ANTIPLATELET DRUGS

Improving the therapeutic window

Antiplatelet therapies are commonly used to lower the risk of heart attack and stroke caused by the formation of blood clots containing aggregated platelets over ruptured or denuded atherosclerotic plaques (atherothrombosis). However, such therapies also impair normal platelet function, and this can cause prolonged or even fatal bleeding. Now, a ligand-based design strategy targeting a G protein-coupled receptor (GPCR) on platelets has been used to identify a novel antiplatelet agent that does not prolong bleeding and which might be used in combination with existing agents to provide more effective antiplatelet therapy.

Platelet aggregation is regulated by multiple GPCRs, ligands for which include thromboxane A_2 (TXA_2) and ADP. Currently, the most widely used antiplatelet therapies are aspirin, which inhibits the production of TXA_2, and clopidogrel, which antagonizes the P_2Y_{12} ADP receptor. Another platelet GPCR — the EP_3 receptor for the inflammatory mediator prostaglandin E_2 (PGE_2) — has also recently been identified as having a key role in atherothrombosis by Fabre and colleagues (see Further reading). PGE_2 production is increased in inflamed atherosclerotic plaques, but the healthy arterial wall produces negligible amounts of PGE_2, suggesting that antagonizing the platelet EP_3 system might not have detrimental effects on normal platelet function, unlike aspirin and P_2Y_{12} antagonists.

To investigate this possibility, Singh *et al.* used a ligand-based design strategy to synthesize EP_3 receptor antagonists. Following detailed structure–activity relationship studies, one compound (DG-041) was selected for further evaluation. DG-041 showed >1,000-fold selectivity for EP_3 receptors in radioligand displacement assays against other PGE_2 receptors, whereas it was inactive against a range of other GPCRs. Furthermore, it blocked the PGE_2-mediated inhibition of cAMP production and inhibited the platelet aggregation response in both rat and human plasma.

The authors then compared the *in vivo* effects of DG-041 on platelet function and bleeding time with those of the P_2Y_{12} antagonist clopidogrel. DG-041 completely inhibited platelet aggregation with no concurrent increase in bleeding time (even at high doses), indicating that EP_3 blockade has a negligible effect on bleeding. Conversely, the minimum effective dose of clopidogrel required to inhibit platelet aggregation significantly increased bleeding time. Furthermore, PGE_2 restored the aggregation response, indicating that the efficacy of P_2Y_{12} antagonists is limited in the context of inflamed plaque.

Finally, as initial clinical trials of DG-041 are likely to require co-administration with current antiplatelet drugs, the effects of combining EP_3 and P_2Y_{12} antagonists were investigated. Adding DG-041 suppressed the PGE_2 facilitation of platelet aggregation seen with clopidogrel alone and did not increase bleeding time, suggesting that co-administration of EP_3 and P_2Y_{12} antagonists could represent a superior antiplatelet therapy.

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ORIGINAL RESEARCH PAPER Singh, J. *et al.* Antagonists of the EP_3 receptor for prostaglandin E_2 are novel antiplatelet agents that do not prolong bleeding. *ACS Chem. Biol.* **4**, 115–126 (2009)
FURTHER READING Gross, S. *et al.* Vascular wall-produced prostaglandin E_2 exacerbates arterial thrombosis and atherothrombosis through platelet EP_3 receptors. *J. Exp. Med.* **204**, 311–320 (2007)