Cyclooxygenase isoforms in health and disease

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Abstract

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have long been used for the treatment of pain and inflammation owing to their inhibitory effects on cyclooxygenase (COX). Ever since NSAIDs have been in use, multiple adverse effects have been noted. Assessment of many of these effects has been complicated due to the discovery of multiple splice variants of the COX gene, greater array of COX and specific COX-2 inhibitor availability. The effect of these drugs on COX cannot be readily explained. This has sparked a new field of investigation on splice variants of COX and effects of COX inhibitors. This review summarizes our current understanding of the role of cyclooxygenase in health and disease.

Introduction

The mechanism of action of NSAIDs has long been proposed based on their inhibition of prostaglandin biosynthesis, enzyme cyclooxygenase (COX or prostaglandin H2 synthase). Two decades after COX discovery the existence of at least two COX isoforms; COX-1 and COX-2 were demonstrated in 1990 (Figure 1). Currently the research is focused on developing safer NSAIDs based on their mechanisms of action and physiological roles in the pathogenesis of inflammation. New classes of COX-2 selective inhibitors have entered the worldwide market. These new medications offer safer alternatives to NSAIDs in
terms of gastrointestinal safety; however, toxicological concerns regarding their renal and cardiovascular safety remain. These COX-2 specific inhibitors benefit arthritic patients, slow down tumor growth, delay the birth process, and impede degenerative changes associated with Alzheimer’s disease and Parkinson’s disease. There has been much speculation in the field on the possibility of a third COX isoform COX-3, that is potently inhibited by some NSAIDs. Thus, inhibition of COX-3 could represent an additional mechanism by which these drugs decrease pain and possibly fever.

Figure 1: Mechanism of Action of COX
Prostaglandins are widely distributed in human tissues (1). PGs encoded by an early response gene not only play a central role in inflammation, but also regulate other critical physiological responses. In humans, PGs are involved in diverse functions, such as blood clotting, ovulation, initiation of labor, bone metabolism, nerve growth and development, wound healing, kidney function, blood vessel tone, and immune responses.

Unlike cortisone or thyroxin, PGs are synthesized in a broad range of tissue types and serve as autocrine or paracrine mediators to signal changes within the immediate environment. Two classes of prostaglandin receptors exist to transduce signals upon binding of ligand. The G-coupled cytoplasmic receptor class (i.e., EP1-4 for PGE2) and the nuclear PPAR receptor class (i.e., PPARα, PPARγ, PPARδ), which act directly as transcription factors upon ligand binding (2). As PGs play broad roles in normal human physiology, it is not surprising that systemic suppression of PG synthesis through inhibition of COX can lead to unwanted side effects. In particular, individuals on NSAIDs treatment for even short periods can experience gastrointestinal and renal side effects (3, 4) in addition to effects on other physiological systems. The different effects of PGs can be explained by considering their varied chemistry, the diversity of PG receptors, and modulation of PG synthesis by local upstream and downstream effects.
Prostaglandin isomers - including thromboxane and prostaglandins D2, E2, F2α, and I2 function in numerous physiological and pathophysiological processes, such as pyresis (fever), analgesia (sensitivity to pain), inflammation, thrombosis, parturition, mitogenesis, vasodilation and vasoconstriction, ovulation, and renal function. Prostaglandin isomers act upon G-protein-coupled receptors (5) and there are multiple receptors for some isoforms (such as prostaglandin E2).
Prostaglandins are short-lived \textit{in vivo} (with half-lives of seconds to minutes), and act in an autocrine or a paracrine rather than an endocrine fashion.

COX-1 was first studied in tissue and cell homogenates, and in this context was shown by Vane (6) to be the inhibitory target of NSAIDs. An intense amount of research conducted in the last decade has been devoted to assign distinguishing role for each type of COX isoforms. Investigators studying cell signaling pathways identified a unique, inducible gene product related to the known COX sequence (7). Concurrently, investigators looking at PG production in response to cytokines and other inflammatory factors noted increases in COX activity that could only be accounted for by increased expression of another COX (8). Both immunoprecipitation of this COX variant with an anti COX antibody, as well as the production of an antibody that precipitated only the COX-2 isoform, allowed for the identification of two different COX isoforms. It was subsequently determined that the COX-1 and COX-2 proteins are derived from distinct genes that diverged well before birds and mammals (9). In a nutshell these early studies revealed that both enzymes carry out essentially the same catalytic reaction and similar protein structures (10). Many of the inflammatory, inducible effects of COX appeared to be mediated by the newly discovered COX-2, while the ‘housekeeping’ effects of COX appear to be mediated by COX-1. This function for each isoform is consistent with their tissue expression patterns. All normal tissues express COX-1 with low to undetectable levels of COX-2 while, COX-2 is constitutively expressed in the brain and kidney of rodents. Other differences between COX-1 and COX-2 include differences in utilization of arachidonic acid substrate pools as well as in mRNA stability (11, 12).

The regions regulating gene expression of COX-1 and COX-2 show little similarity. For example, the promoter and enhancer regions regulating COX-2
contain a variety of response elements which play partial role in their inducibility by hormones, growth factors, phorbol esters, cAMP, inflammatory factors and cytokines. However, much less is known about the elements involved in regulating COX-1 gene expression, although several studies have reported induction of COX-1 in differentiation of macrophages (13–16). COX-1 and COX-2 also show major differences in mRNA splicing, stability, and translational efficiency.

