Effect of Dimephosphon on Lymph Circulation and Microcirculation, Contractility of the Wall and Cusps of Valves in Lymphatic Microvessels, and Cell Composition of the Lymph during Fever

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Stimulation of lymph circulation and microcirculation and increase in contractile activity of the wall and cusps of valves in lymphatic microvessels are the mechanisms for a therapeutic effect of dimephosphon. These changes improve resorption and transport of tissue and cell metabolites from the interstitial space.

Key Words: *fever response; lymphatic microvessels; dimephosphon; lymph circulation*

The lymphatic system plays a role in the pathogenesis of general pathological processes, including fever response (FR) [3]. The development of general principles for lymphotropic correction and the search for new medicinal preparations modulating changes in the lymphatic system during FR are of considerable importance.

Here we studied the effect of vasoactive preparation dimephosphon (DP, Russia) on lymph circulation and microcirculation, contractile activity of the wall and cusps of valves in lymphatic microvessels (LM), and cell composition of central lymph during FR.

MATERIALS AND METHODS

Experiments were performed on male albino rats weighing 200-230 g. Group 1 animals received apyrogenic solution. Pyrogenal in a single dose of 100 μg/kg was injected intraperitoneally to group 2 animals. Group 3 animals were injected with DP in a therapeutic dose of 50 mg/kg. Group 4 animals received DP 30 min after pyrogenal administration.

Acute experiments were conducted on nembutal-anesthetized rats (50 mg/kg intramuscularly) at the stages of temperature rise and drop (2-2.5 and 4-4.5 h after administration of pyrogenal, respectively). The lymph was obtained by puncturing the thoracic lymph duct at the site of junction with the left venous angle. We evaluated lymph flow velocity and cell composition of the lymph. Lymph microcirculation and contractile activity of the wall and valves in rat mesenteric LM were studied by means of vital microscopy. Microscopic images were processed using digital video camera and personal computer. The total number of leukocytes in the lymph and the count of individual cells in lymph smears were estimated routinely. The animals were euthanized with lethal dose of narcotic. The results were analyzed by Student's *t* test.

RESULTS

Administration of DP 1.3-fold accelerated lymph flow and increased the frequency of spontaneous vasomotion in the wall and cusps of valves in rat mesenteric LM. Moreover, DP increased the number of functioning microvessels by 1.5 times (Tables 1 and 2). The amplitude of contractions remained unchanged, while lymph flow velocity in LM and count of lymph cells increased. Administration of DP at the stage of tem-

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perature raise in FR accelerated lymph flow and increased contractile activity of the wall and valves in LM by 2, 2.6 (Fig. 1), and 2 times (Fig. 2), respectively, compared to animals not receiving the drug. The number of vessels with simultaneous function of the wall and valves increased to 72% (*vs*. 52% in pyrogenal-treated rats). The frequency of wall contractions remained high 4-4.5 h after treatment (1.5-fold higher than in the control). However, the frequency of cusp contractions did not differ in treated and untreated animals. Contractions of the wall and valves in DP-receiving rats were more synchronous compared to control animals. Moreover, the amplitude of contractions in rats of the DP group was more stable than in animals not receiving the preparation.

DP had no effect on cell composition of the central lymph in control animals. At different stages of FR, DP increased the number of leukocytes and lymphocytes transported with the lymph to the systemic circulation. These changes were most pronounced at the stage of temperature drop.

DP possesses angioprotective, disaggregation, antiacidotic, antithrombotic, membrane-stabilizing, antiinflammatory, immunomodulatory, and antiarrhythmic properties [2,4,6,7]. Published data show that this preparation decreases the duration of fever during infection [5].

