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Review

Antiplatelet drug resistance: Molecular insights and clinical implications

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ABSTRACT

Antiplatelet drugs are prescribed to patients with cardiovascular disease in order to reduce their risk of clinically important atherothrombotic events. However, a proportion of patients fail to appropriately respond to these drugs in a heterogeneous phenomenon known as 'antiplatelet drug resistance'. Individuals who are identified as being resistant have a higher cardiovascular risk, but currently there is no clinically validated approach to identify and treat these individuals. Large randomised control trials have attempted to personalise antiplatelet therapy based on platelet function testing, but these have failed to demonstrate improved clinical outcomes. An alternative approach to this non-specific assessment of platelet function is to consider whether antiplatelet therapy may be personalised based on the identification of molecular mechanisms that are known to confer resistance. Here we present molecular insights into the mechanisms for aspirin and clopidogrel resistance, with a discussion of their clinical implications.

Contents

Introduction

Aspirin (acetylsalicylic acid) had been a popular synthetic analgesic agent for almost 90 years before its antiplatelet effects were found to confer a significant survival advantage post-myocardial infarction and in the secondary prevention of cardiovascular disease [1–3]. Aspirin is a non-selective inhibitor of the cyclooxygenase enzymes (COX) and acts to prevent the production of thromboxane A_2 (TXA_2) in platelets by irreversibly acetylating a serine residue at position 529 of the COX-1 isoform [4,5]. TXA_2 is a metabolite of arachidonic acid (AA) with the rate limiting step in its synthesis being that catalysed by COX-1 (Fig. 1) [6]. Once synthesised and released by platelets in response to stimuli, TXA_2 binds to its G-protein coupled receptor (the TP receptor) leading to activation of phospholipase C (PLC) and platelet aggregation [7].

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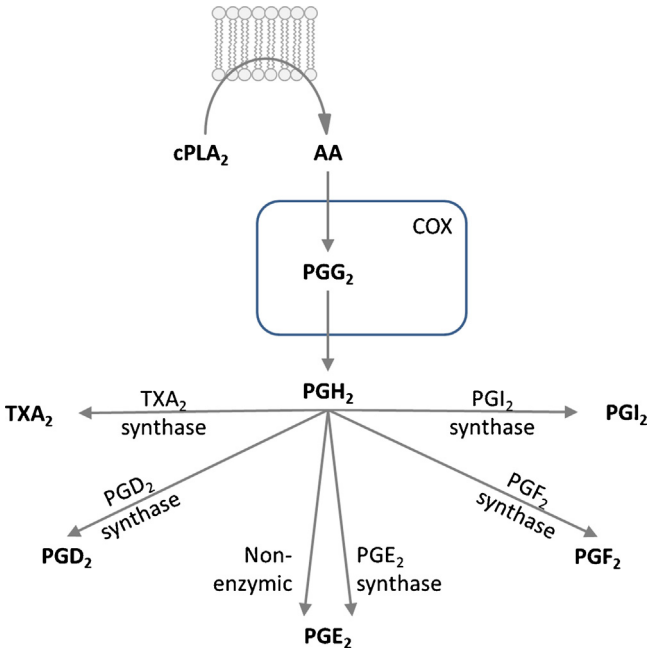

Fig. 1. Cyclooxygenase derived prostanoids. AA, arachidonic acid; COX, cyclooxygenase; cPLA, cytosolic phospholipase A_2; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; PGF_2, prostaglandin F_2; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; PGI_2, prostaglandin I_2 (prostacyclin); TXA_2, thromboxane A_2.

As with many medications, aspirin therapy is not without side effects and these are mediated by the inhibition of prostanoid production in non-platelet tissues. Specifically, a reduction in gastric prostanoid synthesis can lead to life-threatening upper gastrointestinal haemorrhage [8,9], and a reduction in renal prostanoid synthesis can lead to worsening renal function and heart failure [10]. Aspirin's poor specificity for platelet COX combined with a relatively modest potency in inhibiting platelet aggregation, has led to other pathways of platelet activating becoming key pharmacological targets over the past 20 years (Fig. 2).

The thienopyridines are the second most widely used class of antiplatelet drugs and through irreversible antagonism of the $P2Y_{12}$ receptor act to inhibit the activation of phosphoinositide 3 (PI3)-kinase [11]. Antagonism of $P2Y_{12}$ receptors prevents adenosine diphosphate (ADP)-induced platelet activation which, similarly to TXA_2, amplifies multiple pathways of platelet activation through autocrine and paracrine actions [12,13]. The $P2Y_{12}$ antagonists are more potent inhibitors of platelet activation that aspirin, and so their use is associated with a reduction in cardiovascular events when compared to aspirin, but at the cost of an increased rate of major bleeding [14,15].

