

FURTHER STEPS IN THE RESEARCH OF CORTICO-HYPOTHALAMIC INTERACTIONS IN CATS

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Abstract. The cerebral cortex of the cat was systematically stimulated with electric shocks, and the recording of the evoked potentials in the hypothalamus was performed with macro- and microelectrodes stereotactically guided. Stimulation of definite cortical loci evoked potentials in several hypothalamic nuclei studied. Three focuses were found, coincident with the so called "primary sensory area" of the neocortex. Hypothalamic responses elicited by stimulation of the ipsilateral cortex have greater amplitude and shorter latency than those evoked by contralateral stimulation. The "conditioning" stimulus given on the cortex produces on the "test" stimulus response an inhibitory effect if the interstimulus delay is shorter than 0.6 sec, and a facilitatory if it is greater than 0.6 sec.

INTRODUCTION

The "geological model" approach to the brain organization has traditionally induced us to consider the diencephalon, specially its hypothalamic portion, as the highest integrative nervous center for instinctive, vegetative and endocrine activities of the organism (Wheathey 1944, Hess 1948, Clark and Meyer 1950, Strom 1950ab, Folkrow and Euler 1954, Akert 1961, Bleier 1961, Harris and Michael 1964). The cerebral cortex on the other hand seems to be involved in the cognitive aspects of adaptative behavior to the external world (Pribram 1958).

Nevertheless, this point of view is too schematic since, as Dell has pointed out (1952), the telencephalon can also play a role in the integration of vegetative functions. The observations of Papez (1937), Brady (1958) and Azalli et al. (1966) enhanced the role of paleocortical formation in the emotion, instinctive and endocrine functions.

Furthermore, there is evidence that the neocortex also plays a role in

emotional control (Bard and Mountcastle 1947). The orbitofrontal cortex has proved to be related to vegetative (Pinkston et al. 1934, Green and Hoff 1937, Grinker and Serota 1938, Smith 1938, Eliasson and Strom 1950, Chechulin 1958, Covian 1959) and endocrine (Covian et al. 1958, 1959, Azalli et al. 1966) functions of the organism.

On the other hand, experiments on "functional decortication" by chemical stimulation of the cortex with KCl have demonstrated that cortical spreading depression induces excitability changes in several subcortical nuclei, including the hypothalamus (Bureš et al. 1961, Olds 1962, Rüdiger et al. 1962, Rüdiger and Seyer 1965). In the same way, experiments with conditioned reflexes have shown that the cerebral cortex under both exteroceptive and interoceptive stimuli is able to control the activity of the internal organs directly controlled by the hypothalamus (Bykov 1958). Inversely, experiments of stimulation and destruction of the hypothalamus indicate that electrocorticographic activity can be modulated from the hypothalamus. Hypothalamic stimulation mainly produces a synchronizing effect in the cortical EEG (Grinker and Serota 1938, Obrador 1943, Gellhorn and Ballin 1946, Sterman and Clemente 1962ab, Nakamura and Ohye 1964). Finally, the authors have observed that the evoked potentials in the hypothalamus by exteroceptive stimulation can be modified by electrical and chemical stimulation of the cortex (Santibañez and Espinoza 1968). The present paper deals with: (i) physiological characteristics of the connections between the cerebral cortex and the hypothalamus, and (ii) an analysis of the influence of the cortical stimulation upon the exteroceptive evokes activity in the hypothalamus.

METHOD

Thirty adult cats weighing 2.2 to 3.8 kg were used. Chloralose anesthesia in doses of 80 mg/kg was applied. Animals were tracheotomized and the femoral vein was cannulated. Trepanation was carried out to expose the cortex. The dura was removed and the exposed cortex was covered with soft plastic material moistened with saline solution. Different hypothalamic nuclei were recorded through a set of bipolar nichron electrodes 0.3 mm in diameter, electrically insulated except at their tip. The stereotaxic atlas of the hypothalamus of Bleier (1961), was used as a guide. Recording was also performed with 10 to 20 μ Tungsten monopolar microelectrodes mounted on a micromanipulator. A bipolar silver electrode, stereotactically guided, with tips separated about 2 mm, was used to stimulate the cerebral cortex. In all the experiments square monophasic 1 msec electric pulses were used to stimulate the cortex and the paws. In order to avoid post-stimulus effects, the preparation was stimu-

lated at a very slow rate (0.2 cycle/sec). A Grass S-4 stimulator with a stimulus isolation unit was used and needles introduced subcutaneously were permitted to stimulate the paws.

After each experiment, dorsal surface of the cerebral cortex was in an exactly horizontal plane. A map with stereotaxic coordinates was drawn according to the photographs in order to indicate position of cortical electrodes.

After each experiment, brains were perfused through the carotids and fixed in formalin and finally histologically processed to determine location of the recording electrode:

RESULTS

An exploration was made of the relationships of the cerebral cortex and the hypothalamus. We shall first describe the cortical areas whose stimulation produces evoked potentials in the hypothalamus and secondly, the influence of cortical stimulation upon the evoked activity in the hypothalamus. The evoked activity by electrical stimulation was examined in the following hypothalamic nuclei: anterior hypothalamic area (Ha), ventromedial nucleus (Hvm), lateral hypothalamic area (Hl) and mamillary bodies (Mm).

