ROLE OF THE LYMPHATIC SYSTEM IN TRANSPORT OF BIOLOGICALLY ACTIVE SUBSTANCES IN DIFFERENT KINDS OF SHOCK

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Several complex and closely intertwined pathophysiological changes take place in shock. An important role in the changes in vascular permeability, activity of the smooth muscle of organs, and of the cardiovascular system in this condition is played by biogenic amines. It can be postulated that in disorders of the central and, in particular, the peripheral hemodynamics in shock an important role in resorption and transport of biologically active substances from intercellular spaces of tissues and organs into the general circulation is played by the lymphatic system.

The aim of this investigation was to compare concentrations of histamine, serotonin, adrenalin, and noradrenalin in the blood and in lymph from the thoracic duct (TD), and also to investigate the absolute quantity of biogenic amines and mediators transported into the general circulation in the course of anaphylatic and endotoxin shock (AS and ES respectively).

EXPERIMENTAL METHOD

Experiments were carried out on 68 clinically healthy mongrel dogs of both sexes weighing from 6 to 28 kg, anesthetized with thiopental sodium in a dose of 20-25 mg/kg. The animals were sensitized by three subcutaneous injections of normal horse serum in a dose of 6.4 mg/kg. AS was induced on the 18th-21st day by intravenous injection of the reacting dose of antigen, and ES by a single intravenous injection of *Shigella sonnei* endotoxin (batch E7S No. 6747, obtained from the I. I. Mechnikov Research Institute of Vaccines and Sera) in a dose of 3.5 mg/kg. Lymph was obtained by cannulation from TD at the point where it enters the left venous angle. Blood for investigation was taken from the posterior vena cava by introducing a polyethylene cannula through the femoral vein. The velocity of the lymph flow was recorded by a drop recorder (and subsequently converted into ml/kg/min). Throughout the experiment the blood pressure (BP) and respiratory movements of the experimental animals were recorded kymographically. The histamine, serotonin [1], adrenalin, and noradrenalin [4] levels in the lymph and venous blood were investigated. Allowing for changes in the velocity of the lymph flow the absolute quantity of biologically active substances and mediators (adrenalin and noradrenalin) transported by the lymph into the blood stream in unit time was calculated. All parameters were investigated during 3 h after the beginning of shock. In a separate series of experiments the biochemical parameters in the lymph and blood also were studied after 12-15 h. Data on the survival rates of the animals are given in Fig. 1. The numerical results were subjected to statistical analysis [5, 7].

EXPERIMENTAL RESULTS

As will be clear from Fig. 2, an increase in velocity of the lymph flow was a characteristic response to AS and ES. During the first minutes of shock this increase was more than four times greater than the initial values. At the same time there were sudden changes in the concentrations of biologically active substances in the blood and lymph (Table 1). The histamine level in the blood and lymph only 5-8 min after injection of the reacting dose of antigen was over 300% of the initial level. It must be pointed out that the histamine level in the blood of animals dying in the first minutes of AS was not significantly changed, where-

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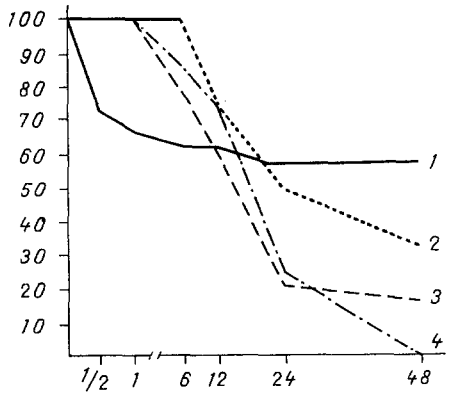

Fig. 1. Survival rate of animals. Abscissa, time after injection of reacting dose of antigen or endotoxin (in h); ordinate, survival rate (in %). 1) AS (n = 30), 2) ES with cannulation of TD 12-15 h after injection of endotoxin, followed by formation of lymphovenous anastomosis (n = 12), 3) ES with ligation of TD (n = 9) or formation of lymphovenous anastomosis (n = 9) after drainage for 3 h, 4) ES + permanent drainage of TD (n = 8).

as in the lymph it was increased by many times (Fig. 3). This indicates directly that the greater part of the histamine released during severe hemodynamic disturbances is resorbed by the lymphatic capillaries.

