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Peter E. Lipsky, M.D.

COX-2 INHIBITORS: SOMETHING NEW OR MORE OF THE SAME

Rheumatic Diseases Division
Simmons Arthritis Research Center
University of Texas Southwestern Medical Center at Dallas

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Peter E. Lipsky, M.D.
Professor of Internal Medicine and Microbiology
Director, Rheumatic Diseases Division
Director, Harold C. Simmons Arthritis Research Center

Dr. Lipsky is the Director of the Simmons Arthritis Research Center. His research interests center on the immunologic basis of autoimmune diseases.

ABSTRACT

Originally suggested to function mainly in inflammatory situations, recent data have implied important roles for the cyclooxygenase-2 (COX-2) isoenzyme in reproductive biology, renal and neurologic function, and the anti-thrombotic activities of endothelial cells. As COX-2 specific inhibitors have recently become available as analgesic and anti-inflammatory drugs, a comprehensive view of this rapidly evolving field is necessary to anticipate both the potential therapeutic benefits and toxicities associated with these agents.

INTRODUCTION

Since the synthesis of aspirin 100 years ago, nonsteroidal antiinflammatory drugs (NSAIDs) have become mainstays in the medical management of pain and inflammation (1). The common but perhaps not the only mechanism underlying NSAID activity, inhibition of the cyclooxygenase enzyme that catalyzes the initial step of arachidonic acid metabolism became clear in the early 1970s (2), and served to encourage the development of an NSAID class that now includes of over 30 compounds. Despite the capacity of these agents to suppress pain, inflammation and fever (3), and the expansion of the use of these agents into one of the most widely used classes of drugs in the world, mechanism-based toxicity related to the suppression of the production of specific arachidonic acid metabolites in individual tissues and organs (4) has limited unmitigated acceptance of these compounds. Moreover, this mechanism-based toxicity has stimulated research into the possibility that less toxic analgesic and anti-inflammatory agents could be developed.

Within the past ten years, COX activity was found to be associated with two distinct isozymes, COX-1 and COX-2 (1,5-7). Initial evidence suggested that COX-1 was expressed constitutively within many tissues and thought to be responsible for homeostatic production of arachidonic metabolites. In contrast, COX-2 was felt not to be expressed normally, but to be rapidly induced in response to inflammatory stimuli and to be responsible for the large amounts of prostaglandin E_2 and other arachidonic acid metabolites produced at inflammatory sites. This generated the hypothesis that the functions of the COX isoforms were mutually exclusive, with COX-1 involved in maintenance of the physiologic function of a variety of organs and COX-2 involved in pathophysiologic processes, including inflammation, pain and fever. This hypothesis was sufficiently compelling that before it was rigorously tested, it served as the rationale to develop specific COX-2 inhibitors, agents that at therpeutic doses block the activity of COX-2 but not COX-1, with the anticipation that these agents would have all of the anti-inflammatory and analgesic properties of standard NSAIDs, but lack the well recognized toxicities related to COX-1 inhibition (8,9). Clinical trials with two of these agents (Figure 1) has produced results that have been consistent with this general paradigm and have lead to the approval of these agents for the treatment for osteoarthritis (celecoxib, rofecoxib), rheumatoid arthritis (celecoxib) and acute pain (rofecoxib) (10,11). However,

newly emerging information has challenged some aspects of the original model, documenting much wider physiologic roles for both COX-1 and COX-2. This information has altered some aspects of the anticipated outcome of treatment with specific COX-2 inhibitors, but also expanded their potential therapeutic indications.

