CONTRACTILE ACTIVITY OF LYMPHATIC MICROVESSELS DURING THE FEBRILE REACTION

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Lymphatic microvessels (LM), which possess a contractile mechanism and a well-developed valve system, are among the most important internal factors for lymph transport and maintenance of homeostasis of the intercellular fluid. The study of the contractile activity of microvessels under pathological conditions is particularly interesting. Yet there have been no investigations into the effect of fever on the function of LM.

EXPERIMENTAL METHOD

In experiments on 89 albino rats of both sexes, weighing 150-200 g, contractile activity of the wall and valves of LM was studied in the mesentery of the small intestine during an experimentally induced febrile reaction (FR) with the aid of intravital microscopy. The FR was induced by intramuscular injection of pyrogenal in a dose of 10 μg/100 g body weight for 1, 3, 5, and 10 days. The body temperature during FR rose on average by 2.0°C. The intact animals were given 1 ml of pyrogen-free physiological saline intramuscularly. Biomicroscopy of the mesentery of the small intestine was carried out by means of a TM-1 television microscope, observing all the demands appropriate for intravital microscopy [6, 11], at the stages of rise and fall of the body temperature and after several days of fever. Throughout the experiment the mesentery was irrigated with pyrogen-free physiological saline, heated to 38°C. Contractions of the wall and valves of LM were recorded and the number of contractions during 1 min was counted by the method described by Aleksandrov and Khugaeva [1]. All the experiments were carried out under pyzogen-free conditions, under pentobarbital anesthesia in a dose of 5 mg/100 g body weight. The experimental results were analyzed on the basis of video recordings and traces of contractile activity of the wall and valves of LM. The numerical data were subjected to statistical analysis by the usual Student's method.

EXPERIMENTAL RESULTS

In intact animals most of the LM in the field of vision were not contracted, and their walls and valves were in a state of relaxation. Meanwhile constant spontaneous rhythmic contractions of the wall were observed in individual LM with a frequency of 8.1 ± 1.03/min, and with equal amplitude. Intervals between individual contractions averaged 6 sec. The cusps of the valves closed with a frequency of 5.7 ± 0.76/min (the mean duration of closure of the cusps was 1 sec, the period of a relaxed state of the valve cusps 10 sec). The walls and valves of LM functioned both synchronously and asynchronously; we recorded LM in which only the walls contracted or the cusps of the valve closed. Contractions of the wall subsequently induced functioning of the valves and, conversely, "working" of the valves stimulated contraction of the vessel wall. The lymph in all the vessels was translucent, although it contained isolated lymphocytes. The lymph flow was in one direction, but sometimes became intermittent and pendulumlike in character, and this type of flow was observed because of the presence of the cells in it. The lymph flow also was observed (by movement of the lymphocytes) during the absence of vasomotor phenomena, i.e., in the noncontracting vessels.

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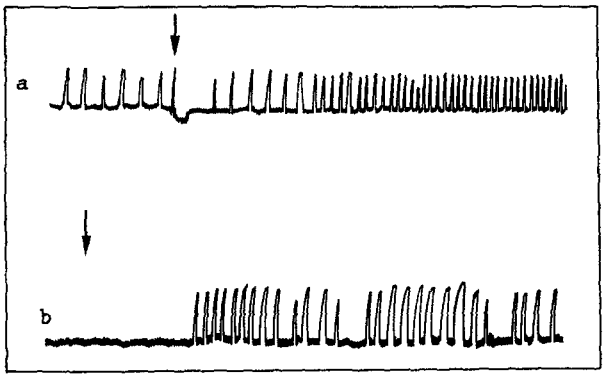

Fig. 1. Action of pyrogenal on contractile activity of wall of LM of intact animals (application in a dose of 0.5 μg in 0.2 ml of physiological saline). a) To contracting vessel, b) to noncontracting vessel. Arrow indicates time of application.

Application of pyrogenal to the mesentery in a dose of 0.5 μg in 0.2 ml of pyrogen-free physiological saline to the contracting LM increased the frequency of spontaneous contractions on average by 2.5 times 30-40 sec after its application. Their amplitude was increased under these circumstances (Fig. 1). Later the contractions became irregular, periodic, and grouped with different time intervals between individual contractions or groups of contractions, or sometimes they were spastic, when a single contraction continued for 4-6 sec. Meanwhile an increase in the velocity of the lymph flow was detected. The uncontracted LM and valves began to contract after application of pyrogenal (Fig. 1).

