Pharmacology & Therapeutics 141 (2014) 69–78

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M. Belvisi

Mechanisms of aspirin resistance

Christopher N. Floyd, Albert Ferro *

Department of Clinical Pharmacology, Cardiovascular Division, King's College London, London, UK

ARTICLE INFO

Keywords:
Aspirin
Resistance
Cardiovascular
Thrombosis
Platelet

ABSTRACT

Aspirin is integral to the secondary prevention of cardiovascular disease and acts to impair the development of platelet-mediated atherothromboembolic events by irreversible inhibition of platelet cyclooxygenase-1 (COX-1). Inhibition of this enzyme prevents the synthesis of the potent pro-aggregatory prostanoid thromboxane A_2. A large number of patients continue to experience atherothromboembolic events despite aspirin therapy, so-called 'aspirin treatment failure', and this is multifactorial in aetiology. Approximately 10% however do not respond appropriately to aspirin in a phenomenon known as 'aspirin resistance', which is defined by various laboratory techniques. In this review we discuss the reasons for aspirin resistance in a systematic manner, starting from prescription of the drug and ending at the level of the platelet. Poor medication adherence has been shown to be a cause of apparent aspirin resistance, and may in fact be the largest contributory factor. Also important is high platelet turnover due to underlying inflammatory processes, such as atherosclerosis and its complications, leading to faster regeneration of platelets, and hence of COX-1, at a rate that diminishes the efficacy of once daily dosing. Recent developments include the identification of platelet glycoprotein IIIa as a potential biomarker (as well as possible underlying mechanism) for aspirin resistance and the discovery of an anion efflux pump that expels intracellular aspirin from platelets. The absolute as well as relative contributions of such factors to the phenomenon of aspirin resistance are the subject of continuing research.

Contents

1. Introduction

Aspirin is the most widely used drug in the world. Developed in the 19th century and subsequently marketed as a panacea for common ailments (Dreser, 1899), during the course of the 20th century its anti-inflammatory effects were recognised and eventually shown to be due to inhibition of cyclooxygenase resulting in impaired prostaglandin

Abbreviations: AA, arachidonic acid; CABG, coronary artery bypass graft; COX, cyclooxygenase; LTA, light transmission aggregometry; MRP4, multidrug resistant protein 4; NSAID, non-steroidal anti-inflammatory drug; PGE_2, prostaglandin E_2; PGH_2, prostaglandin H_2; PGI_2, prostaglandin I_2 (prostacyclin); PPI, proton pump inhibitor; TXA_2, thromboxane A_2; TXB_2, thromboxane B_2.

* Corresponding author at: 3.07 Franklin-Wilkins Building, King's College London, 150 Stamford Street, London SE1 9NH, UK. Tel.: +44 20 7848 4283; fax: +44 20 7848 4500.
E-mail address: albert.ferro@kcl.ac.uk (A. Ferro).

0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.08.005

synthesis (Ferreira et al., 1971; Vane, 1971). Its cardioprotective effect was not established, however, until the 1980s, when it was shown to confer an important survival advantage post-myocardial infarction (ISIS-2 Collaborative Group, 1988). More generally, it has since been shown to be highly effective in the secondary prevention of cardiovascular disease (Patrono et al., 2005).

Aspirin is a non-selective and irreversible cyclooxygenase (COX) inhibitor, and prevents the production of thromboxane A_2 (TXA_2) in platelets by acetylating a serine residue at position 529 of the COX-1 isoform (Roth & Majerus, 1975; Roth et al., 1975). TXA_2 is a metabolite of arachidonic acid (AA), with the rate limiting step in its synthesis being that catalysed by COX-1 (Hamberg et al., 1975) (Fig. 1). 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 and hence platelet aggregation (Nakahata, 2008). TXA_2 is an amplifying signal for other agonists, and so inhibition of COX-1 modulates multiple pathways of platelet activation (FitzGerald, 1991).

Nevertheless, aspirin only prevents approximately 25% of coronary events and ischaemic strokes when used in secondary prevention (Baigent et al., 2009). Much of this can be accounted for by the heterogeneous aetiology of these diseases, especially in the case of ischaemic stroke, where mechanisms may be non-atherothromboembolic and non-platelet mediated (Williams et al., 2011). However, it is estimated that between 5 and 60% of patients on aspirin therapy for secondary prevention do not respond appropriately to aspirin, a heterogeneous phenomenon which has come to be known as aspirin resistance (Hankey & Eikelboom, 2006).

1.1. The definition and classification of aspirin resistance

The term 'aspirin resistance' has not been universally accepted to describe the failure of aspirin to prevent atherothromboembolic events, as the majority of the mechanisms described below do not fit the classical model of drug resistance. Specifically, the pharmacological target COX-1 often remains sensitive to aspirin whilst its ability to suppress systemic levels of TXA_2 and platelet reactivity may be attenuated by a wide range of other factors. Alternative terms such as 'aspirin non-response' and 'aspirin treatment failure' are therefore favoured by some, but are vulnerable to equivalent semantic criticism. For the duration of this article we shall use the term 'aspirin resistance' to describe laboratory-derived findings and 'aspirin treatment failure' to describe the occurrence of clinical events in patients on aspirin.

