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Review Article

Oxidative-stress-related mechanisms affecting response to aspirin in diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a major cardiovascular risk factor. Persistent platelet activation plays a key role in atherothrombosis in T2DM. However, current antiplatelet treatments appear less effective in T2DM patients vs nondiabetics at similar risk. A large body of evidence supports the contention that oxidative stress, which characterizes DM, may be responsible, at least in part, for less-than-expected response to aspirin, with multiple mechanisms acting at several levels. This review discusses the pathophysiological mechanisms related to oxidative stress and contributing to suboptimal aspirin action or responsiveness. These include: (1) mechanisms counteracting the antiplatelet effect of aspirin, such as reduced platelet sensitivity to the antiaggregating effects of NO, due to high-glucose-mediated oxidative stress; (2) mechanisms interfering with COX acetylation especially at the platelet level, e.g., lipid hydroperoxide-dependent impaired acetylating effects of aspirin; (3) mechanisms favoring platelet priming (lipid hydroperoxides) or activation (F_2-isoprostanes, acting as partial agonists of thromboxane receptor), or aldose-reductase pathway-mediated oxidative stress, leading to enhanced platelet thromboxane A_2 generation or thromboxane receptor activation; (4) mechanisms favoring platelet recruitment, such as aspirin-induced platelet isoprostane formation; (5) modulation of megakaryocyte generation and thrombopoiesis by oxidative HO-1 inhibition; and (6) aspirin–iron interactions, eventually resulting in impaired pharmacological activity of aspirin, lipoperoxide burden, and enhanced generation of hydroxyl radicals capable of promoting protein kinase C activation and platelet aggregation. Acknowledgment of oxidative stress as a major contributor, not only of vascular complications, but also of suboptimal response to antiplatelet agents in T2DM, may open the way to designing and testing novel antithrombotic strategies, specifically targeting oxidative-stress-mediated mechanisms of less-than-expected response to aspirin.

Contents

Abbreviations: ASA, acetylsalicylic acid; T2DM, type 2 diabetes mellitus; TX, thromboxane; TP, thromboxane receptor; COX, cyclooxygenase; ROS, reactive oxygen species; AGEs, advanced glycation end products; HO, heme oxygenase; CAD, coronary artery disease

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Aspirin resistance

The maximal antithrombotic efficacy of aspirin (acetylsalicylic acid, ASA) with the lowest bleeding risk has been recorded at 75–100 mg daily and relies on the permanent inactivation of platelet cyclooxygenase (COX)-1 (Fig. 1). This enzyme catalyzes the first step in the conversion of arachidonic acid to thromboxane A_2 (TXA_2), the main prothrombotic prostanoid from human platelets [1]. Variability of platelet response to drug therapy, namely aspirin, has been studied intensively in recent years, though the underlying causes and appropriate actions remain unclear. It appears that both patient-specific and medication-specific factors contribute to the variability of platelet activity and response.

Among the different antiplatelet strategies, over the past years aspirin has been the preferred victim of the inappropriate and largely abused definition of "aspirin resistance," which, far from the pharmacological definition, has been applied both to the clinical issue of occurrence of vascular events despite ongoing treatment and to the laboratory issue of impaired platelet response or residual platelet reactivity in aspirin-treated subjects. Whereas clinical failure is an anticipated event for any preventive strategy, given the multifactorial nature of atherothrombosis, laboratory failure is often biased by the, sometimes unreliable, methods used to assess the response to aspirin. These include single or repeated measurements of platelet function ex vivo using classic light-transmittance aggregation or bedside, whole-blood assays, all exhibiting less than ideal intrasubject and intersubject variability and not reflecting directly its mechanism of action, i.e., platelet COX-1 inactivation. In contrast, serum TXB_2 and urinary 11-dehydro-TXB_2 provide reliable information on the maximal biosynthetic capacity of circulating platelets ex vivo and on the

