Title: RELEASE OF LEUKOTRIENES AND PROSTAGLANDINS DURING ACUTE PANCREATITIS IN PIGS

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INTRODUCTION: The metabolites of the arachidonic acid (AA) cascade are considered to play an important role in acute and chronic inflammatory disorders. Both, the products of the lipoxygenase pathway (leukotrienes), as well as products of the cyclooxygenase cascade (prostaglandins) are also known to excert pronounced hemodynamic effects. To test the hypothesis that arachidonic acid-metabolites are involved in the processes accompanying acute pancreatitis (a disease with a still high mortality in man) we created an animal model, that allowed us to determine prostanoids as well as leukotrienes in pancreatic lymph and ascites fluid.

METHODS: 23 pigs (body-weight 26-35 kg) were anesthetized with fentanyl and enflurane. Following positioning of catheters for hemodynamic monitoring (heart rate, arterial pressure, pulmonary artery pressure, cardiac output) the animals were laparatomized. The pancreatic gland was isolated in-situ to enable sampling of pure pancreatic lymph and ascites fluid. After the control recordings had been obtained, the animals were assigned randomly to three different groups: One control group (n=7) with no specific treatment; a second group (n=8; Na-T) where acute pancreatitis was induced by infusion of a 5% solution of the bile salt sodium-taurocholate into the pancreatic duct; a third group (n=8, FFA) where pancreatitis was induced by infusion of free oleic acid (0.1 mg/kg) into the pancreatic artery. Lymph and ascites samples were collected after 40 minutes, then in hourly intervals. All animals were followed up for 6 hours. Stable hemodynamic conditions were achieved during this period by infusion of cristalloid solutions to maintain pulmonary capillary wedge-pressure at 6 mmHg.

Determination of arachidonic acid metabolites: Thromboxane A_2 and prostacyclin were detected by their stable degradation products TXB_2 and 6-keto-PGF_{1a}, respectively. The leukotrienes C_4 and D_4 were determined in a radioimmunoassay (purchased from New England Nuclear). This had been preceded by a purification procedure by high performance liquid chromatography (HPLC), where leukotriene peaks were separated from each other.

RESULTS: As mentioned above, no changes in hemodynamic parameters were observed, largely due to adequate fluid replacement during the experiment. Pancreatic lymph prostanoid concentrations were not affected significantly during taurochlate pancreatitis. A significant increase in the concentrations of TXB_2 and 6-keto-PGF_{1a} was detected in the animals which received oleic acid in the lymph samples: Whereas concentrations amounted to 0.4 and 2.1 ng/ml during control, they increased significantly to 1.1 and 4.0 ng/ml following onset of pancreatitis and were not subjected to major further changes. Prostanoid levels in pancreatic ascites fluid were elevated in both models of pancreatitits. Only minor changes were detected in the plasma samples. Results of leukotriene determinations in ascites fluid are given in figure. Corresponding results were obtained in pancreatic lymph. No changes of arachidonic acid metabolites were detected in the control group.

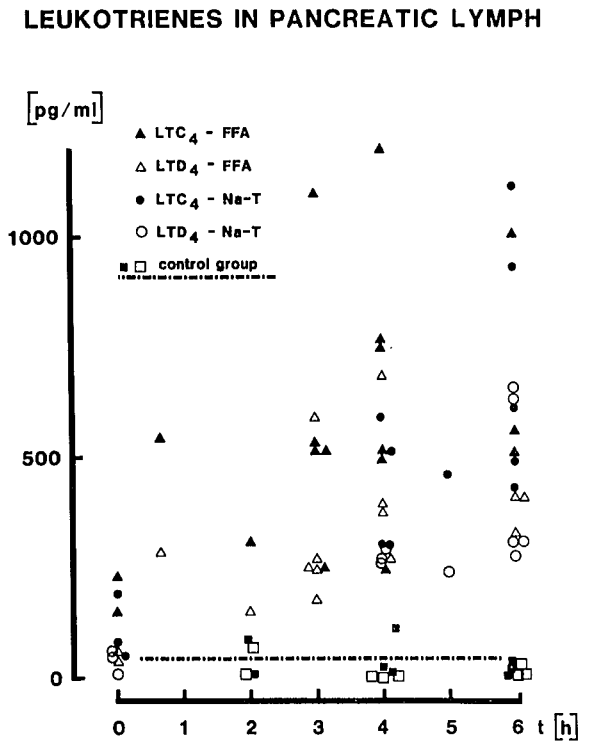

Figure: Leukotriene concentrations in pancreatic lymph during porcine acute pancreatitis. Leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4) were determined by RIA following HPLC purification. Results of the control group were largely below the detection limit of 50 pg/ml.

DISCUSSION: The intrapancreatic activation of enzymes with a consecutive release of mediators is assumed to play an important role for pancreatic necrosis as well as for the systemic complications following acute pancreatitis. The result of our study show a significant release of prostanoids from the cyclooxygenase pathway as well as of leukotrienes from the lipoxygenase pathway in both experimental models of acute pancreatitis: These products were released in considerable quantities into pancreatic lymph and ascites fluid. The significance of these findings and the final role of lipoxygenase products in the progress of pancreatitis remains subject to further investigations.