VESSEL-TISSUE PERMEABILITY IN CENTROGENIC EDEMA OF THE LUNGS

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An increase in the permeability of the lung membrane is of great importance in the pathogenesis of various forms of edema of the lungs [3]. This is shown by the outflow of a large quantity of serum protein into the edema fluid [2, 4-6]. Because in many forms of edema of the lungs the cause has no local action on the lung membrane, it is logical in these conditions to study the state of permeability of the vessel-tissue membranes of some other organs. This is most applicable to centrogenic edema of the lungs. Various agents having a harmful action on the brain spread relatively easily to the region of the hypothalamus, where the regulation of many autonomic functions including permeability is concentrated [1]. It must be assumed that when the cause of the edema acts on this region of the brain, changes in permeability may take place not only in the lung, but also in other tissues. The object of the present investigation was to study the changes in the permeability of certain tissues to macromolecular substances as shown by the elimination of trypan blue, adsorbed by the blood proteins [10] from their vessels in two forms of experimental centrogenic edema of the lungs.

EXPERIMENTAL METHOD

Experiments were carried out on 106 noninbred albino rats of both sexes weighing 180-330 g. Three series of control experiments were carried out on 46 animals, while 60 rats were used for four series of experiments with the production of centrogenic edema. For this purpose, 36 rats with their head fixed in a stereotaxic apparatus in accordance with de Groot's atlas [9], received injection of 0.02 ml of $1:10^6$ aconitine solution bilaterally into the anterior hypothalamus. Pulmonary edema was caused in 24 rats by injection of 0.1-0.2 ml of a stained 5% solution of fibrinogen into the cisterna magna. In some of the first experiments the fibrinogen was injected into the cisterna mixed with thrombin solution to form fibrin clots, irritating the brain tissue [7, 8]. Subsequently, fibrogen alone was injected. After injection of its stained solution, flakes of fibrin also were found in all the ventricles and on the base of the brain, and edema of the lungs developed quickly.

The hematocrit number was determined before the experiment and immediately after death of the animals. The rats were quickly autopsied, and after ligation of the main vessels, the lungs, liver, kidneys, and spleen were extracted, and their relative weight was determined (weight in grams per 100 g body weight). The tissues of these organs, and also the walls of the proximal portion of the small intestine, the thigh muscle, and the skin of the abdomen (without the fatty cellular tissue) were dried to constant weight at 80-90°, and the ratio between their dry weight and the weight of the fresh tissue was calculated in per cent. The same estimations were made in healthy control rats killed by air embolism. In other series of experiments, 3-5 min after the injection of aconitine or fibrinogen, an intravenous injection was given on a 1.0-1.2% solution of trypan blue in a dose of 0.2 ml/100 g body weight. Immediately after death of the animal the chest was opened, blood was taken from the heart, and the vascular system was washed out through the chambers of the heart with 40 ml of physiological saline. The control rats were sacrificed at equal intervals after injection of the dye. After the vessels had been washed out, samples of the lungs, liver, kidneys, small intestine, and muscles, each 100 mg in weight, were taken and thoroughly minced with scissors, homogenized in a microblender, and the trypan blue was extracted with pyridine by the method of Judah and Willoughby [10], and estimated colorimetrically on a FÉK-M photoelectric colorimeter. The concentration of the dye in the tissues, the plasma, and the edema fluid was calculated in mg%.

EXPERIMENTAL RESULTS

The results of all the series of investigations are shown in Tables 1 and 2. Comparison of the relative weight and the dry residue of the lungs in the animals of the control and experimental series shows that both forms of

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TABLE 1. Changes in the Hematocrit Number, Dry Residue, and Gravimetric Coefficients of the Blood and Certain Tissues after Development of Edema of the Lungs Caused by Injection of Aconitine into the Hypothalamus or the Suboccipital Injection of Fibrinogen, M±m

