cluded that the trigger mechanism for the development of pulmonary atelectasis is disturbance of the surface activity of the surfactant.

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BIOLOGICALLY ACTIVE SUBSTANCES OF LUNG TISSUE IN RABBITS WITH BRONCHOPULMONARY INFLAMMATION

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In recent years the lungs have come to be regarded not only as a respiratory, but also as a metabolic organ. One of the most important manifestations of nonrespiratory function of the lungs is their metabolic function in relation to certain biologically active substances (BAS), with marked vasomotor activity. The question of the physiological role of the lungs in the metabolism of BAS has been widely discussed in the literature [1, 2, 10, 11], but there is an almost total absence of data on BAS metabolism in the lungs under pathological conditions. Investigations of this sort could help to shed light on certain stages of the pathogenesis of lung lesions.

The object of this investigation was to study BAS in blood flowing into and out of the lungs, and also in the lung tissue itself during experimental acute and chronic nonspecific bronchopulmonary inflammation.

EXPERIMENTAL METHOD

Experiments were carried out on 68 rabbits of both sexes weighing 2.5 kg, of which 34 were intact. In the other 34 animals chronic inflammation was produced in the lungs by a modified method [3]. A length of Kapron thread, 0.5 mm thick and 7-10 cm long, with a metal bob attached to its end, was introduced by operation into the trachea. The anterior end of the thread was fixed to the anterior wall of the trachea, and its posterior end remained free and reached one of the lobar bronchi or (more frequently) became impacted in one of the small bronchial branches. Biochemical tests were carried out between 1 and 5 months after introduction of the Kapron thread into the trachea. Blood flowing into the lungs was obtained by catheterization of the right atrium under hexobarbital anesthesia (35 mg/kg body weight) and blood flowing from the lungs was obtained by catheterization of the left ventricle. After removal from the thorax the lungs were studied in detail macroscopically. Pieces of lobe of the "affected" lung from some of the rabbits were investigated histologically. To study BAS in lung tissue the bronchi and great vessels were separated on ice and shredded pieces of parenchyma were immersed in liquid nitrogen and homogenized to a fine powder. Adrenalin, noradrenalin, and dopa [6], acetylcholine [8], histamine [7], and serotonin [4] were determined in the tissue homogenate. The same determinations were repeated during blood tests. The total catecholamine concentration in the blood was estimated from the level of adrenalin-like substances (ALS) [5]. The content of BAS in the tissues was expressed in μg/g wet weight of tissues and the concentration of BAS in the blood in μg/ml.

KEY WORDS: bronchopulmonary inflammation; content of biologically active substances.

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TABLE 1. Content of BAS in Lung Tissue (in μg/g) of Rabbits with Bronchopulmonary Inflammation (M ± m)

Group of animals	Time of observation, months	Adrenalin	Noradrenalin	Dopa	Acetylcholine	Histamine	Serotonin
Control	1	(7) 0,015 ±0,006	(7) 0,12 ±0,03	(7) 0,059 ±0,008	(5) 108,0 ±22,1	(5) 0,22 ±0,02	(6) 0,32 ±0,02
Experimental		(7) 0,08* ±0,02	(7) 0,29* ±0,08	(7) 0,033* ±0,004	(11)242,2* ±46,8	(5) 0,88* ±0,22	(9) 1,64 † ±0,23
Control	2	(9) 0,014 ±0,008	(8) 0,106 ±0,014	(9) 0,069 ±0,012	(3) 149,5 ±50,9	(5) 0,23 ±0,02	(5) 0,32 ±0,06
Experimental		(10) 0,06* ±0,015	(10) 0,17† ±0,005	(10) 0,020† ±0,002	(10) 131,5 ±29,5	(3) 0,90 ±0,38	(5) 1,007 † ±0,134
Control	4	(8) 0,012 ±0,008	(8) 0,070 ±0,012	(7) 0,084 ±0,022	(5) 142,0 ±28,7	(5) 0,24 ±0,05	(7) 0,27 ±0,06
Experimental		(6) 0,052 ±0,018	(6) 0,166 ±0,053	(6) 0,013* ±0,005	(6) 101,8 ±22,0	(5) 0,21 ±0,095	(7) 0,73* ±0,13
Control	5	(10) 0,009 ±0,004	(10) 0,125 ±0,037	(10) 0,054 ±0,004	(5) 100,4 ±18,2	(5) 0,20 ±0,005	(5) 0,29 ±0,01
Experimental		(4) 0,052 ±0,031	(4) 0,157 ±0,096	(4) 0,014 † ±0,01	(5) 139,7 ±22,3	(3) 0,28* ±0,02	(4) 1,24 † ±0,15

Note: Here and in Table 2, *P < 0.05, †P < 0.005 compared with control. Number of experiments given in parentheses.