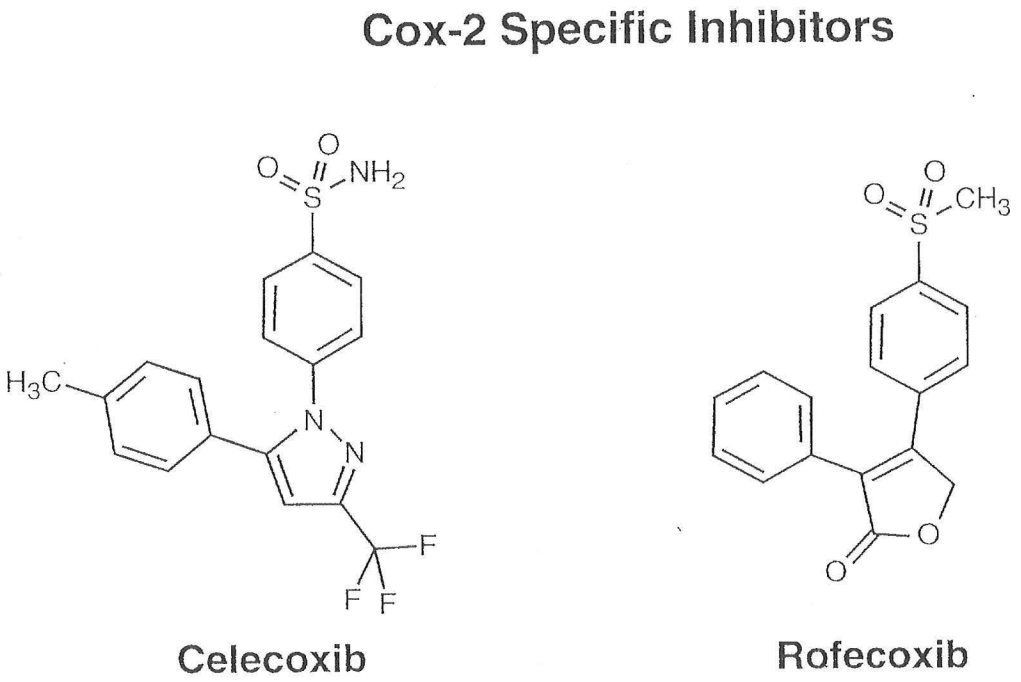

Figure 1

Discovery of COX-2

Although a multitude of NSAID actions have been proposed, the ability of NSAIDs to suppress inflammation and inflammatory pain results primarily from their inhibition of arachidonic acid metabolism and specifically prostaglandin E_2 production (1-4,12,13). Because arachidonic acid metabolites also maintain gastric mucosal integrity (PGE_2, prostacyclin) and platelet function (thromboxane A_2), as well as renal blood flow,

especially in the face of volume contraction, inhibition of arachidonic acid metabolism also explains the mechanism based toxicity of NSAIDs, including gastrointestinal ulceration and bleeding and diminished renal function (4,14-23).

Also called prostaglandin H synthase (PGHS), COX is the first enzyme in the prostanoid biosynthetic pathway catalyzing the conversion of arachidonic acid to PGG_2 and then to PGH_2 (1-7). Subsequent activity by a variety of other specific enzymes results in the characteristic array of arachidonic acid metabolites produced by individual cells and tissues. It is the regulated production of those specific metabolites that determines the unique and often opposing dominant effects of arachidonic acid metabolites at specific tissue sites. For example, platelet derived thromboxane (TXA_2) favors platelet aggregation and thrombosis that is opposed by the vasodilatory effects of endothelial cell derived prostacyclin (PGI_2).

In the late 1980s, it was shown that expression of COX activity could be markedly stimulated by interleukin-1 in fibroblasts and monocytes and inhibited by corticosteroids (24-26). This was important because prostaglandin production was previously thought to be determined only by the amount of arachidonic acid substrate present. Based upon this work, the existence of two distinct forms of COX was proposed, one constitutive and one inducible (25). Since that time, separate genes for the two isoenzymes have been cloned (27-29) and regulation and expression of the two proteins have been delineated, providing clues to their proposed distinct biologic roles (1,5-7).

