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Lymphatic System Transports Creatine Phosphokinase into Blood Circulation in Febrile Animals

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In rabbits, febrile response of various duration produces a drastic increase (in comparison with blood) in the level of creatine phosphokinase in the lymph transported from various regions of the body. Fever-released creatine phosphokinase is resorbed by the lymphatic capillaries and enter the blood circulation.

Key Words: *fever; lymph; lymphatic system; creatine phosphokinase*

Lymphatic system is the drainage apparatus for connective tissue intercellular spaces. Being large molecular aggregates, enzymes after their release can enter blood circulation only after resorption by lymphatic capillaries. This agrees with the notion that enzyme content in the lymph more precisely reflects changes in cell membrane permeability, the extent and severity of cell damage than enzyme level in the blood [5]. Creatine phosphokinase (CPK) is a key enzyme of the energy supply system for various physiological processes (muscle contraction, nonmuscular forms of motility, transmembrane ionic transport, neurotransmitter synthesis, phagocytosis, *etc.*). Guanidine substrates of the CPK-controlled reaction creatine and creatine phosphate participate in the regulation of a number of metabolic transformations: glycolysis, tricarboxylic acid cycle, cell respiration, oxidative phosphorylation, and protein synthesis [1,3]. At the same time, the mechanisms of positive effect of febrile response (FR) include intensification of energy exchange improving the non-specific organism's resistance [12].

In the present study we compared the content of CPK in the lymph and blood effluent from different body regions during febrile response of varying duration.

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MATERIALS AND METHODS

Experiments were performed on 63 Chinchilla rabbits weighing 2.5-4.2 kg. FR was induced by intravenous pyrogenal [6]. Lymph was obtained from thoracic duct, postnodal subdivision of the hepatic duct, and the intestinal lymph trunk. The blood was drawn from the femoral, portal, and hepatic veins. CPK content was measured in the lymph and blood at various times after inducing FR [2]. The controls were injected with apyrogenic physiological solution. Euthanasia was performed with an anesthetic overdose. The data were analyzed statistically [9].

RESULTS

In all lymph samples from control rabbits, activity of CPK was higher than in the serum (Table 1). In both blood and lymph the level of CPK increased during FR. After single injection of pyrogenal the content of CPK in the lymph remained increased even after body temperature drop, while in the blood it returned to initial values. On the next day after 3 injections of lipopolysaccharide, the content of CPK in the intestinal, hepatic, and thoracic duct lymph increased 5-, 3-, and only 2-fold respectively. At the same time, in all serum samples the increase in CPK content was similar. On days 6 and 10 the level of CPK in body fluids

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returned to the control values. After 5-day FR, high CPK level persisted to the 10th day of the experiment. The degree of CPK accumulation directly depended on fever duration. After 10-day FR, lymphatic and blood CPK increased 6- and 3-fold, respectively.

Our data on normal CPK concentration agree with previous report on a higher lymph content of CPK in comparison with its blood level [13]. In febrile rabbits, CPK level in effluent lymph from various body regions surpassed that in the blood. This hyperenzymemia is thought to be associated with energy metabolism disturbance in the cell. Impaired energy metabolism and decreased energy resources can disturb cell structure and selective membrane permeability and induce enzyme release into extracellular space [1]. CPK plays an important role in energy metabolism, in particular in the cardiac and muscle tissues. Energy is primarily transported from mitochondria to utilization sites in myofibrils and extramitochondrial systems by creatine phosphate molecules with participation of various CPK isozymes [4]. High blood level of these isozymes attests to increased permeability of cell membrane [10].

Since CPK is primarily located in the muscular tissue [15], activation of this enzyme, as well as of lactate dehydrogenase [7] in body fluids of febrile animals can result from their release from muscles during tremor. At the same time, the release of large CPK molecules from cells can result from disturbance of myocyte membrane integrity [11]. In addition, this enzyme was detected in mast cells [14]. Presumably, in febrile animals CPK is released by mast cells together with biologically active substances, which also contributes to the increase of its level in the lymph and blood.

We previously found that in febrile animals the content of many enzymes in the blood and lymph increases during fever [7,8]. Therefore, a universal "trigger" in the regulation of enzyme activity in tissues or their release from cells can be proposed. This role can be played by glucocorticoids.

Thus, our data indicate that CPK released during fever is resorbed by the lymphatic system and enters the bloodstream. The pronounced increase of CPK concentration in the lymph more adequately reflects the degree of fever-induced tissue damage than its blood content.

TABLE 1. Content of Creatine Phosphokinase (μmol/liter×sec) in Lymph and Blood of Febrile Rabbits (*M±m*)

Body fluid		Control	Pyrogenal injections									
			1		3			5		10		
			after 2.5-3 h	after 5-5.5 h	on day 4	on day 6	on day 10	on day 6	on day 10	on day 11		
Lymph	thoracic duct	0.85±0.09	1.99±0.24*	1.55±0.30*	1.63±0.16*	1.30±0.22	0.70±0.15	1.64±0.21*	1.13±0.18*	5.92±0.55*		
	hepatic	0.70±0.05	2.94±0.59*	1.44±0.32*	2.03±0.25*	0.74±0.11	0.66±0.12	1.77±0.22*	1.48±0.19*	4.53±0.83*		
	intestinal	0.68±0.07	2.03±0.23*	1.44±0.25*	3.22±0.49*	0.74±0.18	0.70±0.17	2.14±0.23*	1.20±0.20*	4.05±0.92*		
Serum	femoral vein	0.33±0.05	1.00±0.12*	0.59±0.13*	1.22±0.20*	0.45±0.09	0.32±0.06	1.53±0.10*	0.89±0.13*	1.40±0.14*		
	portal vein	0.43±0.08	0.80±0.09*	0.53±0.08*	1.28±0.14*	0.40±0.12	0.36±0.07	1.18±0.14*	0.71±0.11*	1.27±0.21*		
	hepatic vein	0.41±0.12	0.77±0.13*	0.80±0.13*	1.16±0.23*	0.40±0.08	0.36±0.09	1.58±0.28*	0.61±0.11	1.05±0.16*		

Note. *Differences with control are significant.

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