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The cardiovascular biology of microsomal prostaglandin E synthase-1

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Abstract

Both traditional and purpose designed nonsteroidal anti-inflammatory drugs (NSAIDs), selective for inhibition of cyclooxygenase (COX) -2 alleviate pain and inflammation but confer a cardiovascular hazard, attributable to inhibition of COX-2 derived prostacyclin (PGI₂). Deletion of microsomal PGE synthase-1 (mPGES-1), the dominant enzyme that converts the COX derived intermediate product, PGH₂, to form PGE₂, modulates inflammatory pain in rodents. By contrast with COX-2 deletion or inhibition, PGI₂ formation is augmented in mPGES-1^{-/-} mice an effect which may confer cardiovascular benefit, yet undermine the analgesic potential of inhibitors of this enzyme. This review will consider the cardiovascular biology of mPGES1, and the complex challenge of developing inhibitors of this enzyme.

Keywords

Prostaglandin; prostacyclin; PGE synthase-1; cyclooxygenase; cardiovascular; inflammation

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate pain and reduce fever by inhibiting prostaglandin (PG) G/H synthases (commonly known as cyclooxygenases or COXs), pivotal enzymes in the biosynthetic cascade that leads to formation of prostanoids (Figure 1). Metabolism of arachidonic acid by COXs yields the intermediate prostaglandin (PG) endoperoxide product, PGH₂ that is further metabolized to prostanoids by terminal synthases. The analgesic efficacy of NSAIDs is largely attributable to suppression of formation of COX-2 derived PGE₂ and PGI₂ and their serious gastrointestinal (GI) adverse effects result largely from suppression of COX-1 derived PGE₂ and PGI₂ in gastroduodenal epithelium and COX-1 derived TxA₂ formed by platelets. These observations prompted the development of purpose designed (pd) NSAIDs selective for inhibition of COX-2 and

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Conflict of Interest Disclosures

Dr. FitzGerald has consulted in the past year for Astra Zeneca, Daiichi Sankyo, Logical Therapeutics, Lilly and Nicox on NSAIDs and related compounds.

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indeed, they proved less likely to cause serious GI adverse events than the traditional (t) NSAIDs like ibuprofen and naproxen, that inhibited both COX-1 and COX-2. Several tNSAIDs, such as diclofenac and meloxicam, also inhibit preferentially COX-2 at their therapeutic doses. Despite their diminished propensity to cause GI complications, COX-2 inhibitors were shown to increase the risk of myocardial infarction (MI), stroke, systemic and pulmonary hypertension, congestive heart failure and sudden cardiac death (Garcia Rodriguez et al. 2008; Grosser et al. 2006; Grosser et al. 2010). This increased cardiovascular hazard is attributable to suppression of COX-2 derived prostaglandins, particularly, PGI₂ (Grosser et al. 2006; Grosser et al. 2010). Expression of the cardiovascular hazard in an individual patient is likely modulated by drug selectivity, potency and exposure, underlying baseline cardiovascular risk and concomitant therapies, such as low dose aspirin (Garcia Rodriguez et al. 2008; Grosser et al. 2006; Grosser et al. 2010).

The withdrawal from the market and failure of regulatory approval of several pd NSAIDs selective for inhibition of COX-2 prompted interest in microsomal (m)-PGE synthase (PGES) -1 as an alternative drug target (Jakobsson et al. 1999; Samuelsson et al. 2007; Thoren et al. 2003). This enzyme is a member of the MAPEG (membrane-associated proteins in eicosanoid and glutathione metabolism) superfamily and was experimentally identified by Jakobsson et al as microsome-associated and 152 amino acids in length and as exhibiting glutathione-dependent PGE synthase activity (0.25 micromol/min/mg) (Jakobsson et al. 1999). The human PGES-1 gene is localized to chromosome 9q34.3, contains 3 exons and spans 14.8 kb (Forsberg et al. 2000). The human mPGES-1 sequence shows roughly 80% similarity to the enzyme in mouse, rat or cow. Electron crystallography demonstrated that microsomal PGES-1 constitutes a trimer in two-dimensional crystals (Jegerschold et al. 2008; Xing et al. 2009) (Figure 2). Human mPGES-1 inhibitors may not be pharmacologically effective in animals, and such species differences in inhibitor binding efficiency may be attributable to some key residues- Thr-131, Leu-135, and Ala-138 in human mPGES-1 (Pawelzik et al. 2010). These residues are situated in transmembrane helix 4, lining the entrance to the cleft between two subunits in the protein trimer, and regulate inhibitor access to the enzyme. For detail illustration see reference (Pawelzik et al. 2010).

