Cyclooxygenase-2 and atherosclerosis: friend or foe?

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Introduction

Atherosclerosis, manifested by heart disease, stroke, and peripheral vascular disease, remains the leading cause of morbidity and mortality in industrialized countries despite aggressive vascular intervention and myriad blood pressure- and lipid-lowering agents. Over the past decade, however, our understanding of atherogenesis has evolved from one of occlusive lipid accumulation to one of chronic inflammation involving cellular proliferation [1].

Prostaglandins mediate inflammation locally and modulate physiological responses systemically. Nearly all tissues produce prostaglandins and increase production at sites of inflammation. Specifically, arachidonic acid is metabolized to prostaglandin G2 (PGG2) and then to prostaglandin H2 (PGH2) by cyclooxygenase. These moieties are then converted to PGD2, PGE2, PGF2, PGI2, or thromboxane (TX). The specific prostaglandin produced is determined, in part, by the particular cell type under consideration. For example, endothelium primarily produces PGI2 or prostacyclin, while platelets produce TX. Despite recognition of cyclooxygenase’s mechanism of action 30 years ago [2], the enzyme was first cloned in 1988 (cyclooxygenase-1 or COX-1) [3]. A second isoform was reported 3 years later (cyclooxygenase-2 or COX-2) [4].

COX-1 is constitutively expressed, serving a so-called ‘housekeeping’ role, in many tissues under basal conditions. For example, COX-1 helps to maintain normal physiological functions such as mucus production in the gastric mucosa. Conversely, COX-2 is an inducible enzyme, generally not present (or minimally so) in most tissues. Rather, its expression is more often associated with inflammation and other pathophysiological states. This realization has driven the development of COX-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx) for antiinflammatory/analgesic therapy of osteo- and rheumatoid-arthritis as well as acute pain syndromes. Such agents would offer efficacy while minimizing unwanted side effects attributable to COX-1 inhibition (e.g., gastric ulceration).

More recent investigations, however, reveal that COX-2 plays a key role in a wide range of physiological processes including organogenesis, brain and nerve function, reproduction, bone metabolism, salt and water handling, renin release, angiogenesis, cell proliferation and apoptosis. Further, COX-2 has been implicated in several disease states such as: colonic polyposis [5]; various forms of cancer [6,7]; Alzheimer’s disease [8]; and vascular restenosis following angioplasty [9].

This review will focus on the putative role of COX-2 in the development and maintenance of atherosclerosis, emphasizing the ‘inflammatory’ nature of the disease. The role of COX-2 in atherosclerosis, however, may not represent a simple cause-and-effect scenario. Conflicting data exist with regard to the relationship that COX-2 may have with atherogenesis. The following discussion will present arguments for and against COX-2 as an aetiological factor in atherosclerotic cardiovascular disease, as well as the therapeutic potential for its pharmacological manipulation.

COX-2 and atheromatous tissue

A detailed description of atheromatous plaque generation is beyond the scope of this review and can be found elsewhere [1]. As such, a simplified construct of this lesion focuses on three cell types—endothelial, monocyte/macrophage, and vascular smooth muscle. Disruption of the endothelial cell barrier between circulating blood and tissue, monocyte/macrophage sequestration at these sites with elaboration of inflammatory cytokines, and the transmigration and uncontrolled proliferation of vascular smooth muscle cells typify the initial phase of the atherosclerotic process. COX-2 expression has been found in each of these cell types in animal models as well as in human atherosclerotic tissue [10–12]. Similarly, COX-2 can be induced in these cells by many, if not all, of the same proinflammatory mediators implicated in the development of atherosclerosis. Such mediators...
include tumour necrosis factor (TNF), interleukin-1 (IL-1), interferon-γ, free radicals, endotoxin, platelet-derived growth factor, hypoxia, and shear stress as recently reviewed [12]. The presence of COX-2 in cells which comprise the atheromatous lesion as well as its inducibility by mediators of atherogenesis are in keeping with experimental and clinical data showing that prostaglandin production is increased in atherosclerosis; just as it is in other inflammatory conditions [12,13]. Particularly compelling histologically, are the findings of Schonbeck et al. [10] and Baker et al. [11] in which COX-2 expression is found in human atheromatous plaque lesions in diseased coronary arteries resected at the time of surgical revascularization, but not in normal coronary arteries. Furthermore, COX-2 expression colocalizes with that of inducible nitric oxide synthase (iNOS), suggesting an interaction between the two inflammatory mediators. Lastly, augmented COX-2 expression is present in diseased, transplanted coronary arteries to the same extent as that found in diseased native coronary arteries [11]. Again, this emphasizes the inflammatory nature of atherosclerosis as opposed to the ‘degeneration-with-ageing’ model held earlier.

