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PROSTACYCLIN IMPROVES SURVIVAL AND REDUCES MICROCLOT FORMATION IN RABBIT ENDOTOXEMIA. H. Ditter (1), F.R. Matthias (1), R. Voss (1) and P. Röttger (2). Dept. of Internal Medicine, Justus-Liebig-University, D-6300 Giessen, FRG (1), and Dept. of Pathology, General Hospital, D-5160 Düren, FRG (2).

Arachidonic acid metabolites seem to play a pivotal role in the pathophysiology of endotoxin (ET) shock. Therefore, attempts to intervene into the balance of eicosanoids may affect the course of ET shock. Several studies had shown a reduction of ET-induced mortality by non-steroidal antiinflammatory drugs in various animal species.
We investigated whether an infusion of prostacyclin (PGI2) has an effect on survival rates and on the incidence of renal microclots in a rabbit shock model, which is based on an intravenous infusion of ET over 4 hours. Thirty animals being exposed to 75 µg/kg x h of lipopolysaccharide B, were allocated to three groups (E, EI, EA; n=10 each), either receiving ET only (E), or PGI2 (500 ng/kg x min) simultaneously to ET (EI), or aspirin (20 mg/kg) before ET (EA). A control group (C; saline infusion) consisted of 8 animals.
At the end of the observation period (8 hours), the mortality of the treated animals (EI and EA: 4/10 each) was significantly lower than in group E (8/10). However, only in the PGI2-treated group EI a significant reduction of ET-induced glomerular fibrin deposition (GFD) was observed. Indices of GFD after semi-quantitative evaluation of renal slices were 10/27 (E), 1/24 (EI), 3/21 (EA), and 0/24 (C). PGI2 exerted a platelet protective effect as shown by higher blood platelet counts (EI 61.3 % vs. E 33.4 % of initial values), and a better preserved aggregation (EI 60.5 % vs. E 31.7 %) and thromboxane formation capacity (EI 52.0 ng/ml vs. E 23.4 ng/ml) of platelet rich plasma stimulated by 5 µg/ml collagen (all values at six hours after the start of ET infusion). ET caused a profound granulocytopenia which was not prevented by PGI2. Furthermore, PGI2 did not affect the ET-induced metabolic acidosis.
These data confirm a beneficial effect of prostacyclin during a prolonged endotoxemia in rabbits, which may be a consequence of the known vasodilating, platelet inhibiting and cytoprotective properties of the substance.

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ENDOTOXIN INDUCES DIC BY BOTH TISSUE FACTOR (TF) AND PLASMINOGEN ACTIVATOR-INHIBITOR (PA-I) SECRETION. B. Baldus, G. Gehrmann, W. Witt, and P. Donner. Research Laboratories of Schering AG Berlin (West) and Bergkamen, D-1000 Berlin 65, FRG

DIC-induced organ failure represents a major pathomechanism in endotoxemia. To investigate which components of the haemostatic system may be disturbed during endotoxemia anaesthetized male Wistar rats were injected with E. coli endotoxin at dosages of 1 ng/kg to 100 µg/kg body mass. Citrated blood samples were investigated for fibrinolytic activity by a dilute blood clot-lysis time assay (DBC-LT), for PA-I activity by a new functional assay using immobilized rt-PA on 96-well microtiter plates and for TF activity by measuring the rate of thrombin formation after stimulation with a 2000-fold diluted thromboplastin reagent.

Endotoxin induced a decrease in fibrinolytic activity measured as a prolongation of the DBC-LT at dosages from 75 ng/kg to 100 µg/kg. This effect appeared 2 h after the treatment with endotoxin and persisted for > 3 h. In parallel, an increase (up to 7-fold compared to baseline values) in PA-I activity could be measured 2 h after endotoxin application. When the plasma samples were clotted either by kaolin-phospholipid reagent, thrombin or reptilase in the resulting serum PA-I activity was more than 50-fold versus baseline. TF activity generated after stimulation with diluted thromboplastin reagent increased to about 5-fold compared to baseline values. This effect was already significant 1 h after endotoxin injection.

