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Meeting abstract

Prostaglandin E_2 acts via the EP_4 receptor to inhibit platelet aggregation

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Background

Platelets play a central role in haemostasis. Blood vessel injury leads to platelet aggregation and also invokes an inflammatory response leading to the formation of prostanoids like prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2). It is known that low concentrations of PGE_2 enhance and high concentrations inhibit platelet aggregation. PGE_2 mediates its effect through four receptors: EP_1 ($G\alpha_q$ signalling), EP_3 (three isoforms present; signals via G_i, G_s or G_q based on cell type), EP_2 and EP_4 (G_s signalling). PGI_2 is known to inhibit platelet aggregation through its IP receptor (G_s signalling). The role of EP_3 in exacerbating platelet aggregation has been well described. However, the role of EP_4 which acts via the same G protein coupling like IP has not been explored in detail. The aim of this study was to investigate the role of EP_4 in platelet aggregation.

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 AM) by flow cytometry.

Results

As expected, PGE_2 (up to 300 nM) and an EP_3 agonist (sulprostone) enhanced platelet aggregation, whereas an EP_2-selective agonist (butaprost) seemed to have no effect on platelet aggregation. On the contrary, an EP_4 agonist (ONO AE1-329) inhibited platelet aggregation in a concentration-dependent manner, and this effect could be reversed by using EP_4 antagonists (ONO AE3-208 and GW627368x) but not an IP or a DP antagonist. Inhibition of protein kinase C prevented the inhibitory effect of the EP_4 agonist, while inhibition of adenylate cyclase had no effect. The EP_4 agonist ONO AE1-329 also attenuated Ca^{2+} flux in platelets that had been stimulated with ADP.

Conclusion

These results are suggestive of an exclusive EP_4 effect on inhibition of platelet aggregation and EP_4 could be a potential target of antithrombotic therapy.