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An Electrophysiological Study of the Hypothalamic Defense Response *

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In chronic cats with multiple implanted electrodes changes in the electrical activity of the hypothalamus, amygdala, hippocampus and middle ectosylvian cortex simultaneous to or following the hypothalamically elicited defense response were studied. Electrical stimulation of the perifornical hypothalamus consistently elicited a low-threshold defense pattern without the appearance of seizure-like activity. The recording of electrical paroxismal activity from the perifornical hypothalamus elicited by stimulation of neighbouring areas does not lead to the development of the defense response. It is concluded that electrical discharges recorded from the hypothalamic substrate for the expression of emotions are not able to activate this substrate in a suitable manner.

A typical «affective defense response» can be elicited by stimulation of the perifornical region of the hypothalamus (9, 11, 17) and the central gray matter of the mesencephalon (11). Stimulation of the dorsomedial amygdala also evokes a defense response (1, 3, 10, 13). The resemblance between the defense response elicited by stimulation of the amygdala and the hypothalamus and the fact that such response can also be obtained by activating the pathways connecting these structures led some authors (1, 10, 12) to consider the amygdala as an structure able to activate the hypothalamic neural substrate for the expression of emotions. In support of this contention FERNÁNDEZ DE MOLINA and HUNSPERGER (2) found that the amygdaloid defense response was suppressed by coagulation of the ipsilateral hypothalamus.

Electrically elicited rage behaviour has been connected to electrographic seizure activity (5, 8, 16). Emotional states such as fear, anxiety and rage associated with epileptic seizures have been reported in patients who had a discharging focus in the amygdaloid region (6, 7). Symptoms such as twitching of the eyelid and vi-

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brisae and repeated ejection of the tongue have also been reported to develop simultaneously with the defense response after stimulation of the amygdala. These symptoms are know to be associated to seizure-like activity (3, 10, 13, 15). However ROLDÁN *et al.* (19) showed that stimulation of the dorsomedial amygdala consistently elicited a defense response without the simultaneous development of synchronous discharges. Furthermore stimulation of this amygdaloid area superimposed on previously elicited afterdischarges, following activation of the ventromedial amygdala, produced a defense response associated with a reduction in the amplitude and frequency of the afterdischarges. The hypothasis was advanced that the afterdischarges recorded from the dorsomedial amygdala do interfere the amygdaloid substrate for the defense response.

The hypothalamus is one of the structures to which amygdaloid discharges are preferentially projected (4). As most stimulation experiments concerned with the elicitation of emotional patterns of behaviour were performed without EEG recordings one can not know whether the elicited behaviour was caused by the arrival of the electrical discharges to the hypothalamic substrate for the defense response. No specific changes during attack elicited by stimulation of the hypothalamus were recorded from the amygdala, midbrain or hypothalamus contralateral to the stimulated side (20).

This investigation was undertaken to obtain information about the following points: 1) eventual changes in the electrical activity recorded from the hypothalamus and limbic structures during and after the defense response elicited by stimulation of the hypothalamus; 2) behavioural changes developed simultaneously with the appearance of electrical discharges and afterdischarges in the perifornical hypothalamus following the stimulation of neighbouring areas; and 3) the excitability of the emotional hypothalamic substrate during and immediately after the cessation of the afterdischarges projected from the amygdala.

