Evoked potentials in the hypothalamus

SHAAUL FELDMAN, CHARLES S. VAN DER HEIDE, and ROBERT W. PORTER
Departments of Medicine (Neurology) and Anatomy, University of California at Los Angeles School of Medicine, Los Angeles, and the Neurosurgery Section, Veterans Administration Hospital, Long Beach, California

IN THE COURSE OF THE LAST HALF CENTURY there has accumulated a great amount of clinical and experimental evidence indicating the important role of the hypothalamus in the regulation of vegetative, metabolic, endocrine and behavioral activities (1-3). As these vital functions are influenced to a great extent by the internal and external environment, a complete understanding of their hypothalamic control is dependent upon a thorough delineation of the afferent input to the hypothalamus. Although ascending connections to the hypothalamus have been described anatomically (4-6) investigations with regard to their physiologic significance are limited to occasional observations of evoked potentials from peripheral stimulation (7, 8). It is, therefore, the purpose of this report to describe more fully the distribution and some of the properties of responses in the hypothalamus from excitation of afferent nerves.

METHODS

Experiments were performed on 60 cats. Surgical procedures were done under light ether anesthesia, and wound margins infiltrated with 1% procaine. Animals were immobilized with gallamine triethiodide (Flaxedil), respiration being maintained mechanically by means of a Palmer respirator connected to a tracheal cannula. Most experiments were concerned principally with recording in the hypothalamus, mesencephalic reticular formation and medial lemniscus during electrical stimulation of the contralateral sciatic nerve. Single shock stimuli (0.1-2.5 v.; 0.1 or 0.01 msec. duration) were delivered to the isolated nerves through silver bipolar electrodes by means of either a Grass stimulator (S4-A) and isolation unit or a Tektronix pulse generator and reducing transformer for differential fiber stimulation experiments. In the latter studies the induced sciatic nerve action potential was monitored bipolarly 6 cm proximal to the stimulation site. The hypothalamus was screened systematically for evoked potentials with concentric stainless steel electrodes introduced stereotaxically and moved downward in millimeter steps. Hypothalamic potentials were picked up monopolarly and measured with respect to an indifferent potential obtained through a scalp electrode. Responses were amplified by a Tektronix low level preamplifier (type 122), observed on a Dumont dual bcam oscilloscope (series 322) and recorded with a Fairchild camera.

The neuronal recovery in the hypothalamus was studied with paired shocks applied to the sciatic nerve at varying intervals. In a few experiments the effect of high frequency stimulation of the midbrain reticular formation (100/sec.; 17.5 v., 0.01 msec. duration) upon evoked potentials in the hypothalamus was observed. At the end of each experiment various doses of sodium pentobarbital (Nembutal) were administered intravenously in small increments and their influence on hypothalamic and midbrain responses noted. Brains were prepared for histological examination and all electrode placements verified.

RESULTS

Evoked potentials. Stimulation of the contralateral sciatic nerve produced evoked potentials in all regions
explored in the hypothalamus. Responses could be categorized into two main groups on the basis of wave form, latency and anatomical location (fig. 1). The first type was usually a biphasic wave (positive-negative) with a latency of 7–10 msec., although occasionally only the positive portion was seen. These short latency waves occupied a medial position in the posterior hypothalamus, while in the more anterior regions they were found laterally (fig. 2, A–D). A monophasic (rarely biphasic) negative response made up the second type of evoked potentials seen. In most experiments their latencies ranged between 20 and 35 msec., although latencies of 17–45 msec. were observed as well. These long latency responses were found in the medial, dorsal and all of the anterior hypothalamus. The longer latencies were usually in the anterior part of the hypothalamus (fig. 2). The amplitude of both types of evoked potentials ranged between 50 and 150 μV, and their duration from 50 to 100 msec. The distribution of the evoked potentials is shown in figure 2, which represents the six frontal planes of the hypothalamus (Fr. 8 through 13) according to the stereotaxic atlas of Jasper and Ajmone-Marsan (9) which was used as a reference.

