



**Studies of platelet signalling and endothelial cell responses
using unique synthetic drugs.**

av

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Akademisk avhandling

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Abstract

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Haemostasis is a complex and tightly regulated process which protects us from bleeding. Platelets are essential for maintained haemostasis. Under normal conditions platelets are calmed by antithrombotic substances release by the endothelium. During vascular injury, the platelets will activate and form a haemostatic plug to prevent bleeding. Inflammatory processes like atherosclerosis can disturb the haemostatic balance and lead to severe consequences like myocardial infarction and stroke. Inhibition of platelets and coagulation are common treatments to prevent unwanted blood clot formation. There is a great need for increased knowledge on the mechanisms of thrombosis and characterisation of new substances with possible therapeutic potential. This thesis used unique synthetic drugs to study platelet signalling and endothelial responses.

Paper I showed that both sulfated polysaccharides from seaweed and synthetic glycopolymers which mimic their chemical properties caused platelet activation.

Paper II elucidated the molecular mechanism underlying platelet activation by sulfated glycopolymers and polysaccharides. We found that human platelet activation took place via the Platelet endothelial aggregation receptor 1 (PEAR1), while mouse platelet activation was mainly via C-type lectin-like receptor 2.

Aggregation was supported by Glycoprotein Ib α in both species.

Paper III showed the effect of synthetic glycopolymers and natural polysaccharides on cultured human endothelial cells. We found that both the glycopolymers and polysaccharides caused a proinflammatory response after 24h.

In **Paper IV**, the effect of a synthetic purine analogue with a nitrate ester motif was studied. We found that the purine analogue reduced platelet functions by inhibiting Rho-associated protein kinase (ROCK).

This thesis describes unique synthetic drugs that can be used for further studies of the mechanisms underlying the biological processes of thrombosis and inflammation. The synthetic glycopolymers can be used to further elucidate the physiological role of PEAR1, a potential future therapeutic target.

Keywords: Haemostasis, glycopolymers, purine analogue, PEAR1, GPIb α , CLEC-2, inflammation, ROCK.

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