EFFECT OF LITHIUM HYDROXYBUTYRATE ON CHANGES IN LIPID METABOLISM IN PITUITRIN-INDUCED PULMONARY EDEMA

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Increased permeability of the air–blood barrier (ABB) is one of the main components of the pathogenesis of pulmonary edema [4, 10]. In turn, the ABB incorporates a number of biological membranes, consisting of protein–lipid complexes. Their permeability for water and for substances dissolved in it is mainly determined by the lipid component [6, 9]. The writers showed previously that lithium hydroxybutyrate (LHB), in a dose of 400 mg/kg, has a marked prophylactic effect against the edema-inducing action of adrenalin, pituitrin, and bilateral vagotomy in the neck. At the same time, we know that LHB significantly influences lipid metabolism [7].

The aim of this investigation was to study the content of total phospholipids (PL), total, free, and esterified cholesterol (TCh, FCh, and ECh respectively), and total lipids (TL) in the blood plasma and lungs during the formation of pituitrin-induced pulmonary edema under ordinary conditions and against the background of LHB.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats. Pituitrin edema of the lungs was produced by intravenous injection of pituitrin in a dose of 20 U/kg body weight. LHB was injected intraperitoneally in the form of a 20% solution in a dose of 400 mg/kg (3.636 mmoles/kg) 1 h before the injection of pituitrin. The animals were killed by decapitation 30 min after injection of pituitrin. The degree of pulmonary edema was judged by the pulmonary coefficient (PC), the ratio of the weight of the left lung in milligrams to body weight in grams), and the dry residue of the lungs — DR (in per cent). Lipids were extracted from the blood plasma and lungs by the method in [13]. Concentrations of PL, TCh, ECh, FCh, and TL were determined by the usual methods [9, 8]. The experimental results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that injection of pituitrin caused the development of marked pulmonary edema. At the same time the FCh concentration in the blood plasma was increased by 1.6 times and the ECh/FCh ratio was reduced by 1.5 times. The PL and FCh concentrations in the lungs were a little reduced, ECh was increased, and the ECh/FCh ratio was increased by more than 1.8 times (Table 2).

Injection of LHB had virtually no effect on PC or DR. Meanwhile the ECh/FCh ratio of the blood plasma of these rats was increased by 1.6 times and TL in the lungs was increased by 1.2 times.

In response to injection of pituitrin preceded by LHB, pulmonary edema was much less marked than in group 2 (Table 1). Meanwhile no increase in the FCh concentration was observed in the blood plasma of these rats, nor did the ECh/FCh ratio fall. Moreover, in group 4 the FCh concentration was 2.3 times lower and the ECh/FCh ratio was 3.2 times higher than in group 2. No decrease in the FCh concentration and no increase in the ECh/FCh ratio were observed in the lungs of the rats of group 4. Compared with the rats of group 2, the

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TABLE 1. Changes in PC and DR in Rats after Injection of Pituitrin under Ordinary Conditions and after Preliminary Injection of LHB

Group of animals	Experimental conditions	PC	DR, %
1-	Intact animals	1,93±0,10	19,69±0,27
2-	Pituitrin (eight)	4,24±0,46	14,12±0,88
3-	LHB (eight)	1,91±0,12	20,20±0,38
4-	LHB + pituitrin (eight)	2,63±0,34	17,30±0,83
	p_{1-2}	0,001	0,001
	p_{1-3}	0,5	0,2
	p_{1-4}	0,05	0,02
	p_{2-4}	0,02	0,02
	p_{3-4}	0,05	0,01

Legend. Here and in Table 2, number of animals given in parentheses.

TABLE 2. Changes in PL, TCh, FCh, ECh (in mmoles) and TL (in g) in Blood Plasma (per liter) and in Lungs (per kilogram) of Rats after Injection of Pituitrin under Ordinary Conditions and after Preliminary Injection of LHB

Group of animals	Experimeneal conditions	Plasma						
		PL	TCh	FCh	ECh	TL	TCh/PL	ECh/FCh
1	Intact animals (eight)	1,38±0,15	2,33±0,27	0,48±0,04	1,85±0,24	4,89±0,36	1,69±0,07	3,82±0,39
2	Pituitrin (eight)	1,27±0,07	2,35±0,10	0,76±0,10	1,59±0,08	4,87±0,47	1,87±0,06	2,50±0,45
3	LHB (eight)	1,17±0,14	2,14±0,40	0,34±0,08	1,80±0,36	4,16±0,37	1,72±0,16	6,23±1,03
4	LHB + pituitrin (eight)	1,15±0,09	2,13±0,25	0,33±0,08	1,80±0,18	4,76±0,65	1,82±0,09	7,88±1,79
	p_{1-2}	>0,5	>0,5	<0,05	>0,2	>0,5	>0,05	<0,05
	p_{1-3}	>0,2	>0,5	>0,1	>0,5	>0,1	>0,5	<0,05
	p_{1-4}	>0,2	>0,5	>0,1	>0,5	>0,5	>0,2	<0,05
	p_{2-4}	>0,2	>0,2	<0,01	>0,2	>0,5	>0,5	<0,02
	p_{3-4}	>0,5	>0,5	>0,5	>0,5	>0,2	>0,5	>0,2

