QUALITATIVE CHANGES IN PARAMETERS OF ERYTHROPOIESIS IN MAN AND ANIMALS ADAPTED TO PROLONGED HYPOXIA

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Adaptation to hypoxia for three months causes qualitative changes as well as a quantitative increase in the erythropoietic function of the bone marrow. This is shown by: a gradual increase in the proliferative activity of all cells of the erythroid series, including young forms (basophilic normoblasts and erythroblasts); an increase in the intensity of DNA synthesis; a decrease in the maturation time of the reticulocytes and the mean life span of the erythrocytes in the peripheral blood. The whole life cycle of the erythrocytes is apparently speeded up from the time of their appearance in the bone marrow to their death in the peripheral blood.

KEY WORDS: erythropoiesis; hypoxia; life cycle of erythrocytes.

Qualitative changes in mature erythrocytes in the blood of animals adapted to hypoxia have been described previously [1, 2, 5]. A change in the character of erythropoiesis in the bone marrow has been put forward as a possible cause of these new properties of the erythrocytes. Experimental data confirming this hypothesis are presented below.

EXPERIMENTAL METHOD

Noninbred albino rats weighing 150–200 g were adapted to hypoxia in a pressure chamber in which the atmospheric pressure was reduced to a level corresponding to altitudes of between 2500 and 7600 m, increasing by 500 m daily [1]. Tests were carried out on the 5th, 10th, 20th, 30th, 60th, and 90th days of adaptation to hypoxia. The rats were decapitated, blood was collected, and films were prepared from the femoral marrow. The state of the erythropoietic function was determined by differential cell counts of the myeloid and erythroid series in bone marrow films stained by Pappenheim's method. The proliferative activity of the red blood cells was investigated in cultures of bone marrow tissue in a medium with added thymidine-H^3 [4]. The incubation time was 2 h. The type R emulsion (KHIMFOTO Research Institute) was used for autoradiography. Cells of the erythroid series were counted in the developed and stained films, the percentage of labeled cells was calculated, and an idea was thus obtained of the number of cells in the stage of DNA synthesis. By counting the granules in the cells (the mean index of label uptake) the intensity of DNA synthesis was estimated.

The total number of reticulocytes in the peripheral blood and their distribution among four groups (after I. A. Kassirskii) were determined. The maturation time of the reticulocytes was determined by Mosyagina's method [3] and the mean life span of the erythrocytes calculated by the formula: $T=(t\cdot 1000)/(\Delta_r \cdot 24)$ (Δ_r is the number of reticulocytes maturing in time t: 5 h for rats and 4 h for man). The human subjects studied were males aged 18–25 years, permanently resident in the lowland region of Kirghizia (the village of Groznoe, 940 m above sea level), indigenous highlanders of Kirghizia (Tyan'-Shan' moun-

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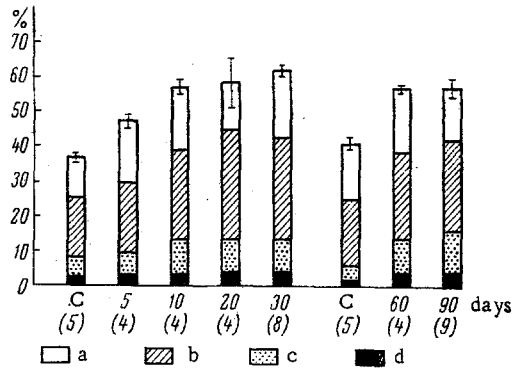

Fig. 1

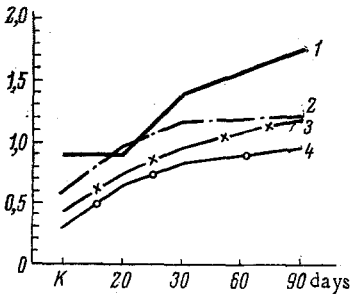

Fig. 2

Fig. 1. Erythropoietic activity of bone marrow of rats adapted to hypoxia at various times: a) oxyphilic normoblasts; b) polychromatophilic normoblasts; c) basophilic normoblasts; d) erythroblasts. Abscissa, time of adaptation to hypoxia; ordinate, number of cells of erythroid series (in percent of total number of cells in bone marrow myelogram). Here and in Figs. 2 and 3: C) control. Here and in Fig. 3: number of animals shown in parentheses. (The reason for the two control groups in this figure was that the animals were tested at different times of year.)

Fig. 2. Intensity of DNA synthesis by erythroid cells of bone marrow of rats during adaptation to hypoxia. Abscissa, duration of adaptation to hypoxia (in days); ordinate, mean index of incorporation of label into erythroblasts (1), basophilic normoblasts (2), and polychromatophilic large (3) and medium (4) normoblasts.