Two other PGE synthases have also been identified, mPGES-2 (Murakami and Kudo 2006) and cytosolic (c) PGES (Pini et al. 2005; Tanioka et al. 2000), however mPGES-1 is the dominant source of PGE₂ biosynthesis (Cheng et al. 2006), as assessed by excretion of its major urinary metabolite, in mice and humans. While cPGES is co-expressed with COX-1, mPGES-1 is often functionally co-regulated with COX-2, such as in the vasculature during zebra fish development (Pini et al. 2005) and in models of inflammation (Claveau et al. 2003). mPGES-1 also predominantly colocalizes with COX-1 in renal distal convoluted tubule and in medullary collecting ducts (Schneider et al. 2004).

Initially, mPGES-1 deletion in mice was found to modulate experimentally evoked pain and inflammation to a degree indistinguishable from treatment with tNSAIDs non-selective for inhibition of COXs (Kamei et al. 2004; Trebino et al. 2003). Although many small molecule inhibitors of mPGES-1 fail to block the rodent enzyme, one inhibitor has been used in mice in which the human enzyme has been overexpressed and shown to inhibit inflammatory pain (Xu et al. 2008). mPGES-1 deletion was shown to upregulate the anti-inflammatory nuclear receptor, PPAR γ (Kapoor et al. 2006), which may also contribute to the efficacy of this strategy. While these results suggested that mPGES-1 might indeed be a promising alternative drug target to COX-2, enzyme deletion has been less impressive in some rodent models of analgesia (Scholich and Geisslinger 2006). This might reflect the contribution of (i) continuing synthesis of PGE₂ by other synthases in mPGES-1^{-/-} mice or (ii) the importance of PGI₂ as a mediator of pain (Chen et al. 2008). Indeed, redirection of

accumulated PGH₂ substrate to PGI₂ synthase can augment PGI₂ biosynthesis in mPGES-1^{-/-} mice (Cheng et al. 2006).

Other areas of potential therapeutic application of mPGES-1 inhibitors have been explored. mPGES-1 was also identified as the central switch during immune-induced pyresis and as a target for the treatment of fever (Engblom et al. 2003; Xu et al. 2008). Enzyme deletion delays and ameliorates the expression of experimental autoimmune encephalomyelitis, thought to be a model of multiple sclerosis (Kihara et al. 2009). By contrast, a note of caution was sounded by a recent provocative study, in which mPGES-1 derived PGE₂, acting via EP2 and EP4 receptors mediates resolution of lipopolysaccharide (LPS)-induced spinal neuroinflammation after initial LPS priming (Brenneis et al. 2011).

mPGES-1 may have therapeutic potential in the chemoprevention of certain cancers (Radmark and Samuelsson 2010), including intestinal tumors (Nakanishi et al. 2008), prostate and lung cancers (Hanaka et al. 2009). Several small molecule inhibitors have been developed and initial experience of human tolerability of some compounds has been acquired. However, it remains a challenge to select an initial target for proof of clinical efficacy. Will these drugs be less likely to confer a cardiovascular hazard than NSAIDs selective for inhibition of COX-2? However, if so, will they be less efficacious than such drugs as analgesics? Might an alternative clinical target offer a more promising route to initial drug approval?

Cardiovascular consequences of mPGES-1 deletion

(i) Thrombosis and blood pressure

It has long been known that NSAID consumption is associated with hypertension and that the magnitude of this response is quite variable (Chan et al. 2009). It is thus unsurprising that disruption of COX-2 dependent formation of PGI₂ and/or PGE₂ will elevate blood pressure in mice and that this effect is highly conditioned by genetic background (Yang et al. 2005). Similarly, genetic deletion or pharmacological inhibition of COX-2 or disruption of the PGI₂ receptor predisposes to accelerated thrombogenesis in rodent models of induced thrombosis (Cheng et al. 2006), consistent with the predisposition to myocardial infarction and stroke observed in placebo controlled trials of pNSAIDs selective for inhibition of COX-2 (Bresalier et al. 2005; Grosser et al. 2006; Solomon et al. 2005). Accelerated thrombogenesis is not observed in mPGES-1 mice which exhibit augmented formation of PGI₂ coincident with suppression of PGE₂ (Cheng et al. 2006). Effects on both prostanoids may be relevant to this phenotype: PGI₂ restrains thrombogenesis while low concentrations of PGE₂ activate platelet aggregation via the EP3 receptor (Fabre et al. 2001).

