1

The Role of COX-2 Inhibitors on Experimental Colitis

Ana Paula R. Paiotti[1], RicardoArtigiani-Neto[1], Daniel A. Ribeiro[1,2], Sender J. Miszputen[3] and Marcello Franco[1]
Universidade Federal de São Paulo, Escola Paulista de Medicina
[1]Departament of Pathology
[2]Departament of Biosciences
[3]Division of Gastroenterology
Brasil

1. Introduction

Since the introduction of acetylsalicylic acid (aspirin) as the first nonsteroidal antiinflammatory drug (NSAID) in 1897, NSAIDs have been widely used in the management of pain and inflammation (Botting, 2010; Vane et al., 1990; Wallace, 1997). Today, they are classified as traditional nonsteroidal antiinflammatory drugs (tNSAIDs), characterized by differing degrees of antiinflammatory, analgesic and antipyretic activity. tNSAIDs are among the most widely used medicines in the world. Unfortunately, they are associated with dose-dependent gastrointestinal (GI) adverse events ranging from dyspepsia (10-20%) to symptomatic and complicated ulcers (1-4%) (Scheiman, 2006; Wolfe et al., 1999). The mechanism of tNSAIDs action is attributed to the cyclooxygenase (COX) inhibition (Botting, 2010; Vane, 1971). Cyclooxygenase is a key rate-limiting enzyme that exists in at least two isoforms: COX-1 is observed constitutively expressed in various tissues, whereas COX-2 does not appear to be expressed except at very low levels in most tissues and is rapidly upregulated in response to growth factors and cytokines. More recently, COX-2 has been implicated in several distinct cellular mechanisms, such as angiogenesis, proliferation and the prevention of apoptosis (Dempke et al., 2001). New antiinflammatory drugs have been synthesized, such as selective COX-2 inhibitors (anti-COX-2), however, these drugs may present side effects, such as the ability to modify the epithelial barrier.

Inflammatory bowel disease (IBD) is a common chronic gastrointestinal disorder characterized by alternating periods of remission and active intestinal inflammation. The precise etiology of IBD, including Crohn´s disease (CD) and ulcerative colitis (UC), remains unclear. However, environmental factors, immunological disturbances, genetic influences and the presence of certain chemical mediators (cytokines) have been established as putative participants in the pathogenesis of the disease (Barbieri, 2000; Lashner, 1995; Podolsky, 2002).

In the last few decades, the development of experimental models for studying IBD has greatly contributed to enhance understanding of the immunological mechanisms involved, such as changes in the gut epithelial barrier (Colpaert et al, 2001; Shorter et al, 1972). IBD seems to occur when luminal antigens from the bacterial flora stimulate the immune system

in the gut barrier towards an exacerbated, genetically defined response. Patients present an increase in the amount of intestinal bacterial antigen compared to healthy individuals (Bonen & Cho, 2003). In particular, some human and animal studies have shown the prime importance of gut epithelial barrier integrity and changes that lead to deregulation of the immune system as a result of the loss of intestinal homeostasis (Élson et al., 1995).

A possible association between the use of NSAIDs and the relapse of IBD has been repeatedly suggested. IBD patients seek relief in NSAIDs for non-IBD-related pains (arthralgias, arthritides) and these drugs are also prescribed for the symptons of extraintestinal manifestations of IBD, such as peripheral arthritis, sacroiliitis, ankylosing spondylitis, and osteoporosis-related fractures. NSAIDs are considered to be the first-line treatment for the abnormalities just mentioned (i.e, relieve pain and treat inflammation).

It has been reported that CD is associated with gut barrier dysfunction and that some patients express an instestinal barrier hyperresponsiveness to NSAIDs (Gornet et al., 2002). Thus, clinicians are concerned that the treatment with NSAIDs could increase the risk of disease aggravation relapse in controlled patients. A large number of people suffering from IBD take NSAIDs and COX-2 inhibitors for various reasons, as the efficiency of these drugs in pain control seems to be unquestioned. In some patients, exacerbation disease happens; however it is uncertain whether NSAIDs are implicated in IBD relapse or whether COX-2 inhibitors are safer than NSAIDs.

NSAIDs have been implicated in the onset or the exacerbation of IBD in a number of studies and case reports, whereas in other studies, no relationship has been found between NSAID treatment and an increase in significant disease flares. On the other hand, COX-2 inhibitors have a smaller incidence of toxicity to the small bowel or colon, as recent studies indicate that COX-2 inhibitors are prescribed more often than NSAIDs in patients who are older, sicker, and have risk factors associated with NSAID gastropathy (Bonner et al., 2000; Bonner et al., 2004; Kurahara et al, 2001; Vane et al., 1998). Is the concept that the use of NSAIDs is associated with relapse of IBD is true? For this reason, many studies are conducted with the use of COX-2 in experimental models. So, the objective of this review is to describe the role of COX-2 inhibitors on different experimental models of colitis.

2. COX-1/ COX-2 concept, biochemistry and structural comparisons

Cyclooxygenase (COX) or prostaglandin H2 synthase (PGHs) is the enzyme that catalyzes the first two steps in the biosynthesis of the prostaglandins (PGs) from the substrate arachidonic acid (AA). These are the oxidation of AA to the hydorxyendoperoxide PGH2. The PGH2 is transformed by a range of enzymes and nonenzymic mechanisms into the primary prostanoids, PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2 (TXA_2) (DeWitt & Smith , 1988) (**Figure 1**).

COX activity has long been studied in preprarations from sheep seminal visicles, and this enzyme was cloned by three separate groups in 1988 (DeWitt & Smith , 1988; Merlie et al, 1988; Yokoyama et al., 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. Induction of this isoform, COX-2, by several stimuli associated with cell activation and inflammation assured the relevance of this finding to inflammatory disease in general. A clear sign of the therapeutic value of this discovery is that in the relatively short time of about five years, several highly effective anti-inflammatory agents and new therapeutic areas have become subjects for

investigation (Bakhle & Botting, 1996; Botting, 2010; Herschman, 1996; Jouzeau et al., 1997; Luong et al., 1996).

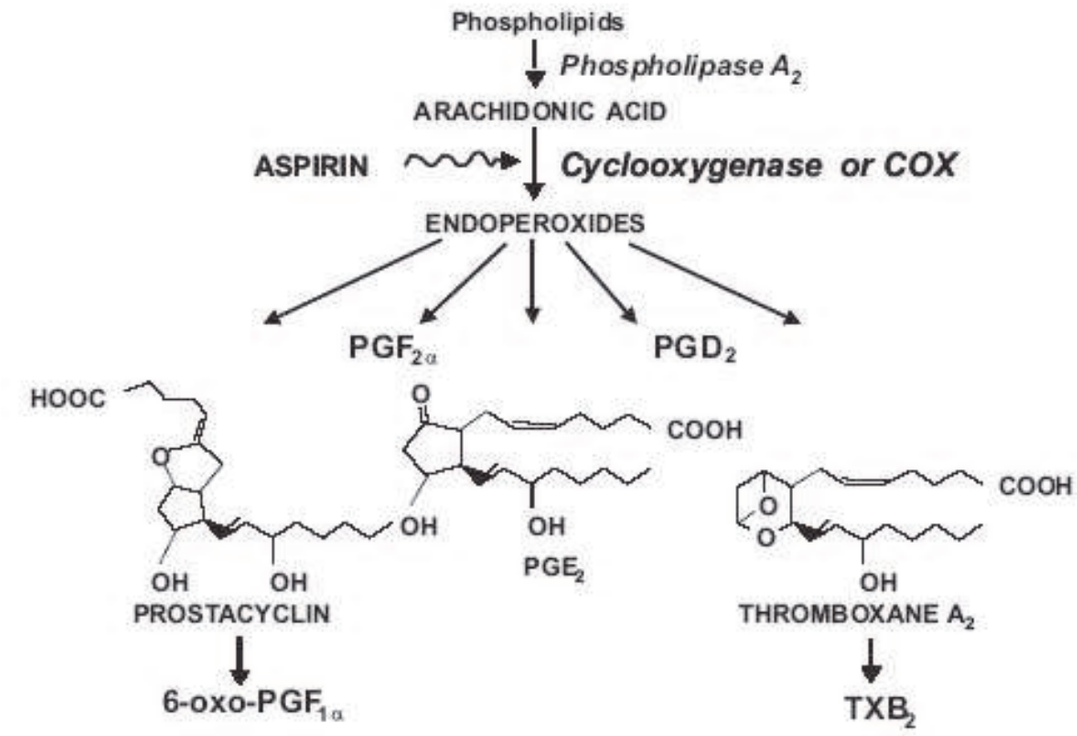


Fig. 1. The arachidonic acid cascade.

