Lymphostimulating Activity of Agents Used in Lung Pathologies

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Lymphostimulating effects of antibiotics and diuretics most commonly used in pulmonology were investigated under conditions of intravital biomicroscopy of the small intestinal mesenterium in rats. Results of the study demonstrated weak or no activation of lymph circulation under the influence of the test agents in comparison with direct-action peptide lymphostimulators.

Key Words: *biomicroscopy; lymphostimulation; antibiotics; diuretics; opioid peptides*

Up to the end of previous century, the role of lymphatic system in pathology seemed to be passive. The contrary was proven to a considerable extent thanks to works of Russian scientists. Fragments of isolated main lymphatic vessels [2] and whole lymphangions [3] exhibit contractive activity.

Adrenergic and cholinergic innervation of lymphatic microvessels (LM) has no substantial effect on motility and lymph circulation rate. It was shown that contractive activity of the wall and valves of mesenterial LM is associated with the presence of opioidergic regulation [4-6].

Experiments on rats showed high efficiency of lymphostimulation with delta-opioid receptor agonist leu-enkephalin (LE) and its analogues in the prophylaxis and treatment of brain ischemia [8] and subcutaneous fat inflammation [1].

Only indirect lymphostimulators, physiological solution, glucose solution, and agents improving central hemodynamics and blood rheology, increasing lymph production and lymph circulation, but not affecting LM wall and valves were hitherto used in clinical practice. Since numerous lung diseases are associated with pulmonary congestion leading to pneumonia and pulmonary edema, the use of agents preventing the development of these conditions for prophylaxis and treatment purposes is of critical importance.

The objective of our study was to investigate microlymphocirculation effects of agents used for the treatment of lung pathologies.

MATERIALS AND METHODS

Experiments were carried out on outbreed albino male rats weighing 200-250 g (n=23). The animals were narcotized with 8% chloral hydrate (0.5 ml/100 g of body weight, 0.4 g/kg intramuscularly).

Biomicroscopy of the small intestinal mesenterium was performed by conventional method [10]. Opioid peptide, antibiotics, and diuretics were applied onto LM mesenterium surface: LE (40 μg/kg), cefotaxime (0.01-100 mg/kg), gentamycin (0.0016-16 mg/kg), ampicillin (0.01-100 mg/kg), furosemide (0.0004-4 mg/kg) in 0.1 ml of isotonic NaCl solution.

Contractive activity of LM wall and valves was evaluated by contraction latency, maximal contraction rate per minute, percentage of activated LM, and contraction duration (Fig. 1). Furthermore, lymph circulation velocity was assessed: weak activity (+) corresponded to pendular lymph movements without propagation toward the center; middle activity (++) reflected pendular lymph movements with propagation toward the center; intense lymph circulation (+++) was characterized by continuous lymph flow. Since LM

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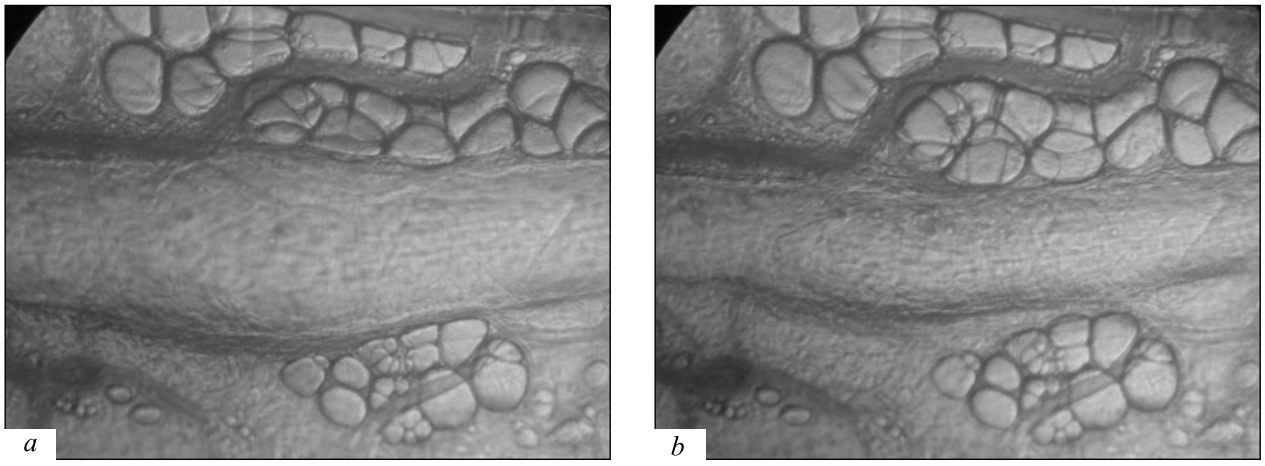

Fig. 1. LM of small intestine mesenterium under biomicroscopy, ×200.
a) LM (200 μ in diameter) during relaxation; *b*) LM (140 μ in diameter) during contraction.

sensitivity depends on their topography in the small intestinal mesenterium, we studied microvessels situated at the border of the adipose tissue and transparent part of the mesenterium. Experiments were carried out on initially non-contracting LM.

RESULTS

At rest, LM wall and valves do not function at all or contract with a frequency from 1.5 to 4 per minute (1.9±0.8) for 5-10 min. LE is a highly effective direct lymphostimulator [4], it was chosen to serve as the etalon of lymphostimulating activity. LE application (40 μg/kg) on mesenterial LM led to activation of LM movements (contraction frequency 20.3±2.7 per minute, $p<0.001$ in comparison with the baseline) and increased lymph circulation velocity (+++) for 40 min and more.

Application of the third-generation semisynthetic cephalosporin antibiotic cefotaxim in doses from 0.01 mg/kg to 100 mg/kg did not activate contractive activity of LM wall and valves in 66.7% cases. In case baseline activity of LM, antibiotic application led to inhibition of wall and valve movements and complete termination of activity in 6 min. In 33.3% cases, insignificant and transient (4-16 min) activation of LM wall contractions was observed (7.33±0.76 contractions per minute, $p<0.001$ in comparison with LE). It should be noted that in this experimental series, the differences from the baseline were significant ($p<0.001$).

Gentamycin (0.0016-16 mg/kg) and ampicillin (0.01-100 mg/kg) did not activate LM motility and did not increase lymph circulation under these conditions.

Furosemide (0.0004-4.0 mg/kg) widely used in clinical practice was unable to stimulate lymph circulation and activate LM movements in 100% of cases. In case of baseline contractive activity of LM wall, furosemide inhibited its movements.

When analyzing the obtained results, we should note that the test agents used in clinics in lung pathologies have no pronounced lymphostimulating effects, and some of them inhibit motility and lymph circulation, what can contribute to edema development in the lung tissue.

Among the studied antibiotics, cefotaxime should be preferred, because it slightly stimulated lymph circulation in 33% of cases. Furosemide possesses no lymphostimulating activity and even inhibits contractive activity of functioning LM, thereby inhibiting baseline lymph circulation.

Considering the importance of the lymphatic system in lung pathologies (detoxification, drainage, water and protein balance regulation, *etc*.) and the absence of agents effectively stimulating the lymphatic system, it is important, when possible, to avoid the agents reducing lymph circulation velocity and inhibiting LM contractive activity.

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