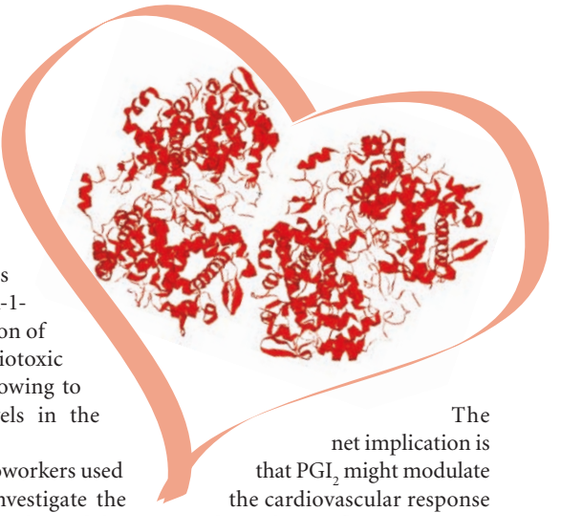
ANTI-INFLAMMATORIES

Heart of the matter



Selective cyclooxygenase-2 (COX-2) inhibitors have been the subject of intensive debate since results from the controversial VIGOR clinical trial indicated a potential link between COX-2 anti-inflammatory agents and myocardial infarction. Now, reporting in *Science*, FitzGerald and colleagues suggest that a disruption in the dynamic balance that exists between the production of the prostacyclin PGI_2 and thromboxane A_2 (TxA_2) in the body might explain these cardiovascular adverse effects.

Both PGI_2 and TxA_2 are synthesized from the prostaglandin precursor PGH_2, which is made from arachidonic acid in a reaction catalysed by the enzyme cyclooxygenase. The synthesis of TxA_2 depends on the COX-1 subtype, which is found in platelets and is involved in protecting the lining of the stomach. COX-2, on the other hand, is involved in the synthesis of PGI_2 in endothelial cells, and mediates pain and inflammation. COX-2 inhibitors, such as rofecoxib (Vioxx) and celecoxib (Celebrex), have been successfully marketed on the basis that the main mechanism by which the non-selective, classical non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and naproxen, cause gastrointestinal toxicity is by inhibiting COX-1. However, the publication of the VIGOR trial results in 2001 raised concerns about the safety of COX-2 inhibitors, as a significantly higher relative risk of cardiovascular toxicity was found for rofecoxib than for naproxen. But was this outcome due to a cardioprotective effect of naproxen, owing to its inhibition of the COX-1-dependent production of TxA_2, or to a cardiotoxic effect of rofecoxib, owing to enhanced TxA_2 levels in the absence of PGI_2?

FitzGerald and coworkers used mouse models to investigate the hypothesis that PGI_2 might modulate the cardiovascular effects of TxA_2 *in vivo*. Deletion of prostacyclin receptors was shown to enhance cellular proliferation and increase platelet activation in response to vascular injury — responses that could cause thrombotic side effects. Prostacyclin-receptor-deficient mice also had raised TxA_2 levels after vascular injury in comparison to wild-type mice, which was indicated by increased urinary secretion of a metabolite of TxA_2.

Conversely, mice in which thromboxane receptor signalling was down-regulated, either by treatment with a TxA_2-receptor antagonist or by knocking out TxA_2 receptors, were shown to have reduced responses to vascular injury. Finally, in mice that lacked both thromboxane and prostacyclin receptors, the increase in cellular proliferation seen in the prostacyclin-receptor knockouts was eliminated, as was the platelet activation, confirming the contribution of enhanced TxA_2 biosynthesis to the vascular response.

The net implication is that PGI_2 might modulate the cardiovascular response through its influence on TxA_2 levels within the body. These findings could be unwelcome to the developers of Vioxx and Celebrex — Merck and Pharmacia, respectively — as they indicate that the increased risk for developing serious cardiovascular defects observed in the VIGOR trial could be a consequence of selective COX-2 inhibition. Caution should be applied in over-emphasizing the significance of these results, however, as the jury is still out on whether naproxen might have contributed a cardioprotective effect to the outcome of the VIGOR trial.

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References and links

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FURTHER READING Pedersen, A. K. & FitzGerald, G. A. Dose-related kinetics of aspirin. Presystemic acetylation of platelet cyclooxygenase. *N. Engl. J. Med.* **311**, 1206–1211 (1984) | McAdam, B. F. *et al.* Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc. Natl Acad. Sci.* USA **96**, 272–277 (1999) | Bombardier, C. *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N. Engl. J. Med.* **343**, 1520–1528 (2000)