Regional fluxes of tissue plasminogen activator in porcine endotoxemia

Akademisk avhandling

som för avläggande av medicine doktorsexamen
vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen
försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3,
fredagen den 16 november 2007, kl. 09.00

av

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Avhandlingen baseras på följande delarbeten

I. Nyberg A, Seeman-Lodding H, Ahlqvist M, Fagerberg A, Jern C, Aneman A. Regionally differentiated fibrinolytic responses during volume-resuscitated acute endotoxemia in pigs.
Acta Anaesthesiol Scand 2003; 47: 1125-31.

II. Nyberg A, Fagerberg A, Ahlqvist M, Jern C, Seeman-Lodding H, Aneman A. Pulmonary net release of tissue-type plasminogen activator during porcine primary and secondary acute lung injury.
Acta Anaesthesiol Scand 2004; 48:845-50.

III. Nyberg A, Jakob S, Seeman-Lodding H, Porta F, Bracht H, Bischofberger H, Jern C, Takala J, Aneman A. Time and dose related regional kinetics of tissue-type plasminogen activator in endotoxemic pigs.
Acta Anaesthesiol Scand in press

IV. Nyberg A, Seeman-Lodding H, Declerck PJ, Fagerberg A, Jern C, Aneman A. Regional differentiation of tPA and PAI-1 kinetics in acute endotoxemia. *Manuscript*

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ABSTRACT

Formation of fibrin clots in the microcirculation during severe sepsis contributes to organ failure, frequently involving the lungs and the splanchnic organs. Tissue type plasminogen activator, tPA, is the key activator of intravascular fibrinolysis with plasminogen activator inhibitor type-1, PAI-1, as its main inhibitor. This thesis focuses on mesenteric, hepatic, renal and pulmonary fluxes of tPA and PAI-1 in response to infusion of endotoxin in anaesthetized, ventilated pigs as a model of experimental gram-negative sepsis. Plasma levels of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) were analysed to assess the host response to endotoxemia.

Endotoxemia resulted in a hypodynamic circulation that in response to resuscitation with volume and vasopressor administration developed into a hyperdynamic circulatory state. Acute lung injury, ALI, was investigated following bronchoalveolar lavage (primary ALI) and in endotoxemia (secondary ALI).
Endotoxemia acutely increased plasma tPA concentrations in all investigated vascular beds and increased mesenteric release and hepatic uptake of tPA. The hepatic uptake effectively prevented a systemic spillover of tPA from the mesenteric circulation. Hemodynamic resuscitation restored mesenteric and hepatic tPA fluxes to baseline. Sustained increases in systemic levels of tPA, notably following administration of noradrenaline, indicated contributions from other vascular regions not studied. Acute changes in mesenteric and hepatic tPA fluxes related to the dose of endotoxin but with a similar temporal pattern up to 18 hours regardless of dose. A pulmonary release of tPA was only observed in secondary ALI. No changes in renal tPA fluxes were observed throughout the studies. Levels of TNF-α correlated to concentrations and fluxes of tPA, whereas data suggested a non-concomitant relation to hepatic PAI-1 release. The molar ratio of active tPA to PAI-1 favoured anti-fibrinolysis at baseline but was reversed into a pro-fibrinolytic balance in hypodynamic endotoxemia, particularly in the mesenteric circulation. Finally, the hyperdynamic state was characterized by a marked anti-fibrinolytic balance of active tPA to PAI-1.

In conclusion, this thesis demonstrated regionally differentiated responses in plasma fluxes of both tPA and PAI-1 in response to endotoxemia. The results support TNF-α as a candidate mediator of tPA and PAI-1 release. Therapeutic strategies to enhance regional tPA fluxes and fibrinolysis in acutely septic patients warrant further investigation.

Key words: pig, endotoxin, tissue type plasminogen activator, plasminogen activator inhibitor, tumor necrosis factor α

ISBN 978-91-628-7322-6 Göteborg 2007