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PROTECTION OF ENDOTOXIN INDUCED DISSEMINATED INTRAVASCULAR COAGULATION IN RATS BY GABEXATE MESILATE. T. Yoshikawa, Y. Furukawa, M. Murakami, S. Takemura and M. Kondo. The 1st Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Gabexate mesilate[methane sulfonic acid salt of ethyl-p-(6-guanidino hexanoyloxy) benzoate : FOY] has recently been developed in Japan, and has been known to have potent inhibitory effects on trypsin, kallikrein, plasmin, thrombin and C1-esterase. Advantage of clinical use of this agent is that FOY has smaller molecular weight than aprotinin so that production of antibody against FOY is hardly observed. In the present investigation, effect of FOY on disseminated intravascular coagulation (DIC) was examined using experimental animal models, in comparison with that of heparin.

Female rats of Wistar strain (8-weeks) were infused with 100mg/kg of bacterial endotoxin (Lipopolysaccharide B; E. coli; 055, Difco) continuously for 4 hours through femoral vein. Blood samples were serially taken from abdominal artery using catheter and examined for plasma fibrinogen, FDP, platelet counts, prothrombin time and partial thromboplastin time. After the experiment, kidneys were removed to examine the deposition of fibrin to glomeruli.

Different concentrations of FOY were intraperitoneally injected to the rats prior to the infusion of endotoxin, and it was found that the administration of 10 mg/kg of FOY showed the most potent inhibitory effect on the development of DIC, either hematologically or histologically. In comparison, heparin showed a strong inhibitory effect on DIC over a dosage of 5 U/kg.

It is concluded that, although inhibitory effect of FOY was less significant than heparin, FOY might be valuable agent for the treatment of DIC especially when heparin is difficult to use in such cases as severe hemorrhagic tendency.

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STIMULATION OF HUMAN PLATELET COAGULANT ACTIVITY BY ENDOTOXIN: A NEW LEUKOCYTE-MEDIATED PATHWAY. N. Semeraro, D. Locati and M. Colucci. Istituto di Ricerche Farmacologiche "Mario Negri", Milan, and Istituto di Microbiologia, Università di Bari, Bari, Italy

Despite the frequent occurrence of thrombocytopenia in patients with Gram-negative sepsis, a direct human platelet-endotoxin interaction in vitro can be hardly demonstrated. We report here that human platelets develop strong coagulant activity after simultaneous incubation with endotoxin and leucocytes in plasma. Whole blood or platelet-rich plasma (PRP) enriched of leukocytes were incubated at 37°C for 4 hours with different endotoxins (E.coli LPS, S. Minnesota LPS and a purified Lipid A, 10 ug/ml final concentration); leukocyte-free washed platelet suspensions isolated from these samples were found to markedly shorten the recalcification time of normal plasma (77 $\pm$ 11 sec, as compared to 359 $\pm$ 47 sec, obtained with platelets isolated from similar samples incubated with sterile saline, n=15). When platelets were challenged with endotoxin in the absence of white blood cells (i.e. in PRP) the subsequentely isolated and washed platelets had no procoagulant activity suggesting that leukocytes are essential mediators in the development of platelet coagulant activity induced by endotoxin. Experiments in which PRP was enriched with mononuclear cells or granulocytes revealed that the former were responsible for this property. "Stimulated" platelets shortened the recalcification time of plasmas deficient in any of the factors of the intrinsic pathway or of factor VII-deficient plasma to the same extent as in normal plasma. The rate of clotting was much lower in factor X-deficient plasma. These data indicate that, in contrast to leukocytes, whose procoagulant activity has well-known tissue factor-like properties, platelets act on coagulation factor X independently of both the intrinsic and extrinsic clotting pathways. Our findings add a new function to circulating mononuclear cells and may be relevant to understanding the postulated role of platelets in the activation of blood coagulation during endotoxemia in man.