ROLE OF THE KIDNEYS IN ERYTHROPOIETIN PRODUCTION

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The erythropoietic activity of blood plasma from the renal vein 24 h after anoxia was increased to a higher level than that in the blood plasma from other vessels.

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Data have been obtained by the use of various experimental models—nephrectomy [9], constriction of the renal artery [8], perfusion of the isolated kidneys [10, 11, 13] and of the kidneys in situ [3, 6, 7, 12]—which demonstrate that the kidneys are the principal site for erythropoietin production when the oxygen supply to the tissues is deficient. However, investigators have failed to discover an increase in erythropoietic activity of the blood following isolated anoxia [4] and perfusion [5] of the kidneys.

In this investigation chronic experiments were carried out to study the erythropoietic properties of blood entering and leaving the kidneys of unanesthetized dogs under normal atmospheric conditions and after anoxia.

EXPERIMENTAL METHOD

Experiments were carried out on 8 dogs. To obtain blood from the renal vein a technique was developed (V. I. Voitkevich) for implantation of a long-stay cannula into the renal vein, its other end being brought out onto the surface of the abdominal wall. Blood from the common carotid artery, preliminarily exteriorized in a skin sleeve, was obtained by puncture. The erythropoietic properties of the plasma were determined by bone marrow cultivation in a liquid medium with the addition of colchicine solution and calculation of the statmokinetic index of the erythroblasts—the number of dividing erythroblasts per thousand erythroid cells capable of division [1, 2].

To produce the anoxic form of anoxia, the dogs were placed in an air-flow chamber supplied with a gas mixture consisting of 6% O_2 and 94% N_2 at normal atmospheric pressure (CO_2 and water vapor in the chamber were absorbed by soda-lime and silica-gel). The total length of the animals' stay in the chamber was 4 h. The dogs were placed in the "anoxic" chamber from one to three times with intervals of 7-10 days between experiments.

In four dogs (7-10 days after the last stay in the "anoxic" chamber) the anemic form of anoxia was produced by repeated bleeding (2% of body weight).

The erythropoietic properties of the plasma were investigated 24 h after exposure to anoxia.

EXPERIMENTAL RESULTS

As Table 1 shows, the original mean indices for the composition of the blood erythrocytes of the dogs were slightly below the accepted normal, evidently because of the preceding surgical operations.

Plasma obtained from the dogs before exposure to anoxia exhibited erythropoietic activity when investigated in this manner, and the statmokinetic index of the erythroblasts, when the test plasma was added to the culture, was significantly higher than the control value shown in Fig. 1 by the zero line. No significant differences between the values of the erythropoietic activity of blood plasma taken from different vessels were found.

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TABLE 1. Changes in Composition of Circulating Blood of Dogs with Anoxic and Anemic Anoxia

Indices studied	Anoxic anoxia					Anemic anoxia				
	before		after			before		after		
	n	M±m	n	M±m	P	n	M±m	n	M±m	P
Hemoglobin (in g%)	10	12,2±0,1	10	13,3±0,6	<0,05	4	12,5±1,1	4	8,3±1,0	<0,05
Erythrocytes (mil/mm³)	10	4,89±0,04	10	5,49±0,35	<0,001	4	5,2±0,61	4	3,00±0,18	<0,001
Reticulocytes (in %)	10	10,2±0,8	10	10,9±1,9	>0,05	4	10,0±2,7	4	19,0±4,5	>0,05
Leukocytes (thousandths/mm³)	10	11,3±0,4	10	21,8±1,5	<0,001	4	12,5±1,2	4	20,3±3,5	>0,05

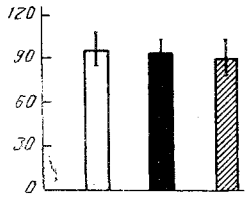

Fig. 1. Erythropoietic activity of blood plasma of dogs taken from common carotid artery (unshaded column), renal vein (black column), and a large subcutaneous vein of the hind limb (obliquely shaded column) as reflected by difference between statmokinetic indices of erythroid cells in a bone marrow culture between tested plasma and Hanks's solution. Horizontal line: statmokinetic index of erythroblasts with Hanks's solution, taken as 0. Ordinate: number of mitoses of erythroid cells. Columns indicate M ± m.

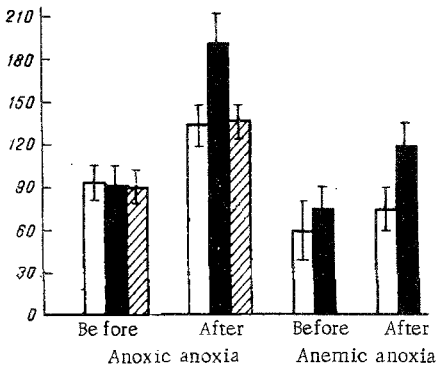

Fig. 2. Erythropoietic activity of blood plasma of dogs after exposure to anoxic and anemic anoxia. Legend as in Fig. 1.

After the dogs had been kept in the "anoxic" chamber the hemoglobin concentration and erythrocyte and leukocyte counts in the circulating blood increased, although no reticulocyte response was present, thus indicating a redistribution of the blood cells.

The erythropoietic activity of the plasma after anoxia was significantly higher in both the arterial and venous blood, the increase in erythropoietic activity being much greater in blood taken from the renal vein (Fig. 2) than in blood obtained from the common carotid artery or a large subcutaneous vein of the hind limb.

The results suggest that erythropoietin enters the blood stream in response to anoxic anoxia mainly from the kidneys.

In response to anemic anoxia (bleeding), the increase in erythropoietic activity of the blood flowing from the kidneys was not significant (Fig. 2). Only in the case of one dog, after the first and the second reading, was the erythropoietic activity in blood obtained from the renal vein higher than that from arterial blood by a statistically significant margin. It may be postulated that in the experiments with anemic anoxia the maximum of the response was missed. However, the possibility is not ruled out that the exposures to anoxia which preceded the bleeding may have modified the animals' reactivity.

Hence, using this method of investigation, no liberation of erythropoietin from the kidneys could be demonstrated under normal atmospheric conditions. Under anoxic conditions (on account of the need for increasing the oxygen capacity of the blood) the erythropoietic activity of blood flowing from the kidneys rises, indicating that it contains erythropoietin essential for the stimulation of erythropoiesis.

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