EFFECT OF HISTAMINE APPLICATION ON THE PULMONARY MICROCIRCULATION AFTER VAGOTOMY

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The action of histamine on the pulmonary microcirculation, especially when the innervation of the lungs is altered, has received less study than its effect on the large pulmonary blood vessels [8, 9]. Speranskii's views on the role of innervation [5] are well known, namely that the nervous system takes part in every response of the organism to a pathogenic factor, and this may lead to a change in its regulatory function. Histamine is one of the principal components of the humoral stage of regulation of microcirculatory systems [10], and in lung pathology its concentration increases [3].

In the investigation described below microcirculatory disturbances arising in the lungs in response to application of histamine after right-sided vagotomy were studied in order to obtain a clearer picture of the pathogenesis of lung diseases.

EXPERIMENTAL METHOD

Experiments were carried out on 140 albino rats weighing 150-200 g. The experimental animals were distributed as follows: for histamine application in doses of 0.5, 1.0, and 5 μg, 20 animals were used for each dose and another 10 rats served as the control; for histamine application in the same doses after right-sided vagotomy, 20 experimental animals were used for each dose and 10 rats again served as the control. Histamine was applied in physiological saline (0.05 ml). Physiological saline alone was applied in the control. The right vagus nerve was divided in its cervical portion. The state of the pulmonary microcirculation was studied by a technique of intravital microscopy suggested previously [2]. Besides microhemodynamic disturbances and changes in diameter of the microvessels, the state of the pulmonary microcirculation was assessed by determining adhesive properties of the capillary endothelium in the lungs relative to leukocytes and ink particles. The number of adherent leukocytes was counted as follows: Every 15 sec for 1 min the same region of the lung was photographed, and if during the interval between photographs a leukocyte remained in the same place on all negatives it was considered to be fixed to the endothelium. Adhesion of ink particles was estimated quantitatively on the basis of their number found in 0.1 mm^2 of the field of vision. Particles were counted 30 min after intravenous injection of 0.2 ml of a 0.1% solution of ink [1]. The ink was injected intravenously 1 min after vagotomy. Histamine was applied 1 min after injection of the ink. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Measurements of the diameter of the pulmonary capillaries showed that their response to histamine application after right-sided vagotomy is not identical with their response to local application of histamine in intact animals. The lumen of both wide and narrow capillaries in the lung [7] was increased by histamine in a dose as low as 0.5 μg (Table 1), but not in doses of 1 and 5 μg, as was observed in the series of experiments in which the nerve was not divided. Whereas in intact animals the increase in diameter of the capillaries was di-

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TABLE 1. Changes in Diameter of Pulmonary Capillaries in Response to Histamine Application before and after Right-Sided Vagotomy

Histamine applied	Dose of histamine, μg	Diameter of wide capillaries, μm		Diameter of narrow capillaries, μm	
		normal	application	normal	application
Before vagotomy	Physiological saline	34,26±1,51	34,11±1,54	8,90±0,23	8,70±0,18
	0,5	36,34±0,90	36,40±1,04	9,21±0,21	9,25±0,22
	1	36,75±0,61	66,54±1,69 ‡	8,80±0,23	9,00±0,10
	5	35,81±0,70	90,30±2,92 ‡	9,17±0,20	11,39±0,27†
After vagotomy	Physiological saline	34,42±1,99	34,70±1,83	8,99±0,99	9,22±0,31
	0,5	35,55±0,88	100,14±2,74 ‡	9,26±0,16	11,63±0,12†
	1	36,12±0,85	90,26±1,85 ‡	9,13±0,22	10,80±0,16*
	5	37,11±0,61	80,69±2,46 ‡	9,60±0,13	10,60±0,12*

*P < 0.05
†P < 0.01
‡P < 0.001

rectly proportional to the increase in histamine concentration, after vagotomy the opposite state of affairs was observed. The lumen of the pulmonary microvessels attained its largest diameter after application of 0.5 μg histamine.

Differences also were found in the microhemodynamic disorders. The blood flow in the pulmonary capillaries in intact animals began to change after local application of histamine in a dose of 1 μg: In 20% of cases the velocity of the blood flow was slowed, in 10% it increased, and in 70% it remained unchanged. Application of 5 μg histamine slowed the blood flow in 60% of cases, causing it to stop completely in 10% of them; in 20% of cases the velocity of the blood flow increased, and only in 20% did it remain unchanged.

