EFFECT OF PHOSPHOLIPASE A_2 ON DEVELOPMENT OF PULMONARY EDEMA AND ON THE PULMONARY HEMODYNAMICS IN INTACT AND VAGOTOMIZED ANIMALS

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Positive correlation is found between the level of phospholipase A_2 (PLA_2) activity in blood plasma from the lungs of rats with experimental pancreatitis and the degree of their involvement and the development of pulmonary edema (PE).

The aim of this investigation was to obtain data relating to the pathogenetic role of PLA_2 in the development of PE and the role of the hemodynamics in this process.

EXPERIMENTAL METHOD

Experiments were carried out on 110 albino rats, 10 guinea pigs, and 30 cats. PLA_2 was injected intravenously into intact or vagotomized animals. The vagus nerves were divided in the neck, and this was followed by tracheotomy. Experiments on the rats and guinea pigs were carried out under local anesthesia, but those on cats and some on rats were carried out under pentobarbital anesthesia (30-40 mg/kg body weight, intraperitoneally). The pulmonary hemodynamics was studied in 10 cats with an open chest and with artificial ventilation of the lungs, by means of an ultrasonic method [3] and of electronic manometers of an original design [6]. The intensity of PE and the degree of filling of the vascular bed of the lungs were estimated by calculating the pulmonary coefficient (PC), the dry residue of the lungs (DR), the volume of edema fluid (EF), and the increase in filling of the blood vessels (BF) in grams per kilogram body weight [10].

EXPERIMENTAL RESULTS

Injection of PLA_2 into rats (1.25, 2.5, and 5 mg/kg) and cats (1.25 mg/kg) did not lead to the development of PE after 1-3 h, although BF in the cats increased (Table 1). In guinea pigs, 2 h after injection of PLA_2 (1.25-2.5 mg/kg) the development of marked PE was observed ($p < 0.01$) without any significant change in the blood volume. According to our data, permeability of the air-blood barrier (ABB) for protein molecules is twice as high in guinea pigs as in rats [4]. Injection of PLA_2 (1.25 mg/kg) into the rats 10-15 min after vagotomy led to death of 100% of these animals during the first hour (on average 37 min after injection), against the background of marked PE ($p < 0.001$) and of an increase in BF ($p < 0.001$). Vagotomy itself slightly increased the volume of EF in the lungs (0.97 ± 0.14). This is 5 times less than after injection of PLA_2 (4.83 ± 0.52). An increase in the dose of PLA_2 accelerated death of the vagotomized rats (2.5 mg/kg caused death after 15 min, 5 mg/kg after 12 min), against a background of marked PE (EF 5.69 ± 0.90 and 6.55 ± 0.37); and it was immaterial whether the PLA_2 was injected before or after vagotomy. Vagotomy on anesthetized cats after 3 h had no significant effect on the degree of hydration and the filling of the blood vessels of the lungs (Table 1). Similar results also were obtained on anesthetized rats. Injection of PLA_2 into cats (1.25 mg/kg) 30 min after vagotomy led to a decrease of 14.6% in DR compared with that after vagotomy alone

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TABLE 1. Effect of PLA_2 on Development of PE in Intact and Vagotomized Animals

Experimental conditions	Group compared	Pulmonary coefficient, g/kg	DR of lungs, %	Volume of EF, g/kg	BF of lungs, g/kg
1. Intact albino rats (16)	—	6,17±0,44	21,85±0,41	0,00±0,12	0,00±0,43
2. PLA_2 (20)	1—2	7,37±0,47	20,52±0,55	0,41±0,32	0,79±0,35
3. Vagotomy (20)	1—3	7,78±0,33*	19,17±0,33*	0,97±0,14*	0,64±0,26
4. Vagotomy + PLA_2	3—4	15,08±0,81*	14,99±0,53*	4,83±0,52*	4,08±0,50*
5. Atropine + PLA_2 (10)	2—5	7,29±0,19	20,74±0,25	0,33±0,10	0,79±0,21
6. Intact guinea pigs (10)	—	8,52±0,89	19,98±0,33	0,00±0,15	0,00±0,86
7. PLA_2 (10)	6—7	14,20±1,41*	15,08±0,54*	3,75±0,72*	1,93±0,77
8. Intact cats (10)	—	6,14±0,35	21,80±0,18	0,00±0,13	0,00±0,52
9. PLA_2 (6)	8—9	9,25±0,40*	22,83±1,73	—0,44±0,67	3,55±0,53*
10. Vagotomy (8)	8—10	6,22±0,42	21,17±0,27	0,18±0,15	—0,10±0,48
11. Vagotomy + PLA_2 (10)	9—11				
	10—11	9,28±0,47*	18,07±0,62**	1,64±0,33**	1,51±0,27**

Legend. Asterisk denotes significant differences (value of p given in text). Number of animals shown in parentheses.