The choice of which antiplatelet drug(s) to prescribe a patient is guided by a risk/benefit analysis, where a balance must be found between the benefit of reducing platelet-mediated ischaemic events and the increased risk of pathological bleeding. In general, the more potent platelet inhibitors are prescribed where the mortality and/or morbidity risk following an ischaemic event is highest, and therefore justifies the increased risk of bleeding [16,17].

Despite the strong evidence base for the benefit of antiplatelet drugs across a patient population, there remain challenges in

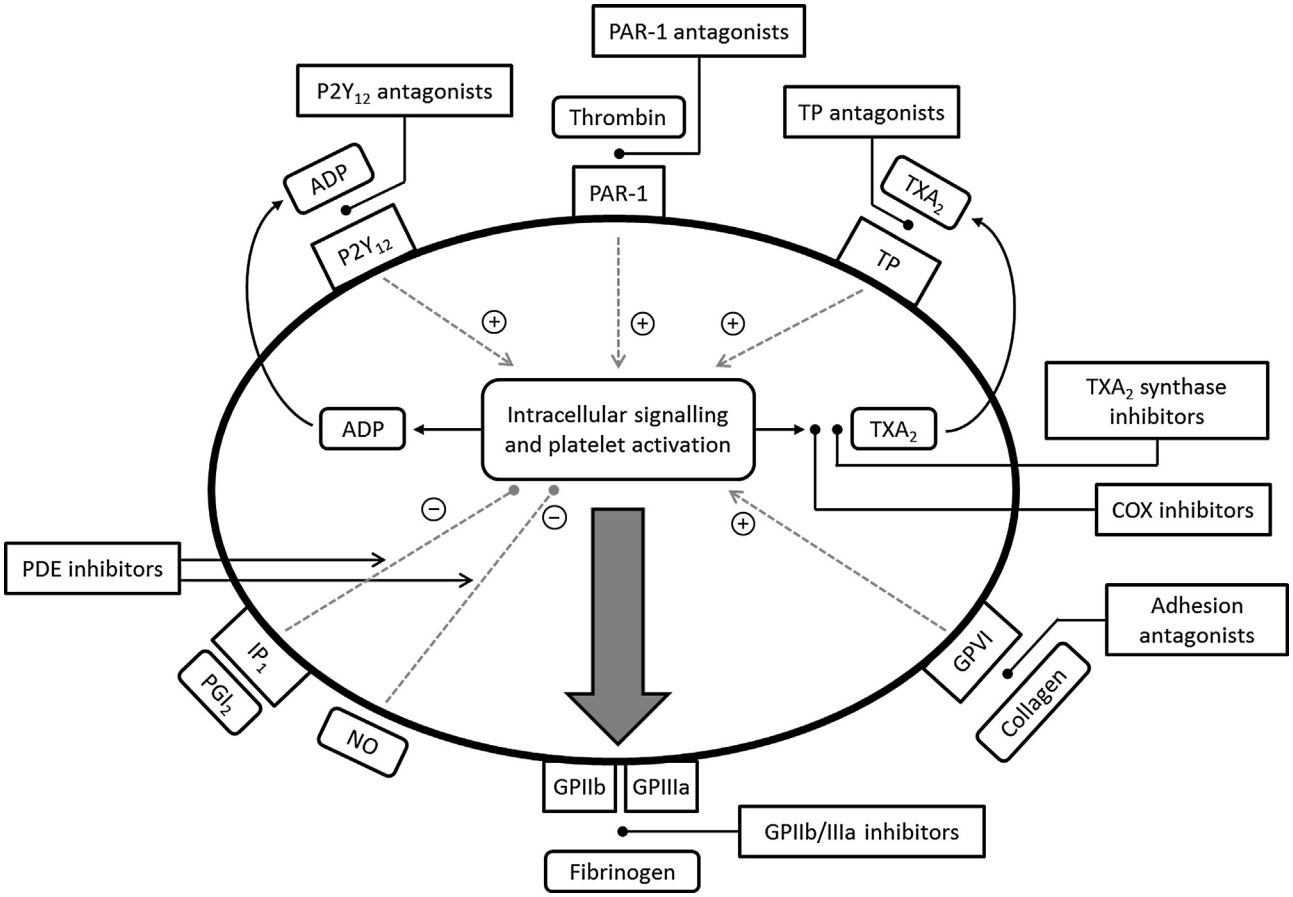

Fig. 2. Therapeutic targets of antiplatelet medication. ADP, adenosine diphosphate; COX, cyclooxygenase; GP, glycoprotein; IP1, prostacyclin receptor; NO, nitric oxide; PAR-1, protease activated receptor 1; PDE, phosphodiesterase; PGI_2, prostaglandin I_2; TP, thromboxane receptor; TXA_2, thromboxane A_2.