The differential impact of mPGES-1 vs COX-2 inhibition on blood pressure is more nuanced. As mentioned, NSAIDs may elevate blood pressure and evidence in rodents suggests that this relates to inhibition of COX-2 and the selectivity with which this is attained (Qi et al. 2002). We and others have reported that deletion of mPGES-1 fails to elevate blood pressure in mice fed either a normal or high salt diet (Cheng et al. 2006; Francois et al. 2007). Hypertension induced by infusion of angiotensin II in hyperlipidemic mice is also uninfluenced by mPGES-1 deletion (Harding et al. 2011; Wang et al. 2008). In contrast to these observations, Jia et al reported that mPGES-1 deletion augmented the hypertensive response to both a more intensive salt loading regimen and to angiotensin II infusion in normolipidemic mice (Jia et al. 2006). This discrepancy may reflect differences in genetic background amongst the strains used in these experiments and differences in the experimental protocols. However, they suggest that any differences in the hypertensive effects of NSAIDs and mPGES-1 inhibitors may turn out to be relative rather than absolute. In contrast to COX-2 deficient mice, no impairment in renal development is observed in

mPGES-1 deficient mice. PGE₂ and PGI₂ promote natriuresis, and thus, may both contribute to blood pressure homeostasis regulated by mPGES-1.

(ii) Vascular inflammation

Inflammation is a hallmark of atherosclerosis, however its functional contribution to disease evolution and, in particular to plaque destabilization and vascular occlusive thrombosis remains speculative. Indeed, the only placebo controlled trials of anti-inflammatory drugs in which cardiovascular endpoints have been assessed have been those involving NSAIDs. Various mutant mice have been developed which result in hyperlipidemia, permitting assessment of drugs or gene deletions on atherogenesis. While the lesions in these mice variably approximate the human condition, they differ in that they are largely resistant to plaque destabilization and consequent thrombosis. Given these caveats, there has been interest in assessing the impact of NSAIDs on atherogenesis in mice, as several clinical trials of COX-2 inhibitors in patients selected to be at low cardiovascular risk resulted in a delayed detection of a drug related increase in myocardial infarction and stroke, consistent with an impact on atherogenesis (Grosser et al. 2006). Indeed, deletion of the PGI₂ receptor promotes initiation and early development of atherosclerosis in hyperlipidemic mice (Egan et al. 2004). By contrast COX-2 inhibitors or enzyme deletion have been shown variously to retard, accelerate, or leave unaltered, development of atherosclerosis in mouse models (Egan et al. 2005; Linton and Fazio 2004). These conflicting results may result from differences in drug specificity or dosing strategy, residual developmental effects of COX-2 deletion or the contrasting effects of COX-2-derived prostanoids that is elaborated in a cell-specific manner over the course of the disease. In any event, the effect of mPGES-1 deletion is quite distinct. Here, atherogenesis in LDL receptor deleted hyperlipidemic mice is retarded by coincident disruption of mPGES-1. Again this may reflect both suppression of PGE₂ and augmentation of PGI₂. Aside from the impact of IP deletion on atherogenesis, deletion of EP4 in macrophages by fetal liver cell transplantation restrains early atherogenesis in LDLR^{-/-} mice (Babaev et al. 2008), suggesting that, as with thrombogenesis, the bivalent effects on formation of these two prostanoids may both have been mechanistically relevant. A note of caution in these studies is that the substrate redirection products consequent to mPGES-1 deletion differs between cell types. Thus, in the setting of atherogenesis, the consequences of vascular smooth muscle cell deletion of mPGES-1 predominates, with augmented formation of PGI₂. However, in lesional macrophages, the dominant redirection products are PGE₂ and TxA₂, both of which may promote atherogenesis (Babaev et al. 2008; Kobayashi et al. 2004), albeit the evidence for myeloid EP4 receptor activation and atherogenesis is contradictory (Tang et al. 2011). Given that adults treated with mPGES-1 inhibitors are likely to have pre-existent atherosclerosis, the more convincing proof of concept would be the induction of lesional regression by a small molecule inhibitor in hyperlipidemic mice expressing the human enzyme with already established atherosclerosis. Lacking this evidence, it is conceivable that administration of an mPGES-1 inhibitor to patients with established atherosclerosis might exacerbate the disease, due to substrate redirection in lesional macrophages.

