PHYSIOLOGY

# FUNCTIONAL ROLE OF THE HYPOTHALAMUS IN ARTERIAL PRESSURE REGULATION

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The principal function at the hypothalamic integration level is correlation of autonomic and motor manifestations of emotional behavior and the linking together of functional systems in an optimal association for a given biological process, rather than the isolated regulation of autonomic functions.

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Numerous investigations have underlined the important role of the hypothalamus in regulation of the cardiovascular system [2, 6, 9, 10, 13] and in the development of vascular pathology [3, 5]. The topographic distribution of the "pressor" and "depressor" zones of the hypothalamus has been studied [9, 13]. However, few attempts have been made to determine the extent of differences between the various nuclear complexes of the hypothalamus, the functional significance of arterial pressure changes associated with these structures, or other manifestations (motor, behavioral) which may be correlated with the vascular effects of the hypothalamus.

In acute and chronic experiments on cats and rabbits an attempt was made by physiological and pharmacological analysis to obtain fresh ideas on this question. The results of these investigations are described below.

## EXPERIMENTAL METHOD AND RESULTS

Types of Vascular Reactions Evoked by Stimulation of Individual Hypothalamic Nuclei. Local stimulation (unipolar insulated electrode 30-80 $\mu$ in diameter) was applied to more than 200 points in various hypothalamic nuclei of cats and rabbits. In each case the elctrolytic marker made by the tip of the active electrode was verified histologically (Nissl's stain), using an atlas of the hypothalamus of the cat and rabbit prepared in our laboratory for identification [4]. The following criteria were analyzed: latent period ($t_1$), amplitude of response (h), time taken for arterial pressure to rise to its maximum ($t_2$), steepness of leading edge (p) of the vascular response (angle of elevation $\alpha$), character of the trailing edge (d), and relationship between intensity of stimulation and response. By grouping all the responses in accordance with these criteria by the superposition method, three principal types of vascular responses were identified (Fig. 1).

Type I was characterized by a short latent period (1-2 sec), with little change when the stimulus was strengthened, and by a steep and rapid rise of pressure exceeding the initial level by 100-150%. With an increase in the strength of stimulation the time during which the pressure rose was increased, not because of steepness of the leading edge (the angle $\alpha$ showed little change), but because of amplitude. The initial level was regained 3-5 sec after stimulation ceased, but in the case of strong stimulation the trailing edge of the vascular response could be drawn out. Changes of this type in the arterial pressure took place during stimulation of the ventro-medial, supraoptic, suprachiasmatic, paraventricular, and medial mammillary nuclei. A low threshold (0.3-0.5 V) of stimulation is a feature distinguishing structures giving a vascular response of type I.

Type II responses were characterized by a long latent period (2-5 sec), and a relatively slow increase in amplitude to the maximum toward the end of stimulation (10-15 sec). The absolute level of the maximum did not exceed the initial level by more than 40-60%. After the end of stimulation the arterial pressure returned to normal within 15-25 sec. Responses of this type arose during stimulation of the lateral and poste-

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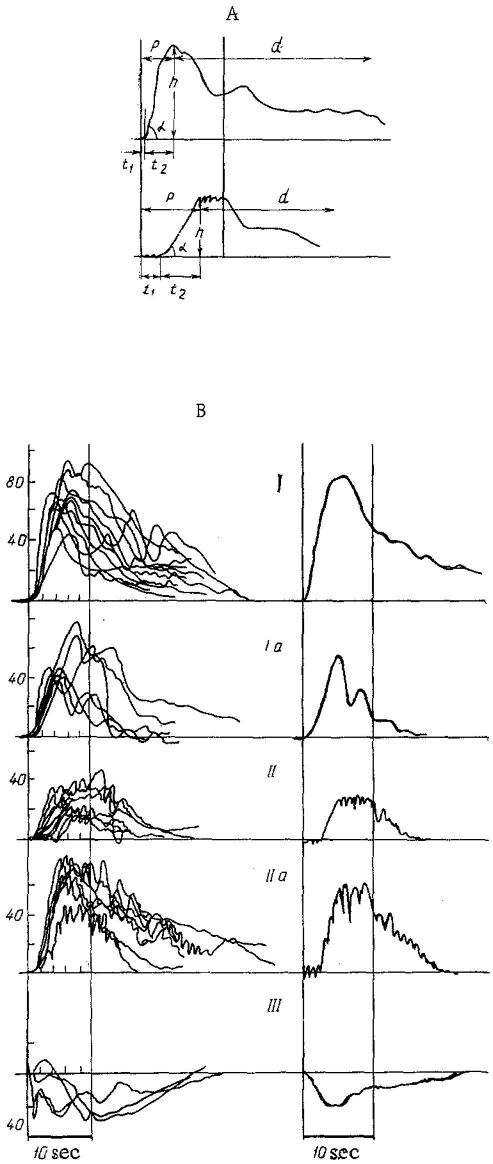