Following intramuscular injection of pyrogenal, an FR developed and was accompanied by considerable quantitative (an increase in the number of contracting LM and of their valves, an increase in their contractile activity) and qualitative changes in the contractile activity of the mesenteric LM of the rat small intestine. At all times of the investigation quickening of spontaneous vasomotor contractions and closing of the cusps of the valves of LM were observed compared with intact animals. These parameters had their highest values at the stage of fall of body temperature. The period of closure of the valves was reduced on average by 2 sec and the period of the relaxed state of the valve was reduced by 5 sec. Meanwhile individual periods of closure of the cusps lasting 8-10 sec could be recorded.

With an increase in the duration of FR qualitative changes in contractile activity of the wall of LM increased: the contractions became asynchronous — intervals between single contractions measured 1-3 sec. "Bursts" of contractions were recorded, with 3-5 to 12-14 per burst, and these were followed by phases of rest lasting from 10-20 sec (in the case of one and three injections of pyrogenal) to 50-60 sec (five and 10 injections of the lipopolysaccharide respectively). Biphasic contractions appeared. Individual vasomotor phenomena lasted up to 12 sec. The amplitude of the contractions varied. In most cases the lymph flow was quickened. During an FR lasting several days, accumulation of blood cells was observed in them (the lymph contained many erythrocytes). Simultaneously, during long-term FR single static LM appeared in the field of vision, together with vessels in which the lymph flow was slow. These vessels had a diameter of 50-70 μ and contained transparent lymph. The lymph flow in LM located in adipose tissue was considerably accelerated. In the late stages after FR, when the body temperature was back to normal (the 6th day after three injections and the 10th day after five injections of pyrogenal) the lymph flow remained fast. The lymph in all these vessels was transparent. During a prolonged FR multiple perilymphatic hemorrhages and extravasations were observed, evidence of increased vascular permeability.

The mechanism of the changes in contractile activity of LM in the mesentery of the small intestine of rats during FR can be provisionally explained as follows. It has been shown that contractile activity of the lymphatic vessels is under metabolic control through the intervention of vasoactive substances. During FR activity of the sympathetic neurons is increased and mobilization of catecholamines (CA) takes place [5]. At the same time, parenteral administration of CA stimulates contractile activity of LM of various animals [7, 9, 14]. Meanwhile fever induces increased functional activity of the mast cells, as shown by our experiments, which demonstrated elevation of biogenic amine levels (histamine and serotonin) in the lymph and blood [8]. Mast cells, located in the outer membrane of the wall of mesenteric LM, have close contacts with myocytes. An increase in their number was found around the lymphatic vessels at a time of their increased contractile activity [2]. The release of biologically

active substances may lead to an increase in the frequency of spontaneous phasic contractions of the wall of the lymphatics, of varied amplitude, and to the transition from a regular, synchronous rhythm of contractions to an asynchronous rhythm [9].

Histamine and serotonin, which are lymphagogues have been shown to increase membrane permeability at the blood vessel – tissue and tissue – lymphatic vessel level, widening contacts at junctions between endothelial cells [3]. Under these circumstances lymph formation is considerably increased, and as a result, rapid filling of the lymphatic bed takes place with new and additional portions, the pressure rises, and the lymph flow increases. Meanwhile, with a rise of lymphatic pressure, the mechanical influence on the vessel wall is strengthened: it stretches, and thereby activates motor function of the lymphatic vessel.

Another factor stimulating contractile activity of LM in our experiments was evidently calcium ions. It has been shown that an increase in the Ca^{2+} concentration stimulates vasomotor function of the lymphatic vessels [4, 9, 15]. On the other hand, we know that excitation of the sympathetic nervous system, taking place in the first stage of FR, increases the content of ionized calcium in the body [10]. Ca^{2+} ions are released from their localization sites under the influence of histamine, CA, and potassium ions [4]. It has been shown that CA, by activating adenylate cyclase, increase cAMP formation, which accelerates the transmembrane Ca^{2+} flow and increases calcium exchange of the subcellular membranes [13]. We also recorded an increase in the calcium concentration in the lymph and blood during a prolonged FR. The investigations also showed that calcium is involved in the release of histamine from mast cells [12].

Thus FR is accompanied by mobilization of biogenic amines from perivascular sympathetic terminals and mast cells, and on the one hand, it acts directly on the contractile apparatus of the wall of the mesenteric LM, activating it, whereas on the other hand, it increases vascular permeability. The latter actively promotes the movement of fluid from the interstitial space into the lymphatics, raising the pressure in them and, as a result, stimulating the contractile activity of the lymphangion, which ultimately leads to optimization of the lymph flow.

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