MECHANISM OF ARTERIAL HYPERTENSION DURING LONG-TERM ELECTRICAL STIMULATION OF EMOTIOGENIC ZONES OF THE RABBIT HYPOTHALAMUS

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The aim of this investigation was to create an experimental model of arterial hypertension (AH), corresponding to essential hypertension (EH) in man, and to study some central and peripheral mechanisms of neurohumoral regulation during the formation of stable hypertension.

EXPERIMENTAL METHOD

Experiments were carried out on 54 male chinchilla rabbits weighing not more than 2.5 kg. To create the model of AH the animals were divided into two groups: group 1 (24 rabbits) served as the control for blood pressure (BP) and heart rate (HR), allowing for seasonal biorhythms and the mechanical effect of the electrodes; group 2 (30 rabbits) was the experimental group, and these animals were subjected to prolonged electrical stimulation of the region of the paraventricular hypothalamic nucleus (PVHN) through implanted electrodes. An independent system of electrical stimulation of brain structures [7] was used to create a generator of pathologically enhanced excitation (GPEE) [4] in the region of PVHN, with the following coordinates taken from a stereotaxic atlas [8]: APO D = 0.5 mm; H = 12.5 mm. The operation of implantation of bipolar electrodes (nichrome, d = 100 μ, distance between electrodes 0.5 mm) was performed under general anesthesia (0.5 ml of 1% trimeperidine solution and 0.5 ml of 2.5% chloropromazine solution, intraperitoneally). BP was recorded by a specially designed instrument in the carotid artery, exteriorized in a skin flap by Van Leersum's method. The maximal pressure in the artery corresponded to the maximal oscillation recorded by a piezoelectric transducer from the cuff as the pressure in it fell after complete occlusion of the artery. Calibration was done in one experiment with simultaneous measurement of BP in the right carotid artery by a Ludwig's manometer and in the left carotid artery by means of the instrument. The experimental schedule consisted of alternation of periods of continuous round-the-clock stimulation for 12 days (a burst of square pulses every 5 min) [7] with periods of rest of the same duration. There were altogether four cycles of stimulation and the total duration of the experiment was 3 months. Throughout this period the animals were kept under normal conditions of diet and maintenance. BP and HR were measured daily, and at the end of each experiment the EEG was recorded in the α- and θ-rhythm bands for 10 sec by unipolar derivation from five fixed electrodes, and averaged electrical activity in the same bands also was recorded by means of an 8-channel "Orion" encephalograph, MN-10M analog computer, and integrator. The EEG was recorded in the left and right frontal and occipital regions and also in PVHN for 3 min. Blood levels of catecholamines were determined polarographically [5], of 11-HCS fluorometrically [6], and of histamine [3] and serotonin [2] fluorometrically, by means of the ninhydrin reaction. The results were subjected to statistical analysis by Student's tests.

EXPERIMENTAL RESULTS

Long-term observation of BP and HR levels in animals of the control group, with electrodes implanted into the region of PVHN revealed no significant differences from the initial values (16.8 ± 0.45 compared with 16.5 ± 0.35 kPa and 235 ± 4.0 compared with 243 ± 2.3 beats/

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TABLE 1. Changes in BP, HR, and Levels of Biologically Active Substances in the Blood during Electrical Stimulation of PVHN in Rabbits (M ± m, n = 26)

Control	BP, kPa	HR, beats/min	Glucocorticoids, μmoles/liter	Adrenalin, nmoles/liter	Noradrenalin, nmoles/liter	Adrenalin/noradrenalin	Histamine, μmoles/liter	Serotonin, μmoles/liter
Control	16,8±0,45	235±4,0	0,15±0,01	1,75±0,,2	2,50±0,14	0,70	54,0±0,6	0,78±0,34
I stimulation	18,83±0,64	247±4,1	0,45±0,04	0,62±0,18	1,20±0,21	0,52	26,9±1,8	0,76±0,07*
Rest	19,21±0,77	245±3,8	0,70±0,23	1,04±0,12	1,55±0,24	0,67	35,0±2,7	0,67±0,06*
II stimulation	18,57±0,63	234±4,8*	0,98±0,15	1,06±0,15	1,55±0,19	0,68	43,2±1,8	0,69±0,06*
Rest	19,22±0,51	241±3,7*	0,95±0,15	0,54±0,14	1,17±0,26	0,46	47,7±2,7*	0,42±0,04
III stimulation	20,28±0,64	245±3,9	1,10±0,12	0,10±0,22	1,13±0,26	0,98	44,1±3,6	0,82±0,07*
Rest	20,22±0,38	236±3,6*	0,46±0,09	0,45±0,14	1,08±0,11	0,42	35,1±1,8	0,68±0,04
IV stimulation	20,48±0,51	242±3,4	0,80±0,16	1,19±0,22	1,64±0,19	0,73	35,9±1,8	0,55±0,05
Rest, 3 months	20,43±0,83	240±5,1*	0,37±0,08	0,38±0,08	1,12±0,08	0,34	45,9±1,8	0,93±0,06

Legend. Asterisk indicates differences compared with control not significant ($p > 0.05$).

min.) The observation showed, however, that BP fluctuated significantly with the change of season. It was lowest in winter (16.1 ± 0.23 kPa) and highest in summer (17.5 ± 0.26 kPa; $p < 0.001$). The results characterizing changes in the BP level at different seasons of the year served as the control for the experimental series of investigations carried out during the corresponding period of the year.

