Effect of Contrykal on Lymph and Blood Kallikrein-Kinin Systems and Contractile Activity of Lymphatic Microvessels during Fever

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Contrykal prevented activation of the kallikrein-kinin system in the lymph and blood during short-term fever, reduced it during long-term fever, and increased contractile activity of the walls and valves of lymphatic microvessels, thus accelerating lymph flow.

Key Words: *fever; contrykal; lymph; kallikrein-kinin system*

Febrile reaction (FR) is accompanied by considerable changes in the functional activity of organs and systems and homeostatic disturbances. An important role in the homeostasis is played by the lymphatic system, which appropriate resorption and transport functions predetermine many qualitative and quantitative changes in metabolic processes at the level of the microcirculatory bed. Taking into account transcapillary exchange of the kallikrein-kinin system (KKS) components (blood—tissue fluid—lymph—blood), we revealed phase shifts in their content in the lymph flowing off from different regions and in the peripheral blood during FR of different duration [7]. It is known, that the kinin system plays an important role in the central mechanisms of fever.

The present study was aimed at investigation of the effect of contrykal on the content of KKS components in the lymph and blood and contractile activity of lymphatic microvessels (LM) during FR.

MATERIALS AND METHODS

Experiments were carried out on 30 Chinchilla rabbits (2.5-4.2 kg) and 23 albino rats (150-200 g). Febrile reaction was induced as described previously [6,7]. In rabbits, the lymph (from the thoracic duct) and blood (from femoral vein) were taken during FR rise and decay after a single injection of pyrogenal and on the next day after 3 or 5 daily injections. The samples were analyzed for the content of kininogenin [10], prekallikrein [2], kallikrein [12], and free kinins [11] and kininase activity [12]. Spontaneous formation and destruction of kinins in samples was prevented. Contrykal in a daily dose of 3000 antitrypsin U/kg in 20 ml apyrogenic saline was intravenously infused 30 min after pyrogenal injection.

In rats, contractile activities of the walls and valvules of mesenteric LM were studied by vital microscopy [1,13] during the rise and decay of FR caused by single injection of pyrogenal after local application of contrykal (100 antitrypsin U in 0.2 ml apyrogenic saline). In control rats, the preparation was administered by the same route. The data were analyzed statistically.

RESULTS

Experiments showed that contrykal did not reduce temperature rise during fever, but prevented activation of both lymph and blood KKS induced by single or triple injections of pyrogenal and reduced it in 5-day FR (Table 1). During short-term FR, the content of free kinins and kallikrein as well as kininase activity in the lymph and blood remained at the baseline level. The contrykal-treated animals receiving 5 injections of pyrogenal showed a less pronounced elevation in

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lymph and blood kinins and a smaller decrease in the content of kininogenin, prekallikrein, and kallikrein than controls.

In the control rats, mesenteric application of contrykal increased the frequency of spontaneous contractions of LM walls and valvules 1.5 times after 20-30 sec. The amplitude of contractions increased; the rhythmical contractions of the walls and valvules were synchronous or asynchronous; all microvessels contained transparent lymph with solitary lymphocytes, lymph flowed in one direction and at higher velocity than in untreated rats. Being applied during FR at the stages of temperature rise and decay, contrykal significantly enhanced contractile activity of LM walls and valvules (2.5-fold after 5-10 sec) and increased the amplitude of contractions without changing their rhythm, the lymph remained transparent, its flow considerably accelerated.

Considering the mechanisms of contrykal-induced inhibition of KKS, it was suggested that contrykal or its peptide metabolites can interact with tissue proteins and form slowly dissociating inactive complexes with kininogenases [16]. In addition, the effects of contrykal on KKS can be realized via inhibition of the synthesis and release of histamine and serotonin and via inhibition of proteolytic enzymes [3,4], the content of which was shown to change [5,7]. We have previously found that long-term (10 days) FR depleted KKS, and that the deficit of its principal components resulted from reduced kinin production [7]. It can be suggested that early treatment of FR with contrykal will preserve the balance between the components of this system and maintain the optimum level of kinin formation.