Series of experiments	Hematocrit number		Blood, D. R.	Lungs		Liver	
	before expt.	death		R. W.	D. R.	R. W.	D. R.
I (control)	—		16,77±0,43	0,75±0,19	20,78±0,21	4,89±0,14	25,39±0,21
II (aconitine edema of lungs)	34±1,55	50±2,08 ($P<0,02$)	23,24±0,39	1,66±0,15	14,12±0,36	4,70±0,15	27,12±0,27
III (fibrin edema of lungs)	39±1,50	47±1,82 ($P<0,01$)	24,16±0,47	1,35±0,05	16,10±0,24	4,62±0,17	26,90±0,34
P for series I and II			<0,001	<0,001	<0,001		<0,001
P for series I and III			<0,001	<0,01	<0,001		<0,001

Continuation

Series of experiments	Kidneys		Spleen		Small intestine	Muscles	Skin
	R. W.	D. R.	R. W.	D. R.	dry residue		
I (control)	0,79±0,16	23,60±0,24	0,44±0,03	22,80±0,23	25,89±0,37	24,51±0,29	35,23—0,58
II (aconitine edema of lungs)	0,83±0,0002	23,77±0,29	0,48±0,03	22,35±0,24	26,36±0,95	24,17±0,17	36,92±0,66
III (fibrin edema of lungs)	0,84±0,02	23,85±0,21	0,41±0,03	22,94±0,33	27,95±0,57	24,65±0,38	38,00±0,73
P for series I and II	<0,02						<0,001
P for series I and III					<0,01		<0,001

Legend: D.R.—dry residue of tissue (in % of weight of fresh tissue); R.W.—relative weight.

Note. The values of P are given only when the difference is significant.

TABLE 2. Concentration of Trypan Blue in Certain Tissues after Development of Edema of the Lungs Caused by Injection of Aconitine into the Hypothalamus or Suboccipital Injection of Fibrinogen, M±m

	Relative wt. of lungs	Dry residue of lung tissue	Time from injection of dye to death (in min)	Concentration of trypan blue (in mg%)						
				plasma	edema fluid	lungs	liver	kidneys	intestine	muscles
Aconitine edema of lungs										
Control	0,65±0,09	21,03±0,56	17 (2—74)	17,49±0,83	—	5,23±0,13	5,98±0,11	8,04±0,20	4,18±0,09	0,94±0,03
Expt.	1,57±0,09	12,30±0,49	17 (2—74)	17,17±0,86	10,95±0,99	17,07±1,72	8,68±0,66	8,23±0,36	5,80±0,24	0,96±0,04
P	<0,001	<0,001				<0,001	<0,001		<0,001	
Fibrin edema of lungs										
Control	0,60±0,01	20,51±0,37	16 (8—43)	13,37±0,80	—	4,53±0,13	5,54±0,29	7,63±0,32	3,24±0,19	1,07±0,09
Expt.	1,39±0,09	14,57±0,41	16 (8—43)	15,23±0,91	16,25±1,20	16,07±0,99	7,50±0,34	8,19±0,43	4,81±0,26	1,11±0,11
P	<0,001	<0,001		<0,001	<0,01	<0,001	<0,001		<0,001	

Note. The control animals were sacrificed at the same times as the experimental animals died.

centrogenic edema were accompanied by an intensive disturbance of the water metabolism in the lungs. A more marked excess accumulation of water in the lung tissue took place in aconitine edema, which in both series (Tables 1 and 2) was a companied by a somewhat greater increase in the relative weight of the lung and a decrease in the dry residue than fibrin edema. The development of pulmonary edema was accompanied by marked disturbances of the water concentration in the blood and in certain tissues. The increase in the dry residue of the blood and the hematocrit number (Table 1) demonstrated loss of water from the blood and hemoconcentration. The increased flow of liquid from the blood into the lungs and the dehydration of the blood in both forms of centrogenic edema was evidently compensated to some degree by an outflow of water from some organs into the blood.

A statistically significant increase in the dry residue took place in both cases in the liver and the wall of the small intestine during fibrin edema (Table 1). To some extent the decrease in the degree of hydration of these tissues may have depended on changes arising in the hemodynamics following brain injury and a decrease in the filling of the tissues with blood, the dry residue of which was rather less than in the investigated tissues. In that case the weight of the corresponding organ must have fallen. In the present experiment the decrease in the relative weight of the liver was small and not significant, the weight of the kidneys rose slightly, but the weight of the spleen showed little change. Following electrolytic injury to the hypothalamus in rats, accompanied by edema of the lungs, Maire and Patton [11] found a considerable decrease in the relative weight of the liver and spleen, which they considered to be a sign of the redistribution of blood from the abdominal organs into the vessels of the pulmonary circulation. In rabbits with aconitine edema in the authors' laboratory, a significant decrease was found in the weight of the liver, kidneys, and spleen. Hence, according to this indirect index, it may be concluded that the filling of many of the internal organs with blood is reduced in the presence of centrogenic edema of the lungs. For reliable conclusions to be drawn, direct determinations must be made of the volume of blood in the organs.