Regulation of COX-2 at the mRNA level appears to be an important mechanism by which some physiological mediators, like corticosteroids, act to regulate PG production. Another major difference between COX-1 and COX-2 appears to be in their ability to choose different substrate pools. For example, in both fibroblasts and immune cells, COX-2 was able to utilize endogenous arachidonic acid, whereas COX-1 does not. In these systems, COX-1 requires exogenous substrate. Soluble PLA₂ can produce an alternative source of substrate for COX-1. Herschman (17) has suggested that release of sPLA₂ in some tissues from neighboring cells might provide the primary regulation of COX-1 activity. Thus, the regulatory elements responsible for increasing PG production are sPLA₂ gene. In summary, the COX-1 and COX-2 genes are regulated by two independent and quite different systems even though the enzymatic reaction they catalyze is identical. The protein encoded by human and rat COX-3 gene has a completely different amino acid sequence than COX-1 and COX-2. It does not have COX activity; and distinguished as COX variant protein (COVAP) to differentiate it from the known prostaglandin synthesizing COX isoforms (18) the results from dog studies were extrapolated to humans and rodents without critical evaluation of the data.
COX Enzymes

Cyclooxygenase-1 (COX-1)

COX-1 is ubiquitously expressed in tissues under basal conditions (19). This implicates that COX-1 plays a major role in providing PG precursors for homeostatic regulation. One important site of COX-1 function is the blood platelets, where it is responsible for supplying precursors for thromboxane biosynthesis (20). This makes sense, since platelets, do not have nuclei, they cannot produce an inducible enzyme in response to activating conditions. Rather, platelets carry a supply of COX-1 in presence of an NSAID like aspirin; platelets are prevented from generating thromboxane during activation and fail to aggregate, inhibiting their thrombogenic potential. In the adjacent vascular endothelium, PGs play a different role. The release of eicosanoids by activated platelets is thought to provide both a substrate and stimulus for the generation of prostacyclin (PGI₂) by the endothelium which stimulates vasodilatation, counteracting thromboxane a vasoconstrictor. COX-1 appears to have role in two other physiological systems: kidney and the stomach, leading to their vasodilatation in the presence of contractile conditions. In these systems, normal physiological stimuli are associated with dramatic changes in blood flow, during times of lowered blood volume, the kidney releases angiotensin and other factors to maintain blood pressure by systemic vasoconstriction (21). At the same time, angiotensin causes PG biosynthesis in the kidney.

COX-1 is expressed in the vasculature, glomeruli, and collecting ducts of the kidney, and it appears to be important in producing the vasodilating PGs, which maintain renal plasma flow and glomerular filtration rate (GFR) during
conditions of systemic vasoconstriction. In the presence of NSAIDs, this protective response fails, leading to renal ischemia and damage in susceptible individuals (22). Similarly, in the gastric antrum, NSAID intake leads to ischemia followed by mucosal damage and ulceration (23). The enzyme blocked by NSAIDs is thought to be COX-1 (24) that produces PGs involved in altering blood flow in the microcirculation of the gastric mucosa. Thus, COX-1 acts in a variety of settings to maintain homeostatic levels of PGs. In some cases, induction of PLA2 is responsible for increased PG biosynthesis and in others, COX-1 levels are modulated (macrophages begin to differentiate). It is not yet clear whether all cells and tissues with COX-1 rely on exogenous supplies of substrate, but this situation would allow for a variety of cooperative mechanisms linking COX-1 activity to neighboring physiological requirements.

**Cyclooxygenase-2 (COX-2)**

In studying a rabbit kidney model of inflammation, (25) it was noted that when one ureter was tied off causing inflammation, that kidney produced high levels of prostaglandins above the normal baseline production of the normal kidney. They also observed that when dermal fibroblasts were stimulated with lipopolysaccharide (LPS) or endotoxin in tissue culture, the same increase in prostaglandin production was observed. This excess prostaglandin could be inhibited by glucocorticoid and indomethacin. The postulation that a second enzyme system existed was based on the fact that excess prostaglandin could be produced in models of inflammation, that it was inhibited by inhibitors of protein synthesis as well as glucocorticoid, and that the baseline prostaglandin production was not affected by glucocorticoid. This second enzyme system COX-
2 was considered to be inducible and upregulated by inflammatory stimuli such as cytokines.

The understanding on the mechanism of action of COX enzyme and its influence on rapid enhancement of PG during inflammation and in other physiological contexts came from studies on cell division. Simmons (26) and Herschman (25) groups independently identified the immediate early genes in fibroblast like cells activated by mitogens. Genes from chicken (27, 29) and mouse (30) were activated by the \textit{v-src} oncogene, phorbol esters and serum. Use of Swiss 3T3 cells showed induction of tetradecanoyl-13-phorbol acetate inducible sequences (or TIS genes) that also induced by other mitogens (31). These workers independently reported that one of their sequences encoded a new inducible COX enzyme, which contributed to the identification of COX-2 in 1991. The inducible enzyme cloned in these studies was frequently referred to as COX-2 and the seminal vesicle form of the enzyme as COX-1.

One of the first studies conducted after the discovery of the isoform of COX was to screen against existing NSAIDs for differential inhibitory effects, and indeed some were found to have a 20 - 70 fold selective preference (28, 29). As a result, studies were conducted to find differential inhibition of COX-1 or COX-2 activities under a variety of experimental conditions (Table 1). While initial studies upheld the concept that COX-2 is mainly an inflammatory, inducible enzyme, more recent studies are beginning to reveal more functions (15).
<table>
<thead>
<tr>
<th>Subcellular location</th>
<th>COX-1 enzyme</th>
<th>COX-2 enzyme</th>
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<tr>
<td>Endoplasmic reticulum</td>
<td>Endoplasmic reticulum and nuclear envelope</td>
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<tr>
<th>Expression</th>
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<tr>
<td>Constitutive</td>
<td>Inducible (by cytokines)</td>
<td>Blocked by glucocorticoids</td>
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<td>Unchanged by glucocorticoids</td>
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<th>Substrate</th>
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<tr>
<td>Endogenous arachidonic acid (fibroblasts and immune cells) released by sPLA2</td>
<td>Exogenous arachidonic acid (fibroblasts and immune cells) released by cPLA2</td>
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<td>39 nmol/min/mg</td>
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<td>Covalent bonding postulated</td>
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<th>Size of active site</th>
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<th>COX-2 enzyme</th>
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<tr>
<td>COX-1 is relatively stable</td>
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<td>COX-2 is induced inflammatory states</td>
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Table 1: Profile of cyclooxygenase (COX) enzymes

**Cyclooxygenase-3 (COX-3)?**
A third isoform of COX, COX-3 was discovered in canine by Dan Simmons and colleagues while looking for the mechanism of action of acetaminophen. Acetaminophen is often categorized NSAID, even though in clinical practice and in animal models it possesses little antiinflammatory activity like NSAIDs (31), however acetaminophen inhibits pain and fever and is one of the world’s most popular analgesic and antipyretic drug. Despite acetaminophen’s long use and popularity it lacks a clear mechanism of action. Flower and Vane showed that acetaminophen inhibited COX activity in dog brain homogenates more than in homogenates from spleen (32). This gave rise to the concept that variants of COX enzymes exist that are differentially sensitive to this drug and acetaminophen acts centrally. Yet, even though two isozymes of COX are known, neither isozyme is sensitive to acetaminophen at therapeutic concentrations of the drug in whole cells or homogenates. Instead, COX-1 and COX-2 in homogenates frequently exhibit the paradoxical property of being stimulated by sub-millimolar concentrations of acetaminophen and inhibited by very high levels of the drug. This finding suggests that neither isozyme is a good candidate for the action of acetaminophen. While analyzing COX-1 and COX-2 RNA expression it was observed that cerebral cortex of dog brain contains two distinct RNAs that hybridized to a canine COX-1 cDNA (32).