Considering the effect of contrykal on contractile activity of the walls and valvules of LM, it should be

TABLE 1. Effect of Contrykal on Components of Blood and Lymph Kallikrein-Kinin Systems in Fever Reaction (*M*±*m*)

Indices	Pyrogenal administration			
	single injection		three injections	five injections
	after 2.5-3 h	after 5-5.5 h		
Lymph from untreated animals				
Kininogen, μg-eq bradykinin/ml	5.36±0.14	5.57±0.30	5.70±0.22	4.72±0.26
Free kinins, nmol/liter bradykinin	2.24±0.19	1.86±0.20	2.61±0.21	2.59±0.16
Prekallikrein, μmol arginine/liter/min	39.12±2.94	35.45±2.76	36.00±1.90	27.26±1.86
Kallikrein, μg-eq bradykinin/ml	1.74±0.12	1.75±0.20	1.26±0.09	0.93±0.07
Kininase activity, μg-eq bradykinin/ml/min	0.108±0.007	0.087±0.01	0.065±0.01	0.114±0.08
Lymph from contrykal-treated animals				
Kininogen, μg-eq bradikinin/ml	5.15±0.34	5.35±0.34	5.68±0.23	4.90±0.27
Free kinins, nmol/liter bradykinin	1.39±0.26*	1.61±0.35*	1.72±0.20*	1.92±0.22
Precallikrein, μmol arginine/liter/min	34.17±3.56	38.21±3.48	34.88±2.54	30.00±1.56
Kallikrein, μg-eq bradykinin/ml	1.42±0.50	1.83±0.41	1.43±0.32	1.55±0.52
Kininase activity, μg-eq bradykinin/ml/min	0.082±0.008*	0.086±0.005	1.095±0.007	0.072±0.008*
Plasma from untreated animals				
Kininogen, μg-eq bradykinin/ml	6.67±0.24	6.96±0.20	6.36±0.15	5.83±0.20
Free kinins, nmol/liter bradykinin	2.23±0.28	2.29±0.19	3.34±0.26	3.80±0.19
Prekallikrein, μmol arginine/liter/min	66.27±2.62	67.89±2.26	66.72±2.21	57.76±1.87
Kallikrein, μg-eq bradykinin/ml	1.29±0.08	1.25±0.10	1.71±0.16	0.95±0.08
Kininase activity, μg-eq bradykinin/ml/min	0.106±0.005	0.114±0.007	0.135±0.009	0.127±0.008
Plasma from contrykal-treated animals				
Kininogen, μg-eq bradykinin/ml	6.50±0.20	6.72±0.41	6.51±0.18	6.37±0.18*
Free kinins, nmol/liter bradykinin	2.08±0.20	2.11±0.23	2.12±0.17*	2.61±0.10*
Prekallikrein, μmol arginine/liter/min	64.15±2.31	62.99±2.96	65.00±1.90	63.88±2.05*
Kallikrein, μg-eq bradykinin/ml	1.33±0.10	1.30±0.18	1.32±0.13*	1.20±0.10*
Kininase activity, μg-eq bradykinin/ml/min	0.122±0.004	0.120±0.005	0.131±0.008	0.134±0.006

Note. *$p<0.05$ in comparison with untreated animals.

taken into account that the development of FR promotes disturbances in lymph circulation despite enhanced lymph production. In turn, disturbed circulation can contribute to the pathogenesis of metabolic changes at the level of lymph microcirculation [9]. At the same time, KKS plays a significant role in microcirculation. Kinins increase the number and diameters of functioning capillaries which leads to enlargement of the vascular bed. In rat mesentery, bradykinin dilates precapillary sphincters, arterioles, and venules, which induced plethora of the microcirculatory bed and decelerates blood flow in venules. Active contraction of endotheliocytes in venules forms gaps between them and increases permeability. High kinin concentrations increase vascular permeability and decelerate blood flow, promote aggregation of blood cells [15]. Bradykinin increases contractile activity of LM [14]. Our study showed that despite the inhibition of lymph and blood KKS, contrykal potentiated contractile activity of the LM, which probably facilitated their dilation. Enhanced contractile activity of smooth muscle structures in lymphatic vessels and their dilation promote lymph flow.

Thus, contrykal induced general inhibition of KKS which affected not only the blood, but also extravascular space and lymph. Simultaneous stimulation of LM contractions facilitates resorption of cell metabolites from the interstitial space and their transport through lymphatic vessels, thus improving exchange between blood and tissues. Our data substantiate one of the pathogenetic mechanisms of the effect of contrykal in FR.

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