Editors' view

TP receptor antagonists (TXRAs): expensive irrelevance or wonder drugs strangled at birth?

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Aspirin (acetyl salicylic acid) is a wonder drug – but does it also have a dark side? We are not referring here only to its adverse effects, important as these are. (A recent meta-analysis leads to the conclusion that in otherwise low risk persons, its harms outweigh its cardiovascular benefits [1] occasioning a re-think among the worried well). Rather, we draw attention to a slowly unfolding drama in which it may yet turn out to play the role, at best, of flawed hero, at worst, of infanticidal villain.

The mechanism of action of aspirin was a total mystery for the best part of a century following its synthesis in the Bayer laboratories in the nineteenth century, and remains incompletely understood to this day. The breakthrough came with the work of Ferreira, Moncada & Vane, published in 1971, which showed that it inhibits prostaglandin biosynthesis [2]. This was subsequently discovered to occur through enzymic oxidation of arachidonic acid by one or other of two cyclo-oxygenase isoenzymes, COX-1 and COX-2 (Figure 1). More recently it was discovered that, unexpectedly, aspirin also *promotes* the synthesis of another class of eicosanoid, the anti-inflammatory lipoxins and resolvins, because COX-2 can still generate hydroxy fatty acids even when acetylated by aspirin [3]. These newish members of the eicosanoid family act as 'stop' signals in inflammation. They are formed by the action of 5-lipoxygenase on 15-hydroxy fatty acids derived from arachidonate (in the case of lipoxin) or eicosapentaenoate (in the case of resolvin), and act on the same G-protein-coupled receptor as does annexin-A1 [4].

The discoveries of thromboxanes by Bengt Samuelsson and of prostacyclin by John Vane and their associates led to the demonstration by Moncada & Vane that doses of aspirin up to 300 mg day⁻¹ alter the balance between thromboxane A₂, which causes platelet aggregation, vasoconstriction and vascular cell proliferation by acting on

thromboxane prostanoid (TP) receptors and prostacyclin (PGI₂) which has opposing actions through IP receptors [5]. Aspirin is particularly effective in inactivating COX-1 in platelets which are exposed to relatively high drug concentrations in the portal circulation following oral administration, compared with systemic vascular tissue which is exposed to much lower concentrations due to extensive pre-systemic metabolism. Furthermore, healthy humans regenerate COX coupled to PGI₂ biosynthesis (presumably in vascular endothelium) within a few hours [6], whereas platelet TXA₂ biosynthesis recovers with the generation of new platelets over several days [7], since platelets do not possess nuclei and lack the macromolecular machinery to direct new protein synthesis. Following oral administration aspirin is de-acetylated within a matter of minutes, so when administered once daily lower doses than are needed for anti-inflammatory activity profoundly (>95%) decrease platelet TXA₂ biosynthesis while having only a transitory action on PGI₂ production, because platelets in the portal circulation are inhibited whereas PGI₂ synthesis occurs mainly in vascular cells in the systemic circulation exposed to much lower aspirin concentrations. Randomized trials of low dose aspirin in secondary prevention have demonstrated unequivocal benefit with reductions in stroke and myocardial infarction of approximately 25% [1].

This familiar success story had a paradoxically chilling effect on the development of drugs that work by closely related but distinct mechanisms to that of aspirin. Despite its cost, synthetic prostacyclin (epoprostenol) found commercial success in several niche indications (for example, to inhibit platelet aggregation during haemodialysis when heparins are unsuitable or contra-indicated, and in patients with primary pulmonary hypertension resistant to other treatments [8]), vindicating Vane's championship. By contrast, thromboxane synthase inhibitors (TXSI) and

Figure 1

Arachidonic acid can be oxidized enzymically (via COX-1 and COX-2) to cyclic endoperoxide intermediates or non-enzymically to isoprostanes. The intermediates are converted to prostanoids (thromboxanes and prostaglandins) by different isomerase enzymes in different tissues (e.g. thromboxane synthase in platelets, prostacyclin synthase present in endothelium, PGE synthase in stomach). Low dose aspirin (ASA) blocks COX-1 in platelets and is an effective antithrombotic drug, but causes gastrointestinal toxicity via inhibition of gastrointestinal PGE₂ biosynthesis. Unlike aspirin, thromboxane receptor antagonists block the actions of all agonists at thromboxane prostanoid (TP) receptors (including endoperoxides and isoprostanes), without inhibiting either PGI₂ or PGE₂. Drugs (aspirin and TXRA) are shown in red

thromboxane receptor antagonists (TXRA) were perceived as too close to aspirin to compete effectively with this inexpensive and effective drug. Their consequent neglect by the industry may yet prove to have been short-sighted.

TXRAs block *all* TP agonists (Figure 1); these include not only TXA₂ (which is effectively and selectively depressed by low doses of aspirin as explained above) but also cyclic endoperoxide (PGH₂) and several isoprostanes, non-enzymic products of fatty acid oxidation formed under conditions of increased oxidative stress [9, 10] and which are not inhibited by aspirin. Endogenous TP agonists are produced by the vascular endothelium, especially under pathological conditions, causing endothelium-dependent contraction and contributing to endothelial dysfunction, a key factor in atherogenesis [11]. Treatment with a TXRA, but *not* treatment with aspirin, inhibits atherogenesis in apo-E deficient mice [12], strongly suggesting that TXRAs not only differ qualitatively from aspirin but could also be superior to aspirin in preventing atheroma. In support of this possibility, acute administration of a single dose of a TXRA (S18886, now known as terutroban) to patients

treated with low dose aspirin for coronary artery disease improved endothelial function assessed by measuring flow-mediated dilatation (FMD) in the brachial artery [13].

In this issue of the Journal we publish a paper [14] by Pierre-François Lesault and colleagues from the same group as authored the earlier paper [13]. This adds a further important chapter to the story. These authors studied 48 patients with carotid atherosclerosis (identified by high resolution B-mode ultrasonography) and treated with aspirin 300 mg once daily. This is near the top end of the 'low-dose' dose regimens, in contrast to the earlier work. Patients were randomly allocated to placebo or to one of three doses of terutroban for 15 days in a double-blind study. FMD was improved by all doses of terutroban both acutely on day 1 (confirming the observations in coronary artery disease patients mentioned above) but also after 2 weeks of chronic treatment, with no hint of tachyphylaxis. The authors discuss several limitations, notably that FMD was measured only at 2 h after dosing (presumed to be near T_{max}), hence leaving open the question of persistence of the pharmacodynamic effects at

trough of the different doses used. The effect of TXRA alone on FMD also needs to be ascertained. Nevertheless we are surely closing in on an unanswerable case for an efficacy trial of a TXRA employing a clinically relevant endpoint. It would be ironic if the wonders of aspirin (or, to be less fanciful, their impact on the mindset of drug development scientists) turn out to have hobbled the development of a related but uniquely distinct class of drugs. There is no pharmacologically based expectation that TXRAs will have adverse direct gastrointestinal effects (although they must inevitably promote gastrointestinal, cerebral or other forms of bleeding in the presence of other pathologies), so the glittering prize would be a drug that not only inhibits thrombosis (like aspirin) but additionally prevents atherosclerosis without causing gastrototoxicity. The worried well might chirp up at that prospect – now there's a market!

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