EFFECT OF ESSENCIALE ON PULMONARY EDEMA AND CHANGES IN LIPID METABOLISM IN RESPONSE TO ADRENALIN

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Increased permeability of the tissue-blood barrier of the lungs is an important stage in the pathogenesis of adrenalin-induced pulmonary edema [4, 11]. This barrier includes several biological membranes, some of the most important structural components of which are phospholipids and cholesterol. Their quantitative and qualitative composition determine properties of the membranes such as microviscosity, permeability for ions and water, and also activity of membrane-bound enzymes: cytochrome oxidase, Mg^{++}-ATPase, Ca^{++}-ATPase, etc. [5, 8, 9].

The preparation essenciale is a drug which has a diverse effect on lipid metabolism and, in particular, on phospholipid and cholesterol concentrations [2, 3].

The aim of this investigation was to study levels of phospholipids, free and esterified cholesterol (ECh), and total lipids in the blood plasma and lungs during the formation of adrenalin-induced pulmonary edema and to examine the effect of essenciale on pulmonary edema and on changes in lipid metabolism.

EXPERIMENTAL METHODS

Experiments were carried out on 65 noninbred albino rats. Pulmonary edema was induced by intravenous injection of 0.1 ml of adrenalin solution in a dilution of 1:5000 per 100 g body weight. Essenciale (from Bosnalijek, Yugoslavia, jointly with Nattermann, West Germany) was injected intravenously, slowly, in a dose of 0.66 ml/100 mg body weight 1 h before adrenalin. Surviving animals were decapitated 30 min after the injection of adrenalin. The degree of pulmonary edema was judged from the rate and duration of survival of the animals, the pulmonary coefficient (PC), the ratio of the weight of the lung, in milligrams, to the body weight (in grams), the dry residue of the lungs (DR, in per cent), the edema fluid index (EFI), and the relative increase in blood volume (IBV) [12]. Lipids were extracted from the blood plasma and lungs by the method in [13]. Total phospholipids (PL), total cholesterol (TCh), free cholesterol (SCh), and ECh, and total lipids (TL) were determined by the usual methods [7, 8].

TABLE 1. Changes in Parameters of Lipid Metabolism in Rats After Injection of Adrenalin with or without Preliminary Administration of Essenciale (M ± m)

Group of animals	Experimental conditions	Number of animals	Parameter			
			PC	DR	EFI	IBV
1-	Control (intact rats)	8/0	6,5±0,35[b]	20,6±0,19[c]	0,0±0,01[b]	0,0±0,35[b]
2-	Adrenalin	9/6	14,7±1,4[a]	14,4±1,1[a,d]	0,87±0,18[a,b]	6,7±1,46[a]
3-	Essenciale	8/0	6,7±0,23[b]	20,6±0,26[b]	−0,003±0,265	0,18±0,43[b]
4	Essenciale + adrenalin	8/1	11,0±1,9	17,6±0,58	0,33±0,10	5,04±1,76

Note. Here and in Table 2: numerator, number of animals used in experiment; denominator, number of animals which died; a) $P < 0.001$ compared with intact rats, b) $P < 0.02$, c) $P < 0.001$, d) $P < 0.05$ compared with group 4.

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TABLE 2. Changes in PL, TCh, ECh, FCh, and TL Levels in Blood Plasma and Lungs of Albino Rats after Injection of Adrenalin with or without Preliminary Administration of Essenciale (M ± m)

Group of animals	Experimental conditions	Number of animals	Plasma						
			PL	TCh	FCL	ECh	TL	TCh/PL	ECh/FCh
1-	Control (intact rats)	8/0	1,22±0,06	1,87±0,19	0,60±0,07	1,26±0,12	2,65±0,24	1,51±0,1	2,13±0,13
2-	Adrenalin	8/6	1,58±0,15[a],[c]	2,51±0,24	0,40±0,050[a][c]	2,11±0,21[a]	4,32±0,6[a]	1,60±0,06[c]	5,48±0,59[b],[c]
3-	Essenciale	8/0	5,65±0,16[b]	2,92±0,05[b]	1,32±0,181[a]	1,60±0,17[d]	6,12±0,15[b]	0,52±0,01[b]	1,44±0,36
4-	Essenciale+ adrenalin	8/1	6,14±0,48[b]	3,25±0,26[b]	1,04±0,13[a]	2,21±0,14[b]	6,71±1,46[a]	0,54±0,05[b]	2,26±0,23