Most experimental data conclude that COX-3 is just another COX-1 splice variant (33, 34). COX-3 is inhibited by acetaminophen but its general low expression level and the available kinetic data indicate that it is unlikely to be clinically relevant. Although several years have passed since the original publication (35), there is no any follow up study which would confirm the COX activity of the canine COX-3 and its sensitivity to acetaminophen. In human and rodents the mRNA transcript of COX-3 is potentially targeted by nonsense mediated decay,
which explains its low expression level. The exact function of the COX-3 protein is currently unknown. COX-3 proteins from dog, human and rodents do not show substantial homology. Although COX-3 encoded proteins are known in rodents (33) and in human, their biological roles are unclear. The protein encoded by human and rat COX-3 gene has a completely different amino acid sequence than COX-1 and COX-2. Further COX-3 does not have usual COX activity hence it was distinguished as COX variant protein (COVAP) to differentiate it from the known COX isoforms (18). But evidence does not support claims (36, 37, 38) that acetaminophen is a selective COX-3 inhibitor in rodent studies. It is also important to note that commercially available anti-COX-3 antibodies can only be used in a species selective manner because of considerable differences among amino acid sequences of COX-3 from different species. The exact mechanism of acetaminophen still remains a mystery. Thus studying the transcription of COX genes might help us to better understand the function of alternative splicing mechanisms in eukaryotes.

**Systemic Functions Of COX**

**Isoforms**

**Kidney Physiology**

Prostaglandins serve as important physiological modulators of vascular tone and sodium and water homeostasis in the mammalian kidney. COX-1 is recognized to be involved in normal kidney function, while COX-2 has a specific role. The localization studies indicate that COX-2 is expressed both in the macula densa of the kidney (39) and in the interstitial cells of the medulla in rats (40). The macula
Nerve and Brain Physiology

COX-2 seems to have some role in regulating brain function (45). PGs have long been known as mediators of fever, inflammatory reactions in neural tissue and more recently in brain function. Each of these processes involves induction of PG biosynthesis and COX-2 especially plays an important role. While NSAIDs are commonly used to control fever, the actual mechanism of fever induction has only recently been described. Intraperitoneal injection with lipopolysaccharide
(LPS) causes a marked fever response in rats. In an elegant dissection of molecular and tissue interactions, Cao and colleagues have shown how COX-2 induction in brain endothelial cells temporally correlates the fever response (45, 46). This leads to the synthesis of PGs, which then act on temperature sensing neurons in the preoptic area. In turn, COX-2 inhibition by an isoform-specific NSAID can effectively block fever (47). Communication between local inflammatory sites and the brain endothelium is mediated by cytokines such as IL-1, which can directly induce COX-2 expression in these cells (48). These investigators have also shown induction of COX-2 expression in other parts of the brain, but these areas are not directly associated with the fever pathway. A separate inflammatory pathway is one mediated by microglial cells, tissue specific macrophage that lies dormant until needed for defense or tissue remodeling (49). The microglial cell does not show induction of COX-2 in response to cytokines, in strong contrast with other inflammatory cells. In the microglial COX-2 response is limited to direct LPS exposure by bacterial infection of the brain. Thus, the microglial defensive response is segregated from systemic inflammation by its limited repertoire of inducers. This segregation is important because COX-2 also plays a central role in neural development and adaptation. In the earlier stages of brain development, neural genes and proteins are developmentally induced that play an important role in the maturation process. During later stages of maturation, environmental influences as represented by neural responses and synaptic activity, play an increasingly important role in determining brain structure. It is in these final stages of development and brain modeling that COX-2 becomes active in a manner that coincides with the imprinting of environmental influences (50). COX-2 remains an important modulator of neural response throughout adult life. Seizures and N-methyl-D-aspartate mediated activity increase COX-2 levels (51). The sites of induction being the postsynaptic
dendritic arborizations (52) of specific excitatory neurons located in the major processing centers of the brain. The actual role of COX-2 and PGs in these sites is to be understood. However the association of COX-2 induction and neural degeneration after glutamate stimulation (53), seizures, and spreading depression waves (54) suggest that COX-2 may play more of a role in the selective loss of neural connections than in their formation.

**Role of COX isoforms in Alzheimer’s disease (AD)**

AD is a neurodegenerative disorder of unknown etiology that accounts for two-thirds of all dementia in the elderly. Although the inciting event responsible for initiation of the disease remains unclear, pathological studies of early to late stage AD demonstrate prominent neuronal and synaptic loss in concert with amyloid deposition and astrocytic and microglial activation. In AD, neuronal COX-2 levels have been found to be either elevated (55, 56) or unchanged (57). Recent studies suggest that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a significantly lower risk of developing AD (58, 59), raising the possibility that in normal aging populations, inhibition of COX activity may be protective against the development of AD. However, the precise pharmacological actions of anti-inflammatory drugs in the brain are still unclear. Several studies are attempting to identify a role for COX in the etiology of AD. Cytokines such as IL-1 or IL-6, as well as acute-phase proteins such as 1-antichymotrypsin (ACT), participate in the etiopathology of AD. Tepoxalin, a novel NSAID, markedly inhibited IL-1 induced IL-6 and ACT synthesis in astrocytes (60). Lipopolysaccharide stimulated microglial cells treated with tepoxalin also exhibited decreased synthesis of IL-1 and IL-6 (59). This effect was mediated
known to through inhibition of NF-B via decreased IB degradation. NF- activate COX-2 expression under some circumstances. The amyloid stimulated secretion of proinflammatory products by microglia and monocytes, mediating neurotoxicity and astrocyte activation, was also inhibited by NSAIDs, reportedly through PPAR activation (61). Recognition of COX-2’s key role in inflammation led to the hypothesis that it may represent a primary target for NSAIDs in AD, consistent with inflammatory processes occurring in AD brain (62, 63).