The genes for the two COX isoforms are approximately 65% homologous in their coding regions and, as a result, the proteins are quite similar with comparable enzymatic activities and substrate specificities. One potential difference in the enzymatic activities of the two isoforms is the source of the arachidonic acid substrate, with COX-2 utilizing intracellular arachidonic acid and COX-1 employing extracellular substrate (5,30,31). Soluble phospholipase A_2 ($sPLA_2$), produced by a variety of cells, appears to be important in providing extracellular arachidonic acid substrate for COX-1 (5,30,31). As the amount of substrate might be an essential contributor of arachidonic acid metabolite production by COX-1, regulation of $sPLA_2$ rather than COX-1 itself may provide the crucial influence of the metabolic activity of the COX-1 isoform.

One additional difference between COX-1 and COX-2 emerged from analysis of the three dimensional structures of the molecules (32,33-35). A subtle difference in the structures of the hydrophobic channel leading to the active site of the COX-2 molecule has been identified, with a somewhat larger orifice and an additional pocket pointing away from the catalytic site. This has permitted the development of inhibitors that block the activity of COX-2 specifically at concentrations that have only minimal effects on COX-1 (8,9). In general, COX-2 inhibitors differ from classic competitive inhibitors in that they require time to fit into the active site of the enzyme, after which their inhibitory effects may become persistent. Of note, the same compound may function as a competitive inhibitor of COX-1 at high concentrations and a "timed inhibitor" of COX-2 at markedly lower concentrations, owing to the unique configuration of the hydrophobic channel leading to the active site of the COX-2 isoform. Of importance, the differences

between the mechanisms of inhibition of COX-1 and COX-2 can influence the estimation of the activity of a putative inhibitor when analyzed only with isolated enzymes or intact or broken cells.

The homeostatic versus pro-inflammatory theory of cyclooxygenase actions:

Analysis of the expression of COX-1 using monoclonal antibodies and molecular probes has documented that this isoform is expressed constitutively in many cells and tissues (36). Of importance, in certain tissues and cells such as the normal gastric mucosa and the platelet, COX-1 is the only isoform expressed. In the gastric antrum, local production of PGE_2 and PGI_2 synthesized via the action of COX-1 promotes vasodilatation thereby promoting the maintenance of mucosal integrity (21-23). Similarly, in the kidney, COX-1 is important in producing vasodilatory prostaglandins that maintain renal blood flow and the glomerular filtration rate, especially during periods of systemic vasoconstriction (37,38). Finally, in platelets, the action of COX-1 is essential for the production of thromboxane A_2 (TXA_2) that promotes platelet aggregation (39). These findings stimulated the concept that the major, if not the only, function of COX-1 was to maintain homeostasis and promote specific physiologic activities.

In contrast to the constitutive expression of COX-1 and its putative role in homeostatic regulation of physiologic processes, the COX-2 enzyme was initially noted to be undetectable in most normal tissues and cells (5-7,36). However, when a variety of cells, such as macrophages and endothelial cells, were challenged with various inflammatory mediators, COX-2 expression was rapidly induced. Moreover, at sites of inflammation, such as the rheumatoid synovium, COX-2 was dramatically upregulated (40-42). Finally, in animal models of inflammation, COX-2 mRNA and protein, but not COX-1, were dramatically upregulated at the inflammatory site by the evoking stimulus and just before the marked increase in local prostaglandin production and clinical manifestation of inflammation (43). This evidence suggested the hypothesis that COX-2 was an inducible enzyme that was markedly upregulated at sites of inflammation and accounted for the increased production of arachidonic acid metabolites locally and the resultant vasodilitation, edema and pain.

This information provided the basis for the hypothesis that COX-1 was involved in cellular "housekeeping functions" necessary for normal physiologic activity whereas COX-2 acted primarily at sites of inflammation to amplify pain and pro-inflammatory manifestations. The clinical corollary to this hypothesis was that highly specific inhibition of COX-2 would exert beneficial antiinflammatory and analgesic effects without influencing the important physiologic functions of COX-1. Since all currently available non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2 to varying degrees (16,17) by competing with arachidonate for binding to the active site of the enzyme, this line of reasoning suggested that the toxicity of these agents might be related to their capacity to inhibit COX-1, whereas their analgesic, anti-inflammatory and anti-pyretic effects might depend on their ability to inhibit COX-2. The potential of segregating the "good" from the "bad" actions of NSAIDs stimulated the search for agents that inhibited COX-2 specifically.

