbamazepine Dose (mg/kg) 2.5	5.0	10.0	Response	Effect	Blood Levels (μg/ml)
1			X	AD	S*	10.7
1	X			AD	NS	1.2
2			X	AD	S*	10.0
2	X			AD	NS	1.4
3			X	AD	S*	6.5
3		X		AD	S*	2.8
4			X	AD	S*	6.3
4'			X	AD	S*	7.5
5			X	AD	S*	4.3
5'			X	AD	S*	3.0
5'		X		AD	S*	2.9
6		X		AD	S*	2.4
7		X		AD	S*	3.9
7	X			AD	NS	1.4
8	X			AD	NS	—
9	X			AD	NS	1.0
10		X		AD	S*	1.8
2'			X	QBA	NS	10.0
2'		X		QBA	NS	2.8
4''			X	QBA	NS	4.2
4'''			X	QBA	NS	7.5
4'''		X		QBA	NS	2.8
5''			X	QBA	NS	9.7
5'''			X	QBA	NS	—
5'''		X		QBA	NS	2.8
10'			X	QBA	NS	8.6
10''			X	QBA	NS	—
10''		X		QBA	NS	2.9

AD, affective defense; QBA, quiet biting attacks.

*$p<0.001$; '–''', a second to fourth attack site utilized in drug testing from the same animal; S, response suppression; NS, not significant.

affective defense and quiet biting (predatory) attack behavior elicited by electrical stimulation of midbrain periaqueductal gray were examined. The principal finding of this study was the observation that carbamazepine powerfully suppressed affective defense behavior while having little or no effect on quiet biting attack behavior at the dose levels tested. It is of interest to note that carbamazepine administration at the maximum dose level utilized in this study (i.e., 10 mg/kg) resulted in a long-lasting suppression of the affective defense response relative to that observed after adminstration of a lower dose (i.e., 5 mg/kg). Such results would suggest that, at higher dose levels, carbamazepine is retained in brain tissue for long periods of time in which the drug remains effective in modulating the attack response. This long-lasting effect is consistent with an earlier report which indicated the presence of carbamazepine in brain tissue 360 min after drug administration [26].

That the suppressive effects of carbamazepine are not due to either a generalized inhibition of the motor system or to interference with sensory processing mechanisms can be inferred from the observation that, even at the maximum dose (10 mg/kg), carbamazepine had no effect upon quiet biting attack behavior. Such observations were most clearly indicated in the cases where the selective effects of carbamazepine upon both affective defense and quiet biting attack behavior were demonstrated in the same animals (Table 1, Fig. 3).

Since carbamazepine specifically suppresses the affective form of aggressive behavior, it is plausible to suggest that such an effect is achieved by its action upon neuronal pathways which serve as anatomical substrates for this form of attack. In fact, it has recently been established that the hypothalamic and brain stem pathways which mediate affective defense and quiet biting attack behavior are distinctly different [13–15, 32]. Thus, it is suggested that carbamazepine acts upon such neural populations as the medial preoptico-hypothalamus and dorsal aspect of the midbrain periaqueductal gray matter from which affective defense (but not quiet biting attack) can be elicited by electrical stimulation [14,31].

Concerning the possible mechanisms of action of carbamazepine upon the synaptic regions noted above, little information is available. Although previous reports in the literature deal with the effect of carbamazepine upon neuronal systems other than those considered in the present study, such results, nevertheless, raise the possibility that carbamazepine might modulate affective defense behavior by depressing discharge of those neurons associated with affective attack [17,20], perhaps as a result of blockade of sodium channels [30]. Although the neurotransmitter substances utilized in the diencephalic-mesencephalic regions involved in aggressive behavior have not been identified, it is possible that carbamazepine may act through an adenosine receptor system. Skerritt *et al.* [34] demonstrated that carbamazepine could inhibit the binding of an adenosine analog to rat brain membranes. In a second study [35], it was shown that high concentrations of carbamazepine reduced the inhibition of electrically stimulated contractions in the isolated guinea pig ileum by the adenosine agonist 1-methylisoguanosine. These authors also showed that the adenosine antagonist, theophylline, significantly decreased the anticonvulsant effects of carbamazepine. Alternatively, carbamazepine might regulate affective defense by modulating monoamine or peptide transmitter release and uptake in key regions associated with affective defense behavior. Transmitter candidates include norepinephrine, somatostatin and dopamine, all of which are known to be present in regions associated with affective defense [23, 39, 40], and which have also been shown to be affected by carbamazepine [2, 19, 29]. In addition, it has recently been shown that suppression of shock-induced fighting in mice by carbamazepine can be reversed by the GABA antagonists bicuculline and picrotoxin [27]. This result would suggest that carbamazepine might also act by enhancing GABAergic transmission.

From previous studies, it was not possible to discern whether the effectiveness of carbamazepine in the treatment of episodes of aggression was the result of its anticonvulsant actions or to a selective action of this drug upon aggressive responses [16, 33, 37]. However, the present study suggests that the psychotropic effects of carbamazepine seem to be independent of its anticonvulsant properties since no convulsions were induced during the course of the study. Therefore, it is possible that the neural mechanisms by which carbamazepine regulates aggressive behavior are different from those by which seizures are controlled.

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