Elevated CSF PGE2 levels are observed in patients with probable AD (64). COX-2 was elevated in the hippocampal pyramidal layer in sporadic AD and was correlated with amyloid plaque density (65). In vitro studies using COX-2 over expressing neurons derived from transgenic mice suggest that elevation of COX-2 may potentiate A-beta mediated oxidative stress (65). Further analyses of 54 post mortem brain specimens from patients with normal or impaired cognitive status suggested that neuronal COX-2 expression in subsets of hippocampal pyramidal neurons may be a marker of progression of dementia in early AD (66). IL-1 and synthetic amyloid peptides induced COX-2 expression and PGE2 release in the human neuroblastoma cell line SK-N-SH (67, 68). In human breast cancer cells (69), neuroblastoma cells also exhibit increased COX-2 expression mediated by p38 mitogen activated protein kinase (MAPK), suggesting p38 MAPK as a potential therapeutic target in AD (68). However, COX-1 and COX-2 may be involved in different cellular processes in the pathogenesis of AD, as indicated by their different distribution profile. An overall increase of COX-1 expression in AD has also been suggested COX-1 expression was detected in microglial cells, whereas COX-2 expression was found in neuronal cells (70). In AD brains, COX-1 positive microglial cells were primarily associated with the amyloid plaques, and AD fusiform cortex exhibited increased density of COX-1 immunopositive
microglia (70, 71). Furthermore, more COX-2 positive neurons were detected in AD brains than in control brains (70). Although in vitro studies use astrocytes to investigate the role of COX in AD, no COX expression was detected in astrocytes in vivo. Therefore, COX-1 could also contribute to central nervous system pathology, which brings up the issue of whether non-selective inhibitors would be more effective. The possible implication of COX-1 in AD is further substantiated by the Alzheimer’s disease Cooperative Study (ADCS) (72). A multicenter clinical trial found that a repressor of COX-2 expression, prednisone neither prevented nor accelerated cognitive decline in AD, although interpretation of these data is complex because glucocorticoids are fairly nonspecific and affect many other pathways. Nevertheless, the ADCS has initiated a trial to compare a nonselective NSAID and a selective COX-2 inhibitor for effectiveness in slowing the rate of cognitive decline in AD. Indomethacin showed promising results in a pilot clinical trial (73). Whether COX-2 inhibitors will be more effective is uncertain, since the enzyme is constitutively expressed in neurons and may play some role in normal brain function (74). Animal experiments suggest that COX-2 may be responsible for the regulation of adaptive functions associated with normal neurons and protective functions associated with stressed neurons. Other mechanisms for NSAID neuroprotective potency unrelated to their ability to inhibit COX-1 or COX-2, such as inhibition of monocyte cytotoxicity, have been suggested based on in vitro neurotoxicity assays (75). The antithrombotic activity of PGs may also be important for protection against AD. De la Torre (76) hypothesizes that AD is caused by the development of tortuous and flow-impeded capillaries in the brain. This would presumably promote intravascular coagulation, leading to ischemic damage in the brain that could promote the development of AD. Platelets contain which may contribute to the perivascular amyloid depositionβ both APP and A- seen in AD. Protein kinase C (PKC) in
human platelets is involved in the secretory cleavage of APP, whereas COX plays only a minor role in this process (77). The precise role of the COX isoenzymes in AD is not clear, but the use of NSAIDs that inhibit both COX-1 and COX-2 activity appears to be beneficial. Non-selective NSAIDs can reduce inflammation associated with activation of microglia, but they seem ineffective in reversing the degenerative process in AD. A recent study suggests that naproxen, ibuprofen, and aspirin may reduce the risk of Alzheimer’s disease. Nevertheless, the effects of NSAIDs are likely to be mediated through a combination of mechanisms. Although reduced microglial or monocyte activation has been shown to be effective in various cell culture and animal models, clinical studies have yet to be performed. Mechanistic studies already under way will provide insight and directions for further development.

**Role of COX isoforms in Parkinson’s disease (PD)**

PD is another common neurodegenerative disease which is characterized by motor abnormalities causing tremors, muscle stiffness, paucity of voluntary movements, and postural instability (78). Its main neuropathological feature is the loss of the nigrostriatal dopamine containing neurons, whose cell bodies are in the substantia nigra pars compacta (SNpc) and nerve terminals in the striatum (79). Except for a handful of inherited cases related to known gene defects, PD is a sporadic condition of unknown pathogenesis (78). Epidemiological studies suggest that inflammation increases the risk of developing a neurodegenerative condition such as AD (80). Hence, inflammatory processes associated with increased expression of COX-2 and elevated levels of prostaglandin E2 (PGE2) have been implicated in the cascade of deleterious events leading to
neurodegeneration in PD associated pathological settings (81–83). COX in
general convert arachidonic acid to PGH2, the precursor of PGE2 and several
other prostanoids, and exists in eukaryotic cells in two main isoforms: COX-1,
which is constitutively expressed in many cell types; and COX-2, which is
normally not present in most cells, but whose expression can readily be induced
in inflamed tissues in PD also (84). Although both isoforms synthesize PGH2,
COX-1 is primarily involved in the production of prostanoids relevant to
physiological processes, whereas COX-2 is mainly responsible for the production
of prostanoids linked to pathological events (84). COX-2 expression is induced
specifically within SNpc dopaminergic neurons in postmortem PD specimens and
in the 1-methyl-4-phenyl-1,2,3,6- terahydropyridine (MPTP) mouse model of
PD during the destruction of the nigrostriatal pathway and COX-2 induction
occurs through a JNKyc-Jun dependent mechanism and that COX-2 ablation and
inhibition attenuate MPTP induced nigrostriatal dopaminergic
neurodegeneration, not by curtailing inflammation, but possibly by mitigating
oxidative damage which is evident of COX-2 involvement in the pathogenesis of
PD and suggest a potential mechanism for the selectivity of neuronal loss in this
disease (Figure 2). Collective data thus provide evidence for COX-2 up regulation
in MPTP and PD and support a significant role for COX-2 in both the mechanism
and the specificity of MPTP and PD induced SNpc dopaminergic neuronal death.
The present studies suggest that inhibition of COX-2 may be a valuable target for
the development of new therapies for slowing the progression of the
neurodegenerative process during PD.
Figure 2. Higher COX-2 expression (blue stain) in neurons from Parkinson’s disease

Increasing evidence suggests that neuroinflammation is an active process in PD that contributes to ongoing neurodegeneration. PD brains and experimental PD models show elevated cytokine levels and up regulation of inflammation associated factors as COX-2 and inducible nitric oxide oxidase. Antiinflammatory treatment reduced neuronal degeneration in experimental models.

