EFFECT OF THE FEBRILE REACTION ON THE KALLIKREIN–KININ SYSTEM OF LYMPH AND BLOOD

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Despite much convincing data to show that the activity of many systems and organs is modified during the development of a febrile reaction (FR) [1, 2, 5, 12], the role of the lymphatic system in the pathogenesis of this process is completely ignored in the literature. Since the functions of the lymphatic system (maintenance of the volume and composition of the extracellular fluid, resorption and transport of tissue fluid, plasma proteins, and other high-molecular-weight compounds, participation in defensive reactions of the body and in hematopoiesis, etc.) are directly related to the maintenance of homeostasis, it can be postulated that changes in them are a definite stage in the mechanism of compensation and disturbances of homeostasis during FR.

The aim of this investigation was to study the dynamics of components of the kallikrein–kinin system of the lymph and blood of rabbits after FR of varied duration. If allowance is made for continuous transcapillary exchange of the components of the kallikrein–kinin system (KKS): blood → tissue fluid (and cells of the reticuloendothelial system of the internal organs) → lymph → blood, in our view changes in the activity of this system during fever ought to be reflected in the lymph as well as in the blood. In turn, the resorptive and transport functions of the lymmphatic system may bring about changes in the blood levels of individual components of the kinin system.

EXPERIMENTAL METHOD

Experiments were carried out on 80 chinchilla rabbits weighing from 3.2 to 3.4 kg. The animals were kept under identical conditions and on the ordinary animal house diet. Before the beginning of the experiment the body temperature of the rabbits was measured daily for ten days. Only those animals whose fluctuations of rectal temperature did not exceed 0.2°C were chosen for the experiments.

Fever was produced by daily intravenous injection (into the marginal vein of the ear) of pyrogenal (produced by the N. F. Gamaleya Institute of Epidemiology and Microbiology, Academy of Medical Sciences of the USSR, 1000 MPD*/ml, batch No. 51) in a dose of 5 μg/kg body weight (50 MPD/kg) for 1, 3, 5, and 10 days. After daily injection of pyrogenal in the specified dose, the temperature reaction weakened starting with the 7th day. To maintain the reaction at the same level, the dose of the preparation was therefore increased after the 7th day to 7 μg/kg body weight. Animals receiving injections of pyrogen-free physiological saline, made up in bidistilled water, served as the control. Lymph was obtained from the thoracic duct (TD) where it empties into the venous angle. Blood for investigation was taken from the marginal vein of the ear. Levels of kininogen [9, 13], kallikrein [10], and kininase activity [10, 14] were determined in the lymph and blood. The experimental material was subjected to statistical analysis. After the experiment the animals were killed by injection of a lethal dose of general anesthetic.

EXPERIMENTAL RESULTS

The investigations showed that the kininogen level and kininase activity in the lymph of intact animals were lower than in the blood; only in the case of kallikrein was there no significant difference between its concentrations in the peripheral blood and lymph (Table 1).

*Minimal pyrogenic doses.

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TABLE 1. Time Course of Concentrations of Components of Kallikrein–Kinin System in Thoracic Duct Lymph (A) and Blood Plasma (B) of Intact Rabbits and during Febrile Reaction of Varied Duration (M ± m)