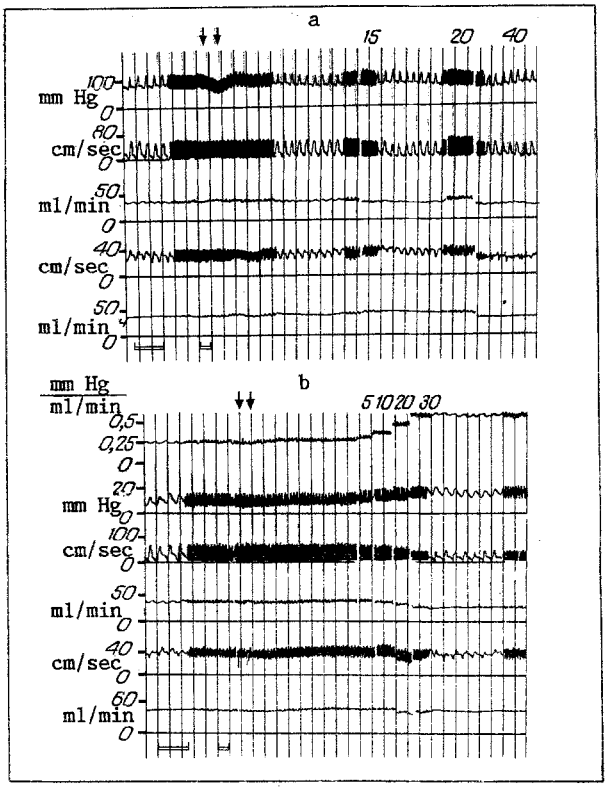

Fig. 1. Changes in parameters of pulmonary and systemic circulation after vagotomy. a: From top to bottom) blood pressure in femoral artery (mm Hg), phased blood flow in lower lobar pulmonary artery, mean values of flow in lower lobar pulmonary artery, phased blood flow in lower lobar pulmonary vein, mean flow rates in lower lobar pulmonary vein; b: from top to bottom) vascular resistance of lobe of lung, blood pressure in pulmonary artery, phased blood flow in lower lobar pulmonary artery, mean values of flow in lower lobar pulmonary artery, phased blood flow in lower lobar pulmonary vein, mean flow rates in lower lobar pulmonary vein. Here and in Fig. 2: thin lines beneath each curve indicate zero levels. Arrows indicate time of procedure. Numbers in top part of figures give time (in min) elapsing after procedure. Time scale: 1 and 10 sec.

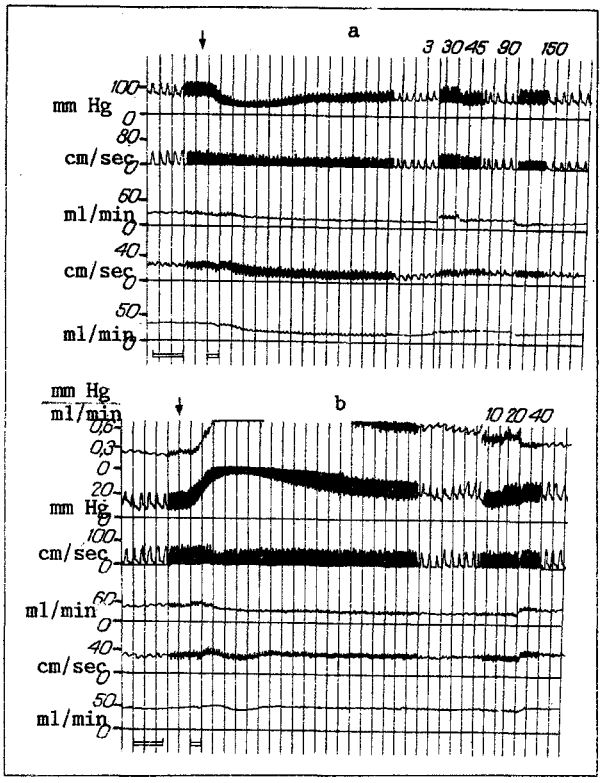

Fig. 2. Changes in parameters of pulmonary and systemic circulation after intravenous injection of PLA_2. Legend as to Fig. 1.

