GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

The Response of Granulocyte Precursors to Experimental Neurotic Stimuli

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Immobilization stress and experimental neurosis caused by conflict situation, deprivation of REM sleep, or their combination caused hyperplasia of the granulocytic stem in the bone marrow. Pronounced changes in hemopoietic tissue resulted from increased secretion of hemopoesin-producing cells of the microenvironment.

Key Words: *neurotic stimuli; granulocytopoiesis; hemopoesin-inducing microenvironment*

Different responses of the erythroid stem to different neurotic stimuli [5] are controlled by hemopoesin-inducing microenvironment (HIM). Psychoemotional tension is one of the major causes of stress-related diseases [8]. It was demonstrated that leukocytes play an important role in the maintenance of homeostasis during the development of these diseases.

Our objective was to study the reactions of the granulocyte-monocyte precursor cells to experimental neurotic stimuli in comparison with immobilization stress.

MATERIALS AND METHODS

Experiments were performed on 574 CBA/CaLac mice aged 2-2.5 months. The mice were obtained from Tomsk Research Center for Biomedical Modeling. Stress was modeled by immobilization in supine position [4], conflict situation [6], deprivation of REM sleep [9], and combination of conflict situation and REM sleep deprivation. The segmented neutrophil count in peripheral blood was determined 1-7 days after the stress. The mice were then killed by cervical dislocation, and the contents of CFU-GM, immature and mature neutrophils in the bone marrow, and colony-stimulating activity (CSA) of culture medium conditional by adherent and nonadherent myelokaryocytes [2] were determined. The results were analyzed by the standard methods of variational statistic. The significance of differences was evaluated by Student's test for pairs and groups, nonparametric Wilcoxon test, and two-dimensional correlation analysis.

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RESULTS

Pronounced changes in peripheral blood and bone marrow were observed in all stressed mice. Immobilization stress activated the formation of granulocytes and monocytes. The number of CFU-GM (days 5-6), mature (day 6) and immature (days 1-3 and 6-7) neutrophils in the bone marrow increased simultaneously with peripheral blood neutrophilia (days 2-5 and 7) (Fig. 1). Colony-stimulating activity of conditional media from adherent and nonadherent myelokaryocytes (Fig. 2) increased. These shifts are due to activation of the hypophysial-adrenal system and autonomic nervous systems during stress, which changes the proliferation and differentiation status of committed myelopoietic cells via stimulation of HIM. These changes manifest them-

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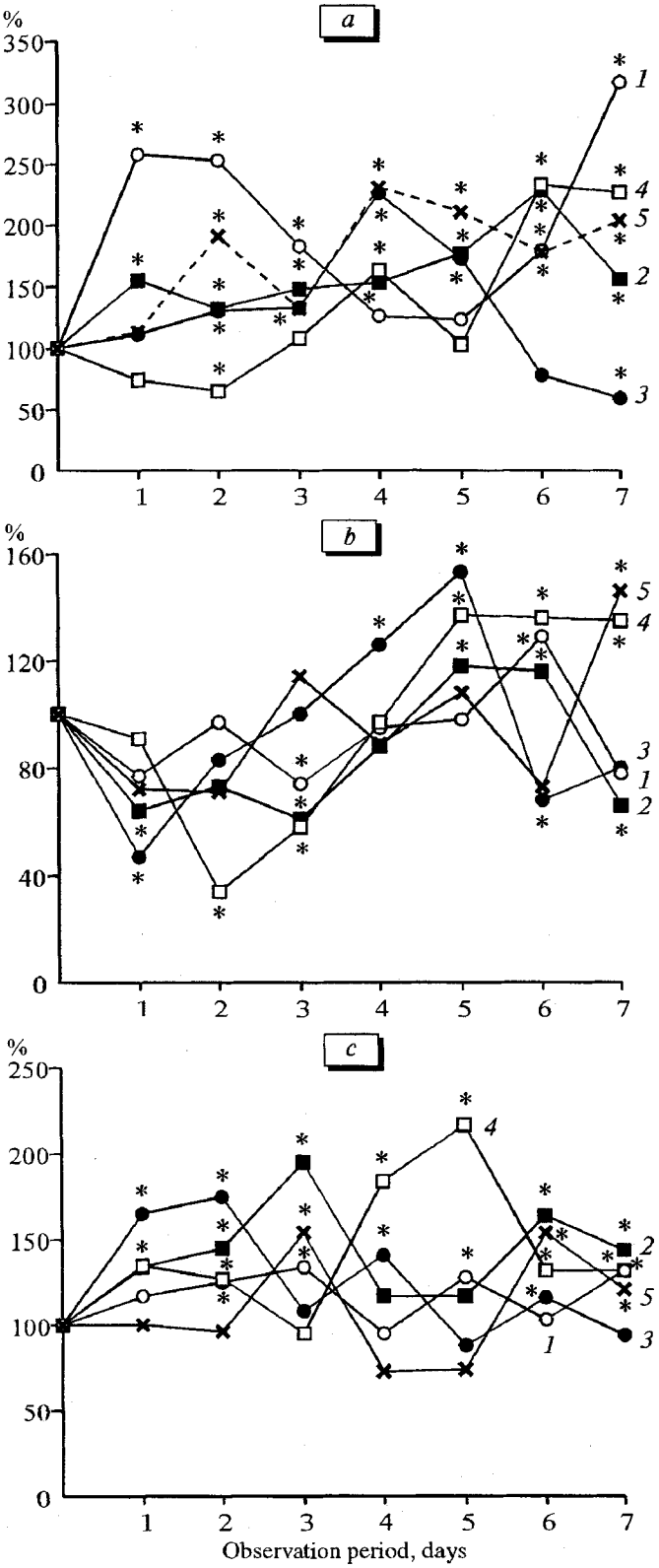

