GENERAL PATHOLOGY AND PATHOPHYSIOLOGY

Role of the Central Nervous System in Hemopoiesis Regulation during Experimental Neuroses

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Pharmacological blockade of dopamine- and serotoninergic structures with haloperidol and cyproheptadine, respectively, attenuated hyperplasia of the bone marrow granulocytopoiesis and erythropoiesis (cyproheptadine) caused by conflict situation. At the same time, haloperidol and, especially, cyproheptadine normalized erythropoiesis and modulated granulocytopoiesis under conditions of paradoxical sleep deprivation. These results indicate that central regulation of hemopoietic stems is mediated by different neurotransmitter mechanisms. Erythropoiesis depends on the state of serotoninergic structures, while granulocytopoiesis is regulated both by the dopamine- and serotoninergic systems.

Key Words: *experimental neuroses; granulomonocytopoiesis; erythropoiesis; haloperidol; cyproheptadine*

Our previous studies showed that changes in activity of the adrenergic system contribute to pronounced blood reactions during experimental neuroses [3,9,10]. Central adrenergic structures regulate hemopoiesis via adrenoceptors on hemopoietic cells and committed precursors of myelopoiesis [3,9]. Changes in the production of local humoral factors, proliferation, and differentiation of hemopoietic precursors [2,9,10], affect the cellularity of the erythroid and granulomonocytic hemopoietic stems [5,6]. The central mechanisms of hemopoiesis regulation are probably realized not only via the adrenergic system. Disorders of the higher nervous activity and somatic manifestations of emotional stress are related to dopamine and serotonin [9].

Here we studied the role of dopamine- and serotoninergic structures in adaptive reactions of the blood system to conflict situation (CS) and paradoxical sleep deprivation (PSD).

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MATERIALS AND METHODS

Experiments were performed on 320 CBA/CaLac mice aging 2-2.5 months (collection of the Laboratory of Experimental Biological Modeling, Institute of Pharmacology, Tomsk Research Center). CS [7] and PSD [14] served as the models of experimental neuroses. To modulate blood changes, the animals were injected with serotonin and dopamine receptor antagonists, cyproheptadine (30 μg/kg, Serva) and haloperidol (3 mg/kg, Gedeon Richter A. O.), respectively, 20 min before and 5 h after the start of the experiments [8]. Control mice received an equivalent volume of isotonic NaCl. On days 1-7, peripheral blood segmented neutrophils and reticulocytes were counted. After blood tests, the animals were euthanized by cervical dislocation, and the contents of immature and mature neutrophilic granulocytes, erythrokaryocytes, and committed precur-

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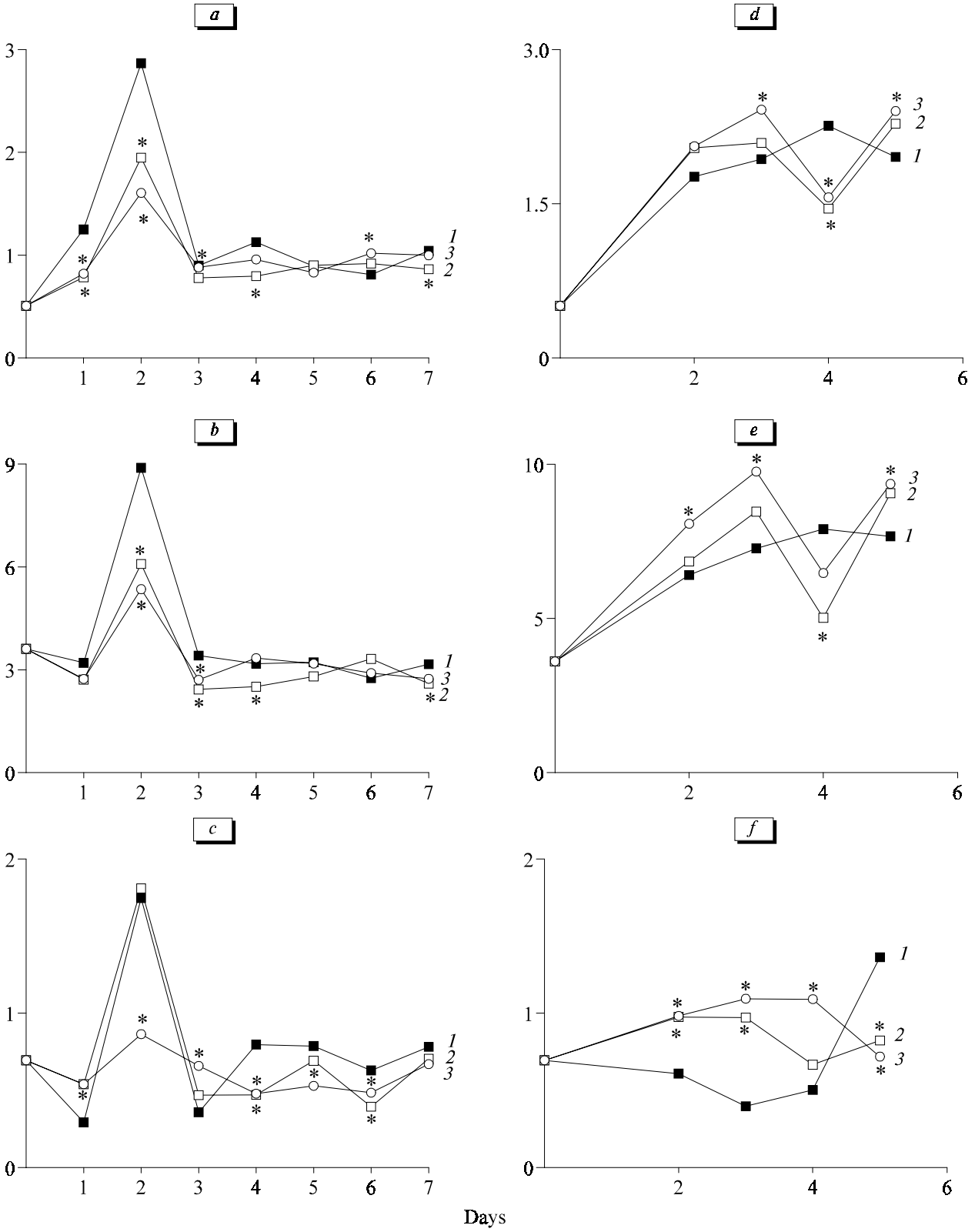