The most marked disturbances of the microcirculation were observed when histamine was applied after division of the right vagus nerve. In doses of 0.5-1 μg, histamine caused even more profound changes than it did in its highest concentration (5 μg) in intact animals. In all the experimental animals in response to these doses the velocity of the blood flow was slowed; in 80% of cases the blood flow subsequently stopped (Fig. 1), and this occurred 5-10 sec after application. Application of 5 μg histamine caused a rather different response of the microhemodynamics. Slowing of the blood flow was observed in 60% of animals, in 25% it was increased, and in 15% it remained unchanged.

The velocity of movement of the blood cells returned to its initial level sooner (40-60 sec) after application of histamine to intact animals. In the vagotomized animals this process was delayed until 1.5 min.

Right-sided vagotomy followed by application of physiological saline (control animals) caused virtually no increase in diameter of the pulmonary capillaries (Table 1), but changes in the microhemodynamics were observed in 10% of cases (the velocity of the blood flow was very slightly reduced).

The study of the adhesive properties of the endothelium of the pulmonary microvessels showed that the number of "fixed" ink particles in 0.1 mm^2 of the field of vision increased after histamine application in the intact animals with an increase in histamine concentration: 8.4 ± 0.8 in the control, 28.7 ± 0.9 after application of 0.5 μg histamine, 43.0 ± 0.8 after application of 1 μg, and 59.9 ± 2.4 after application of 5 μg. The opposite relationship was observed when histamine was applied locally after right-sided vagotomy: 27.7 ± 1.6 in the control, 56.9 ± 2.5 after application of 0.5 μg, 47.9 ± 2.0 after application of 1 μg, and 42.4 ± 3.0 after application of 5 μg histamine.

Approximately the same situation also was observed when leukocyte adhesion was studied. In the intact animals the number of leukocytes adherent to the endothelium of the pulmonary capillaries was increased after application of 1 μg histamine (1.52 ± 0.12 in the control; 2.66 ± 0.36 after application) and reached its highest values after application of 5 μg histamine, namely 3.08 ± 0.49 (Fig. 2). Meanwhile the highest values of leukocyte adhesion were found when histamine was applied after vagotomy in a dose of 0.5 μg, namely 3.18 ± 0.27 (control 1.43 ± 0.13). The time taken for this parameter to return to its original values also differed. The number of white blood cells fixed to the endothelium 30 min after histamine application corresponded to a number in the control at the time of its application to intact animals and 45 min after its application to vagotomized animals.