Fever is accompanied by accumulation of the main lipid peroxidation (LPO) products in the plasma and decrease in activity of the antioxidant system. It was hypothesized that LPO products decrease contractile activity of lymphangions. DP contributes to transformation of reduced glutathione into oxidized glutathione and, therefore, activates the antioxidant system during LPO. The glutathione buffer in cells is the major component of the antioxidant system. DP increases activities of antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase under pathological conditions accompanied by activation of LPO [6,7]. Moreover, DP activates oxidative synthesis of ATP in mitochondria. These changes increase pacemaker activity and sensitivity of smooth muscle cells in the LM wall to mediators and bioactive substances, whose synthesis is activated during FR. Glucose-6-phosphate dehydrogenase is a key enzyme of the pentose-6-phosphate pathway, which serves as a major source of NADP-H_2 for the transmembrane potassium current. DP increases activity of this enzyme and maintains a sufficient amount of potassium in smooth mus-

TABLE 1. Effect of DP on Lymph Flow Velocity in Rat Thoracic Lymph Duct (*M*±*m*)

Group of animals	*n*	Time after pyrogenal administration, h	Lymph flow velocity, 10^{-2} ml/100 g/1 sec
1	8		0.45±0.04
2	8	2.0-2.5	0.75±0.07***
	8	4.0-4.5	0.83±0.09*
3	7		0.62±0.07**
4	9	2.0-2.5	1.59±0.13^{+}
	9	4.0-4.5	0.89±0.09

Note. *p<0.001, **p<0.05, and ***p<0.01 compared to group 1; ^{+}p<0.01 compared to group 2. Here and in Table 2: *n*, number of animals.

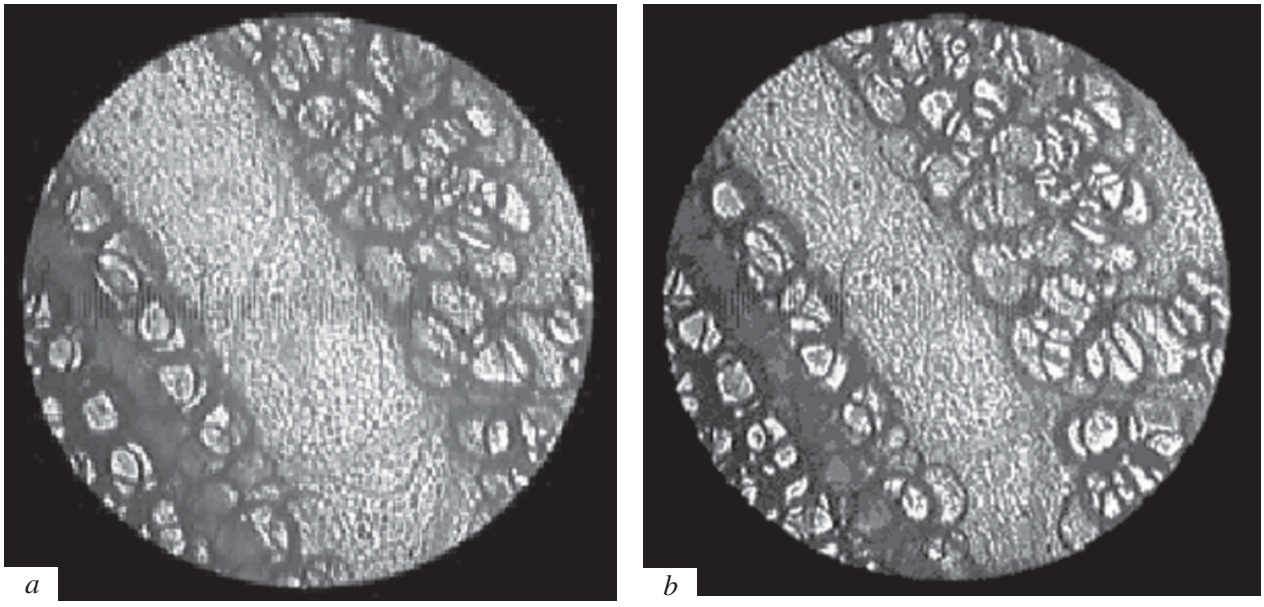

Fig. 1. Phasic contractions of the wall in mesenteric lymphatic microvessels of dimephosphon-receiving rats: relaxation (*a*) and contraction of the wall (*b*). Biomicroscopy, ×96.