Group of animals	Experimental conditons	Number of animals	Plasma						
			PL	TCh	FCh	ECh	TL	TCh/PL	ECh/FCh
1-	Control (intact rats)	8/0	23,55±0,70	13,55±0,70	6,43±0,87	7,12±0,68	25,91±1,71	0,58±0,03	1,14±0,22
2-	Adrenalin	8/6	19,14±0,28[a] [d]	10,92±0,46[a]	4,02±0,61[a]	6,92±0,49	21,46±1,26	0,57±0,03	1,92±0,31
3-	Essenciale	8/0	26,47±1,02 [d]	10,99±0,78[a]	3,61±0,83[a]	7,37±0,43	27,66±1,39	0,42±0,03[b]	2,68±0,68[a]
4-	Essenciale+ adrenalin	8/1	21,63±0,80	11,1±1,44	4,29±0,70	6,80±1,12	23,32±3,01	0,51±0,04	1,74±0,32

Note. Concentrations of PL, TCh, FCh, and ECh expressed in mmoles/liter (Plasma) and mmoles/kg (lungs); TL) in g/liter (plasma) and in g/kg (lungs). a) $P < 0.05$, b) $P < 0.001$, compared with control, c) $P < 0.001$, d) $P < 0.02$ compared with group 4.

RESULTS

Injection of adrenalin caused the development of marked pulmonary edema (Table 1). Most animals died within 3.0 ± 0.5 min. Meanwhile the PL level in the blood plasma of these rats was raised by 1.3 times, ECh by 1.7 times, and TL by 1.6 times, whereas the FCh level fell by one-third (Table 2). The PL and TCh concentrations in the lungs were reduced on account of a decrease in the quantity of FCh.

Injection of essenciale caused no changes in the content of water and blood in the lungs. However, essenciale increased the plasma TL concentration by 4.6 times and, unlike adrenalin, increased the FCh concentration by 2.2 times. The TCh/PL ratio showed a three-fold decrease. Essenciale, like adrenalin, reduced the FCh concentration in lung tissue. However, unlike the rats of group 2, a decrease in the TCh/PL ratio and an increase in the ECh/FCh ratio were observed at the same time in these animals.

When injection of adrenalin was preceded by administration of essenciale the intensity of the pulmonary edema was much less than in the rats of group 2; however, the blood volume in the lungs was increased by virtually the same degree (Table 1). Just as after injection of adrenalin under ordinary conditions, the ECh concentration in the plasma of the rats of group 4 increased, but the plasma FCh level was 1.7 times higher than in intact animals and 2.5 times higher than in the animals of group 2. As a result of this the ECh/FCh ratio did not rise as in the rats of group 2, but remained at the control level. The TCh/PL ratio also was three times lower than in the control. Just as in group 3, this was due to an increase in the PL concentration. The PL level was lower in the lungs of the rats of group 4 than in those of group 3, but higher than in the animals of group 2.

The mechanism of the observed changes can be represented as follows. Injection of adrenalin induces activation of phospholipase A [1]. As a result, lyso forms of PL, which are surface-active (have a detergent action) and can significantly increase permeability, are formed. In addition, lyso derivatives of PL, which are sufficiently soluble in water, may leave the lung tissue, as a result of which its permeability also will increase. As the

result of intensification of cholesterol esterification the FCh level in the plasma and lung tissue falls. A decrease in the FCh concentration in the membranes, on the one hand, increases their permeability for ions and water, and on the other hand increases the mobility of the fatty acids of PL and makes them more accessible for phospholipases and active radicals [5]. Adrenalin is known to potentiate lipid peroxidation [6].

Administration of essenciale sharply increases the molar concentration of PL in the blood plasma. This facilitates extraction of FCh from the tissues and, in particular, from the lungs. As a result the molar fraction of PL in the lipid phase of the lungs increases. As a result of this structural change there is a smaller decrease in the PL concentration in the lungs after injection of adrenalin, a less severe disturbance of permeability of the alveolar-capillary barrier, and less hydration of the lungs. The effect of essenciale on the cardiovascular system plays a definite role in the mechanism of its protective action [10].

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