ADAPTIVE CHANGES IN THE BLOOD TO HYPOXIA OF VARIED DURATION

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During exposure to hypoxia changes directed toward increasing the oxygen capacity of the blood take place. The mechanisms of adaptation of the respiratory function of the blood to a low ambient partial pressure of oxygen are known to differ considerably in different animals. The most typical response to hypoxia is stimulation of erythropoiesis, reflected in an increase in the number of erythrocytes (E) and the hemoglobin (Hb) content per unit volume of blood. On the other hand, a study of the redblood indices in little Caucasian susliks, whose natural habitat is in the mountains (2200 m), showed that their E count and Hb concentration were significantly lower than in lowland animals [6, 7]. Investigations by the present writers [2] confirmed this fact. Meanwhile it was shown that a decrease in the E count and Hb concentration in the blood is connected with a considerable increase in the relative plasma volume in mountain animals. Since this indicated a different form of adaptation to hypoxia, it was decided to study the phenomenon in more detail and, in particular, to study correlation between the duration of exposure to hypoxia and the character of adaptive changes in the blood.

EXPERIMENTAL METHOD

Noninbred albino rats, and spotted and little susliks were studied. Before investigation of their blood the rats were adapted in a pressure chamber to hypoxia at an "altitude" of 7000 m for 1-2 months in accordance with the training program described previously [1]. The spotted susliks were progeny of animals artificially introduced from the lowlands to the region of Mt. El'brus at an altitude of 3000 m 20-25 years ago. The little susliks were natives of the mountains, having always lived at an altitude of 2200 m. Animals living in the lowlands constituted the control group.

The state of the blood was evaluated on the basis of E count, Hb concentration, and hematocrit index, determined by the usual methods. The volume of the blood and plasma was determined by Porath's method in Beloshitskii's modification [4] by injection of Evans' blue into the bloodstream. The total number of E and Hb content circulating in the bloodstream and per 100 g body weight, and the Hb content and concentration in the E were calculated. Direct morphometry of E was carried out. The state of erythropoiesis in the bone marrow was studied by the usual methods.

EXPERIMENTAL RESULTS

As a result of adaptation to hypoxia the E count and Hb content in 1 ml blood were significantly increased (Table 1). A marked increase in the total circulating blood volume took place as a result of the increase in mass of E with no change in the total volume of plasma. This response, as we know, is characteristic of laboratory animals adapted to hypoxia, of the blood of mountain dwellers, and also of the blood of persons going up into the mountains for the first time [8-11].

In spotted susliks which had lived in the mountains for 20-25 generations, adaptive changes in the blood system were of a rather different character. An increase in the E and Hb content in 1 ml blood was observed, the blood volume was increased and, correspondingly,

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TABLE 1. Some Blood Indices of Animals Adapted to Hypoxia of Varied Duration (M ± m)

Index	Rats		Susliks			
			little caucasian		spotted	
	control (n=10)	adaptation (n = 14)	lowland (n = 10)	mountains (n = 12)	control (n=21)	mountains (n = 10)
Erythrocytes:						
millions/mm³	7,24±0,16	9,54±0,3	7,11±0,15	5,48±0,11	7,25±0,14	8,53±0,14
P	<0,001		<0,001		<0,001	
millions/100 g body wt.	$6,5 \cdot 10^4$	$11,4 \cdot 10^4$	$4,6 \cdot 10^4$	$4,6 \cdot 10^4$	$5,9 \cdot 10^4$	$10,6 \cdot 10^4$
Hemoglobin:						
g%	11,2±0,25	14,4±0,27	12,9±0,25	11,6±0,20	12,2±0,24	14,1±0,24
P	<0,001		<0,01		<0,001	
g/100 g body wt.	1,0±0,028	1,72±0,14	0,83±0,04	0,97±0,09	1,01±0,04	1,75±0,08
P	<0,001		n/s		<0,001	
Hematocrit, vol.%	40,9±0,76	54,8±1,47	48,1±0,74	43,8±1,01	44,8±0,72	54,2±0,98
P	<0,001		<0,01		<0,001	
Blood volume, ml/100 g body wt.	8,98±0,22	11,9±0,51	6,47±0,27	8,37±0,44	8,3±0,32	12,38±0,31
P	<0,001		<0,002		<0,001	
Plasma volume, ml/100 g body wt.	5,32±0,17	5,37±0,16	3,38±0,16	4,71±0,31	4,52±0,18	5,69±0,13
P	n/s		<0,002		<0,001	
Volume of erythrocyte, μ^3	56,6±0,87	57,7±1,83	67,8±1,09	80,0±1,57	61,9±0,22	63,6±0,89
P	n/s		<0,001		n/s	
Hemoglobin content of erythrocytes, pg	15,5±0,25	15,1±0,24	18,2±0,41	21,4±0,39	16,8±0,25	16,6±0,18
P	n/s		<0,001		n/s	
Hemoglobin concentration in erythrocytes, pg	0,27±0,002	0,26±0,05	0,27±0,001	0,27±0,003	0,27±0,003	0,26±0,002
	n/s		n/s		0,02	

Note: n/s) Not significant.

there was an even greater increase in the E and Hb content calculated per 100 g body weight. In contrast to rats, however, the total plasma volume was significantly increased.

