CHARACTERISTICS OF EXPERIMENTAL ALLERGIC MYOCARDITIS

Chang Lyu, A. I. Polyak, and V. S. Otlivshchikova

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Repeated immunization with antigen from heart muscle with Freund's adjuvant for 1.5-2 months causes allergic myocarditis in rabbits. This condition is characterized by changes in the ECG (a decrease in voltage of the R and T waves and the QRS complex), dysproteinemia (a decrease in the albumin concentration, an increase in that of the γ- and β-globulins), the appearance of microprecipitins and antiheart hemagglutinins, an increase in the complementary activity of the serum and the accumulation of C-reactive protein, and also by degenerative changes in the muscle fibers and disorganization of the connective-tissue basis of the heart. Considerable changes in the activity of succinate dehydrogenase, adenosine triphosphate, and alkaline and acid phosphatases take place in the myocardium. After preliminary bilateral destruction of the posterior hypothalamic nucleus all the above-mentioned changes were aggravated.

Increased interest has been shown in recent years in lesions of the myocardium in whose pathogenesis allergic processes played a decisive role [9, 12, 13, 22, 25, 28]. Correlations have been studied between changes in the heart muscle in myocarditis and the clinical picture of this disease [3, 6, 19, 20, 23, 27]. However, only one or two papers have been devoted to functional changes in the activity of the cardiovascular system and their comparison with the dynamics of the pathomorphological manifestations. The problem of the role of central mechanisms in the regulation of immunological and allergic reactions likewise remains unsolved [1, 2, 5, 7, 8, 14-16, 24, 30].

The object of this investigation was to study the information of allergic myocarditis and its distinguishing features after bilateral coagulation of the posterior hypothalamic nucleus.

EXPERIMENTAL METHOD

Experiments were carried out on 60 rabbits weighing 2.5-3.0 kg. The rabbits (35) of group 1 were immunized with antigen (AG) prepared from heart tissue with Freund's adjuvant and with the addition of an equal volume of a killed streptococcal culture (2 billion cells/ml). The first injection was given simultaneously into the plantar pads and in four places on the abdominal wall (subcutaneously), in doses of 0.5 mg (as protein) AG per injection, and also intravenously (2 mg AG). The second injection of 2 mg AG was given intravenously 3-4 days after the first; the third injection (5 mg AG, intraperitoneally) was given 3-4 days after the second, and the last injection (2 mg AG, intravenously) 4-5 days after the third. The 25 rabbits of group 2 were immunized in accordance with the same scheme 5-7 days after bilateral coagulation of the posterior hypothalamic nucleus (dc, 1 mA, 30 sec): the unipolar electrode was inserted into the brain by a stereotaxic apparatus using coordinates of Fifkova and Marsal's atlas.

Before and during the experiment (on the 3rd, 7th, 14th, 21st, 30th, 45th, and 60th days after the fourth injection of AG) the total protein and protein fractions, C-reactive protein, complementary activity for 50%

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TABLE 1. Changes in Complementary Activity of Blood Serum (in 50% hemolysis units) in the Course of Experimental Allergic Myocarditis (M ± m)

Group of rabbits	Day of experiment				
	3-rd	7-th	14-th	21-st	60-th
Control	24,10±0,52				
1-	33,50±1,72	37,10±2,01	47,80±2,52	44,50±3,10	26,50±1,40
	P_{K-1}<0,001	<0,001	<0,001	<0,001	>0,4
2-	31,00±1,85	47,40±2,65	36,00±1,83	37,50±1,45	21,80±1,12
	P_{K-2}<0,001	<0,001	<0,001	<0,001	>0,1
	P_{1-2}>0,4	<0,01	<0,01	<0,05	<0,05

Legend: P_{K-1} and P_{K-2}) significance of differences between experimental groups 1 and 2 and the control respectively; P_{1-2}) the same between groups 1 and 2.

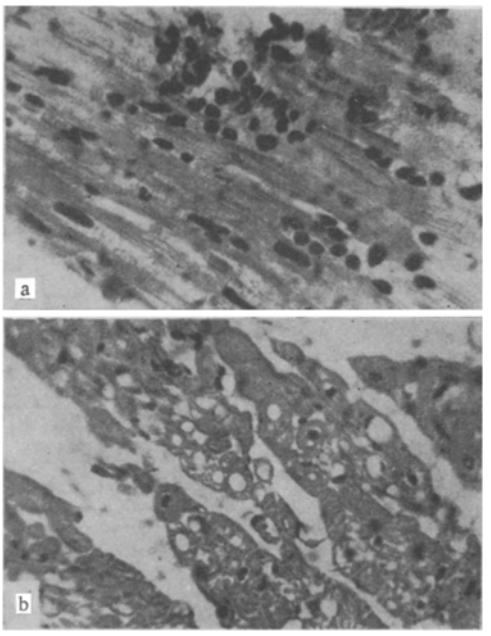

Fig. 1. Morphological changes in heart muscle in experimental myocarditis (hematoxylineosin): a) monocytic infiltration (14 days, group 1; 420×); b) vacuolar degeneration (7 days, group 2; 280×).

hemolysis, microprecipitating antibodies, and antiheart hemagglutinins were determined in the blood and the ECG was recorded in three standard leads (paper winding speed 50 mm/sec; 1 mV = 10 mm).

Pieces of myocardium were stained with hematoxylin-eosin and by Van Gieson's and Selye's methods; the activity of adenosine triphosphatase (ATPase; after Padykula and Herman), succinate dehydrogenase (SDH; after Shelton and Schneider), and alkaline and acid phosphatase (by Gomori's method) were determined in the tissue. The results were analyzed by the method of indirect differences.