Materials and Methods

Experiments were carried out in fourteen cats from 2.5 to 3 kg. Under sodium pentobarbital antesthesia (Nembutal 35 mg/kg) multilead needle electrodes for stimulation and recording were implanted into the brain following stereotaxic coordinates of the REINOSO-SUÁREZ atlas (18). One needle assembly of four electrodes with 0.3 mm contacts and spaced 1 mm apart was implanted on one side in the hypothalamus and preoptic region and bilaterally in the amygdala. A two electrodes needle was implanted in the hippocampus and two ball electrodes from silver wire were placed on the pial surface of the middle ectosylvian cortex. The experimental procedure has been published elsewhere (19). Bipolar stimulation and recording were used. The stimulus consisted of a train of square wave monophasic pulses 0.7 msec duration delivered by a Grass S88 stimulator through an stimulus isolating unit. Frequencies ranged from 20 to 40 c/sec. Train duration never exceded 30 sec. To record the electrical activity the electrodes were connected via low noise shielded cables (Microdot) to EEG preamplifiers in a Grass Model 7 poligraph. Filters attenuated frequencies below 1 and above 75 c/sec. After the completion of the experimental period the animals were killed by an overdose of Nembutal and perfused with saline and formaline. The brains were removed and frontal sections were made and stained following the NISSL method. The needle tracks were microscopically examined. In those cases where there was no histological evidence of the positions of the contacts, the position of each stimulated point was calculated by reference to the preserved electrode needles array. An

illustrative example of the location of four needle tracks in one of the brains is shown in figure 1. A defense response was elicited from the right amygdala by stimulating through the dorsal pair of contacts and from the hypothalamus (close to the fornix) through the ventral pair of electrodes.

Results

Once more it was confirmed that low-threshold stimulation of portions of the area preoptica and of the perifornical hypothalamus evokes an «affective defense response» (9, 11) characterized by lowering of the head, laying back of ears, hunching of the back accompanied by growling and hissing and signs of sympathetic discharge such as dilatation of pupils and piloerection. This threat pattern strikingly resembles the natural reaction seen when a cat meets a dog or an unfriendly fellow cat (9). Sometimes tha cat raises a forepaw ready to strike or resorts to flight. Latencies for the first hissing vary from 3 to 20 seconds, depending upon the site of electrode and the intensity of stimulation. Figure 2 illustrates a series of records obtained before, during and after stimulation with a pair of electrodes located close to the fornix (fig. 1, ventral pair of contacts in RHyp.) at stereotaxic coordinates AP—, 11, L— 1.6 and H —4 and —3. A defense response gradually developed culminating in repeated hissing (filled squares) after 12 seconds of stimulation. No changes can be seen in the electrical activity recorded from the stimulated hypothalamus, right and left amygdale, preoptic region, hippocampus and middle ectosylvian cortex. This result was consistently obtained when the electrodes were well placed within the hypothalamic field for the defense response and stimulating with threshold intensity. Higher intensities produced hissing with a shorter latency and a more intense display of sympathetic activity but no changes whatsoever appeared in the electrical activity recorded in the mentioned structures.

However stimulation with electrodes located more dorsally and with higher intensities produced a different behavioural and electrical response. In the example illustrated in figure 3 the stimulating electrodes were placed at stereotaxic coordinates AP— 11, L— 1.8 and H at —2 and —1. The animal lifted its head, looked around in an inquisitive manner with a moderate tachipnea and dilatation of pupils. Then the cat fixed its gaze attentively through the observation window

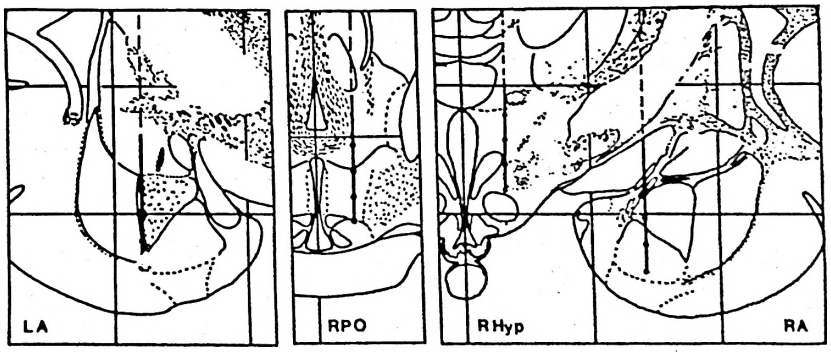

Fig. 1. *Illustrative example of the locations of multilead needle assemblies in both amygdalae (LA-RA), right hypothalamus (RHyp) and right preoptic region (RPO).* Filled circles indicate electrode contacts. Drawings following the stereotaxic atlas from REINOSO-SUÁREZ.

