ROLE OF ADRENALIN AND BLOCKING OF α-RECEPTORS IN RESPONSES OF HEMATOPOIETIC ORGANS TO STRESS

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After injection of adrenalin the number of cells in the spleen and thymus is reduced, while in the bone marrow the number of lymphocytes is increased and the number of mature neutrophils reduced. Administration of the sympatholytic dihydroergotoxin caused similar changes in the thymus and bone marrow although the number of cells in the spleen was unchanged. Preliminary injection of dihydroergotoxin (before adrenalin) prevented the response of a decrease in the number of spleen cells observed after injection of adrenalin alone. It is concluded that the sympathetic nervous system plays the decisive role in the mechanism of the early response of the spleen to extremal factors. Blocking the α-adrenergic receptors had no significant effect on the bone marrow and thymus.

Responses of the hematopoietic organs to the action of various factors inducing a stress response have been studied in the writers' laboratory for several years [3, 7, 11, 13].

Previous investigations have shown that each type of extremal stimulus acts in its own special way, although the changes in the blood system obey certain general principles. These changes have been studied in different stages of the stress response [5]. Contrary to the generally accepted view, the writers have shown that cell depopulation of the thymus and spleen takes place not only on account of disintegration of the cells but also, and mainly, on account of migration of lymphocytes [8, 10, 11].

An increase in the number of lymphocytes is always observed in bone marrow tissue during the first few hours after exposure to an extremal stimulus. This suggests that the bone marrow is one of the places to which lymphocytes migrate. Following the increase in the number of lymphocytes, activation of myelopoiesis accompanied by a stage of resistance and by the appearance of transient hyperplasia of the bone marrow takes place. In experiments with nonuniform irradiation of rats it has been shown that lymphocytes can migrate from screened areas of the body, with probable dedifferentiation and subsequent formation of myeloid tissue [13]. Experiments on adrenalectomized rats have shown that adrenalectomy prevents activation of myelopoiesis but does not prevent the increase in the number of lymphocytes in the bone marrow after exposure to stress. The problem of the mechanisms affecting migration of lymphocytes thus remains unsolved [1, 5].

Since an increase in tone of the sympathetic nervous system and secretion of catecholamines always take place in the initial phase of the stress response it was natural to consider whether the rapid increase in the number of lymphocytes in the bone marrow is the result of the action of the sympathetic nervous system on the hematopoietic organ. To investigate this problem the action of adrenalin and the consequences of its pharmacological blocking by dihydroergotoxin on hematopoiesis were studied.

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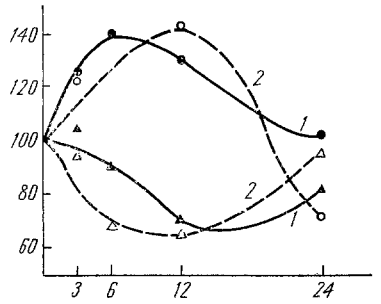

Fig. 1

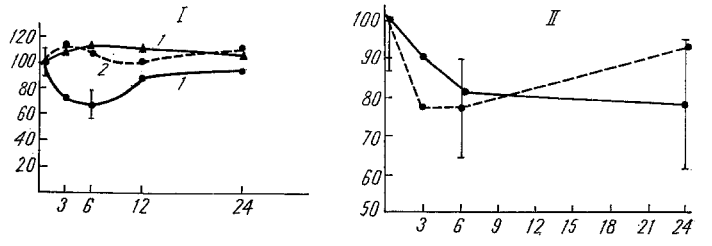

Fig. 2

Fig. 1. Changes in cell composition of the bone marrow after injection of adrenalin (1) and dihydroergotoxin (2). Maximal differences are significant ($P < 0.05$). Legend: circles denote lymphocytes, triangles mature granulocytes. Here and in Fig. 2: abscissa, time after injection of substances (in h); ordinate, number of cells (in % of initial level).

Fig. 2. Number of cells in spleen (I) and thymus (II) after injection of adrenlin (1) and dihydroergotoxin (2). ▲) Denotes injection of adrenalin after administration of dihydroergotoxin. Vertical lines represent confidence limits.

EXPERIMENTAL METHOD

Experiments were carried out on Wistar rats aged 10 weeks of both sexes weighing 160-180 g. Adrenalin hydrochloride was injected subcutaneously in a dose of 1 mg/kg. The dose of the sympatholytic dihydroergotoxin (Spofa, Czechoslovakia) required to block the sympathetic nervous system for 2 h was determined by the usual pharmacological method. Subcutaneous injection of dihydroergotoxin prevented for 2 h the elevation of blood pressure which follows intravenous injection of 10 μg adrenalin.

The number of cells in the spleen and thymus gland was counted by the method described previously [2, 7]. The number of nucleated cells in the femoral marrow was counted by Mantz's method. The absolute numbers of cells of different generations were determined from the myelogram counted on impression films. The hematopoietic organs were investigated in rats sacrificed 3, 6, 12, 24, and 72 h after injection of the drugs. From 10 to 15 rats were used at each time.

EXPERIMENTAL RESULTS

Bone Marrow. After injection of adrenalin the number of lymphocytes was increased (up to 40%), reaching a maximum after 6 h. During the first day the number of mature granulocytes fell. This reaction could not be neutralized by preliminary injection of dihydroergotoxin, for dihydroergotoxin itself produces the same response of the bone marrow as adrenalin, presumably because of its toxicity, as is shown by the changes in cell composition of the bone marrow (Fig. 1). The number of cells of the early generations of the myeloid series (myeloblasts-myelocytes) 72 h after injection of adrenalin and also of dihydroergotoxin showed an increase of 50 and 58% respectively ($P < 0.05$). These changes in the cell composition of the bone marrow were completely identical to those observed in the stress response of the bone marrow described by the writers previously [4].

Spleen. The number of cells in the spleen was significantly reduced 6 h after injection of adrenalin, and the normal level was restored after 12 h. Injection of dihydroergotoxin did not affect the changes in the cell composition of the spleen. In the next series of experiments it was shown that preliminary injection of dihydroergotoxin completely prevents the effect of subsequent injection of adrenalin. The mean results obtained are shown in Fig. 2, I.

Thymus. The number of lymphocytes fell significantly after injection of adrenalin and dihydroergotoxin. The action of both compounds was similar (Fig. 2, II).

DISCUSSION

Changes in the cell composition of the bone marrow arising after injection of comparatively large doses of adrenalin were indistinguishable from changes observed in the stress responses to a variety of extremal stimuli. Blocking the α-receptors by injection of dihydroergotoxin did not prevent the development of a characteristic stress reaction to the bone marrow. Evidently because of its toxicity, dihydroergotoxin itself gives rise to the same changes in cell composition in the bone marrow as exposure to other extremal stimuli. It is worth noting that dihydroergotoxin completely abolished the effect of adrenalin on the spleen. Probably the decrease in the cell population of the spleen was attributable to the ability of adrenalin to cause concentration of the smooth muscle of the capsule of this organ. The influence of the sympathetic nervous system on contraction of the spleen was demonstrated in exsanguination experiments [15]. This effect can be blocked by blocking the α-receptors. The possibility that α-blocking agents would act in this way was demonstrated by the work of Davies et al. [14]. It can be concluded from the results of these experiments that the sympathetic nervous system plays a decisive role in the mechanism of the early response of cell depopulation of the spleen, the effect being achieved through participation of the α-receptors. The results thus provide evidence that the mechanisms of cell depopulation differ in the spleen and thymus.

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