The inducible enzyme COX-2 is very similar in structure and catalytic activity to the constitutive COX-1. The biosynthetic activity of both isoforms can be inhibited by aspirin and other NSAIDs (Botting, 2010; Vane, 1971). Both isoforms have a molecular weight of 71 K and are almost identical in length, with just over 600 aminoacids, of which 63% are in an identical sequence. However, the human COX-2 gene at 8.3 kb is a small immediate early gene, whereas human COX-1 originates from a much larger 22-kb gene. The gene products also differ, with the mRNA for the inducible enzyme being approximately 4.5 kb and that of the constitutive enzyme being 2.8 kb (Bakhle & Botting, 1996; Botting, 2010; Jouzeau et al., 1997).

The three-dimensional X-ray crystal structure of human or murine COX-2 (Mancini et al, 1994; Picot etal., 1994) can be superimposed on that COX-1 (Lecomte et al., 1994); the residues that form the substrate binding channel, the catalytic sites, and the residues immediately adjacent are all identical except for two small variations. In these two positions, the same substitutions occur: Ile in COX-1 is exchanged for Val in COX-2 at positions 434 and 523 (the residues in COX-2 are given the same number as their equivalent aminoacids in COX-1).

In spite of this structural identify, there are clear biochemical differences between the isoforms in substrate and inhibitor selectivity. For example, COX-2 will accept a wider

range of fatty acids as substrates than will COX-1 (Bakhle & Botting, 1996; Botting, 2010). Thus, although both enzymes can utilize AA and dihomo-γ-linolenate equally well, COX-2 oxygenates other fatty acid substrates, such as eicosapentaenoic acid, γ-linolenic acid, α-linolenic acid, and linoleic acid more efficiently than does COX-1. Also, COX-2 acetylated by aspirin on Ser 530 will still oxidize AA but to 15-HETE, whereas similarly acetylated COX-1 will not oxidize AA at all (Griswold & Adams, 1996; O'Neill et al., 1994; Wong et al., 1997). In addition (see below), inhibitors will differentiate between COX-2 and COX-1 with over 1000-fold selectivity (Gierse et al., 1996; Luong et al., 1996).

Supporting evidence is strongest from the work on COX-2-selective inhibitors; mutation of Ile 523 to Val in the COX-1 protein allows COX-2-selective inhibitors to bind and inhibit PGH_2 formation without altering the K_m for AA (Guo et al., 1996), and the reverse mutant of COX-2 in which Val 523 is exchanged for Ile shows inhibitor binding and selectivity profiles comparable to those of wild-type COX-1 (Bhattacharyya et al., 1996; Mancini et al., 1995). The structural basis for this has been shown clearly in the crystal analyses of COX-2, which have used either the human or the murine protein, each bound to a nonselective COX-1 or COX-2 inhibitor. The smaller size of Val 523 allows the inhibitor access to a side pocket off the main substrate channel in COX-2-access that is denied sterically by the longer side chain of Ile in COX-1. Selective inhibitors of COX-2 do not bind to Arg 120, which is used by the carboxylic acid ot the substrate AA and by the COX-1-selective or-nonselective NSAIDs, all of which are carboxylic acids (Ren et al., 1995a; Ren et al., 1995b).

Another striking structural difference between the isoforms, but of unknown significance, is the absence of a sequence of 17 amino acids from the N terminus and the insertion of a sequence of 18 amino acids at the C terminus of COX-2 i comparison to COX-1. This accounts for the different numbering for the analogous residues in the two isoforms (e.g. the acetylatable serine is Ser 530 in COX-1 but Ser 516 in COX-2). The C-terminal insert in COX-2 does not alter the last four amino acids residues, which in both proteins form the signal for attachment to the membrane of the endoplasmic reticulum (ER). However, COX-2 is located on the nuclear membrane as well as on the ER, while COX-1 is found attached only to the membranes of the ER. The reason for this selective localization may lie in the different sequence of the C terminus. It is relevant that in the X-ray structural analysis of either isoform, the three-dimensional structures of the last 18 C-terminal residues in COX-1 and the last 30 residues in COX-2 were not resolved, implying a marked flexibility in this region of the proteins even in the crystalline form (Hudson et al., 1993; Mitchell et al., 1993; Morita et al., 1995; Otto & Smith, 1994; Regier et al., 1993). Although emphasis has been placed here on the differences between isorforms, the extensive overall structural and biochemical similarity between COX-1 and COX-2 must be reiterated. Both use the same endogenous substrate, AA, and form the same product by the same catalytic mechanism. Their major difference lies in their pathophysiological functions.

2.1 Physiological and pathological functions of COX-1 and COX-2

Chronic inflammation is an excellent example of a disease that represents a malfunction of normal host defense systems. Thus, rather than classifying PG biosynthesis into physiological and pathological, it may be better to use the classification applied to the COX isoforms: either constitutive or induced. COX-1 activity is constitutive, present in nearly all cell types at a constant level; COX-2 activity is normally absent from cells, and when induced, the protein levels increase and decrease in a matter of hours after a single stimulus (Bakhle & Botting, 1996; Botting, 2010; Jouzeau et al., 1997).

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 alpha (TNF-α). The anti-inflammatory cytokines, IL-4, IL-10, and IL-13, will decrease induction of COX-2, as will the corticosteroids (Bakhle & Botting, 1996; Luong et al., 1996). 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, hemorrhage and ulceration.

2.2 Mechanisms of NSAID injury to the gastrointestinal mucosa

For evaluation of the validity of new potentially less toxic NSAIDs it is mandatory to clearly understand the pathogenesis of NSAID induced ulceration (**Figure 2**). Both aspirin and non-aspirin NSAIDs inhibit the COX pathway of prostaglandin synthesis (Botting, 2010; Hudson et al., 1993; Mitchell et al., 1993; Vane, 1971). This represents the basis of anti-inflammatory action but is also responsible for the development of side effects in the gastrointestinal tract and kidney as well as inhibition of platelet aggregation. Inhibition of prostaglandin synthesis can exert injurious actions on the gastric and duodenal mucosa as it abrogates a number of prostaglandin dependent defence mechanisms. Inhibition of COX leads to a decrease in mucus and bicarbonate secretion, reduces mucosal blood flow, and causes vascular injury, leucocyte accumulation, and reduced cell turnover, all factors that contribute to the genesis of mucosal damage. Within this broad spectrum of events, the microvascular damage appears to play a central role. Prostaglandins of the E and I series are potent vasodilators that are continuously produced by the vascular endothelium. Inhibition of their synthesis by an NSAID leads to vasoconstriction (Gana et al., 1987). Furthermore, inhibition of prostaglandin formation results in a rapid and significant increase in the number of neutrophils adhering to the vascular endothelium in both gastric and mesenteric venules (Asako et al., 1992 a;b; Wallace et al., 1993). Adherence is dependent on expression of the â2 integrin (CD11/CD18) on neutrophils and intercellular adhesion molecule on the vascular endothelium (Wallace et al., 1993). Neutrophil adherence in turn causes microvascular stasis and mucosal injury through ischaemia and release of oxygen derived free radicals and proteases (Vaananen et al., 1991).

The severity of experimental NSAID gastropathy was markedly reduced in rats rendered neutropenic by pretreatment with antineutrophil serum or methotrexate (Lee et al., 1992; Wallace et al., 1990) Recently, Wallace et al (2000) provided evidence for an isoenzyme specific role of COX in the homeostasis of the gastrointestinal microcirculation. Thus in rats, the selective COX-1 inhibitor SC-560 decreased gastric mucosal blood flow without affecting leucocyte adherence to mesenteric venules. In contrast, the selective COX-2 inhibitor celecoxib markedly increased leucocyte adherence but did not reduce gastric mucosal blood flow. Only concurrent treatment with the COX-1 and COX-2 inhibitor damaged the gastric mucosa, suggesting that reduction of mucosal blood flow and increase in leucocyte adhesion have to occur simultaneously to interfere with mucosal defence. Inhibition of prostaglandin synthesis thus plays a key role in induction of mucosal injury but does not represent the only pathway by which NSAIDs can damage the gastrointestinal mucosa. NSAIDs can also induce local damage at the site of their contact with the gastrointestinal mucosa. Topical

application of NSAIDs increases gastrointestinal permeability allowing luminal aggressive factors access to the mucosa. Aspirin and most non-aspirin NSAIDs are weak organic acids. In the acidic milieu of the stomach, they are converted into more lipid soluble unionised acids that penetrate into the gastric epithelial cells. There, at neutral pH, they are reionised and trapped within the cell causing local injury. Having entered gastric mucosal epithelial cells, NSAIDs uncouple mitochondrial oxidative phosphorylation. This effect is associated with changes in mitochondrial morphology and a decrease in intracellular ATP and therefore a reduced ability to regulate normal cellular functions such as maintenance of intracellular pH. This in turn causes loss of cytoskeletal control over tight junctions and increased mucosal permeability. The ability of NSAIDs to uncouple oxidative phosphorylation stems from the extreme lipid solubility and position of a carboxyl group that acts as a proton translator (Mahmud et al., 1996; Somasundaram et al., 2000). A further mechanism involved in the topical irritant properties of NSAIDs is their ability to decrease the hydrophobicity of the mucus gel layer of the gastric mucosa. NSAIDs can convert the mucus gel from a non-wettable to a wettable state and in experimental animals this effect has been shown to persist for several weeks or months after discontinuation of NSAID administration. Gastric mucosal lesions can also occur in a non-acidic milieu, such as following rectal application. With oral administration, gastric acid however appears to enhance NSAID induced damage. More extensive and deeper erosions occur at low pH and an elevation in gastric pH above 4 is necessary to prevent this acid related component. Prostaglandins do not represent a unique pathway to protect the gastric mucosa. Nitric oxide (NO) has the potential to counteract potentially noxious effects of inhibition of