1. *Evoked activity in the hypothalamus induced by electrical stimulation of the cerebral cortex*

a) *Hypothalamic evoked responses by stimulation of the cerebral cortex.* The stimulation of certain areas evoked responses in the different hypothalamic nuclei. Figure 1 shows an experiment in which the lateral gyrus of the cortex was electrically stimulated and different diencephalic points were recorded. The recording electrode was moved downwards in 1 mm steps in horizontal planes. The anterior and lateral planes were maintained constant. Points from horizontal 0 to -6 were recorded in the same stimulated hemisphere. As it can be appreciated, the response progressively increases in amplitude reaching the highest intensity when the point of the recording electrode reaches the horizontal planes from -3 to -5. This zone corresponds closely to the location of the ventromedial nucleus, between -2 to -5. If the recording electrode is placed in the hypothalamus in the point of maximal activity, and a penetrating needle electrode is used to stimulate cortex, maintaining the voltage of the stimulus constant, we find that the hypothalamic response can be elicited only from the gray cortical matter, and completely disappears when the stimulating electrode reaches the fibers of the internal capsule.

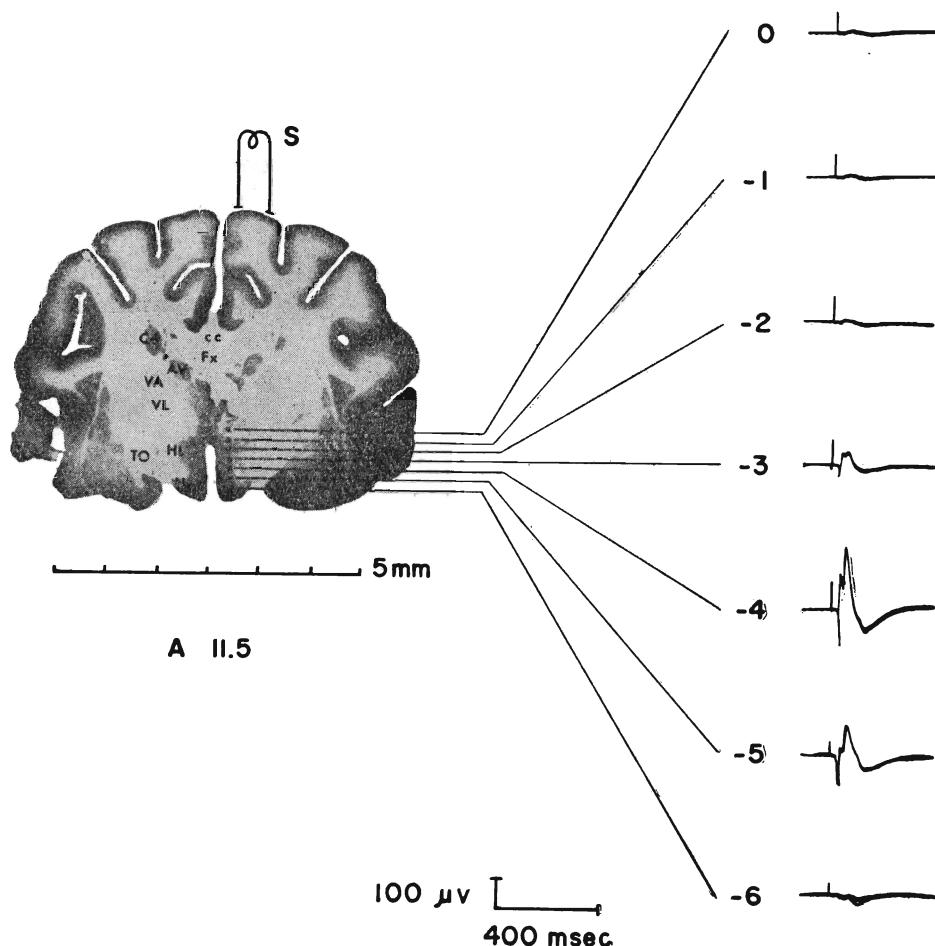


Fig. 1. Normal cat under chloralose anesthesia. A frontal slice of the brain is shown. The left cortex was stimulated with square monophasic 1 msec duration, 5 v electric pulses. The oscillographic recording of different points in the horizontal plane from 0 to -6 are shown. Each record has five superimposed traces. Cd, caudate nucleus; cc, corpus callosum; Fx, fornix; AV, anteroventral thalamic nucleus; VA, nucleus ventralis anterior; VL, ventrolateral thalamic nucleus; Hvm, ventromedial hypothalamic nucleus; HI, lateral hypothalamic area; TO, optic tract.

b) Hypothalamic evoked response and ipsilateral cortical active areas. If we now examine which are the most effective cortical areas whose stimulation produces maximal response in a given responsive hypothalamic area, the pattern shown in Fig. 2 is obtained. In this experiment, the recording electrode was located in the left ventromedial nucleus and the whole ipsilateral cortex was electrically stimulated in 1 mm steps. The external aspect of the cerebral cortex and a sample of the hypothalamic