In ES no significant changes were observed in the blood and lymph histamine levels in the early periods of shock. There was a small increase in its concentration in the lymph (by 133%) but not until 3 h after injection of the endotoxin, and in the blood shortly before death of the animals (after 12-15 h). Data in the literature on the role of histamine during the action of bacterial endotoxins are contradictory [2, 6, 9-11]. Although we found no increase in its concentration in the biological fluids of the organism in the initial periods of ES, the role of histamine as a local vasoactive principle in primary hemodynamic disturbances cannot be completely ruled out. It is not by accident that an important place in the mechanism of ES is ascribed to a high histamine concentration in the region of the hepatic venules, leading to stasis in the hepatoceliac vessels, to a decrease in the venous return, and a fall of BP. When the hemodynamics in the liver is severely disturbed, transport of biologically active amines from it is probably effected mainly through the lymphatic system. The absolute quantity of histamine transported by the lymph (allowing for changes in the lymph flow per unit time) during the first minutes of ES rose sharply to 346% of the initial level. At the same time it was found that in the early stages of shock the lymph of TD consists mainly of lymph from the liver; transudation was intensified in Disse's spaces [8].

The rise in the histamine level in the blood and lymph in the later stages of shock can be explained by increased synthesis. Activation of histidine decarboxylase in many organs has been described during shock by a number of workers [6, 13]. There is also evidence of inhibition of histaminase activity [3, 6].

In AS a marked increase in the serotonin concentration was observed in the lymph and blood. In the lymph, however, these changes arose earlier and were prolonged. In ES the blood serotonin level, on the contrary, was depressed during the first minutes of development of shock, whereas in the lymph, just as in AS, its level was considerably raised. The maximal increase in the serotonin concentration in the blood and lymph was found 12-15 h after injection of the endotoxin, namely by 160 and 240% respectively. The dynamics of serotonin transport by the lymph into the general circulation (absolute quatity per unit time) in AS and ES was similar to that of histamine and its concentrations were sharply increased at all times of the investigation. The increase in the serotonin concentration in the biological fluids in AS was evidently due to its release from platelets (which were aggregated by the action of catecholamines), to massive release from depots (mast cells, enterochromaffin cells of the gastrointestinal tract, etc.), a fall of monoamine oxidase activity,

TABLE 1. Dynamics of Blood and Lymph Levels of Biologically Active Substances and Their Transport by Lymph of TD in AS and ES (M ± m)