Evolving knowledge of the biology of COX-1 and COX-2 has suggested that the initial paradigm is an oversimpli-fication. Although COX-2 is induced at sites of inflammation, a critical role for COX-2 in a number of other physiologic processes has emerged. Moreover, in certain circumstances COX-1 has been shown to be induced (44-46) and to play a protective function (47), or to contribute to inflammatory responses (48). Thus, a more complex interplay of COX-1 and COX-2 in physiology and pathophysiology has emerged with certain unexpected outcomes resulting from targeted disruption or inhibition of specific COX isoforms. Moreover, a role for COX isoforms in unanticipated physiologic or pathophysiologic processes has emerged, suggesting unexpected therapeutic opportunities or consequences of specific COX-2 inhibition.

Emerging Complexity: Diverse Physiological and Pathophysiological Roles for COX-1 and COX-2

Emerging information suggests that both COX-1 and COX-2 play broad and complex physiologic and pathophysiologic roles. Animal data, for example, demonstrate that COX-2 is expressed constitutively in the kidney (49,50) and brain (51-53) and can be induced by physiologic stimuli in the kidney, brain, the ovary, uterus, cartilage, and bone (49,54-66). Conversely, COX-1 can be induced in response to injury, as for example in the crypt cells of the small intestine after radiation injury and play a role in regeneration (47). COX-2 appears to play an important role in a number of essential physiologic functions such as ovulation and implantation (55,57), whereas COX-1 may play a critical role in inflammation, especially when it is induced by extracellular arachidonic acid or occurs in the skin (48). These findings have provided a more complex model of the interplay of COX-1 and COX-2 in both normal physiology and in pathophysiologic conditions than the "homeostasis versus inflammation" paradigm of COX-1 and COX-2 action originally suggested.

Renal Function

COX-1, expressed in the vasculature, glomeruli, and collecting ducts of the kidney, appears to produce vasodilating prostaglandins that maintain renal plasma flow and glomerular filtration rate especially during conditions of angiotensin-stimulated systemic vasoconstriction (37,38). NSAIDs, known to have multiple clinical effects on kidney function (37,67), are thought to block this COX-1 protective response and lead to renal ischemia and functional damage in some individuals (37,38).

Recent studies have suggested that COX-2 may also play a role in the development of the renal cortex and in maintaining kidney function. Mice that do not express COX-2 because of targeted gene disruption (COX-2 null mice) show severe disruption of kidney development (68-70), COX-2 is expressed in the interstitial cells of the medulla of the rabbit kidney (50) and in the macula densa and the thick ascending loop of Henle in the rat kidney (49). Moreover, recent work suggests that COX-2 is also expressed in the human kidney, but not in the macula densa, but rather in the podocytes of the glomerulus and the endothelial cells of arteries and veins(71,72).

Chronic sodium deprivation or experimental hyperfiltration states increase COX-2 expression in the rat kidney, suggesting that the prostaglandin produced by COX-2 may function to increase sodium reabsorption in response to volume contraction or hyperfiltration that may occur with progressive renal failure (49). Renal COX-2 is also upregulated in the rat by long term administration of ACE inhibitors or type I angiotensin II receptor antagonists, suggesting feedback inhibition of COX-2 expression by the renin-angiotensin system. Moreover, a specific COX-2 inhibitor blocked the increase in plasma and kidney renin levels induced by captopril and also in a model of renovascular hypertension. As shown in figure 2, these results suggest that COX-2 plays a role in the regulation of renin production. Thus, in the rat, angiotensin II appears to down regulate COX-2 expression, whereas, COX-2 is involved in the increased production of renin in response to inhibition of angiotensin II production.

