Possible Correction of Lymph Flow and Contractile Activity of Lymphatic Microvessels during Febrile Response

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In experiments on dogs and rats dimephosphon considerably enhanced contractile activity of walls and valves in lymphatic microvessels, thus accelerating lymph flow and improving exchange between blood and lymph.

Key Words: *febrile response; lymph flow; dimephosphon; lymphatic microvessels*

Our previous studies showed that impairment of the resorption and transport functions of the lymphatic system plays an important role in the mechanisms of febrile response (FR) [6]. Lymphatic microvessels (LM) with their contractile activity and well-developed valves is an important factor regulating lymph flow and interstitial fluid homeostasis [8]. At the same time, the effects of many drugs on lymph flow under normal conditions and during FR are poorly studied.

Here we studied the effects of dimephosphon on the lymph flow and LM contractile activity during FR.

MATERIALS AND METHODS

Experiments were carried out on 14 outbred dogs (5-15.2 kg) and 15 albino rats (150-200 g). FR was induced as described previously [4,5]. In dogs, dimephosphon (200 mg/kg in 20 ml saline) was intravenously injected 30 min after FR induction. The rate of lymph flow was determined by measuring the volume of lymph collected from the thoracic duct (TD) via a cannula. In rats, the contractile activity of walls and valves in mesenteric LM was assessed by vital microscopy [1,10] 3 h after a single injection of pyrogenal against the background of dimephosphon (15 mg/100 g in 0.2 ml apyrogenic saline). Control rats received the preparation by the same route. The animals were sacrificed by narcotic overdose.

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RESULTS

In control dogs, lymph flow in the TD 30 min after dimephosphon injection increased 1.7-fold and remained at this level for 1.5 h (Table 1). The drug alleviated FR symptoms reducing both the peak (body temperature increased by 2.1°C *vs.* 2.9°C in untreated animals) and duration (5.8 *vs.* 7 h) of fever.

We previously found that FR is accompanied by a 2.8-fold increase in the lymph flow rate, most pronounced at the stage of body temperature decrease [4]. Dimephosphon administered during FR increased lymph flow 2.5- and 1.5-fold compared to the control and untreated animals, respectively. The effect of dimephosphon during fever persisted for a longer time.

In control rats, the frequency of spontaneous contractions of LM walls and valves 40-55 min after dimephosphon application increased 1.3 fold without changes in their amplitudes. Contractions of lymphatic vessel walls were accompanied by both synchronous and asynchronous contractions of valves. Lymph flow was accelerated compared to that in intact rats. All microvessels contained transparent lymph with solitary lymphocytes. Vasomotor reactions appeared in functionally inactive LM. Dimephosphon applied during FR significantly (2.3-fold compared to untreated animals) enhanced the contractile activity of LM walls and valvules as soon as after 20-25 sec and increased the amplitude of contractions without affecting their arrhythmicity observed during fever in untreated rats [5]. Lymph flow was accelerated, but sometimes

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pendulum pulsation of the lymph was observed. The lymph remained transparent despite increased cell content. Effect of dimephosphon remained at this level for 20-25 min.

When analyzing the mechanisms of the effect of dimephosphon on lymph flow, its angioprotective, disaggregating, membrane stabilizing, antiinflammatory, antithrombotic, immunomodulatory, and antiacidotic properties should be taken into account. The latter properties are related to activation of metabolic mechanisms involved in the regulation of acid-base balance, rather than to direct neutralization of acidic compounds [2,3]. In addition, dimephosphon reduces the duration of fever accompanying infectious pathology [9].

The effect of dimephosphon on lymph flow during FR can be explained as follows. The initial acceleration of TD lymph flow can be associated with enhanced contractile activity and relaxation of LM. The tone of LM considerably increased during fever due to intensive sympathoadrenal stimulation. These changes increase the capacity of lymphatic bed and facilitate lymph outflow. Stimulation of contractile activity and dilatation of LM considerably accelerate lymph flow. It can be assumed that this effect is further potentiated by stimulation of lymph production due to increase in the total area of functioning blood and lymphatic capillaries, elevation of the colloid-osmotic pressure in the terminal regions of the lymphatic system, and by the increased filtration and resorption capacities of LM. This assumption is confirmed by more long-lasting effects of dimephosphon on lymph flow in animals with fever compared to controls in our *in vivo* experiments. Stimulation of lymph production increases lymph pressure and therefore accelerates lymph flow. At the same time, elevated lymph pressure exerts mechanical (stretching) effects on the lymph vessel wall and activates its vasomotor responses.

It can be concluded, that apart from other well-known mechanisms, the effect of dimephosphon in FR is mediated via enhanced contractile activity of LM, stimulation of lymph production, and acceleration of lymph flow. These stimulatory effects of dimephosphon improve resorption of products of cell metabolism from the interstitial space and their transport via the lymphatic system. Our data substantiate the use of dimephosphon in FR.

TABLE 1. Effect of Dimephosphon on Lymph Flow Rate (10^{-6} liter/kg/sec) in Thoracic Duct during Febrile Reaction in Dogs ($M \pm m$)

Term of observation	Intact	Pyrogenal
Before injection	0.50±0.06	1.00±0.11
Postinjection, min		
0-30	0.55±0.08	1.12±0.14
30-60	0.88±0.10**	2.18±0.20*
60-90	0.90±0.12*	2.48±0.15*
90-120	0.77±0.07**	1.56±0.15**
120-150	0.60±0.09	1.58±0.11**
150-180	0.55±0.07	0.98±0.12

Note. *$p<0.001$, **$p<0.05$ compared to the corresponding parameters before dimephosphone injection.

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