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Review Article

Remembering Cyclooxygenases: A Brief Review

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ABSTRACT

Non-steroidal anti-inflammatory drugs are the competitive inhibitors of cyclooxygenase, the enzyme which bioconvert the arachidonic acid to inflammatory prostaglandins. Although their use is associated with the side effects such as gastrointestinal and renal toxicity they are one of the widely prescribed drugs. The therapeutic anti-inflammatory action of NSAIDs is produced by the inhibition of COX-2, while the undesired side effects arise from inhibition of COX-1 activity. Based upon that, a number of selective COX-2 inhibitors (Rofecoxib, Celecoxib, Valdecoxib etc.) were developed as safer NSAIDs. However, the recent market removal of some COXIBs such as Rofecoxib due to its adverse cardiovascular side effects clearly encourages the researchers to explore and evaluate alternative templates with COX-2 inhibitory activity. Recognition of new avenues for selective COX-2 inhibitors in cancer chemotherapy and neurological diseases such as Parkinson and Alzheimer's diseases still continues to attract investigations on the development of COX-2 inhibitors. This review highlights the therapeutic profile as well as the future therapeutic potential of COX inhibitors with highlighting their disadvantages as well.

Key-words: Cyclooxygenases, NSAIDS, Prostanoids, Prostaglandins

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Introduction

Professor John Vane won the Nobel Prize for elucidating the mechanism of action of aspirin. He reported that aspirin act by blocking the enzyme called cyclooxygenase (COX-1) that was responsible for the conversion of arachidonic acid to prostaglandins. Prostaglandins liberated from arachidonic acid by cyclooxygenase are short-lived substances that act as local hormones (autocoids) important in normal physiology and pathologic conditions.[1,2]

Since that discovery, many nonsteroidal anti-inflammatory drugs (NSAIDs) have come on the market, and they represent the most widely prescribed class of drugs in the world. The success of NSAIDs in treating various inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA) validated inhibition of the enzyme prostaglandin H synthase (PGHS) orcyclooxygenase (COX) as a highly suitable target in anti-inflammatory therapies.[3,4]

The term 'eicosanoids' designate a group of oxygenated twenty carbon fatty acids.[5] The major precursor of these compounds is arachidonic acid (all cis 5, 8,11,14-eicosatetraenoic acid), and the pathways leading to the eicosanoids are known collectively as the 'arachidonate cascade'. There are three major pathways within the cascade, including the cyclooxygenase, lipoxygenase, and epoxygenase pathways. In each case, these pathways are named after the enzyme(s) that catalyzes the first committed step. The prostanoids, which include the prostaglandins and thromboxanes, are formed via the cyclooxygenase pathway.[6]

Prostanoids particularly prostaglandins (PG's) are end products of fatty acid metabolism produced via the COX pathway. PG's have long been known to behave as important physiological and pathological mediators implicated in a number of therapeutic areas of interest including inflammation, pain, pyrexia, cancer, glaucoma, male sexual dysfunction, osteoporosis, cardiovascular disease, labour and asthma.[7]

Arachidonic acid (AA), an unsaturated 20-carbonfatty acid embedded in cell membranes as a phospholipid ester, is the precursor for PG synthesis. In response to a wide variety of stimuli, free AA is released which is subsequently converted via COX, lipoxygenase (LOX) and cytochrome P450 enzyme catalysis to various lipid mediators known collectively as eicosanoids.[5] In the COX pathway, the two known COX isoforms catalyse the first committed step in the biosynthesis of PG's, thromboxanes (TxA) and other eicosanoids.[5,7,8] The production of these eicosanoids is dependent on the availability of AA. The release of AA from membrane phospholipids is mediated by either secretory (sPLA2) or cytoplasmic (cPLA2) phospholipases. Once AA is released, the COX isoforms catalyze two sequential reactions. The initial COX reaction converts AA to prostaglandin G2 (PGG2). The subsequent peroxidase (POX) reaction reduces PGG2 to prostaglandin H2 (PGH2) which is then converted by various cell specific isomerases and synthases to produce five biologically active primary PG's that include prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostacyclin (PGI2) and thromboxane A2 (TxA2).These products act as secondary messengers by interacting with prostanoid G-protein coupled receptors and other receptors.[5]

COX activity has long been studied in preparations from sheep seminal vesicles and this enzyme was cloned by three separate groups in 1988. The discovery of a second form of COX in the early 1990s was the most important event in prostanoid biology in almost 20 years.[9]