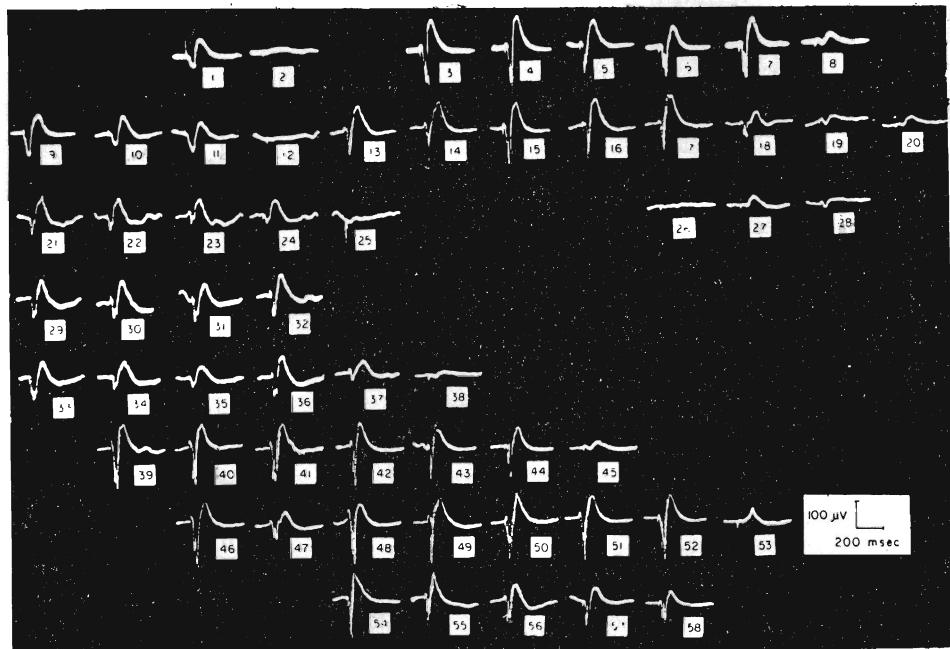
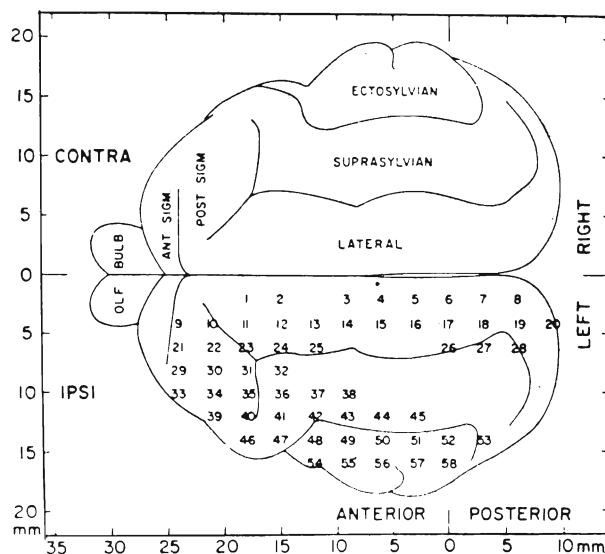


Fig. 2. Normal cat under chloralose anesthesia. Schematic drawing of the external aspect of the cortex in stereotaxic coordinates. The left hemisphere was systematically stimulated with 1 msec duration, 5 v electric pulses. The recording electrode was located in the left hypothalamus. Oscillographic traces obtained through stimulation of the corresponding cortical points are shown. Note the focal character of the active areas.

responses evoked by stimulation of the corresponding cortical points, are shown in the figure. It can be observed that there are certain cortical focuses that stimulated, produce maximal evoked hypothalamic responses. Hypothalamic responses evoked from the focal areas have the following characteristics:

1. Maximal amplitude.
2. The most complex pattern.
3. Maximal duration.
4. Maximal recording stability.

Three focuses of maximal activity can be observed: the first in the posterior sigmoidean gyrus; the second, in the medial portion of the lateral gyrus; and the third, in the middle ectosylvian gyrus. When the stimulating electrode is separated from the focal areas, the response progressively diminishes in amplitude, pattern complexity, and recording stability, until it completely disappears.

c) *Hypothalamic evoked activity by ipsilateral and contralateral stimulation.* Figure 3 shows the responses obtained in the left ventromedial nucleus by stimulation of the contra- and ipsilateral gyri of the cortex.

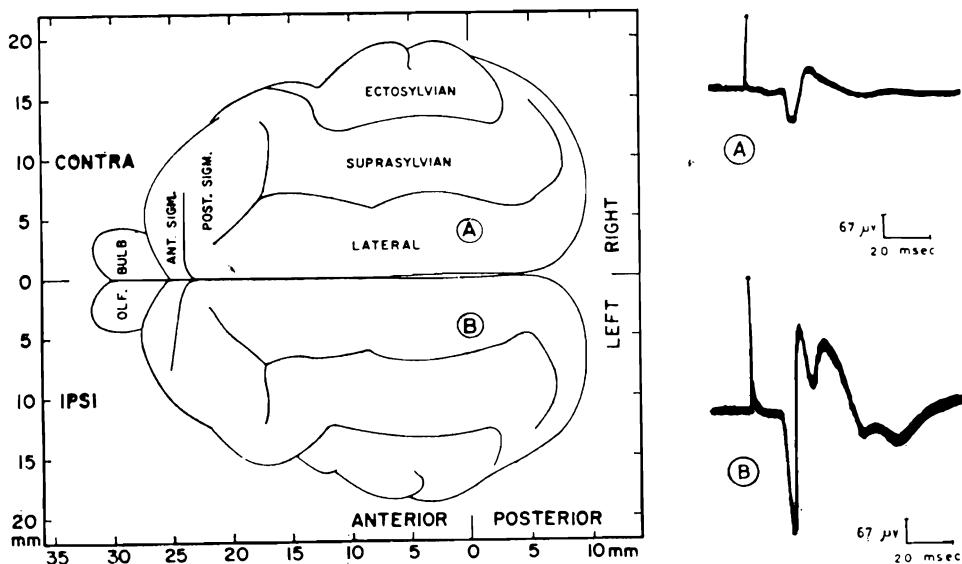


Fig. 3. Normal cat under chloralose anesthesia. Schematic drawing of the cerebral cortex in stereotaxic coordinates. The recording electrode was located in the left ventromedial hypothalamic nucleus. The cerebral cortex was stimulated with square monophasic 1 msec duration, 6 v electric pulses. Oscillographic recording of the hypothalamus through stimulation of A (contralateral) and B (ipsilateral) cortex is shown. Note greater amplitude and complexity and smaller latency of the ipsilateral response.