In the healthy animals sacrificed 2-74 min after the intravenous injection of trypan blue, definite traces of dye were found in the blood plasma and the investigated tissues, and the amounts did not depend on the time after its injection when the rats died. They were equal in different tissues and corresponded to the degree of permeability of their vessel-tissue membrane. In the series with aconitine edema the dye was injected in a rather higher concentration (1.2%). Correspondingly, the concentration of the dye in the plasma and organs of the control rats of this series was slightly higher than in the animals of the other control group. Comparison of the concentrations of dye in the lung tissues in the edematous and control animals showed that in both forms of centrogenic edema the permeability of the lung membrane for proteins adsorbing the dye was considerably increased. The fact was noted that the greater (by dry residue and by relative weight) accumulation of water in the lungs in

aconitine edema than in the fibrin form was accompanied by a relatively smaller outflow of dye into the lung tissue and edema fluid. It is clear from Table 2 that in aconitine edema the concentration of dye in the lungs rose significantly to 326% of its concentration in the control group; in fibrin edema it also reached 355%. Evidently, injection of aconitine into the brain tissue was accompanied by more severe disturbances of the pulmonary hemodynamics and an increase in filtration pressure, whereas after irritation of the brain by fibrin clots deposited on the walls of the ventricles, the increase in permeability of the lungs was predominant. This hypothesis is supported by the higher protein concentration in the edema fluid in aconitine edema than in fibrin edema, as the authors' special experiments showed.

It is clear from Table 2 that in both forms of centrogenic edema the concentration of dye increased in all the investigated tissues. The degree of increase in the concentration of dye was independent of its concentration in normal conditions. The increase in its concentration in all the organs was not so marked as in the lung tissue, but in the liver and in the wall of the small intestine it was significant. The more intense staining of the tissues by the finely dispersed particles could only be attributed to an increase in the permeability of their membranes independent of changes in their hemodynamic conditions, because the gravimetric coefficients and indices of the water content indicated rather a decrease in the filling of the investigated tissues with blood.

Hence, by acting upon the brain to cause the development of fatal pulmonary edema in albino rats, an increase in the vessel-tissue permeability resulted not only in the lungs, but also in other tissues, accompanied by redistribution of the water between them. Evidently, the mechanisms of regulation of this property of the various organs show certain specific features and procedures directed toward them produce disturbances of different intensity. The increase in the permeability of the lung membrane was much greater than the changes taking place in the other investigated tissues.

LITERATURE CITED

1. N. I. Grashchenkov, The Hypothalamus, Its Role in Physiology and Pathology [in Russian], Moscow (1964).
2. I. I. Islamov, Doklady Akad. Nauk SSSR, 97, No. 6, 1089 (1954).
3. Ya. A. Lazaris and I. A. Serebrovskaya, Edema of the Lungs [in Russian], Moscow (1962).
4. I. A. Serebrovskaya, Pat. Fiziol., No. 3, 60 (1960).
5. I. A. Serebrovskaya, Abstracts of Proceedings of the 3rd All-Union Conference of Pathophysiologists [in Russian], Moscow (1960), p. 151.
6. G. R. Cameron, Brit. med. J., Vol. 1 (1958), p. 965.
7. G. R. Cameron and S. N. De, J. Path. Bact., Vol. 61 (1949), p. 375.
8. S. Cruchaud and G. Vermeil, Helv. med. Acta, Vol. 17 (1950), p. 525.
9. J. de Groot, J. comp. Neurol., Vol. 113 (1959), p. 389.
10. J. D. Judah and D. A. Willoughby, J. Path. Bact., Vol. 83 (1962), p. 567.
11. F. W. Maire and H. D. Patton, Am. J. Physiol., Vol. 184 (1956), p. 351.