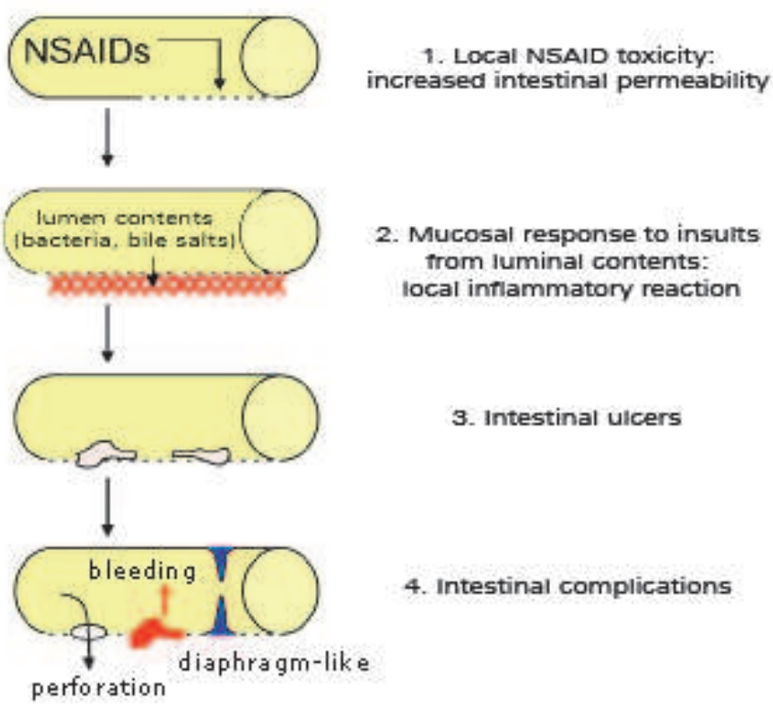


Fig. 2. Pathogenesis of NSAID-induced intestinal lesions (Taken from Thiéfin & Beaugerie, 2005).

prostaglandin synthesis, such as reduced gastric mucosal blood flow and increased adherence of neutrophils to the vascular endothelium of the gastric microcirculation. NO has well characterised inhibitory effects on neutrophil activation/adherence demonstrated in various tissues.

2.3 Chronic inflammatory bowel disease and COX-2

The potential role for prostaglandins in the inflammatory process underlying chronic IBD has been a focus of controversy. Under the hypothesis that prostaglandins may be protective, treatment with exogenous prostaglandins was investigated but found to exacerbate the diarrhea. The possibility that proinflammatory mechanisms might be involved prompted trials of NSAID therapy. However, studies of various NSAIDs in patients with ulcerative colitis showed either no improvement or an exacerbation of the symptoms (Rampton & Sladen, 1981). In keeping with these early findings, some reports suggested a deleterious effect of NSAIDs on the course of IBD (Evans et al., 1997; Felder et al., 2000). The magnitude of the risk, however, remains controversial (Bonner et al., 2002; Nion-Lamurier et al., 2003). The recent review article meets different studies including original papers, case reports, reviews, controlled trials and databases about exacerbation of IBD associated with the use of NSAIDs (Kefalakes et al., 2009). The **Table 1** showed the mechanisms of action of NSAIDs and COX-2 inhibitors in patients with IBD.

2.4 Development of the "COXIBs"

The identification of the COX-2 isoenzyme opened the door to development of NSAIDs which selectivity inhibit COX-2. The main goal of which was to decrease the GI toxicity. The first generation of selective COX-2 inhibitors came from animal models in which compounds were sought that were potent anti-inflammatory agents with minimal side effects on the stomach (Nimesulide, etodolac and meloxicam) (Carvalho et al., 2004). The discovery of the specificity these products was in reality found after the sale, being due, mainly on clinical and experimental observations reduced incidence of gastrointestinal side effects, and subsequently confirmed by *in vitro* studies. The nimesulide is considered an aberrant example of NSAIDs, with good power in vivo inflammatory models, but with weak inhibition in vitro preparations of COX. The nimesulide and display specificity of action on COX-2, has other effects that further enhance their anti-inflammatory activity, as inhibition of neutrophil activation and antioxidant properties. Based on in vitro studies initially suggested that meloxicam selectively inhibited COX-2. However, when tested in *vivo*, in humans, its specificity for COX-2 was only about ten times higher than that for COX-1, with further platelet inhibition (Panara et al., 1999). The molecular modification of these drugs, especially those of nimesulide, in order to increase its COX-2 selectivity, resulted in structures without a carboxylic group and the presence of a sulphonamide or sulphone group, resulting specific inhibitors in the second generation. This group includes celecoxib, rofecoxib, valdecoxib, parecoxib (pro-drug of valdecoxib), APHS [o-(acetoxyphenyl)hept-2-ynyl sulfide] and etoricoxib (Fitzgerald & Patrono, 2001; Kulkarni et al., 2000).

Coxib spare COX-1 and firstly inhibit COX-2 function therefore decrease but do not eliminate NSAIDs associated GI toxicity and are efficacious as tNSAIDs in relieving pain. Data from large GI outcomes studies have characterised the GI effects of coxib. The Celecoxib Longterm Arthritis Safety Study (CLASS Study) that compared high dose Celecoxib (400 mg bid), diclofenac (75 mg bid), and ibuprofen (800 mg 3 times daily)

showed that symptomatic ulcers were significantly less common among celecoxib users than tNSAIDs users; however ulcer complication rates were not significantly different (which was probably due to the confounding factor of concomitant low-dose aspirin use which was present in 22% of patients) (Silverstein et al., 2000). However, a recent meta-analysis of available trials of the Cochrane collaboration confirms that celecoxib at any dosewas associated with statistically less GI events (Moore et al., 2005). Moreover, the results of another large outcomes study, celecoxib vs naproxen and diclofenac in osteoarthritis patients (SUCCESS I Study), confirmed the significantly better safety profile of celecoxib compared with tNSAIDs (Singh et al., 2006). The Vioxx Gastrointestinal Safety of Rofecoxib trial (VIGOR Study) concluded that rofecoxib users had 50% fewer GI events compared with naproxen users (Bombardier et al., 2000). Later, in the comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and

Drug	**Mechanism of action**
Conventional NSAIDs	COX-1 and COX-2 → PGE reduction Surface membrane phospholipid interaction Effect on mitochondrial energy metabolism (oxydase phosphorilation inhibition → ATP deficiency → ↑ mucosal permeability) Escalation of intestinal inflammatory activity Enhancement of enterohepatic circulation Formation of drug enterocyte adducts COX-independent damage to the small intestine Small-bowel enteropathy → blood loss → hypoalbuminemia ↑ TNF-α, IL-1, NO release Lower the thromboxane production
COX-1 inhibitors	Impairs mucosal microcirculatory blood flow Lower the thromboxane production Impairs mucous secretion and acid regulation Impair renal blood flow and platelet aggregation
COX-2 inhibitors	Imunomodulatory and anti-inflammatory role on the GI tract (selective COX-2 inhibition → PGE reduction) Loss of vasodilation Increased of vascular permeability May delay epithelial proliferation Delay wound healing ↑ Oxygen metabolites (LTB4, TNF) ↑ Leukocyte adherence to the vascular endothelium

Table 1. Mechanisms of action of NSAIDs and COX-2 inhibitors in patients with IBD (Taken from Kefalakes et al., 2009).

Gastrointestinal Event Trial (TARGET), showed a 75% decrease in adverse GI events with the coxib (Schnitzer et al., 2004). It is important to emphasise that although the incidence of adverse GI events increased in relation to the presence of GI risk factors, the differences from NSAIDs were maintained in subgroups of patients with and without risk factors (Skelly et al., 2003).