If we compare ipsi and contralateral hypothalamic responses, we find that the ipsilateral response has more amplitude, greater pattern complexity and smaller latency than the contralateral one.

d) *Ipsi and contralateral active areas for different hypothalamic nuclei.* The aim of this experiment was to study whether the cortical active areas are the same for all the hypothalamic nuclei, or if there are differences between them. To this purpose, a set of recording electrodes was located in a sample of the following hypothalamic nuclei: Ha, Hl, Hvm, and Mm,

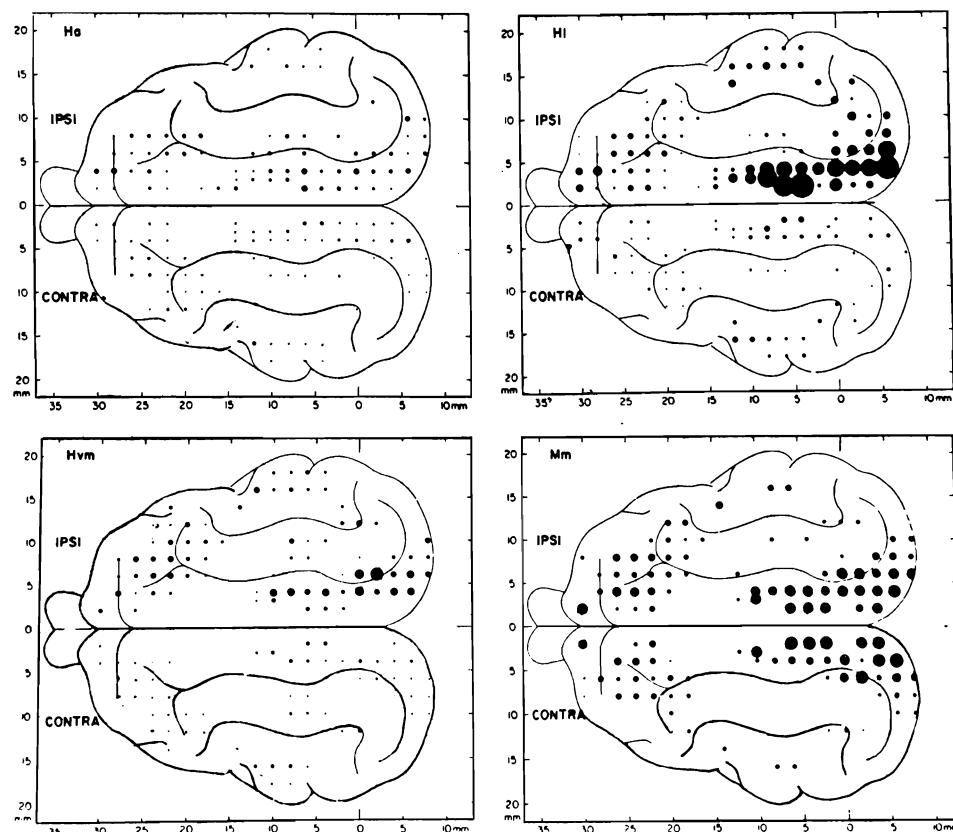


Fig. 4. Normal cat under chloralose anesthesia. Schematic drawing of the cortex in stereotaxic coordinates. The whole cortex was electrically stimulated at 2 mm steps laterally anteroposteriorly. A set of recording electrodes was placed in the left and right hemisphere, in Ha (anterior hypothalamic area), Hl (lateral hypothalamic area), Hvm (ventromedial hypothalamic nucleus) and Mm (mammillary bodies). Dots represent cortically active points. The six of each dot indicates the amplitude of the hypothalamic response recorded in each hypothalamic nucleus through stimulation of the corresponding cortical points. Note the focal character of the active areas, as well as the fact that ipsilateral focuses are more active than contralateral ones.

Also note the similarity in the patterns for the different nuclei studied.

of both hemispheres in a given preparation. The whole cortex shown in the figures was stimulated at 2 mm steps laterally and anterioposteriorly. The responses to stimulation in each particular point of the cerebral cortex was recorded in each hypothalamic nuclei of both sides. Results are shown in Fig. 4. A dot has been placed in each stimulated cortical point, the size of which indicates the amplitude, measured peak to peak, of the evoked hypothalamic response produced by the stimulation of the corresponding cortical point. If the stimulation of a given cortical point produces no response, then no dot was placed, so, clear zones correspond to silent areas. In this case, as it can be seen, there are also three definite focuses of maximal activity. The first, in the anterior and posterior sigmoidean gyrii, the second in the middle and caudal portion of the lateral gyrus and the third in the middle ectosylvian gyrus. If we compare hypothalamic responses to stimulation of the ipsi- and contralateral cortex, we see that ipsilateral responses are of greater amplitude than those evoked by contralateral stimulation of the corresponding cortical point. Latencies of ipsilateral responses are smaller than those of contralateral. This is the case for all nuclei studied. If we compare the cortically active areas for the different nuclei, we note that there are no definite differences in their location. There are differences in amplitude, latency and shape of the evoked responses in each nucleus.

e) *Hypothalamic evoked activity by stimulation of the interhemispheric and orbital cortex.* Some control experiments were run to explore these cortical areas. In the case of the interhemispheric cortex it was necessary to remove one hemisphere to get a good exposure; this operation was traumatic. Nevertheless, it was possible to prove that there are two focuses of maximal activity in the hemispheric faces, the first corresponding to the continuation of the lateral gyrus, and the second to the continuation of the posterior sigmoidean gyrus beside the sulcus cruciatus. In the case of the orbital cortex, it was necessary to remove the eye. This manipulation was also traumatic, but it was possible to prove that stimulation of this area does not produce evoked response in the hypothalamus.

f) *Control experiments* were also performed in the chloralose and "encephale isolé" preparations (Fig. 5 and 6) stimulating the hypothalamus and recording the evoked activity in different control points. In both preparations, as it can be appreciated, active control points are coincident and correspond to the same cortical areas whose stimulation evoked responses in the hypothalamus.

g) *Statistical measurements.* The t-test was used to see if the differences in amplitude and latency between ipsilateral and contralateral hypothalamic responses to stimulation of the different focuses for each nucleus were statistically significant. Such differences were found in all the cases