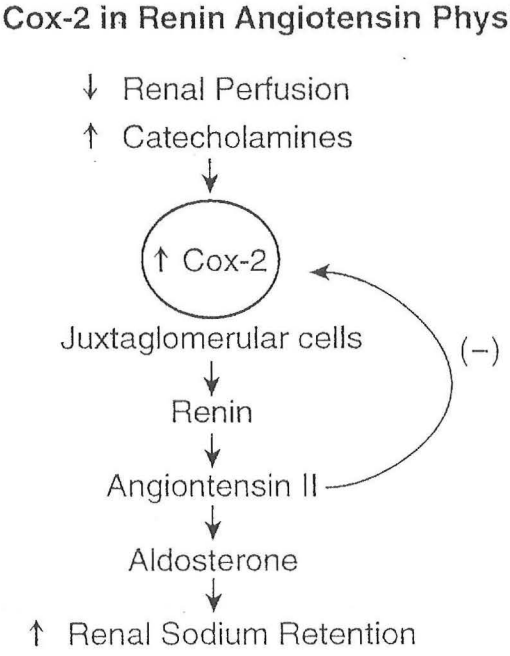

Figure 2

In normal humans, specific COX-2 inhibitors induce a transient sodium retention associated with a marked decrease in 6-keto-$PGF_{1\alpha}$ excretion, a measure of renal prostacyclin production, but no alteration in glomerular filtration rate (73). These results are consistent with the conclusion that a major fraction of renal prostacyclin production is

dependent on COX-2 activity presumably in the renal vasculature and that this may contribute to renal sodium balance independently of an effect on renal hemodynamics. Of importance, glomerular filtration rate in normals, even the normal elderly, does not appear to depend on renal COX-2 function. Whether this is also the case in individuals with intrinsic renal disease or those with hypertension or volume contraction remains to be determined.

Gastrointestinal Tract Integrity

COX-1 is the only COX isoform identified in the gastric mucosa of normal animals, including humans, and is intimately involved in protecting the stomach from erosions and ulceration (21-23,74). As a result of inhibiting COX-1, all currently available traditional NSAIDs impose a risk of gastric ulceration and the major complications of gastrointestinal bleeding, perforation, and obstruction (16-23). Gastrointestinal bleeding caused by NSAIDs appears to relate to two events, inhibition of platelet COX-1 activity that increases the tendency to bleed (75,76) and inhibition of gastric COX-1 that increases the likelihood of ulceration (16,21). The net result is a relative risk for gastrointestinal bleeding of approximately 4 for currently available NSAIDs (18,19). Since COX-2 is not detectable in the normal gastric mucosa nor in the platelet (36,74), inhibition of Cox-2 would not be anticipated to impose a risk of gastric ulceration or bleeding. However, COX-2 is expressed during the acute stages of gastric erosion and ulceration in animal models and might play a role in facilitating ulcer healing (77). Therefore, COX-2 specific inhibitors may increase the risk of major gastrointestinal adverse effects not by increasing the likelihood of developing an ulcer or bleeding, but by decreasing ulcer healing induced by other stimuli, such as H. pylori or concomitant aspirin administration. The potential clinical impact of this effect of specific COX-2 inhibition has not yet been reported in clinical trials and, therefore, the relative risk of gastrointestinal bleeding associated with these agents is not certain.

COX-2 may also play an important physiologic role in other parts of the gastrointestinal tract. In response to invasion by pathogenic microorganisms, epithelial cells express COX-2, which leads to increased prostaglandin production. This appears to play a protective role in the stimulation of the chloride and fluid flux that flushes bacteria from the intestine (78). Thus, COX inhibitors block the rapid intestinal secretion of fluid that accompanies Salmonella infection of Rhesus monkeys (79). Moreover, antibodies to PGE_2 block the accelerated production of chloride from bacterially infected intestinal cells (78). Together the data indicate that invasion by pathogenic microorganisms leads to the production of COX-2 by intestinal cells that catalyzes the production of PGE_2 which governs the chloride and fluid secretion involved in expelling the intestinal pathogen. The potential protective role of COX-2 in the intestine is emphasized by the observation that COX-2 is increased in inflammatory diseases such as ulcerative colitis, whereas selective inhibition of COX-2 may exacerbate inflammation in animal models of colitis (80). The exact role of COX-2 in maintaining intestinal integrity in humans remains to be completely resolved, but specific COX-2 inhibitors could limit intestinal healing or diminish resistance to invasive microorganisms.

