First Vienna Shock Forum

Part A: Pathophysiological Role of Mediators and Mediator Inhibitors in Shock

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INFLUENCE OF THE LYSOSOMAL ELASTASE INHIBITOR EGLIN ON THE DEVELOPMENT OF INTERSTITIAL LUNG EDEMA IN E.COLI BACTEREMIA IN PIGS

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INTRODUCTION

The importance of unspecific proteolysis in inflammatory disease processes is currently gaining common interest. An imbalance between the endogenous inhibitor/protease ratio in favour of the proteases might be the reason for extensive proteolysis of tissue structures and humoral factors. Eglin c, an 8100 Da miniprotein from the medical leech, is a potent inhibitor of the lysosomal proteinases elastase and cathepsin G. Its resistance against oxidation and proteolysis (Seemüller et al. 1981) suggested its use for an antiproteolytic therapy. The production of sufficient amounts of eglin c (r-eglin c) by recombinant DNA technology (Rink et al. 1984) made such studies possible. We wanted to examine whether eglin medication could be of potential benefit during a complex inflammatory situation such as an experimentally induced E.coli septicemia with respiratory failure in pigs.

MATERIALS AND METHODS

Weaned domestic pigs (body weight around 20 kg) spontaneously respirating under pentobarbital anesthesia were used. Catheters were placed to monitor blood pressures, cardiac output and extravascular lung water (EVLW, double indicator method, Lewis et al. 1979) and to collect blood and urine samples. All pigs (n = 14) were given an in-

fusion of 3 x 10^{10} live cells obtained from freshly cultured E.coli (ATCC 20399), in 24 ml saline over a period of 2 hrs. In addition, 7 animals were given 200 ml 0.9% saline (group 1) and 7 animals r-eglin c in a dosis of 3.85 mg / kg x h in 200 ml 0.9% saline (group 2), each for 4 hrs. All intravenous infusions were started simultaneously, 60 min after the end of the operation. r-Eglin c concentration in plasma and urine samples was determined by radial immunodiffusion. Alpha-2-macroglobulin (alpha-2-M) and antithrombin III (AT III) levels were estimated by chromogenic substrate assays (Boehringer, Mannheim), factor XIII (F XIII) by a coagulation method (Behringwerke, Marburg). Observation was terminated at death or after 30 hrs and lung tissue was fixed immediately. Severity of lung tissue damage was assessed in hematoxyline-eosine stained sections and graded into severe, moderate, or absent interstitial edema. For comparison of lung damage, the Mantel-Haenszel test was used. Unpaired data were compared with the two-tailed t-test.

RESULTS

Antithrombin III and Factor XIII. Significant consumption of these proteins was observed in the bacteremia group 1 but was clearly reduced by administration of r-eglin c (group 2). The mean of the last measured AT III level was 80.9 $\pm$ 12.8% in group 1 vs. 97.4 $\pm$ 10% in group 2 ($p < 0.02$). The mean of the last measured FX III level was 53.9 $\pm$ 15.7% in group 1 and 76.3 $\pm$ 13.2% in group 2 ($p < 0.015$).

Light microscopical evaluation of lung tissue. Severe interstitial edema (3 cases) or moderate interstitial edema (4 cases) and accumulation of nucleated cells was noted in all tissue sections of group 1 animals. Other typical features were not constant, e.g. peribronchial, perivascular and alveolar edema, atelectasis and intravascular clot formation. In group 2, moderate edema was found in 2 animals and 5 animals showed no sign of increased vascular permeability. The difference was significant (Fisher's exact $p < 0.01$).

Plasma levels and urinary excretion of eglin. Maximum levels of r-eglin c in plasma were attained after 4 hrs and ranged from 1.9 to 5.1 µmol/l. Plasma levels remained high in animals with impaired renal elimination. In animals with normal renal function, maximum plasma levels

ranged from 2.9 to 3.7 µmol/l and eglin was not detectable any more after 6 to 12 hrs. In these animals, 75 up to 95% of the total administered eglin doses were found in the urine within 12 hrs.

Mortality. In group 1, 3 out of 7 animals survived the observation period, 4 died after 3.5, 6.7, 6.8, and 8.4 hrs, respectively. In group 2, 4 out of 7 animals survived the 30 hrs observation period, 3 died after 15.1, 15.3 and 18.4 hrs, respectively.

Mean arterial blood pressure (AP). In all animals, AP dropped initially by 20 to 30 mm Hg. However, after the first 2 to 3 hrs AP recovered in group 2 animals and declined further until death in group 1 animals (n.s.).

Extravascular lung water. In group 1, EVLW rose steeply from 16 $\pm$ 4.2 ml/kg at zero hrs to 24 $\pm$ 10 ml/kg at 7 hrs whereas it increased only slightly during this time interval in group 2 from 13 $\pm$ 1.8 ml/kg to 17 $\pm$ 3.7 ml/kg (n.s.).

Alpha-2-macroglobulin. alpha-2-M decreased significantly in all experiments indicating activation of proteolysis. However, consumption of alpha-2-M was considerably less severe in group 2 animals.

Other parameters. The following measurements displayed a typical response of the animals to septicemia: White blood cells showed a deep initial leucocytopenia followed by leucocytosis. Platelet counts dropped to 11% up to 50% of the starting values. Arterial blood gas analyses showed hypoxemia, acidosis and hypocapnia. The pulmonary circulation reacted with an enormous pulmonary arterial hypertension and decreased cardiac output. All these parameters were not substantially influenced by eglin administration. Urine output decreased and was better maintained in group 2 than in group 1 animals.

DISCUSSION

The light microscopical observations and the measurements of EVLW clearly indicate that the accumulation of interstitial fluid can be prevented by r-eglin c treatment. This favours the assumption that at least elastase from polymorphonuclear granulocytes (PMN) is involved in the pathophysiology of lung tissue damage during septicemia (Lee et al. 1981). AT III and F XIII plasma levels were better maintained under eglin treatment. We prefer to interpret this finding as an indication of an effectively

inhibited unspecific proteolysis (Fritz et al. 1984) rather than an inhibition of coagulation. In humans and in dogs, fatal septicemia was also associated with an extensive systemic proteolysis as assesssed by F XIII and AT III activity in plasma (Jochum et al. 1981, Jochum et al. 1984). Correspondingly, protection of these proteins from proteolysis as tried in this study apparently improves prognosis. Alpha-2-M, a potent inhibitor of various lysosomal and other proteinases, is also a highly susceptible substrate for both PMN elastase and PMN cathepsin G. The observed difference between the groups in the plasma levels of alpha-2-M may be explained therefore by a reduced consumption of this inhibitor due to the protective effect of eglin c. Remarkably, eglin c levels in plasma between 2 and 5 µmol/l seem to be sufficient to inhibit the liberated lysosomal proteinases substantially. The actual eglin c level is, however, strongly influenced by the kidney function because elimination of this inhibitor occurs chiefly by renal excretion.

SUMMARY

Infusion of 3 x 10^{10} live E.coli cells into anesthetized piglets induced severe septicemia with characteristic alterations in systemic and pulmonary circulation, lung function and morphology, blood cell counts and plasma protein composition. The simultaneous infusion of the elastase-cathepsin G inhibitor, r-eglin c, in a dosis of 3.85 mg / kg x h for 4 hrs, reduced mortality, plasma protein consumption, and accumulation of interstitial fluid in the lungs. These findings are in favour of the concept that during septicemia the balance between liberated lysosomal proteinases and their extracellular inhibitors is severely disturbed. It can be at least partially restored by administration of an exogenous elastase inhibitor.

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