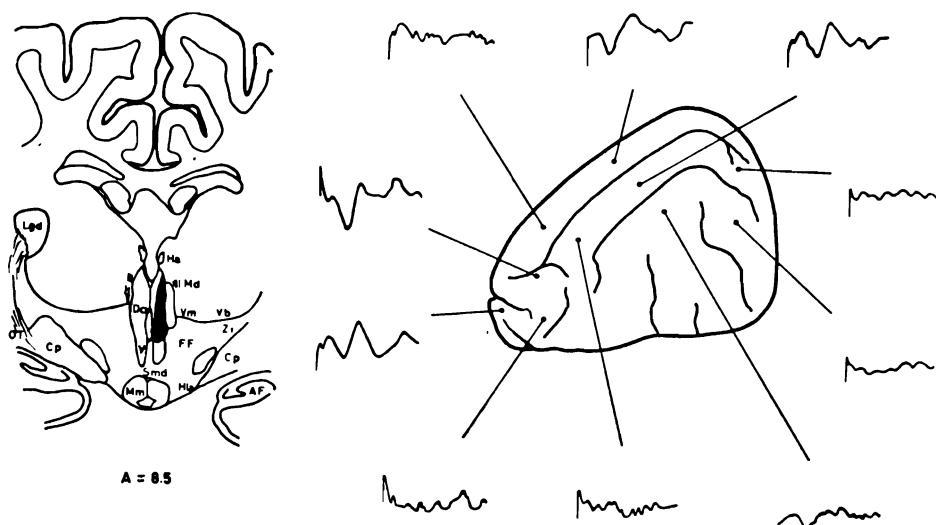


Fig. 5. Cortical evoked potentials elicited by hypothalamic electrical stimulation in the "encephale isolé" preparation.

amplitude values were greater and latency values smaller in the ipsilateral side.

Table I shows latency values of the responses recorded in several nuclei through stimulation of the corresponding cortical points. It can be observed that latencies of the ipsilateral responses are, in every case, shorter than those contralateral ones. Each value is the mean of the latency value of hypothalamic response evoked through stimulation of a given cortical focus in at least two different cats. If we consider the mean of the response latency in all of the nuclei through stimulation of

TABLE I

Latencies in (msec) of hypothalamic evoked responses by cortical stimulation

| Nucleus | Sigmoidal gyrus | | Lateral gyrus | | Ectosylvian gyrus | |
|---------|------------------|------------------|------------------|------------------|-------------------|------------------|
| | ipsi | contra | ipsi | contra | ipsi | contra |
| Ha | 9.0 | 10.0 | 17.5 | 25.0 | 14.0 | 17.5 |
| Hpv | 18.6 | 19.3 | 16.6 | 22.5 | 22.5 | 40.0 |
| Hvm | 14.5 | 15.0 | 16.5 | 20.0 | 20.0 | 20.0 |
| Hl | 11.0 | 37.5 | 20.0 | 52.5 | 32.5 | 45.0 |
| Hp | 22.0 | 25.5 | 22.5 | 25.0 | 40.0 | 50.0 |
| MM | 12.0 | 15.0 | 17.0 | 20.0 | 17.5 | 40.0 |
| | $\bar{x} = 14.5$ | $\bar{x} = 20.4$ | $\bar{x} = 18.4$ | $\bar{x} = 27.5$ | $\bar{x} = 24.4$ | $\bar{x} = 35.4$ |

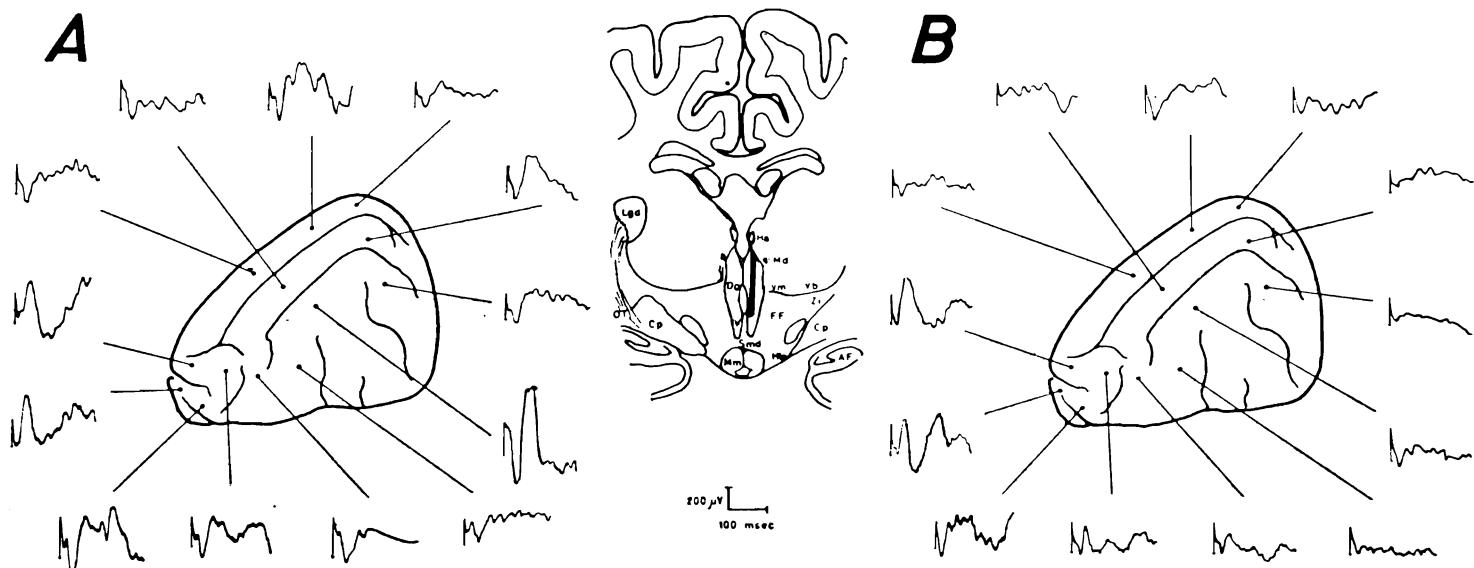


Fig. 6. Cortical evoked potentials elicited by ipsilateral (A) and contralateral (B) electrical hypothalamic stimulation in a normal cat under chloralose.

the different focuses, we can see that the latencies from the anterior and posterior sigmoidean gyri are the shortest for both ipsi and contralateral sides. The responses evoked through stimulation of the ectosylvian gyrus show the greatest latency, and responses evoked from the lateral gyrus show intermediate values.