Fig. 1. Changes in the contents of immature (*a*) and mature (*b*) granulocytes in the bone marrow and the segmented neutrophil count (*c*) in peripheral blood of CBA mice. Ordinate: cell content, %. Here and in Fig. 2: *1*) immobilization stress, *2*) conflict situation, *3*) deprivation of REM sleep (DRS), *4*) conflict after DRS, *5*) DRS after conflict. *$p<0.05$ compared with the background level (100%).

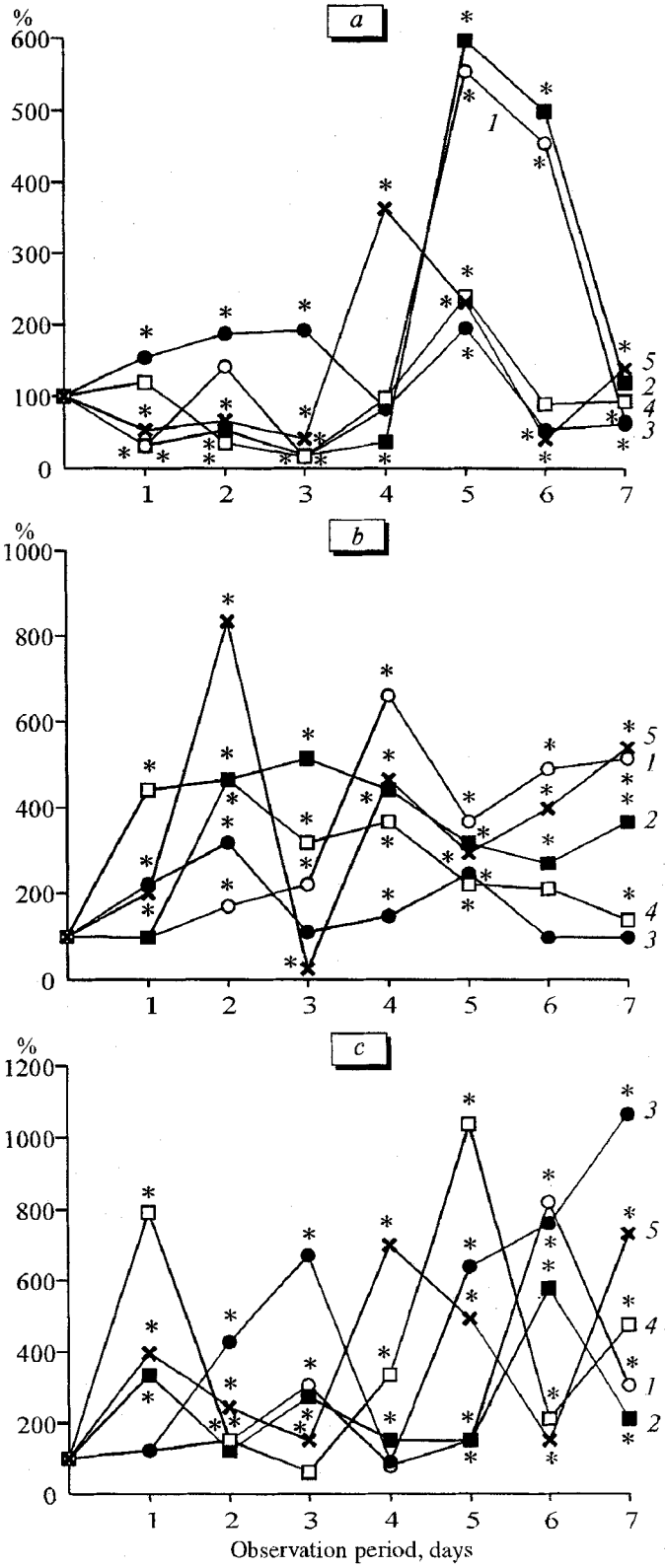

Fig. 2. Changes in the content of CFU-GM (*a*), CSA of culture media conditional by adherent (*b*) and nonadherent (*c*) bone marrow cells. Ordinate: CFU-GM content, %.

selves in hyperplasia of bone marrow tissue and increased number of specialized blood cells [1].

