Monoaminergic Regulation of Hemopoiesis under Extreme Conditions

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The role of the adrenergic, dopaminergic, and serotoninergic systems in the regulation of hemopoiesis was evaluated on various models of pathological processes (restraint stress, experimental neurosis, and cytostatic treatment). The proliferation, differentiation, and maturation of polypotent, multipotent, partially determined, and oligopotent hemopoietic precursors and functional activity of microenvironmental cells (stromal cells, macrophages, and Thy1,2$^+$ cells) were shown to be under the control of a complex system of monoaminergic regulation. Central monoamines have a direct or indirect (mediated by microenvironmental cells) regulatory effect on hemopoietic precursors of various classes, which is realized via specific receptors. The system of colony-stimulating factors is characterized by selective sensitivity to catecholamines. It should be emphasized that the effects of erythropoietin are mainly associated with serotonin. Irrespective of experimental conditions (hyperplasia of hemopoiesis, myelosuppression, and dysregulation of precursor cell proliferation and differentiation), the erythroid hemopoietic stem is more sensitive to serotoninergic influences. Granulocytopoiesis was revealed to be more sensitive to central catecholamines.

Key Words: *monoamines; stem cell; committed hemopoietic precursors; hemopoiesis-inducing microenvironment; extreme conditions*

The regulation of hemopoiesis under normal and pathological conditions is an urgent problem of modern hematology. There is a general agreement on the existence of the so-called hemopoietic (hemopoiesis-inducing) microenvironment (HIM). The complex of cellular, extracellular, and humoral factors that are located close to hemopoietic cells has a function of short-range regulation of blood cells [2,5-10,20,22,23,33-35]. Microenvironmental cells (stromal cells, macrophages, and T lymphocytes) regulate the proliferation, differentiation, and maturation via components of the extracellular matrix, glycosaminoglycans, and various hemopoietic cytokines and trophic factors. The regulatory effects are also realized due to a direct contact with hemopoietic cells [2,5-10,20,22,23,33-35,58,63,67,76,80].

A large body of evidence indicates that the bone marrow parenchyma contains sympathetic, peptidergic, and other nerve endings (*e.g.*, opioidergic terminals) [36,64,71,72,78,79,82,83]. They secrete epinephrine, norepinephrine, dopamine, and tachykinins (substance P, neurokinins A and B, and compounds with opiate-like properties). Nerve endings were found on various stromal cells of the bone marrow, including sinusoid and periarterial adventitial and reticular cells [36,83]. Catecholamine receptors were identified on the plasma membrane of mature blood cells [65,66,74,75,77,84]. However, little is known about the monoaminergic biological bases of hemopoietic stem cells (HSC) and committed hemopoietic precursors in various parts of the body. Our studies of polypotent, multipotent, partially determined, and oligopotent hemopoietic pre-

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cursors were performed with neuropharmacological agents on various experimental models of pathological processes. Moreover, we evaluated the regulatory effect of monoamines on functional activity of microenvironmental cells (fibroblasts, macrophages, and Thy1,2^+ cells).

The first experiments were designed to evaluate possible involvement of the sympathetic autonomic nervous system in the development of hyperplasia of bone marrow hemopoiesis, peripheral blood leukocytosis, and reticulocytosis in CBA mice after restraint stress. During long-term immobilization of animals in the supine position (6-10 h), activation of proliferation and differentiation of granulocyte-macrophage (CFU-GM) and erythroid precursors (CFU-E) is mainly provided by high activity of the sympathetic nervous system [18,23,70]. The cells of individual hemopoietic stems were shown to be characterized by specific regulation. CFU-E and CFU-GM are more sensitive to β-adrenergic and α-adrenergic influences, respectively. The role of autonomic ganglia and peripheral adrenergic structures in adaptive reactions of the blood system was confirmed in further experiments on the models of neuroses (conflict situation and paradoxical sleep deprivation) and myelosuppressions (cytostatic treatment in various doses) [11,16,46,62,68]. Our results illustrate general biological type of these processes.