The lumiracoxib is a novel highly selective COX-2 inhibitor. Lumiracoxib differs structurally from others drugs in the class of selective COX-2 inhibitors (**Figure 3**) (Brune & Hinz 2004; Mangold et al., 2004). Differently, the lumiracoxib is a phenyl acetic acid derivative. It has the highest selectivity (selective for COX-2 compared with COX-1 in the human whole blood assay with a ratio of 515:1 in healthy subjects and a fairly short plasm half-life (3-6 hours) compared with other COX-2 selective inhibitors (Esser et al., 2005). In endoscopic studies, lumiracoxib has been associated with a rate of acute gastric injury and chronic ulcer formation that does not differ form placebo (Rordorf et al., 2003) and which was significantly lower than with the NSAID ibuprofen and with celecoxib (Hawkey et al., 2004; Kivitz et al 2004).

Notwithstanding, it is important to note that 3 of the above commented outcome studies (CLASS, TARGET and SUCCESS studies) (Schnitzer et al., 2004; Silverstein et al., 2000; Singh et al., 2006), one endoscopy study (Solomon et al., 2005) and several epidemiological studies (Lanas et al., 2005) have shown that the concomitant use of low-dose aspirin and coxib or tNSAIDs increases further the risk of upper GI bleeding in NSAIDs users and attenuates the GI advantage of a coxib over an tNSAID.A recent meta-analysis of RCTs has shown that coxib plus low-dose ASA use was associated with a lower risk of upper GI complications when compared to non-selective NSAID plus low-dose ASA (Rostom et al., 2009). These gastrointestinal benefits have to be balanced against the known cardiovascular risks, particularly with long-term use. The VIGOR and Adenomatous Polyp Prevention on Vioxx Trial Investigators (APPROVe) studies showed that rofecoxib were associated with increased risk of cardiovascular events after 12 and 36 months of treatment when compared to naproxen (VIGOR) or placebo (APPROVe) (Bombardier et al., 2000; Bresalier et al., 2005). Other outcome studies have shown also that celecoxib at doses of 400 mgbid or 200 mgbid (Laine et al., 2004), but not 400 mg once a day (Arber et al., 2006) is associated with increased risk of cardiovascular events. Observational studies have shown, however, that celecoxib at 200 mg/day dose was not associated with increased risk of cardiovascular events (Bombardier et al., 2000; Silverstein et al., 2000). Recent observational studies have shown that also most NSAIDs (including nonselective) may be associated with increased cardiovascular risk and this may be different for the different compounds, dose and length of treatment (Chan et al., 2006; Lanas et al., 2005; McHippisley-Cox & Coupland, 2005). Of all traditional NSAIDs, diclofenac have been found to be the one increasing the CV risk the most (Mc Gettigan & Henry, 2006). In the MEDAL program etoricoxib at the dose of 60–90 mg/day was found to be not different to diclofenac in the incidence of CV events (Cannon et al., 2006). The study also showed no differences in the incidence of upper GI complications between these 2 compounds, although the total number of events (symptomatic ulcers and complications) was statistically lower in etoricoxib users (Laine et al, 2007). Lastly, both tNSAIDs and coxib may also increase blood pressure and reduce kidney function. Following, we describe the effects of these COX-2 inhibitors on differents studies on experimental colitis models.

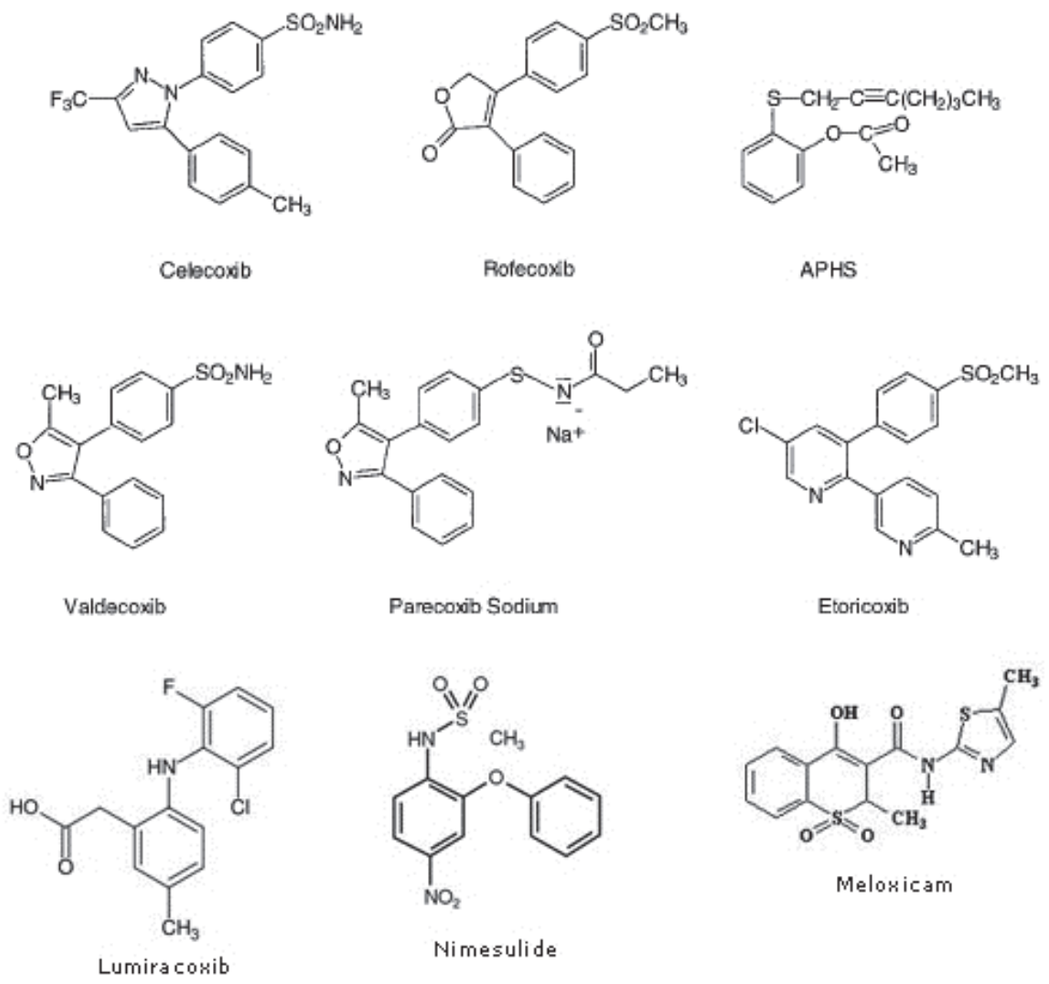


Fig. 3. The chemical structures of some COX-2 inhibitors.

2.5 COX-2 inhibitors on experimental colitis models

The role of selective inhibition of COX-2 for the inflammatory process and the course of experimental and human colitis is controversially discussed, even though increased levels of prostaglandins (PGE_2 and PGI_2) and other eicosanoids were detected in both colitis models and patients with chronic inflammatory bowel disease, which correlates well with the disease activity. PGE_2 is produced by mononuclear cells in the lamina propria and is dependent on COX-2 expresion. It modulates the intestinal immune response, including the differentiation of T cells and the production and release of proinflammatory cytokines. During the course of inflammatory bowel disease and experimental colitis, some prostanoids are released and subsequently modulate the course of the disease.

Animal models are used extensively to study the pathogenesis and pathophysiology of IBD and to evaluate therapies. The more extensively used models were: acetic acid colitis, dextran sodium sulphate (DSS) and 2,4,6′-trinitrobenzene sulphonic acid (TNBS). Acetic-acid-induced colitis in rats resembles human ulcerative colitis in histology, eicosanoid

production and excessive oxygen-derived free radicals release by inflamed mucosa (Millar et al., 1996). DSS-induced ulcerative colitis is accompanied by erosion and ulceration as well as inflammatory cell infiltration, characteristics resembling those of human ulcerative colitis (Okayama et al., 2007). TNBS-induced colitis is accompanied by marked thickening of the colonic wall, infiltration of polymorphonuclear leukocytes and ulceration, resembling the human Crohn´s disease (Morris et al., 1989). A number of animal studies have reported the positive effect of COX-2 inhibition, others exacerbation of colitis (**Table 2**).

