TISSUE SEROTONIN LEVELS IN ACUTE HYPOXIA (A DESCRIPTION OF THE PHENOMENON AND ITS POSSIBLE IMPORTANCE)

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The serotonin (5-HT) concentration in the bone marrow and kidney cortex fell immediately after hypoxia lasting 1 h, but the 5-HT blood level rose. After hypoxia for 6 h a fall in the 5-HT level also was observed in the kidney medulla, spleen, and thymus. In the posthypoxic period phasic changes in 5-HT took place. Hypoxia evidently mobilizes 5-HT and stimulates its biosynthesis. The possible role of 5-HT in the regulation of hematopoiesis at the kidney level and actually in the cells of the hematopoietic tissues is discussed.

KEY WORDS: serotonin; hypoxia; hematopoiesis.

On the basis of the marked erythropoietic effect of exogeneous serotonin (5-HT) [7, 12, 14] and the high concentrations of endogenous 5-HT in hematopoietic tissue [3, 6] the authors postulated a role of the latter in the regulation of hematopoiesis [3, 6].

To test this hypothesis it was necessary to discover whether hypoxia induces changes in the 5-HT concentration primarily in organs participating in or regulating hematopoiesis.

EXPERIMENTAL METHOD

Experiments were carried out on 62 female CBA mice aged 2-4 months. Hypoxia was produced in a pressure chamber by lowering the pressure to 230 mm Hg, equivalent to an altitude of 9 km. 5-HT was determined by the ninhydrin method [4, 5]. Statistical analysis was carried out with the aid of the Student–Fisher criterion [1].

EXPERIMENTAL RESULTS AND DISCUSSION

The results are illustrated in Fig. 1. After hypoxia for 1 h a hyperserotoninemia developed and it continued during a stay of 6 h in the pressure chamber. The persistent character of this phenomenon shows that 5-HT is constantly being mobilized from the tissue depots and entering the blood stream. Limitation of monoamine oxidase (MAO) activity by the oxygen deficiency could be a contributory factor.

It is well known that the gastrointestinal tract is almost the only source of circulating 5-HT [10, 11]. Maintenance of the normal 5-HT concentration during hypoxia in both portions of the intestine was evidently the result of parallel stimulation of its biosynthesis, to compensate for mobilization of 5-HT. This is also confirmed by the fact that during hypoxia for 6 h a significant ($P < 0.025$) decrease in 5-HT was observed in five of the six organs incapable of forming 5-HT [10, 11] (the right half of Figure 1) and it was not found in all the four organs which synthesize 5-HT (left half of Figure 1).

Hyperserotoninemia usually leads to marked 5-HT accumulation in the bone marrow, spleen, lymph glands, and thymus [6]. The development of the opposite phenomenon, a fall of the 5-HT level, during hypoxia shows that 5-HT is mobilized in the hematopoietic tissue in an intensity greater than that of the supply of 5-HT from the blood stream. The alternative explanation – activation of metabolism – seems unlikely

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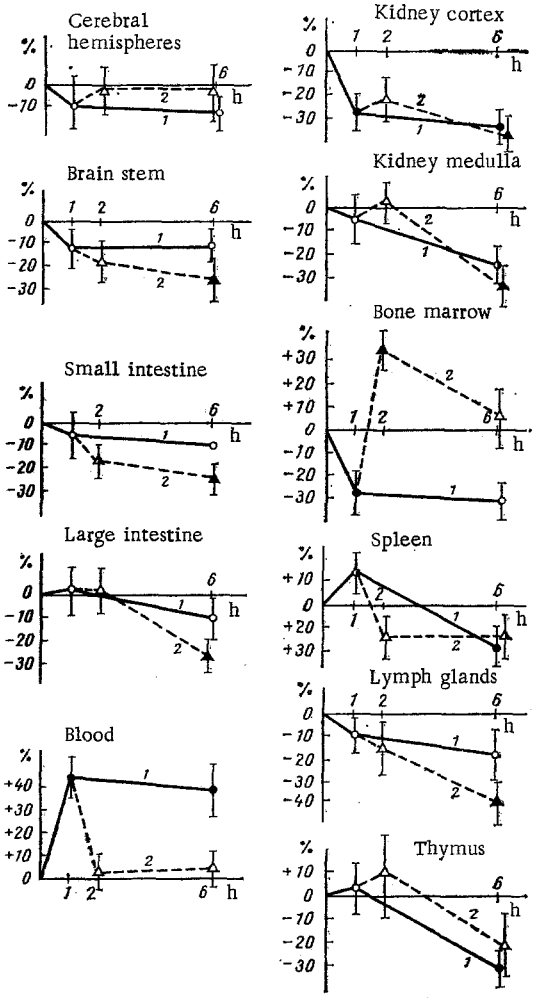

