CHANGES IN COMPONENTS OF THE KININ SYSTEM AND STRUCTURE OF MYOCARDIUM CAUSED BY ANTIKININ PREPARATIONS IN RABBITS WITH ALLERGIC MYOCARDITIS

M. S. Surovikina, V. A. Odinokova,
N. R. Paleev, M. A. Gurevich,
and M. O. Yankovskaya

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The effect of anginin, contrical, aspirin, indomethacin, and ε-aminocaproic acid on the kininogen content and kininase activity in the myocardium and on its morphological structure was studied in rabbits with experimental allergic myocarditis. Anginin and contrical depressed the activation of the kinin system of the myocardium much more than the other substances and facilitated restoration of the morphological structure of the heart muscle. By inhibiting the kinin system of the plasma and the myocardium by antikinin substances it is possible to arrest the development or reduce the severity of allergic inflammation in the myocardium.

KEY WORDS: *Allergic myocarditis; kinin system; antikinin substances.*

Previous investigations have shown that during the development of experimental allergic myocarditis in rabbits the increase in the kinin level in the general circulation [2] and directly in the myocardium itself [3] is accompanied by functional and morphological changes in the heart muscle.

The object of this investigation was to continue the study of the state of the myocardial kinin system during the development of allergic myocarditis and after administration of therapeutic substances.

EXPERIMENTAL METHOD

Experiments were carried out on 49 chinchilla rabbits weighing 2.5-5 kg. By the method described previously [1] allergic myocarditis was produced in 37 animals; 25 of these animals received antikinin (anginin and contrical) and anti-inflammatory [ε-aminocaprioc acid (ε-ACA), aspirin, or indomethacin] preparations daily starting with the first day of immunization. All the substances except contrical were given by mouth in therapeutic doses; anginin 6 mg/kg, ε-ACA 400 mg/kg, aspirin 50 mg/kg, and indomethacin 2 mg/kg. Contrical was given intraperitoneally or intravenously to the animals in a dose of 3000-5000 antitrypsin units /kg. During and after the end of the courses of immunization and treatment (2-2.5 months from the beginning of the experiment) the animals were killed and the kininogen content and kininase activity in the myocardium were determined. After fixation of the heart in Lillie's solution histological survey sections were cut and stained with hematoxylin-eosin, picrofuchsin-fuchselin, toluidine blue, azan by Mallory's method, iron-hematoxylin by Heidenhain's method, by Selye's, Brachet's, Einarson's, and Feulgen methods and by Shabadash's method with amylase control. The number of muscle cells showing necrobiotic changes was counted in 100 fields of vision in sections through the myocardium under the light microscope (magnification 120×).

The following preparations were used: bradykinin triacetate (Reanal, Hungary), anginin (pyridinol carbamate; Wapui, Japan), contrical (Germed, East Germany), and ε-aminocaproic acid (Chemapol, Czechoslovakia).

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TABLE 1. Changes in Kininogen Content and Kininase Activity of Myocardium during Experimental Treatment of Allergic Myocarditis in Rabbits (M±m)

Component of kinin system studied	Healthy animals (control, 12)	Rabbits with allergic myocarditis					
		untreated (12)	treated with				
			anginin (7)	contrical (3)	aspirin (6)	ε-ACA (4)	indomethacin (5)
Kininogen, μg/ml:							
Initial content	1,02±0,12	—	—	—	—	—	—
4th-5th immunizations	—	0,075±0,007	—	—	—	—	—
8th immunization	—	0,25±0,07	0,75±0,14	0,94±0,15	0,72±0,11	0,71±0,08	0,60±0,07
Kininase, μg/ml/min:							
Initial content	25,2±0,85	—	—	—	—	—	—
4th-5th immunizations	—	11,8±2,80	—	—	—	—	—
8th immunization	—	24,4±0,37	28,5±0,48	27,3±0,49	12,3±1,59	15,0±2,65	15,1±0,94

Legend. Number of animals shown in parentheses.

EXPERIMENTAL RESULTS AND DISCUSSION

The results given in Table 1 show that the kininogen content in the untreated animal after 4 or 5 immunizations was only 7.3% of its initial level. By the 8th immunization the kininogen content started to increase, but it remained far below the control (24%). In the treated animals the kininogen content in the myocardium at the end of the course of immunization was higher than in the untreated animals (92.5% of the control after contrical; 73.5% after anginin, 70.6% after aspirin, 68.6% after ε-ACA, and 58.8% after indomethacin).