Role of COX isoforms in maintenance of Gastrointestinal integrity

The intestinal epithelium is a tissue that undergoes constant regeneration in response to both insult and normal use. The use of NSAIDs causes irritation and ulceration of the stomach lining of the gastrointestinal tract (85). Under these circumstances, COX-1 appears to play a major role in maintaining proper glandular architecture. Gastrointestinal epithelium is also the target of numerous infectious and parasitic organisms. In response to infection or invasion, COX-2 expression is induced in epithelial cells (86), which leads to increased PG
production. The PGs then stimulate chloride and fluid secretion from the mucosa that flush bacteria from the intestine. In addition, COX-2 is expressed during inflammation and wound healing, and in animal models, treatment with COX-2 inhibitors can exacerbate inflammation and inhibit healing. Nevertheless, COX-2 selective inhibitors appear to be associated with less gastrointestinal damage than conventional NSAIDs (87). Many of the diverse roles of PGs in the intestine have been revealed by studying the effects of indomethacin or other NSAIDs. Giannella et al. (88) have found that indomethacin could effectively suppress the rapid intestinal fluid secretion accompanying Salmonella infection of Rhesus monkeys. More recently, Eckmann et al. (89) have shown that Salmonella infection of cultured intestinal epithelial cells gives rise to a rapid induction of COX-2, and associated rise in PGs, and increase in chloride secretion. With such response of infected cells, uninfected cells also acquired the property of enhanced fluid secretion, demonstrating the paracrine nature of the PG response.

**Role of COX isoforms in Ovaries and Uterus**

The uterus epithelium is a tissue that undergoes constant regeneration in response to both insult and indomethacin as a treatment for premature labor with dramatic results. Out of 50 women, 80% experienced cessation of uterine contractions. However, five infants from the treated mothers died because of premature closure of the ductus arteriosus, a circulatory shunt in the fetus that allows the output of the left ventricle to bypass the fetal lungs, which is maintained by PGs (90). Prenatal indomethacin is sufficient to block PG production leading to premature duct closure and disruption of fetal circulation (90). Ovulation, the process by which oocytes are released from the pre ovulatory follicle in the ovary is accompanied by induction of prostaglandin synthesis as a
consequence of the LH surge. This marked response led to the first observation of COX-2 induction during a normal physiological event (91). One of many molecular events associated with ovulation (92), the induction of COX-2 is necessary for the successful rupture of the follicle, probably mediating directly the generation or activation of proteolytic enzymes necessary for this process (93). Induction of COX-2 can be modulated by the gonadotropins LH and FSH, and by TGF-a, IL-1, or other cellular signaling pathways (94). After fertilization, COX-2 again plays a role, this time during implantation of the embryo in the uterine endometrium. During the pre-implantation period, uterine COX-1 (95) and the PGE2 receptors, EP1, EP3, and EP4 (96), may modulate preparation of the uterus for interaction with the embryo, and COX-2 (95) and the EP2 receptor (97) appear to mediate the embryo uterine interactions during implantation. COX-2 null mice show multiple failures in reproductive function, including ovulation, fertilization, implantation, and decidualization, underscoring the multiple roles of PGs during these processes (98). Finally, at the completion of pregnancy, PGs again act in the ovary and uterus to help mediate the delivery process. As mentioned above, PGs have long been known to stimulate uterine contraction. In mice, the production of PGF2a by the fetal and/or uterine tissues signals the ovary to induce luteolysis (99), leading to a decline in maternal progesterone and the induction of oxytocin receptors in the myometrium. This induction in turn increases the myometrial response to oxytocin and brings on parturition. One of the earliest noted sites of PG accumulation was amniotic fluid (100), and one of the first known biological responses to a prostaglandin was the rhythmic contraction of the uterine myometrium. These associations with pregnancy and labor led to the recognition of PGs as a major effector in induction of labor. Indeed, administered indomethacin as a treatment for premature labor with dramatic results (101).
COX isoforms and Bone

PGs were initially characterized by stimulating bone resorption in culture, human and animal responses to PGs often include stimulation of bone formation (102). Collagen synthesis by osteoblasts can be both stimulated (103) or inhibited by PGs. Mechanical stress on bone cells leads to an increase in PG synthesis, suggesting that immobilization would be characterized by low PG levels (104). Nevertheless, immobilization is associated with PG mediated bone loss, an effect that is slowed by NSAIDs. PGs act on the modeling of bone in several ways. They stimulate the differentiation of precursors of both the bone resorbing cells (osteoclasts) and the bone forming cells (osteoblasts), they stimulate bone resorption in vitro, and they stimulate bone growth when given exogenously in vivo (105). While little is known of how PG synthesis affects the balance between bone loss and formation, COX-2 induction in osteoblasts is reported to be essential to the acute stress response in a bone remodeling system (106). Bone loss is associated with inflammation in periodontal disease (107) and NSAIDs can slow this process (108). Cytokines associated with inflammation, including IL-1b and IL-6 (109) have been found to induce both COX-2 and increase PG production when added to bone marrow cells in culture. In response, osteoclasts are induced to differentiate from their stem cell precursors. Osteoblasts and marrow stromal cells are the site of COX-2 induction and are further activated by the increased production of PGs. Other cytokines, for example IL-4 and IL-13 appear to suppress this response (110). Other inducers of COX-2 include parathyroid hormone (111), an important regulator of calcium metabolism, vibrational forces (112) and pulsating fluid flow (104), both of which are thought to model physical forces associated with mechanical stress on bone. Thus, it appears that stimuli that lead to both breakdown and building of bone use the
same basic pathways to activate the bone remodeling system and that in bone
PGs are responsible for ensuring that this resorption and formation occur
coordinately, preventing an imbalance between these two processes.

