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ROLE OF LEUKOTRIENES IN SHOCK OF IMMUNE GENESIS

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The writer showed previously that immune damage to the heart is accompanied by a shock reaction, due to disturbance of the contractile function of the myocardium and mediated humorally through stored blood [2-5].

One possible humoral intermediary in the development of disturbances of the cardiodynamics and hemodynamics of immune genesis may be a slow reacting substance A (SRSA) — a vasoactive mediator of hypersensitivity reactions of immediate type [1, 6, 14]. It has recently been shown that SRSA consists of leukotrienes C_4, D_4, and E_4 — representatives of a new class of biologically active substances, which are derivatives of arachidonic acid by the lipoxygenase metabolic pathway [11, 13]. Leukotrienes are formed and secreted from the heart in considerable amounts during cardiac anaphylaxis [10]. When introduced into the body they can cause considerable disturbances of the cardio- and hemodynamics [12], with the development of coronary spasm, focal ischemia, and contractile failure of the myocardium [8, 9].

To determine the role of leukotrienes in the development of disturbances of the cardio- and hemodynamics associated with cardiac lesions of immune genesis, in the investigation described below the response of the circulatory system to immune trauma of the heart, with and without blockade of leukotriene biosynthesis was compared *in vivo*.

EXPERIMENTAL METHOD

Acute experiments were carried out on mongrel dogs weighing 17-22 kg under chloralose-urethane anesthesia (0.05 and 0.3 g/kg, respectively). There were two series of experiments: I) Control, in which changes in the hemodynamics and cardiodynamics were studied in intact dogs subjected to immune trauma to the heart, and II) experimental, in which changes in the same parameters under similar conditions were studied in dogs after preliminary blockade of lipoxygenase, i.e., of leukotriene biosynthesis. Lipoxygenase was blocked by means of quercetin, a solution of which was injected intravenously in a dose of 10 mg/kg [15]. Immune trauma to the myocardium of the left ventricle was inflicted 10-15 min after injection of quercetin, and changes in the cardio- and hemodynamics were observed for 1 h. The heart was traumatized by injection of 1 ml of a solution of immune anticardiac γ-globulin (1 mg/kg) into one branch of the left coronary artery, without opening the chest.

The globulin was obtained from an anticardiac serum with anticardiac antibody titer in the complement fixation test of 1:320-1:640.

The following parameters of the cardio- and hemodynamics were recorded in the experiments: The systemic blood pressure (BP), the central venous pressure (CVP), the perfusion pressure

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of the coronary artery and femoral artery, the venous outflow pressure in the femoral vein, the pressure in the left ventricle, its end-diastolic component and first derivative (dp/dt), the cardiac output, and the thermodilution curve to calculate the volumes of the left ventricle, and the ECG.

Using the parameters mentioned above, a number of indices of the pumping function of the heart were calculated: cardiac and systolic indices, end-diastolic and end-systolic volumes (EDV and ESV, respectively), the ejection fraction, and indices of contractility of the left-ventricular myocardium ($dp/dt_{max}/p$), the relaxation index, and the total peripheral resistance (TPR) of the vascular bed.

The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Preliminary injection of quercetin into the dogs caused less marked disturbances of the cardio- and hemodynamics of animals with immune trauma to the heart (Fig. 1). For instance, whereas intracoronary injection of anticardiac antibodies in intact animals was accompanied by a fall of BP by almost 50%, after preliminary injection of quercetin the corresponding injection was followed by a fall of BP by 19-26%. The differences (after 15 min) between the two series were significant ($P < 0.05$).

Significant differences between the responses of the intact animals and animals receiving preliminary quercetin to immune trauma were observed also in the response of the coronary vascular bed. Immune trauma in intact animals was accompanied in all experiments, during the first minutes, by marked constriction of the coronary vessels, with an increase in coronary perfusion pressure from 153 ± 4.8 to 192 ± 6.1 mm Hg ($P < 0.01$). After quercetin constriction was slight and the rise of the coronary perfusion pressure during the first minutes of the reaction averaged +10 mm Hg, and in 37% of the experiments the initial constrictor reaction was absent and the coronary vessels dilated after injection of anticardiac γ-globulin. Differences between the mean values of the reaction of the coronary vessels in the control and experimental series were significant. In the animals of the experimental series there was likewise no tendency toward constriction of the coronary vessels such as occurred in the control in the late period of the reaction, namely after 30-60 min.