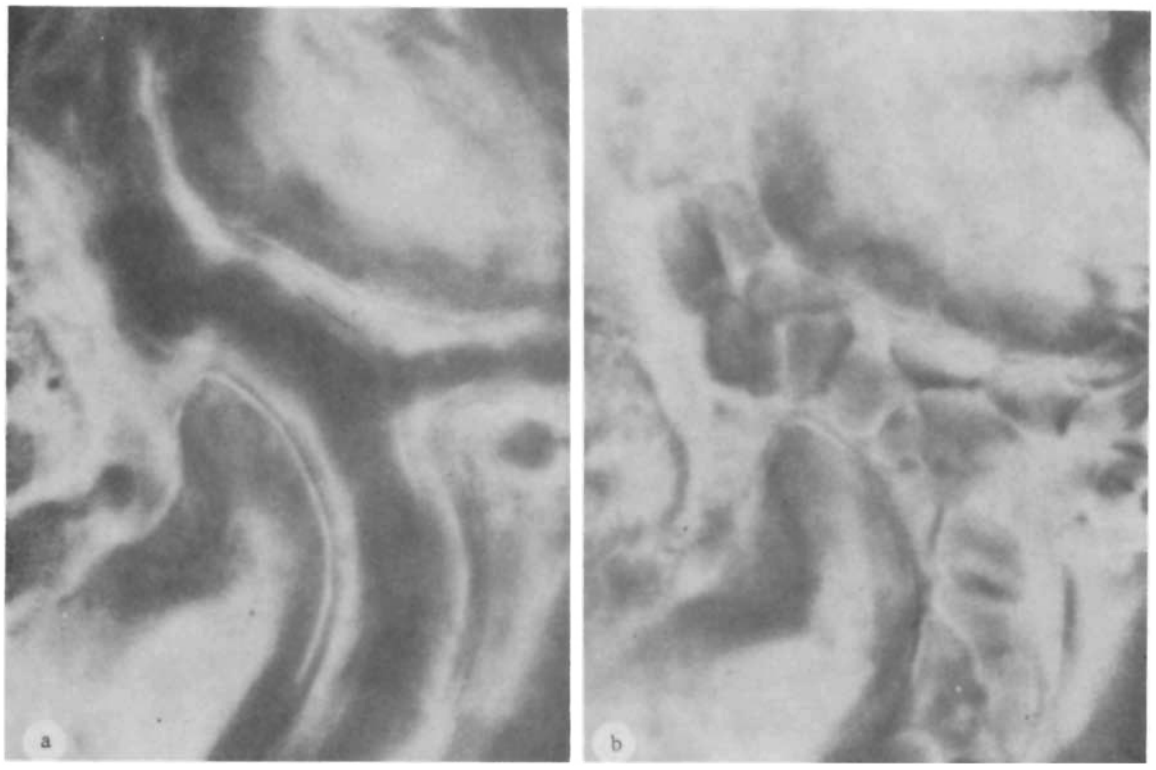

Fig. 1. Arrest of blood flow in pulmonary capillaries in response to application of 1 µg histamine after right-sided vagotomy. a) Normal, b) application. Objective 95, ocular 4.

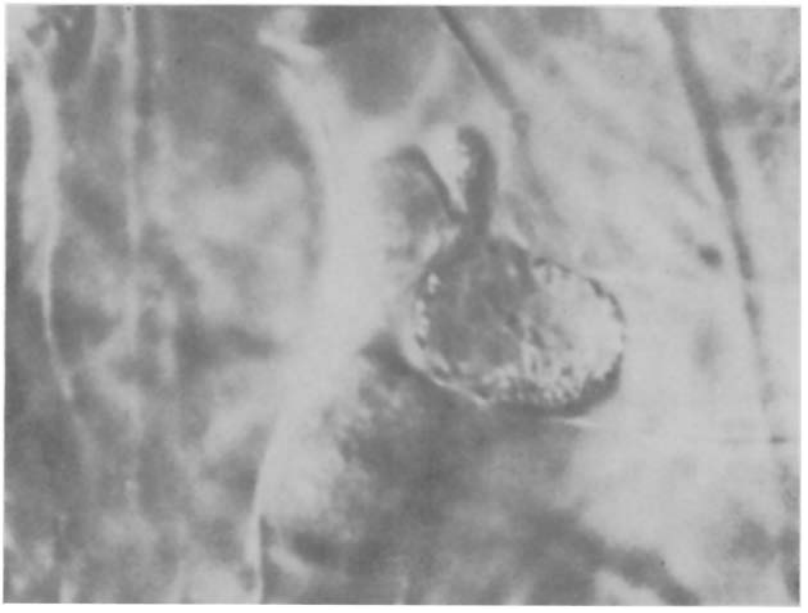

Fig. 2. Leukocyte held up in endothelium of pulmonary capillary after application of 1 µg histamine. Objective 95, ocular 7.

Consequently, the severity of the disturbances arising in the pulmonary microcirculation in response to local application of histamine after right-sided vagotomy did not correlate with the rise in its concentration. The severest changes were observed in response to smaller doses of this biologically active substance. It must also be pointed out that compared with changes observed in intact animals after application of histamine, their duration was longer, i.e., division of the right vagus nerve lowered the "threshold dose" for the action of histamine on the pulmonary microcirculation.

Partial or total denervation of an organ and tissue is known to increase their sensitivity to the action of various types of factors, including biologically active substances, as has frequently been confirmed experimentally [4, 6]. The increase in sensitivity usually arises a few hours or weeks after the disturbance of innervation. The results of the present experiments indicate that this occurs much sooner at the level of the microcirculation.

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