When the response was examined at successive depths (the electrode moving vertically downward) the long latency monophasic response in the lateral part of the tuberal hypothalamus became biphasic and the short latency positive waves appeared (fig. 1A). The negative wave which followed, corresponded in latency in most experiments to the negative monophasic wave recorded more dorsally, but in some experiments the latencies of the two waves were quite different. The appearance of the positive wave apparently signaled the approach of the recording electrode to a source of incoming impulses into the hypothalamus as in a number of experiments progressive lowering of the electrode in the lateral hypothalamus caused a clear increase in the amplitude of the positive wave, to be followed later by a drop in the potential (fig. 1B). Also, usually the long latency negative wave was larger in amplitude in the posterior than in the anterior hypothalamus.

The short and long latency responses in the hypothalamus evoked from sciatic stimulation were compared with those seen in the midbrain reticular formation and the medial lemniscus. The reticular formation evoked potentials were similar in general to the long latency responses in the anteromedial hypothalamus (fig. 3), whereas the lemniscal responses were usually similar to those of the short latency evoked potentials in the posterior and lateral hypothalamic areas (fig. 4A and B). Furthermore the short latency responses could be reproduced from stimulation of the medial lemniscus.

**Nerve activation threshold for hypothalamic potential.** In some experiments the evoked potentials appeared in the hypothalamus at the group A alpha-beta threshold for nerve stimulation and grew in amplitude with higher voltage (fig. 5), while in other experiments the hypothalamic evoked potential appeared only when the gamma-delta group fibers were stimulated. The thresholds of activation were essentially the same for the long latency potentials in the anterior and the short latency potentials in the posterior hypothalamus. In these experiments it seemed therefore that activation of all group A fibers was necessary to obtain the full evoked potentials like in the midbrain reticular formation (10).

**Recovery cycles.** Neuronal recovery in the hypothalamus was studied by paired shocks to the sciatic nerve the second following the first at varied intervals from 20 to 2000 msec. The recovery of the neurons was estimated by expressing the amplitude of the response to the second of a pair of shocks as a percentage of the amplitude of the response to the first of the same pair. Usually up to 80–100-msec. intervals between the first and second shocks, there was complete inhibition of the latter; in one of the experiments there was complete inhibition even at 160-msec. interval. At longer intervals partial recovery of the second response took place. In the recovery cycle (fig. 6B) sometimes recovery peaks were observed, but usually even at 1000 and in other experiments at 2000-msec. in-
Distribution of evoked potentials in the 6 frontal planes of the hypothalamus from Fr. 8 (A) to Fr. 13 (F) elicited by stimulation of contralateral sciatic nerve. Dots denote monophasic, long latency (7-45 msec.) negative waves. Crosses indicate occurrence of a biphasic wave: a negative wave similar to above, preceded by a short latency (7-10 msec.) positive wave.

Effect of pentobarbital. In some cases small doses of sodium pentobarbital (5 mg/kg) caused a slight decrease in the long latency negative waves in the hypothalamus. Ten milligrams per kilogram always caused a depression, and 15-20 mg/kg abolished the evoked potentials completely (fig. 4). Further increase in anesthesia caused the appearance of high voltage evoked potentials of 60-160 msec. latency, which were recorded throughout the anterior brain stem the characteristics of which will be described in detail separately. The negative wave of the short latency biphasic response behaved similarly, but the preceding positivity was much more resistant to pentobarbital (fig. 4) and persisted sometimes even at surgical levels of anesthesia (35-40 mg/kg). When the effect of a single dose of pentobarbital (50 mg/kg) upon the long latency evoked potentials in the hypothalamus was compared with its effect upon the midbrain reticular formation potentials it was observed in most experiments that the hypothalamic response was abolished before that of the reticular formation (fig. 3). On the other hand, comparison of the hypothalamic evoked potentials with those of the medial lemniscus showed that the positive wave of the latter which represents the presynaptic component was resistant to high doses of pentobarbital, which abol-
ished completely the hypothalamic negative potentials (fig. 4).

Effect of high frequency stimulation of the reticular formation. Stimulation of the midbrain reticular formation with pulses of 100/sec. and of 0.01 msec. duration abolished completely the evoked potentials in the hypothalamus.