Fig. 1. Contents of immature (*a*, *d*) and mature (*b*, *e*) neutrophilic granulocytes and erythrokaryocytes (*c*, *f*) in the bone marrow of CBA/CaLac mice in conflict situation (*a-c*) and after paradoxical sleep deprivation (*d-f*): NaCl (control), haloperidol (*2*), and cyproheptadine (*3*). *$p<0.05$ compared to the control. Ordinate: number of bone marrow cells, 10^6 myelokariocytes per femur.

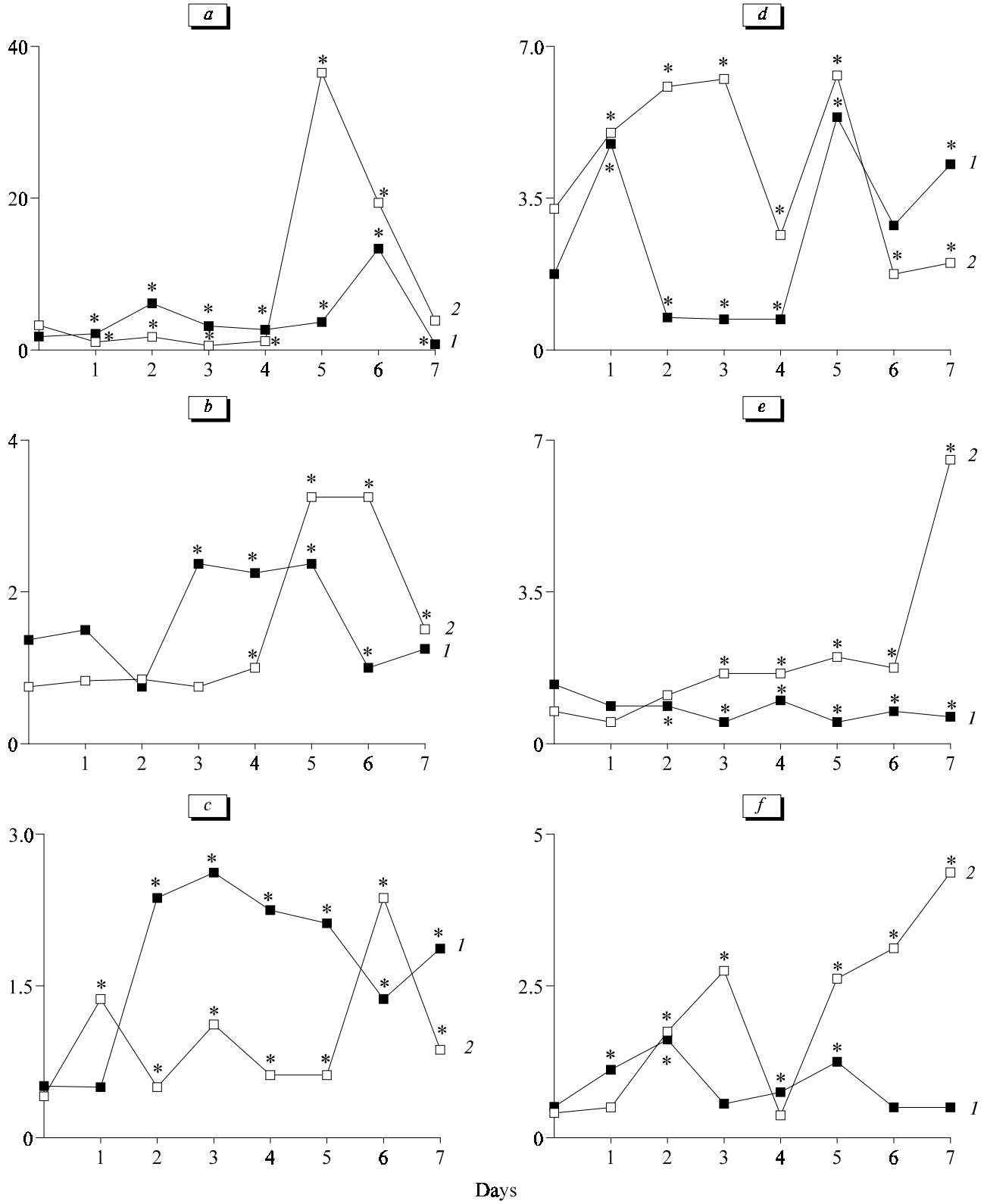

Fig. 2. Parameters of erythropoiesis in conflict situation (*a-b*) and after paradoxical sleep deprivation (*d-f*): content of erythroid (*1*) and granulomonocytic (*2*) precursors (*a*, *d*); erythropoietic activity (*b*, *e*); colony-stimulating activity of conditioned media containing adherent (*1*) and nonadherent (*2*) myelokaryocytes (*c*, *f*). *$p<0.05$ compared to the control. Ordinate: number of precursor cells, 10^5 myelokariocytes.

sors of granulomonocyto- (CFU-GM) and erythropoiesis (CFU-E) in the bone marrow were estimated. Colony-stimulating (CSA) and erythropoietic activities of conditioned media containing adherent and nonadherent myelokaryocytes were measured [1]. The results were analyzed by standard methods of variational statistics. The significance of differences was evaluated by Student's *t* test and Wilcoxon nonparametric rank test.

RESULTS

CS increased the count of immature (days 1, 2, and 4) and mature (day 2) neutrophilic granulocytes and erythrokaryocytes (days 1, 4, and 5) in the bone marrow (Fig. 1) and caused neutrophilic leukocytosis (days 3-7) and reticulocytosis in the peripheral blood (days 3-6). These changes attested to an increase in the number of CFU-E (days 2-6) and CFU-GM (days 5-6) in the hemopoietic tissue and high activity of humoral regulators of erythro- and granulomonocytopoiesis produced by adherent and nonadherent myelokaryocytes (Fig. 2).

PSD increased the count of CFU-GM (days 1, 2, 3, and 5), bone marrow immature and mature neutrophilic granulocytes, peripheral blood segmented neutrophils (Fig. 1), and CSA of adherent and nonadherent myelokaryocytes (Fig. 2). At the same time, PSD produced other reactions of the erythroid hemopoietic stem. Suppressed production of local erythropoiesis regulators by adherent nuclears (days 1-7) was accompanied by inhibition of CFU-E growth (days 2-4, Fig. 2), which decreased the count of erythroid elements in the bone marrow (days 2-4) and peripheral blood (days 2-3, Fig. 1). Secretion of erythropoietic activity by nonadherent myelokaryocytes increased on days 2-7.