Fig. 1. Amplitude and temporal characteristics of type I (above) and II (below) responses of arterial pressure (A) and different types of vascular responses arising during stimulation of the hypothalamus (B). A; $t_1$) latent period (in sec); $t_2$) time for arterial pressure to rise to maximum (in sec); h) amplitude of response (in mm); $\alpha$) angle of inclination of leading edge; p) leading edge of pressor response; d) trailing edge.
B: on the left–grouping of response changes of arterial pressure obtained in different experiments at optimal intensity of stimulation for obtaining full range of specific behavioral response; on the right–averaged curves characterizing different types of vascular responses: I, Ia (type I), II, IIa (type II) and III (type III). Ordinate–arterial pressure (in mm), abscissa–time (in sec). Duration of stimulation 10 sec.

rior hypothalamic regions and the lateral mammillary nucleus. Type III responses were depressor in character and arose much less frequently during stimulation of the preoptic and oral portions of the anterior hypothalamic region.

Nembutal, in doses of 3-5 mg/kg, produced negligible changes in the amplitude and latent period of the type I pressor responses arising during stimulation of the medial mammillary and ventro-medial nuclei. Meanwhile the pressor responses to stimulation of the posterior hypothalamic region, the lateral mammillary nucleus, and the lateral hypothalamic region (responses of type II) were reduced by 50-80% after administration of Nembutal. In this case, however, after injection of Nembutal in a dose of 1-3 mg/kg, the decrease in amplitude of the response was accompanied by an increase in its latent period (by 1.5-2 sec). An increase in the intensity of stimulation (applied to the posterior and lateral hypothalamic region) after injection of Nembutal did not result in the appearance of the initial response, in contrast to what was observed with the type I responses, when an increase in the intensity of stimulation evoked the initial change of arterial pressure.

In experiments with morphine, a relationship between the dose of the drug and the type of vascular response was discovered. In small doses (of the order of 0.01-0.05 mg/kg) morphine caused facilitation of the pressor responses, mainly responses of type I. In doses of 4-5 mg/kg, the pressor responses of type I were almost completely suppressed, while the amplitude of the type II responses was reduced by only 30%.

