COMPONENTS OF THE PLASMA KININ SYSTEM IN RABBITS WITH ACUTE INFLAMMATION

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At the height of development of acute aseptic inflammation of the subcutaneous cellular tissue the plasma kinin system in the general circulation becomes activated, as reflected in an increase of 1.5-2 times in kallikrein activity, an increase of 1.5-3 times in kininase activity, and a decrease of 25-26% in the kininogen level. The conditions are created for increased generalized formation and accumulation of free kinins, the mediators of the second phase of the disturbances of vascular permeability in inflammation.

KEY WORDS: blood plasma, bradykinin, acute inflammation, kinin system.

Regular biphasic changes in the content of free kinins in the general circulation of rabbits during acute inflammation were established previously. In the first 5-6 h the blood kinin concentration fell by 4-5 times, but from the 2nd to the 5th days their concentration increased by 5-6 times. The kinin level in venous blood draining from the inflammatory focus was increased by 6-9 times with effect from the first hour of development of the inflammatory reaction [5]. No results of a combined study of the principal components of the kinin system in the general circulation during the development of acute inflammation can be found in the literature. There are only reports of a change in the concentration of kininogen and of kinin-forming and kinin-destroying enzymes in the lymph flowing from the region of inflammation, or in the exudate or perfusion fluid obtained from the surface of the affected organs and tissues.

The object of this investigation was to study the character of changes in the principal components of the plasma kinin system regulating the level and metabolism of free kinins in the peripheral blood at different times during the development of acute inflammation.

EXPERIMENTAL METHOD

Experiments were carried out on 17 chinchilla rabbits weighing 2-3.5 kg. Inflammation was produced in the animals by injection of 1 ml turpentine or a mixture consisting of 0.2 ml turpentine and 0.8 ml mineral oil into the subcutaneous cellular tissue of the anterior abdominal wall. During the first 5-6 h and the next 1-7 days, samples of 2-3 ml blood were taken from the marginal vein of the ear and the concentrations of protein, total BAEE-esterase [3], and the three components of the kinin system – kininogen [3], kininase (the writer's modification of Erdös's biological method) [2], and kallikrein (a biological method devised by the writer and based on activation of plasma kininogenase, which catalyzes the reaction of "spontaneous" bradykinin formation) [6] were investigated in oxalated or heparinized plasma. Bradykinin (Sandoz, Switzerland) and bradykinin triacetate (Reanal, Hungary) were used as the standard.

EXPERIMENTAL RESULTS AND DISCUSSION

In all the experimental animals local hyperemia of the skin and swelling began to develop 1 h after the injection of turpentine; with the passage of time the changes increased and by the end of the first day a soft inflammatory focus of infiltration measuring up to 6 × 10 cm was formed in the anterior abdominal

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TABLE 1. Content and Activity of Components of Kinin System, BAEE-Esterase, and Protein in Blood Plasma of Rabbits with Acute Inflammation (M±m)

Parameter studied	Initial concentration	Time after injection of inflammatory agent								
		h				days				
		1	3	5	1	3	4	5	7	
Kininogen (in μg bradykinin/ml plasma)	3,54±0,30	3,61±0,85	3,34±0,78	3,04±0,26	3,09±0,30	2,65±0,36*	—	2,63±0,27*	3,31±0,35	
Protein (in g %)	5,89±0,07	5,45±0,13*	5,36±0,15*	5,41±0,19*	5,24±0,13*	5,55±0,13*	—	5,62±0,11*	5,92±0,23	
Kininase (in μg bradykinin/ml plasma/min)	1,50±0,14	1,34±0,28	0,93±0,17*	0,52±0,06*	0,46±0,08*	0,50±0,13*	—	0,88±0,16*	1,39±0,26	
Kallikrein (in μg bradykinin/ml plasma)	0,40±0,06	—	—	0,23±0,13	0,33±0,16	0,63±0,16	1,56±0,20*	0,61±0,16	0,67±0,20	
BAEE-esterase (in μ moles BAEE/ml plasma/min)	0,37±0,08	0,27±0,04	0,24±0,04	0,19±0,06	0,12±0,02*	0,15±0,03*	—	0,29±0,02	—	
Free kinins (in ng/ml plasma)†	4,2±0,43	1,3±0,06	0,8±0,07*	1,1±0,30*	1,9±0,40	14,3±2,92*	23,1±3,12*	21,7±5,87*	9,1±1,41	

* $P < 0.05$.

† Data on the concentration of free kinins are taken from the previous paper [5].

wall. In some animals an area of necrosis measuring up to 2 × 3 cm was present in the center of the zone of infiltration. In the next 3-5 days, the zone of infiltration increased still more in volume, it became demarcated from the surrounding tissues, and began to grow firm.

The results of tests carried out during the development of the inflammatory reaction are given in Table 1. Clearly the kininogen level in the peripheral blood showed a tendency to fall during the first 3-5 h of development of inflammation, but the decrease in its concentration became statistically significant (by 25-26%) only on the 3rd-5th day of inflammation. The plasma protein concentration also fell but no strict parallel could be drawn between the changes in these two parameters. The lowest kininogen level was found on the 3rd-5th day and the lowest protein concentration 24 h after administration of the inflammatory agent. The kininase activity started to fall after the first hour of development of inflammation, and ability to split bradykinin remained reduced by 1.5-3 times during the first 3-5 days of the inflammatory reaction. The plasma kallikrein activity was lowered by 1.5-2 times in the first 5-24 h after injection of the irritant, but starting from the 3rd day and, in particular, on the 4th day, a 3-4-fold in kinin-forming activity was observed.

Data on the content of total BAEE-esterase, the activity of which is frequently used [1, 2, 4] to judge the plasma kallikrein level, were in contradiction with the dynamics of the parameters described above. In the present experiments, BAEE-esterase activity fell starting from the first hour of development of the inflammatory reaction, to reach a minimum (a threefold decrease) 1-3 days after injection of the turpentine. These results indicate that changes in total plasma BAEE-esterase activity do not reflect the true content of kallikrein in the plasma. Of the two methods used to determine activity of the kinin-forming enzyme, the method based on the reaction of "spontaneous" bradykinin formation was the most reliable.

Analysis of the results showed that the formation of a local inflammatory focus in the body is accompanied by quantitative and qualitative changes in the components of the kinin system in the general circulation. These changes are purposive in character and at the height of development of inflammation (3-5 days) they amount to an increase in kallikrein activity, a decrease in kininase activity, and a lowering of the kininogen level, i.e., conditions are created for increased generalized formation and accumulation of free kinins [5]. The decrease in concentration of free kinins in the general circulation detected in the writer's previous experiments after the action of a harmful agent [5] evidently arises through a decrease in kallikrein activity, possibly caused by a compensatory increase in the synthesis of inhibitor.

According to Wilhelm's classification [7], aseptic turpentine inflammation may be characterized by an acute inflammatory reaction of the 4th type (of the six principal types), the second phase of which lasts about 100 h (3-5 days). It was in that period that activation of the plasma kinin system was found. On the 3rd-5th days of inflammation the conditions are favor-

able for increased formation and accumulation of free kinins in the general circulation. The results point to the role of bradykinin as the mediator of the second phase of the acute inflammatory reaction.

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