Thus, changes in functional activity of the hemopoietic microenvironment regulated by central neuroendocrine mechanisms underlie the stimulation or inhibition of hemopoietic stems during experimental neuroses [3,8,9]. We evaluated the contribution of serotonin- and dopaminergic structures into hemopoiesis regulation during experimental neuroses.

Haloperidol and cyproheptadine decreased the count of immature and mature neutrophilic granulocytes in the bone marrow during CS. The content of erythrokaryocytes more drastically decreased after blockade of serotoninergic structures (Fig. 1). During PSD, these agents, especially cyproheptadine, normalized erythropoiesis and modulated activated granulocytopoiesis (Fig. 1).

These results indicate that central regulation of hemopoietic stems is realized via different neurotransmitter mechanisms. Erythropoiesis depends on the state of serotoninergic structures, while granulocytopoiesis is regulated both by the dopamine- and serotoninergic systems.

Our previous studies showed that pharmacological blockade of α- and β-adrenoceptors abolishes hyperplasia of erythropoietic stem in CS, its inhibition after PSD [2], and hyperplasia of granulomonocytopoietic stem [9]. Exhaustion of catecholamine stores caused by reserpine produces similar changes; the only exception was more pronounced inhibition of erythrokaryocyte proliferation and differentiation during PSD. These data indicate coregulation of hemopoiesis by various neurotransmitter systems. Changes in erythro- and granulomonocytopoiesis depend on activity of two neurotransmitter systems, but not on the model of experimental neurosis. Granulomonocytopoiesis is regulated by dopamine, catecholamines, and to a lesser extent by catecholamines, while the regulation of erythropoiesis is mediated by serotonin and catecholamines. It should be emphasized that if the adrenergic system transfers the information via adrenoceptors on hemopoietic cells and committed precursors [3,9], serotonin and dopamine modulate activity of adrenergic structures. At the same time, these biogenic amines are not the only neurotransmitters involved in these processes. In our previous experiments, cholinolytic scopolamine normalized erythropoiesis, but did not modulate granulocytopoiesis during experimental neuroses [2]. It should be noted that activation of the adrenergic system in PSD is preceded by activation of the cholinergic system [11]. Moreover, the very early disturbances in higher nervous activity during CS are associated with acetylcholine [12,13]. Thus, the cholinergic system probably triggers the formation of specific properties and plastic reconstruction of neuronal metabolism.

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