The nature of stimulating agents determines the interaction of the sympathetic nervous system with blood cells. Sympathetic activation of precursor cells for erythropoiesis and granulomonocytopoiesis in a conflict situation is similar to that observed under stress conditions. However, sympathetic stimulation during paradoxical sleep deprivation is followed by dysregulation of CFU-GM proliferation and differentiation and suppression of CFU-E division and maturation [10,11,16,17,46]. After treatment with cyclophosphamide or 5-fluorouracil, catecholamines (α- and β-adrenergic mechanisms) potentiate the damaging effect of toxic agents on CFU-GM, CFU-E, and granulocyte CFU (CFU-G). These changes increase the severity of bone marrow hyperplasia [18,26,38].

According to the modern views, hemopoiesis involves not only partially determined and oligopotent hemopoietic precursors. GSC and cells of various compartments in polypotent and multipotent hemopoietic precursors play an important role in this process [2,7,10,19]. The development of prolonged myelosuppression, leukopenia, and reticulocytopenia in the peripheral blood of CBA/CaLac mice after treatment with cyclophosphamide in a dose of 83 mg/kg was related to a significant decrease (2% of the baseline) in the number of mature precursor cells (CFU-GM, CFU-G, and CFU-E) and functional suppression of microenvironmental cells (stromal cells, macrophages, and Thy1,2^+ cells). These extreme conditions are accompanied by transition of bone marrow polypotent and granulocyte-erythroid-macrophage-megakaryocyte (multipotent) hemopoietic precursors from the G0 phase to the state of proliferation and multistage differentiation into specialized nucleated cells (CFU-GM, CFU-G, and CFU-E). Granulocyte-macrophage, granulocyte, and erythroid precursors undergo rapid maturation, which restores the cellularity of individual hemopoietic stems [26].

Apart from cytokines (IL-1, IL-3, IL-6, IL-11, Steel factor, Flt3 ligand, G-CSF, and GM-CSF), various peripheral monoaminergic mechanisms (adrenergic, dopaminergic, and serotoninergic processes) play a role in division and differentiation of primitive hemopoietic CFU [25,26,38,61]. Our experiments on the model of toxic damage to the hemopoietic tissue with cyclophosphamide showed that adrenergic influences (mainly β-adrenergic factors) and dopamine accelerate the G-CSF-induced differentiation of polypotent hemopoietic precursors into CFU-GM. The newly formed and partially determined CFU-GM differentiate into CFU-G and macrophage precursors under conditions of peripheral adrenergic stimulation (α- and β-adrenergic stimulation) [61]. These processes underlie one of the neurotransmitter mechanisms for the recovery of partially determined and oligopotent precursors that are most sensitive to the adverse effect of alkylating agents (Fig. 1).

Serotonin has the inhibitory effect on blood cells. Functional activity of primitive precursors (differentiated into the granulocytic stem) is reduced under the influence of serotonin. Moreover, serotonin treatment is accompanied by a decrease in mitotic activity of committed precursors for CFU-G and CFU-E (most sensitive to the inhibitory effect of this agent) [38,61].

Similar results were obtained in experiments with 5-fluorouracil-treated animals. It should be emphasized that mitotic activity of CFU-E in these animals is reduced not only under conditions of adrenergic stimulation, but also after treatment with serotonin and dopamine [39].

We compared the *in vitro* and *in vivo* effects of agonists and antagonists of α- and β-adrenoceptors on hemopoietic cells after cytostatic treatment. The type of the cellular response to catecholamines is shifted from positive to negative reaction with the hierarchical progression of cells from polypotent precursors to mature cells.

Monoamines have an indirect effect on hemopoietic precursors, which is mediated by microenvironmental cells. The development of cyclophosphamide-induced (cytostatic) myelosuppression is accompanied by an increase in differentiation of bone marrow mesenchymal stem cells into stromal precursors. These cells form