Study	Model of colitis	Drug	Results
Reuter et al. (1996)	TNBS	diclofenac (10mg/kg) naproxen (5mg/kg) etodolac (10 or 50mg/kg) nabumetone (25 or 75mg/kg) L745,337 (1 or 5mg/kg)	unfavorable
Lesch et al. (1999)	TNBS	NS-398* SC-58125* PD-138387* *dose of 100mg/kg	unfavorable
Karmeli et al. (2000)	Acetic-acid or iodoacetamide	nimesulide (10mg/kg) SC-236 (6mg/kg)	favorable
Cuzzocrea et al. (2001)	DNBS	celecoxib (5mg/kg)	favorable
Martin et al. (2003)	TNBS	rofecoxib	favorable
Martin et al. (2005)	DSS	Rofecoxib (2.5-10mg/kg)	favorable
Singh et al. (2003)	Acetic-acid; LTB4-induced IBD)	nimesulide (9 and 18mg/kg)	favorable
Zhang et al. (2004)	TNBS	celecoxib (1.25mg/kg)	unfavorable
El-Medany et al. (2005)	Acetic-acid	celecoxib (5mg/kg) rofecoxib (2.5mg/kg)	favorable
Kruschewski et al. (2006)	TNBS	NS-398 (10mg/kg)	favorable
Tsubouchi et al. (2006)	DSS	rofecoxib	unfavorable
Dudhgaonkar et al. (2007)	TNBS	rofecoxib (10mg/kg)	favorable
Okayama et al. (2007)	DSS	celecoxib (3mg/kg)	unfavorable
Paiotti et al. (2009)	TNBS	lumiracoxib (6mg/kg)	unfavorable

Table 2. COX-2 inhibitors on experimental colitis.

Karmeli et al. (2000) reported that nimesulide, ameliorates the extent of tissue damage in acetic acid and iodoacetamide-treated rats. The decrease in the extent of colitis induced by nimesulide was accompanied by a significant decrease in mucosal MPO and nitric oxide synthase (NOS) activities.

There is good evidence that an enhanced formation of reactive oxygen species contributes to the pathophysiology of IBD (Guo et al., 1999; Kruidenier & Verspaget, 2002). Quantitatively, the principal free radical in tissues is superoxide anion (O_2^-), which is converted to H_2O2 by superoxide dismutase. Superoxide anion (O_2^-) can be produced by activated neutrophils through NADPH oxidase, which reduces molecular oxygen to the O_2^- radical through the enzyme myeloperoxidase. Nitric oxide (NO), a reactive free radical gas, is generated enzymatically in a variety of cells from the L-arginine pathway by three isoforms of NO synthetase (Yue et al., 2001). In the GI tract, NO can be either protective or damaging to tissues, depending on what type of NOS is involved in the pathological condition. In experimental colitis, NO derived from iNOS, together with other free radicals, contribute significantly to the inflammatory response in the colon. The mechanism for this inflammatory response is likely explained by the interaction of NO with superoxide to produce peroxynitrite, which is a strong oxidizing agent that initiates lipid peroxidation (El-Medany et al., 2005). Combination of rofecoxib and aminoguanidine hydrochloride has protective effect on colonic injury by TNBS which is probably, via mechanism of local inhibition of iNOS and COX-2 activity in colonic mucosa (Dudhgaonkar et al., 2007).

Cuzzocrea et al. (2001) have provided evidence for the potential protective effect of celecoxib in reducing the severity of colonic injury induced by dinitrobenzene sulfonic acid (DNBS). They observed reduction of the degree of colonic injury, the MPO activity, hemorrhagic diarrhoea and the weight loss. Martin et al. (2003; 2005) have demonstrated that rofecoxib seems to have beneficial effects in TNBS-induced colitis in rats and in acute DSS-induced colitis in mice; probably by the initial diminishing the initial stage of inflammation by a mechanism related to inhibition of PGE_2 by the COX-2 pathway as well by reducing neutrophil infiltration and inhibiting up-regulation of IL-1β. The use of nimesulide in two different models (acetic acid -and LTB4-induced IBD) significantly prevented development of inflammatory changes, decreased MPO activity, and also restored the altered contractility response of the isolated colon segment (Singh et al., 2003). In addition, El-Medany et al. (2005) showed that treatment with the celecoxib and rofecoxib reduced the inflammation and subsequent tissue damage to the colon induced by acetic acid, as verified by macroscopic, histological and biochemical findings. They demonstrated that these drugs exert a significant attenuation of the extent and severity of the histological signs of cell damage, significant reduction in tissue PGE_2 production, as well reduction in NOS activity.

The acute phase of TNBS colitis is characterized by a significant reduction of capillary blood flow, capillary density, diuresis, and weight and a significant increase in capillary permeability, leukocyte sticking, and hematocrit (Kruschewski et al., 2006). Kruschewski et al. (2006) demonstrated that the selective COX-2 inhibitor NS-398 leads to a significant improvement of all microcirculatory parameters and clinical findings compared to the (untreated) colitis.

On the other hand, Reuter et al. (1996) reported that administration of three types of COX-2 inhibitors with moderate to high selectivity significantly exacerbated the severity of colonic damage in experimental colitis. Continued twice-daily administration of these

compounds for one week resulted in perforation of the colon, leading to death in a substancial number of the animals. Lesch et al. (1999) evaluated three highly selective COX-2 inhibitors (NS-398, SC-58125 and PD-138387) on TNBS-induced colitis and observed that these three compounds do not seem to have any beneficial effect in this model. Zhang et al. (2004) showed that celecoxib resulted in exacerbation of inflammation-associated with colonic damage and even led to perforation, megacolon and death of the rats, with the mortality rate reaching 50%. Tsubouch et al. (2006) demonstrated that daily administration of indomethacin and rofecoxib significantly delayed the healing of colitis with deleterious influences on histological restitu as well as mucosal inflammation. Okayama et al. (2007) showed that celecoxib aggravated the severity of colonic ulceration and inflammation, as represented by the gross injury and the shortening of colon length as well as the myeloperoxidase activity (MPO) on dextran sulfate sodium (DSS) induced colitis.

Although lumiracoxib interacts with the COX-2 enzyme via mechanisms different from other COX-2 selective inhibitors and is associated with improved gastrointestinal tolerability, Paiotti et al. (2009) showed this did not reduce inflammation-associated colonic injury in TNBS-induced colitis. They demonstrated that macroscopic and the histopathological assessment on the TNBS nontreated induced-colitis and lumiracoxib-treated induced-colitis were similar.

3. Conclusion

The ability of selective COX-2 inhibitors to significantly exacerbate colonic injury in differents models of colitis suggests that prostaglandins derived from COX-2 are beneficial in the setting of colonic inflammation. There is a strong body of evidence to suggest that prostaglandins do exert anti-inflammatory and mucosal protective effects in experimental colitis. It is known that PGE_2 inhibits inflammatory cytokines and stimulates mucus secretion in the GI mucosa through activation of EP4 receptors (Kabashima et al., 2002; Nitta et al., 2002). Nitta et al reported that a selective EP4 agonist decreased the levels of IL-1β and cytokine-induced neutrophil chemoattractant in the colorectal mucosa with marked downregulation of the corresponding cytokine mRNA expression. They also found that the IL-10 concentration was higher following administration of the EP4 agonist. These findings may suggest that endogenous PGE_2 ameliorates the severity of dextran sodium sulphate colitis (DSS), presumably by suppressing the induction of proinflammatory cytokines. Prostaglandins are capable of reducing the production of reactive oxygen metabolites and a number of inflammatory mediators suggested to contribute to the pathogenesis of human and experimental colitis, included leukotriene B_4 and TNF-α. In addition prostaglandins increase the secretion of water and electrolytes into the intestinal tract and in the acute stage of UC and CD, activated monocytes promote the increased concentration of PG in the enteric mucosa, which in turn suppresses the effect of the Na^+, Ka^+-ATP enzyme and prevents the reabsorption of Na^+, resulting in diarrhea. Some studies demonstrated that pretreatment with intraluminal PGE analogs (e.g. 16,16′-dimethyl PGE_2) caused a reduction in the severity of injury induced by TNBS and acetic acid (Feng et al., 1993; Nitta et al., 2002; Sasaki et al., 2000 Tso et al., 1995).

In conclusion, the relative role of COX-2 selective inhibitors on human and experimental colitis to be explored. Thus, the use of COX-2 inhibitors in IBD should be considered with caution.

4. References

Arber N, Eagle CJ, Spicak J, et al. (2006). Pre-SAP Trial Investigators. Celecoxib for de prevention of colorectal adenomatous polyps. *N Engl J Med*, Aug; 355(9):885-95. ISSN 1533-4406.

Asako H, Kubes P,Wallace JL, et al. (1992). Indomethacin-induced leukocyte adhesion in mesenteric venules: role of lipoxygenase products. *Am J Physiol*, 262:G903-8; a. ISSN 0363-6119.