The results of this study indicate, that endotoxin induces a destruction of the balance of the haemostatic system by increasing coagulability via stimulation of TF activity and by decreasing fibrinolytic activity by secretion of PA-I. Furthermore the present data provide evidence for activation of a latent form of PA-I during the clotting process.

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MINI PLASMINOGEN-LIKE MOLECULE IN SEPTIC PATIENTS. L.Kordich (1,2), P.Porterie (2), O.Lago (1), G.Bergonzelli (1), B.Sassetti (1) and J.C.Sanchez Avalos (2). Facultad de Ciencias Exactas y Naturales Universidad de Buenos Aires (1) and Hospital Privado Güemes, Buenos Aires, Argentina (2).

We have previously described (Thromb.Res.44(6),1986) an altered relation Plasminogen (Plg)/α_2-antiplasmin (APL)(Plg/APL<0.6) in the plasma of septic patients. A probable explanation of the mechanism whereby this alteration takes place would be the degradation of Plg to fragments of lower molecular weight due to the action of leukocyte elastase. In order to confirm this we studied 10 patients with sepsis, which did not have clinical or laboratory evidence of disseminated intravascular coagulation or septic shock, with positive blood cultures for bacterial germs. Elastase-α_1-proteinase inhibitor complexes were measured by an enzyme-linked immunosorbent assay (mean: 510±181.9ug/l; normal range: 86±28.5ug/l). Plg and APL functional activities were assayed by the amidolytic method; Plg: 40±8.9%; normal range: 100±20%. APL: 95±10.1% normal range 100±20%. Two different behaviors were observed in the plasma Plg of these patients with regard to their capacity to bind to Lysine-Sepharose 4B. On the basis of this observation the patients were divided into two group. Group A (4 patients) only presented Plg activity in fraction 1 (Plg without lysine binding sites : LBS). Group B (6 patients) presented Plg activity in fraction 1 and in fraction 2 (Plg with LBS). The normal controls presented Plg activity only in fraction 2. All the fractions which presented functional Plg activity also presented immunologic Plg activity and developed areas of lysis in heated fibrin plates after activation with urokinase.

PLASMINOGEN PATIENTS	GROUP A				GROUP B						% NORMAL CONTROLS
	1	2	3	4	5	6	7	8	9	10	N = 10
FRACTION 1	20	17	20	18	20	10	10	18	17	20	0
FRACTION 2	0	0	0	0	30	20	35	17	20	25	140 - 180

It seems tenable the hypothesis that the action of the leukocyte elastase is responsible for the degradation of Plg and this modification in the molecule would give rise to a greater depuration thus explaining the marked drop of the plasmatic levels seen in septic patients.

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PLASMINOGEN ACTIVATOR INHIBITOR ACTIVITY IN SEPTICAEMIA. J.A. Páramo, B. Cuesta, M. Hernández, J. Fernández, M.J. Paloma and E. Rocha. Hematology Service. University Clinic. University of Navarra. Pamplona. Spain.

In vitro and in vivo studies have shown that endotoxin induces a marked increase in plasma plasminogen activator inhibitor (PAI) activity. Plasma PAI and endotoxin concentration (limulus lysate chromogenic peptide substrate) were determined in 61 patients with sepsis: temperature greater than 38° and either positive blood cultures (n= 32) or negative blood cultures in neutropenic patients. Thirty age-matched healthy subjects served as control group. There was a marked increase in PAI in patients (7.1 ± 10.5 U/ml) as compared to controls (0.9 ± 0.8 U/ml) with statistical differences ($p < 0.002$). Mean endotoxin concentrations in patients was 1779 pg/ml (Ref. = no detectable). PAI concentration was significantly higher in patients with positive blood cultures ($p < 0.009$). Such an increase was higher in patients with Gram-negative bacteria (n= 26) than in those with Gram-positive bacteria (n= 6), but without statistical differences. The highest PAI concentration was found in 9 patients with disseminated intravascular coagulation (DIC) as compared with those without DIC ($p < 0.002$). No correlation was found between PAI and endotoxin concentrations. We conclude that there is a marked increase of PAI activity in septicaemia which may contribute to the pathogenesis of DIC-associated sepsis.