COX, originally called prostaglandin H synthase (PGHS), is the major enzyme responsible for oxidation of AA to PGG2 and PGH2. The COX-1 and COX-2isoforms both catalyze a cyclooxygenase reaction in which the substrate AA and two molecules of molecular O2 are converted to PGG2 and a peroxidase reaction in which PGG2 is reduced toPGH2 by a two electron reduction. These two

reactions occur at distinct but structurally and functionally interconnected sites. The COX isoforms are heme containing enzymes that exhibit distinct expression profiles and roles in several physiological processes. The primary structure of COX-1 is comprised of 602 amino acids whereas COX-2 has 604 amino acids. [10]

TheCOX-1 and COX-2 isoforms share 60-65%sequence identity within species and about 85-90% sequence identity among different species (Yokoyama et a;,1988). The COX isoforms are homodimers, with each monomer comprised of three structural domains; aN-terminal epidermal growth factor (EGF) domain, a membrane binding domain and a large Cterminal catalytic domain.[10]

Both COX-1and COX-2 isoforms are attached to the endoplasmic reticulum (ER) and nuclear envelope. N-glycosylation of the COX isoforms is required for enzyme folding and activity.[5,12]

The COX-1 isoform is constitutively expressed at high levels in cells and tissues such as endothelium, monocytes, platelets, renal collecting tubules and seminal vesicles indicating that it is developmentally regulated.[13] The COX-2enzyme is induced by mediators of inflammation such as lipopolysaccharides (LPS), interlukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α) in a wide variety of cells and tissues such as vascular endothelium, osteoclasts, rheumatoid synovial endothelial cells, monocytes and macrophages. Recent studies have indicated that constitutively expressed COX-2 plays specific functions in reproduction, renal physiology, bone resorption and neurotransmission.[14,15]

COX-2 is constitutively expressed under basal conditions in many areas of the central nervous system too. Most information on localization is based on animal studies. The highest levels in the CNS have been found in the hippocampus associated with granule and pyramidal cell layers. Moderate levels have been found in pyramidal cell, piriform cortex, neocortex, and amygdala. Lower levels have also been found in caudate-putamen, thalamus, hypothalamus, striatum, and preoptic levels. Increased levels have also been found in cortical neurons in response to natural N-methyl D-aspartic acid (NMDA) receptor-mediated neuronal activity. Expression here may be involved in modulation of pain which suggests that blocking COX-2 centrally may be important in control of pain.[16,17]

The genes for COX-1 and COX-2 are located on separate chromosomes, with COX-1 on chromosome 9 and COX-2 on chromosome 1. The COX-2 gene is smaller than COX-1.

Exons 1 and 2 of COX-1 (containing the translation site and original peptide) are condensed into a single exon in COX-2. The introns of COX-2 are smaller than COX-1. COX-2 has a TATA box promoter and COX-1 lacks a TATA box. These features differentiate the gene for COX-1 into a gene consistent with rapid transcription and mRNA processing for processing a continuously transcribed stable message. This provides for a constant level of enzyme in most cell types to synthesize prostaglandins responsible for homeostatic functions. In contrast, the features of the COX-2 gene are those of an "immediate-early" gene that is not always present but is highly regulated and upregulated during inflammation or pathological processes.

Traditional NSAIDs prescribed to control joint pain and treat inflammatory conditions such as RA and OA produce their anti-inflammatory and analgesic effects by nonselective inhibition of COX activity. During the inflammatory process, the COX-1mRNA and protein activity do not change whereas a dramatic increase in COX-2 levels occurs leading to increased production of proinflammatory PGs. The GI side effects associated with traditional NSAIDs are due to the inhibition of gastroprotective PGs synthesized via the COX-1 pathway. [18,19] The baseline production of prostaglandins not inhibited by glucocorticoids was considered to be the constitutive or "housekeeping" prostaglandins important in the protection of the gastrointestinal tract, regulators of renal blood flow, and functioning in platelet aggregation.

Induction of COX-2 enzyme is associated with inflammation. The COX-1 enzyme does not appear to be affected by the inflammatory process since similar levels of mRNA and protein are detected in both normal and inflamed tissue in animal models.[10]

PGs such as PGE2 and PGI2 produced via the COX-2 pathway magnify the degree of inflammation initiated by other mediators of inflammation such as histamine and bradykinin leading to increased vascular permeability and edema. Inhibition of COX-2 by NSAIDs gives an anti-inflammatory effect, whereas inhibition of COX-1 would result in adverse effects such as gastrointestinal toxicity and nephrotoxicity.