2. Influence of cortical stimulation of exteroceptive responses in the hypothalamus

Since the stimulation of the paws evokes responses in the hypothalamic nuclei, the modification of these evoked responses by electrical stimulation of the cerebral cortex can serve as an experimental model to study interactions. Observations described here were made in several hypothalamic nuclei, and behavior of the mammillary bodies will serve as an example. Figure 7 show typical responses of the mammillary body.

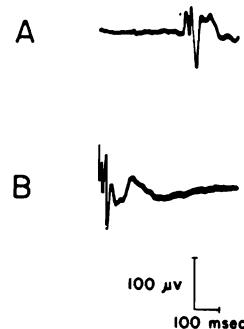


Fig. 7. The response evoked in the mammillary body through stimulation of the ipsilateral forepaw is shown in A. In B, the response in the mammillary body to stimulation of the cerebral cortex.

In A, the response to the stimulation of the ipsilateral forepaw is shown. The latency from the stimulus artifact to the beginning of the first deflection is about 35 msec. In B, the response to stimulation of the ipsilateral "visual cortex" (medial portion of the lateral gyrus) is shown. The latency to the beginning of the first deflection is about 20 msec.

In the experiments to be described now, the "conditioning-testing" technique was used. The "conditioning" stimulus was the cortical one, and the "test" stimulus was the exteroceptive one. The modifications of the exteroceptive response were tested at different interstimulus delays. Figure 8 shows the sequence of the experiment. In 1, the exteroceptive response is alone observed. When a cortical stimulus is delivered 600 msec before the exteroceptive one, 2, an increment of the amplitude of the hypothalamic exteroceptive response with respect to control is observed. When the interstimulus delay is reduced (3, 4, 5, 6 and 7), the response to the test stimulus progressively diminishes. With a 400 msec delay, the response to the test stimulus has the same amplitude of the control. With

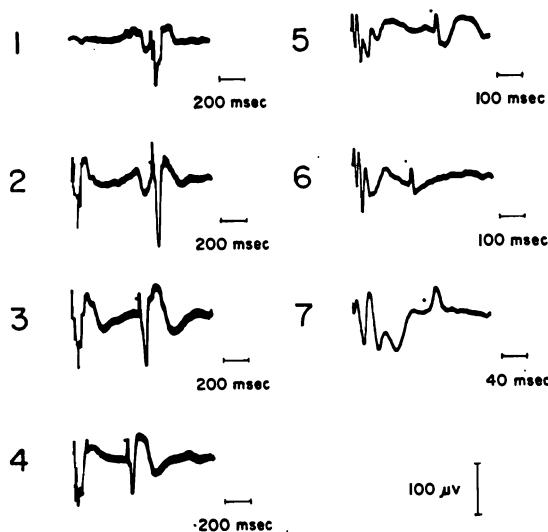


Fig. 8. Facilitation and inhibition of hypothalamic evoked activity through cortical stimulation (1). Hypothalamic response evoked through exteroceptive stimulation ("test" stimulus). A "conditioning" cortical stimulus applied (2) 600 and (3) 500 msec before the "test" stimulus increases exteroceptive responses amplitude. (4) With 400 msec delay, the response amplitude is unchanged. (5) With 300, (6) 200 and (7) 100 msec interstimulus delay the "test" diminishes with respect to control.

shorter delays a diminution of the amplitude of the response to the test stimulus with respect to control is observed, until it almost completely disappears with a 100 msec delay.

This phenomenon is graphically shown in Fig. 9. As it can be appreciated there is a critical moment, that in this case was about 450 msec interstimulus delay, in which the response to the test stimulus has the same amplitude with respect to control. With greater delays, an increase of the amplitude is observed, and with shorter delays, a decrease of the amplitude can be seen. In the control experiments we observed that this critical point could be found between 400 msec to 1.2 sec interstimulus delay. This seems to depend on the physiological state of the preparation as well as on the hypothalamic nuclei studied. This phenomenon was observed in at least 10 different experiments with different cats controlling different hypothalamic nuclei.

Other experimental facts observed are the following:

1. If cortical stimuli are used, both as conditioning and test stimulus, the same sequence just described is observed. In other words, the effects of a cortical stimulus on the response to another stimulus is the same as that of a cortical stimulus on the response to an exteroceptive one. The time course of the sequence is also the same.

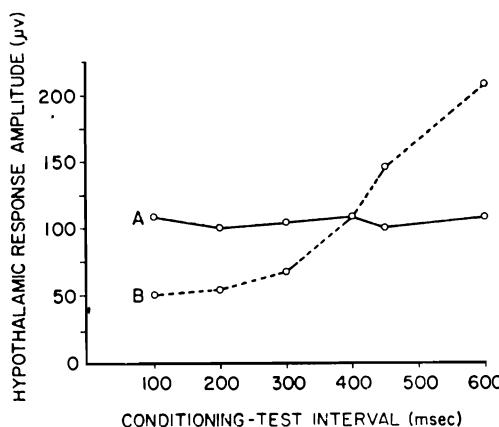


Fig. 9. Graphic representation of facilitation and inhibition of hypothalamic evoked activity through cortical stimulation. *A*: amplitude values of "test" response. *B*: values of the "test" response when cortical "conditioning" stimuli are delivered at different interstimulus delays. Each values is a means of three measurements. Note decrease of the values in *B* with delays shorter than 400 msec and their increase with delays greater than 400 msec.