Prolonged electrical stimulation of the region of PVHN, alternating with a period of rest, led to the development of hypertension in 26 of the 30 animals, starting with first cycle of stimulation (Table 1). Whereas in cycles I and II of the experiment the pressure exceeded the initial value by 12-13%, after cycles III and IV of stimulation, it exceeded it by 20.7-21.9%, BP fell a little during the rest period, but it was always significantly higher than initially. Observation of the BP level for 3 months after the end of stimulation revealed a persistently raised level.

In the course of the experiment HR did not exhibit such significant changes as BP. Only in periods I and II of stimulation was HR increased by 5.1% compared with the initial level. However, analysis of the changes in HR showed that a rise of BP in 50% of animals was accompanied by the development of tachycardia, whereas in the rest it was accompanied by bradycardia. It can be postulated that hypertension was formed in the animals on the basis of different mechanisms, in agreement with the hemodynamic heterogeneity of EH in man [1].

The study of brain electrical activity in the α- and θ-rhythm bands showed that depression of the α-rhythm, evidence of the appearance of a focus of excitation in the corresponding parts of the brain, began to be formed only from the II cycle of stimulation (Fig. 1). Subsequent periods of the experiment were characterized by persistent depression of the α-rhythm (to 67% of its initial value, $p < 0.001$), evidence of the existence of a stable focus of excitation in the corresponding parts of the brain. Moreover, more marked depression of the α-rhythm was observed in the region of stimulation of the right PVHN and in the right frontal and occipital regions, i.e., on the side of electrical stimulation. Changes in the θ-rhythm were not statistically significant.

Thus electrical stimulation of the region of PVHN creates a GPEE in the subcortical region of the brain starting with the 3rd week of the experiment, leading to excitation of the corresponding brain system.

To study the mechanisms of the effect of GPEE in the region of PVHN, blood levels of biologically active substances were studied in rabbits. Starting with the I cycle of electrical stimulation, the concentration of glucocorticoids arose to 3 times its initial level. This high concentration was maintained throughout the experiment (Table 1) and even after a long rest it was still 2.8 times higher than initially. The blood catecholamine levels gradually fell during the experiment, and by its end they have reached 22% of the initial level for adrenalin and 45% for noradrenalin. The adrenalin/noradrenalin ratio rose during periods of stimulation and fell after periods of rest compared with initially. The histamine concentration was low from the time of the first stimulation and throughout the experiment, namely 67% of the initial value by the end of the experiment and 85% after a period of rest. The serotin concentration similarly was low (Table 1), but during rest it rose by 19%.

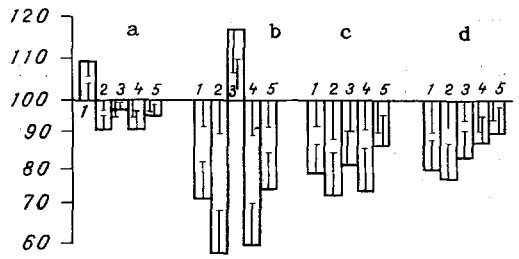

Fig. 1. Changes in α-activity on EEG of different parts of the rabbit brain during electrical stimulation of PVHN. Abscissa: a-d) I-IV cycles of stimulation, 1) hypothalamus, 2 and 3) right and left frontal regions of cortex, 4 and 5) right and left occipital regions of cortex respectively; ordinate, change in α-activity on EEG (in % of initial value, taken as 100).

Thus in response to creation of a pathological system of brain excitation through the formation of a GPEE in the region of PVHN, fundamental changes take place in the pressor and depressor systems of the body leading to the development of arterial hypertension [4].

LITERATURE CITED

1. I. A. Gundarev, E. N. Konstantinov, and A. N. Britov, Ter. Arkh. No. 12, 34 (1983).
2. V. S. Il'in and E. M. Stabrovskii, Methods of Investigation of Neuroendocrine Systems [in Russian], Leningrad (1971), p. 78.
3. N. V. Klimkina and S. I. Platman, Biochemical Methods of Investigation in Hygiene [in Russian], Moscow (1973).
4. G. N. Kryzhanovskii, Determinant Structures in Pathology of the Nervous System. Generator Mechanisms of Neuropathological Syndromes [in Russian], Moscow (1980).
5. A. R. Maslova, Biokhimiya, No. 2, 181 (1959).
6. I. Ya. Usvatova and Yu. A. Pankov, Modern Methods of Determination of Steroid Hormones in Biological Fluids [in Russian], Moscow (1968), pp. 38-48.
7. P. S. Khomulo and N. A. Dmitrieva, Models and Methods of Studying Experimental Emotional Stress [in Russian], Volgograd (1977), pp. 319-320.
8. I. P. Tsvetkova, The Rabbit Hypothalamus [in Russian], Leningrad (1978).