The results thus show that the coronary constrictor response, accompanying immune trauma to the heart, is due mainly to the action of endogenously formed leukotrienes. This is in agreement with data in the literature. A strong coronary-constrictor action of the leukotrienes, which may amount to complete arrest of the coronary blood flow, has been described in various animals [8, 9].

The marked protective action of quercetin was observed when indices of the contractile and pumping function of the heart were studied. Their fall after immune trauma to the heart was less in animals of the experimental series. For instance, the rate of rise of pressure in the left ventricle decreased by 25-30% compared with 38-55% in the control (Fig. 1). The ejection fraction of the left ventricle was virtually unchanged. The fall in cardiac output also was much less in these animals (Table 1). This effect of quercetin on changes in the contractile function of the myocardium and the pumping function of the heart was evidently due to a reduction in leukotriene biosynthesis and, as a result of that, the weaker negative inotropic and coronary-constrictor action which, as we know, is a property of the leukotrienes [7, 16].

The significant difference between responses of the animals of the two series to immune trauma from the standpoint of the peripheral vascular bed and, in particular, its capacitive

TABLE 1. Changes in Hemodynamic Indices during Shock of Immune Genesis in Dogs before and after Blockade of Leukotriene Biosynthesis

Parameter	Series of experiments	Changes in index (in % of initial) after				
		5 min	15 min	30 min	45 min	60 min
Cardiac index	I	−43,2±4,5	−45,6±4,6	−42,5±4,6	−38,1±6	−48,1±7,7
	II	−27,0±8,0	−26,1±6,6	−25,6±5,0	−22,1±5,8	−28,5±6,1
Systolic index	I	−43±4,9	−40,1±4,9	−34,8±5,8	−33,1±5,8	−38,1±6,2
	II	−15,1±7,3	−14,7±12,7	−22,2±6,6	−24,5±7,6	−28,5±6,0
TPR	I	−11,3±9,7	−9,9±7,1	−8,6±6,8	−2,2±8,8	+0,7±10,1
	II	+14,7±17,3	+18,4±12,3	+10,3±8,2	+4,4±7,6	+19,0±8,9

