COX-2 in Cardiovascular Disease

David Bishop-Bailey, Jane A. Mitchell, Timothy D. Warner

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 be lacking their toxic actions on the gastrointestinal tract.1,2

Subsequently, however, a shorter 12-week study, SUCCESS-I, has 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

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 risk of thrombotic events, particularly when taken at high doses for prolonged periods of times.1,2,7

The fact that COX-2–selective inhibitors reduce circulating PGI2 levels is intriguing, as although healthy blood vessels are known to contain abundant amounts of both COX-1 and PGI2 synthe there is little evidence for COX-2.2,10 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 PGI2 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 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, 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-
Potential roles of COX enzymes in large vessel vascular disease. Top panel, The healthy vessel. COX-1 is expressed in the endothelium producing protective PGI2. PGI synthase (PGIS) is expressed in both the endothelium and vascular smooth muscle. Middle panel, The acute response stress or injury. Along with endothelial COX-1, COX-2 is induced in the endothelium and underlying vascular smooth muscle to produce protective PGI2 from the constitutively expressed PGIS. Lower panel, The chronic inflammatory vascular lesion. COX-2 along with PGE synthase is induced in macrophages and vascular smooth muscle producing large amounts of deleterious PGE2, which in turn induces tissue destructive metalloproteinases (MMPs) and cell death.

References

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 al21 together with others2,11–17 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 PGI2 constitutively. As an acute response to change or injury protective PGI2 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 PGE2 and alternative prostanooids (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 prostanooids at different sites.


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