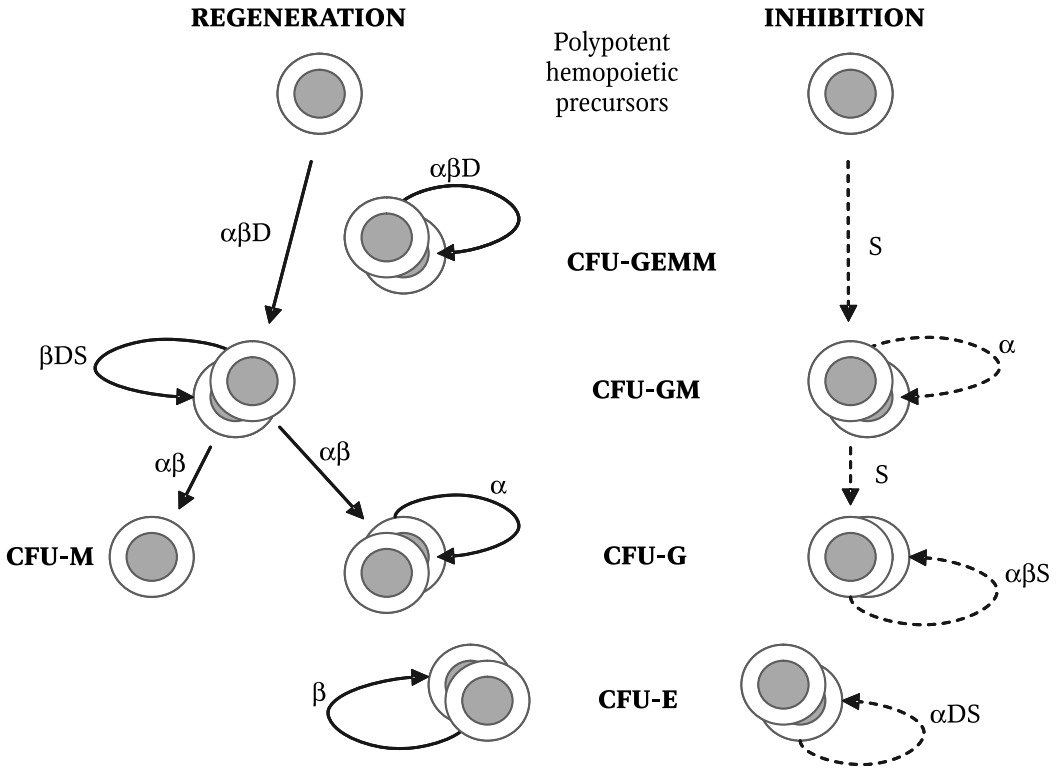

Fig. 1. Effect of peripheral monoaminergic stimulation on bone marrow hemopoietic precursors during cytostatic treatment. Solid line: stimulation; dotted line: inhibition. Here and in Figs. 2 and 3: α- and β-adrenergic stimulation, dopamine (D), serotonin (S).

hemopoietic tissue stroma essential for hemopoiesis and function of hemopoietic cells after toxic treatment [61]. Catecholamines (mainly β-adrenergic stimulation) reduce the pool of stromal cells and decrease feeder activity of these cells in relation to granulomonocytopoiesis precursors. These changes are accompanied by the inhibition of CFU-G growth, which results from the interaction of CFU-F with Thy1,2$^+$ cells. By contrast, serotonin increases the fibroblast-mediated stimulation of granulomonocytopoiesis precursors (Fig. 2).

Analysis of the erythroid stem showed that β-adrenergic and serotoninergic stimulation has a normalizing effect on activation of CFU-E by macrophages, which is suppressed by the alkylating agent.

Extracellular matrix components play a role in the mechanisms of action of monoamines on blood cells. Cell culture studies showed that the isoprenaline-induced and serotonin-induced recovery of binding capacities of macrophages for erythroid precursors was abolished by alkylating agent, but increased in the presence of N-acetylneuraminic acid (glycosaminoglycan component) [38]. The potentiating effect of sialic acid is associated with the fact that this agent provides high concentration of hemopoietic growth factors and monoamines in the area adjacent to hemopoietic precursors and mononuclear phagocytes. Moreover, sialic acid increases affinity of these cells for specific receptors (Fig. 2).