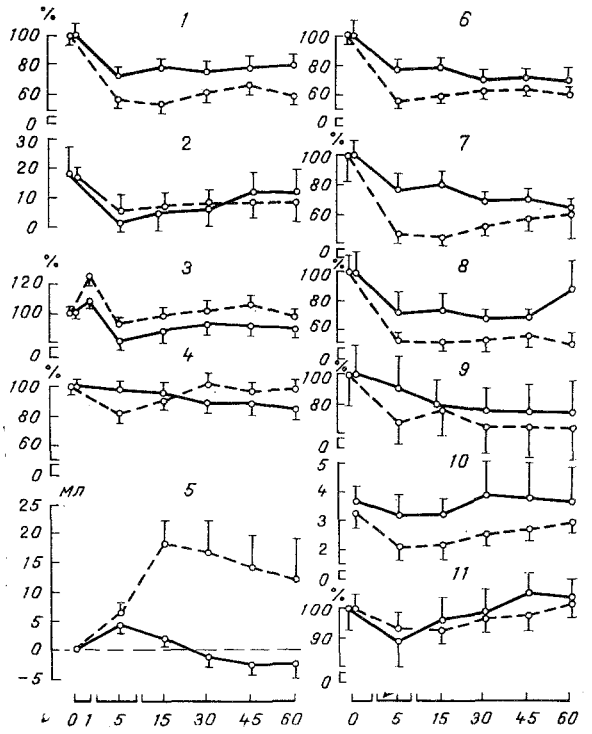

Fig. 1. Effect of blocking leukotriene biosynthesis on changes in cardio- and hemodynamics after immune trauma. Abscissa, time after beginning of reaction (in min). 1) Systemic BP, 2) CVP, 3) coronary perfusion, 4) perfusion pressure of femoral artery, 5) volume of blood stored in skin and muscle region (of hind limb), 6) systolic pressure in left ventricle, 7) maximal rate of rise of intraventricular pressure, 8) maximal rate of fall of pressure in left ventricle, 9) index of myocardial contractility, 10) end-diastolic pressure (EDP) in left ventricle, 11) heart rate, beats/min. Continuous line — experiment, broken line — control. CVP, EDP, and volume of stored blood expressed in absolute values, remaining parameters in % of initial value.

function, revealed by the present investigation, is of fundamental importance. For instance, after premedication with quercetin, the blood storage response during the first 15-60 min was virtually absent in the animals, and there was even a tendency for the capacity of the vascular bed in the peripheral region which was studied (the system of femoral vessels, Fig. 1) to decrease.

Differences between the two series of experiments with respect to this parameter after 30-60 min were significant ($P < 0.05$). This indicates that the blood storage reaction observed after immune trauma to the heart is evidently largely due to the action of leukotrienes on capacitive vessels. Since there are as yet no direct data on the action of leukotrienes on the veins, these experimental results can be regarded as indirect evidence of the ability of leukotrienes to dilate the venous bed. Since storage of blood plays the leading role in the combination of cardiac and vascular reactions during the development of shock, abolition of this reaction by blockade of biosynthesis of leukotrienes or of their receptors is of great importance in connection with the prevention and treatment of shock reactions.

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DYNAMICS OF STRUCTURAL METABOLISM IN THE LIVER DURING HYPERBARIC OXYGENATION IN THE RECOVERY PERIOD AFTER ACUTE MASSIVE BLOOD LOSS

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An important role in the course and outcome of terminal and other hypoxic states has been shown to be played by changes in nucleic acid metabolism in the liver [3, 5, 6, 14, 15]. Profound disturbances of nucleic acid metabolism in the liver have a definite effect on formation of irreversible changes after massive blood loss [5, 14, 15]. The development of a terminal state (agony) after acute massive blood loss is accompanied by inhibition of synthesis of nuclear and cytoplasmic RNA and by a fall in the concentrations of both RNA and DNA in the liver tissue. The wide use of hyperbaric oxygenation (HBO) in the treatment and prevention of hypoxic states [2, 12] has necessitated the study of its effect on the dynamics of metabolism of highly important biopolymers in the liver tissues and on the outcome of severe hypoxic states. It has been shown that oxygen, given by HBO, has a varied effect on nucleic acid metabolism in the tissues [4, 7, 12, 14, 15]. The amplitude of the oxygen effect is known to be extremely wide. On the one hand, it may lead to severe poisoning, on the other hand it may give a powerful therapeutic effect [8, 12]. The biological effect of oxygen depends both on the conditions of HBO and on the state of the patient or animal treated with oxygen. Experimental data and clinical observations show that HBO has different effects on the healthy organism and in pathology accompanied by hypoxia [8, 12]. It has been shown experimentally that when healthy animals are subjected to HBO, profound disturbances of nucleic acid metabolism are observed in the tissues, and are expressed as increased activity of lysosomal enzymes (RNase, DNase) and a fall in nucleic acid concentrations in the tissues [7]. As a result of exposure of a healthy organism to hyperbaric oxygenation, the regenerative activity of the cells is depressed [8]. The use of HBO in the early stages after acute massive blood loss has been shown to prevent the inhibition of synthesis of nuclear and cytoplasmic RNA, the fall in the nucleic acid (RNA and DNA) concentrations, and also the development of a terminal state in most animals [14, 15]. However, the effect of HBO on nucleic acid and protein metabolism in the liver has not been studied in the recovery period after massive blood loss, yet this is important for an understanding of the pathogenesis of complications which develop in the postresuscitation period, in which disturbances of nucleic acid and protein metabolism in the tissues play an important role [6, 11].

This paper describes a study of the effect of HBO on structural metabolism in the liver in the recovery period after acute massive unreplaced blood loss.

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