**Role of COX isoforms at Joints and in Arthritis**

Although the importance of COX activity in the production of PGs has been
known since long (113), the inducibility of this activity and the central role of this
induction in the amplification of inflammation have been fully appreciated only
recently (114). Evidence provided by animal models of inflammatory arthritis
strongly suggests that increased expression of COX-2 is responsible for increased
PG production seen in inflamed joint tissues (115). COX-2 induction has been
observed in both human osteoarthritis affected cartilage (116) as well as in
synovial tissue taken from patients afflicted with rheumatoid arthritis (117). Cell
culture experiments utilizing primary cells derived from human synovial tissue or
cell types (monocytes) important in inflammatory processes have been critical to
an understanding of factors involved in modulating this induction. The pro-
inflammatory agents IL-1, TNF-a, and LPS, as well as the growth factors TGF-b,
EGF, PDGF, and FGF, have all been shown to induce COX-2 expression in this
system. On the other hand, the antiinflammatory cytokines IL-4 and IL-13, as
well as the immunosuppressive glucocorticoids, were shown to decrease COX-2
levels. Although the synovial tissues of patients with osteoarthritis express lesser
amounts of COX-2, primary *in vitro* cultures of human osteoarthritis affected
cartilage spontaneously express large amounts of COX-2 and PGs (116). Nitric
oxide, another important inflammatory modulator, has been shown to regulate
PG production in osteoarthritic cartilage, though not in synovial cells. Whether
this modulation attenuates or enhances COX activity remains controversial (116,
118). The rapid expansion of knowledge about the role of COX-2 in inflammation led to drug screens attempting to identify antiinflammatory agents selective for COX-2 as well as to the rational design of highly selective COX-2 inhibitors (119). The availability of these COX-2 inhibitors has now allowed for the design of studies that could directly determine the importance of COX-2 in inflammatory disease. COX-2 is reported to be central to the inflammatory process and COX-2 inhibition is sufficient to achieve the same therapeutic endpoints found with less specific inhibitors that also target COX-1(120).

**Role of COX isoforms in Pain**

Local tissue injury and inflammatory diseases like osteoarthritis are associated with increased PGs, and pain receptors are known to be sensitized to lower levels of stimulus by PGs (121). Thus, the action of COX at the site of injury or inflammation is hyperalgesic, and the pain relieving action of NSAIDs at the local site is easily explained by this mechanism. In addition, PGs are thought to act in the spinal cord to facilitate the transmission of pain responses, though there is little known about how they might do this (122). NSAIDs can also act at these central sites (123–125). COX-2 is induced in both local and central sites (126), and the question of whether COX-2 mediates pain reception or transmission is being investigated, primarily through the use of COX-2 specific NSAIDs. Intrathecal injection of both the COX-2 specific inhibitor NS-398 and the nonspecific NSAID indomethacin suppressed a formalin mediated pain response (which measures a central response), but neither suppressed a high temperature induced local pain response (122). In contrast, systematically administered meloxicam, an NSAID more specific for COX-2 than COX-1, suppressed the inflammatory pain response locally (127) without affecting central pain
transmission. In neither of these studies was the drug introduced into both sites to allow an internal comparison, but together they show that COX-2 can act both locally and centrally to mediate pain. In fact, the COX-2 specific inhibitor Celecoxib was shown in short term human studies to effectively suppress the pain associated with dental work, osteoarthritis, or rheumatoid arthritis without causing any significant gastro duodenal lesions (127, 128).

**Role of COX isoforms in Cancer**

Cyclooxygenase (COX), a key enzyme in the prostanoid biosynthetic pathway, has received considerable attention due to its role in human cancers. Observational and randomized controlled studies in many different population cohorts and settings have demonstrated protective effects of nonsteroidal anti-inflammatory drugs for colorectal cancers (CRCs). COX-2, the inducible isoform of COX, is over-expressed in early and advanced CRC tissues. Experimental studies have identified important mechanisms and pathways by which COX-2 plays an important role in carcinogenesis. Selective COX-2 inhibitors have been approved for use as an adjunctive therapy for patients with familial polyposis. The role of COX-2 inhibitors is currently being evaluated for use in wider populations. The connection between inflammation and cancer was proposed long ago by Rudolph Virchow. The cancerous tissue also contains the cells and factors responsible for the features of the body's inflammatory response. Therefore, Virchow hypothesized that cancer begins at sites of chronic inflammation. Since that time the scientific community disavowed the idea that infection could also cause harm. The NSAIDs act by blocking COX-1 and COX-2, thus inhibiting the conversion of arachidonic acid to thromboxane and prostaglandins (129). Whilst COX-1 is expressed in platelets and the gastric mucosa, COX-2 is specifically induced in
sites of inflammation and neoplasia. Over expression of COX-2 was found to stimulate angiogenesis in tumors (130). Angiogenesis is an essential step in the transition of in situ cancers to invasive forms (131,132) and in the development of distant metastasis (133–135). COX-2 stimulates angiogenesis via multiple mechanisms.

The current understanding of the role of cyclooxygenase in cancer can be concluded as (i) promotion of the production of vascular endothelial growth factor, a potent angiogenic growth factor, by increasing its mRNA transcription (136, 137); (ii) production of thromboxane A2, prostaglandin E2 (PGE2) and prostacycline, products of arachidonic acid which are direct stimulants of endothelial cells (138–140); (iii) up regulation of matrix metallo-proteinases, which are endopeptidases essential for tumour and vascular cell invasion (141, 142) and (iv) inhibition of the production of interleukin-12, a potent antiangiogenic cytokine (143, 144). Another pro-cancerous effect of the over expression of COX-2 is the increased resistance to apoptosis (145). This resistance is caused by the increased production of Bcl-2, an antiapoptotic protein, in response to high levels of PGE2 – a product of COX-2 (146, 147).

Another pro survival effect of COX-2 is the activation of the Akt system which is essential for vascular endothelial cell survival (1480. The increased production of prostaglandins by COX-2 can cause local immune suppression by decreasing the activity of both lymphocytes and natural killer cells and inhibition of the production of TNF- that can alter the antitumour immune response (149,150). In several types of cancer, over expression of COX-2 is correlated with advanced disease and poor prognosis (151, 152). COX-2 inhibitors were found both in vitro and in vivo to be antiangiogenic agents and to induce apoptosis (130, 153). These studies have provided further evidence for the role of COX-2 in carcinogenesis.
Some studies have suggested that their anticancer effect may also be through COX-2 independent mechanisms, such as by increasing the level of endostatin an endogenous angiogenesis inhibitor (154) and by interference with DNA binding of transcription factors (155). COX-2 is induced by procarcinogens found in tobacco smoke and in turn, its peroxidase activity converts these chemicals into highly reactive mutagens that bind to DNA (156). This data has kindled interest in the possible effects of NSAIDs as anticancer agents, and also encouraged many studies on the preventive roles COX-2 selective and non-selective NSAIDs in many types of cancers.