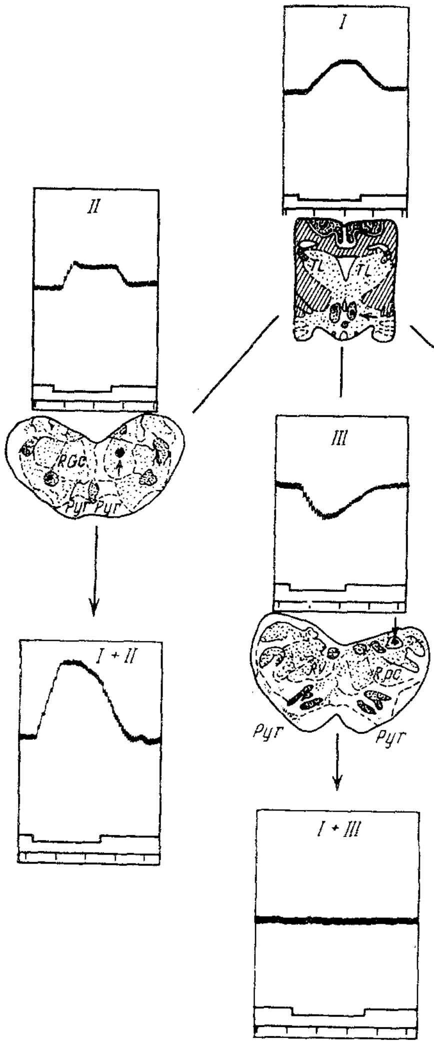


Fig. 2. Effect of paired stimulation of hypothalamus and medulla on magnitude of pressor responses. I) Response to stimulation of posterior hypothalamic region; II) gigantocellular reticular nucleus (RGc); III) motor nucleus of vagus nerve (RV); IV) parvocellular reticular nucleus (Rpc); I+II, I+III, I+IV) effects of paired stimulation of posterior hypothalamic region with above-mentioned reticular nuclei. Arrows on diagrams indicate location of electrodes. TL) Hypothalamus; Pyr) pyramids.

Neuropharmacological analysis thus confirmed the existence of different types of vascular responses with well-marked functional differences.

Role of the Hypothalamus in the Tonic and Phasic Regulation of Arterial Pressure. Comparison of the doses of neurotropic drugs producing total suppression of the pressor responses evoked by electrical stimulation with doses modifying the initial background level of the arterial pressure revealed considerable divergence. Nembutal, in doses of 7-10 mg/kg, reduced the amplitude of the pressor responses of arterial pressure by 80-100%. After injection of this narcotic in the same doses, the initial arterial pressure level showed practically no decrease. Consequently, at the level of the hypothalamus, just as of the rhombencephalon [1], two independent systems from this point of view may be distinguished.

Dividing of the brain stem at the level of the optic chiasma, followed (or preceded) by division of the fibers of the cranial nerves (pairs VII-XII), was performed in order to study the role of tonic impulses from the hypothalamic region and the afferent inflow at the bulbar level in maintenance of the initial neurogenic vascular zone.

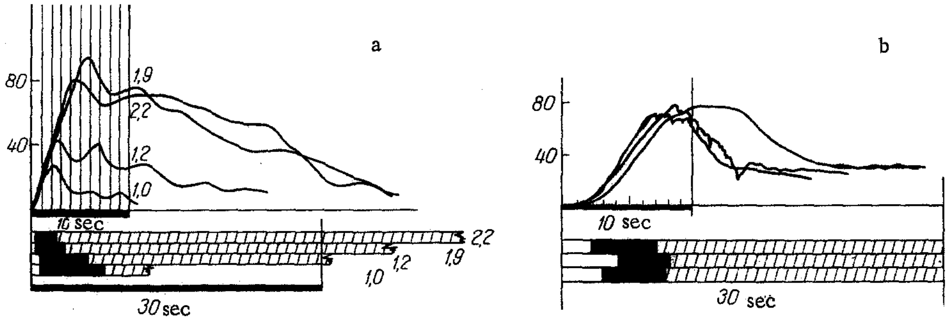


Fig. 3. Comparison of changes in arterial pressure and phases of development of aggressive-defensive behavioral response during gradually increasing intensity of stimulation (a) and response of "searching" type (b). Abscissa—time (in sec), ordinate—amplitude of pressor response (in mm). Numbers denote amplitude of stimulation (in V). Unshaded area—latent period of behavioral response; black areas—duration of alertness response; shaded—emotional behavioral response.

Separation of the hypothalamus from the rhombencephalon, as is well known [11,12], produced no essential changes of arterial pressure. However, additional deafferentation (division along the lateral border of the rhomboid fossa, maintaining the integrity of the medulla and pons), preventing the arrival of impulses from the receptors of cranial nerve VII-XII, was accompanied by a sharp decrease (by 50-60 mm) in systemic arterial pressure. If the bilateral division along the lateral border of the rhomboid fossa was performed first, the systemic pressure was unchanged. Subsequent separation of the hypothalamus again led to a fall of pressure.

Hence, in the case of a sharp decrease in the flow of afferent impulses to the vasomotor structures of the medulla and a decrease of their tonic activity, the hypothalamus compensates for the loss of afferent impulses and stabilizes the arterial pressure. If the bulbar vasomotor center is functioning normally, the hypothalamus has no significant role in maintaining the initial level of arterial pressure.