2. The same is observed when an exteroceptive stimulus is used as "conditioning and as test".
3. The same is also observed when the exteroceptive stimulus is used as "conditioning" and a cortical one is used as "test".
4. It is not possible to obtain addition of the exteroceptive and cortical responses when the stimuli are simultaneously delivered, whether the stimuli were subliminal or maximal.
5. When the conditioning stimulus voltage is diminished, its effects on the response of the test stimulus also diminishes.
6. If different hypothalamic nuclei are tested, the same general results are obtained.

DISCUSSION

We shall discuss separately the two types of results obtained. First, those related to the exploration of cortical areas capable of eliciting hypothalamic evoked activity, and secondly, the results obtained with the "conditioning-testing" technique.

The stimulation of definite zones in the neocortex is effective to elicit evoked responses in the different hypothalamic areas or nuclei studied. As it has been shown three focuses have been found: The first, comprises both anterior and posterior sigmoidean gyrus (area I); the second, the medial and caudal part of the gyrus lateralis (area II); and the third, the middle ectosylvian gyrus (area III).

We see two possible objections to the results. The first is that the evoked response is not really the activity of a nucleus but of a neighbouring tract or bundle. Nevertheless, we have shown that the response is produced only when the tip of the recording electrode reaches the nucleus. We could observe in other cases, if, for instance a thalamic nucleus was recorded, that the potential evoked changes its features as soon as the electrode was moved downwards reaching a hypothalamic nucleus. We could observe a polarity inversion of the first deflection and changes in the latency of the response. If we refer to Fig. 1, we can clearly see that the response appears when the tip is near the fornix, but in control experiments we observed that although the tip was near this tract and at a comparable distance with the example, the responses were not observed if the tip was not in the ventromedial nucleus. Another fact that rejects this observation are the results obtained in some control experiments performed with tungsten microelectrodes (10–20 μ at the tip), which in any case record from distance greater than 0.2 mm.

The second possibility is that the responses are not due to cortical stimulation but to the activation of some subcortical (for instance thalamic) nucleus, elicited by the spreading of the stimulation current. But, stimulating the cortex with a bipolar needle electrode, the responses are elicited only from the gray matter, and completely disappear when the stimulating electrode reaches the fibers of the internal capsulae, in such a way this possibility can be rejected.

Another important technical problem is that related to stimulation thresholds. The value in each experiment correspond to the maximal stimulus in the focuses of maximal activity. The surface of the active areas increases when the supramaximal stimuli are used, and inversely, with threshold and suprathresholds stimuli, the surface diminishes.

According to the latencies of the responses, we can assume that the cortical information comes to the hypothalamus through polysynaptic pathways. Comparing the latencies of responses from the different areas, we can conclude that area I is communicated by more direct pathways. Areas II and III would be communicated through pathways with greater number of synapses.

If we consider that the ipsilateral focuses are of greater extension than contralateral ones, and that the ipsilateral responses have greater amplitude and shorter latency than the contralateral one, we can conclude that the cortico-hypothalamic communications, being bilateral, are principally ipsilateral. This difference, as has been pointed out, is statistically significant. These results suggest that in the ipsilateral focuses there are a greater number of cortical active neuronal elements and that the corticohypothalamic pathways originating them are shorter and have a small-

ler number of synapses. These results confirm those of Bleier et al. (1966) and those of Rüdiger and Seyer (1965). The former authors, using the technique of isolation of the hypothalamus and studying cell degeneration in the different hypothalamic areas, found that the hypothalamus receives bilateral information. The latter, studying thermosensitive behavior as indicator of hypothalamic activity, and combining functional decortication (by topical stimulation of the cortex with KCl) with the destruction of certain hypothalamic nuclei, have found that cortical influences on the hypothalamus are ipsilateralized. Our results also agree with those of Baklavezhyan and Astvatsatryan (1968), who found evoked activity in the hypothalamus stimulating the same cortical focuses described here, in cats immobilized with dithyline.

An important point to be discussed is that the cortical focuses described in this paper are located in the neocortex and correspond strictly to the so called "primary sensory areas" in the cat (Woolsey 1958). So, area I corresponds to the "somatic area". Area II to the "visual area", and area III to the "auditory area". The stimulation of the so called "associative area" does not elicit evoked responses in the hypothalamus.

Lozoya (1967) found in a series of experiments in cats, that electrical stimulation of the hypothalamus produces cortical evoked responses on the same cortical focuses described here in this paper. Hypothalamic influence on the cerebral cortex also has a focal character. Our control experiments of stimulation of the hypothalamus and recording in the chloralose and "encephale isolé" preparations agree with this author. According to those findings we may conclude that primary sensory area of the neocortex are intergration sites of information coming from and going to the hypothalamus.

It is necessary to discuss the possible anatomic pathways followed by information coming from the neocortex and reaching the hypothalamus. Pathways coming from the mamillary bodies, the anterior thalamic nuclei, and the gyrus cinguli to the hippocampus, have long been known (Clark and Meyer 1950, Cowan and Powell 1954, Fry et al, 1963, Peacock and Combs 1965).