**Role of COX-2 in Atherosclerosis**

COX is the rate limiting enzyme catalyzing the conversion of arachidonic acid into prostanoids, the lipid mediators critically implicated in a variety of physiological and path physiological processes, including inflammation, vascular and renal homeostasis, and immune responses. In the setting of acute ischemic syndromes it has been recognized that COX pathway plays an important role. The function of platelet COX-1 in acute ischemic diseases is firmly established, but the role of COX-2 in atherothrombosis remains controversial. The complex role of COX-2 in this setting is also confirmed by the unexpected cardiovascular side effects of long-term treatment with COX-2 inhibitors (157).

The COX-2 influences the construction of atheromatous tissue. The lesion involves three cell types; endothelial, monocyctic/macrophage, and vascular smooth muscle cells. Disruption of the endothelial cell barrier between circulating blood and tissue, monocyte/macrophage sequestration at these sites with elaboration of inflammatory cytokines, and the transmigration and uncontrolled proliferation of vascular smooth muscle cells typify the initial phase
of the atherosclerotic process. COX-2 expression has been found in each of these cell types in animal models as well as in human atherosclerotic tissue (158–160). Similarly, COX-2 can be induced in these cells by many, of the same proinflammatory mediators implicated in the development of atherosclerosis. Such mediators include tumour necrosis factor (TNF), interleukin-1 (IL-1), interferon- , free radicals, endotoxin, platelet-derived growth factor, hypoxia, and sheer stress as recently reviewed (160). The presence of COX-2 in cells which comprise the atheromatous lesion as well as its inducibility by mediators of atherogenesis are in keeping with experimental and clinical data showing that prostaglandin production is increased in atherosclerosis; just as it is in other inflammatory conditions (160,161).

The histological findings show COX-2 expression is found in human atheromatous plaque lesions in diseased coronary arteries resected at the time of surgical revascularization, but not in normal coronary arteries (158, 159). Furthermore, COX-2 expression co-localizes with inducible nitric oxide synthase (iNOS), suggesting an interaction between the two inflammatory mediators. Lastly, augmented COX-2 expression is present in diseased, transplanted coronary arteries to the same extent as that found in diseased native coronary arteries (159).

Accumulation of low-density lipoprotein (LDL) in the sub endothelial region of the vascular wall is a primary event in the initiation of atherosclerotic injury. Monocytes attracted to these areas of accumulated LDL by increased expression of adhesion molecules on endothelial cell membranes, aggregate on the surface of the lumen and subsequently transmigrate into the intimal layer. Here they differentiate into macrophages which scavenge lipoproteins, ultimately forming foam cells. LDL, however, is first oxidatively modified which facilitates its uptake
by the macrophage (162). Oxidized LDL (oxLDL) accelerates the formation of foam cells that contribute their lipid contents to fatty streak formation, the histological hallmark of the initial stage of atherosclerosis. Experimentally, the ability of oxLDL to activate a macrophage is not only dependent on oxidation of either the protein moiety or lipid moiety of the LDL molecule, but also requires fully differentiated macrophages derived from monocytes (163). The relationship between COX-2 and oxLDL is not straightforward. Activated macrophages produce a variety of inflammatory mediators, including prostaglandins. Thus, increased COX-2 activity would be expected in oxidatively stressed macrophages given its inducible nature. In animal models, however, macrophages exposed to oxidized lipoproteins decrease their prostaglandin production (PGE2 and PGI2) when stimulated by inflammatory cytokines such as lipopolysaccharide (LPS) (164). As such, cholesterol rich macrophages and foam cells appear to have an impaired or reduced inflammatory response, rather than an augmented one, following oxLDL exposure (165). Recently, Eligini et al. (166) reported that oxLDL inhibited LPS induced COX-2 expression in human macrophages.

The pathophysiological significance of oxLDL's ability to down regulate COX-2, specifically, and to diminish macrophage responsiveness to inflammatory stimuli, globally remains unclear. One argument highlights the negative feedback exerted on macrophage colony stimulating factor (M-CSF) by PGE2 and PGI2 (167). Enhanced M-CSF secretion by monocytes could foster proliferation and accumulation of macrophages in areas of atheroma formation, potentiating the atherosclerotic process. Another argument contends that normal resolution of inflammatory processes requires intact and robust cellular responses to such stimuli, ‘effective clean-up’ in essence. Blunted inflammatory responses by macrophages exposed to oxLDL, early in the development of atheromatous
lesions, could limit tissue repair and result in a low grade state of chronic inflammatory injury which is unable to repair itself. Pharmacological intervention with selective COX-2 inhibitors may help to delineate the relationship between oLDL, COX-2, and the activated macrophage. Another lipoprotein, high-density lipoprotein or HDL, exerts an ‘antiatherogenic’ or protective effect on the cardiovascular system. A strong inverse correlation exists between levels of HDL and the frequency as well as mortality of atherosclerotic disease (168). Functionally, HDL is known to remove excess cholesterol from the circulation and inhibit oxidation of LDL. The latter function is accomplished by paraoxonase; an esterase that degrades oxidized phospholipids and which uses HDL as its carrier protein (169). What is not clear is whether HDL’s angioprotective effect is attributable to these or to other unrelated functions. Cockerill et al. have reported on the inhibitory effect of HDL on cytokine induced adhesion molecule expression by human endothelial cells (170). Based upon previous observations that HDL stimulates endothelial cell PGI2 synthesis (171), these investigators also reported that HDL can synergistically increase COX-2 expression in human endothelial cells following cytokine stimulation with either IL-1β or TNF. The synergistic increase in COX-2 protein is mirrored by increased PGI2 production in these cytokine stimulated cells (172). Although HDL clearly has opposing effects on two cytokine stimulated responses by human endothelium, the results may be additive. On one hand, an increase in PGI2, mediated by a HDL induced increase in COX-2 expression, serves to inhibit platelet aggregation, cholesterol accumulation, and vascular smooth muscle cell proliferation/contraction and thus may be vasoprotective. Concurrently, decreased expression of adhesion molecules on cytokine-induced endothelial cell membranes may also be consistent with an antiatherogenic effect of HDL.
PGI2 is a metabolite of arachidonic acid and the major prostaglandin produced by endothelial cells. As mentioned earlier, PGI2 is a potent inhibitor of leukocyte activation and adhesion, platelet aggregation, and vascular smooth muscle cell proliferation, migration and contraction. Its role in vitro, however, has remained unclear. Recently, a knockout mouse deficient in the PGI2 receptor IP, has demonstrated an antithrombotic as well as antiinflammatory role for PGI2 (173). It is also well established that PGI2 excretion is increased in patients with ‘activated platelet’ conditions such as unstable atherosclerotic disease as well as following vascular interventional procedures (161). On one hand, it would not be unreasonable to predict a facilitative role for COX-2 in these conditions of increased PGI2 production, given its inducible nature and the fact that COX-2 is responsible for the majority of PGI2 produced in the body (174). On the other hand, nonselective NSAID therapy (sulindac and indomethacin) inhibits intimal proliferation and prevents or slows vascular changes in atherosclerosis prone mice while aspirin and nimesulide (a selective COX-2 inhibitor) do not (175).