The main reason for labeling COX-1 and COX-2 as physiological and pathological, respectively, is that most of the stimuli known to induce COX-2 are those associated with inflammation, for example, bacterial lipopolysaccharide(LPS) and cytokines such as interleukin (IL)-1, IL-2, and tumor necrosis factor(TNF)-α. The anti-inflammatory cytokines, IL-4, IL-10, and IL-13, will decrease induction of COX-2, as will the corticosteroids.[20,21] The physiological roles of COX-1 have been deduced from the deleterious side effects of NSAIDs, which while inhibiting PG biosynthesis at inflammatory sites, also inhibit constitutive biosynthesis. Thus, COX-1 provides PGs in the stomach and intestine to maintain the integrity of the mucosal epithelium and its inhibition leads to gastric damage, haemorrhage, and ulceration.[9]

Gastrointestinal ulceration and bleeding, renal damage, and platelet dysfunction—were accepted as inevitable consequences of the inhibition of COX activity required to prevent synthesis of PGs in inflammatory conditions such as rheumatoid orosteo-arthritis. Now with COX-2 clearly associated with inflammation but not with the physiological synthesis of PGs, selective inhibitors of COX-2 offered the possibility of inhibition of inflammatory PGs without affecting PGs generated by COX-1 in the stomach, kidney or platelet: "an aspirin without ulcers."This possibility has generated a great deal of effort and a considerable degree of success in pharmaceutical research.[9]

But ,in addition to its implication in the kidney development, COX-2 plays an important role in the regulation of renal function (perfusion, water handling, and renin release) in both normal and paraphysiological conditions (i.e., in patients with liver cirrhosis, renal insufficiency or congestive heart failure). These patients are, therefore, at risk of renal ischemia when NSAIDs and/or selective COX-2 inhibitors reduce vasodilatory PG synthesis.[22] Moreover, cyclic hormonal induction of COX-2 is important for ovulation and, at the end of pregnancy, high uterine levels of COX-2 are necessary for the onset of labor. As a result, like for classical NSAIDs, the use of selective COX-2 inhibitors should be avoided in the early stages of pregnancy whereas they should be useful in delaying premature delivery.[23,24]

Further, COX-2 may be involved in the ''adaptative cytoprotection'' response in GI mucosa. When the latter is inflamed or ulcerated, COX-2 is rapidly induced at sites of injury where it produces large amounts of PGs involved in the healing process. So, selective COX-2 inhibitors should be avoided in patients with gastric susceptibility.[25]

In addition, selective inhibitors of COX-2 depress prostacyclin (PGI2), an atheropro-tective agent. Thus, the use of these compounds in cardiovascular diseases still requires vigilance. [26] Rofecoxib (Vioxx) was withdrawn voluntarily by Merck from the market in September 2004 following the increased cardiovascular risks observed in Adenomatous Polyp Prevention on Vioxx (APPROVe) study. Subsequently, the sale of Bextra (valdecoxib) was also suspended by Pfizer in 2005. This raised a question on the safety of selective COX-2 inhibitors. However, no increased risk of cardiovascular

thrombotic events was evident in Celecoxib Long Term Arthritis Safety Study (CLASS) trial conducted on celecoxib.[27]

A meta-analysis of published and unpublished tabular data from randomized trials revealed that selective COX-2 inhibitors and traditional NSAIDs (high dose regimens of ibuprofen and diclofenac) have similar incidence of adverse cardiovascular events.[28]

The mechanism underlying the adverse cardiovascular effects associated with the use of COX inhibitors is due to an imbalance between COX-1 derived thrombotic thromboxane A2 (TXA2) in platelets and COX-2 derived vasoprotective prostacyclin (PGI2) in endothelium.[27]

Currently available NSAIDs have the ability to inhibit both COX-1 and COX-2 by binding reversibly or irreversibly to the enzyme. The major toxicities of NSAIDs are thought to be due to their ability to block synthesis of the housekeeping prostaglandins (those in the kidney, stomach, and platelets) by inhibition of COX-1. Inhibition of COX-2 does not affect these prostaglandins but stops the synthesis of prostaglandins involved in inflammation. Most of the current NSAIDs exhibit some degree of selectivity in their ability to differentially block COX-1 or COX-2.[29]

COX2 beyond inflammation

Carcinogenesis — COX-2 may be upregulated in some forms of cancer including colon cancer. Epidemiologic studies have demonstrated a decreased rate of colon cancer inpatients taking NSAIDs. Research is ongoing to determine if COX-2 inhibition may be beneficial in prevention of cancer. In a neural model of multiple prognosis, COX-2 is upregulated in the precancerous areas compared to normal tissue.