In the next series we studied the role of central monoaminergic structures in regulation of hemopoietic compartments under conditions of experimental neuroses (conflict situation [3,4,43,45] and paradoxical sleep deprivation [37,73]). These experimental models were selected due to the fact that the pathogenesis of neurosis involves various neurotransmitter systems. Moreover, our studies revealed an unexpected response of the blood system. Conflict situation and immobilization stress were followed by similar stimulation of the bone marrow erythropoiesis and granulomonocytopoiesis. By contrast, sleep disorders were shown to cause suppression of the erythron and abortive hyperplasia of the granulocytic hemopoietic stem [15,24,30-32,42,44,47,57]. Experiments with neuropharmacological agents of the central action (sympatholytic, neuroleptic, and antiserotonin products) showed that plastic reconstruction of the blood system during neuroses is regulated by the adrenergic, dopaminergic, and serotoninergic systems [10,12,13,24,29,42,48,49,52,54,56,59,60]. The intensity of bone marrow erythropoiesis is mainly associated with serotoninergic regulation. However, variations in the number of granulocytes in the bone marrow and peripheral blood depend on activity of central catecholamines.

It was interesting to evaluate the mechanisms of interaction between central catecholamines and hemopoietic cells. Under neurotic conditions the transduc-

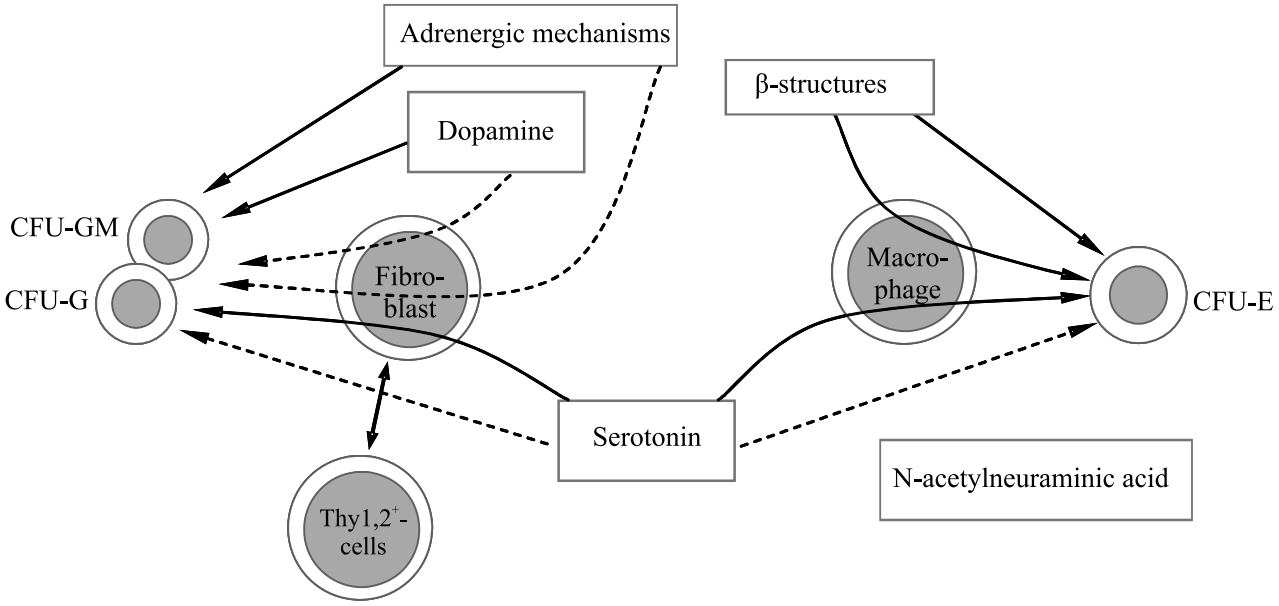

Fig. 2. Peripheral monoaminergic regulation of hemopoietic activity of stromal cells and macrophages in the bone marrow during cytostatic treatment. Solid line: stimulation; dotted line: inhibition.

tion of instructive information from central parts of the adrenergic system to CFU-GM and CFU-E is realized not only via α- and β-receptors (direct pathway), but also via adrenergic receptors on microenvironmental cells (indirect pathway) [11,12,121].

