# Effect of Orthophen on Microlymphocirculation during Fever Reaction

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Orthophen improved lymph flow during fever reaction via stimulation of contractile activity of the wall and valves in mesenteric lymphatic vessels of rat small intestine. These changes constitute the pathogenetic mechanism for the effect of orthophen during fever.

**Key Words:** *fever reaction; lymph flow; lymphatic microvessels; orthophen*

The lymphatic system eliminates excess of bioactive substances, enzymes, metabolic products, and toxins from the internal medium, continually replenishes the pool of lymphocytes, and maintains homeostasis during fever reaction (FR). Directed stimulation of lymph flow is a way to restore homeostasis and improve metabolic processes in the extracellular space [5]. At the same time, the effects of commonly accepted drugs on the lymph flow under normal conditions and during FR remain unknown.

Here we studied the effect of nonsteroid antiinflammatory drug orthophen on lymph flow and contractile activity of lymphatic microvessels (LM) during FR.

## MATERIALS AND METHODS

Experiments were performed on 34 male and female albino rats weighing 150-230 g. FR was modeled as described elsewhere [4]. Orthophen in a dose of 15 mg per 100 g body weight was injected intramuscularly 30 min after FR modeling. Lymph flow rate was determined by the amount of lymph released from the thoracic duct (TD). Contractile activity of the wall and valves in mesenteric LM of the small intestine was estimated by vital microscopy according to requirements [1,7]. Examination was performed 3 h after single injection of pyrogenal and application of orthophen (2 mg per 100 g body weight) in 0.2 ml apyrogenic physiological saline. Control animals received the preparation according to the same scheme. The rats were killed by administration of a narcotic drug in the lethal dose. The results were analyzed by methods of variational statistics [6].

## RESULTS

The rate of lymph flow in TD of intact animals increased by 1.6 times 1 h after administration of orthophen (Table 1). The rate of lymph flow increased similarly in untreated rats with FR. It should be emphasized that in dogs the rate of lymph was 2.8 times higher [2]. The rate of lymph flow increased by 2.3 and 3 times 30 min and 1 h after administration of the preparation, respectively (compared to animals not receiving orthophen). In animals with experimental fever the effect of this preparation persisted throughout the experiment.

In intact rats the amplitude of spontaneous contractions in LM increased 25-30 sec after application of orthophen to the small intestinal mesentery. The frequency of contractions in the wall and valves increased by 1.5 times 60-70 sec after treatment. Lymph was transparent and flowed unidirectionally. The rate of lymph flow in treated rats was higher than in intact animals. However, the number of functioning vessels

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did not increase in these rats. Contractile activity of the wall and valves in LM increased by 3 times 30-40 sec after application of orthophen during FR (compared to untreated animals). We observed high-amplitude rhythmic contractions. However, contractions of vessels were arrhythmic in untreated animals with fever. The number of functioning LM, rate of lymph flow, and count of lymph cells increased. The effect of orthophen persisted for 1 h.

Orthophen inactivates the key enzyme of arachidonic acid metabolism cyclooxygenases 1 and 2, intensifies utilization of substrates by the lipoxygenase pathway, and promotes the formation of leukotrienes. Inactivation of cyclooxygenase in the microsomal fraction of brain cells prevents the increase in intracellular cAMP level, accumulation of $Ca^{2+}$ in cells, changes in the Na/Ca ratio, and functional modification of heat production and heat dissipation centers. Nonsteroid antiinflammatory drugs suppress free radical reactions and production of macroergic phosphates (ATP) and cyclic nucleotides during oxidative and glycolytic phosphorylation, inactivate lysosomal hydrolases, prevent platelet aggregation, inhibit the release of biogenic amines and kinins, and reduce activity of neutrophils (guanosine triphosphate-binding protein). These preparations have anionic properties and permeate the membrane phospholipid bilayer in immunocompetent cells, directly modulate protein-protein interactions, and decrease cell activity at the early stage of the disease (*e.g.*, fever) [3,8].

FR contributes to the impairment of lymph flow (despite the increase in the rate of lymph secretion). Microlymphocirculatory disturbances play a role in the pathogenesis of metabolic changes in the microcirculatory bed [5]. We hypothesized that orthophen-induced changes during FR are mediated by the following mechanisms. Intensive lymph outflow from LM is provided by increased contractile activity of walls and valves and increased capacitance of lymphatic vessels. Further stimulation of lymph secretion is determined by increased colloid-osmotic pressure in terminal regions of the lymphatic system and increase in the area of functioning lymphatic and blood vessels. These changes promote the increase in filtration and resorption capacities of LM. The lymphatic bed is rapidly filled with new portions of the lymph, the pressure and lymph flow increases. The increase in lymphatic pressure is accompanied by an increase in mechanical influence on the vascular wall. The vessel is stretched, which results in pronounced activation of motor function in LM.

**TABLE 1**. Lymph Flow Rate ($10^{-2}$ ml/100 g/sec) in Rat TD and Influence of Orthophen on Lymph Flow during FR ($M\pm m$)

| Period | Group of animals | |
|---|---|---|
| | intact | fever reaction |
| Before orthophen administration | 0.43±0.07 | 0.69±0.08 |
| After administration, min | | |
| 0-30 | 0.40±0.05 | 0.67±0.09 |
| 30-60 | 0.43±0.02 | 1.85±0.25* |
| 60-90 | 0.66±0.10* | 2.00±0.27* |
| 90-120 | 0.60±0.09* | 1.72±0.30* |
| 120-150 | 0.45±0.06 | 1.37±0.11* |
| 150-180 | 0.39±0.04 | 1.22±0.10* |

**Note.** *$p<0.05$ compared to indexes before orthophen administration.

Our results show that orthophen produces positive therapeutic effects, which is manifested in modulation of thermoregulation, stimulation of lymph flow, and improvement of metabolic processes in the interstitial spaces.

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