Others have found connections between the frontal cortex and the ventromedial nucleus, lateral gyrus, mammillary bodies and posterior areas of the hypothalamus (Beck 1951, Clark and Meyer 1950, Ward and McCulloch 1947). Niemer and Jimenez-Castellanos (1950) and Adey and Meyer (1952) have described connections between the temporal cortex and the ventromedial nucleus and mammillary bodies. Nevertheless, since both neuronal degeneration and "physiological neuronography" techniques outline only direct pathways, it is difficult to decide if they are involved in the phenomenon described here, where the existance of multisynaptic path-

ways seems probable. It might be useful to consider the communication of Carruthers et al. (1964) who observed evoked potentials of neocortical (temporal) origin in the amigdalae. The latency of these responses is shorter than that of hypothalamic responses from this focus (area II). So, the amigdalae could be considered one of the possible relays. We think that the organization of the active cortical areas described here is very suggestive. The existence of neocortical focuses receiving and sending information to the hypothalamus speaks for itself of a delicate system of specific intercommunications between both structures.

The results obtained in experiments with the "conditioning-testing" technique, show that "conditioning" stimulus produces two effects on hypothalamic cells in a precise time course. First, an inhibitory effect lasting 400 msec to 1.2 sec can be observed, and from then on a facilitating effect takes place. We can assume that both effects are present from the first moment, but that at the beginning the inhibitory influences are predominant. Then the facilitating influences progressively increase, and there is a moment when both are of the same magnitude, therefore, the amplitude of the response to the test stimulus remains the same. This does not mean that in this moment there is no influence at all, because with greater delays, the facilitating influence becomes predominant and an increment in the amplitude of the response to the test stimulus is observed. Finally, with about 2 or 3 sec interstimulus delay, both influences tend to disappear and no modification of the response is observed.

It might be objected that the inhibitory influence observed at the beginning is not really an active process, but merely due to the refractory period of the hypothalamic units. This possibility is rejected because the refractory period lasts the same as the duration of the neuron spike, i.e. only a few milliseconds. Nevertheless, in spinal motoneurons a period of about 100 msec after the spike is necessary for the neuron membrane to recover the resting potential. During this period an hyperpolarization of about 5 mv, affecting the membrane and perhaps its excitability has been observed (Eccles 1957). Since, so far as we know, there are no measurements of this kind in hypothalamic units, it is difficult to decide in favor of this possibility.

Considering that the period of both inhibition and facilitation observed in our experiment is considerably longer than that determined by others in monosynaptic models (Lloyd 1946), we think that in this case we must assume the participation of multisynaptic chains as those proposed by Lorente de Nó (1938). As he has pointed out, these neuronal circuits can prolong the period of facilitation and inhibition, as well as modify the functional interrelations between facilitatory and inhibitory pathways.

The facts under discussion can be tentatively explained as follows:

the stimulation of both the cerebral cortex and the exteroceptive pathways produces a volley that reaches a hypothalamic pool through a synaptic pathways and the evoked potential is observed. The fact that it is not possible to obtain addition when cortical or exteroceptive maximal or sublimi or subthreshold stimuli are simultaneously delivered, indicates that both pathways converge at a relay before reaching the hypothalamus, getting to it by a final common pathway, or that they converge to the same hypothalamic neuronal pool. This pathway also exerts a subliminal influence on another cellular pool changing its excitability. On the other hand, both stimuli exert different effects on the whole hypothalamic neuronal population through a multisynaptic pathway: in the first 400 msec to 1.2 sec an inhibitory or hyperpolarizing effect is produced, and subsequently a facilitating or depolarizing one. So, when the test stimulus is delivered in the first period, a decrease in the evoked potential is observed because a great number of elements are inhibited. When it is delivered in the second period, the excitability of the whole population is increased and a greater number of neurons are fired, the response being increased with respect to control.

Even if this interpretation is not correct, we can conclude that the hypothalamic neurons are receiving facilitatory and inhibitory influences, of neocortical as well as exteroceptive, and perhaps interoceptive origin, through multisynaptic neuronal models, and that these influence have a definite time course.

SUMMARY

The present paper deals with: a) The physiological organization of cortico-hypothalamic connections, and b) The effects of cortical stimulation on the evoked activity in the hypothalamus by exteroceptive stimulation. The experiments were performed in acute cat preparations, under chloralose anesthesia. The cerebral cortex was systematically stimulated with electric shocks, and the recording of evoked potentials in the hypothalamus was performed with macro- and microelectrodes stereotactically guided. Results can be summarized as follows:

1. *Hypothalamic activity in the hypothalamus by cortical stimulation.* Stimulation of definite cortical areas produces evoked potentials in several hypothalamic nuclei studied. When the electrode for cortical stimulation is withdrawn from the focal areas, the hypothalamic response progressively diminishes in amplitude until it completely disappears.
2. Three cortical focuses were found, coincident with the so called "primary sensory areas" of the neocortex, namely: the anterior

and posterior sigmoidean gyrus or "somatic area" (area I); the middle and caudal part of the lateral gyrus or "visual area" (area II); and the middle ectosylvian gyrus or "auditory area" (area III).

3. Hypothalamic responses elicited by stimulation of ipsilateral cortex have greater amplitude and shorter latency than those evoked by contralateral stimulation. Ipsilateral active areas have greater surface than contralateral ones.
4. These facts suggest the existence of a specific cortico-hypothalamic projection system, which has its origin in the primary sensory areas of the neocortex of both hemispheres, being principally ipsilateral.

B) *Effects of cortical stimulation on exteroceptive activity in the hypothalamus.*

1. The "conditioning" stimulus (cortical or exteroceptive) produces two effects on the response to the "test" stimulus (cortical or exteroceptive) whichever combination was used: a) with about 600 msec or shorter delays, a decrease in the amplitude of the hypothalamic response to the "test" stimulus is observed; b) with greater delays, an increase of the hypothalamic response to the test stimuli is observed.
2. Results are discussed in relation to physiological data, and hypothalamic neuronal pool are assumed to be receiving influence, both facilitatory and inhibitory, of cortical as well as exteroceptive origin in a definite time course.

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