Nerve and Brain Function

Prostaglandin production plays a central role in the fever response and is thought to play a role in certain specific manifestations of brain function. The mechanism underlying the fever response, appears to involve the COX-2 enzyme. In rats, intraperitoneal injection of lipopolysaccharide causes a marked fever response that temporally parallels COX-2 induction in the endothelial cells of the brain vasculature(81,82). This is thought to be mediated by interleukin 1β and perhaps other cytokines produced in response to lipopolysacharide that stimulate brain endothelium (83). The resulting prostaglandins then act on temperature-sensing neurons in the preoptic area to produce the fever response. Cyclooxygenase-2 specific inhibition effectively blocks the fever response (84). Moreover, pyrexia in response to lipopolysaccharide stimulation does not occur in mice rendered COX-2 deficient by targeted gene disruption. By contrast, COX-1 deficient mice have a normal fever response (85).

COX-2 also appears to play an essential role in neural development and adaptation. While early-stage brain formation seems to be internally crafted by developmentally induced neural genes and proteins, the final stages of brain maturation are more environmentally imprinted by neural responses and synaptic activity and coincide with the local expression of COX-2 activity (86). COX-2 is expressed most notably during ontogeny in the cortex and hippocampus. Throughout adult life, COX-2 may remain an important modulator of specific neural responses. Seizures, for example, strongly induce COX-2 in the post-synaptic dendritic arborization of excitatory neurons in major processing centers of the brain (51,52). Associations between COX-2 induction and neural degeneration following stresses, such as glutamate stimulation (53), seizures and spreading depressive waves (54), suggest that the role of COX-2 and arachidonic acid metabolites produced may be involved in selective loss, but not formation, of neural connections. The role of COX-2 in human brain function and the potential impact of specific COX-2 inhibitors is unknown and requires evaluation, especially in view of the well-known negative impact of non-specific COX inhibitors on cognitive function in the elderly (87).

COX-2 may also play a specific role in local inflammation in the brain. In this regard COX-2 can be upregulated by specific stimuli in microglial cells, the tissue-specific macrophages that reside in the brain in a dormant condition until activated during host defense or tissue remodeling (88). Unlike other inflammatory cells, the microglial cell upregulates COX-2 only in response to direct lipopoly-saccharide exposure and not to cytokines, a rare event linked with direct bacterial infection of the brain. Thus, the microglial defense is usually not part of the systemic response to inflammation, but may play a critical role during brain infection.

Ovarian and Uterine Function

Although classically associated with parturition (89), prostaglandins and COX-2 have now been implicated as mediators of other stages of pregnancy, including ovulation and implantation. Studies with COX-2 null mice have documented reproductive failures at

ovulation, fertilization, implantation, and decidualization (55), indicating the essential role of COX-2 at each of these stages.

Induction of COX-2 immediately following the luteinizing hormone surge was the first observation suggesting that this COX isoform may play a role in a normal physiological events (90). This COX-2 induction accompanies normal oocyte development and appears to be necessary to produce the proteolytic enzymes that rupture the follicles (91). The inductive trigger for COX-2 during ovulation may involve luteinizing hormone and follicle stimulating hormone, transforming growth factor α (92), or interleukin-1β (56), leading to increased COX-2 gene transcription (58). Inhibition of COX-2 by NSAIDs may explain the infertility secondary to delayed or blocked follicular rupture associated with their use (93-96).