Clinically, a question arises regarding the lack of inhibition by selective COX-2 inhibitors of thromboxane (TBX), a COX-1 mediated prostaglandin, produced primarily by platelets. Given TBX’s procoagulant and vasoconstricting effects, long term therapy with COX-2 inhibitors may create a state of chronic, ‘unopposed’ TBX activity with potentially deleterious cardiovascular outcomes. In the VIGOR trial, for example, over 8000 patients with rheumatoid arthritis were randomized to receive either naproxen (500 mg po bid) or rofecoxib (50 mg po q day) for 12 months (176). Aspirin therapy was excluded in all subjects since the mucosa of the GI tract was being evaluated. Although rofecoxib demonstrated a marked gastro protective effect, a significantly increased incidence of myocardial infarction occurred in the rofecoxib treated group. A large percentage of these
adverse events occurred in a small subset of patients who were at risk for myocardial infarction and should have been receiving aspirin therapy but were unaware of their risk factors at the time of randomization. These results have been attributed to the lack of antiplatelet activity demonstrated by selective COX-2 inhibitors. As noted recently, selective COX-2 inhibition may offer gastro protection but not cardio protection (177). COX regulates the production of eicosanoids, which modulate physiologic processes in the vessel wall contributing to atherosclerosis and thrombosis, including platelet aggregation, control of vascular tone, and the local inflammatory response. Cyclooxygenase-1 mediates production of platelet thromboxane A2, a potent vasoconstrictor and platelet agonist, whereas both COX 1 and 2 contribute to production of endothelial prostacyclin, a vasodilator that inhibits platelet activation. Concerns have been raised that COX-2 inhibitors may increase thrombotic cardiovascular events by disturbing the balance between platelet thromboxane A2 and endothelial prostacyclin, but this controversial issue will only be resolved by prospective clinical trials. Because COX-2 is upregulated in activated monocyte/macrophages, which play a key role in the pathogenesis of atherosclerosis, it is recently tested hypothesis that pharmacological inhibition of COX-2 in LDL receptor deficient mice would reduce early atherosclerosis. After 6 weeks on a Western-type diet, male LDL receptor deficient mice treated with either rofecoxib (a selective COX-2 inhibitor) or indomethacin (a non-selective COX inhibitor) had significant reductions in atherosclerosis when compared with control mice. Also, LDL-receptor deficient mice null for macrophage COX-2 were generated by fetal liver cell transplantation and developed significantly less atherosclerosis than control LDL-receptor deficient mice transplanted with fetal liver cells wild type for COX-2, providing genetic evidence in support of a pro atherogenic role for macrophage COX-2 expression. These results support the
potential of antiinflammatory approaches for the prevention of atherosclerosis and identify cyclooxygenase-2 as a target for intervention (178).

**Conclusion**

This review highlights the role of COX isoforms in many physiological systems. The precise mechanisms by which this biosynthetic pathway can mediate such diverse functions are still being understood and will likely continue until researchers fully characterize the biology of the various PG synthases and receptors downstream of COX. Nevertheless, identifying an inducible COX was a major breakthrough in this area. What evolved from this discovery was a paradigm in which one isoform, COX-1, was mainly responsible for the biosynthesis ofPGs involved in homeostatic regulation, while the second isoform, COX-2, was primarily involved in producing PGs in response to a wide spectrum of environmental insults and internal stimuli. Such a mechanism appears to explain, at least in part, both the therapeutic and toxic effects of NSAIDs in humans. The major side effects of NSAIDs, gastro duodenal erosion and disruption of normal renal function, appear to be caused by the inhibition of COX-1, while the antiinflammatory and analgesic activity of these drugs rests largely on their ability to inhibit COX-2. Investigations into the role of COX-2 in disease have suggested that chronic activation of this enzyme may be pathological in the colon, where there is strong evidence to suggest that inhibition of COX-2 can limit the progression ofcolorectal cancer. Thus, a little more than a century after the discovery of aspirin, the potential clinical indications for NSAID use appear to be widening from their original purpose as analgesic agents. COX-3 is considered a new and important lead in the generation of anti-inflammatory and analgesic agents. However, a frame shift caused by complete retention of intron 1
in the human sequence questions its relevance to human pathophysiology
Ongoing studies to more clearly delineate the role of each COX isoform will be
crucial in defining the use of these drugs in the next century. COX-2 is now
considered as a viable target for chemotherapy, especially since selective COX-2
inhibitors have improved safety profiles compared with nonselective NSAIDs and
are much less toxic than most chemotherapeutic agents. There is increasing
evidence for the involvement of COXs in the development and progression of
cancer, Alzheimer’s disease, Parkinson’s disease and other pathophysiological
states. Development of therapeutic and diagnostic tools to treat these diseases is
being actively investigated. Moreover, variants of cyclooxygenase derived from
alternative splicing have been reported. Elucidation of the roles played by these
variants could provide greater insight into the roles of COXs in health and
disease.

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