TABLE 2. Effect of DP on Contractile Activity of the Wall and Valves in Intestinal LM of Rats with FR (*M*±*m*)

Group of animals	*n*	Time after pyrogenal administration, h	Frequency of wall contraction, min^{-1}	Frequency of closure of valve cusps, min^{-1}
1	10-6	—	8.10±1.03	5.70±0.76
2	9-6	2.0-2.5	12.30±1.74**	11.10±1.88*
		4.0-4.5	16.10±1.05***	13.50±1.48*
3	7	—	12.10±1.56***	8.50±0.72***
4	9	2.0-2.5	31.90±3.91^{+}	22.60±2.38^{+}
	8	4.0-4.5	24.80±2.55^{+}	15.00±1.98

Note. *p<0.002, **p<0.05, and ***p<0.01 compared to group 1; ^{+}p<0.001 compared to group 2.

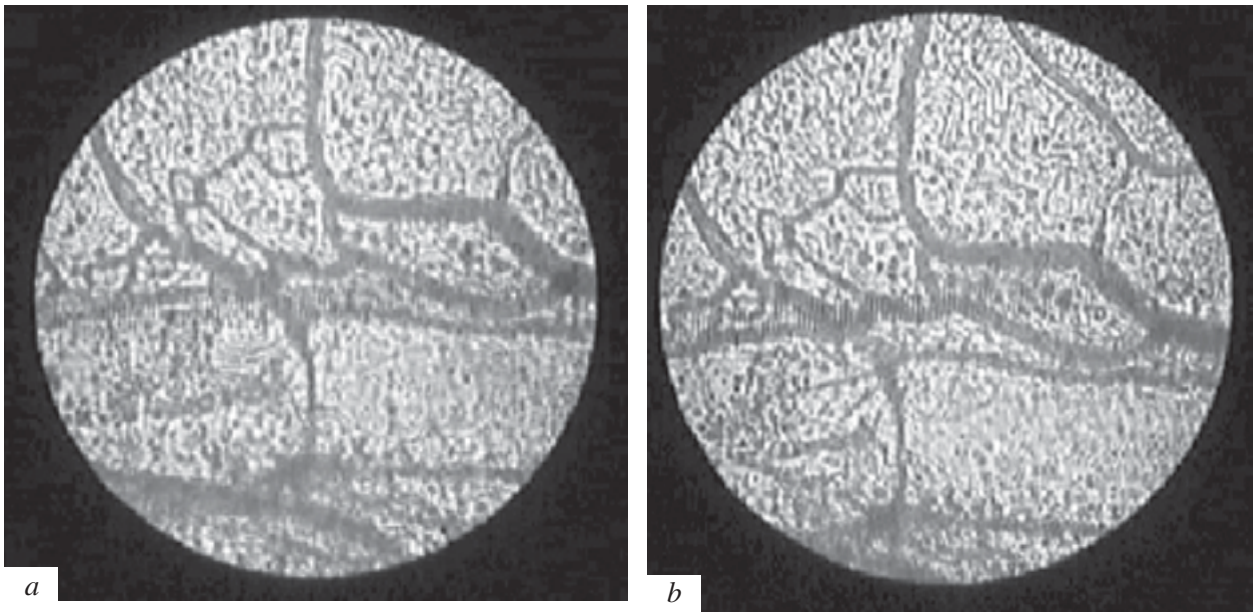

Fig. 2. Function of valve cusps in mesenteric lymphatic microvessels of dimephosphon-receiving rats: closed (*a*) and open cusps (*b*). Biomicroscopy, ×96.

cle cells. It provides adequate response of these cells to contractile stimulation.

The membrane-stabilizing effect of DP is realized via Ca^{2+} binding and decrease in intracellular Ca^{2+} concentration [8]. Some authors reported that extracellular calcium ions provided phasic contractions of LM [9]. The increase in the number of cells transported with the lymph is probably associated not only with acceleration of lymph flow, but also with activation of lymphopoiesis, release of lymphocytes from lymph nodes, and decrease in aggregation of blood cells under the influence of DP.

Our results show that the effect of DP during FR is realized apart from known mechanisms via its complex action on lymph flow. On the one hand, DP stimulates contractile activity of the wall and cusps in valves of LM. On the other hand, DP activates lymph production, which improves resorption and transport of tissue and cell metabolites from the interstitial space.

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