EFFECT OF STIMULATION OF THE HYPOTHALAMUS ON THE ACTIVITY OF THE CARDIOVASCULAR SYSTEM IN LONG-TERM EXPERIMENTS

V. A. Tsybenko

Department of Human and Animal Physiology (Head, Corresponding Member AN Ukr. SSR Professor A. I. Emchenko), Order of Lening T. G. Shevchenko Kiev University
(Presented by Active Member AMN SSSR V. V. Parin)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 2, pp. 11-16, February, 1964
Original article submitted October 23, 1962

The role of the hypothalamic region in the regulation of cardiac activity and vascular tone has been the subject of many investigations [3, 6, 9, 11, 12, 16]. Experimental stimulation of the hypothalamus has shown that reactions of sympathetic type (increased blood pressure, increase of the heart rate) are most frequently elicited from its posterior portion, and of parasympathetic type (a fall in blood pressure and slowing of the heart rate) from the anterior portion. Nearly all these investigations have been conducted in animals under anesthesia and in acute experimental conditions. However,anesthesia has a marked effect on the normal activity of the central nervous system and cardiovascular apparatus [13]. The only observations made on unanesthetized dogs under chronic experimental conditions are those of Rushmer and co-workers [14], who found an increase in the strength and frequency of the cardiac contractions and an increase in the pressure inside the left ventricle. No investigations of the vascular system, especially of the changes in blood pressure, during stimulation of the hypothalamus have been carried out because of the difficulty in recording this index in waking, unanesthetized animals.

The results of experiments involving extirpation or destruction of the hypothalamus are contradictory. Some investigators found no changes in the activity of the cardiovascular system after removal of the hypothalamus in acute experiments [7, 8], while others, studying the problem in chronic experimental conditions, found definite disturbances in the vascular system and heart of the animals [10, 15]. These differences were evidently not entirely attributable to the effects of anesthesia, but also to the duration of the observations.

In previous investigations [4, 5], in acute experimental conditions, we observed an increase in arterial pressure by 20-80 mm and an increase in the heart rate by 10-50 beats/min during stimulation of the posterior hypothalamus and a fall in arterial pressure of 20-60 mm, sometimes accompanied by a slowing of the pulse by 8-30 beats/min, during stimulation of the anterior hypothalamus. It was interesting to discover the nature of these relationships in unanesthetized animals. In the present investigation we studied the effects of stimulating various parts of the hypothalamus on the arterial pressure and the heart rate in the course of chronic experiments on waking animals.

EXPERIMENTAL METHOD

Experiments were carried out on 5 dogs. In 2 animals electrodes were implanted into the middle and posterior portions of the hypothalamus, using the method of Bogach and Kosenko [1] with an approach through the temporal region, and in the other 3 animals they were implanted into the anterior hypothalamus using a transoral approach. The active electrode, 0.1 mm in diameter, was insulated throughout its length except at the end, so that its stimulating surface did not exceed 0.1 mm^2 in area. The indifferent electrode, 20 cm^2 in area, was applied to the shaven skin of the forehead. Unipolar stimulation was carried out with a sinusoidal current from a type ZG-1 audiofrequency generator, with a frequency of 50 cps, a strength of 0.05-2.0 mA and a voltage of 0.4-6 V. The duration of stimulation was 15-60 sec. The pressure was recorded in the carotid artery, exteriorized in a skin flap. Since all the methods of prolonged bloodless recording of the pressure that were tried show only the character and direction of the reaction, and give no idea of its magnitude, we recorded the arterial pressure directly by puncture of the carotid artery where it lay in the skin flap. In 2 dogs the pressure was recorded in a subcutaneous artery on the medial aspect of the knee joint by Pavlov's method [2]. The arterial pressure was recorded by a membrane manometer. During the experiment the dog was strapped to an ordinary frame. The position of the electrodes was verified roentgenographically and in histological sections of the brain at the end of the experiments.