COMMENT

The outstanding properties of the evoked potentials recorded in the anterior and medial hypothalamus were long latencies and a great sensitivity to repetitive stimulation and to anesthesia. As the hypothalamus is considered to be a rostral continuation of the brain stem reticular formation (7) it is not surprising that these evoked potentials in the hypothalamus were found to have properties quite similar to those described in the multisynaptic systems in the midbrain reticular formation and the intralaminar nuclei of the thalamus. These are usually attributed to the highly complex interneuron organization of these structures (8, 10-12). However, the latencies in the hypothalamus were generally longer, showed a more delayed recovery on double stimulation, than reported for the midbrain reticular formation (13) and seemed to be more susceptible to pentobarbital. These properties might be due to the fact that a greater number of synapses are involved in the hypothalamic response or they may indicate that the multisynaptic organization of the hypothalamus is still more complex than that of the midbrain reticular formation. However, this greater pentobarbital sensitivity and longer recovery on double stimulation do not necessarily imply a greater multisynaptic organization as there may be factors of neuronal selectivity involved.

There is evidence to suggest that the positive deflection of the short latency potentials observed in our experiments in the posterior and lateral portions of the hypothalamus, arises from activity at the terminals of lemniscal axons (14). The similarity of the responses recorded in the posterior and lateral hypothalamic areas from sciatic and from lemniscal stimulation and the resistance of the hypothalamic positive wave to pentobarbital would strongly suggest the existence of an important direct sensory inflow into the posterior and lateral hypothalamus. These short latency responses are probably analogous to the collateral afferent system of the reticular formation previously described (7).

The relation of the medial lemniscus to the hypothalamus is not clear. There is some evidence that part of the fibers of the mammillary peduncle come from the medial lemniscus (4) and thus provide a direct path for sensory

![Figure 5](http://ajplegacy.physiology.org/)

**FIG. 5.** Above figures indicate the threshold for evoked potentials in the anterior and posterior hypothalamus (B) from sciatic nerve stimulation. The sciatic nerve action potential is monitored proximal to stimulation site (A). While activation of the alpha-beta fibers (0.5 v.) caused the appearance of hypothalamic potentials, this full amplitude was attained only on activation of the gamma-delta group (0.6 v.).

![Figure 6](http://ajplegacy.physiology.org/)

**FIG. 6.** A. Effect of repeated stimulation of the sciatic nerve upon the amplitude of the evoked potentials in the medial and lateral hypothalamus. Increasing the frequency causes a progressive diminution in the amplitude of hypothalamic potentials. B. Lower figure shows graph of the recovery cycle of hypothalamus on paired pulse stimulation of sciatic nerve. Hypothalamic response to second of each pair is expressed as fraction of response to the first of each pair of stimuli. Typical examples are shown above at various intervals. Note that recovery is still not complete at 1200 msec.

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impulses from the brain stem into the hypothalamus. In fact it was suggested by Clark that its relation to the hypothalamus is the same as that of the medially lemniscus to the thalamus (5). Additional studies based on a number of species have shown that some fibers of the mammillary peduncle continue forward beyond the mammillary body to reach a more rostral level of the hypothalamus (6, 10).

Two alternative connections to be considered as possible pathways of the short latency responses into the hypothalamus are the periventricular system of thalamohypothalamus which is known to receive lemniscal fibers (5).

The presence of such an extrathalamic collateral from the lemniscal pathway has been suggested by Magoun and McKinley from electrophysiological studies (11).

The question arises as to the origin of the long latency responses recorded in the thalamus (5). Additional studies based on a number of species have shown that some fibers of the mammillary peduncle continue beyond the mammillary body (14). This extrathalamic collateral from the midbrain reticular formation into the hypothalamus is known to have intimate connections with the reticular formation (6).

In fact, our observations on the blocking effect of high frequency stimulation of the reticular formation on the activity of the latter. Such a reticular influence has been demonstrated on postsynaptic potentials of most specific evoked potentials of the hypothalamus (15). It may be assumed therefore that the afferent impulses reaching the hypothalamus directly from the sensory pathways as described in the present investigation as well as those from the midbrain reticular formation, play an important role in modifying the autonomic and endocrine activity of this region of the brain and supply the information for elaboration and integration of emotional reactions.

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