EFFECT OF A MEMBRANE MODULATOR OF THE 3-HYDROXYPYRIDINE CLASS ON DEVELOPMENT OF PULMONARY EDEMA

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Lipid peroxidation (LPO) has been shown to proceed at an extremely low level in intact lungs. Reduction of antiradical activity of the lung tissue with enhancement of LPO is combined in some cases with the development of pulmonary edema (PE) [11]. Considering the marked damaging action of LPO products on cell membrane structures [6], it can be tentatively suggested that the use of active inhibitors of free-radical processes would be an effective means of prevention and treatment of PE.

EXPERIMENTAL METHOD

Experiments were carried out on 280 albino rats. The effect of the water-soluble antioxidant emoxipin [9] on the degree of hydration and congestion of the lungs [12], permeability of the air-blood barrier for protein molecules [14], and its effect on the development of hemodynamic and neurogenic forms of PE were investigated. Emoxipin (100 mg/kg) was given as a single injection by the intratracheal, intravenous, or intraperitoneal routes (for 4 days). PE was produced by intravenous injection of noradrenalin, and pituitrin and by suboccipital injection of a solution of aconitine (1×10^5), or by bilateral cervical vagotomy. Injections were given or vagotomy performed under local procaine anesthesia, whereas aconitine was injected under superficial ether anesthesia. In order to provoke edema, physicological saline was injected in a dose of 10 ml/kg into the vagotomized animals 15 min after the operation. The rats were killed 30-40 min after induction of edema or 2 h after vagotomy by decapitation on a guillotine. To estimate the mechanism of action of emoxipin, preparations with a strong membrane-modulating action were used: the β-adrenomimetic euspiran, and prostacycline. The intensity of PE was assessed by the pulmonary coefficient (PC), the dry residue of the lungs (DR), the quantity of edema fluid (EF), and the increase in congestion (IC), expressed in grams per kilogram body weight [12]. In each series 10 animals were used.

EXPERIMENTAL RESULTS

Intravenous or intraperitoneal injection of emoxipin did not affect the degree of hydration or congestion of the lungs compared with intact animals (Table 1). Intratracheal injection of emoxipin likewise caused no significant differences with the control group, receiving the corresponding volume of physiological saline (5 ml/kg). Intraperitoneal injections of emoxipin for 4 days did not affect the permeability of the pulmonary vessels for protein molecules (48.5 ± 5.8 mg in the experiment, 67.5 ± 8.9 mg Evans' blue/kg dry weight of lung tissue in the control). On intratracheal injection of a solution of albumin labeled with Evans' blue, no changes likewise were observed in its plasma concentration (2.5 ± 0.7 mg in the experiment compared with 1.3 ± 0.6 mg Evans' blue/liter plasma in the control). Intravenous injection of emoxipin 30 min before injection of noradrenalin (0.5 mg/kg) or pituitrin (10 units/kg) did not affect the development of these forms of PE (Table 1). Intraperitoneal injection of emoxipin for 4 days increased the intensity of development of PE after injection of noradrenalin (0.25 mg/kg), aconitine (0.04

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TABLE 1. Effect of Emoxipin, Prostacycline, and Euspiran on Development of PE ($M \pm m$)