Changes in Arterial Pressure and Heart Rate during Stimulation of Various Parts of the Hypothalamus

Dog. No.	Electrode	Site of stimulation	Strength of current (in mA)	Voltage (in V)	Maximal arterial pressure (in mm Hg)		Pulse rate, per min		Accompanying reactions
					before stimulation	during stimulation	before stimulation	during stimulation	
1	3	Between mamillary bodies	0.8	2.5	108	152	78	114	Upward lifting of head
	3	The same	0.5	2.0	106	132			Constriction of pupils
	4	Posterior part of tuber cinereum	0.2	1.4			84	144	Strengthening of respiration, weak motor restlessness
2	1	Lateral part of tuber cinereum	0.1	0.7	120	120	92	100	Constriction of pupils, yelping
	2	Lateral mamillary body	0.8	4.0	110	156	80	96	Twitching of neck and head
	4	Between mamillary bodies	0.2	5.0	110	136	84	124	Absence of motor reactions
	4	The same	0.5	6.0	104	170			Dog paws with its forelimbs
3	1	Paraventricular nucleus	0.2	3.0	110	134	78	118	Licks itself
	3	Anterior supraoptic nucleus	0.6	6.0	122	126	72	68	Movement of head, sniffs and urinates
4	1	Paraventricular nucleus	0.2	2.5	110	106	76	78	Constriction of pupils, restlessness
	1	The same	1.1	4.0	138	158	80	96	Turning head to the side
	2	Medially to anterior supraoptic nucleus .	0.2	3.0	120	114	74	76	Motor restlessness, yelping
5	1	Laterally to paraventricular nucleus . . .	0.07	2.8	82	62	76	88	Constriction of pupils, sniffing
	1	The same	0.1	3.0	106	94			Urination
	2	Posterior supraoptic nucleus	1.2	5.0	92	124	76	104	Chewing, urination
	2	The same	1.5	5.5	96	162	70	118	Dilatation of pupils, defecation

EXPERIMENTAL RESULTS

In 2 dogs electrodes were applied to the middle and posterior parts of the hypothalamus and to the region of the tuber cinereum and the mamillary bodies. In both animals threshold stimulation as a rule caused an increase in arterial pressure and in the heart rate (see table, dogs Nos. 1 and 2). The arterial pressure began to rise 2-4 sec after the beginning of stimulation and returned to normal quickly after its end; during stimulation it rose by 20-40 mm (Fig. 1). With stronger stimulation (0.5-2.0 mA) the pressure sometimes rose by 60 mm or more, and then its return to its initial level after the end of stimulation was considerably protracted. In 24% of cases the arterial pressure was unchanged in these dogs in response to stimulation of the hypothalamus.

It was far more difficult to obtain a fall in arterial pressure during stimulation of the anterior hypothalamus than a pressor reaction of the posterior hypothalamus. Of the 3 animals in which electrodes were implanted into the region of the supraoptic and paraventricular nuclei (see table, dogs Nos. 3, 4, and 5), only in one was a clear depressor reaction to stimulation observed (Fig. 2, A). In the other cases stimulation of the anterior hypothalamus caused insignificant fluctuations of arterial pressure, which sometimes fell after stimulation had ended (Fig. 2, B). It should be noted that a depressor reaction could not be elicited in dog No. 5 (see Fig. 2, A) in every experiment. On some

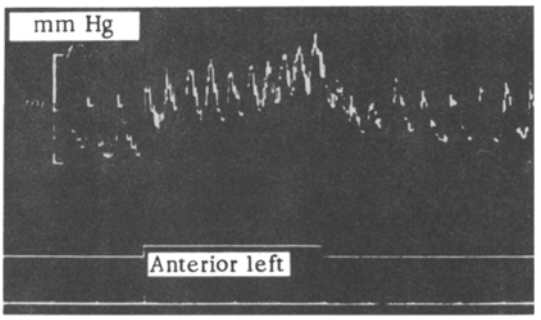

Fig. 1. Elevation of arterial pressure in dog No. 2 during stimulation of posterior hypothalamus. Tracing of pressure in carotid artery. Electrode 4 situated between mamillary bodies, in their caudal part. Current strength 0.2 mA, voltage 5 V. Significance of curves (from top to bottom) here and in other figures: arterial pressure, stimulation marker, time marker (15 sec).