Asako H,Kubes P,Wallace JL, et al. (1992). Modulation of leukocyte adhesion in rat mesenteric venules by aspirin and salicylate. *Gastroenterology*, Jul; 103(1):146-52;b. ISSN 1440-1746.

Bakhle YS, Botting RM. (1996). Cyclooxygenase-2 and its regulation in inflammation. *Mediat Inflamm*, Oct; 5(5):305-23. ISSN 0962-9351.

Barbieri D. (2000). Inflammatory bowel diseases. *J Pediatr (Rio J)*, Jul; 76(suppl 1):S173-S180. ISSN 0021-7557.

Bhattacharyya DK, Lecomte M, Rieke CJ, et al. (1996). Involvement of arginine 120, glutamate 524 and tyrosine 355 in the binding of arachidonate and 2-phenylpropionic acid inhibitors to the cyclooxygenase active site of ovine prostaglandin endoperoxide H synthase-1. *J Biol Chem*, Jan; 271(4):2179-84. ISSN 0021-9258.

Bombardier C, Laine L, Reicin A, et al. (2000). Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Méd*, Nov; 343(21):1520-8. ISSN 1533-4406.

Bonen DK, Cho JH. (2003). The genetics of inflammatory bowel disease. *Gastroenterology*, Feb; 124(2):521-536. ISSN 1440-1746.

Bonner GF, Fakhri A, Vennamaneni SR. (2004). A long-term cohort study of nonsteroidal anti-inflammatory drug use and disease activity in outpatients with inflammatory bowel disease. *Inflamm Bowel Dis*, Nov; 10(6):751-757. ISSN 1078-0998.

Bonner GF, Walczak M, Kitchen L, et al. (2000). Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol*, Aug; 95(8):1946-1948. ISSN 0002-9270.

Botting RM. (2010). Vane's discovery of the mechanism of action of aspirin changed our understanding of its clinical pharmacology. *Pharmacol Reports*, 62:518-25. ISSN 1734-1140.

Bresalier RS, Sandler RS, Quan H, et al. (2005). Adenomatous polyp prevention on Vioxx (APPROVe) trial investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*, Marc; 352(11):1092-102. ISSN 1533-4406.

Brune K, Hinz B (2004). Selective cyclooxygenase-2 inhibitors: similarities and differences. *Scand J Rheumatol*, 33(1):1-6. ISSN 03009742.

Cannon CP, Curtis SP, FitzGerald GA, et al. (2006). MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: A randomized comparison. *Lancet*, Nov 18; 368(9549):1771-81. ISSN 0140-6736.

Carvalho WA, Carvalho RDS, Rios-Santos F. (2004). Specific cyclooxygenase-2 inhibitor analgesics: Therapeutic advances. *Rev Bras Anestesiol*, Aug; 54(4):448-64. ISSN 0034-7094.

Chan AT, Manson JE, Albert CM, et al. (2006). Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation* 2006 Mar; 113(12):1578-87. ISSN 0009-7322.

Colpaert S, Liu Z, De Greef B, et al. (2001). Effects of anti-tumour necrosis factor, interleukin-10 and antibiotic therapy in the indometacin-induced bowel inflammation rat model. *Aliment Pharmacol Ther*, Nov; 15(11):1827-1836. ISSN 0269-2813.

Cuzzocrea S, Mazzon E, Serraino I, et al. (2001). Celecoxib , a selective cyclooxygenase-2 inhibitor reduces the severity of experimental colitis induced by dinitrobenzene sulphonic acid in rats. *Eur J Pharmacol*, Nov; 431(1):91-102. ISSN 0014-2999.

Dempke W, Rie C, Grothey A, et al. (2001). Cyclooxygenase-2: a novel target for cancer chemotherapy? *J Cancer Res Clin Oncol*, Jul; 127(7):411-417. ISSN 0171-5216.

DeWitt DL, Smith WL. (1988). Primary structure of prostaglandin G/H synthase from sheep vesicular gland determined from the complementary DNA sequence. *Proc Natl Acad Sci USA*, Marc; 85(5):1412-1416. ISSN 0027-8424.

Dudhgaonkar SP, Tandan SK, Kumar D, et al. (2007). Influence of simultaneous inhibition of cyclooxygenase-2 and inducible nitric oxide synthase in experimental colitis in rats. *Inflammopharmacology*, Oct 15(5):188-95. ISSN 09254692.

El-Medany Azza, Mahgoub Afaf, Mustafa ali, et al. (2005). The effects of selective cyclooxygenase-2 inhibitors, celecoxib and rofecoxib, on experimental colitis induced by acetic acid in rats. *Eur J Pharmacol*, Jan; 507(1-3):291-299. ISSN 0014-2999.

Élson CO, Sartor RB, Tennyson GS, et al. (1995). Experimental models of inflammatory bowel disease. *Gastroenterology*, Oct; 109(4):1344-1367. ISSN 1440-1746.

Esser Ronald, Berry Carol, Du Zhengming , et al. (2005). Preclinical pharmacology of lumiracoxib: a novel selective inhibitor of cyclooxygenase-2. *Br J Pharmacol*, Feb; 144(4):538-550. ISSN 0007-1188.

Evans JM, McMahon AD, Murray FE, et al. (1997). Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* , May; 40(5):619-22. ISSN 0017-5749.

Felder JB, Korelitz BI, Rajapakse R, et al. (2000). Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol*, Aug; 95(8):1949-54. ISSN 0002-9270.

Feng L, Sun W, Xia Y, et al. (1993). Cloning two isoforms of rat cyclooxygenase: Differential regulation of their expression. *Arch Biochem Biophys*, Dec; 307(2):361-8. ISSN 00039861.

Fitzgerald GA, Patrono C. (2001). The coxibs, selective inhibitors of cyclooxigenase-2. *N Engl J Med*, Aug; 345(6):433-442. ISSN 1533-4406.

Gana TJ, Huhlewych R, Koo J (1987). Focal gastric mucosal blood flow in aspirininduced ulceration. *Ann Surg*, Apr; 205(4):399-403. ISSN 0003-4932.

Gierse JK, McDonald JJ, Hauser SD, et al. (1996). A single amino acid difference between cyclooxygenase-1 and -2 reverses the selectivity of COX-2 specific inhibitors. *J Biol Chem*, Jun; 271(26):15810-14. ISSN 0021-9258.

Gornet JM, Hassani Z, Modiglian R, et al. (2002). Exacerbation of Crohn's colitis with severe colonic hemorrhage in a patient on rofecoxib. *Am J Gastroenterol*, Dec; 97(12):3209-3210. ISSN 0002-9270.

Griswold DE, Adams JL. (1996). Constitutive cyclooxygenase (COX-1 and inducible cyclooxygenase (COX-2): rationale for selective inhibition and progress to date. *Med Res Rev*, Mar; 16(6):181-206. ISSN 1077-5587.

Guo Q, Wang L, Ruan K, et al. (1996). Role of Val509 in time-dependent inhibition of human prostaglandin H synthase-2 cyclooxygenase activity by isoform-selective agents. *J Biol Chem*, Aug; 271(32):19134-39. ISSN 0021-9258.

Guo X, Wang WP, Ko JK, et al. (1999). Involvement of neutrophils and free radicals in the potentiating effects of passive cigarette smoking on inflammatory bowel disease in rats. *Gastroenterology*, Oct; 117(4):884-92. ISSN 1440-1746.

Hawkey CJ, Svoboda P, Fiedorowicz-Fabrycy IF, et al. (2004). Gastroduodenal safety and tolerability of lumiracoxib compared with ibuprofen and celecoxib in patients with osteoarthritis. *J Rheum*, Sep; 31(9):1804-1810. ISSN 0315-162X.

Herschman HR. (1996). Prostaglandin synthase 2. *Biochim Biophys Acta*, Jan; 1299(1):125-40. ISSN 0006-3002.

Hudson N, Balsitis M, Everitt S, et al. (1993). Enhanced gastric leukotriene B4 synthesis in patients taking non-steroidal anti-inflammatory drugs. *Gut*, Jun; 34(6):742-7. ISSN 0017-5749.

Jouzeau J-Y, Terlain B, Abid A, et al. (1997). Cyclooxygenase isoenzymes. How recent findings affect thinking about nonsteroidal anti-inflammatory drugs. *Drugs*, Apr; 53(4):563-82. ISSN 0012-6667.

Kabashima K, Saji T, Murata T, et al. (2002). The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. *J Clin Invest*, Apr; 109(7):883-93. ISSN 0021-9738.

Kafalakes H, Stylianides TJ, Amanakis G, et al. (2009). Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatpry drugs: myth or reality. *Eur J Clin Pharmacol*, Oct; 65(10):963-70. ISSN 0031-6970.

