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A biological target for antiplatelet therapy: the prostaglandin E_2 receptor EP_4

Sonia Philipose, Martina Ofner, Ákos Heinemann, Rufina Schuligoi*

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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 PGI_2, PGE_2 and PGD_2 are released which are also involved in thrombosis. Lower concentrations of PGE_2 enhance platelet aggregation whereas higher concentrations inhibit aggregation. PGE_2 acts via 4 receptors: EP_1, EP_2, EP_3 and EP_4 (G_s signalling). The role of the EP_3 receptor in enhancing platelet activation and aggregation has been looked at in detail but the role of the EP_4 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 platelet-rich plasma. Aggregation was induced using ADP or collagen. Different agonists and antagonists were added to investigate their effects on platelet aggregation. Ca^{2+} flux changes caused by addition of agonists were also examined using a fluorescent Ca^{2+} dye (Fluo-3) by flow cytometry. Expression of the EP_4 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 dyne/cm^2 using the Mirus nanopump.

Results

We observed that human platelets express EP_4 receptors. A selective EP_4 agonist potently inhibited the platelet aggregation as induced by ADP or collagen. This effect could be completely reversed by using an EP_4 antagonist, but not by PGI_2, PGD_2 TXA_2 receptor antagonists. Moreover, an EP_4 antagonist enhanced the PGE_2-induced stimulation of platelet aggregation, indicating a potent anti-aggregatory activity of the EP_4 receptors. Interestingly, the inhibitory effect of the EP_4 agonist was brought about by protein kinase C but not adenylyl cyclase, accompanied by attenuated Ca^{2+} flux, decreased activation of glycoprotein IIb/IIIa and down-regulation of P-selectin. Most importantly, *in vitro* thrombus formation was effectively reduced by the EP_4 agonist and this effect was reversed using the EP_4 antagonist.

Conclusions

These findings indicate that the EP_4 receptor is a potential biological drug target in anti-platelet therapy.

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* Correspondence: rufina.schuligoi@medunigraz.at
Institute of Experimental and Clinical Pharmacology, Medical University of Graz, 8010 Graz, Austria