Oxidative stress and COX-2

Accumulation of low-density lipoprotein (LDL) in the subendothelial region of the vascular wall is a primary event in the initiation of atherosclerotic injury. Monocytes, attracted to these areas of accumulated LDL by increased expression of adhesion molecules on endothelial cell membranes, aggregate on the surface of the lumen and subsequently transmigrate into the intimal layer. Here they differentiate into macrophages which scavenge lipoproteins, ultimately forming foam cells. LDL, however, is first oxidatively modified which facilitates its uptake by the macrophage [14]. Oxidized LDL (oxLDL) accelerates the formation of foam cells that contribute their lipid contents to fatty streak formation, the histological hallmark of the initial stage of atherosclerosis. Experimentally, the ability of oxLDL to activate a macrophage is not only dependent on oxidation of either the protein moiety or lipid moiety of the LDL molecule, but also requires fully differentiated macrophages derived from monocytes [15].

The relationship between COX-2 and oxLDL is not straightforward. Activated macrophages produce a variety of inflammatory mediators, including prosta-
glandins. Thus, increased COX-2 activity would be expected in oxidatively stressed macrophages given its inducible nature. In animal models, however, macrophages exposed to oxidized lipoproteins decrease their prostaglandin production (i.e. PGE2 and PG12) when stimulated by inflammatory cytokines such as lipopolysaccharide (LPS) [16]. As such, cholesterol-rich macrophages and foam cells appear to have an impaired or reduced inflammatory response, rather than an augmented one, following oxLDL exposure [17]. Recently, Eligini et al. [18] reported that oxLDL inhibited LPS-induced COX-2 expression in human macrophages.

The pathophysiological significance of oxLDL’s ability to downregulate COX-2, specifically, and to diminish macrophage responsiveness to inflammatory stimuli, globally, remains unclear. One argument highlights the negative feedback exerted on macrophage colony stimulating factor (M-CSF) by PGE2 and PG12 [19]. Enhanced M-CSF secretion by monocytes could foster proliferation and accumulation of macrophages in areas of atheroma formation, potentiating the atherosclerotic process. Another argument contends that normal resolution of inflammatory processes requires intact and robust cellular responses to such stimuli, ‘effective clean-up’ in essence. Blunted inflammatory responses by macrophages exposed to oxLDL, early in the development of atheromatous lesions, could limit tissue repair and result in a low-grade state of chronic inflammatory injury which is unable to repair itself. Pharmacological intervention with selective COX-2 inhibitors may help to delineate the relationship between oxLDL, COX-2, and the activated macrophage.

Another lipoprotein, high-density lipoprotein or HDL, exerts an ‘antiatherogenic’ or protective effect on the cardiovascular system. A strong inverse correlation exists between levels of HDL and the frequency as well as mortality of atherosclerotic disease [20]. Functionally, HDL is known to remove excess cholesterol from the circulation and inhibit oxidation of LDL. The latter function is accomplished by paraoxonase, an esterase that degrades oxidized phospholipids and which uses HDL as its carrier protein [21]. What is not clear is whether HDL’s angioprotective effect is attributable to these or to other unrelated functions.

Cockerill et al. [22] have reported on the inhibitory effect of HDL on cytokine-induced adhesion molecule expression by human endothelial cells. Based upon previous observations that HDL stimulates endothelial cell PG12 synthesis [23], these same investigators reported that HDL can synergistically increase COX-2 expression in human endothelial cells following cytokine stimulation with either IL-1β or TNFz. The same synergistic increase in COX-2 protein is mirrored by increased PG12 production in these cytokine-stimulated cells [24]. Although HDL clearly has opposing effects on two cytokine-stimulated responses by human endothelium, the results may be additive. On one hand, an increase in PG12, mediated by a HDL-induced increase in COX-2 expression, serves to inhibit platelet aggregation, cholesterol accumulation, and vascular smooth muscle cell proliferation/contraction and thus may be vasoprotective. Concurrently, decreased expression of adhesion molecules on cytokine-induced endothelial cell membranes may also be consistent with an antiatherogenic effect of HDL.
Prostacyclin (PGI2) and thromboxane (TBX)