Karmeli F, Cohen P, Rachmilewitz D. (2000). Cyclo-oxygenase-2 inhibitors ameliorate the severity of experimental colitis in rats. *Eur J Gastroenterol Hepatol*, Feb 12(2):223-31. ISSN 0954-691X.

Kivitz AJ, Nayiager S, Schimansky T, et al. (2004). Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. *Aliment Pharmacol Ther*, Jun; 19(11):1189-1198. ISSN 0269-2813.

Kruidenier L, Verspaget HW. (2002). Oxidative stress as a pathogenic factor in inflammatory bowel disease-radicals or ridiculous? *Aliment Pharmacol Ther*, Dec; 16(12):1997-2015. ISSN 0269-2813.

Kruschewski M, Anderson T, Burhr HJ, et al. (2006). Selective COX-2 inhibition reduces leukocyte sticking and improves the microcirculation in TNBS colitis. *Dig Dis Sci*, Apr 51 (4):662-70. ISSN 0002-9211.

Kulkarni SK, Jain NK, Singh A. (2000). Cyclooxygenase isoenzymes and newer therapeutic potential for selective COX-2 inhibitors. *Methods Find Exp Clin Pharmacol*, Jun; 22(5):291-298. ISSN 0379-0355.

Kurahara K, Matsumoto T, Iida M, et al. (2001). Clinical and endoscopic features of nonsteroidal antiinflammatory drug-induced colonic ulcerations. *Am J Gastroenterol*, Feb; 96(2):473-480. ISSN 0002-9270.

Kurumbail RG, Stevens AM, Gierse JK, eta l. (1996). Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. *Nature*, Dec; 384(6610):644-48. ISSN 0028-0836.

Laine L, Curtis SP, Cryer B, et al (2007). MEDAL Steering Committee. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis

and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: A randomized comparison. *Lancet*, Feb 10;369(9560): 465-73. ISSN 0140-6736.

Laine L, Maller ES, Yu C, et al. (2004). Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. *Gastroenterology*, Aug; 127(2):395-402. ISSN 1440-1746.

Lanas A, Garcia-Rodriguez LA, Arroyo MA, et al. (2005). Coxibs, NSAIDs, aspirin, PPIs and the risks of upper GI bleeding in common clinical practice. *Gastroenterology*, 128:629. ISSN 1440-1746.

Lashner BA. (1995). Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am*, Sep; 24(3):467-474. ISSN 0889-8553.

Lecomte M, Laneuville O, Ji C, et al. (1994). Acetylation of human prostaglandin endoperoxide synthase-2 (cyclooxygenase-2) by aspirin. *J Biol Chem*, May; 269(18):13207-15. ISSN 0021-9258.

Lee M, Aldred K, Lee E, et al. (1992). Aspirin-induced acute gastric mucosal injury is a neutrophil-dependent process in rats. *Am J Physiol*, Dec; 263(6PT1):G920-6. ISSN 0363-6135.

Lesch CA, Kraus ER, Sanchez B, et al. (1999). Lack of beneficial of COX-2 inhibitors in an experimental model of colitis. *Methods Find Exp Clin Pharmacol*, Marc 21(2):99-104. ISSN 0379-0355.

Luong C, Miller A, Barnett J, et al. (1996). Flexibility of the NSAID binding site in the structure of human cyclooxygenase-2. *Nat Struct Biol*, Nov; 3(11):927-933. ISSN 1072-8368.

Mancini JA, O'Neill GP, Bayly C, et al. (1994). Mutation of serine-516 in human prostaglandin G/H synthase-2 to methionine or aspirin cetylation of this residue stimulates 15-R-HETE synthesis. *FEBS Lett*, Mar; 342(1):33-37. ISSN 0014-5793.

Mancini JA, Riendeau D, Falgueyret JP, et al. (1995). Arginini 120 of prostaglandin G/H synthase-1 is required for the inhibition by nonsteroidal anti-inflammatory drugs containing a carboxylic acid moiety. *J Biol Chem*, Dec; 270(49):29372-77. ISSN 0021-9258.

Mangold JB, Gu H, Rodriguez LC, et al. (2004). Pharmacokinetics and metabolism of lumiracoxib in healthy male subjects. *Drug Metab Dispos*, May; 32(5):566-571. ISSN 0090-9556.

Martin AR, Villegas I, La-Casa C, et al. (2003). The cyclooxygenase-2 inhibitor , rofecoxib, attenuates mucosal damage due to colitis induced by trinitrobenzene sulphonic acid in rats. *Eur J Pharmacol*, Nov; 481(2-3):1-10. ISSN 0014-2999.

Martin AR, Villegas I, Alarcon de la Lastra C. (2005). The COX-2 inhibitor, rofecoxib, ameliorates dextran sulphate sodium induced colitis in mice. *Inflamm Res*, Apr 54(4):145-51. ISSN 1023-3830.

Mc Gettigan P, Henry D. (2006). Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and non selective inhibitors of cyclooxygenase 2. *J Am Med Assoc*, Oct;296(13):1633-44. ISSN 0002-9955.

McHippisley-Cox J, Coupland C. (2005). Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BM*J, Jun; 330(7504):1366. ISSN 09598138.

Merlie JP, Fagan D, Mudd J, et al. (1988). Isolation and characterization of the complementary DNA for sheep seminal vesicle prostaglandin endoperoxidase synthase (cyclooxygenase). *J Biol Chem*, Mar; 263(8):3550-53. ISSN 0021-9258.

Millar AD, Rampton DS, Chander CL, et al. (1996). Evaluating the antioxidant potential of new treatments for inflammatory bowel disease using a mouse model of colitis. *Gut*, Sep; 39(3):407-15. ISSN 0017-5749.

Mitchell JA, Akarasereenont P, Thiemermann C, et al. (1993). Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci USA*, Dec; 90(24):11693-7. ISSN 0027-8424.

Moore RA, Derry S, Makinson GT, et al. (2005). Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from company clinical trial reports. *Arthritis Res Ther*, Mar; 7(3):R644-65. ISSN 1478-6354.

Morita I, Schindler MS, Regier MK, et al. (1995). Different intracellular locations for prostaglandin endoperoxide H synthase 1 and 2. *J Biol Chem*, May; 270(18):10902-8. ISSN 0021-9258.

Morris GP, Beck PL, Herridge MS, et al. (1989). Hapten-induced model of chronic inflammation and ulceration in the rat colon. *Gastroenterology,* Mar; 96(3):795-803. ISSN 1440-1746.

Nitta M, Hirata I, Toshina K, et al. (2002). Expression of the EP4 prostaglandin E2 receptor subtype with rat dextran sodium sulphate colitis: colitis suppression by a selective agonist, ONO-AE1-329. *Scand J Immunol*, Jul; 56:66-75. ISSN 0300-9475.

Okayama M, Hayashi S, Aoi Y, et al. (2007). Aggravation by selective COX-1 and COX-2 inhibitors of dextran sulfate sodium (DSS)-induced colon lesions in rats. *Dig Dis Sci*, Sep; 52(9):2095-2103. ISSN 0163-216.

O'Neill GP, Mancini JA, Kargman S, et al. (1994). Overexpression of human prostaglandin G/H synthase-1 and -2 by recombinant vacinia virus: inhibition by nonsteroidal anti-inflammatory drugs and biosynthesis of 15-hydroxyeicosatetraenoic acid. *Mol Pharmacol*, Feb; 45(2):245-54. ISSN 0026-895X.

Otto JC, Smith WL. (1994). The orientation of prostaglandin endoperoxide synthases 1 and 2 in the endoplasmic reticulum. *J Biol Chem*, Aug; 269(31):19868-75. ISSN 0021-9258.

Paiotti APR, Miszputen SJ, Oshima CTF, et al. (2009). Effect of COX-2 inhibitor after TNBS-induced colitis in wistar rats. *J Mol Hist*, Aug; 40(4):317-24. ISSN 1567-2379.

Panara MR, Renda G, Sciulli MG, et al. (1999). Dose-dependent inhibition of platelet cyclooxygenase-1 and monocyte cyclooxygenase-2 by meloxicam in healthy subjects. *J Pharmacol Exp Ther*, Jul; 290(1):276-280. ISSN 00223565.

Picot D, Loll PJ, Garavito RM. (1994). The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. *Nature*, Jan; 367(6460):243-49. ISSN 0028-0836.

Podolsky DK. (2002). Inflammatory bowel disease. *N Engl J Med*, Aug; 347(6):417-429. ISSN 1533-4406.

Rampton DS, Sladen GE. (1981). Prostaglandin synthesis inhibitors in ulcerative colitis: flurbiprofen compared with conventional treatment. *Prostaglandins*, Mar; 21(3):417-25. ISSN 1098-8823.