Exptl. conditions	PC		DR		EF		IC	
	control	experiment	control	experiment	control	experiment	control	experiment
Emoxipin i.v. + noradrenalin	14,33±1,02*	14,25±0,39	14,49±0,60*	15,16±0,28	4,85±0,61*	4,34±0,22	3,31±0,66*	3,74±0,42
Pituitrin	12,48±0,38*	14,14±1,08	15,48±0,28*	15,26±0,42	3,59±0,22*	4,34±0,23	2,69±0,31*	3,63±0,56
Emoxipin i.p. + noradrenalin	12,35±0,60*	13,52±1,05	17,31±0,52*	16,62±0,40	2,57±0,33*	3,59±0,32**	3,61±0,58*	3,76±0,97
Aconitine	11,57±1,10*	15,34±1,16**	18,03±0,75*	14,74±0,64**	2,29±0,65*	5,22±0,59**	3,11±0,54*	3,96±0,67
Vagotomy	14,73±1,53*	18,45±1,20	16,62±0,35*	15,65±0,30**	4,10±0,32*	5,20±0,38	4,46±0,89*	7,09±0,82**
Prostacycline + pituitrin	12,06±1,25*	12,71±0,95	16,66±0,56*	16,27±0,73	3,02±0,59*	3,37±0,62	2,57±0,74*	3,18±0,59
Aconitine	15,86±1,12*	10,66±0,60**	13,78±0,46*	17,43±0,63**	5,95±0,62*	2,22±0,40**	3,75±0,62*	2,27±0,32**
Euspiran + pituitrin	14,73±1,53*	10,43±1,05**	16,62±0,35*	17,77±0,92	4,10±0,32*	2,09±0,62**	4,46±0,89*	2,16±0,68
Aconitine	15,86±1,12*	10,00±1,04**	13,78±0,46*	18,72±0,69**	5,95±0,62*	1,54±0,43**	3,75±0,62*	2,24±0,71**
Intact animals	17,77±1,37*	10,33±1,32**	14,51±0,34*	18,64±0,86**	5,91±0,54*	1,67±0,59**	5,69±0,97*	2,49±0,78
Emoxipin	6,17±0,44		21,85±0,44		0,00±0,12		0,00±0,43	
	6,42±0,45		20,79±0,36		0,28±0,26		0,00±0,52	

Legend. Control — induction of edema; experiment — preparation + induction of edema. *$p < 0.05$ For comparison of intact and control animals, **$p < 0.05$ for comparison of control and experimental animals.

ml) and, in particular, pituitrin (5 units/kg) and did not affect the development of postvagotomy PE (Table 1). The degree of congestion of the lungs in the group with aconitine rose by 59%. Mortality was increased to 100% compared with 60% in the control. Emoxipin, which possesses antiradical activity [2, 4], at the same time inhibits thromboxane A_2 formation, increases the prostacycline concentration, inhibits phosphodiesterase, increases the content of cyclic nucleotides in the cell, increases the content of polar lipid fractions (phosphatidylserine and phosphatidylinositol), and thereby reduces the viscosity of the lipid layer [3, 9]. Preliminary intravenous injection of prostacycline (1 mg/kg) followed after 5-10 min by injection of pituitrin (10 units/kg) had an inhibitory action on the development of this form of PE (Table 1). A similar result was obtained after injection of prostacycline (2 mg/kg) followed by suboccipital (0.04 ml) injection of aconitine. Injection of euspiran (10 mg/kg), an adenylate cyclase stimulator, 10-15 min beforehand inhibited the development of PE by an even greater degree after injection of pituitrin (10 units/kg) or suboccipital injection (0.08 ml) of aconitine (Table 1).

Thus the intensification of development of pituitrin-induced and centrogenic PE after injection of emoxipin cannot be connected with its ability to raise the prostacycline concentration or to inhibit phosphodiesterase. On the contrary, these properties of the preparation ought to inhibit PE. The effect of emoxypin may perhaps be linked with its antioxidant properties. According to our data [8], injection of pituitrin led to the accumulation of primary LPO products in the lung tissue, whereas preliminary injection of the powerful antioxidant ionol increases the development of pituitrin- and, in particular, of noradrenalin-induced PE. Polyunsaturated fatty acids, the substrate for LPO, are known to have a protective effect on the development of lethal adrenalin-induced PE [5]. It has been shown that gamma-irradiation, a powerful activator of free-radical processes, significantly inhibits the development of PE induced by adrenalin, chloramine, and vagotomy [1]. Blockade of beta-adrenoreceptors by propranolol sharply enhances the edemogenic effect of noradrenalin on the lungs [7]. Activation of LPO with weakening of antiradical protection of the lung tissue has been established in many pathological processes [10], unaccompanied by the development of PE. We know that one result of activation of LPO is a sharp decline in the fraction of readily oxidized phospholipids (phosphatidylserine, phosphatidylinositol [13]), essential for signal transmission from the receptor inside the cell. It can be tentatively suggested that peroxides, by acting on the lipid component of the membrane, uncouple the receptor from its submembrane component. Emoxipin, by inhibiting free-radical oxidation, and by reacting with peroxide radicals of lipids, increasing the activity of antioxidant enzymes and raising the phosphatidylinositol concentration, may increase the sensitivity of the cell to the action of vasopressin and noradrenalin, and may thereby bring about an increase in PE.

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