COX-2 affects many processes that have been implicated in different stages of carcinogenesis. These include xenobiotic metabolism, cell proliferation, angiogenesis, apoptosis, immune function and tumor invasiveness.[30,31]The peroxidase part of COX can convert the procarcinogens to carcinogens and thus initiate tumor formation. Substantial amounts of xenobiotics (natural non-human organic compounds) can be co-oxidized into mutagens by the peroxidase activity of COX.[32]

Apoptosis — Apoptosis, the morphologically defined form of programmed cell death, plays a crucial role in the carcinogenesis. The disegulation of this process can lead to abnormal survival of cells and the increased risk of mutagenesis and oncogenesis.[31]

COX-2-derived PGs regulate programmed cell-death and reduce the apoptotic rate via inhibition of the mitochondrial apoptotic pathway characterized through reduced cytochrome c release, attenuated caspase-9 and -3 activation and upregulation of bcl-2.[31,33]

Over expression of COX-2 in some cell lines is associated with the expression of Bcl-2, a protein that acts to make cells resistant to apoptosis. In addition, overexpression of COX-2 is associated with decreased expression of transforming growth factor-beta (TGFbeta).TGF-beta is important for transducing signals that inhibit cell growth. Both of these effects were blocked with NSAIDs. It is hypothesized that if cells were resistant to apoptosis and/or allowed to grow indefinitely, such cells may be responsible for either autoimmune disease or neoplasia.[34]

Further, MDR-1 (or P-glycoprotein), is an efflux pump for chemotherapeutic drugs and thereby contributes to multidrug resistance. Overexpression of COX-2 has been found to increase the production and function of MDR-1 in cells in culture, an effect that was prevented by treatment with a selective COX-2 inhibitor. Although much work is required to establish the clinical significance of this interaction, it is appealing to speculate that selective COX-2 inhibitors will enhance the anti-tumor activity of cancer chemotherapy by reducing the multidrug resistance.[35]

COX-2 in CNS may have an ambivalent functionality since the basal production of PGs through COX-2 may participate in neuronal homeostasis, whereas the expression of COX-2 is associated with brain development.[36]

Since COX-2 expression in the brain and PGE2 content in the cerebrospinal fluid have been reported to be elevated in Alzheimer's disease together with the finding that COX-2 protein levels in the brain correlate with the severity of amyloidosis and clinical dementia, thus COX-2 inhibition by NSAIDs might be involved in the apparent protection in this setting.

COX-2 is constitutively expressed at high levels in brain and is specifically concentrated in pyramidal neurons which are vulnerable to AD pathology. On the other hand, COX-1 is not constitutively expressed in brain at high levels but is upregulated in reactive microglia, the target for inflammatory suppression. So far, COX-2 has not been detected in astrocytes and microglia in AD and is barely induced with the inflammatory mediators in AD. It would be anticipated, therefore, that NSAIDs 1 rather than selective COX-2 inhibitors would be more likely to reduce the brain inflammation selectively.[37,38]

However, recent studies have shown that the relation between the two isoforms is not so straightforward. Indeed, COX-1 may contribute to the inflammation processes whereas COX-2 is constitutively expressed in several tissues and organs such as brain,[39] kidneys,[40] and reproductive tract.[41]

In 2002, the group of Daniel Simmons characterized and cloned a COX enzyme in dog brain which, unlike COX-1 and COX-2, was sensitive to inhibition with paracetamol (acetaminophen). This COX enzyme was a variant of COX-1 and derived from the same gene; it was designated as COX-3. This variant is produced by alternative splicing of the COX-1 gene. The only difference is the retention of intron 1 of the COX-1 gene in COX-3.[36]

COX-3, which contributes about 5% of total COX-1, is a 65-kDa membrane protein whose cyclooxygenase activity is about 80% lower than that of COX-1. This suggests that intron 1 retention may modify the conformation of the active site. Preferential expression of COX-3 in the brain and heart has been reported.[42,43] In addition to COX-3, two shorter variants without cyclooxygenase activity have been identified, PCOX-1a and PCOX-1b. The function of these two inactive, truncated COX-1 variants is unknown.[44] COX-3 is considered to play a key role in the biosynthesis of prostanoids known to be important mediators in pain and fever. Drugs that preferentially block COX-1 also appear to act on COX-3.[42]

Conclusion

NSAIDs are the most widely prescribed drugs on the market and are effective for decreasing pain, inflammation and related pathologies. Their mechanism of action was discovered to be the inhibition of cyclooxygenase. Prostaglandins derived from the action of COX-1 are considered to be the constitutive or "housekeeping" and are important for platelet aggregation, renal blood flow in the impaired kidney and cytoprotection in the stomach etc. Prostaglandins derived from COX-2 are inducible and upregulated in areas of inflammation. They do not exist in the basal state. Although they share 60% structural homology, they constitute two completely different systems with different functions in the human body. New and exciting roles in humans for inhibition of COX synthesis other than pain control are now being investigated. The powerful techniques of molecular biology have rapidly provided detailed knowledge of the COX-1 and COX-2 proteins. Now, COX 3 has come to limelight and more physiological roles of COX 2 are being investigated which soundly implies that the importance and COX as therapeutic opportunity seems too difficult to ignore.

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