Abdominal aortic aneurysm (AAA) is an inflammatory disorder, characterized by localized connective tissue degradation and smooth muscle cell (SMC) apoptosis, leading to aortic dilatation and rupture. Although both often coexist, the pathology of AAA differs from that of atherosclerosis (Golledge et al. 2006; Sakalihasan et al. 2005). Human aortic aneurysm biopsies stain strongly for COX-2 *ex vivo* and a preliminary cohort study in patients suggest that use of tNSAIDs retarded aneurysmal growth (Walton et al. 1999). Deletion or selective inhibition of COX-2, but not inhibition of COX-1 decreases AAA formation in hyperlipidemic mice (King et al. 2006). We reported that deletion of mPGES-1 also retards formation of AAA induced by an angiotensin II infusion in LDLR^{-/-} mice. This occurs

concomitant with suppression of aortic and systemic indices of oxidative stress and matrix metalloproteinase 2 expression, themselves previously implicated in the pathogenesis of AAA (Sakalihasan et al. 1996; Thomas et al. 2006). Deletion of mPGES-1 inhibited production of PGE₂, but also resulted in substrate redirection to augment production of PGI₂ and PGD₂, both of which might upregulate antioxidant enzymes and restrain oxidant stress (Alvarez-Maqueda et al. 2004; Egan et al. 2004).

A third vascular phenotype associated with evidence of inflammation is the response to injury. Both COXs and PGs differentially modulate the response to vascular injury. For example, wire induced vascular proliferation is enhanced in mice that are genetically deficient in the IP, while deletion of the TxA₂ receptor (TP) depresses this response (Cheng et al. 2002). There are conflicting reports of the impact of disrupting COX-2 on vascular remodeling. For example, pharmacological suppression of COX-2 derived PGI₂ with nimesulide promotes adverse vascular remodeling in a flow-induced injury model, an effect replicated by deletion of the IP (Rudic et al. 2005). However, COX-2 inhibition by celecoxib reduces neointimal hyperplasia in balloon-injured carotid arteries in rats and rabbits (Wang et al. 2005; Yang et al. 2004). It is unclear whether this discrepancy reflects off target effects of celecoxib or species differences in the response to vascular injury. Furthermore, despite the risk of myocardial infarction conferred by celecoxib in placebo controlled trials (Solomon et al. 2008), preliminary evidence suggests that in patients who underwent angioplasty and received platelet inhibitors to limit this risk, in-stent late luminal loss is reduced by this COX- selective inhibitor (Koo et al. 2007). Deletion of mPGES-1 in mice attenuates neointimal hyperplasia after vascular wire-injury (Wang et al. 2011) (Figure 3). Again, both suppression of PGE₂ and redirection of the accumulated PGH₂ substrate to PGI₂ seem mechanistically relevant. Both modulate the injury induced upregulation of tenascin-C — an abundant extracellular matrix glycoprotein, which affords a scaffold along which vascular smooth muscle cells migration to proliferate in the neointima.

(iii) Cardiac function

An increased incidence of congestive cardiac failure has been observed in placebo controlled trials of NSAIDs (Grosser et al. 2006). Although this may in part reflect NSAID induced hypertension, it appears that COX-2 dependent formation of PGI₂ in cardiomyocytes affords cardioprotection. Thus, selective deletion of COX-2 in cardiomyocytes results in mild heart failure and cardiac fibrosis in mice (Wang et al. 2009) demonstrating the direct role of COX-2-derived prostanoids in cardiac function. The primary COX-2-derived mediators implicated in cardioprotection are PGI₂ and PGE₂, which, acting on the IP or the EP₃, respectively (Dowd et al. 2001; Shinmura et al. 2005), can protect against oxidative injury in cardiac tissue. Wu et al (Wu et al. 2009a) found that celecoxib decreased survival in mice after acute MI, while mPGES-1 deletion did not change the survival rate due to increased PGI₂ signaling (Wu et al. 2009b). On the other hand, Degousse et al observed that deletion of mPGES-1 leads to eccentric cardiac myocyte hypertrophy, left ventricle (LV) dilation, and impaired LV contractile function after acute MI. This adverse LV remodeling contrasts with the favorable PGI₂ dependent vascular remodeling in mPGES-1 knockout mice and is due to suppression of PGE₂ formation by inflammatory cells in the infarct and peri-infarct regions (Degousse et al. 2008). Others reported that depletion of mPGES-1 impairs the compensatory hypertrophic response to prolonged angiotensin II infusion and reduces the ejection fraction (Harding et al. 2011). These studies raise the possibility of adverse cardiac effects of mPGES-1 inhibitors in patients who had recently suffered a myocardial infarction or exhibit cardiac decompensation. In contrast with the results following myocardial ischemia or infarction, deletion of mPGES-1 attenuates brain injury and promotes functional recovery after experimentally induced stroke (Kapoor et al. 2006).