Parameter studied	Test object	Intact animals	Number of injections of pyrogenal			
			1	3	5	10
Kininogen, μg-eq bradikinin / ml	A	5,42±0,12	—	—	—	—
	B	6,51±0,29				
4th day	A	—	5,36±0,12	5,70±0,17	—	—
	B	—	6,67±0,15	6,36±0,17	—	—
6th day	A	—	5,57±0,12	5,76±0,19	4,72±0,11	—
	B	—	6,96±0,13	6,85±0,21	5,83±0,15*	—
10th day	A	—	5,54±0,11	5,71±0,16	4,83±0.13	4,18±0,26*
	B	—	6,60±0,17	7,00±0,23	6,21±0.15	6,95±0.16
Kallikrein, μg-eq bradykinin/ ml	A	1,58±0,15				
	B	1,31±0,11				
4th day	A	—	1,74±0,12	1,26±0,09*	—	—
	B	—	1,29±0,08	1,71±0,15*	—	—
6th day	A	—	1,72±0,20	1,04±0,09*	0,93±0,07*	—
	B	—	1,25±0,10	1,97±0,12*	0,95±0.008*	—
10th day	A	—	1,71±0,15	1,57±0,12	1,68±0.15	1,05±0,07*
	B	—	1,40±0,14	1,05±0,08*	2,08±0,21*	1,07±0.10
Kininase activity, μg-eq bradykinin/liter	A	0,086±0,005	—	—	—	—
	B	0,121±0,006	—	—	—	—
4th day	A	—	0,108±0,006*	0,065±0,010	—	—
	B	—	0,106±0,005	0,135±0,009	—	—
6th day	A	—	0,087±0,010	0,087±0,010	0,114±0.008*	—
	B	—	0,114±0,007	0,136±0,006	0,127±0.008	—
10th day	A	—	0,123±0,008*	0,111±0,009*	0,101±0,011	0,065±0,009*
	B	—	0,122±0,005	0,120±0.008	0,089±0.006	0,087±0,004*

Legend. Here and in Table 2: *$p < 0.05$.

A single injection of pyrogenal was sufficient to induce a marked FR in the rabbits. The maximal rise of rectal temperature was 2.3°C and the total duration of the FR was 7 h. In the postfebrile period (24 h after injection of pyrogenal) the rabbits' body temperature was the same as initially.

After a single injection of pyrogenal the kallikrein and kininogen concentrations in the lymph and blood were unchanged at all times of investigation, but two "peaks" of kininase activity were observed in the lymph — on the 4th and 10th days (Table 1).

Three injections of lipopolysaccharide likewise did not affect the kininogen concentration in the biological fluids. Meanwhile elevation of the kallikrein level in the blood was observed on the 4th and 6th days after FR, followed by a fall until the 10th day of investigation. Its level in the lymph fell at later stages. A significant increase in kininase activity was found only in the lymph, and only toward the 10th day after fever.

After five injections of pyrogenal, on the 6th day after the beginning of the experiment, the kininogen and kallikrein levels were observed to fall, and on the 10th day this was followed by a fall in the blood kininase activity. Later during the experiment the kallikrein concentration rose significantly and was almost twice its initial value, whereas the kininogen gradually returned to normal. Significant changes in the lymph were found only for kallikrein (a decrease) and kininase activity (an increase), toward the 6th day of investigation.

Ten injections of pyrogenal were followed by a decrease in the concentration of all components of the KKS studied in the lymph, whereas in the blood only kininase activity fell.

The investigations thus showed that FR, depending on its duration, is accompanied by considerable changes in activity of the KKS. These changes are integral in character, i.e., they are observed in all stages of humoral transport — in both blood and lymph, an indication of close interconnections and unity of KKS with the body fluids.

Quantitative and qualitative differences in the time course of individual parameters of KKS in the lymph and blood during fever can be explained on the grounds that the level of its components in the central lymph is determined not only by permeability of the blood–tissue–lymphatic barriers, but also by the metabolic activity of cells of the internal organs (mainly the liver and intestine) and the reticuloendothelial system of the intercellular connective-tissue spaces.

On the whole, while noting that the KKS possesses definite "resistance" to injury, it can be tentatively suggested that the model of fever over a period of several days, used in this investigation, evidently induces a type of response of the KKS in which qualitative disturbances are observed in the ratio between its components, evidence of a "failure" of the regulatory connections in this system, its exhaustion, and the change from physiological into pathogenetic reactions [3, 4, 8, 11]. These changes arise much earlier in the thoracic duct lymph, moreover, than in the blood. The facts described above are in agreement with the results of our previous investigations, showing that disturbance of the function of the lymphatic system is an essential component in pathology, and the biochemical composition of the lymph is the earliest indicator of disturbances of permeability of the blood–tissue–lymphatic barriers, and also of the quantitative and qualitative changes in metabolic processes in the tissues and organs in typical pathological processes such as inflammation and shock [6, 7].

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