Regier MK, DeWitt DL, Schindler MS, et al. (1993). Subcellular localization of prostaglandin endoperoxide synthase-2 in murine 3T3 cells. *Arch Biochem Biophys*, Mar; 301(2):439-44. ISSN 0003-9861.

Ren Y, Loose-Mitchell DS, Kulmacz RJ. (1995). Prostaglandin H synthase-1: evaluation of C-terminus function. *Arch Biochem Biophys*, Feb; 316(2):751-57. ISSN 0003-9861.

Ren Y, Walker C, Loose-Mitchell DS, et al. (1995). Topology of prostaglandin H synthase-1 in the endoplasmic reticulum membrane. *Arch Biochem Biophys*, Oct; 323(1):205-14. ISSN 0003-9861.

Reuter BK, Asfaha S, Buret, et al. (1996). Exacerbation of inflammatory associated colonic injury in rat through inhibition of cyclooxygenase-2. *J Clin Invest*, Nov; 98(9):2076-2085. ISSN 0210-573X.

Rordorf C, Kellett N, Mair S, et al. (2003). Gastroduodenal tolerability of lumiracoxib vs placebo and naproxen: a pilot endoscopic study in healthy male subjects. *Aliment Pharmacol Ther*, Sep; 18(5):533-541. ISSN 0269-2813.

Rostom A, Muir K, Dube C, et al. (2009). Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. *Drug Healthc Patient Saf*, Oct; 1:1-25. ISSN 1179-1365.

Sasaki S, Hirata I, Maemura K, et al. (2000). Prostaglandin E2 inhibits lesion formation in dextran sodium sulphate-induced colitis in rats and reduces the levels of mucosal inflammatory cytokines. *Scand J Immunol*, Jan; 51:23-28. ISSN 0300-9475.

Scheiman JM. (2006). Unmet needs in non-steroidal antiinflammatory drug-induced upper gastrointestinal diseases. *Drugs*, 66 (Suppl 1):15-21, discussion 29-33. ISSN 0012-6667.

Schnitzer TJ, Burmester GR, Mysler E, et al. (2004). Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet*, Aug; 364(9435):665-74. ISSN 0140-6736.

Shorter RG, Huizenga KA, Spencer RJ, et al. (1972). Inflammatory bowel disease. The role of lymphotoxin in the cytotoxicity of lymphocytes for colonic epithelial cells. *Am J Dig Dis*, Aug; 17(8):689-696. ISSN 0002-9211.

Silverstein FE, Faich G, Goldstein JL, et al. (2000). Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial.

Celecoxib Long-term Arthritis Safety Study. *J Am Med Assoc*, Sep; 284(10):1247-55. ISSN 0002-9955.

Singh G, Fort JG, Goldstein JL, et al. (2006). Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am J Med*, Mar; 119(3):255-66. ISSN 0002-9343.

Singh VP, Patil CS, Jain NK, et al. (2003). Effect of nimesulide on acetic acid- and leukotriene-induced inflammatpry bowel disease in rats. *Prostaglandins Other Lipid Mediat*, Jul; 71(3-4):163-75. ISSN 1098-8823.

Skelly MM, Hawkey CJ. (2003). Dual COX inhibition and upper gastrointestinal damage. *Curr Pharm Des*, 9(27):2191-5. ISSN 1381-6128.

Solomon SD, Mc Murray JJ, Pfeffer MA, et al. (2005). Adenoma Prevention with Celecoxib (APC) study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*, Mar; 352(11):1071-80. ISSN . ISSN 1533-4406.

Suenaert P, Bulteel V, Vermeire S, et al. (2005). Hyperresponsiveness of the mucosal barrier in Crohn´s disease is not tumor necrosis factor-dependent. *Inflamm Bowel Dis*, Jul; 11(7):667-673. ISSN 1078-0998.

Thiéfin G, Beaugerie L. (2005). Review: Toxic effects of nonsteroidal antiinflammatory drugs on the small bowel, colon and rectum. *Joint Bone Spine*, Jul; 72(4):286-94. ISSN 1297-319X.

Tso JY, Sun X-H, Kao T-H, et al. (1995). Isolation and characterization of rat and human glyceraldehyde-3-phosphate dehydrogenase cDNAs: Genomic complexity and molecular evolution of the gene. *Nuclei Acids Res*, Apr; 13(7):2485-2502. ISSN 0305-1048.

Tsubouch R, Hayashi S, Aoi Y, et al. (2006). Healing impairment effect of cyclooxygenase inhibitors on dextran sulfate sodium-induced colitis in rats. *Digestion*, Dec 74(2):91-100. ISSN 0012-2823.

Vaananen PM, Meddings JB, Wallace JL. (1991). Role of oxygen-derived free radicals in indomethacin-induced gastric injury. *Am J Physiol*, Sep; 261(3 Pt 1):G470-5. ISSN 0002-9513.

Vane JR, Bakhle YS, Botting RM (1998). Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol*, 38:97-120. ISSN 0362-1642.

Vane JR, Flower RJ, Botting RM. (1990). History of aspirin and its mechanism of action. *Stroke,* Dec; (Suppl 12):IV12-IV23. ISSN 00392499.

Vane JR. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirine-like drugs. *Nat New Biol*, Jun; 231(25):232-235. ISSN 0090-0028.

Wallace JL, Keenan CM, Granger DN. (1990). Gastric ulceration induced by nonsteroidal anti-inflammatory drugs is a neutrophil-dependent process. *Am Jphysiol*, Sep; 259(3 Pt 1):G462-7. ISSN 0002-9513.

Wallace JL, McKnight W, Miyasaka M, et al. (1993). Role of endothelial adhesion molecules in NSAID-induced gastric mucosal injury. *Am J Physiol*, Nov; 265(5 Pt 1):G993-8. ISSN 0002-9513.

Wallace JL,McKnight W, Reuter BK, et al. (2000). NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. *Gastroenterology*, Sep; 119(3):706-14. ISSN 1440-1746.

Wallace JL. (1997). Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology*, Mar; 112(3):1000-1016. ISSN 1440-1746.

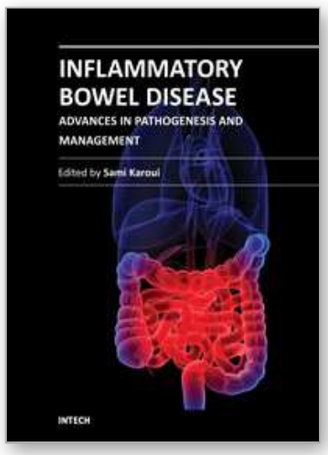
Wolfe MM, Lichtenstein DR, Singh G. (1999). Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*, Jun; 340(24):1888-1899. ISSN 1533-4406.

Wong E, Bayly C, Waterman HL, et al. (1997). Conversion of prostaglandin G/H synthase-1 into an enzyme sensitive to PGHS-2 selective inhibitors by a double His513 to Arg and Ile523 to Val mutation. *J Biol Chem*, Apr; 272(14):9280-86. ISSN 0021-9258.

Yokoyama C, Takai T, Tanabe T. (1988). Primary structure of sheep prostaglandin endoperoxidase synthase deduced from cDNA sequence. *FEBS Lett*, Apr; 231(2):347-51. ISSN 0014-5793.

Yue G, Pi-Shiang L, Kingsley Y, et al. (2001). Colon epithelial cell death in 2,4,6 trinitrobenzene sulfonic acid induced colitis is associated with increased inducible nitric-oxide synthase expression and peroxynitrite production. J *Pharmacol Exp Ther*, Jun; 297(3):915-25. ISSN 0022-3565.

Zhang L, Lu YM, Dong XY. (2004). Effects and mechanism of the selective COX-2 inhibitor, celecoxib, on rat colitis induced by trinitrobenzene sulfonic acid. *Chin J Dig Dis*, 5(3):110-114. ISSN 1443-9611.



Inflammatory Bowel Disease - Advances in Pathogenesis and Management

Edited by Dr. Sami Karoui

ISBN 978-953-307-891-5
Hard cover, 332 pages
Publisher InTech
Published online 27, January, 2012
Published in print edition January, 2012

This book is dedicated to inflammatory bowel disease, and the authors discuss the advances in the pathogenesis of inflammatory bowel disease, as well as several new parameters involved in the etiopathogeny of Crohn's disease and ulcerative colitis, such as intestinal barrier dysfunction and the roles of TH 17 cells and IL 17 in the immune response in inflammatory bowel disease. The book also focuses on several relevant clinical points, such as pregnancy during inflammatory bowel disease and the health-related quality of life as an end point of the different treatments of the diseases. Finally, advances in management of patients with inflammatory bowel disease are discussed, especially in a complete review of the recent literature.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen