

EFFECT OF RESERPINE ON ERYTHROPOIETIN CONSUMPTION IN WHITE RATS

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Vegetative system studies in modern erythropoiesis research are very scanty. Many of the valuable in terms of physiological action pharmaceuticals, enabling the performing of a thorough and accurate analysis, are insufficiently investigated. The role played by the adrenergic mediator unit in erythropoietin consumption by bone marrow is by no means studied. The data concerning the influence of the sympathetic nervous system on erythropoiesis are conflicting. Some of the authors find inhibition of erythropoiesis after operative sympathectomy (3, 8, 14), whereas others establish enhanced erythropoiesis and increased number of erythropoietins (4, 15). A third group of authors claim that there are no changes whatsoever (1, 12). Incomplete operative sympathectomy is a common shortcoming of all the research studies cited above.

Reserpine reduces catecholamine content in a number of tissues and in the adrenergic neurons by blocking their deposit in the amine granules. Under the influence of background impulsion, the axonal norepinephrine depot, responsible for adrenergic mediation, is also depleted. All this results in a strong inhibition of the adrenergic transmission of impulses, i. e. in a post-reserpine blocking within the adrenergic neuroreflectory synapses (6, 10, 11, 13). The «chemical sympathectomy» produced is accomplished at axonal level, and represents a feasible model for studying the influence exerted by the axonal linkage of the adrenergic mediator unit on erythropoietin effect. The fact that epinephrine sensitive fibers are present within the bone marrow (9), as well as the considerations referred to above, have served as a basis for undertaking a study on the post-reserpine adrenergic block effect upon the exogenous erythropoietin action.

Material and Method

The experiments were conducted on 47 white Wistar rats, divided up in two groups: donors — 27, and recipients — 20. Plasma, rich in erythropoietin, was obtained from the donors within 20 hours of blood letting in quantity 1.5 ml/100 g body weight. Furthermore, the animals-recipients, after starvation for 72 hours, were divided into two subgroups: an experimental group of 10 rats, treated with 3 mg/kg weight Serpasil «CIBA», daily i. m. injections over a period of 6 days. Erythropoietic plasma (2 ml) from the donors was injected two times — at 3 and 4 days from the beginning of the experiment. The control group (ten rats) were

injected with the same quantity physiologic saline solution and erythropoietic plasma.

Forty eight hours after the last erythropoietic plasma injection, the animals were sacrificed, and bone marrow from the femurs was obtained for swabbing and myelokaryocyte study. Prior to plasma injection and at the end of the experiment, blood was obtained from all the animals for erythrocyte, hemoglobin and reticulocyte study according to routine techniques. Along with that, the total myelogram, erythroblastogram and the mitoses of red cells were also studied, and calculations made of the granulocyte-erythroblast and erythroblast maturation indices.

Results and Discussion

The results of the study on erythrocytes are presented in fig. 1. From 5.310 ± 0.162 m/mm³ before injection of the erythropoietic plasma in the experimental group, they fall to 4.140 ± 0.414 m/mm³ at the end of the expe-

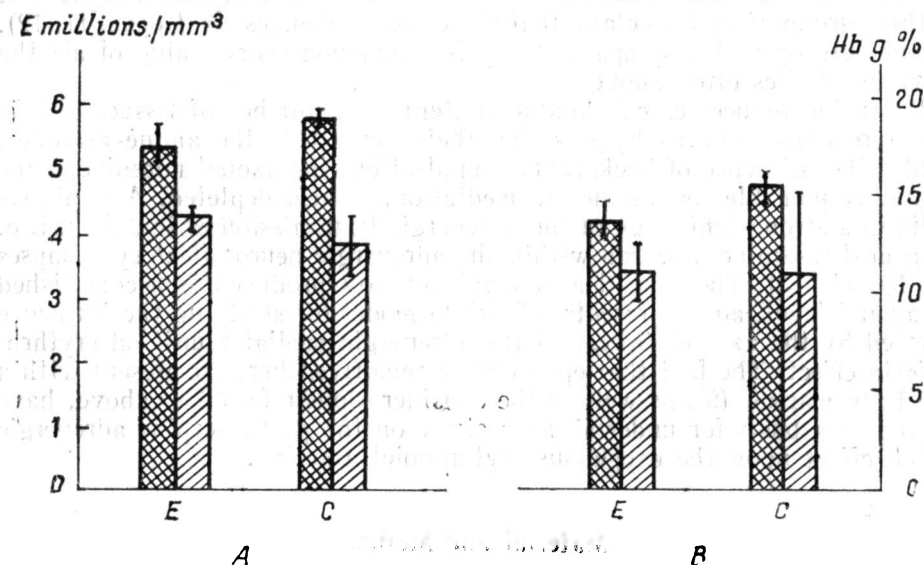


Fig. 1. Values of erythrocytes and hemoglobin in the experimental and control group. The two leftside columns of A — erythrocytes before and after injecting erythropoietic plasma (Ep) into the animals experimented upon. Rightside columns — the same for the controls; B — hemoglobin in g% in the experimental and control group. The other designations are the same as above.

