ROLE OF THE MAMILLARY NUCLEI OF THE HYPOTHALAMUS IN REGULATION OF ERYTHROPOIESIS

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Bilateral electrolytic coagulation of the posterior hypothalamus in rabbits in the region of the mamillary nuclei causes a periodic anemia, most marked in the 3rd and 16th weeks after the operation. The first wave of anemia is accompanied by increased erythropoietin activity of the blood, and at the height of the second wave, the content of erythropoietins in the blood of the animals is unchanged.

Studies of the role of subcortical structures, notably the hypothalamus, in the regulation of erythropoiesis have been published only recently [2, 4, 6-9]. Many aspects of this problem are still far from solution.

In the present investigation changes in the system of humoral regulators of erythropoiesis (erythropoietins) and some indices of the peripheral blood and bone marrow were studied after destruction of the mamillary nuclei of the posterior hypothalamus in rabbits.

EXPERIMENTAL METHOD

Bilateral destruction of the mamillary nuclei of the hypothalamus was carried out in 25 rabbits at the level P-3 according to the atlas of Sawyer and co-workers [10]; 20 rabbits, in which bilateral destruction of the subcortical white matter was carried out, acted as controls; the blood picture for a period of 16 weeks was investigated in a further 20 rabbits in the absence of operative procedures.

The appropriate brain structures were destroyed stereotaxically through a monopolar electrode by a direct electric current of 2 mA acting for 1 min. The operation was carried out under nembutal anesthesia. Before the operation, tests were carried out on all animals to determine the erythrocyte, leukocyte, and reticulocyte counts, the blood hemoglobin concentration, and the leuko-erythroblastic ratio between bone marrow cells, in percent. After operation the same blood indices were studied every 3-4 days. Bone marrow puncture was carried out before, and on the 17th-18th and 105th-110th days after the operation.

TABLE 1. Erythropoietic Activity of Plasma of Intact, Control, and Experimental Rabbits on 15th-18th and 105th-110th Days after Operation (percentage of mitoses of erythroid series in bone marrow culture)

Group of rabbits	15-18th day					105-111th day				
	Hank's solution		Protein-free extract			Hank's solution		Protein-free extract		
	n	M±m	n	M±m	P	n	M±m	n	M±m	P
Intact	6	4,2±1,0	10	5,1±1,0	>0,05	6	4,4±1,0	10	6,0±0,7	>0,05
Control	6	5,0±1,1	12	6,8±1,1	>0,05	8	5,0±1,1	8	7,0±1,3	>0,05
Experimental	6	6,0±0,8	10	13,0±0,8	<0,001	6	5,5±0,8	10	7,5±1,1	>0,05

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TABLE 2. Rate of Incorporation of Fe^{59} into Erythrocytes of Polycythemic Recipient Mice Receiving Physiological Saline and Protein-Free Extract of Plasma of Intact and Experimental Rabbits pulses/min

Substances tested		n	M±m	P
Physiological saline		6	320.0±60.9	–
Protein-free extracts of plasma	of intact rabbits	5	339.0±59.8	> 0.05
	of experimental rabbits	5	321.0±39.3	> 0.05

The erythropoietic activity of the blood was investigated at the same times in vitro using a bone marrow culture [3, 5], and in vivo by recording the rate of incorporation of Fe^{59} into erythrocytes of polycythemic recipient mice [1]. The magnitude and location of destruction of the hypothalamic tissue were verified histologically.

EXPERIMENTAL RESULTS

After destruction of the mamillary nuclei of the hypothalamus the rabbits developed prolonged and periodic anemia, which was most severe on the 15th-18th and 100th-105th days after the operation. On the 15th-18th day the erythrocyte count fell from 5,240,000± 77,500 to 4,230,000±34,320 ($P < 0.001$), the leukocyte increased from 11,200±386 to 12,900±643 ($P < 0.05$), the reticulocyte count rose from 17.5±0.9 to 27 ±1.5‰ ($P < 0.001$), and the hemoglobin concentration fell slightly. The number of cells of erythroblastic series in the bone marrow increased from 18.5±0.5 to 30.4±2.5% ($P < 0.001$). The blood picture began to recover 22-23 days after the operation, and on the 66th day the indices studied had almost returned to their initial levels.

On the 100th-105th day after destruction of the mamillary nuclei of the hypothalamus a second wave of anemia occurred (the erythrocyte count fell to 4,150,000±219,000; $P < 0.001$), with a decrease in the relative percentage of cells of the erythroid series in the bone marrow (13.6±1.2%; $P < 0.001$), but with no significant changes in the reticulocyte count and hemoglobin concentration.

In animals subjected to bilateral destruction of the subcortical white matter, only a transient decrease in the erythrocyte count was observed on the 6th and 11th days after the operation (from 5,160,000±97,590 to 4,550,000±176,600; $P < 0.01$). No appreciable deviation of the hematological indices from the initial level was observed in the intact rabbits.

Investigation of erythropoietic activity in vitro (Table 1) showed that at the height of the first wave of neurogenic anemia the content of erythropoietins in the blood of rabbits with foci of destruction in the posterior hypothalamus was considerably higher than in control and intact rabbits. At the height of the second wave, the level of erythropoietic activity was about the same in all groups investigated.

Similar results were obtained by the study of erythropoietic activity of the blood of experimental rabbits at the height of the second wave (105th-110th day) in experiments in vivo (Table 2).

It can be concluded from the results of these experiments that following destruction of the mamillary nuclei of the hypothalamus, a marked anemia develops and follows a periodic course. The mechanism of this neurogenic anemia is highly complex: it is accompanied by characteristic changes in the composition of both the peripheral blood and bone marrow. Erythropoietins play a role in the complex chain of compensatory mechanisms.

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