Lymphotropic Effect of Mexidol in Reactive Fever

R. Kh. Khafiz'yanova and D. A. Mukhutdinov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 140, No. 10, pp. 433-435, October, 2005
Original article submitted May 17, 2005

Single injection of mexidol (drug with antioxidant and membranotropic effects) to animals with reactive fever produces a multicomponent effect on the lymph circulation. The drug increased the number of functioning lymph capillaries and contractile activity of wall and valvular leaflets in rat small intestinal mesenteric lymphangion, accelerated lymph drainage, thus stimulating lymph formation and lymph flow.

Key Words: *reactive fever; lymph capillaries; mexidol; lymph circulation*

Almost all pathological changes (including reactive fever, RF) are associated with intensification of free radical processes [4,6]. LPO products are released from the interstitium into the lymph and are thus transported into common circulation. However, the lymphotropic mechanisms underlying the effects of many drugs remain little studied until now. Evaluation of the contribution of the "lymph" component into realization of drug therapeutic effect is therefore an important problem.

We studied the effect of mexidol (a drug with antioxidant and membranotropic effects) on lymph formation, contractile activity of the lymph capillary walls and valves in the rat small intestinal mesentery and on the cytological composition and toxicity of the central lymph in RF.

MATERIALS AND METHODS

Experiments were carried out on albino rats (200-230 g) divided into 4 groups. Group 1 animals were injected (intramuscularly) with apyrogenic solution, group 2 rats received a single (100 μg/kg) dose of pyrogenal, group 3 received mexidol (Ellar Company) parenterally in a single therapeutic dose (5 mg/kg), and group 4 animals received the same dose of mexidol 30 min after pyrogenal injection. Experiments were carried out on narcotized (50 mg/kg sodium ethaminal intramuscularly) animals at the stages of temperature rise and drop (2.0-2.5 and 4.0-4.5 h after pyrogenal injection, respectively). Lymph flow rate was evaluated by the volume of the lymph released from the thoracic lymph duct (TLD). Leukocyte count and toxicity of the lymph were evaluated [14]. Microcirculation of the lymph and contractile activity of the wall and valvular leaflets in small intestinal mesenteric lymph capillaries were studied by vital microscopy. The image was transferred from the microscope into PC through a digital videocamera. Standard Adobe Premier 6.0 videocapture software was used. Euthanasia was carried out by injection of a lethal dose of narcotic. The data were statistically processed using Student's *t* test.

RESULTS

Injection of mexidol 1.6 times accelerated the lymph flow from the TLD of intact animals and did not modify contractile activity and amplitude of contractions of the capillary walls and valvular leaflets in mesenteric lymphangions (Table 1), while the number of functioning vessels increased significantly (by 35%). The ratio of lymphangions with different functional activity (presence of phasic contractions of wall myocyte and valvular work) after a single injection of the drug remained the same as in intact animals. No wall contractions and closure of valvular leaflets was recorded in 47% cases, wall contractions and valve closure in 22%, contractions of the wall alone in 26%, and valvular leaflet closure alone in 5% cases. Mexi-

Department of Pharmacology, Kazan State Medical University. ***Address for correspondence:*** muha-med@mail.ru. D. A. Mukhutdinov

0007-4888/05/1404-0432

dol did not modify cell composition of the central lymph and the lymph toxicity (Table 2).

Drug injection in RF significantly (2.5 times) increased lymph flow during the stage of body temperature rise, increased contractile activity of myocytes in lymph capillary wall (3-fold) and valvular leaflets (2.5 times) in comparison with animals receiving no mexidol. Later (4.0-4.5 h after pyrogenal injection) the number of spontaneous vasomotions in walls and valves in animals injected with mexidol increased 1.9 times and lymph flow rate from TLD 1.8 times. Contractions of the walls and valves had similar amplitude and became synchronous during all periods of the experiment; burst vasomotions disappeared. The number of lymph capillaries with simultaneously functioning walls and valves was 12% higher in the group of animals injected with mexidol. The content of leukocytes transported with the lymph into common circulation remained elevated (by 15%) in rats with RF. Mexidol reduced TLD lymph toxicity during RF: by 21 and 36% during temperature rise and drop, respectively.

Mexidol, a 3-hydroxypyridine derivative and structural analog of vitamin B_6, carrying succinate (a tricarbonic acid cycle metabolite) in its chemical composition, is a so-called "duplicator" of endogenous bioenergetic reactions under conditions of hypoxic stress; it is considered as an antioxidant. Mexidol inhibits free radical LPO processes, increases activities of antioxidant enzymes, and produces positive effects on the physicochemical characteristics of membranes by increasing the content of polar lipid fractions (phosphatidylserine and phosphatidylinositol) and reducing the cholesterol/phospholipid ratio and viscosity of the lipid bilayer. The drug modifies activities of phosphodiesterase, acetylcholinesterase, optimizes the content of cyclic nucleotides, improves energy metabolism in cells. On the whole, mexidol produces a membrane-modulating effect improving membrane sensitivity to drugs. At the whole-body level mexidol is characterized by antiatherogenic (hypocholesterolemic) effect due to inhibition of LDL oxidation and platelet aggregation. It stabilizes erythrocyte membranes and improves microcirculation. The drug is characterized by cardio-, stress-, and myeloprotective effects. Due to its antihypoxic, antiischemic, nootropic, anxiolytic effects, mexidol increases dopamine content in the brain, optimizes synaptic neurotransmission, and corrects CNS dysfunctions during aging. Mexidol promotes a decrease in oxygen consumption, thus stimulating the adaptive compensatory functions of the body [1-3,5-10,12,13].