EXPERIMENTAL RESULTS AND DISCUSSION

As a result of immunization a severe dysproteinemia developed; it was particularly marked in the animals of group 2, with a decrease in the albumin concentration and an increase in the globulin fraction on account of γ- and β-globulins. From the third day after the last immunization microprecipitins, specific hemagglutinins, and C-reactive protein were found in the animals of both groups, but their level was considerably higher in the rabbits of group 2. Meanwhile an increase in the complementary activity of the blood serum was recorded (Table 1).

During the experimental reproduction of autoallergic myocarditis changes corresponding to those observed in the active phase of rheumatoid myocarditis were thus found in the blood serum [3, 10, 11, 18, 31]. The severest changes occurred in rabbits in which the autoimmune process was reproduced after bilateral destruction of the posterior hypothalamic nucleus.

In the rabbits of group 1, on the seventh day after the last injection of AG a sharp decrease ($P < 0.001$) was observed in the voltage of the QRS complex and the R wave in all leads. Later the QRS complex was transformed by omission of the R wave into a QS complex. An increase in the duration of electrical cystole and a sharp decrease ($P < 0.001$) in voltage of the T wave were observed, and in some cases the latter became negative. Similar but still more marked changes in the ECG were found in animals immunized after preliminary destruction of the posterior hypothalamic nucleus.

These data showing changes in the ECG correspond to results obtained experimentally [4] and clinically [17, 21, 26, 29] in local and diffuse lesions of the myocardium and in rheumatic carditis.

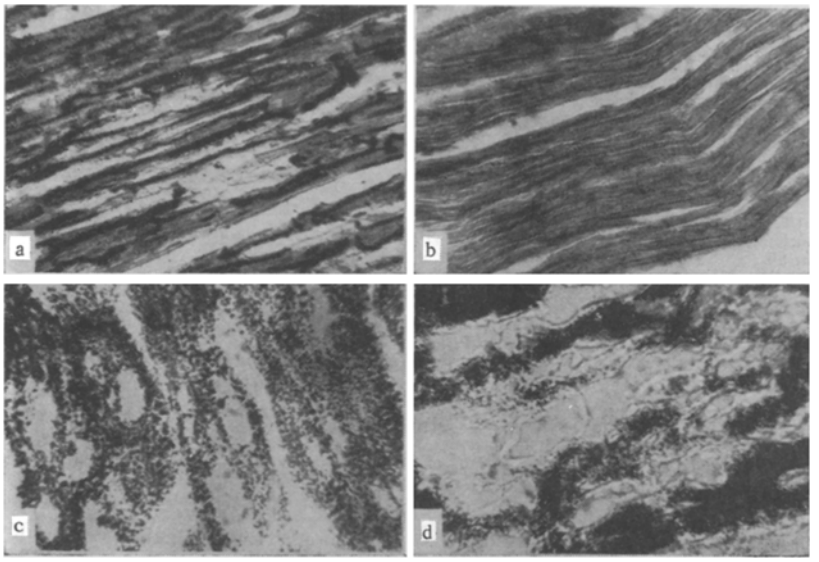

Fig. 2. Disturbance of enzyme activity in the myocardium (14th day): a and b) increase (group 1) and decrease (group 2) respectively in alkaline phosphatase activity in capillary walls (Gomori; 140×); c and d) uneven SDH activity in myocardium of rabbits of groups 1 and 2 respectively (Shelton and Schneider; 280×).

In a microscopic study of the myocardium from animals of both groups microcirculatory disturbances were found as early as on the seventh day (edema of the interstitial connective tissue, congestion of arteries and veins, and plasmostasis). Groups and even whole fields of muscle fibers were affected by degenerative and destructive changes resembling myolysis, vacuolation, and cloudy swelling, while here and there were solitary foci of necrosis. The nuclei were pycnotic, swollen, or in a state of partial or total lysis. Some fibers were without nuclei and the internal structure of the sarcoplasm was obliterated. The muscle fibers in the walls of some arteries were homogenized. The staining properties of the fibrous structures of the interstitial connective tissue were altered (decrease in uptake of fuchsin when stained by Van Gieson's method). Diffuse cellular infiltration, more intensive in the necrotic areas of the myocardium, was observed in both groups of rabbits. The infiltrating cells were monocytes, histiocytes, and lymphocytes (Fig. 1a). The myocardial degeneration was more severe in the animals with destruction of the hypothalamus, as reflected in the extensive areas of muscle fibers in a state of myolysis, vacuolation, and homogenization (Fig. 1b) and extensive foci of necrosis of muscle fibers. Later, in the animals of both groups proliferation of the nuclei of the muscle fibers, endothelial cells, and fibroblasts took place. Proliferation of connective tissue was observed at the sites of the dying fibers. In some places the layers of connective tissue were infiltrated by monocytes. In sections stained by Selye's method large groups and whole fields of muscle fibers were fuchsinophilic; in the course of time the number of groups and the size of the fields of fuchsinophilic fibers increased, and the structure of the fibers could not be made out.

From the first week and until the end of the experiments activity of SDH, ATPase, and alkaline and acid phosphatases in the heart muscle and also of ATPase and alkaline phosphatase in the walls of the capillaries and in the structures of the muscle fibers fell appreciably, and its distribution was irregular. In the animals of group 2 the activity of these enzymes was more strongly depressed (Fig. 2). From the first time of testing hardly any ATPase or alkaline phosphatase activity could be found in most of their capillaries. A decrease in ATPase activity also was found in larger blood vessels, whereas in the rabbits of group 1 no significant changes in enzyme activity were found in the corresponding vessels.

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