Summary

The mPGES-1 enzyme represents an intriguing target for drug development. Given the limitations of presently available data on analgesic efficacy in animals we will not know how the analgesic efficacy of its inhibition compares with NSAIDs until such studies are performed in humans. Will augmented PGI₂ formation dilute the analgesic potency of mPGES-1 inhibitors and if so, will this only apply to certain types of pain? Limited evidence, at the preclinical level, suggests an improved adverse effect profile of this therapeutic strategy compared to a tNSAID (Xu et al. 2008). Preclinical studies favor the cardiovascular profile of mPGES-1 inhibitors. However, while they may confer limited cardiovascular hazard per se, their use may be injudicious in patients who have suffered a myocardial infarction or are in heart failure. A comparative evaluation of their impact relative to NSAIDs selective for inhibition of COX-2 on blood pressure in mildly hypertensive individuals would seem a priority early in clinical development. Local delivery of mPGES-1 inhibitors from endovascular stents might limit the consequences of vascular injury in patients subject to angioplasty while limiting systemic adverse effects and merits consideration as a route to initial drug approval. Similarly, an impact of mPGES-1 inhibition on progression to surgery in patients with AAA might represent an orphan indication. Meantime, further preclinical experimentation with tool compounds will provide valuable information concerning substrate redirection to PGD₂, and its implications for patients with asthma (Wang et al. 2010), the relative GI tolerability of mPGES-1 inhibitors versus NSAIDs and whether the major products formed via substrate redirection change with functional consequence during chronic therapy where lesional infiltrations alter during the natural history of disease.

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Fig. 1. Biosynthetic/response pathway for prostanoids

Arachidonic acid is released from membrane phospholipids upon physiological or inflammatory stimulation, and then catalyzed by cyclooxygenases (COXs) to form the intermediate product, PGH_2 . Terminal isomerases, PGI_2 synthase (PGIS), thromboxane synthase (TxS), microsomal (m) or cytosolic (c) PGE_2 synthase (PGES), mPGES (microsomal PGE_2 synthase), hematopoietic (h) - or lipocalin (l)- type PGD_2 synthase (PGDS) and $\text{PGF}_{2\alpha}$ synthase (PGFS), convert PGH_2 to form PGI_2 , TxA_2 , PGE_2 , PGD_2 and $\text{PGF}_{2\alpha}$, respectively. Prostanoids exert their action mainly via corresponding G-protein coupled receptors, for example, PGI_2 via I prostane (P) receptor, IP, TxA_2 via TP (two TP isomers, α and β are spliced from same gene), and PGE_2 via four receptors (EP1, EP2, EP3 and EP4). Among the three identified PGESs, mPGES-1 is the dominant source of PGE_2 formation in inflammation.

Fig. 2.

Overall structure of human mPGES-1 trimer. The three mPGES-1 monomers are colored in grey, red and green, respectively. Three glutathione molecules are complexed with mPGES-1 trimer at the intermonomeric interfaces, and they are represented by space-filling model in (a) and stick model in (b). (a) Top view from the cytoplasmic side of the membrane. (b) Side view from the membrane. Top and bottom are respectively the cytoplasmic and luminal phase. This figure is reproduced with permission from J Comput Aided Mol Des. 2009;23(1):13–24.

Fig. 3. Deletion of mPGES-1 reduced neointimal formation

Mice were subjected to wire injury in femoral artery and assessed 4 weeks later. Wild type (WT) mice developed extensive neointima as compared to sham operated control mice (A and D), while this mPGES-1^{-/-} (KO) mice demonstrate significantly reduced neointima area (A), ratio of intima to media (B) and lumen occlusion (C and D). Representative H&E staining of cross sections from sham operated or wire-injured arteries is shown (D). N denotes neointima; M denotes media; ► indicates internal elastin; ◄ indicates external elastin. Scale bar denotes 20 μm. This figure is reproduced with permission from Circulation(Wang et al. 2011).