Following fertilization in the mouse, COX-2 also plays a role in embryo implantation in the uterine myometrium. Whereas COX-1 and specific prostaglandin receptors apparently prepare the wall for interaction with the embryo (59,60), the COX-2 enzyme, leading to the production of prostacyclin, seems to be necessary for the implantation event itself (59,97). Transient induction of COX-2 has been shown in the uterus of many species, including humans.

Thrombosis

Maintenance of normal blood flow and the appropriate thrombogenic response to injury requires a delicate balance between the activities of platelet produced thromboxane A_2 and endothelial cell derived prostacyclin (Table 1).

Table 1.
Cyclooxygenase Activity and Thrombosis

	Platelet	Endothelial Cell
Cyclooxygenase Isoform	Cox-1	Cox-2
Active Arachidonic Acid Metabolite	Thromboxane A_2	Prostacyclin
Function	• Activate IIb-IIIa receptors for fibrinogen • Induce vasoconstriction	• Inhibit platelet function • Stimulate smooth muscle relaxation and vasodilation

After activation, platelets produce thromboxane A_2 via the action of COX-1, the only COX isoform they contain (39,75,76). Thromboxane A_2 plays an essential role in the aggregation of platelets. The release of eicosanoids by activated platelets is thought to provide a substrate and a stimulus for the production of prostacyclin by endothelial cells (75). Prostacyclin stimulates vasodilatation, thereby, counteracting the vasoconstrictive action of thromboxane A_2(3). It has recently been shown that shear stress induces COX-2 expression in endothelial cells and that substantial amounts of eicosanoid production by endothelial cells results from the action of COX-2 (98). In fact, recent studies have shown that excretion of 2,3 dinor 6-keto $PGF_{1\alpha}$ a metabolite of prostacyclin that is indicative of systemic prostacyclin production in man was significantly inhibited by the administration of a specific COX-2 inhibitor (73, 99). These results indicate that a substantial proportion of systemic prostacyclin production derives from the action of COX-2. These data are all consistent with the conclusion that platelet thromboxane A_2 production is uniquely regulated by the action of COX-1, whereas a substantial portion of endothelial cell-derived prostacyclin is produced as a result of the action of COX-2. Since currently available NSAIDs inhibit both COX-1 and COX-2, a balanced impact on these pro- and anti-thrombotic activities is expected. However, specific COX-2 inhibitors may limit the production of prostacyclin by endothelial cells while having no effect on the production of thromboxane A_2 by platelets. The resulting imbalance may then favor platelet aggregation and vasoconstriction with a resulting increase in the tendency for vascular occlusion and tissue ischemia. The potential clinical impact of this imbalance has not been explored, but should be examined, especially in patients at risk for ischemic events.

Summary

A full awareness of the physiologic and pathophysiologic roles of COX-1 and COX-2 continues to emerge (Table 2).

Clinical Effects of Specific COX-2 Inhibitors

- Similar to non-specific COX inhibitors
  - Anti-inflammatory
  - Analgesic
  - Anti-pyretic
  - Some renal effects, e.g. sodium excretion, blood pressure

- Different from non-specific COX-inhibitors
  - No anti-platelet effects
  - Reduced endoscopic GI erosion and ulceration
  - Some renal effects, e.g. possibly less alteration of RBF and GFR

Although the initial paradigm that COX-1 was homeostatic, whereas COX-2 was pro-inflammatory provides a general framework for thought, more recent investigation has clearly indicated more complex roles for these isoforms in both health and disease. As specific Cox-2 inhibitors are used in the clinic, attention should be given to potential adverse effects related to the kidney, gastrointestinal tract, bone and brain as well as a potential negative impact on pregnancy and thrombogenic potential. On the other hand, new potential therapeutic targets for specific COX-2 inhibitors have emerged as a role for COX-2 in development and progression of adenomatous polyposis and colon cancer has been shown (100-113). Moreover, the possibility that COX-2 may play a role in the progression of Alzheimer's disease has also been suggested (114-120). Thus, developing information about the biology and function of COX-2 has presented the clinician with new challenges as well as new opportunities.

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