Apart from general features, we revealed the existence of model-specific characteristics for monoaminergic regulation of hemopoiesis. In a conflict situation, high concentration of norepinephrine and "positive" effect of the serotoninergic system in regulatory "contours" of the erythroid and granulocytic stem induce the formation of an active microenvironment, stimulation of the division and maturation of committed hemopoietic precursors, and hyperplasia of hemopoiesis [10-12,17,21]. During paradoxical sleep deprivation, the inhibition of adrenergic mechanisms (deficiency of the central neurotransmitter and suppression of the sympathetic nervous system) plays a major role in the reduction of CFU-E proliferation and differentiation, decrease in the concentration of serum erythropoietin, dysfunction of T lymphocytes and macrophages, and dysregulation of hemopoiesis. Central dopamine and serotonin also contribute to a decrease in the number of morphologically distinguishable nucleated cells in the blood system.

The dependence of hemopoiesis on central adrenergic, dopaminergic, and serotoninergic structures was confirmed on the models of cytostatic-induced myelosuppressions after treatment with cyclophosphamide and 5-fluorouracil [28,38,40,50,53,55]. Similarly to experimental neuroses, the regulatory effect of central monoamines is realized via specific receptors on primitive and mature hemopoietic precursors or mediated by functional changes in microenvironmental cells. Regeneration of the erythron is mainly related to serotonin (formation of erythroid cell complexes, secretion of erythropoietic activity by adherent microenvironmental cells, and differentiation of CFU-E). Central catecholamines play a greater role in white blood cell recovery (formation of granulocytic hemopoietic islets, secretion of colony-stimulating activity by adherent microenvironmental cells, proliferation and differentiation of CFU-GM, and maturation of CFU-G; Fig. 3). It should be emphasized that the cytokine system is characterized by a specific regulation. The effects of erythropoietin are mainly associated with serotoninergic structures. By contrasted, the influence of G-CSF is mediated by adrenergic and dopaminergic mechanisms [14,27,51].

Apart from general features of long-range regulation of hemopoiesis, we revealed model-specific differences in cytostatic-induced myelosuppressions. For example, catecholamines (primarily adrenergic mechanisms) potentiate the toxic effect of an alkylating agent on the blood system [28,38,53]. It results in impaired formation of granulocytic hemopoietic islets and reduced production of erythropoietic activity by adherent microenvironmental cells. These changes are accompanied by a decrease in the number of proliferating granulocytopoietic precursors (mediated mainly by peripheral and central adrenergic structures and G-CSF-associated mechanisms). It should be noted that the cooperation of stromal cells and T lymphocytes under conditions of adrenergic stimulation practically did not differ from normal. The inhibitory influence of the dopaminergic system on erythropoiesis is manifested