A parallel study of erythropoiesis in the bone marrow of rats adapted to hypoxia in a pressure chamber and in susliks introduced into the mountains showed considerable stimulation of the erythroid branch: an increase in the number of cells of the erythroid series to 40-45% (from 18-25% in the control), a decrease in the percentage of mature forms, a significant increase in the mitotic index, acceleration of maturation of the reticulocytes, and a shift to the left of the formula of their distribution.

A different form of adaptation to hypoxia was observed in the blood and bone marrow of animals native to the mountains. Lowering of the red blood indices per unit volume was found to be the result of a considerable increase in the plasma volume. The total number of E circulating in the blood, calculated per 100 g body weight, was the same as in the lowland animals. Despite the high plasma erythropoietic activity, the relative percentage of erythroid cells in the bone marrow and their mitotic index were indistinguishable in these animals from the control. Meanwhile, the relative number of young cells of the erythroid branch was significantly increased. Mitoses were found in the mature polychromatophilic normoblasts. The maturation times of the reticulocytes were shortened, but their number was the same as in the control, although the formula of distribution of the reticulocytes showed a shift to the right.

Morphometric analysis of the dimensions of E (Fig. 1) showed that the blood of the mountain susliks contained E whose main fraction (up to 75%) had a mean diameter of 7.3 μ. In the control 78% of cells had a mean diameter of 6.3 μ. This marked macrocytosis could perhaps be directly connected with the considerable increase in plasma volume which, in turn, could prevent any excessive increase in blood viscosity.

In susliks introduced into the mountains the mean E diameter also was greater than in the control, but the character of distribution of E by size differed from that in the susliks native to the mountains. Considerable heterogeneity of the cell population and the presence of an E fraction with a diameter of over 8 μ (up to 25% of the cells) were observed. The increase found in the plasma volume can also evidently be regarded as an adaptive reaction aimed at preventing excessive viscosity of the blood, although it was less well marked.

The modal class of E in the rats adapted to hypoxia was identical in value with the control, but the number of macrocytes circulating in the blood also was increased. However, de-

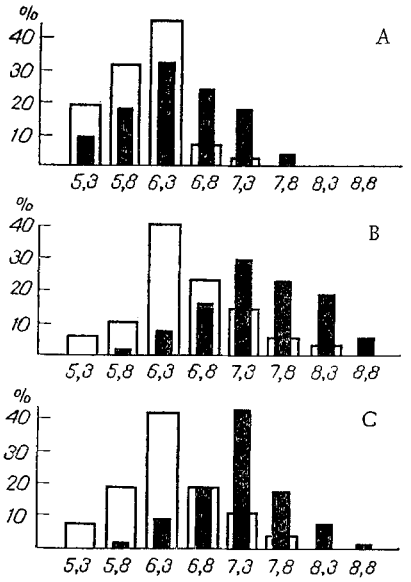

Fig. 1. Distribution of erythrocytes (by diameter) in blood of animals adapted to hypoxia of varied duration. Abscissa, diameter of erythrocyte (in μ); ordinate, number of cells (in %). Unshaded columns — control; black columns — adapted animals. A) Rats; B) spotted susliks; C) little susliks.

spite the considerable polycythemia and the presence of a number (over 40%) of large cells, no increase in the plasma volume was found.

These results suggest that during relatively short-term adaptation to hypoxia considerable, chiefly quantitative, changes take place in the bone marrow. As a result of sustained erythropoiesis, many E with increased energy-sustaining activity, whose properties in many respects are similar to the properties of neonatal E [3], appear in the bloodstream.

During long-term adaptation a genetically determined change in erythropoiesis evidently takes place, as a result of which E with different oxygen-binding properties are formed. As Table 1 shows, the Hb content in the E of the animals native to the mountains was significantly higher than in the lowland animals, whereas in rats and susliks with relatively short-term adaptation this index was the same as in the control. In this connection some interesting results were obtained by Grigor'eva [5], who studied the electrophoretic properties of Hb and the regulation of its affinity for O_2 in the same groups of animals and found clear differences in the fractional composition of Hb only in susliks native to the mountains. The 2,3-diphosphoglycerate content remained unchanged. On the other hand, during short term adaptation to hypoxia only the accumulation of 2,3-diphosphoglycerate was observed, with no change in the fractional composition of Hb.

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