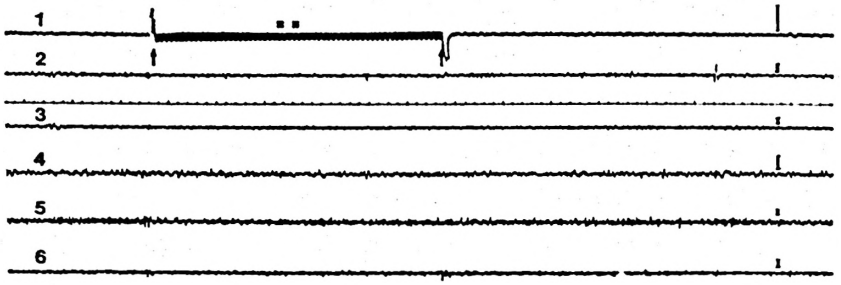

Fig. 2. *Series of records showing the electrical activity before, during and after stimulation of the right perifornical hypothalamus (trace 1).*
Filled squares show the moment of appearance of repeated hissing. Trace 2, right amygdala; trace 3, left amygdala; trace 4, preoptic region; trace 5, hippocampus, and trace 6, ectosylvian cortex. In this and the following figures: time calibration in seconds; voltage calibration: vertical bars, 100 microvolts. Arrows: period of stimulation.

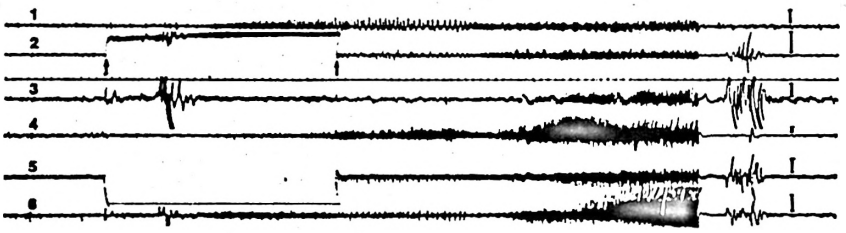

Fig. 3. *Electrical discharges and afterdischarges generated by stimulation of the dorsal hypothalamus (dorsal pair in RHyp. Fig. 1).*
1, ectosylvian cortex; 2, preoptic region; 3, left amygdala; 4, hippocampus; 5, perifornical hypothalamus, and 6, right amygdala; no defense response.

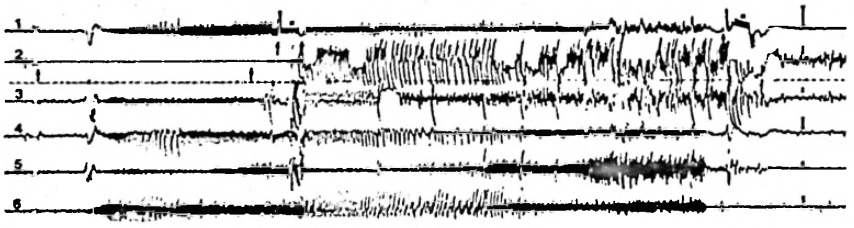

Fig. 4. *Stimulation of the perifornical hypothalamus (second and third pair of arrows) during and after the cessation of afterdischarges elicited by stimulation of the ventromedial right amygdala (first pair of arrows).*
Electrical activity recorded from: 1, perifornical hypothalamus; 2, right ventromedial amygdala; 3, right dorsomedial amygdala; 4, preoptic region; 5, hippocampus, and 6, ectosylvian cortex. Filled squares: hissing.