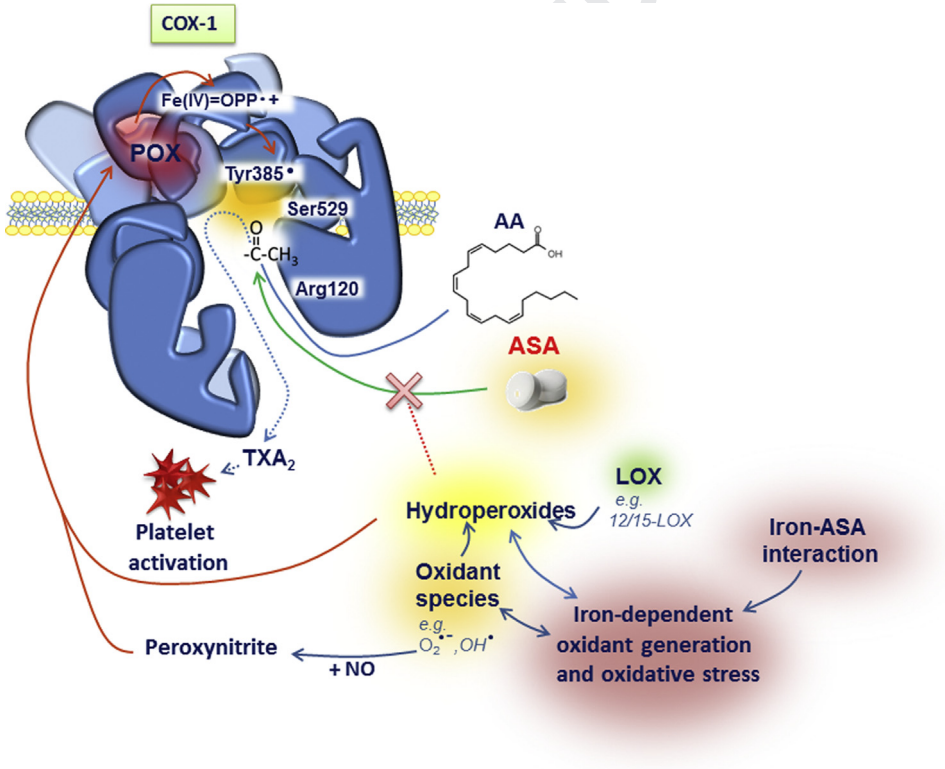

Fig. 1. Platelet prostaglandin H (PGH) synthase 1, also referred to as cyclooxygenase (COX)-1, catalyzes the first committed step in the conversion of arachidonic acid to thromboxane A_2 (TXA_2), the main prothrombotic prostanoid from human platelets. The best-characterized mechanism of action of aspirin at low doses consists in the permanent inactivation of the COX activity of platelet PGH-1. PGH synthase has a bifunctional nature, because it contains both a COX and a heme-containing peroxidase (POX) at the catalytic site. By diffusing through cell membranes, aspirin enters the COX channel, a narrow hydrophobic channel connecting the cell membrane to the catalytic pocket of the enzyme. Aspirin first binds to an arginine 120 residue and then acetylates a serine residue (serine 529 in human COX-1 and serine 516 in COX-2) located in the narrowest section of the channel, thereby preventing arachidonic acid (AA) from gaining access to the COX catalytic site of the enzyme. Especially in diabetic patients, oxidative stress-related mechanisms may impair COX-1 (and COX-2) acetylation by aspirin. In this regard, interaction of hydroperoxides with PGH synthase POX leads to the formation of the protoporphyrin radical cation ($Fe(IV)=OPP^{\bullet+}$) and then of the tyrosine 385 radical ($Tyr385^{\bullet}$) characterized by specific oxidizing properties; thus, hydroperoxide-dependent oxidation of critical COX amino acid residues results in impaired acetylating effects of aspirin with decreased drug antiplatelet activity in the case of COX-1. Moreover, in the case of COX-2, the hydroperoxide-dependent impaired acetylating effects of aspirin may prevent aspirin-triggered lipoxin and resolvin formation compromising the anti-inflammatory effects of aspirin (see *Hydroperoxides*). Lipid hydroperoxides can be formed enzymatically by lipoxygenases, such as 12/15-LOX, or nonenzymatically owing to oxidant species often generated iron-dependently and capable of inducing lipid peroxidation (see Fig. 2); the interaction of ASA with iron may favor oxidant generation, iron-dependent lipid peroxidation, and lipid hydroperoxide generation. Moreover, ASA–iron interaction may alter pharmacokinetic and pharmacodynamic properties of ASA, eventually resulting in its impaired therapeutic effects. Notably, peroxynitrite, formed from the reaction of superoxide anion ($O_2^{\bullet-}$) with nitric oxide (NO), can also act as an efficient substrate for POX of COX-1 and COX-2. ASA, acetylsalicylic acid or aspirin; LOX, lipoxygenase; $OH^{\bullet}$, hydroxyl radical.

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