of aspirin to its binding sites inside the COX-1 channel by substrate competition. This type of drug interaction with the antiplatelet effects of aspirin was recognised for several anti-inflammatory drugs, including indomethacin and ibuprofen, many years ago.[10-11] Interestingly, recent data also suggest similar interactions for the non-inflammatory pyrazoles, including dipyrone (metamizole)[12] which is a frequently used and potent analgesic.[13] Mechanistically, NSAIDs and pyrazoles will compete with arachidonic acid for access to the catalytic site inside the hydrophobic channel of COX-1 and might also prevent the initial binding of the salicylate moiety of aspirin. This type of interaction may become significant in patients at increased risk of myocardial infarction because of chronic diseases, such as rheumatoid arthritis.[14]

Pharmacodynamic reasons for aspirin resistance include COX-1 gene polymorphisms and alterations in COX-1 sensitivity to aspirin, which might be overcome by increasing aspirin doses. Several prothrombotic genetic variations relevant to antiplatelet effects of aspirin have been described,[15] including those in COX-1.[16] These heritable factors are assumed to contribute prominently to the variability in residual platelet activity which accounts for insensitivity to aspirin.[17]

Disease-related mechanisms

Clearly, treatment failure is caused much more often by lack of compliance and platelet hyperreactivity[18] than by true pharmacological resistance to aspirin. These factors are frequently confused.[19]

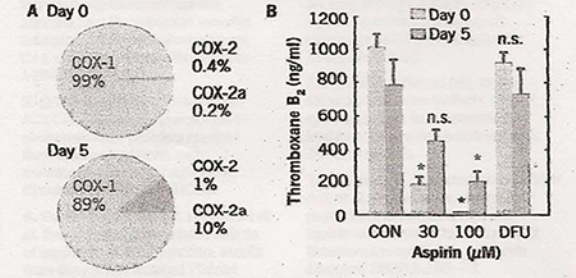
Disease-related mechanisms of aspirin resistance include platelet hyperreactivity (as postulated to occur in patients with atherosclerosis), platelet stimulation by mechanisms insensitive to aspirin (such as adenosine diphosphate [ADP] agonism and shear stress), COX-2-dependent thromboxane formation (which will occur in inflammatory states such as atherosclerosis) and platelet sensitisation by isoprostanes (for example, in patients with diabetes) which cause platelet activation which is not sensitive to aspirin.[20]

Fresh insights into possible mechanisms for aspirin "resistance" came from the discovery that platelets contain an immunoreactive COX-2.[21] This was thought to offer an explanation for the different findings on aspirin resistance *in vivo*. We have shown that, in patients undergoing coronary artery bypass grafting (CABG) with extracorporeal circulation, inhibition of arachidonic acid-induced platelet aggregation by aspirin was reduced after five days; this corresponded with the expression of immunoreactive COX-2.[13] However, the selective COX-2 inhibitor celecoxib did not block this effect. This apparent contradiction was resolved when a COX-2 isoform, COX-2a, was identified.[22] COX-2a is normally present in very low concentrations (constituting 0.2% of total COX, compared with 0.4% for COX-2 and >99% for COX-1) but is induced in patients undergoing cardiac surgery so that it accounts for as much as 10% of total COX (compared with 1% for COX-2). This is associated with significant levels of thromboxane B_2 even in the presence of aspirin (**figure 1**). The reduced responsiveness to aspirin in stroke patients may be overcome by increasing the aspirin dosage.[23-24] It is not known whether an upregulation of an enzymatically active COX-2 occurs in other situations of increased platelet turnover, such as diabetes or essential thrombocythaemia, and how it compares to upregulation of COX-2a.