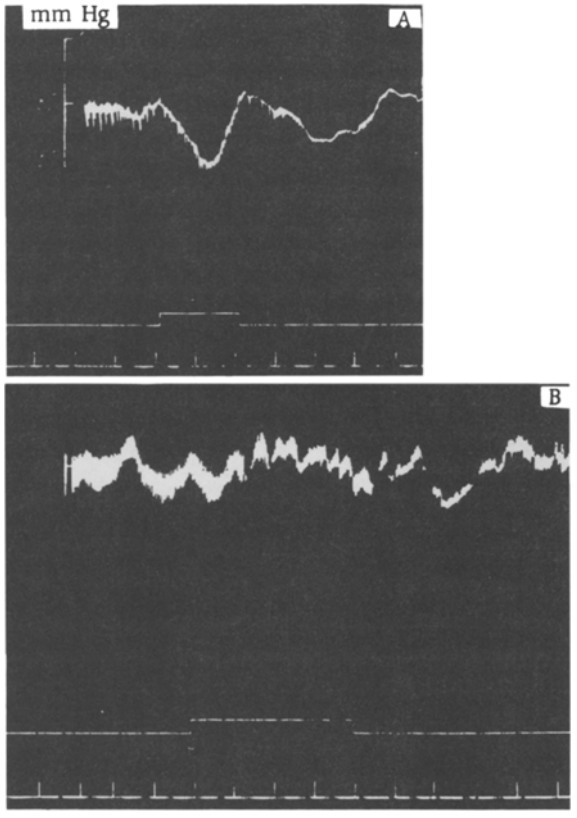

Fig. 2. Effect of stimulation of anterior hypothalamus on arterial pressure. Recording from subcutaneous artery of knee joint. A) dog No. 5; electrode 1 in region of left paraventricular nucleus; strength of current 0.007 mA, voltage 3 V; B) dog No. 4; electrode 1 in region of right paraventricular nucleus; current 0.4 mA, voltage 5 V.

days stimulation of the same region of the hypothalamus caused no changes in arterial pressure, probably as a result of changes in the functional state of the animal not taken into consideration.

With an increase in the strength of stimulation of the anterior part of the hypothalamus pressor reactions may arise, sometimes fairly considerable in degree (Fig. 3). An increase in the strength of the current during unipolar stimulation was accompanied by an increase in the area of the excited region of the brain around the electrode. In several of our experiments stimulation of two neighboring areas of the hypothalamus with 2 electrodes situated not more than 2 mm apart caused different reactions. It may therefore be concluded that unipolar stimulation with a current of 1-2 mA stimulates an area of the hypothalamus within a radius of 2 mm around the electrode and that the pressor effect during such stimulation is due to excitation of the pressor elements found in the anterior hypothalamus and not to the spreading of loops of current to the posterior hypothalamus.

Stimulation of the posterior part of the hypothalamus caused an increase in the heart rate by 16-40 (sometimes by 60) beats per minute. During stimulation of the anterior part of the hypothalamus a smaller increase in the heart rate (by 12-20 beats per minute) was usually observed; in some cases the heart rate was unchanged, and only in isolated experiments was a very slight slowing of the pulse observed – by 4-8 beats per minute. The absence of a parallel between the character and magnitude of the changes in arterial pressure and in the heart rate, also observed in our previous acute experiments [4], was a noteworthy feature.

During stimulation of the hypothalamus, besides changes in the arterial pressure and heart rate, other autonomic and somatic reactions also were observed: constriction or dilatation of the pupils, changes in respiration, sniffing, licking, chewing movements, chattering the teeth, turning the head, and so on. Stronger stimulation caused, besides the above, urination, defecation with corresponding changes in the position of the body, and generalized motor restlessness. In several experiments we observed only changes in the arterial pressure and heart rate, without any other visible reactions, and in some experiments, in the absence of changes affecting the cardiovascular system, various autonomic and somatic reactions were recorded. It may therefore be postulated that the motor reactions arising during stimulation of the hypothalamus are not the cause of the changes in arterial pressure (with maintenance of constance of the manometer levels and of the condition of the blood vessel to be tested), but are merely some-

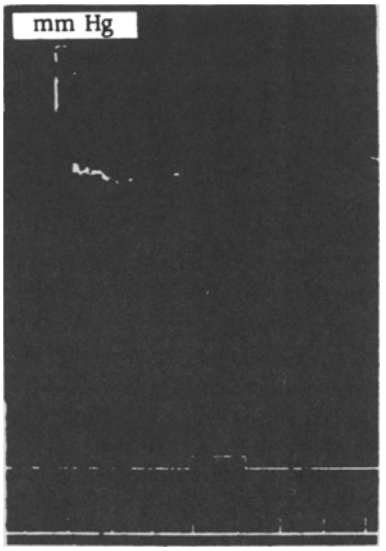

Fig. 3. Effect of strong stimulation of the anterior hypothalamus on arterial pressure in dog No. 5. Recording made in subcutaneous artery of the knee joint. Electrode 2 in the region of the posterior supraoptic nucleus; strength of current 1.2 mA, voltage 5 V.