Parameter	Type of shock	Material studied	Initial value	After injection of reacting dose of antigen or of endotoxin					
				5–8 min	30 min	1 h	2 h	3 h	12–15 h
Histamine, μmoles/liter	ES	lymph	0,368 ± 0,057 (0,111)	0,315 ± 0,053 (0,394)	0,419 ± 0,089 (0,265)	0,442 ± 0,091 (0,193)	0,471 ± 0,097 (0,214)	0,491 ± 0,098* (0,211)	3,462 ± 1,396* (1,648)
		blood	0,358 ± 0,019	0,317 ± 0,067	0,415 ± 0,087	0,393 ± 0,089	0,361 ± 0,066	0,377 ± 0,062	5,318 ± 2,004*
	AS	lymph	0,333 ± 0,047 (0,133)	0,973 ± 0,169* (1,514)	0,565 ± 0,089* (0,424)	0,327 ± 0,041 (0,182)	0,325 ± 0,039 (0,156)	0,324 ± 0,054 (0,132)	—
		blood	0,382 ± 0,029	1,152 ± 0,281*	0,500 ± 0,054*	0,371 ± 0,039	0,395 ± 0,047	0,427 ± 0,040	—
Serotonin, μmoles/liter	ES	lymph	1,135 ± 0,227 (0,376)	2,153 ± 0,335* (2,691)	1,871 ± 0,245* (1,182)	1,882 ± 0,281* (0,882)	2,472 ± 0,317* (1,122)	2,511 ± 0,211* (1,077)	2,719 ± 0,631* (1,294)
		blood	1,719 ± 0,189	1,128 ± 0,188*	1,438 ± 0,211	1,708 ± 0,222	1,839 ± 0,221	1,881 ± 0,173	2,748 ± 0,409*
	AS	lymph	1,529 ± 0,201 (0,517)	3,188 ± 0,501 (4,961)	2,276 ± 0,350* (1,709)	2,916 ± 0,311* (1,621)	2,545 ± 0,180* (1,224)	1,983 ± 0,227 (0,809)	—
		blood	1,468 ± 0,145	1,994 ± 0,201*	3,078 ± 0,352*	2,635 ± 0,164	2,186 ± 0,395	1,591 ± 0,314	—
Adrenalin, nanomoles/liter	ES	lymph	1,089 ± 0,508 (0,338)	1,566 ± 0,967 (1,959)	7,887 ± 3,389* (6,604)	—	—	3,149 ± 1,397* (1,354)	2,931 ± 1,059 (1,397)
		blood	1,190 ± 0,393	3,073 ± 0,928	5,622 ± 1,381*	—	—	5,174 ± 1,987*	2,336 ± 0,568
	AS	lymph	1,594 ± 0,464 (0,802)	2,156 ± 0,519 (3,357)	5,453 ± 1,779* (4,121)	—	—	—	—
		blood	2,780 ± 0,759	1,801 ± 1,075	13,896 ± 4,999*	—	—	—	—
Noradrenalin, nanomoles/liter	ES	lymph	1,064 ± 0,526 (0,330)	0,904 ± 0,473 (1,129)	3,676 ± 1,353* (2,323)	—	—	3,280 ± 1,578* (1,407)	0,508 ± 0,260 (0,242)
		blood	2,334 ± 0,851	1,548 ± 0,845	5,620 ± 1,684*	—	—	2,813 ± 0,916*	0,296 ± 0,165
	AS	lymph	0,751 ± 0,313 (0,254)	1,430 ± 0,674 (2,228)	2,204 ± 1,064* (1,655)	—	—	—	—
			0,898 ± 0,715	2,126 ± 1,235	3,020 ± 1,472	—	—	—	—

Legend. Absolute quantity of biologically active substance transported by lymph: μmoles (nanomoles)/min × 10^{-4}, allowing for velocity of lymph flow. *P < 0.05.

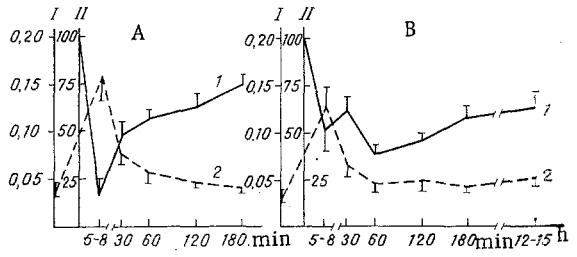

Fig. 2

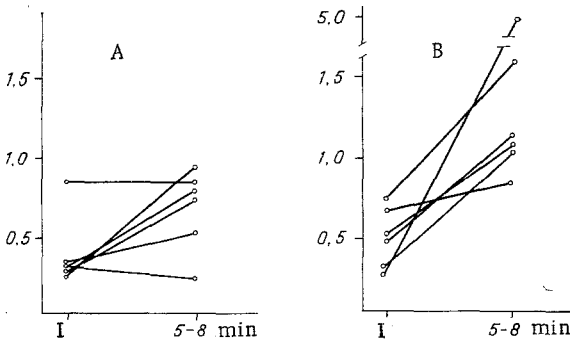

Fig. 3

Fig. 2. Time course of BP and velocity of lymph flow in AS (A) and ES (B). Abscissa, time of investigation; ordinate: I) velocity of lymph flow (in ml/kg/min); II) BP (in % of initial value). 1) BP, 2) velocity of lymph flow.