As a result of the conflict situation, the number of immature (1-7th day) and mature (5-6th day) neutrophils in bone marrow increased in parallel with the development of neutrophilia (days 2-3 and 6-7) in peripheral blood. An increase in the CFU-GM content was observed on the 5-6th days after a tendency toward a decrease (from the 1st till the 4th day). The time course of changes in CSA of conditional media from both fractions of karyocytes repeated that of the CFU-GM content. Thus, conflict situation led to activation of the granulocyte-monocyte stem cells. The differences in the hemopoiesis alterations caused by conflict situation and immobilization stress were quantitative rather than qualitative.

In mice deprived of REM sleep, the number of immature and mature granulocytes (days 4-5 and 1-6, respectively) in the bone marrow increased, which led to neutrophilia. These changes were associated with the rise in the number of CFU-GM (1-3rd and 5th days) and high CSA of adherent (days 1-2 and 4-5) and nonadherent (days 2-3, 5, and 7) bone marrow cells. These findings point to the activation of granulocyte and monocyte formation in the bone marrow.

The myelopoietic response to the combination of conflict situation with deprivation of REM sleep similar to that caused by deprivation of REM sleep. Neutrophilia in peripheral blood (days 1-2 and 4-7) developed against the background of increased number of immature (days 4 and 6) and mature (days 5-7) neutrophilic granulocyte in the bone marrow. The number of CFU-GM increased considerably (day 5) after its reduction (days 2-3). The CSA of culture media conditioned by adherent (days 1-5 and 7) and nonadherent (days 1-2 and 4-7) HIM cells increased, which indicated stimulation of granulocyte and monocyte formation.

Conflict situation and deprivation of REM sleep stimulated hemopoiesis, as evidenced by increased contents of granulocyte-monocyte precursors of all types: immature (days 2-7), mature (day 7), and neutrophil granulocyte (days 6-7) and the monocytic series cells (days 1-7t). The number of segmented neutrophils (days 3 and 6-7) in peripheral blood increased. The increase in CSA activity of culture media conditioned by bone marrow cells was observed on the 4-5th and 7th days of the experiment. Pronounced changes in hemopoietic tissue were associated with increased functional activity of HIM.

Thus, proliferation and differentiation of CFU-GM are activated in response to experimental neurotic stimuli of different nature. The control over the activity of hemopoietic cells under these conditions is probably realized by the HIM cells [1]. The data on the changes in the adrenergic system activity in the emotiongenic brain structures [3,8] and the involvement of the bone marrow adrenal receptors in the transmission of information from the upper regulatory centers [7] in emotional stress suggest that specific reorganization of neurochemical properties and plastic reorganization of the catecholamine metabolism are the major mechanisms responsible for the regulation of hemopoiesis.

REFERENCES

1. E. D. Gol'dberg, A. M. Dygai, and I. A. Chlusov, *Role of the Autonomic Nervous System in the Regulation of Hemapoiesis*, [in Russian], Tomsk (1997).
2. E. D. Gol'dberg, A. M. Dygai, and V. P. Shakhov, *Methods of Culture and Tissues in Hematology*, [in Russian], Tomsk (1992).
3. L.V. Devoino and R.Yu. Il'yutchenok, *Neurotransmitter Systems in Psychoneuroimmunomodulation*, [in Russian], Novosibirsk (1993).
4. A.M. Dygai and N.A. Klimenko, *Inflammation and Hemapoiesis*, [in Russian], Tomsk (1992).
5. A.M. Dygai, N.I. Suslov, E.G. Skurikhin *et al.*, Byull. Eksp. Biol. Med., **123**, No. 2, 158-161 (1997).
6. T.A. Kligul' and V.A. Krivopalov, *Pharmacol. Toksicol.*, No. 2, 241-244 (1966).
7. E.G. Skurikhin and N.V. Provalova, in: *Modern Problems of Pharmacology and the Search for New Drugs*, Ed. E.D. Gol'dberg, [in Russian], Vol. 9, 105-107 (1997).
8. *Emotional Stress: Theoretical and Clinical Aspects* [in Russian], Pril. Vestn. Volgograd. Med. Akad., Eds: K.V. Sudakov, V.I. Petrov, **53**, No. 3 (1997).
9. M. Thakkar and B.N. Mallick, *Sleep*, **16**, No. 8, 691-694 (1993).