ROLE OF THE THYMUS IN REGULATION OF MEDULLARY HEMATOPOIESIS DURING STRESS

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The use of clonal research methods has now proved quite conclusively that the thymus and, in particular, lymphocytes of thymic origin, are able under certain experimental conditions to exert a regulatory influence on the proliferation and differentiation of different types of hematopoietic precursor cells [6-8]. However, the problem of the role of the thymus in the regulation of medullary hematopoiesis in the intact organism, which is of fundamental importance to the solution of the problem as a whole, still remains largely unexplained. Experiments carried out by the writers previously on a model of local irradiation of bone marrow demonstrated the important role of the thymus in the regulation of hematopoiesis during exposure of an animal to extremal factors, accompanied by the development of hypoplasia of the hematopoietic tissue [2]. In the light of these data it was natural to suggest that the thymus may play an important role in the regulation of hematopoiesis also during exposure to extremal factors which have no myeloinhibitory action, i.e., which do not depress medullary hematopoiesis.

The aim of the present investigation was to study the role of the thymus in the regulation of myelopoiesis during stress induced by immobilization.

EXPERIMENTAL METHOD

Experiments were carried out on 150 hybrid (CBA × C57BL)F_1 mice weighing 18-20 g. The animals were immobilized in the supine position for 10 h. The thymus was removed from some of the mice 1 month before immobilization, or a mock thymectomy was performed. The mice were killed by cervical dislocation at different times after the beginning of immobilization. The total number of karyocytes was counted in the thymus and femoral marrow. Bone marrow films were stained and the myelogram counted. The numerical results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

In mice immobilized but not subjected to any operation marked hyperplasia of medullary hematopoiesis developed 6-8 days after the beginning of immobilization (Table 1), and it was preceded by a decrease in the number of karyocytes in the thymus down to 64.2% of its initial level on the 5th day of the experiment. This phenomenon (stimulation of hematopoiesis), it will be noted, also develops regularly under the influence of other extremal stimuli (electrical stimulation, muscular exertion, and so on) and it is accompanied by an increase in nonspecific resistance [3]. The total number of myelokaryocytes in mice not undergoing operation reached a maximum on the 7th day of the experiment (Table 1). A similar time course of the absolute number of nucleated bone marrow cells also was observed in mice immobilized after undergoing a mock operation (Table 1). Analysis of the myelograms showed that the increase in the number of cells observed in the bone marrow was due to stimulation of both erythropoiesis and granulocytopoiesis (Fig. 1).

To determine the role of the thymus in the mechanisms of development of this phenomenon experiments were carried out on thymectomized animals. They showed that hyperplasia of the

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TABLE 1. Time Course of Total Number of Myelokaryocytes in Mice Subjected to Immobilization (M ± m)

Time after immobilization, days	No operation	P	Mock operation	P	Thymectomy	P
Control (before immobilization)	19,5±1,1	—	18,3±1,1	—	20,5±1,4	—
4	19,5±0,5	>0,5	—	—	15,5±1,9	>0,05
5	19,8±1,4	>0,5	18,6±1,7	>0,5	17,3±1,4	>0,1
6	25,5±1,3	<0,01	21,5±1,0	<0,05	20,1±1,4	>0,5
7	30,2±1,4	<0,001	25,9±0,6	<0,001	18,6±1,0	>0,5
8	22,6±0,9	<0,05	23,4±1,1	<0,02	19,5±1,6	>0,5
9	—	—	—	—	16,4±0,3	<0,05