Fig. 3. Changes in blood (A) and lymph (B) histamine levels in animals dying during first minutes of anaphylactic shock. Abscissa, time of investigation (in min); ordinate histamine concentration (in μmoles/liter). I) Initial values.

the serotonin-pectic properties of the plasma, and a disturbance of its inactivation by the liver. The fall in the blood serotonin level in the first minutes of ES can probably be explained by changes in the adsorption properties of the platelets. Platelets, as we know, cannot form serotonin from tryptophan, but can actively adsorb serotonin during passage through the vessels of the gastrointestinal tract.

When the hemodynamics is disturbed in the capillaries (through disseminated intravascular clotting, shunting, and hypotonia, and also thrombocytopenia) resorption and transport of serotonin from the tissues and organs and, in particular, from the abdominal organs, probably take place directly into the lymphatic capillaries. In the present experiments an increase in the serotonin concentration in the lymph and in its transport by lymph of the TD was discovered during ES.

From the first minutes of AS and ES a tendency was observed for the catecholamine levels to rise in the blood and lymph. Their concentrations were increased many times over at the 30th minute of shock. The adrenalin level in the lymph and blood was raised at all times of observation in ES, whereas the noradrenalin level showed a tendency to fall in the late stages of ES development, after 12-15 h. Investigation of the absolute quantity of catecholamines transported by the lymph into the general circulation per unit time showed a sharp increase in its transport during the very first minutes of shock. Elevation of the catecholamine levels in the body fluids in AS and ES was probably due to their mobilization from the adrenals and other chromaffin cells. At the same time we know that the biogenic amine histamine stimulates adrenalin secretion directly from the adrenal medulla [14], and also through a reflex mechanism, on account of the developing hypotension and stimulation of baroreceptors of the vascular zones [12].

The investigations thus showed that both AS and ES are accompanied by considerable changes in the hemodynamics, lymphatic circulation, concentrations of biologically active substances in the blood and lymph, and their transport by the lymph into the blood stream.

The most profound and earliest changes in concentrations of biologically active substances in AS and ES were discovered in the lymph, evidence of the important role of the lymphatic system in their resorption and transport from the organs and tissues into the general circulation, and also of the lymphogenous source of their presence in the blood in shock of varied etiology.

The results provide evidence of adsorption of lymph in shock combined with goal-directed stimulation of lymph formation in order to regulate an adequate influence of biogenic amines and mediators on the various functional systems and organs, and also to mobilize the extracellular fluid and to abolish manifestations of stasis in the organs.

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INCREASED RESISTANCE OF THE MYOCARDIUM TO STRESS AND TO EXCESS CALCIUM IN SPONTANEOUSLY HYPERTENSIVE RATS

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Animals of different genetic lines differ in their sensitivity to stress [3] and in their resistance to injuries caused by prolonged stress [2]. The further study of the mechanism of genetically determined resistance to stress is undoubtedly of great importance for an understanding of the pathogenesis of stress injuries and their prevention.

This paper describes a study of the mechanisms of increased resistance of the myocardium of spontaneously hypertensive rats (SHR) to stress injury and evaluation of the role of calcium transport in this mechanism.

EXPERIMENTAL METHOD

Male normotensive Wistar-Kyoto (WKY) and August lines of male rats and SHR rats aged 7-8 months were used. Half of the animals of each line served as the control, and the rest were subjected to immobilization stress (IS) by fixation in the supine position for 6 h. The animals were decapitated after 2 h of IS, the heart was removed, the left ventricle and right atrium were weighed, and these were used for subsequent physiological study. Contractility of the isolated atrium was recorded in oxygenated Krebs–Henseleit solution on an F-50 "Physiograph DMP-4B" myograph (Narco-Biosystems, USA), by the method fully described previously [1]. The atrium contracted spontaneously for 40-50 min, after which it was gradually stretched by stepwise increasing loads to a length of l_{max}, at which it developed maximal tension. Extensibility of the atrium was judged from the increase in its length in response to a standard load of 100 mg, and this increase of length was described as Δl. Contractility of the atrium was judged from the maximal value of developed tension (T_d) during isometric contraction and from the graph of length versus developed tension, i.e., the Starling curve. To assess calcium transport the response of the atrium to an excess of this ion in the working so-

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