P057

Antithrombotic Effect of Rimonabant – Selective CB1 Cannabinoid Receptor Antagonist in Experimental Models of Thrombosis

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Introduction

An increasing number of clinical observations indicates that thrombotic events, e.g. coronary thrombosis, stroke and peripheral arterial thrombosis (cannabis arteritis) occur in the young following consumption of cannabinoids. It was shown that cannabinoids play a role in activating rabbit and human platelets through the stimulation of CB1 cannabinoid receptors [Braud S et al, FEBS Lett 471:12, 2000; Catani MV et al, Cell Mol Life Sci 67:601, 2010]. Moreover, there is evidence from clinical trials (STRADIVARIUS) that rimonabant (RIM) – a selective CB1 receptor antagonist reduces cardiovascular risk and cardiovascular and all-cause mortality [Nissen SE et al, JAMA 299:1547, 2008].

We hypothesize that benefits observed after RIM treatment depend on its influence on acute intravascular thrombosis. So far there have been no data confirming the effect of RIM on experimental thrombosis in vivo.

Aim

The purpose of the study was to test the antithrombotic effect of RIM in experimental animal models.

Materials and methods

Male Wistar rats (300-350g) were used (n=15-18). Arterial thrombosis was induced by a constant current electrical stimulation of the common carotid artery which caused artery wall damage and occlusive thrombus development.

Venous thrombosis in rats was induced by ligation of the inferior vena cava which caused stasis of flow, local hypoxia, changes in endothelial function and activation of clotting. After 1 hour, thrombus and blood from the right ventricle of the heart were collected. The thrombus weight, incidences of thrombosis and bleeding time (BT) were measured. The washed platelet adhesion to fibrillar collagen ex vivo was determined as well.

To assess thrombus formation in the mesenteric blood vessels in mice we used intravital microscopy in green fluorescent protein (GFP)-transgenic mice C57BL/6J (17-20g, n=4-7). This method enables simultaneous monitoring of platelet aggregation and its procoagulant activity after injury to the mesenteric venous endothelium by argon laser.

In all experiments, the animals received rimonabant (RIM, 1 mg/kg) or vehiculum (VEH), as a bolus into the femoral vein 10 min before induction of thrombosis.

Results

In rat arterial thrombosis experiments, RIM prolonged time to occlusion (7.0±1.8 min VEH vs. 11.0±2.0 min RIM), decreased incidences of occlusion (50% VEH vs. 25% RIM), but did not change the thrombus weight (0.61±0.13 mg VEH vs. 0.72±0.11 mg RIM).

In rat venous thrombosis experiments, RIM reduced incidence of thrombosis by 27% and decreased thrombus weight (p<0.05). RIM injection significantly diminished adhesion of platelets to collagen (28.6±1.6 % VEH vs. 19.1±2.8 % RIM; p<0.05). BT was significantly shortened by RIM, too (103±4 sec. VEH vs. 85±4 sec. RIM; p<0.01).

In laser-induced thrombosis in murine mesenteric veins, RIM decreased the volume of the thrombus by about 69% (p<0.05) and decreased the extent of platelet aggregation by about 22%, but did not change the procoagulant activity of platelets.

Conclusion
In conclusion, the antithrombotic effect of RIM in the experimental models of arterial and venous thrombosis has been demonstrated. The antithrombotic effect of RIM is at least partially platelet-dependent.

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