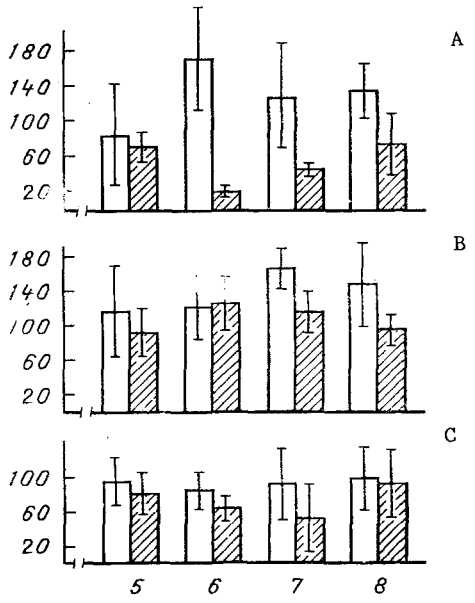

Fig. 1. Time course of number of erythroid cells (A), granulocytes (B), and lymphoid cells (C) in bone marrow of mice subjected to immobilization. Abscissa, time after irradiation (in days); ordinate, number of cells (in % of control). Unshaded columns — mice undergoing mock operation, shaded columns — thymectomized mice. Confidence intervals at P = 0.05.

bone marrow does not develop in thymectomized mice subjected to immobilization (Table 1). On the contrary, in this case marked inhibition of the erythroid branch of hematopoiesis took place. Incidentally, the times of maximal depression of erythropoiesis in thymectomized animals and of stimulation of the erythron in mice undergoing mock thymectomy coincided (Fig. 1).

The results described in this paper, like those obtained previously on a model of local irradiation of bone marrow [2, 4], are thus evidence of the important role of the thymus in the regulation of medullary erythropoiesis during exposure to extremal factors. It must be emphasized that no significant increase in the number of cells of the granulocytic branch of hematopoiesis was observed in thymectomized mice, unlike in animals undergoing the mock operation, on the 6th-8th days of the experiment, i.e., under the conditions described above, the thymus exerts its regulatory influence on granulocytopoiesis also. The mechanisms lying at the basis of the observed effects require further interpretation. It can be tentatively suggested that in immobilization stress, just as during local irradiation of hematopoietic tissue, lymphocytes of thymic origin migrate into the bone marrow and stimulate proliferation and differentiation of committed precursor cells and of more mature hematopoietic cells [1, 5].

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MECHANISM OF DEPRESSION OF THE SPINAL PAIN SYNDROME BY SEROTONIN DERIVATIVES

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Serotonin (5-hydroxytryptamine, 5-HT) is an inhibitory mediator of the supraspinal descending system [6], and when applied ionotophoretically it inhibits discharges of spinothalamic neurons of the dorsal horn [8] and causes analgesia if applied directly to the spinal cord [16]. 5-HT derivatives may be a promising series of compounds for the relief of pain, but in order to select potentially effective preparations we need to have a deeper understanding of the molecular mechanisms of serotoninergic analgesia. From this point of view there are some interesting data showing that the inhibitory effects of 5-HT on neurons, unlike excitatory effects, are mediated by receptors coupled with adenylate cyclase (ATP-pyrophosphate lyase, cyclizing, EC 4.6.1.1) [13, 15]. On the assumption that receptors of this last type are involved in the antinociceptive action of 5-HT, it was decided to compare the ability of 5-HT derivatives to stimulate adenylate cyclase in the nervous system with their action on the intensity of the spinal pain symdrome (SPS), induced by the creation of a generator of pathologically enhanced excitation (GPEE) in the lumbar segments of the spinal cord [2].

EXPERIMENTAL METHOD

An SPS was induced in rats weighing 200-250 g by applying the sodium salt of benzylpenicillin to the dorsal surface of the lumbar segments of the spinal cord. The intensity of the SPS and its depression by the preparations were assessed according to a 3-point scale [1]. An SPS with a strength of 3 points was characterized by paroxysmal attacks of very severe pain, accompanied by a cry, by motor excitation, flexion of the hind limb, and attempts to bite the skin in an area corresponding to the trigger zone [1]. The preparations were injected intraperitoneally (time of maximal manifestation of the SPS).

The effect of 5-HT derivatives on activity of serotonin-sensitive adenylate cyclase was estimated from the change in cAMP concentration in the synaptosomes, which can be regarded as

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