TABLE 2. Content of ALS, Acetylcholine, Histamine, and Serotonin in Blood Flowing into and out of Lungs of Rabbits with Bronchopulmonary Inflammation (M ± m)

Group of animals	Time of observation, months	ALS, μg%		Acetylcholine, μg/ml		Histamine, μg%		Serotonin, μg/ml	
		inflowing blood	outflowing blood	inflowing blood	outflowing blood	inflowing blood	outflowing blood	inflowing blood	outflowing blood
Control	1	(5) 11,8 ±1,8	(5) 9,4 ±0,9	(5) 194,0 ±11,5	(4) 154,1 ±5,9	(5) 11,6 ±4,8	(5)12,0 ±5,0	(6) 0,115 ±0,038	(5) 0,073 ±0,01
Experimental		(5) 13,3 ±2,07	(6) 14,2** ±0,8	(7) 203,0 ±42,7	(5) 331,1** ±45,3	(4)10,0 ±0,36	(4) 16,0 ±2,8	(4) 0,186 ±0,016	(4) 0,22** ±0,0065
Control	2	(7) 14,9 ±2,2	(7) 9,06 ±1,6	(6) 194,6 ±11,4	(6) 162,0 ±22,6	(5) 12,0 ±3,0	(5) 11,0 ±2,0	(6) 0,122 ±0,093	(5) 0,066 ±0,006
Experimental		(4) 14,5 ±4,4	(3) 20,5* ±2,9	(6) 142,7 ±28,1	(4) 245,7 ±51,7	(4) 19,0 ±6,3	(4) 21,0 ±7,9	(4) 0,153 ±0,02	(3) 0,19* ±0,038
Control	4	(4) 12,5 ±2,5	(4) 9,5 ±1,3	(6) 212,2 ±56,3	(3) 211,5 ±33,5	(5) 10,7 ±3,7	(5) 11,0 ±3,0	(8) 0,12 ±0,011	(4) 0,093 ±0,019
Experimental		(3) 11,4 ±0,19	(3) 12,5 ±0,63	(4) 286,2 ±56,3	(3) 305,5 ±104,0	(4) 6,0 ±2,1	(3) 8,5 ±2,3	(3) 0,192 ±0,033	(3) 0,212 ±0,05
Control	5	(5) 15,1 ±1,7	(5) 7,8 ±1,6	(4) 190,3 ±15,9	(4) 144,8 ±11,0	(5) 14,0 ±3,0	(5) 11,0 ±2,0	(8) 0,122 ±0,009	(4) 0,072 ±0,013
Experimental		(4) 14,2 ±2,64	(4) 15,0* ±1,08	(4) 240,1 ±79,2	(5) 359,9* ±58,8	(5) 9,6 ±2,6	(5) 12,4 ±3,3	(5) 0,147 ±0,015	(5) 0,146* ±0,016

EXPERIMENTAL RESULTS

The results of the biochemical tests, given in Tables 1 and 2, indicate that the development of acute bronchopulmonary inflammation in rabbits is accompanied by marked changes, in the same direction, in the content of the tissue mediators. For instance, at the first month of development of inflammation a considerable increase was observed in the content of adrenalin and noradrenalin in the tissue; the tissue dopa (a precursor of catecholamines) level fell under these circumstances, reflecting the more rapid conversion of dopa into noradrenalin (Table 1). Meanwhile an increase was observed in the concentrations of acetylcholine, histamine, and serotonin (by 2-5 times compared with the control).

Similar changes in the BAS content also were found in blood flowing from the lungs (Table 2). There was a distinct venoarterial gradient in the acetylcholine and serotonin concentrations and, to a lesser degree, in the histamine concentration. The level of ALS in blood flowing from the lungs also was higher than in venous blood, evidently because of the entry of noradrenalin from pathological tissue into the blood.

Consequently, the development of acute inflammation in the lungs was accompanied by a sharp increase in the tissue hormone content in the pathological focus. The severity of the changes in BAS depended on the character of the developing lesion. The following observation, based on biochemical and morphological investigations, can serve as an illustration.

Rabbit No. 508 (one month from the beginning of the experiment). Suppurative tracheitis with focal infiltration of the walls, edema and marked hyperemia of the mucosa, and accumulation of many lymphocytes in the walls of individual bronchi, was diagnosed. Meanwhile multiple small acute abscesses were found in the affected lobe of the lung, against the background of bronchiostasis of varied severity. Biochemical investigation revealed a marked increase in the adrenalin concentration in the lung tissue to 0.12 μg/g, noradrenalin to 0.30 μg/g, and dopa to 0.036 μg/g. A marked increase was found in the acetylcholine concentration to 412.2 μg/g, histamine to 0.90 μg/g, and serotonin to 1.68 μg/g.

Later, when the bronchopulmonary inflammation had become chronic in character (2-3 months after the operation) the BAS content in the inflammatory focus gradually fell, but still remained higher than normally. For instance, the concentrations of acetylcholine, serotonin, and noradrenalin were clearly reduced but the histamine level was unchanged. The reserves of biological precursors of catecholamines (dopa) continued to decline. Meanwhile the BAS level fell in blood entering and leaving the lungs, but compared with the control the BAS concentration in the blood, like that in the tissues, remained high. As before, a distinct negative venoarterial gradient was noted in the acetylcholine, serotonin, and ALS levels, and a less clear gradient in the histamine concentration.

