THE ROLE OF FIBRIN IN THE MECHANISM OF VASCULAR PERMEABILITY

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In 1894-1897, V. V. Voronin [2, 3] suggested that the plasma proteins block the spaces between the cells of the vascular endothelium, and thereby affect their permeability. In 1940, Danielli again drew attention to the importance of the plasma proteins in the mechanism of vascular permeability [8, 13, 14]. No experimental proof of these assertions has been given, and the character of the adsorbed protein has not been precisely identified. Much interest has therefore been shown in the recent suggestions that in normal conditions the inner surface of the blood vessels is lined with a fibrin film, providing a nonwetting vascular surface, facilitating the blood flow [7]. The constant formation of fibrin has been reported at the sites of physiological injuries to the blood vessels [6]. Fibrin, according to these writers [6, 7], is constantly formed and decomposed under the control of the fibrinolytic system.

To investigate the presence of a fibrin film and to study its importance, we examined the vascular permeability in dogs in which the fibrinolytic activity of the blood was increased by administration of heparin [9] or nicotinic acid [12].

EXPERIMENTAL METHOD

Nicotinic acid (1 mg/kg) was injected into the femoral or jugular vein of dogs. Heparin was also injected intravenously in a dose of 5 units/ml of blood.

The clotting power of the blood was determined by the Lee–White method, the fibrinolytic activity by the degree of lysis of a fibrin clot [1] and by the time of lysis of the euglobulin fraction [1, 11].

The vascular permeability was determined by the rate of removal of Evans blue, injected intravenously [4]. The dye was injected into the dogs in a dose of 0.6 ml of 0.2% solution per 1 kg body weight. Blood for estimation of the concentration of Evans blue was taken 30, 60, 90, 120, 150, and 180 min after injection. The concentration of Evans blue in heparinized plasma was measured in a universal photometer (0.5 cm dish, M_{61} filter). The time taken to clear half the Evans blue from the blood (an index of vascular permeability) was calculated from a semilogarithmic curve (ordinate–log concentration of Evans blue, abscissa–time) of the removal of the dye from the blood. In view of the lack of standardization of preparations of Evans blue (variations in the half-clearance time), the same preparation was used for the whole investigation, experiments being conducted simultaneously on the experimental and control dogs. The animals were of different sexes and breeds, and weighed from 10 to 20 kg.

EXPERIMENTAL RESULTS

The effect of heparin on the vascular permeability was studied in experiments on 8 dogs (including 4 controls). Before injection of heparin the clotting time of the blood was between 5 and 8 min, and 5 min after the injection it was over 5 h. This prolonged clotting time was maintained throughout the full 3 h of the observations. The dye was injected into the blood stream 30 min after the heparin. At this time the fibrinolytic activity of the blood was increased by 25%. The half-clearance time of Evans blue in the experimental dogs (205, $\sigma = \pm 21$ min) and the controls not receiving heparin (205, $\sigma = \pm 26$ min) was the same. Consequently, heparin had no effect on the vascular permeability.

The action of nicotinic acid on the vascular permeability was studied in experiments on 15 dogs, of which 5 were controls and did not receive the acid. In the 30 min after injection of nicotinic acid, i.e., before the intravenous injection of Evans blue, the fibrinolytic activity of the blood was doubled on the average (degree of lysis of

the fibrin clot) or multiplied by 2.5 (time of lysis of the euglobulin fraction). At this time the clotting power of the blood showed no statistically significant difference from the initial level. The results of the determinations of the rate of removal of Evans blue from the blood are shown in the table.

Nicotinic acid had no effect on the rate of clearance of Evans blue from the blood, i.e., it did not alter the vascular permeability. The exponential curves of the removal of Evans blue from the blood were indistinguishable in the experimental and control dogs.

The circulation of fibrinogen in the blood stream takes place more rapidly than the cycle of the other plasma proteins; its half-life period in the blood of dogs is about 2.5 days [5, 10]. The velocity of destruction of fibrinogen in dogs' blood is unaffected by administration of heparin and dicumarol, which disturb the process of conversion of fibrinogen into fibrin; on this basis the continuous formation and lysis of fibrin cannot be accepted [10]. Our results also supported this view. If the vessel wall were covered on its inner surface with a fibrin film, the removal of this film would lead to an increase in the vascular permeability.

Time of Removal of Half the Evans Blue from the Blood of Dogs (in minutes) after Injection of Nicotinic Acid

Statistical criteria	Experimental dogs	Control dogs
N	160	160
$\sigma \pm$	24.5	14.4
$m \pm$	7.6	6.5

In our experiments the injection of heparin intensified fibrinolysis; a particularly sharp increase in the fibrinolytic activity was caused by nicotinic acid. In this way conditions were evidently created which favored the dissolving of the fibrin film and prevented the formation of new fibrin (in experiments with heparin). Evans blue forms complexes with the plasma albumin, and its penetration through the membranes thus reflects their permeability to proteins. The rate of removal of Evans blue from the blood in our experiments was the same in dogs receiving nicotinic acid or not. It has recently been reported [12] that nicotinic acid accelerates the removal of Evans blue from the blood stream of dogs; no mention is made in the report of the dose of nicotinic acid used. The variation in the results may possibly be explained by differences in the doses of nicotinic acid used. The variation in the results may possibly be explained by differences in the doses of nicotinic acid.

We gave nicotinic acid and heparin in doses stimulating fibrinolysis. Under these circumstances the vascular permeability was not disturbed. This result casts doubt on both the presence of a fibrin film on the inner surface of the vessels, and the participation of fibrin in the mechanism of normal vascular permeability.

SUMMARY

The effect of nicotinic acid and heparin on vascular permeability was studied in dogs. The state of vascular permeability was determined by the rate of Evans blue elimination from the blood. Nicotinic acid and heparin had a marked intensifying effect on the fibrinolytic activity of the blood. Notwithstanding the intensified fibrinolysis, no disturbance of the vascular permeability was detected. This casts doubt both on the literature data concerning the presence of fibrin film on the internal surface of normal vessels and on the supposition concerning the fibrin participation in the mechanism of normal vascular permeability.

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