The myocardial kininase activity of the untreated rabbits after 4 or 5 immunizations was reduced by more than half compared with the control, but recovered towards the end of the experiment. Anginin and contrical activated kininase a little; under the influence of aspirin, ε-ACA and indomethacin, however, the myocardial kininase activity continued to remain low throughout the period of immunization.

Analysis of the morphological changes developing in the myocardium of the immunized rabbits showed that the therapeutic substances also affected the myocardium. Under the influence of these preparations the microcirculation was restored in the heart and the permeability of the walls of the capillaries, arterioles, and venules was reduced. Under their influence the edema diminished and the number of mast cells and the dimensions of the foci of lymphocytic and histiocytic infiltration were reduced. The cytoplasm of the mast cells became PAS-negative and gave γ-metachromasia on staining with toluidine blue. The accumulation of glycogen, RNA, and DNA in the muscle cells was intensified but the number of cells in the various phases of myolysis (discoid degeneration, homogenization of the cytoplasm) decreased.

As regards their normalizing effect on the structure of the myocardium anginin and contrical were the most effective substances. At the end of immunization only very slight changes (uneven filling of the capillaries, arterioles, and venules with blood; a reduction in the glycogen content and very slight cloudy swelling in solitary muscle fibers) could be observed in the myocardium of the rabbits treated with anginin and contrical. The number of muscle fibers with necrobiotic changes was 12.26±2.10 after administration of angin and 13.62±2.37 after contrical, whereas in the untreated animals a picture of allergic myocarditis was seen with extensive lympho-histiocytic infiltration in the stroma and with numerous muscle cells with necrobiotic changes (17.52±2.32; $P<0.05$).

After administration of aspirin and indomethacin to the rabbits the foci of cellular infiltration in the stroma became widespread. The number of muscle cells in the various phases of myolysis was 15.44±2.92 and 16.88±2.23 respectively. ε-ACA also was less effective than anginin and contrical. After its administration hemorrhagic foci remained, perivascular and intermuscular edema continued to be fairly severe, and foci of lympho-histiocytic infiltration persisted. The number of muscle fibers with necrobiotic changes was 14.87±2.04.

Specific antikinin substances, namely anginin and contrical, which normalized the myocardial kinin system, thus depressed the inflammatory-allergic reaction in it much more than the other substances used. Nonspecific anti-inflammatory agents, although retarding the process of normalization of the myocardial kininase, inhibited the pathological process by a lesser degree. Since the mechanism of action of these substances differs from that of con-

trical and anginin (they act predominantly on the activation of the plasmin and prostaglandin systems), the quantitative difference in their effectiveness points to a predominant role of the kallikrein-kinin system in the pathogenesis of allergic myocarditis.

Some decrease in the intensity of the morphological manifestations of experimental myocarditis also was found when such anti-inflammatory agents as butadione and mephenamic acid were used [4].

The results of these investigations are evidence that activation of the myocardial kinin system occurring during the first five weeks of development of the inflammatory process leads to marked local hyperproduction of kinin, an important factor in the development of allergic myocarditis. The activation of the plasma kinin system discovered previously at these same times of development of myocarditis [2] evidently leads to summation of the harmful action of the plasma and myocardial kinins on the structure and function of the heart. The manifestations of allergic myocarditis can be considerably reduced by inhibition of the kinin system of the plasma and myocardium.

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EFFECT OF ALLERGIC PROCESSES OF IMMEDIATE AND DELAYED TYPES ON THE INTENSITY OF CORTISOL METABOLISM IN THE GUINEA PIG LIVER

V. I. Pytskii and Yu. P. Syusyukin

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The intensity of cortisol metabolism was studied during perfusion of the liver in situ with solutions containing different concentrations of cortisol. Under these circumstances metabolism was shown to take place chiefly in the direction of cortisone formation. With an increase in the cortisol concentration in the perfusion fluid the intensity of its metabolism in the liver tissue also increased. During anaphylactic changes in the liver tissue the intensity of conversion of cortisol into cortisone was reduced, indicating a disturbance of the oxidation of cortisol. In experimental allergic encephalomyelitis the intensity of cortisol metabolism also was reduced.

KEY WORDS: *Allergy; glucocorticoids; metabolism of cortisol in the liver.*

In allergic diseases the half-elimination time of injected cortisol is increased, evidence of delay in its metabolism [7, 8]. Experiments on dogs have shown that during allergic changes in the liver tissue the intensity of cortisol metabolism is reduced [3], whereas no such disturbance has been found in dogs' kidneys [4]. Marked changes in cortisone metabolism have also been discovered in the liver of guinea pigs [5]. However, the general principles governing the change in corticosteroid metabolism in the liver during allergic processes are not yet known.

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