

MEETING ABSTRACT

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A biological target for antiplatelet therapy: the prostaglandin E₂ receptor EP₄

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Background

Acute myocardial infarction is one of the leading causes of death in the world which is caused by coronary artery thrombosis. Platelets play a central role in cardiovascular thrombosis. Platelet aggregation caused due to a ruptured artherosclerotic plaque could eventually lead to vascular occlusion. Another important component of vascular diseases is inflammation. During inflammation, prostaglandins (PG) like PGI2, PGE2 and PGD2 are released which are also involved in thrombosis. Lower concentrations of PGE2 enhance platelet aggregation whereas higher concentrations inhibit aggregation. PGE₂ acts via 4 receptors: EP1, EP2, EP3 and EP4 (Gs signalling). The role of the EP₃ receptor in enhancing platelet activation and aggregation has been looked at in detail but the role of the EP₄ receptor is largely unknown. We were interested in how this receptor modulates platelet aggregation and what are the signalling mechanisms involved in this process.

Methods

Platelet aggregation assays were performed *ex vivo* using a platelet aggregation analyser (Aggregometer II). Blood from healthy human donors was used to obtain plateletrich plasma. Aggregation was induced using ADP or collagen. Different agonists and antagonists were added to investigate their effects on platelet aggregation. Ca²⁺ flux changes caused by addition of agonists were also examined using a fluorescent Ca²⁺ dye (Fluo-3) by flow cytometry. Expression of the EP₄ receptor on the surface of platelets was established using indirect flow cytometry whereas expression of CD62P, PAC1 and CD41 was examined using direct flow cytometry. *In vitro* thrombus

formation was assessed by flowing whole blood on collagen-coated Cellix biochips at $-30~\rm dyne/cm^2$ using the Mirus nanopump.

Results

We observed that human platelets express EP₄ receptors. A selective EP₄ agonist potently inhibited the platelet aggregation as induced by ADP or collagen. This effect could be completely reversed by using an EP4 antagonist, but not by PGI2, PGD2 TXA2 receptor antagonists. Moreover, an EP4 antagonist enhanced the PGE2-induced stimulation of platelet aggregation, indicating a potent anti-aggregatory activity of the EP₄ receptors. Interestingly, the inhibitory effect of the EP4 agonist was brought about by protein kinase C but not adenylyl cyclase, accompanied by attenuated Ca²⁺ flux, decreased activation of glycoprotein IIb/IIIa and downregulation of P-selectin. Most importantly, in vitro thrombus formation was effectively reduced by the EP₄ agonist and this effect was reversed using the EP4 antagonist.

Conclusions

These findings indicate that the EP₄ receptor is a potential biological drug target in anti-platelet therapy.

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