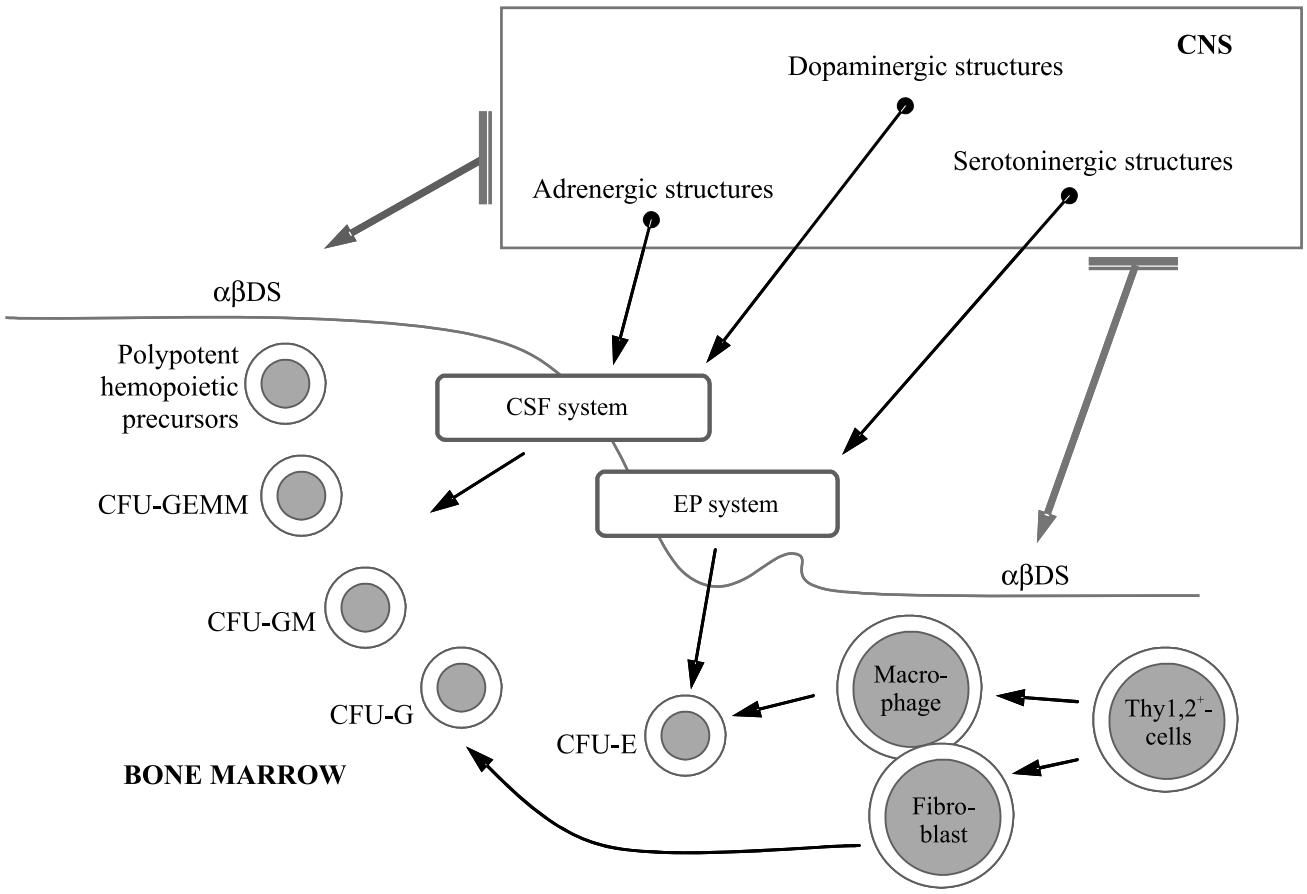

Fig. 3. Central monoaminergic regulation of hemopoietic precursor cells during cytostatic treatment. EP: erythropoietin.

in functional suppression of microenvironmental cells and erythropoietin system [38-40]. Central serotonin delays the recovery of erythroid cell complexes and activity of erythroid precursors (*i.e.*, erythropoietin-associated mechanisms).

As differentiated from the alkylating agent, central catecholamines counteract the damaging effect of antimetabolites on adherent microenvironmental cells, increase the production of erythropoietic activity by nonadherent cells, and normalize the function of CSF and erythropoietin [28,38,53]. Peripheral adrenergic mechanisms play an important role in activation of hemopoiesis regeneration. High rate of CFU-E division and maturation is provided by β-adrenergic structures. Activity of CFU-GM and CFU-G is associated with α- and β-receptors. On the one hand, under these conditions the dopaminergic system causes erythropoietin-dependent activation of CFU-E proliferation. On the other hand, this system decreases secretion of colony-stimulating activity by stromal cells [39,50]. Central serotonin has various effects on hemopoiesis. Serotonin aggravates the suppression of erythropoiesis, which is related to the impaired production of erythropoiesis-stimulating activity by microenvironmental cells and decrease in serum erythropoietin concentration [40,55]. This amine prevents the destruction of granulocytic hemopoietic islets and accelerates the CSF-mediated division and differentiation of CFU-GM.

These results of experimental studies are of considerable importance for basic and applied sciences. Nonspecific stimulators of the blood system (zymosan, splenin, vitamins C, B_1, and B_6, Siberian ginseng extract, hormones, and lithium salts) were ineffective in various dysfunctions of hemopoiesis. The products of recombinant cytokines (G-CSF, GM-CSF, erythropoietin, and thrombopoietin) are used instead of these agents [10,41]. The directed effect of growth factors on hemopoietic cells determines high activity of these agents and development of differentiated approaches to the therapy of cytostatic-induced myelosuppressions. However, blood-stimulating agents (*e.g.*, G-CSF and erythropoietin) can produce the undesirable effects (musculoskeletal pain, arthralgia, allergic reactions, *etc*.) [1,69,81]. Short-term treatment with cytokine products is low effective, while prolonged administration of these agents has some complications.

