ROLE OF THE LYMPHATIC SYSTEM IN THE MECHANISM OF MEDIATOR ACTION IN IMMEDIATE ALLERGY

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The role of the lymphatic system in the pathogenesis of allergic reactions has been examined from the immunologic aspect. Yet in allergy and, in particular, in systemic allergic reactions of immediate type, real grounds are created for disturbance of the circulation of lymph, its transport, and changes in its qualitative composition. It can be tentatively suggested that an essential role is played by the lymphatic system in the resorption and transport of mediators of immediate allergy from the intercellular spaces of tissues and organs into the general circulation.

The object of this investigation was to study the comparative dynamics of mediators of immediate allergy: components of the kallikrein-kinin system and biogenic amines, namely histamine and serotonin, in the lymph and blood of dogs during sensitization and anaphylactic shock (AS).

EXPERIMENTAL METHOD

Experiments were carried out on 58 dogs. To determine biologically active substances, 65 virgin rats, 12 cats, and 36 guinea pigs were used. The animals were sensitized by three subcutaneous injections of normal horse serum in a dose of 6.4 mg/kg body weight. On the 18th-23rd day after the last sensitizing injection the dogs were used for the acute experiment under thiopental anesthesia (20 mg/kg body weight). Lymph was obtained by cannulation of the thoracic duct at the point where it empties into the venous angle. Blood for testing was taken from the femoral vein. AS was induced by intravenous injection of the reacting dose of antigen (32 mg/kg body weight). The levels of histamine [7, 15], serotonin [8, 10], kininogen [3, 11], kallikrein [6], and free kinins [5, 13], and kininase activity [6, 12] were determined in the lymph and blood. Throughout the experiment the arterial blood pressure and respiration of the experimental animals were recorded on a kymograph. Numerical values of biochemical blood and lymph determination were expressed in SI units. The experimental results were subjected to statistical analysis. After the experiment the animals were killed by injection of a lethal dose of the anesthetic.

EXPERIMENTAL RESULTS

The concentration of biogenic amines and of components of the kallikrein-kinin system (kininogen and free kinins) in the lymph of the intact animals were considerably less (2-3 times) than in the peripheral blood (Table 1). Significant differences were not found only in the kallikrein concentration and kininase activity between blood and lymph.

Protein sensitization was accompanied by an increase in the kininogen and kallikrein concentrations and a fall in the serotonin level in the lymph, whereas a fall in the serotonin level in the blood was accompanied by a decrease in the kininogen concentration. No changes in the concentrations of histamine and other components of the kallikrein-kinin system were observed in the lymph and blood.

In AS there was a massive, "explosive" release of biologically active substances (histamine and serotonin) and activation of the kallikrein–kinin system in the body fluids,

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TABLE 1. Concentrations of Biologically Active Substances in Lymph and Blood of Intact Dogs (M ± m)

Parameter tested	Lymph	Blood
Histamine, μmoles/liter	0,88±0,09	1,78±0,13
Serotonin, μmoles/liter	0,36±0,04	0,68±0,08
Free kinins, nmoles/liter bradykinin	0,95±0,08	2,96±0,26
Kininogen, mg/liter	1,49±0,14	4,26±0,20
Kallikrein, mg/liter	0,99±0,05	1,14±0,06
Kininase, mg/liter/min	0,089±0,005	0,107±0,011

TABLE 2. Dynamics of Histamine, Serotonin, and Components of Kallikrein–Kinin System in Lymph and Blood of Dogs during AS (M ± m)

Parameter tested	Before injection of reacting dose of antigen	After injection of reacting dose of antigen, min			
		5–8	30	60	120
Free kinins, nmoles/liter bradykinin:					
Lymph	0,99±0,13	2,12±0,39****	3,59±0,18*	2,67±0,29*	1,78±0,16***
Blood	3,27±0,42	3,94±0,46	5,06±0,45***	4,19±0,38**	3,09±0,18
Kininogen, mg/liter:					
Lymph	1,96±0,16	1,13±0,15*	1,12±0,20*	1,90±0,11	1,79±0,11
Blood	1,79±0,13	1,24±0,10*	0,61±0,09*	0,70±0,12*	0,90±0,12*
Kallikrein, mg/liter:					
Lymph	1,34±0,12	1,66±0,11**	2,19±0,20*	1,84±0,20**	1,58±0,15
Blood	1,39±0,13	1,83±0,21**	2,69±0,22**	2,36±0,26***	2,07±0,25**
Kininase, mg/liter/min:					
Lymph	0,087±0,003	0,134±0,011***	0,153±0,006*	0,124±0,007*	0,112±0,014
Blood	0,104±0,005	0,132±0,013**	0,158±0,005*	0,138±0,007*	0,109±0,005
Histamine, μmoles/liter					
Lymph	0,91±0,03	3,34±0,36*	1,66±0,22***	0,90±0,12	0,80±0,12
Blood	1,70±0,15	3,54±0,32*	2,32±0,16***	1,65±0,13	1,45±0,18
Serotonin, μmoles/liter:					
Lymph	0,23±0,03	0,79±0,06*	0,77±0,07*	0,87±0,05*	0,47±0,04*
Blood	0,39±0,03	0,54±0,05****	0,55±0,06**	0,62±0,06***	0,42±0,04