PGI2 is a metabolite of arachidonic acid and the major prostaglandin produced by endothelial cells. As mentioned earlier, PGII2 is a potent inhibitor of leukocyte activation and adhesion, platelet aggregation, and vascular smooth muscle cell proliferation, migration, and contraction. Its role in vivo, however, has remained unclear. Recently, a knockout mouse deficient in the PGII2 receptor, IP, has demonstrated an antithrombotic as well as antiinflammatory role for PGII2 [25]. It is also well established that PGII2 excretion is increased in patients with ‘activated platelet’ conditions such as unstable atherosclerotic disease as well as following vascular interventional procedures [13]. On one hand, it would not be unreasonable to predict a facilitative role for COX-2 in these conditions of increased PGI2 production, given its inducible nature and the fact that COX-2 is responsible for the majority of PGI2 produced in the body [26]. On the other hand, nonselective NSAID therapy (sulindac and indomethacin) inhibits intimal proliferation and prevents or slows vascular changes in atherosclerosis-prone mice while aspirin and nimesulide (a selective COX-2 inhibitor) do not [9,27].

Clinically, a nagging question arises regarding the lack of inhibition by selective COX-2 inhibitors of thromboxane (TBX), a COX-1 mediated prostaglandin, produced primarily by platelets. Given TBX’s procoagulant and vasoconstricting effects, long-term therapy with COX-2 inhibitors may create a state of chronic, ‘unopposed’ TBX activity with potentially deleterious cardiovascular outcomes. In the VIGOR trial, for example, over 8000 patients with rheumatoid arthritis were randomized to receive either naproxen (500 mg po bid) or rofecoxib (50 mg po q day) for 12 months [28]. Aspirin therapy was excluded in all subjects since the mucosa of the GI tract was being evaluated. Although rofecoxib demonstrated a marked gastroprotective effect, a significantly increased incidence of myocardial infarction occurred in the rofecoxib-treated group. A large percentage of these adverse events occurred in a small subset of patients who were at risk for myocardial infarction and should have been receiving aspirin therapy but were unaware of their risk factors at the time of randomization. These results have been attributed to the lack of antiplatelet activity demonstrated by selective COX-2 inhibitors. As noted recently, selective COX-2 inhibition may offer gastroprotection but not cardioprotection [29].

Conclusion

Clearly, many questions remain to be answered before the role of COX-2 in the atherosclerotic process is understood. COX-2 would be expected to play a role in an inflammatory condition such as atherosclerosis given its inducible nature yet some findings outlined above would contradict such a role (Table 1). Large, long-term trials involving patients at risk for atherosclerotic disease as well as those who require chronic analgesic therapy with COX-2 inhibitors for arthritic and other inflammatory conditions are warranted.

Table 1. Evidence for and against COX-2 inhibition in ASCVD

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<th>Data supporting therapeutic benefit of COX-2 inhibition in ASCVD:</th>
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<tr>
<td>1. Induction of COX-2 by mediators of atherogenesis</td>
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<td>2. Expression found in vascular endothelium, smooth muscle cells, and macrophage/fibrous cells</td>
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<td>3. Expression found in diseased, human coronary arteries as well as allograft vessels</td>
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<td>4. Increased urinary excretion of PGE2 and PGI2 in patients with unstable angina or postangioplasty</td>
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<th>Data contradicting therapeutic benefit of COX-2 inhibition in ASCVD:</th>
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<tr>
<td>1. oxLDL-stressed macrophages decrease prostaglandin production</td>
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<td>2. oxLDL decreases LPS-induced COX-2 expression</td>
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<td>3. oxLDL attenuates cytokine-induced COX-2 mRNA levels</td>
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<td>4. PGE2 and PGI2 exert negative feedback on M-CSF</td>
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<td>5. HDL increases COX-2 expression in human endothelial cells</td>
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<td>6. Noneffective NSAIDs prevent or slow intimal proliferation in ASCVD-prone mice while selective COX-2 inhibitors do not</td>
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ASCVD, atherosclerotic cardiovascular disease.

References

5. Eberhart CE, Hall RJC, Evans TJ et al. 1998; 30: 3–21


