Marked thrombin generation and depression of fibrinolysis result in fibrin deposition that may further compromise the intestinal microvasculature and hence, contribute to irreversible intestinal injury.

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Antithrombin III Substitution Inhibits Local Intravascular Coagulation and Fibrin Deposition after Intestinal Ischemia in Rats.

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Introduction: In a previous study, we demonstrated local intravascular coagulation and inhibition of fibrinolysis with subsequent fibrin deposition following intestinal ischemia and reperfusion in rats. These phenomena resulted in epithelial dysfunction of the intestine. The aim of this study was to investigate the salvaging effect of systemic heparin and antithrombin III (ATIII) administration upon local intravascular coagulation and thrombotic obstruction in the splanchnic microvasculature following intestinal ischemia.
Methods: Rats were divided into 3 groups: control (n=24), heparin (n=18) and ATIII (n=18). Intestinal ischemia was induced by superior mesenteric artery occlusion (SMAO) for 0, 20 or 40 min. Saline, heparin (375 IU/kg) or ATIII (250 IU/kg) were administered 15 min before reperfusion. During reperfusion, portal (local) and systemic blood samples were analysed for activation of coagulation and fibrinolysis.
Results: SMAO resulted in mild to moderate intestinal injury as assessed by histological analysis, biochemical markers, absorptive capacity and barrier function. 20 and 40 min of intestinal ischemia and 3 hours reperfusion resulted in local intestinal thrombin generation and fibrinogen to fibrin conversion, reflected by a 2.9- and 4.1-fold increase in thrombin-antithrombin (TAT) complex levels (15.6±0.7 and 21.6±2.4 vs. 5.4±0.8 ng/ml) and a 2.9- and 2.8-fold elevation of fibrin degradation products (D-dimer) (154.6±7.4 and 147.9±15.2 vs. 53.9±6.5 ng/ml), respectively. Administration of ATIII resulted in reversion of ischemia/reperfusion-induced activation of coagulation, as shown by a 1.9- and 2.1-fold reduction of portal TAT levels and in a 1.5- and 3.2-fold decrease of portal D-dimer levels, after 20 min and 40 min of ischemia, respectively. Heparin infusion did not result in significant changes of activation of coagulation. After a short-lasting, initial activation of local fibrinolysis in the control group, plasminogen activator activity was subsequently suppressed after 20 and 40 min ischemia, as a result of an almost 4-fold increase in portal plasma levels of plasminogen activator inhibitor-1 during reperfusion. Both, heparin and ATIII administration did not change fibrinolytic activity or its inhibition. In the control group, activation of coagulation and depression of fibrinolysis resulted in fibrin formation, as confirmed by intravascular fibrin deposits at histological examination. No such fibrin deposition could be detected in the antithrombin-treated rats. Intestinal structural characteristics and functional parameters were however not improved.
Conclusion: Systemic substitution of ATIII but not heparin inhibits local activation of coagulation and reduces fibrin deposition in a model of 20-40 min ischemia and reperfusion in the rat. Intestinal dysfunction was however not improved.

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Antioxidants and Ischemia-Reperfusion of the Rat Intestine in the Absence of Leucocytes

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Introduction: Antioxidant drugs (AO) have proved to be quite effective at decreasing both the mucosal damage to the intestine and the mortality rate following reperfusion of the ischemic gut in the rat. We have also proved that AO improve all the hemodynamic parameters following reperfusion. Leucocytes are said to be the main responsible for all the reperfusion damage. We are assessing the effect of AO in a model of intestinal reperfusion *in vitro* without blood cells.
Methods: Male Wag rats have been used. The superior mesenteric artery and the portal vein are cannulated and the whole small intestine is excised, perfused with heparinized Ringer solution, and placed into a warming chamber for 60 minutes. Using a solution previously presented to this Society (which includes glucose, insulin and oxygen), the intestine is perfused during 30 minutes (12 ml/min; 100/60 mm Hg) restoring the cellular metabolism in the absence of white blood cells. Twelve rats were allocated to the control group, while 18 received folinic acid (0.21 µl/ml), α-tocopherol (1.6 µl/ml) and SOD (0.58 µl/ml) in the perfusate. Samples from the perfusate and the portal drainage were collected at 0, 5, 15 and 30 minutes of reperfusion. Afterwards, three samples of terminal ileum were obtained and embedded in paraffin.
Results: No statistically significant differences could be found between control and AO-treated groups, regarding analysis of the effluent fluid. The initial hyperkaliemia was reduced to normal values 15 minutes after starting reperfusion. The initial acidosis was also reduced after 15 minutes, stabilising at 0.06 below the perfusate's pH. Though [Ca^{++}] was initially low, by the end of the experiment it was within the normal range. The oxygen pressure of the effluent increased from 90 mm Hg at the initial moment to over 130 mmHg for the last 15 minutes. Damage to the intestine is being assessed on histological sections and by biochemical analysis of the effluent (LDH, CK).
Conclusion: When reperfusing the ischemic intestine without white blood cells, antioxidant treatment showed no benefit, which reinforces the hypothesis of these cells being the main agents of reperfusion injury to the intestine.