Cyclooxygenase-2 Induction in Congestive Heart Failure

Friend or Foe?

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Cyclooxygenase-2, like the other member of the COX family, COX-1, is a bifunctional enzyme that catalyzes the conversion of arachidonic acid to PGG$_2$ via COX activity and PGG$_2$ to PGH$_2$ via peroxidase activity. PGH$_2$ is the precursor for PGs, prostacyclin, and TXA$_2$. Hence, COX-2 occupies a central position in the biosynthesis of proinflammatory PGE$_2$ and vasoactive prostacyclin and TXA$_2$. COX-2 shares with COX-1 most of its catalytic and structural properties. The crystallographic structure of COX-2 reveals a branched substrate channel, as contrasted to a nonbranched, more rigid COX-1 channel structure. This difference in substrate channel structure forms the basis for selective inhibition of COX-2 by newly developed compounds containing a side chain that snugly fits the substrate channel of COX-2 but not COX-1. COX-2 is encoded by a gene $\approx$8 kb in size located on the long arm of chromosome 1 (q25.2–q25.3). The COX-1 gene, on the other hand, is $\approx$22 kb and is located on chromosome arm 9q32–q33. In contrast to COX-1, which is constitutively expressed in most tissues, COX-2 expression is induced in inflammatory cells by a variety of agents, including cytokines, mitogenic factors, PGs, and hypoxia. These agents induce COX-2 transcription by involving different regulatory elements and putative binding sites on the 5’-flanking untranslated region of the COX-2 gene. It has been shown in murine 3T3 cells that COX-2 induction by v-src, platelet-derived growth factor, or serum is mediated by the cAMP response element at -59 to -53. COX-2 induction in bovine endothelial cells by phorbol 12-myristate 13-acetate involves both the cAMP response element and the NF–IL-6 site ($\approx$12 to -124). Induction of COX-2 by tumor necrosis factor-α in a murine osteoblastic cell line, the MC 3T3-E1 cell, requires both the NF–IL-6 site and an NF-κB site at -401 to -393. In the human COX-2 promoter, there is an additional NF-κB site at a more proximal region ($\approx$213 to -222). Preliminary data from our laboratory indicate that this site is required for IL-1–mediated COX-2 induction in cultured human dermal fibroblasts and umbilical vein endothelial cells.

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COX-2 induction in animal inflammation models and human rheumatoid tissues has been investigated extensively. Selective COX-2 inhibitors have been shown to suppress inflammation in these animal models, indicating that COX-2 plays a key role in mediating inflammation. Little is known about COX-2 induction in cardiovascular diseases. In this issue of Circulation, Wong et al have provided intriguing findings of increased COX-2 expression in myocardium of patients with congestive heart failure. They reported increased COX-2 immunostaining in endothelial cells and myocytes of the infarcted myocardium secondary to coronary heart disease. COX-2 staining was also evident in myocytes of myocardial fibrosis due to dilating cardiomyopathy. In myocardium of sepsis, COX-2 was positively stained in myocytes and inflammatory cells. There was a general correlation between COX-2 and NF-κB staining in these cells, implying that COX-2 induction may be mediated by NF-κB activation in the diseased myocardium. These findings suggest that COX-2 induction plays a pathophysiological role in congestive heart failure.

When the COX-2 isoform was discovered and its inducibility was characterized, there was a general acceptance that COX-2 induction is deleterious whereas COX-2 expression is protective. However, this distinction has become less clear as recent studies suggest that under certain circumstances, COX-2 induction may have a protective function. The pathophysiological role that COX-2 plays may depend on a number of factors, among which the cell types and their inherent prostanoid synthetic pathways appear to be the key determinants. Vascular and probably endocardial endothelial cells are endowed with PGIS, which catalyzes the conversion of PGH$_2$ to prostacyclin (PGI$_2$). PGIS is constitutively expressed, and a recent study has shown that it is induced by cytokines. Hence, in endothelial cells, an overexpression of COX-2 increases the synthesis of vasoprotective PGI$_2$. PGI$_2$ inhibits platelet aggregation and vasoconstriction and synergizes with nitric oxide in suppressing monocyte activation and its adhesion to the endothelial surface. A concept is emerging that COX-2 induction in endothelial cells represents an important compensatory mechanism to defend against vascular injury. COX-2 induction in endocardial endothelial cells may be cardioprotective, as suggested by increased cardiac fibrosis in COX-2–deleted mice. In contrast, monocyte-macrophages and fibroblasts do not express PGIS, and induced COX-2 expression in these cells results in increased synthesis of PGE$_2$ and TXA$_2$, which mediate inflammatory change, vasoconstriction, and platelet aggregation. Increased synthesis of these 2 prostanoids is considered to play an important role in inflammation and tissue injury. Hence, induction of COX-2 in macrophages and fibroblasts, as detected in the myocardium of patients with sepsis, is expected to contribute significantly to myocardial inflamma-
tion, injury, and fibrosis. On the other hand, induced expression of COX-2 in endothelial cells, as observed in myocardial infarct tissues, may represent a compensatory protective mechanism. It would be interesting and important to determine whether selective COX-2 inhibitors have a differential effect on congestive heart failure due to various etiologies.

References

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