The potential of specific COX-2 inhibition

Continued laboratory breakthroughs and ongoing clinical trials suggest a new important role for the cyclooxygenase enzyme (COX) in biomedical research. COX is the rate-limiting enzyme in the production of prostaglandins and, as such, is a key target for anti-inflammatory drugs. Indeed, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are COX inhibitors. There are two known COX isoforms, COX-1 and COX-2, with distinct expression patterns and biological activities. COX-1 is a constitutively expressed protein found in most tissues, while COX-2 expression can be induced by a variety of mitogens, including cytokines, hormones and phorbol esters. Inflammatory stimuli have little effect on COX-1 expression, but lead to a rapid rise in COX-2 expression, suggesting a primary role for COX-2 in inflammation. The clinical significance of COX-2 and therapeutic strategies for targeting this isoform were discussed at the IBC's *Second Annual Conference on COX-2 Inhibitors* in Coronado (CA, USA). Information presented at the conference is summarized below.

As most cells appear to express constitutive COX-1, why do cells need an inducible COX-2 gene?

Harvey Herschman (University of California, Los Angeles, CA, USA) presented evidence showing that in mast cells, two pools of arachidonate are released by distinct phospholipases from cells following stimulation, and are differentially presented to COX-1 and COX-2 (Ref. 1). Thus, for the mast cell, and presumably for other cell types as well, COX-1 and COX-2 might differentially compartmentalize or channel prostaglandin synthesis in the cell.

Recent studies suggest that COX-2 might be important in many clinical disorders. For example, in ischaemia-mediated neurodegeneration, COX-2 is induced in injured neurons that are likely to die, and the time course of this induction is prolonged in the neuronal population that undergo delayed neuronal death[2]. Furthermore, in colon cancer, COX-2 is constitutively expressed in early neoplastic cancer[3], while COX-2 is not expressed in the normal colon or small bowel. In the Alzheimer's disease brain, COX-2 content is elevated by nearly twofold in comparison to non-AD controls, and COX-2 induction correlates strongly with β-amyloid (Aβ)-plaque density and Aβ1-40 content in the same brain region[4].

How COX-2 might contribute to such varying types of apparently unrelated disorders is a timely question. In general, it is recognized that the action of COX-2 products and the patterns of prostanoid release depend on the availability of secondary metabolizing enzymes for prostaglandin H_2, as well as on the type of prostanoid receptors present on the target tissue. For example, human vascular smooth muscle cells are a rich source of prostacyclin synthetase, but normally contain little COX activity. Under challenges of injurious stimuli, human vascular smooth muscle cells respond by inducing COX-2 expression to support the enhanced release of the vasoprotective prostacyclin[5]. With respect to nociceptive pain, prostanoid receptor-mediated sensitization of sensory nerve fibres is a key contributor to the generation of hyperalgesia. Both PGE_2 and PGI_2 prostanoid receptors are present on sensory neurons[6].

Therapeutic efficacy of COX inhibition

Recent studies have revealed possible therapeutic efficacy of COX inhibition. Epidemiological studies have demonstrated that COX inhibitors (active against both COX-2 and COX-1) appear to reduce the risk of colorectal cancer[7] and slow down the course of dementia in Alzheimer's disease[8]. In animal model systems, COX inhibitors provide neuroprotection in brain ischaemia[9] and radiation injury in the brain [Kyrkanides, S.J.A. *et al.* (University of Rochester, New York, NY, USA), unpublished observation]. Based on the role of COX-2 in these disorders, it has been postulated that COX-2 should be the specific therapeutic target. As COX-1 appears to be involved in the maintenance of essential physiological functions such as platelet aggregation, cytoprotection in the stomach and maintenance of normal kidney function, specific COX-2 inhibitors, by virtue of sparing COX-1, should possess a markedly improved side effect profile. Two COX-2 specific drugs, Rofecoxib (Merck & Co.) and Celecoxib (Searle & Pfizer) have demonstrated their potential for the same clinical efficacy as the standard non-specific COX inhibitors, without the associated gastrointestinal toxicity or platelet and renal activity. These, and related, COX-2 specific inhibitors represent promising therapies for ischaemia, cancer and Alzheimer's disease, as well as for pain management.

In addition to COX-2 inhibitors, therapeutic strategies directed against COX-2 might also be exerted at the level of either COX-2 transcription or prostanoid receptors. Hiroyasu Inoue (National Cardiovascular Centre Research Institute, Osaka, Japan) presented evidence that COX-2 gene expression in different cell types is distinctly regulated through identical *cis*-acting elements[10]. Understanding COX-2 gene regulatory mechanisms could provide clues for the development of a novel COX-2 inhibitor at the transcription level. Lastly, although activation of the EP or IP prostanoid receptors contributes to pain conditions, it is not known which prostanoid receptor dominates. Should one of the four PGE_2 receptor subtypes or the PGI_2 receptor be shown to the major mediator of sensitization process, then an important pain drug discovery target will have been identified.

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Collaborations...

A development, commercialization and collaboration agreement has been signed by **Bristol-Myers Squibb Co.** (BMS, Princeton, NJ, USA) and **Otsuka Pharmaceutical Co.** (Tokyo, Japan) for aripiprazole, a novel drug currently in Phase III trials as a treatment for schizophrenia. As part of this agreement, BMS will market and promote the drug under Otsuka's trademark in the US and the EU, but will have an exclusive license in all other countries except Japan and some Asian and Middle-Eastern countries. The two companies will collaborate to complete the clinical trials for schizophrenia and BMS will conduct additional studies for new dosage forms and new indications. A regulatory filing for schizophrenia in the US is planned for late 2001.

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