* $P<0,001$.
** $P<0,05$.
*** $P<0,01$.
**** $P<0,02$.

reflected in a fall in the kinogren level and an increase in the concentrations of kallikrein and free kinins and in kininase activity. In the lymph of the thoracic duct, however, changes in the concentrations of biogenic amines and free kinins took place sooner, they were greater in magnitude, and more prolonged in character than those in the peripheral blood (Table 2). Within 5-8 min of the beginning of the clinical picture of shock, for instance, a more than threefold increase was observed in the concentrations of biogenic amines in the lymph, whereas the increase in the blood was by only 1.5-2 times. Absolute values of the serotonin concentration in the lymph, despite the quite low (compared with blood) initial level, were higher at all times of the investigation than in the blood. The fact must be emphasized that changes in the histamine level in the lymph during AS occurred only in the first 30 min after the beginning of the clinical picture of AS, whereas the serotonin level in the lymph was considerably and significantly raised throughout the period of observation (2 h); during the first hour after the beginning of AS, moreover, the increase in the serotonin concentration in the lymph was close on fourfold, whereas in the blood it was increased by only about 1.5 times.

The increase in the level of free kinins in the lymph was significant at all times of the period (2 h) of observation whereas in the blood it was significant only 30 min and 1 h after the beginning of shock. The maximal increase in the kinin concentration in the lymph was considerably greater than in the blood (by 3.5 and 1.5 times respectively). Elevation of the free kinin level in the lymph and blood was accompanied by an increase in

activity of the kinin-catabolizing enzyme kininase; activity of the enzyme in the lymph, moreover, was higher than initially.

It is interesting to note that the greatest changes in concentrations of components of the kallikrein–kinin system in the lymph took place 30 min after injection of the reacting dose of antigen, whereas the greatest increase in the histamine and serotonin level occurred as early as 5-8 min after the beginning of shock. Since the "shock organ" in dogs with AS is the liver and the splanchnic bed, the greater increase in the concentration of biogenic amines in the lymph than in the blood can be explained by their arrival from the abdominal organs followed by resorption by the lymphatic capillaries. On the other hand, the biochemical composition of lymph in the thoracic duct is a sensitive indicator of the functional state of organs of the gastrointestinal tract and it reflects changes in permeability of cell and intracellular membranes and the degree in depth of cell damage more accurately than the peripheral blood [9, 14].

Biogenic amines, stimulating activation of the kinin system of the intercellular fluid, lymph, and blood, probably play a trigger role in the pathogenesis of AS. The mechanism of this process can be represented as follows. Massive release of primary mediators (histamine and serotonin) facilitates the entry of plasma proteins into the extravascular space, where tissue kinins are activated and intracellular hydrolytic enzymes are released into the blood and lymph, where they increase the proteolytic activity in the body fluids. In turn the proteolytic enzymes increase vascular permeability directly, through their action on the endothelium of the vessel walls, and also directly, by inducing the further formation of permeability mediators. Activation of proteolytic enzymes is accompanied ultimately by increased activity of the kinin system.

Elevation of the level of biologically active substances in the blood and lymph observed in these experiments correlated with a marked increase in the velocity of lymph flow, in agreement with data in the literature on intensification of the lymphatic circulation in experimental animals following injection of biogenic amines and bradykinin [1, 2, 4].

An important role in the circulation of mediators of immediate allergy is thus played by the lymphatic system, and it is manifested mostly clearly in systemic allergic reactions.

LITERATURE CITED

1. É. I. Ainson, Izv. Akad. Nauk Ést. SSR, 29, No. 1, 1 (1980).
2. G. N. Kotova, Nauchn. Tr. Bashkir. Med. Inst., 17, 470 (1968).
3. T. S. Paskhina, T. P. Egorova, V. P. Zykova, et al., in: Modern Methods in Biochemistry [in Russian], Vol. 2, Moscow (1968), p. 232.
4. I. A. Potapov, Outlines of Physiology of the Lymphatic Circulation (Mechanisms of Participation of the Lymphatic System in Regulation of the Blood Circulation) [in Russian], Alma-Ata (1977).
5. M. S. Murovikina, Byull. Éksp. Biol. Med., No. 5, 123 (1971).
6. M. S. Surovikina, Kardiologiya, No. 2, 119 (1973).
7. V. I. Uspenskii, Histamine [in Russian], Moscow (1963), p. 117.
8. G. A. Chernov and A. A. Lipats, Patol. Fiziol., No. 3, 80 (1962).
9. L. Arvy, Presse Med., 79, 915 (1971).
10. C. E. Dalgliesh, C. C. Toh, and T. C. Work, J. Physiol. (London), 120, 298 (1953).
11. C. R. Diniz and I. F. Carvalho, Ann. N. Y. Acad. Sci., 104, 77 (1963).
12. E. G. Erdös and F. M. Sloane, Biochem. Pharmacol., 11, 585 (1962).
13. S. H. Ferreira and I. R. Vane, Br. J. Pharmacol. Chemother., 29, 367 (1967).
14. G. P. Lewis, J. Physiol. (London), 205, 619 (1969).
15. O. H. Riesser, Arch. Exp. Pathol. Pharmak., 187, 1 (1937).