MECHANISM OF DEVELOPMENT OF DISSEMINATED MICROTHROMBOSIS IN THE GENERALIZED SCHWARTZMANN REACTION

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UDC 616.151.511-092:616-005.6-031.86

The development of disseminated intravascular blood clotting in the generalized Schwartzmann reaction is due to activation of viscous metamorphosis of the platelets and to thromboplastic and thrombin formation, developing as the result of lysis of the platelets under the influence of antigen–antibody complexes (immunoallergic conflict).

The pathogenesis of the generalized Schwartzmann reaction (GSR) is associated with intravascular blood clotting [12, 16]. The mechanism of its activation has not yet been finally explained [6, 10, 17].

The object of the present investigation was to study the mechanism of development of intravascular blood clotting in the GSR.

EXPERIMENTAL METHOD

The effect of staphylococcal endotoxin on aggregation of the platelets in vitro, on viscous metamorphosis of the platelets, on the blood clotting system, and on pathomorphological changes in the internal organs of intact and heparinized dogs and rats during the GSR was studied. Aggregation of the platelets under the influence of staphylococcal endotoxin was investigated by mixing 0.2 ml of citrated donor's plasma (substrate) with 0.1 ml endotoxin (Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Batch No. 487 dated July 25, 1967). To study the role of thrombin in the mechanism of the platelet-aggregating action of the endotoxin the substrate plasma was first mixed with 500 i.u. antithrombin–heparin (Gedeon Richter). The GSR was induced in dogs by two intravenous injections of endotoxin (0.15 ml/kg) at an interval of 24 h. The role of thrombin in the pathogenesis of the GSR was studied in another series of experiments on six dogs, which received an intravenous injection of heparin (420 units/kg) shortly before the second injection of toxin. Blood was tested before the second injection of toxin and also 5 min and 1, 2, 4, and 24 h thereafter. Viscous metamorphosis of the platelets was studied by counting them, determining the aggregation time during recalcification of the plasma [1] and under the influence of their contact with the surface of a glass flask [9] in the author's modification [1], and determining the index of adhesiveness [7]. The study of the system of pro-and anticoagulants included determination of the blood clotting time, the plasma recalcification time [8], the plasma heparin tolerance [14], thromboplastin formation [4], the prothrombin consumption during clotting of the plasma [15], thrombin formation [13], the fibrinogen concentration in the plasma (by a gravimetric method), and determination of the plasma antithrombin III level [3]. The immunological changes were determined from the serum complement titer [8].

Statistical analysis of the results was carried out by the Student–Fisher method. The internal organs were investigated histologically during the GSR in 14 intact and 14 heparinized (40 i.u./100 g body weight) rats. The GSR was induced in the animals by two injections of endotoxin (0.03 ml/100 g body weight) at an interval of 24 h. The first injection was given intraperitoneally and the second intravenously. The rats were then sacrificed in pairs after 10 and 30 min and 1, 2, 24, 48, and 72 h. Pieces of tissue from the heart,

L'vov Research Institute of Hematology and Blood Transfusion. (Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Fedorov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 73, No. 5, pp. 20-22, May, 1972. Original article submitted May 24, 1971.

lungs, liver, spleen, and kidneys were fixed in 10% formalin solution. Sections were stained with hematoxilin-eosin and some of them for fibrinogen by Weigert's method.

EXPERIMENTAL RESULTS

Staphylococcal endotoxin induced aggregation of platelets in citrated plasma in the course of 55 sec. Under the influence of heparin (500-125 i.u./ml) its platelet-aggregating action was inhibited.

The platelet count in the dogs was considerably reduced (about 11,000/mm^3 blood) 5 min and 1, 2, and 4 h after the second injection of endotoxin. Because of the thrombocytopenia, the aggregation time of the platelets could not be determined. The index of adhesiveness of the platelets was increased. A decrease was found in the combined activity of the clotting system (thromboplastin, plasma prothrombin index, thrombin, fibrinogen concentration, and serum complement titer) and the fibrinolytic activity of the blood was increased.

The number of platelets, their adhesiveness, their aggregating activity, and the indices of the system of pro- and anticoagulants were close to their initial values again after 24 h.

In the heparinized dogs 5 min after injection of endotoxin the platelet count was reduced from 298,000 ± 45,000 to 106,000 ± 35,000/mm^3 blood. Their aggregation was retarded and the index of adhesiveness increased. However, 1 h after injection of the endotoxin the platelet count reached its initial level. The combined activity of the blood clotting system, and thromboplastin and thrombin formation were sharply reduced. The injected heparin was inactivated after 24 h and the state of the clotting system returned to normal. No significant changes were found in the serum complement titer.

On histological examination of the rats sacrificed 10 and 30 min, and also 1-2 h after the 2nd injection of endotoxin, slight congestion of the internal organs was observed; but 24-72 h after injection, degenerative changes were found in the myocardium, liver, and kidneys and multiple thrombi in the vessels. Congestion of the internal organs developed in the heparinized rats, and extravasation of fluid was found in the lungs and myocardium. No degenerative changes or microthrombosis were observed. The results indicate that changes in the functional state of the blood clotting system in the GSR are phasic in character: the phase of hypercoagulation developing initially is quickly replaced by hypocoagulation of the blood. The development of hypercoagulation is due to activation of viscous metamorphosis of the platelets, and of thromboplastin and thrombin formation, thus giving rise to disseminated microthrombosis.

The hypocoagulation phase is the result of deficiency of platelet and plasma procoagulants, thrombocytopenia, heparinemia, and increased fibrinolysis.

Immunoallergic conflict is the activator of viscous metamorphosis of the platelets and of thromboplastin formation in the GSR: it leads to agglutination and lysis of the platelets, as a result of which the platelet-aggregating substance ADP [5] and phospholipids possessing thromboplastic properties (factor 3) are liberated from them into the surrounding medium.

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