and started a repeated mewing retracting the corners of the mouth. A gradually built-up synchronous activity developed in the recording from the middle ectosylvian cortex (trace 1), ipsilateral hippocampus and ipsilateral amygdala (trace 6). No change can be seen in the records from the preoptic region (trace 2) and hypothalamus (trace 5) due to the stimulus artefact. On cessation of the stimulus the mewing persisted all the time the afterdischarges were being recorded from all the structures and for 20 seconds more after the sudden and simultaneous cessation of the paroxismal activity. Gradually the animal recovered from the seizure and started to licking the forelimbs. The highest amplitude afterdischarges were recorded from the ipsilateral amygdala and hippocampus. There were neither facial twitching nor repeated ejection of the tongue. It is worth noting the different shape and frequency in the course of the afterdischarges. In the ectosylvian cortex and ipsilateral amygdala the intrastimulatory built-up discharges have a frequency of 4 c/sec changing first to a slower 2 c/sec spiking afterdischarge and then to a much faster frequency of 8-10 c/sec which is the frequency shown by the hippocampus from the initiation of its synchronous activity towards the end of the stimulating period. The same two phases as regards to the shape and frequency of afterdischarges can be seen in the preoptic region and the hypothalamus. It appears that the amygdaloid and ectosylvian cortex paroximal activity predominates during the first phase of slow spiking afterdischarge and then the hippocampus seems to pacemake the rhythm. This view is supported by the fact that the ipsilateral amygdala afterdischarge reversed its polarity during the second phase of faster rhythm.

ROLDÁN *et al.* (19) demonstrated that seizure activity recorded from the dorsomedial amygdala does not necessarily lead to the development of the defense response. Their evidence favoured the suggestion that what is occurring in thes situation is some interfering action which lead to the functional suppression of the amygdaloid substrate for the defense response. They also observed that recording of intrastimulatory discharges and of afterdischarges from the hypothalamus, both projected from the amygdala, did not lead to the activation of the hypothalamic substrate for the expression of emotion. It was then important to test the excitability of the hypothalamic neuronal agregates under this condition to see to what extent the projected paroxismal activity was interfering with the integrative action for the expression of the defense response (fig. 4). The ventromedial amygdala (nucleus basalis pars parvocellularis) was first stimulated (first pair of arrows) in order to produce electrical discharges which were then projected to the hypothalamic neuronal agregates (trace 1) besides the dorsomedial amygdala (trace 3), preoptic region (trace 4), hippocampus (trace 5) and middle ectosylvian cortex (trace 6). During this stimulation there was first a cessation of activity, the animal remaining fixed. Then it appeared a tonic closing of the ipsilateral eye, piloerection and tachypnea followed by a contraversive movement of the head, twitching of the ipsilateral eyelid and vibrisae, repeated ejection of the tongue and salivation. Three seconds after the end of this stimulus the hypothalamus was stimulated (second pair of arrows). After three seconds the cat started to hiss repeatedly and the stimulus was switched off. During this brief period of stimulation the animal showed a greater degree of excitement, arching of the back and piloerection; a clear desynchronizing effect can be seen in the electrical activity recorded from the dorsomedial amygdala (trace 3) masked by movement artefact during the second part of the stimulus. After cessation of the hypothalamic stimulation the facial twitching persisted

for 28 seconds. Electrical spiking afterdischarges with a frequency of 3 and 2 c/sec accompanied the motor symptoms. This slow activity was then replaced by a much faster rhythm of 10 c/sec until its sudden cessation first in the hypothalamus, hippocampus and ectosylvian cortex and a few seconds later in both the dorso and ventromedial amygdala. The hypothalamus was again stimulated (third pair of arrows). There was an inmediate hissing and no further alterations could be detected in the electrical activity of the recorded structures except in the trace from the hippocampus where a small amplitude and irregular spiking can be seen during the stimulus.

