Prostanoids are a large family of lipid mediators derived from the arachidonic acid metabolites of the cyclooxygenase (COX) enzymes. Therapeutically, COX is the target of the nonsteroid antiinflammatory drugs (NSAIDs), a chemically diverse group that includes ibuprofen, naproxen, and diclofenac, among dozens of others. Inhibition of prostanoid production by traditional NSAIDs accounts for all their major therapeutic effects, such as the dampening down of inflammation and the reduction of fever, and their potentially severe adverse side effects, most commonly within the gastrointestinal tract.1,2

Since the early 1990’s it has been clear there are two distinct enzymes responsible for the production of prostanoids: a constitutive COX-1 found in all tissues and an inflammation-associated enzyme COX-2.1,2 COX-2 is constitutively expressed in only a few sites, such as parts of the kidney and central nervous system, but is highly upregulated and active at sites of inflammation. These findings led to the hypothesis that selective COX-2 inhibitors could be antiinflammatory without the major side effects associated with traditional NSAIDs. Against this background several COX-2–selective inhibitors have been produced and brought to market, the first two being celecoxib (Celebrex) and rofecoxib (Vioxx).

Preclinical studies of these COX-2–selective inhibitors were extremely promising. In animal models, for example, they were demonstrated to be as efficacious as traditional NSAIDs but to be lacking their toxic actions on the gastrointestinal tract. Clinical trials have, however, been marred by controversy. The CLASS trial for celecoxib, a 12-month osteoarthritis study of celecoxib, demonstrated celecoxib to have improved safety relative to ibuprofen but not diclofenac at 6 months, but this advantage was absent at 12 months.1–3 Subsequently, however, a shorter 12-week study, SUCCESS-I, has demonstrated celecoxib to have reduced gastrointestinal toxicity compared with naproxen and diclofenac.4 However, the major controversy surrounding the COX-2–selective drugs arose as a consequence of the VIGOR study comparing rofecoxib to naproxen in patients experiencing rheumatoid arthritis.5 Although data from the VIGOR study clearly demonstrated that rofecoxib produced fewer severe adverse events in the gastrointestinal tract than naproxen, it also indicated that significantly more thrombotic events, notably myocardial infarctions, occurred in those taking rofecoxib than in those taking naproxen.1,2,6 More recently data from a placebo-controlled trial for rofecoxib in the prevention of colon cancer recurrence also suggested an excess of thrombotic events after long term, >18 months consumption of rofecoxib, and the drug was withdrawn by the manufacturer.6 Because of the very large scale consumption of NSAIDs and COX-2–selective drugs and the accordingly large potential risk to public health the cardiovascular side effects of COX-2 inhibitors have been under scrutiny over these last few years. Much current evidence suggests that COX-2–selective inhibitors, traditional NSAIDs, and acetaminophen (which also inhibits COX) may all increase the risk of thrombotic events, particularly when taken at high doses for prolonged periods of times.1,2,7

The mechanism, or mechanisms, underlying the increase in thrombotic events associated with the NSAIDs is unclear. One explanation may be found in the observation that COX-2–selective drugs and traditional NSAIDs reduce the body’s production of prostaglandin (PG) I2.8,9 PG I2 is a local hormone that reduces platelet reactivity and increases bleeding time so inhibition of its production could well increase the risk of thrombosis.1,2

The fact that COX-2–selective inhibitors reduce circulating PG I2 levels is intriguing, as although healthy blood vessels are known to contain abundant amounts of both COX-1 and PG I2 synthase there is little evidence for the existence of COX-2,10 In contrast, COX-2 is present after vascular damage, and is highly expressed in atherosclerotic lesions and aortic aneurysms in animal models and human tissue.1,2,11–17 PG I2 is generally protective within the vasculature irrespective of whether it derives from COX-1 or COX-2. It is easy therefore to conceive that as a response to injury COX-2 is induced in the vessel to produce protective vascular PG I2.18 But circumstances may be different in highly inflamed or diseased vessels in which COX-2 is highly expressed and potentially producing large amounts of alternative prostanoids, eg, endoperoxides and PGE2. PGE2 can promote the expression of matrix metalloproteinasises and the cell death associated with tissue destruction and vascular lesion instability.16,19 The roles of COX-2 in inflamed or highly diseased vascular lesions are far from clear, though some limited clinical evidence suggests that COX-2, rather than being protective, produces prostanoids with detrimental actions. PGE2 synthase, for example, is particularly localized in unstable atherosclerotic plaques.19 Interestingly, in patients with acute coronary syndromes dosing with the COX-2–selective drug meloxi-
vasculature tissue, as celecoxib affected neither elevations in blood pressure induced by angiotensin II nor circulating total cholesterol levels.

The role of COX enzymes in chronic inflammatory vascular lesions clearly needs more investigation. COX enzymes are often described as isolated entities, when in reality their functions are controlled by their environment, the level of substrate available, the expression of individual prostanoid synthase enzymes, and the expression and cellular targets of the prostanoid receptors which mediate their actions. The findings of King et al\textsuperscript{21} together with others\textsuperscript{1,2,11–17} indicate that vascular COX enzymes have multiple and varying roles depending on vascular location and environment. Immunohistochemical analyses of large blood vessels shows us that in healthy states COX-1 produces protective PGI\textsubscript{2} constitutively. As an acute response to change or injury protective PGI\textsubscript{2} may also come from induced COX-2. However, in complex chronic inflammatory lesions the environment changes, and COX-2 is expressed at high levels that may lead to the production of deleteriously large amounts of PGE\textsubscript{2} and alternative prostanoids (see the Figure). Within an individual’s vascular tree, under dynamic conditions, all such circumstances could conceivably apply at the same time, with different COX isoforms associated with the production of both protective and deleterious prostanoids at different sites.

### References


COX-2 in Cardiovascular Disease
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