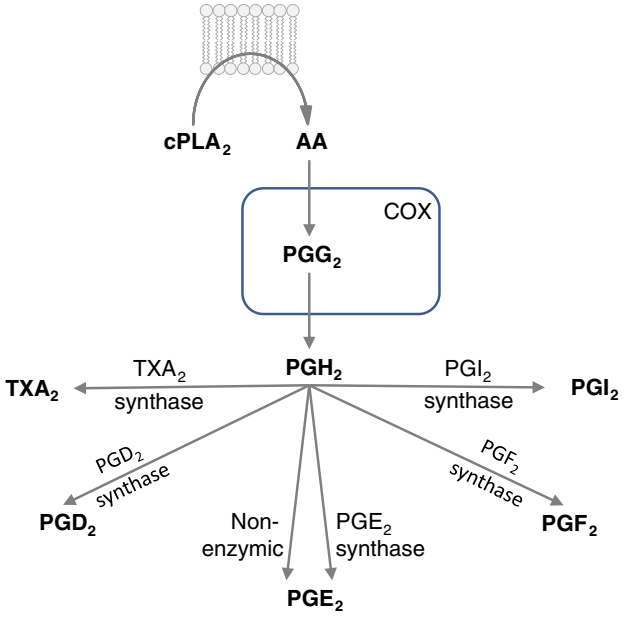

Fig. 1. Cyclooxygenase derived prostanoids. $cPLA_2$ = cytosolic phospholipase A_2, AA = arachidonic acid, COX = cyclooxygenase, PGG_2 = prostaglandin G_2, PGH_2 = prostaglandin H_2, TXA_2 = thromboxane A_2, PGD_2 = prostaglandin D_2, PGE_2 = prostaglandin E_2, PGF_2 = prostaglandin F_2, PGI_2 = prostaglandin I_2 (prostacyclin).

In addition to a lack of consensus on nomenclature, there is no accord regarding the classification of aspirin resistance beyond the distinction between clinical and laboratory resistance (Bhatt & Topol, 2003). Laboratory resistance is best described as a failure of aspirin to prevent the production of platelet COX-1-derived TXA_2, and is generally assessed either by the measurement of metabolites (e.g. serum thromboxane B_2; TXB_2) or by platelet function testing. Assays used for the detection of laboratory resistance are to varying degrees subject to inherent biases in sensitivity and/or specificity, resulting in poor agreement (Lordkipanidze et al., 2007), and thus the use of a single assay for defining aspirin resistance within a population is unlikely to produce truly meaningful results. A number of approaches have been suggested to aid in the diagnosis and classification of aspirin resistance, but these either lack clinical utility or do not facilitate reliable sub-categorisation of potential mechanisms (Weber et al., 2002; Pulcinelli & Riondino, 2006).

1.2. Pharmacokinetics and pharmacodynamics of aspirin

Before considering the mechanisms of aspirin resistance, it is helpful to briefly review its pharmacokinetic and pharmacodynamic profiles. After oral administration, aspirin crosses the mucosal lining of the stomach and upper small intestine in its lipophilic state with a bioavailability of 40–50% (Fig. 2) (Pedersen & FitzGerald, 1984). It undergoes substantial pre-systemic hydrolysis to salicylic acid by plasma and endothelial esterases before entering the systemic circulation (Harris & Riegelman, 1969), and demonstrates a plasma half-life of approximately 15–20 min across the range of treatment doses (Costello & Green, 1982). The portal circulation is the primary location at which platelet COX-1 inhibition occurs, as demonstrated by a fall in serum TXB_2 levels being detectable prior to the detection of aspirin within the systemic circulation (Pedersen & FitzGerald, 1984), and due to approximately 50% of absorbed aspirin being conjugated during first-pass hepatic metabolism (Rowland et al., 1972).

Once daily dosing has been found to achieve adequate inhibition of platelet COX-1 in aspirin-sensitive healthy individuals and those with cardiovascular disease (Patrignani et al., 1982; Antithrombotic Trialists' Collaboration, 2002). This is perhaps surprising given the normal platelet survival time of 10 days that should theoretically result in approximately 10% of circulating platelets being aspirin-naïve prior to each daily dose (Dale, 1997). However, the ability of aspirin to inhibit COX-1 in megakaryocytes (Demers et al., 1980) is likely to result in platelets entering the circulation already COX-1-inhibited, as proto-platelets in the final stages of development are unlikely to be able to re-generate COX-1 prior to release (van Pampus et al., 1993).

The extent to which platelet COX-1 and hence TXA_2 synthesis must be inhibited before platelet aggregation is impaired remains the subject of debate. The observation that the capacity of platelets to generate TXA_2 in vitro greatly exceeds the systemic production of TXA_2 measured in vivo suggested that substantial inhibition of platelet COX-1 would still allow full TXA_2 mediated aggregation (Patrono et al., 1986). Further work measuring in vivo urinary metabolites of TXA_2 and ex vivo assays of platelet reactivity led to the development of the '95% hypothesis', which states that >95% inhibition of COX-1-derived TXA_2 is necessary to inhibit aggregation (Hennekens et al., 2004). More recent work, however, using a wide range of agonist concentrations, has revealed that for the TXA_2-dependent agonists AA and low-dose collagen, a linear relationship exists between inhibition of platelet TXA_2 generation and suppression of TXA_2-mediated platelet aggregation (Armstrong et al., 2008). These findings are more consistent with the observation that