Experiments on the model of cytostatic-induced myelosuppression showed that the sympatholytic agent potentiates the stimulating effect of G-CSF on

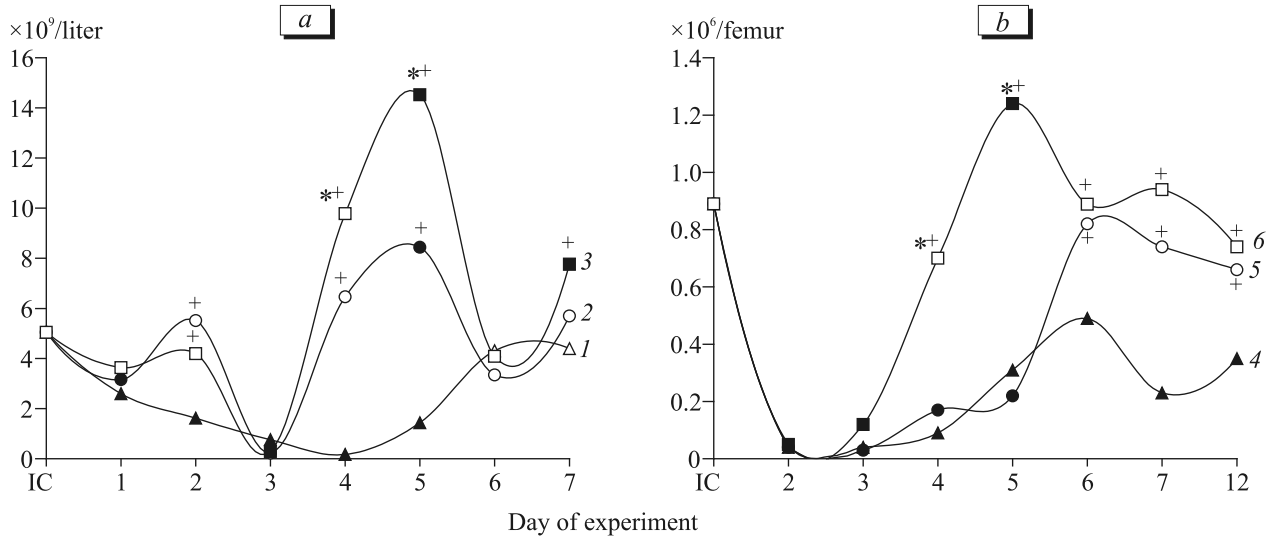

Fig. 4. Effect of a sympatholytic agent on granulocytopoiesis-stimulating activity of G-CSF after treatment with cyclophosphamide (*a*). Effect of antiserotonin agent on erythropoiesis-stimulating activity of erythropoietin after treatment with 5-fluorouracil (*b*). Cyclophosphamide (*1*); administration of G-CSF after treatment with cyclophosphamide (*2*); administration of a sympatholytic agent and G-CSF after treatment with cyclophosphamide (*3*); 5-fluorouracil (*4*); administration of erythropoietin after treatment with 5-fluorouracil (*5*); administration of an antiserotonin agent and erythropoietin after treatment with 5-fluorouracil (*6*). Ordinate: (*a*) number of peripheral blood neutrophilic leukocytes; (*b*) number of bone marrow erythrokaryocytes. IC, intact control. $p<0.05$: compared to IC (dark symbols); +compared to cytostatic-treated animals; *compared to animals receiving G-CSF or erythropoietin.

granulocytopoiesis. Antiserotonin agent potentiates the stimulation of erythropoiesis by erythropoietin (Fig. 4). Central neuropharmacological agents that protect the hemopoietic tissue (*e.g.*, precursor cells) from the toxic effect of cytostatics should be used in combination with hemopoietin products for the therapy of cytostatic-induced suppression of the blood system [14,27,51].

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