($p < 0.001$) and a decrease of 20.8% compared with PLA_2 alone ($p < 0.05$), and also to accumulation of EF. Experiments on vagotomized rats showed that preliminary administration of pentobarbital in the same doses as for cats sharply inhibited the development of PE and prevented their death after injection of PLA_2 (EF 1.25 ± 0.42). An increase in the dose of PLA_2 (5 mg/kg) led to the development of marked PE in these rats (EF 5.61 ± 0.71), but their death was prevented by artificial ventrilation of the lungs. Thus division of the vagus nerves leads to manifestation of the edemogenic action of PLA_2 on the lungs, although general anesthesia significantly depresses the effect of vagotomy. This effect is unconnected with the blocking of efferent impulsation along the vagus nerves, for preliminary injection of atropine into the rats (250-500 mg/kg subcutaneously 1 h beforehand) followed by injection of PLA_2 (2.5-5 mg/kg) did not repeat the action of vagotomy (Table 1).

After vagotomy the systemic arterial blood pressure of the cats was unchanged or very slightly raised (on average by 20% toward the 10th minute) (Fig. 1a). A similar response was observed in rats and guinea pigs [4]. The heart rate (HR) of the cats was increased by 15.4% by the 5th minute, but in rats it was slowed (335.00 ± 39.20 compared with 468.20 ± 11.67, $p < 0.01$). In most experiments vagotomy had no significant effect on the pulmonary hemodynamics. All that could be observed was a transient rise of pulmonary arterial pressure (PAP) on average by 20.3% toward the 10th minute. In some experiments, however, PAP was maintained at a high level for longer (Fig. 1b). The volume velocity of the blood flow in the lower lobar artery during the first minutes after vagotomy was only slightly increased or unchanged, but later it gradually decreased toward the 30th minute. The resistivity of the pulmonary vessels increased proportionally to time and to the degree of reduction of the blood flow along the lobar artery, and was increased on average by 28.6% toward the 30th minute. In separate experiments there was a more marked increase in the pulmonary vascular resistance (Fig. 1b).

Injection of PLA_2 (1.25 mg/kg) against this background led to lowering of the systemic blood pressure and to an increase in HR followed by its restoration to the level which was found before vagotomy (Fig. 2a). Changes in the pulmonary hemodynamics were biphasic in character. The first phase was an immediate response to injection of PLA_2 with a sharp rise of PAP and an increase in the resistance of the pulmonary vascular bed. PAP was partially or completely restored after 3-5 min but the pulmonary vascular resistance remained high until the end of the experiment (Fig. 2b). At the same time a decrease was observed in the volume velocity of the blood flow along the lobar artery. This reduction of the blood flow persisted throughout the period of observation (until 3 h), the inflow of blood along the lobar artery usually being less than its outflow along the

analogous vein. This is indirect evidence of an increase in the blood flow along the bronchial arteries, for we know that much of the venous outflow from the system of the bronchial arteries takes place along the pulmonary veins [1, 9]. We observed a similar response previously in experimental pulmonary embolism [7]. After 40-90 min there was a second rise of PAP. By this time, spontaneous respiratory movements had begun to appear in the animals against the background of continuing artificial respiration, evidence of the development of marked hypoxia, the most probable cause of the secondary rise of PAP [1]. Starting from this time, the systemic BP fell and bradycardia developed. The action of PLA_2 is evidently realized through an increase in permeability of the air-blood barrier and injury to the phospholipid layer of the alveoli. It cannot be concluded from these results that changes in the hemodynamics play the leading role in the development of PE in this particular model. However, we know from data in the literature that in a situation in which pulmonary vascular permeability is increased, an increase in the pulmonary capillary hydrostatic pressure can considerably increase the degree of pulmonary edema [11]. The increase of pressure in the pulmonary artery and the increase in pulmonary vascular resistance in the present experiments lead to the conclusion that the capillary hydrostatic pressure under these conditions was increased in the lungs [11]. The writers demonstrated previously that vagotomy leads to an increase in permeability of ABB [4]. This is associated with blocking of vagal afferent impulsation [5] and with the appearance of a humoral factor [2], not yet identified, but whose production is evidently inhibited by general anesthesia, in the blood of vagotomized animals. The fact revealed by this investigation that vagotomy can influence the manifestation of the edemogenic action of PLA_2 may help to explain the mechanism of development of pulmonary edema arising after vagotomy.

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