The role of inflammation

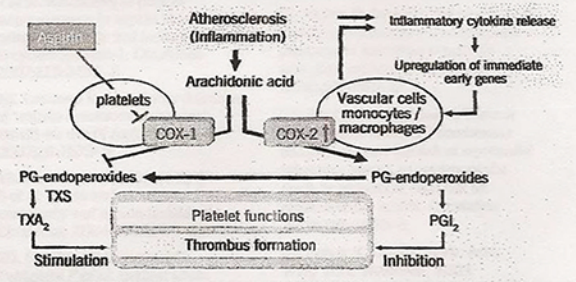
For many years, atherosclerosis has been recognised as an inflammatory condition. This implies that atherosclerosis, particularly in its advanced stages, might be associated with an upregulation of inflammatory genes and gene products, including COX-2 and prostaglandins.[25] A subgroup analysis from the Heart Outcomes Prevention Evaluation (HOPE) study found a relationship between vascular outcomes and urinary excretion of the thromboxane metabolite 11-dehydro-thromboxane B_2.[26] It was suggested that urinary 11-dehydro-thromboxane B_2 might be an index of aspirin resistance but in reality it is more likely to reflect a systemic inflammatory state.[27] Interestingly, the excretion of thromboxane metabolites correlates well with the measurement of platelet function,[3] suggesting a significant contribution of non-platelet-COX-1-derived thromboxane to overall thromboxane production. Thus, chronic inflammatory conditions and/or advanced atherosclerosis, chronic heart and renal failure or hypertension might well be associated with an increased expression of COX-2, i.e. an aspirin-"resistant" form of PG-endoperoxide formation. In turn, this would provide

Figure 1. A: proportions of COX-1, COX-2 and COX-2a mRNA and B: inhibition of AA-induced thromboxane formation by aspirin and a selective COX-2 inhibitor at days 0 and 5 post cardiac surgery



Key: CON=control; COX=cyclooxygenase; DFU=a COX-2-selective inhibitor; n.s.=non significant

Figure 2. COX-2 dependent, aspirin-insensitive thromboxane formation as a result of myocardial ischaemia



Key: COX=cyclooxygenase; PG=prostaglandin; PGI_2=prostacyclin; TXA_2=thromboxane A_2; TXS=thromboxane synthase

endoperoxides for platelet thromboxane synthase not blocked by aspirin and will generate thromboxane A_2 independent of the effective prevention of COX-1-dependent thromboxane formation by aspirin.

Figure 2 summarises this hypothesis. In the non-inflammatory state, arachidonic acid is metabolised first to prostaglandin endoperoxides and then to thromboxanes via a COX-1-dependent pathway and to prostaglandins via a COX-2 pathway. This balance between thromboxane and prostaglandin production is altered when an acute event causes the release of inflammatory cytokines. These upregulate COX-2 in inflammatory cells, such as monocytes and macrophages, but also in vascular cells including the endothelium and smooth muscle cells. COX-2 upregulation results in an increase in metabolism of arachidonic acid to prostaglandin endoperoxides, which are taken up by platelets and converted to thromboxane by their thromboxane synthase.

Aspirin blocks only the COX-1 pathway in this system, leaving the COX-2 pathway as a source of endoperoxides which are subsequently converted by platelets to thromboxanes. This model provides a mechanism for the diminished therapeutic response to aspirin prophylaxis and suggests that inflammation may have an important role in maintaining residual platelet activity. Patients who suffer from more advanced stages of atherosclerosis are likely to have more acute ischaemic/inflammatory events.

Summary

Insufficient pharmacological inhibition of platelet COX-1 by aspirin may exist but it is likely to be very rare (about 1%). The term aspirin "resistance" does not adequately explain treatment failures with low-dose aspirin which occur more often but have no direct pharmacological relationship to COX-1 inhibition by the drug. 'Treatment resistance' is a frequently used term for this phenomenon but of greater relevance in this context are patient adherence and "residual" platelet reactivity. Aspirin "resistance", however it is defined, is not a matter of concern[28] and – excepting individual cases of aspirin intolerance – has no clinical consequences since no appropriate alternatives are available. Moreover, even if platelet function is incompletely inhibited, the drug may have effects on autocrine and paracrine functions of platelet-derived thromboxane. Thus, there is no reason to withhold aspirin alone or in dual antiplatelet therapy because of concerns regarding possible "resistance"

Conflict of interest

KS has received research funding, honoraria for lectures or acted as a consultant to Bayer-Schering, Lilly/Daiichi Sankyo, Sanofi-Aventis and UCB.

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