In the later stages the character of the change in the BAS concentration in the lung tissue were phasic in character. For instance, in the 4th month of the pathological focus the acetylcholine, histamine, and noradrenalin levels in the lung tissue were almost completely back to normal and no venoarterial gradient of BAS in the blood was found. Five months after the operation, an increase in the values of most biochemical indices in the lung tissue (serotonin, histamine, and acetylcholine concentrations) was again found. These changes in the tissue were combined with preservation of a negative venoarterial gradient in the acetylcholine, histamine, serotonin, and ALS levels. At the same time, the dopa reserves continued to fall (sometimes to the trace level). The following case will serve as an example of the principal metabolic changes in the lungs of rabbits with chronic bronchopulmonary inflammation.

Rabbit No. 571 (5 months from the beginning of the experiment). Besides suppurative tracheobronchitis and moderately severe papillary growths of the mucosa, chronic abscesses with perifocal sclerosis and adenoma-like structures in the zones of sclerosis, were found in the affected lobe of the lung on histological examination, against the background of multiple chronic bronchiectases and of bronchiectases with suppuration of their walls; multiple foci (in all lobes) of dysatelectasis of the lung tissue, predominantly peribronchial in location, and marked lymphoid infiltration of the bronchial walls and lung tissue also were observed. The BAS content in the lung tissue in this period was 0.035, 0.26, and 0.005 μg/g, respectively for adrenalin, noradrenalin, and dopa, and 162, 0.3, and 0.5 μg/g for acetylcholine, histamine, and serotonin, respectively. BAS thus plays a direct part in the pathological reaction of the lung tissues. The phasic character of changes in the content of tissue mediators of inflammation, probably reflecting the picture of repeated exacerbations connected with abscess formation or the development of bronchiectasis, must be emphasized. Changes in the acetylcholine and histamine concentrations were maximal in the first and fifth months of the pathological process, suggesting that they play a role in triggering reactions and in the development of exacerbations. Morphological and functional changes in the affected lung tissues were most completely reflected by serotonin, changes in the content of which in the course of the pathological process differed sharply from the corresponding changes in the control. In the present writers' opinion they are evidently the most specific of all and they participate in stabilization of irreversible changes in the lungs. So far as catecholamines and dopa are concerned, judging from data in the literature their role in inflammation can be reduced to the repair of microcirculatory disturbances caused by the mediators of inflammation — acetylcholine, histamine, and serotonin [9, 12]. In the early stages of chronic bronchopulmonary inflammation an important role is evidently played by a change in the ratio between mediators of inflammation and mediators exerting an antiinflammatory action, in favor of the former.

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LIFE SUPPORT BY OXYGEN BREATHING AFTER TOTAL BLOOD REPLACEMENT BY DEXTRAN

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Artificial hemodilution, or treatment of blood loss by transfusion with blood substitute, invariably leads to the development of acute anemic hypoxia. The problem arises of whether life can be supported with this degree of blood dilution, when so few erythrocytes remain in the blood stream that they cannot ensure the transfer of the necessary quantity of oxygen.

To answer this question, experiments were carried out with replacement of blood by dextran, a blood substitute which can maintain constancy of the circulating blood volume (CBV) for a long period of time. Under these circumstances an extreme degree of hemodilution was produced, with a hematocrit index of below 5. It was shown previously that if the hemoglobin concentration is below 2-3 g% [2] or the hematocrit index below 5 [4-6] death from anemic hypoxia takes place. In the present experiments, to overcome or alleviate the hypoxia, the animals breathed oxygen at normal barometric pressure.

EXPERIMENTAL METHOD

Sixteen cats (9 experimental and 7 control) were anesthetized with pentobarbital (30 mg/kg body weight, intramuscularly). Blood replacement by dextran was carried out by means of 2 or 3 fractional exchange transfusions. Blood was withdrawn from an artery and the blood substitute was injected intravenously at the same rate. With this method, 94-98% of the recipient's blood was replaced [1]. The cats were intubated: The experimental animals breathed pure oxygen and the control animals atmospheric air. The following parameters were determined in the experiment: the arterial blood pressure (BP) in the femoral artery, the central venous pressure (CVP) in the mouth of the posterior vena cava, the pulmonary ventilation and oxygen consumption by the method of Douglas and Haldane, the partial pressure of oxygen (pO_2) in arterial and venous blood, the CBV by means of ^{51}Cr-labeled erythrocytes, the hematocrit index, and hemoglobin concentration. The cardiac output (CO) was calculated by Fick's method and the arterio-venous (A-V) difference in O_2 concentration, total peripheral resistance (TPR), and coefficient of oxygen utilization were determined. The various parameters were determined before, immediately after, and 1, 2, and 4 h after exchange transfusion.

EXPERIMENTAL RESULTS

In both experimental and control animals the hematocrit index after exchange blood transfusion did not exceed 2-3 and the hemoglobin concentration was 2 g%. Under these conditions the animals of the control group died 10-15 min after the end of blood replacement whereas the experimental animals did not die before the end of the experiment, which lasted 8-9 h.

KEY WORDS: hemodilution; oxygen therapy; blood substitutes.

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