Endogenous t-PA release and pharmacological thrombolysis
Experimental animal studies of the coronary circulation

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This thesis is based on the following papers:

I. Björkman J-A, Jern S, Jern C**.** Cardiac sympathetic nerve stimulation triggers coronary t-PA release**.**
Arteriosclerosis, Thrombosis & Vascular Biology 2003;23(6):1091-7.

II. Mattsson C, Björkman J-A, Ulvinge JC. Melagatran, hirudin and heparin as adjuncts to tissue-type plasminogen activator in a canine model of coronary artery thrombolysis.
Fibrinolysis & Proteolysis 1997;11(3):121-8.

III. Mattsson C, Björkman J-A, Abrahamsson T, Nerme V, Schatteman K, Leurs J, Scharpe S, Hendriks D**.** Local proCPU (TAFI) activation during thrombolytic treatment in a dog model of coronary artery thrombosis can be inhibited with a direct, small molecule thrombin inhibitor (melagatran).
Thrombosis & Haemostasis 2002;87(4):557-62.

IV. Björkman J-A, Abrahamsson TI, Nerme VK, Mattsson CJ**.** Inhibition of carboxypeptidase U (TAFIa) activity improves rt-PA induced thrombolysis in a dog model of coronary artery thrombosis.
Thrombosis Research 2005;116(6):519-24.

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Abstract

The physiologically most important activator of intravascular fibrinolysis is tissue-type plasminogen activator (t-PA) released from endothelial cells. In man, sympathomimetic drugs increase the systemic concentration of t-PA. It is therefore of interest to investigate whether cardiac sympathetic activation can induce a local t-PA release, which could counteract intra-coronary clot formation.

Thrombolytic therapy with recombinant t-PA (rt-PA) is effective in acute myocardial infarction, but the treatment is limited by a fairly slow reperfusion rate and frequent early reocclusions. A potential mechanism behind early reocclusions might be that active thrombin is released from the thrombus during thrombolytic therapy. Thrombin has recently been shown to activate pro-carboxypeptidase U, which in its active form (CPU) down-regulates endogenous fibrinolysis. Therefore, one way of improving thrombolytic efficacy may be to combine rt-PA with a low-molecular weight direct thrombin inhibitor, which theoretically could have a pro-fibrinolytic effect, either by inhibition of fibrin-bound thrombin and/or by inhibition of CPU activation. An alternative way may be direct inhibition of CPU.

In a porcine model, experimental activation of cardiac sympathetic nerves by electrical stimulation at 1 and 8 Hz induced 5- and 20-fold increase in the release of both total and active t-PA together with frequency-dependent increases in heart rate, blood pressure, and coronary blood flow. The t-PA release was independent of the heart rate and coronary flow response, but local infusion of isoprenaline suggested that part of the t-PA response was mediated by stimulation of β-adrenergic receptors. Next, we studied the combined effect of rt-PA and thrombin inhibitors (melagatran, hirudin and heparin) in a canine model of copper coil-induced coronary thrombosis. The pro-fibrinolytic effect of rt-PA, either measured as patency rate or time-to-patency, was significantly enhanced with the low-molecular weight direct thrombin inhibitor melagatran, but to a lesser degree by hirudin and heparin. In the same model it was shown that active CPU is produced locally in the coronary vascular bed during both thrombus formation and clot lysis. Inhibition of thrombin attenuated CPU formation and improved patency. A similar effect was obtained with a direct inhibitor of CPU.

In conclusion, the coronary t-PA response to sympathetic stimulation may constitute a thrombo-protective defence mechanism to counteract its prothrombotic effects on the systemic level. Furthermore, direct thrombin and/or CPU inhibition may be potential targets for prevention of thrombus formation via facilitation of the endogenous fibrinolytic system.

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