It was then confirmed that the recording of electrical discharges or afterdischarges from the hypothalamus following the stimulation of the amygdala does not necessarily lead to the production of the defense response. It seems that that the excitability of the hypothalamic agregates is higher than under control condition — without electrical discharges — as the latency for hissing was systematically reduced from 12-14 to 3 seconds when the hypothalamus was stimulated during the first phase of intense afterdischarges or immediately after its cessation.

Discussion

The present results demonstrate that an «affective defense response» can be elicited by stimulating the active field in the hypothalamus, as outlined by HESS and BRUGGER (9) and HUNSPERGER (11), without the simultaneous development of synchronous electrical activity, under experimental conditions which allowed to control the moment of appearance of such discharges not only at the stimulated hypothalamus but also in the preoptic region, both amygdalae, hippocampus and ectosylvian cortex. These data confirm and exted previous observations (19) concerning the production of a seizure uncontaminated defense response when the dorsomedial amygdala is electrically stimulated. In both experimental situations when stimulating the active field for the defense response either at the dorsomedial amygdala or at perifornical hypothalamus level no changes could be seen in the electrical activity recorded from the stimulated structures or from structures known to be connected to them. Present results further extend the results obtained by WASMANN and FLYNN (20) who showed that no specific changes were produced in the electrical activity recorded from the ipsilateral amygdala, midbrain and contralateral hypothalamus during the attack of cat upon a rat elicited by stimulation of the hypothalamus.

Due to the stimulus artefact it was not possible to follow the development of synchronous activity in both the perifornical hypothalamus and preoptic region simultaneous with the stimulation of the dorsal hypothalamus. However the recording of gradually built-up discharges both from the ipsilateral amygdala and the middle ectosylvian cortex and the recording of afterdischarges immediately after cessation of the stimulus from the hypothalamus and preoptic region strongly indicates that the hypothalamic field for the defense response have been discharging during the period of stimulation. Yet the animal did not show any vocalizations or the adequate posture characteristic of the defense response. The behavioural change was characterized by a prolonged mewing during and after cessation of the afterdischarges, a symptom which seems to be due to the invasion of the hippocampus by the paroxismal activity (14). This invasion may have been through the amygdala itself but the activation through the fornix system can not be ruled out.

The same result was obtained when the electrical discharges were being recorded from the hypothalamus perifornicalis following the stimulation of the amygdala.

No defense response developed following the invasion of the hypothalamus by amygdaloid discharges. However it was shown that the excitability of the hypothalamic neuronal agregates was enhanced during the time the afterdischarges were recorded and even some time after its cessation as the latency of the hissing was much reduced when stimulation of the perifornical hypothalamus was superimposed on a background of afterdischarges.

Two conclusions can be reached from the present results: 1) the generation of electrical synchronous activity is not an esential condition to evoke the affective defense response following the stimulation of the perifornical hypothalamus, and 2) the recording of electrical discharges or afterdischarges from the perifornical hypothalamus elicited by stimulation of nearby structures does not lead to the development of the defense response. It seems that although the electrical discharges can be recorded from the neural substrate which serves emotional behaviour these discharges are not able to activate this substrate in an adequate manner.

Resumen

Se ha estudiado la actividad eléctrica registrada a nivel de hipotálamo, amígdala, hipocampo y corteza ectosylviana media en preparaciones crónicas con múltiples electrodos durante y después de la reacción afectiva de defensa producida por la estimulación del hipotálamo perifornical. Esta estimulación genera una típica reacción de defensa en el gato que no se acompaña de alteración alguna de la actividad eléctrica. El registro de actividad paroxística del hipotálamo perifornical generada por estimulación de áreas vecinas no conduce nccesariamente al desarrollo de la respuesta de defensa. Se concluye que las descargas eléctricas registradas del substrato hipotalámico responsable de la expresión de las emociones no es capaz de activar dicho substrato de manera adecuada.

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