periment, while in the control group — from 5.797 ± 0.094 m/mm³ to 3.747 ± 0.414 m/mm³. The reduction of erythrocytes in the control group is stronger — 35.36 per cent, than in the experimental — 22.03 per cent. The data concerning hemoglobin in g% are as follows: for the experimental

group — 13.88 ± 0.39 before, and 11.08 ± 0.58 after the injection of erythropoietic plasma, and for the control group, 15.53 ± 0.30 and 10.94 ± 1.65 respectively. The hemoglobin fall is likewise more pronounced in the control group — 29.55 per cent, as compared to the experimental — 20.17 per cent. Hemoglobin and erythrocytes' decrease in the experimental group is partially in line with the pertinent literature data (4, 8). Prolonged fasting, despite erythropoietic stimulation, has an essential practical bearing on the lowering of these indices in both animal groups.

Reticulocytes in the peripheral blood in either of the groups (Fig. 2) show an increase at the end of the experiment. In the experimental group it ranges from 51.5% to 103% , i. e. 100.97 per cent increase ($P < 0.001$). The increase in the control group was less pronounced: from 47.9% to 71.2% , i. e. 48.64 per cent. The data reported comply to a varying degree with the results published by Partev (4), and are in indirect disagreement with those of Tartakovskii (7).

The study of myelograms (Fig. 3 B) shows a pronounced increase of the red row cells among the animals experimented upon, and close values of the total number of nucleated cells. The absolute amount of erythroblasts is with 40.1 per cent higher in the experimental group ($P < 0.001$). The erythroblastogram (Fig. 3 A) demonstrates a considerable increase of polychromatophilic erythroblasts and normoblasts in the experimental group, and equal number of proerythroblasts and oxyphilic normoblasts ($P < 0.001$). Basophilic erythroblasts proved to be substantially more numerous in the control group. The granulocyte-erythroblast index (Fig. 4 A) is 0.38 in the experimental, and 1.13 in the control group. It is decreased whenever the red cells prevail over the granulocyte elements. The maturation index of erythroblasts is 21.3 in the experimental, and 4.5 in the control group. Its increase reflects the prevalence of polychromatophilic erythro- and normoblasts. In this context, our data are partly correlated with the data submitted by Fedorov and associates (8), who found accumulation of polychromatophilic erythroblasts following sympathetic denervation in cats. Mitoses and dividing erythroblasts display higher values in the experimental group — 59.50% , relative to 46.88% for the controls.

Interpretation of the results described is rather difficult owing to the variable reserpine effect. Apart from the liberation of serotonin and catecholamines in the CNS and in a number of other tissues, and the occurrence of adrenergic axonal block, reserpine accounts for an increase of the para-

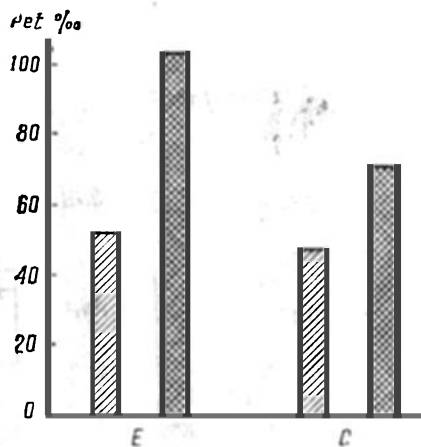


Fig. 2. Reticulocytes per 1000 erythrocytes in the experimental and control group. The markings are the same as in Fig. 1.

sympathicus tone, stimulates the adreno-hypophyseal system and exerts influence on a number of metabolic processes (2, 6, 13, 16). Operative removal of the sympathetic nerve, in the opinion of some authors, results in the increase of bone marrow cells (15). In the latter case, against the back-