(Continued)

Group of animals	Experimental conditions	Lungs						
		PL	TCh	FCh	ECh	TL	TCh/PL	ECh/FCh
1	Intact animals (eight)	22,53±0,56	13,83±0,76	10,02±0,36	3,81±0,48	30,67±1,64	0,61±0,02	0,38±0,06
2	Pituitrin (eight)	20,35±0,52	13,13±0,70	8,02±0,77	5,11±0,27	30,70±3,29	0,64±0,02	0,69±0,09
3	LHB (eight	23,3±0,96	14,11±0,61	10,58±0,54	3,53±0,52	35,76±1,37	0,61±0,01	0,35±0,06
4	LHB + pituitrin (eight)	20,48±0,76	12,62±0,78	8,64±0,56	3,98±0,22	27,73±0,82	0,61±0,02	0,46±0,01
	p_{1-2}	<0,02	>0,5	<0,05	<0,05	>0,5	>0,2	<0,02
	p_{1-3}	>0,5	>0,5	>0,2	>0,5	<0,05	>0,5	>0,5
	p_{1-4}	<0,05	>0,2	>0,05	>0,5	>0,1	>0,5	>0,2
	p_{2-4}	>0,5	>0,5	>0,5	<0,01	>0,2	>0,2	<0,05
	p_{3-4}	<0,05	>0,1	<0,05	>0,2	<0,001	>0,5	>0,05

ECh/FCh ratio in these animals was actually 1.5 times lower. This was due both to a smaller concentration of ECh in the lungs of the rats of group 4 and to prevention of their FCh level from falling. Meanwhile the PL concentration in the lungs of the animals of group 4 was reduced, as it was also in the rats of group 2.

The following mechanisms of the increased permeability of ABB in the lungs with pituitrin-induced pulmonary edema can be postulated on the basis of these results. We know that vasopressin stimulates hydrolysis of membrane lipids and increases the concentration of lyso-forms of phospholipids [11]. This effect is evidence of activation of phospholipase A_2, possibly due to vasopressin directly, or indirectly through catecholamines, the secretion and action of which are intensified after injection of pituitrin [11]. As a result of activation of phospholipase A_2 the formation of lyso-derivatives of phospholipids in the lung

tissue is intensified; since these are water-soluble compounds, they can leave the lung tissue. In turn, this reduces the PL content in the lungs, and on the other hand, it increases the permeability of the ABB. Another factor increasing the permeability of ABB may be the intensification of lipid peroxidation through an increase in the content of free fatty acids. Another important result of the action of vasopressin in the present experiments was a decrease in the FCh content in the lungs and an increase in the ECh/FCh ratio. Removal of FCh from the plasma membranes of the tissues is effected mainly by high-density lipoproteins with the participation of the enzyme lecithin:cholesterol acyltransferase [6]. Vasopressin modifies the functional activity of this complex. This is shown by the absence of any increase in cholesterol esterification in the blood plasma despite elevation of the FCh level. Reduction of the content of FCh, the most hydrophobic components of membranes, in the lungs increases their permeability for water and substances dissolved in it. Furthermore, a decrease in the FCh concentration leads to increased mobility of the fatty acids of PL, which makes them more accessible for phospholipases [6]. Further activation of phospholipases also is facilitated by an increase in surface tension of the membranes due to the development of edema and swelling of cellular structures [1]. Incidentally, similar changes in lipid metabolism in the lungs also were observed by the present writers during the formation of adrenalin edema [12].

It must be recalled that all the changes in lipid metabolism described above, leading to increased permeability of ABB, were combined after injection of pituitrin with marked disturbances of function of the cardiovascular system. This is manifested by spasm of the coronary vessels, arrhythmias, reduction of left ventricular contractility, and increased peripheral resistance [11]. This combination of hemodynamic disturbances, leading to a rise to hydrostatic pressure in the lung capillaries and changes in lipid metabolism, increasing the permeability of ABB, ultimately leads to the development of pulmonary edema.

LHB prevents the fall of the FCh level and rise of the ECh/FCh ratio in the lungs. LHB also depresses lipase and lipoprotein-lipase activity in the blood and tissues and reduces the content of free fatty acids and the intensity of lipid peroxidation [7]. In the present experiments reduction of lipase activity was manifested by a significant increase in the TL content in the lungs under the influence of LHB. All this largely prevents the increased permeability of ABB under the influence of pituitrin. Another factor in the mechanism of the protective action of the compound to be taken into account is that LHB reduces activity of the sympathicoadrenal system [2], synthesis and secretion of vasopressin [14], and the renin activity of the blood plasma considerably [5], and also improves the coronary circulation and prevents arrhythmias [2, 3]. The results of these effects are reduction of the hemodynamic disturbances and a smaller increase in hydrostatic pressure in the lungs, and this also plays an important role in the prevention of pulmonary edema.

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