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 PGG2 via COX activity and PGG2 to PGH2 via peroxidase activity. PGH2 is the precursor for PGs, prostacyclin, and TXA2. Hence, COX-2 occupies a central position in the biosynthesis of proinflammatory PGE2 and vasoactive prostacyclin and TXA2. 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 ∼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 ∼22 kb and is located on chromosome arm 9q32–q33.3. 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 (−124 to −122). 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 the 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 (−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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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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