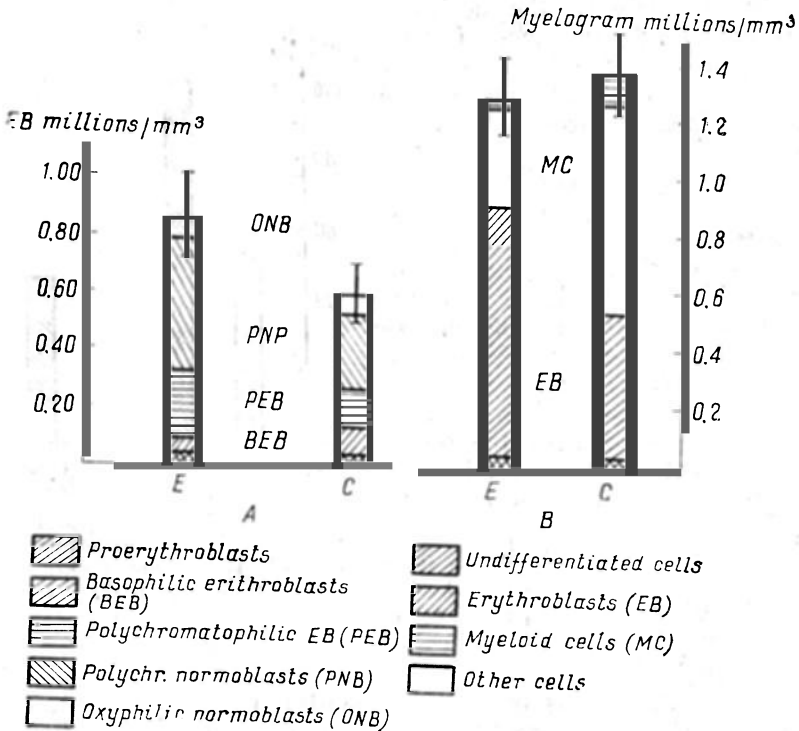


Fig. 3

A — bone marrow erythroblasts in absolute values millions/mm³ in the experimental and control group; B — myelogram in the experimental and control group — millions/mm³.

ground of inhibited sympathetic and accordingly, increased parasympathetic tone, the erythropoietic plasma stimulates erythroid hyperplasia within the bone marrow. There is evidence that serotonin accounts for an increase of bone marrow activity, and is furthermore an important cellular proliferation factor in many organs, bone marrow inclusive (5). It is difficult to say whether or not the liberated serotonin played a role in the experiments described. The accumulation of polychromatophilic erythro- and normoblasts points to a certain degree of hemoglobin synthesis inhibition, and may be explained by an eventual glandular metabolism disorder (4).

Our results suggest a stimulating effect of the post-reserpine adrenergic axonal block on erythropoietin consumption in the bone marrow. The increase of erythroblasts and mitoses in the bone marrow, and of reticulo-

cytes in the peripheral blood of the animals experimented upon gives us sufficient reason to reach such an inference. Along with that, emphasis should be laid on a certain degree of interference with the maturation of erythroblasts — accumulation of polychromatophilic erythro- and normoblasts

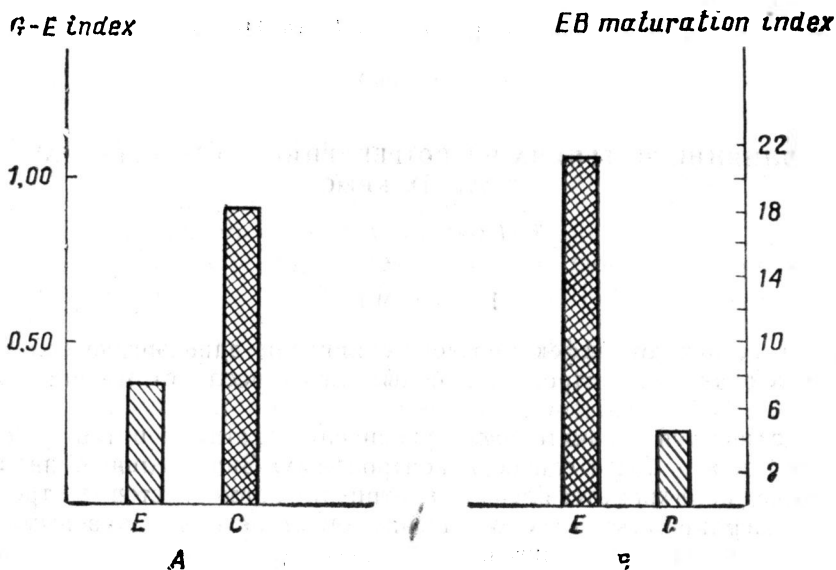


Fig. 4

A — granulocyte-erythroblast index in the experimental and control group; B — the maturation index of erythroblasts in the experimental and control group.

at equal number oxyphilic normoblasts in either of the groups. In our opinion, a disturbance in hemoglobin synthesis is the most probable cause.

On the ground of the results obtained the conclusion is reached that reserpine induced inhibition of the axonal functional link in the adrenergic mediator complex augments the susceptibility of red bone-marrow elements to exogenous erythropoietic stimulation.

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ВЛИЯНИЕ РЕЗЕРПИНА НА ПОТРЕБЛЕНИЕ ЭРИТРОПОЕТИНА У БЕЛЫХ КРЫС

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РЕЗЮМЕ

Авторы исследуют эффект послерезерпиновой адренэргической аксональной блокады на эритропоез у белых крыс после стимуляции эритропоеза.

Устанавливается значительное увеличение ретикулоцитов у опытных животных и более слабое в контрольных. Значительным является увеличение полихроматофильных эритро- и нормобластов у третируемых резерпином крыс. Соотношение между белыми и красными элементами в костном мозге опытных животных — в пользу красных, в то время как в контролях это соотношение обратное. Индекс созревания эритробластов в опытной группе гораздо выше чем таковой у животных контрольной группы. Более высоким является и процент митозов делящихся эритробластов в костном мозге опытных крыс.

Авторы считают, что адренэргическая послерезерпиновая аксональная блокада усиливает эффект экзогенного эритропоетина на эритропоез. Кроме этого, описанные изменения могут являться и результатом увеличенного парасимпатического тонуса. Весьма возможно участие эндокринно-метаболических эффектов резерпина, а также и освобожденного серотонина.