MECHANISM OF THE IMMUNOTROPIC EFFECT OF ASPARTIC ACID

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The immunoactive properties of aspartic acid, manifested as stimulation of differentiation of precursor T cells and mature cells, and activation of the immune response to thymus-dependent antigens, have recently been established [2]. The aim of this investigation was to study parameters of the functional and metabolic state of thymic cells (content of cyclic nuelcotides, DNA synthesis) following administration of aspartic acid to animals with experimental iron-deficiency anemia (IDA). The choice of IDA as model was due to the fact that in this pathology disturbances of lymphoid regulation of erythropoiesis as well as other immunologic disorders arise [1, 4], from which it may be assumed that immunocorrection has a positive effect on these conditions.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats from the "Rappolova" nursery, Academy of Medical Sciences of the USSR. IDA was produced by repeated bleeding and administration of the complexone desferal ("Ciba," Switzerland). The presence of iron deficiency was confirmed by determination of the serum iron level and its iron-binding capacity; the characteristic blood and bone marrow picture also was observed. To correct the anemia, Ferrum-lek (Yugoslavia) was injected intraperitoneally (control group 1) into animals with anemia, or Ferrum-lek combined with aspartic acid ("Reanal," Hungary) was injected 5 times in a dose of 0.1 mg/100 g(group 2). On the 5th day after the last injection, parameters of the peripheral blood, the number of karyocytes in the thymus and bone marrow, and the myelogram were determined.

The intensity of DNA synthesis in the thymocytes and myelokaryocytes was determined with the aid of methyl-^{3}H-thymidine. For this purpose, $2 \cdot 10^6$ cells in 0.5 ml of medium 199 were introduced into sterile plastic plates and an equal volume of radionuclide (activity 37 kBq) was added. The samples were incubated for 2 h at 37°C. Next, 200 µl of 20% formic acid was added to each well, and the contents of the well were then filtered on a semiautomatic apparatus, sedimenting the cells on millipore filters (450 nm). Radioactivity was counted on an SBS-2 scintillation counter in toluene scintillator. The results was expressed in becquerels per 10^6 karyocytes.

The content of cyclic nucleotides cAMP and cGMP was determined by radioimmunoassay using commercial kits (Czechoslovakia).

The results were subjected to statistical analysis with the use of parametric tests, on the Élektronika DZ-28" minicomputer.

EXPERIMENTAL RESULTS

The experiments showed that injection of aspartic acid into intact animals led to no significant changes in their blood or bone marrow, but the cell content of the thymus was increased. In rats with IDA, when this preparation was used in conjunction with Ferrum-lek treatment, the number of lymphocytes in the bone marrow did not change significantly, whereas their number in the blood was increased. Aspartic acid also caused a decrease in the cAMP concentration in the thymocytes, whereas the cGMP concentration did not change significantly although it had a tendency to fall (Table 1).

It is important to note that the cAMP/cGMP ratio in the thymus cells increased under the influence of aspartic acid, i.e., cAMP accumulated, and this is an early molecular

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TABLE 1. Some Parameters of the State of the Lymphocytes after Administration of Aspartic Acid

Parameter	Group of animals	
	1-	2-
Number of lymphocytes in myleogram, %	16,3±1,8	18,0±3,1
Number of lymphocytes in blood, 10^9/liter	5,78±0,50	7,54±0,07*
cAMP, pmoles/10^6 thymocyte	0,243±0,034	0,119±0,018*
cGMP, pmoles/10^6 thymocytes	0,010±0,001	0,003±0,001
cAMP/cGMP	24,3	39,7**
Incorporation of ^{3}H-thymidine into DNA, Bq/10^6 thymocytes	210,2±2,1	264,0±4,2*

Note. *$p < 0.05$, **) Parameter determined by calculation based on means.

response of activation of the lymphocytes [3]. Increased incorporation of ^{3}H-thymidine into the thymic cells is also linked with cAMP accumulation and is evidence of stimulation of DNA synthesis in these cells. Together with the increase in the number of karyocytes in the thymus, this leads to the conclusion that proliferative processes are stimulated in the thymus. Similar changes also were observed in the bone marrow cells. This suggests that common mechanisms are involved in the response of lymphocytes to aspartic acid.

Thus administration of aspartic acid leads to increased production of immunocompetent cells in the thymus and metabolic changes in these cells (accumulation of cAMP, stimulation of DNA synthesis), leading to stimulation of lymphocyte function. These data may serve as a basis for the pathogenetic treatment of immunologic disturbances, especially accompanied by IDA.

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