Fig. 1. Changes in tissue serotonin concentration in acute hypoxic hypoxia: 1) during hypoxia; 2) after end of hypoxia for 1 h; $P < 0.05$ for values $\geq \pm 25\%$. Abscissa, time from beginning of hypoxia (in h); ordinate, changes in 5-HT concentration (in % of control).

because MAO activity in hematopoietic tissues is low [11], and in hypoxia the activity of this enzyme must also be reduced.

After the end of hypoxia lasting 1 h the 5-HT concentration in most tissues fell gradually. The previously activated mobilization processes evidently continued into the posthypoxic period, and in most tissues they predominated over the formation and accumulation of 5-HT. On the whole, however, 5-HT mobilization in the body also fell, as shown conclusively by the rapid disappearance of the hyperserotoninemia. The temporary (1 h after hypoxia) accumulation of 5-HT in the bone marrow supports this conclusion. Mobilization of 5-HT in the bone marrow probably ceased most quickly of all, whereas accumulation still continued.

To determine the causes of the decrease in the 5-HT concentration in the tissues special investigations are necessary. A decrease in active 5-HT transport into the depots because of ATP deficiency or the liberating action of H^+ ions can naturally be suggested. However, the selectivity of this phenomenon (after hypoxia for 1 h the decrease in 5-HT took place only in the kidney cortex and bone marrow) and, in particular, its greater intensity in the posthypoxic period, when the changes in metabolism had already been corrected, rather than during hypoxia itself agrees better with a physiological mechanism of mobilization.

The results confirm the hypothesis of a possible role of endogenous 5-HT in hematopoiesis [3, 6]. The presence of early (immediately after hypoxia for 1 h) and marked changes in 5-HT in organs which actually participate in erythropoiesis (bone marrow) or its regulation (kidney) is particularly interesting from this standpoint. In the other eight organs studied the fall in the 5-HT level took place later. Its absence in the early period in the brain, small intestine, and spleen is in agreement with data in the literature [2].

The authors consider that there may be two different points of application of the action of 5-HT: at the distant regulation level and actually at the level of the hematopoietic cells. Support for the first mechanism is shown by the much earlier development of changes in the content of erythropoietin in the kidney cortex than its accumulation in the blood: Under similar conditions (267 mm Hg) such accumulation began only 1 h after hypoxia lasting 1.5 h [13]. The maximal erythropoietin concentration was reached 4.5 h [13] or, according to other data, 18-24 h after the beginning of acute hypoxia [8, 16]. Judging from the intensity of the changes in the 5-HT concentration in those tissues that may participate in the control of hematopoiesis [9] the peripheral component (kidneys) responds earlier and more strongly than the central component (the brain stem and, in particular, the cerebral hemispheres). The much earlier response of the kidney cortex than of its medulla will also be noted.

Mobilization of the endogenous 5-HT of the bone marrow and the supply of new molecules from the blood stream both play an important role in the second hypothetical mechanism. It will be noted that of the 11 tissues it was only in the bone marrow and blood that the dynamics of 5-HT during hypoxia differed clearly from those during the posthypoxic period. The action of 5-HT at both levels may be mediated by cyclic 3', 5'-AMP [3], for 5-HT increases its concentration in the kidneys [15]. The marked changes in the 5-HT concentration in the bone marrow and blood during acute hypoxia may be responsible for the increased radioresistance characteristic of that state.

Changes in 5-HT exchange between the organs can take place in widely different forms of hypoxia (for example, high-altitude sickness, blood loss, cardiovascular failure, asphyxia neonatorum) and, because of the high physiological activity of 5-HT [10, 11], this may be reflected in the functions of various systems, especially of the brain, the gastrointestinal tract, the excretory system, and the system of immunity, in all of which changes in the 5-HT concentration were demonstrated in the investigation described above.

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