A dual antiplatelet and anticoagulant compound inhibits collagen-induced platelet aggregation in mice and protects against arterial thrombosis

Bonetti N1; Jouppila A2; Stivala S1; Gobbato S1; Camici GG1; Lassila R3; Beer JH1,4

1 Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland; 2 Helsinki University Hospital Research Institute, Helsinki, Finland; 3 Coagulation Medicine, HU, Helsinki, Finland; 4 Department of Internal Medicine, Cantonal Hospital Baden, Baden, Switzerland

INTRODUCTION

Antithrombotic treatments are key for preventing detrimental ischemic complications in vascular disease. APAC mimics natural heparin proteoglycans and has dual antiplatelet (AP) and anticoagulant (AC) actions in vitro and at vascular injury sites in vivo.

Upon local intraluminal application, APAC was seen to preserve vascular integrity in a rat femoral anastomosis model1.

APAC intravenously protected against renal ischemia/reperfusion injury in rats2.

Furthermore, APAC has been observed to yield anti-proliferative effects.

These properties combined within one compound, may make for an attractive novel antithrombotic drug.

In this study, we aimed to test APAC’s anti-platelet effects in mice and to assess its anti-thrombotic potential in a mouse model of arterial thrombosis.

METHODS

RESULTS

CONCLUSION

Figure B: APAC i.v. significantly inhibited in vivo thrombus formation in a mouse model of photochemically induced laser injury, expressed by a significantly lengthened time to occlusion compared to PBS and UFH treated animals [APAC vs PBS $p < 0.0001$; APAC vs UFH $p = 0.0031$]. The pre-surgical baseline measurements of bodyweight, initial blood flow and heart rate remained unchanged. The groups were compared by one-way ANOVA with Tukey multiple comparisons. Error bars show SEM. N ∼ 8/8.

In conclusion, we observed that:

- The synthetic heparin proteoglycan, APAC, but not UFH, inhibits murine collagen-induced platelet aggregation in vitro.
- Intravenous application of APAC, but not UFH, significantly delayed thrombocytic occlusion in an in vivo mouse model of arterial thrombosis.
- This supports APAC’s anti-thrombotic efficacy even after systemic application.

Based on previous findings showing APAC adhering to the site of vascular injury, a mechanism of self-targeting may be involved. These findings imply the compounds’ attractiveness as a potential novel, antithrombotic drug.

Further studies will address APAC’s local distribution at the site of vascular injury and other mechanisms, including local tissue factor expression and activity.

Contact: nicole.bonetti@uzh.ch