times coexistent; the effect observed during stimulation should probably be regarded as the result of simultaneous excitation of different groups of nerve cells, connected by certain quantitative relationships. In response to threshold stimulation a minimal number of specialized reactions may be obtained, whereas in response to stronger stimulation a whole series of autonomic and somatic reactions is observed.

The main difference between the results of the acute and chronic experiments is the less frequent manifestation of depressor responses in chronic experimental conditions, and it may be attributed to the absence of the anesthetic effect. Further investigation is required in order to determine why anesthesia does not affect the manifestation of the pressor, but only of the depressor reactions. No chronic changes were observed in the cardiovascular system of the experimental animals during the period of observation (from 10 to 40 days after insertion of the electrodes).

The investigation confirmed the results obtained in acute experiments: stimulation of the posterior part of the hypothalamus usually caused a marked rise in arterial pressure and an increase in the pulse rate, while stimulation of the anterior part led to a fall in arterial pressure, although less often than in the acute experiments.

SUMMARY

In chronic experiments on waking unanesthetized dogs a study was made of the effect produced by stimulating various portions of the hypothalamus on the blood pressure and the frequency of cardiac contractions. Blood pressure was recorded in the coronary artery or in the subcutaneous artery of the knee joint. As demonstrated, stimulation of the posterior hypothalamus (caudal portion of the tuber cinereum and of the mamillary body) increased the blood pressure by 20-40 mm Hg, whereas stimulation of the anterior hypothalamus (the area of the supraoptic and paraventricular nuclei) decreased the pressure in a number of cases by 10-20 mm Hg. The frequency of cardiac contraction usually increased by 10-14 (at times by 60 beats) per minute; the rise in response to stimulation of the anterior hypothalamus was less pronounced. In individual cases there was an insignificant deceleration of the cardiac rhythm by 4-8 contractions per minute. Other autonomic and somatic reactions often accompanied the blood pressure and pulse changes, i.e., the pupil size changes, those of respiration, of the smelling reaction, licking, urination, defecation, general motor excitation, etc.

LITERATURE CITED

1. P. G. Bogach and A. F. Kosenko, Fiziol. zh. SSSR, 11, 989 (1956).
2. I. P. Pavlov, Complete Collected Works [in Russian], 1, p. 72, Moscow-Leningrad (1951).
3. N. P. Smirnova, Fiziol. zh. SSSR, 2, 185 (1961).
4. V. O. Tsibenko, Visn. Kiivsk. Univ. za 1959, seriya biol., 2, 79 (1959).
5. V. O. Tsibenko, Fiziol. zh. (Ukrain.), 2, 178 (1961).
6. A. van Bogaert, Arch. int. Pharmacodyn. (1936), 53, p. 137.
7. E. Braun Menendez, Rev. argent. Cardiol. (1934), 1, p. 337.
8. D. W. Bronk, R. F. Pitts, and M. G. Larrabee, Ass. Res. Dis. Proc. (1939), 1940, 20, p. 323.
9. W. R. Hess, Das Zwischenhirn und die Regulation von Kreislauf und Atmung. Leipzig (1938).
10. H. Hoff and H. Urban, Klin. Wschr. (1933), 12, p. 1366.
11. H. Kabat, H. W. Magoun, and S. W. Ranson, Arch. Neurol. Psychiat. (1935), 34, p. 931.
12. J. P, Karplus and A. Kreidl, Pflüg. Arch. ges. Physiol. (1927), 215, p. 667.
13. H. L. Price, Physiol. Rev. (1960), 40, p. 187.
14. R. F. Rushmer, O. A. Smith, and E. P. Lasher, ibid., Suppl. 4, p. 27.
15. J. W. Watts and J. F. Fulton, Ann. Surg. (1935), 101, p. 363.
16. S. J. Weinberg and J. M. Fuster, Arch. int. Physiol. (1959), 67, p. 699.