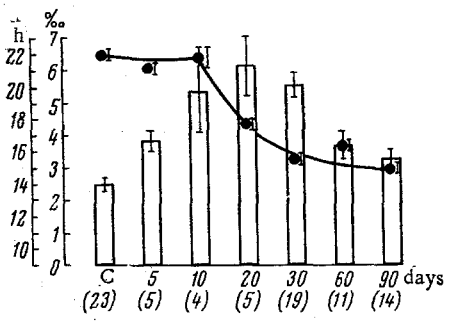

Fig. 3. Number of reticulocytes and times of their maturation in blood of rats adapted to hypoxia at different times. Columns show number of reticulocytes (in ‰); circles show times of maturation of reticulocytes (in h).

tains, the village of Kyzyl-Dzhar, 2500 m above sea level), and also a group of people born in the lowlands but resident in the village of Kyzyl-Dzhar for 2-3 years.

EXPERIMENTAL RESULTS

During adaptation to hypoxia, for 3 months a considerable erythrocytosis was observed in the peripheral blood of the rats, indicating activation of the erythropoietic function of the bone marrow. Hyperplasia of cells of the erythroid series of the bone marrow was observed from the 5th day of adaptation to hypoxia (Fig. 1) and reached a maximum after 20-30 days. The phasic changes in the erythrograms will be noted. From the 5th to the 20th-30th day of adaptation the increase in erythropoiesis took place chiefly on account of an increase in the number of the most mature cells: oxyphilic and polychromatophilic normoblasts. The number of younger cells of the erythroid series (basophilic normoblasts) increased after the 10th day and the number of the youngest cells (erythroblasts) after the 20th day. By the end of the 3rd month, erythropoiesis was accounted for chiefly by an increase in the number of the youngest cells, a feature that distinguishes the character of erythropoiesis qualitatively in rats adapted to hypoxia and normal rats. This state of medullary hematopoiesis should possibly be regarded as a stage of extreme stress of the erythropoietic function, leading to its subsequent exhaustion.

Analysis of the dynamics of DNA synthesis by cells of the erythroid series, as reflected in the number of labeled cells, showed the greatest increase in the polychromatophilic normoblasts (from 34.8 ± 4.7% in the control to 66.0 ± 4.6% on the 30th day and 78.0 ± 3.3% on the 90th day of adaptation) and a smaller increase in the basophilic normoblasts (from 47.2 ± 4.4 to 77.0 ± 4.9 and 75.5 ± 2.2% respectively). The number of labeled erythroblasts was slightly increased only toward the end of the 3rd month (from 61.8 ± 7.3 to 76.0 ± 4.3%). If the intensity of DNA synthesis was judged from the mean index of incorporation of the

label, although qualitatively the dynamics of the process remained unchanged, quantitative changes were particularly conspicuous, especially for the erythroblasts (Fig. 2). The increase in the intensity of DNA synthesis in all cells of the erythroid series suggested a more rapid maturation of these cells to the mature forms. It is logical to suppose that the change in the character of erythropoiesis led to the formation of reticulocytes and erythrocytes with different properties from the red blood cells of the control animals.

Corresponding to the dynamics of medullary erythropoiesis, phasic changes were found in the number and quality of the reticulocytes (Fig. 3). An increase in the number of reticulocytes was observed after the 5th day of adaptation. The reticulocytosis reached a maximum on the 20th-30th day. Despite a further slight decrease in the number of reticulocytes, it remained at a high level until the end of the 3rd month. A shift to the left was observed in the composition of the reticulocytes (the number of cells of group 1 was increased from 2.06 ± 0.77% in the control to 5.93 ± 1.10% on the 30th day and 6.76 ± 2.47% on the 60th day of adaptation; and the number of cells of group 2 increased from 11.16 ± 2.19 to 17.68 ± 1.14 and 17.60 ± 2.15%, respectively). This parameter returned to normal by the end of the 3rd month, but the properties of the reticulocytes were considerably modified: starting from the 20th day a decrease in the maturation time of the reticulocytes to the stage of mature erythrocytes was observed (Fig. 3).

The more rapid maturation of the reticulocytes also was observed in the human subjects at high altitudes. Just as in animals [5], residence at altitudes of 2500 m not only leads to a quantitative stimulation of erythropoiesis in man, but also to a change in its character. This change was particularly marked in the indigenous highlanders: the maturation time of the reticulocytes was almost halved (20.2 ± 1.30 h in lowlanders and 11.4 ± 0.34 h in highlanders). In persons temporarily resident at the same altitudes, the figure was 15.2 ± 1.65 h. Corresponding changes were observed in the mean life span of the red blood cells of the persons studied: 78.43 ± 7.50 days in lowlanders, 40.29 ± 5.67 days in the indigenous highlanders, and 55.12 ± 10.0 days in persons temporarily resident in the mountains. The life span of the erythrocytes in the experimental rats was reduced from 36.16 ± 3.15 to 14.89 ± 3.63 days on the 20th day, and 13.26 ± 1.62 days on the 30th day of adaptation to hypoxia.

These results indicate an acceleration of the whole life cycle of the erythrocytes – from the time of their appearance in the bone marrow to their death in the peripheral blood.

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