Interaction between Hypothalamus and the Bulbar and Spinal Levels of Vasomotor Regulation. A detailed examination of the functional connection between the hypothalamus, on the one hand, and the bulbar and spinal levels of vasomotor regulation, on the other, was made on 62 cats using a method of paired stimulation of the hypothalamus and medullar or hypothalamus and lateral horns of the spinal cord. Series of square stimuli were applied to the paired structures through unipolar electrodes.

Subthreshold stimulation of the hypothalamus (not evoking a pressor response) strengthened the pressor response evoked by stimulation of the lateral horns of the spinal cord. During paired stimulation of the hypothalamus and medial nuclei of the medullary reticular formation (Fig. 2), as a rule mutual potentiation of the response was observed. The paired responses from the lateral portions of the reticular formation (parvocellular nucleus) in half of the cases were smaller than the separately evoked pressor responses. If the pressor change evoked from the hypothalamus was combined with the depressor response arising during stimulation of the dorsal nuclei of the vagus nerve, mutual extinction of the responses took place (Fig. 2).

Nembutal behaved variously toward the effects of paired stimulation. If the vascular response was greater in amplitude than the responses evoked by separate stimulation, it was depressed by a larger dose of Nembutal than the separately evoked responses. When the paired response was smaller in amplitude than the separate responses, it was depressed by smaller doses of Nembutal than the responses evoked by single stimulation.

Hence, the various levels of regulation of arterial pressure are linked by complex relationships manifested not merely by facilitation, but also by depression of their functional activity.

Correlation between Various Types of Vascular Responses and Various Types and Components of Hypothalamic Behavioral Responses. Zones of the hypothalamus, stimulation of which can give rise to arterial pressure changes, coincide topographically with the integrative centers of various behavioral responses [9]. As we have shown previously [4], behavioral responses of the "rage," "running away," "searching," and "orientation" arrive during stimulation of clearly demarcated nuclear structures of the posterior hypothalamus. To understand the functional significance of the arterial pressure changes arising during stimulation of the posterior zones of the hypothalamus, it is important to determine with which component of the total complex of the behavioral response the vascular response correlates.

Details of the course of behavioral responses arising in rabbits during unipolar stimulation of different points of the hypothalamus through implanted electrodes were studied in chronic experimental conditions. By applying stimuli of gradually increasing intensity, differences in the thresholds of appearance of the individual autonomic and motor components of the complex behavioral responses could be determined. In acute experiments on the same animals, without anesthesia and with the same parameters of stimulation, changes in arterial pressure and respiration corresponding to the different levels of the behavioral response were recorded.

Pressor responses of type I were found to coincide with the threshold of onset of behavioral responses of the nature of "aggressiveness," "rage," or "precipitous flight," which were clearly emotional in character. Responses of type II corresponded to behavioral responses of the "searching," or "orienting behavior" type. Responses of type III corresponded to changes in the animal's behavior with the character of "depression, low-spiritedness, and prostration."

It is clear from Fig. 3 that the ascending phase of the pressor response of types of I and II coincides in time (latent period, time of development) with the initial alerting response preceding each behavioral response. Periods of "alerting" differing in the character of their course corresponded to different types of behavior. These results were described more fully in an earlier paper [4].

The pressor response thus precedes the emotional behavioral response proper. It has been shown [7] that stimulation of zones of the hypothalamus from which defensive responses (flight-fight) arise in cats is accompanied by considerable vasodilatation in the skeletal muscles. The opinion has been expressed [8] that this process takes place through sympathetic vasodilators. The rise of systematic arterial pressure is thus of adaptive importance, on the one hand creating better conditions for increasing the blood flow to the skeletal muscles, and on the other hand preventing possible disturbances of the hemodynamics connected with redistribution of the blood. It must therefore be concluded that the principle function of the hypothalamic level of integration is in correlating autonomic and motor manifestations of emotional behavior, in linking together the various functional systems into an optimal association for a given biological process, and not in the isolated regulation of autonomic functions.

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