The mechanism of its effect on lymph circulation and contractile activity of myocytes in walls and valves of the lymphangion in RF seems to be due to modification of microenvironment of membrane receptors on the cell surface. This treatment can modify the conformation and capacity of these proteins to bind bioactive substances generated during fever. Diffuse distribution of the antioxidant in the cell results in

TABLE 1. Effects of Mexidol on Lymph Flow Rate in TLD and Contractile Activity of Rat Lymph Capillary Walls and Valvular Leaflets Normally and in RF (*M*±*m*)

Parameter	Group 1	Group 2		Group 3	Group 4	
		2.0-2.5 h	4.0-4.5 h		2.0-2.5 h	4.0-4.5 h
Lymph flow rate, 10^{-2} ml/100 g/sec	0.45±0.04 (*n*=8)	0.75±0.07* (*n*=8)	0.83±0.09* (*n*=8)	0.76±0.08* (*n*=8)	1.79±0.25$^+$ (*n*=7)	1.43±0.19$^+$ (*n*=6)
Wall contraction rate, min	8.10±1.03 (*n*=10)	12.30±1.74* (*n*=9)	16.10±1.05* (*n*=9)	8.43±1.67 (*n*=7)	35.91±3.62$^+$ (*n*=7)	29.77±3.09$^+$ (*n*=8)
Valvular leaflet closure rate, min	5.70±0.76 (*n*=6)	11.10±1.88* (*n*=6)	13.50±1.48* (*n*=6)	6.17±0.81 (*n*=7)	27.29±3.03$^+$ (*n*=7)	23.87±2.76$^+$ (*n*=8)

Note. Here and in Table 2: $p<0.05$ compared to: *group 1, $^+$group 2.

TABLE 2. Cytological Composition and Toxicity of Thoracic Duct Lymph Normally and in RF during Mexidol Treatment (*M*±*m*)

Parameter	Group 1 (*n*=8)	Group 2		Group 3 (*n*=8)	Group 4	
		2.0-2.5 h (*n*=8)	4.0-4.5 h (*n*=8)		2.0-2.5 h (*n*=7)	4.0-4.5 h (*n*=6)
Leukocyte count, 1 µl lymph	13 176±859	12 675±387*	19 371±563*	12 528±649	14 878±451$^+$	22 193±485$^+$
Toxicity, arb. units	1.60±0.28	1.55±0.25	2.04±0.31*	1.48±0.18	1.23±0.19$^+$	1.31±0.22$^+$

modification of membrane structures, which leads to inhibition of LPO processes and deceleration of metabolite release into intercellular space. The drug stimulates the release of metabolites forming during RF [11] from the interstitium into the lymph, initiating stimulation of lymph production and lymph outflow. Presumably, activation of microcirculation, increase of hydraulic conduction of the interstitium, and improvement of interstitial fluid rheology play an important role in the mechanisms of acceleration of lymph drainage under the effect of this antioxidant. We suppose that the number of cells transported with the lymph in RF increases not only due to lymph flow acceleration, but also due to increased lymphopoiesis and lymphocyte "washout" from the lymph nodes and to decrease of blood cell aggregation under the effect of mexidol.

Hence, mexidol due to its direct and indirect lymphotropic effects protects the lymph circulation: stimulates contractile activity of lymph capillary walls and valves and intensifies lymph formation, which improves resorption and transporting functions of the lymph system.

REFERENCES

1. T. A. Voronina and S. B. Seredenin, *Eksp. Klin. Farmakol.*, No. 4, 3-9 (1998).
2. T. A. Voronina and L. D. Smirnov, *Ros. Psikhiatr. Zh.*, No. 1, 32-34 (2000).
3. V. V. Gatsura, V. V. Pichugin, L. N. Sernov, *et al.*, *Kardiologiya*, No. 11, 59-62 (1996).
4. V. N. Gurin, *Mechanisms of Fever* [in Russian], Minsk (1993).
5. K. M. Dyumaev, T. A. Voronina, and L. D. Smirnov, *Antioxidants in Prevention and Therapy of Diseases of the Central Nervous System* [in Russian], Moscow (1995).
6. V. V. Zinchuk, M. V. Borisyuk, and V. N. Korneichuk, *Byull. Eksp. Biol. Med.*, **121**, No. 1, 44-47 (1996).
7. A. V. Zor'kina, Ya. V. Kostin, V. I. Inchina, *et al.*, *Khim.-Farm. Zh.*, No. 5, 3-5 (1998).
8. E. V. Levitina, *Eksp. Klin. Farmakol.*, No. 5, 34-36 (2001).
9. L. D. Luk'yanova, R. I. Atabaeva, and S. Yu. Shepeleva, *Byull. Eksp. Biol. Med.*, **115**, No. 3, 259-260 (1993).
10. I. I. Miroshnichenko, L. D. Smirnov, A. E. Voronin, *et al.*, *Ibid.*, **121**, No. 2, 170-173 (1996).
11. F. I. Mukhutdinova, *Kazansk. Med. Zh.*, No. 3, 219-222 (1994).
12. A. K. Sariev, I. A. Davydova, G. G. Neznamov, *et al.*, *Eksp. Klin. Farmakol.*, No. 3, 17-21 (2001).
13. O. N. Smirnov, V. I. Inchina, A. V. Zor'kina, *et al.*, *Ros. Onkol. Zh.*, No. 5, 25-27 (2000).
14. V. F. Stashchuk and V. Ya. Tsudechkis, *Lab. Delo*, No. 1, 15-18 (1986).