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Review

Anti-inflammatory and side effects of cyclooxygenase inhibitors

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Abstract:
Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs in inflammatory diseases, since they are effective in management of pain, fever, redness, edema arising as a consequence of inflammatory mediator release. Studies have shown that both therapeutic and side effects of NSAIDs are dependent on cyclooxygenase (COX) inhibition. COX isoforms have been named constitutive (COX-1) and inducible (COX-2). COX-1 catalyzes formation of cytoprotective prostaglandins in thrombocytes, vascular endothelium, stomach mucosa, kidneys, pancreas, Langerhans islets, seminal vesicles, and brain. Induction of COX-2 by various growth factors, proinflammatory agents, endotoxins, mitogens, and tumor agents indicates that this isoform may have a role in induction of pathological processes, such as inflammation. It is well known that therapy with COX inhibitors is associated with a number of side effects including gastrointestinal erosions, and renal and hepatic insufficiency. Such critical adverse reactions are mostly dependent on COX-1 inhibition. As a result of research focused on reduction of the adverse effects of NSAIDs, selective COX-2 inhibitors, such as celecoxib and rofecoxib have been developed. However, many data demonstrate that mechanisms of action of these drugs are multidirectional and complex. These drugs or their derivatives, which belong to the same group, have distinct pharmacological effects, side effects and potencies which implies that there may be more than two, five or even tens of COX isoforms.

Key words:
NSAIDs, COX enzymes, inflammation, COX-2 selective inhibitors, non-selective inhibitors

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs in inflammatory diseases, since they are effective in management of pain, fever, redness, edema arising as a consequence of inflammatory mediator release [22, 57]. Studies have shown that both therapeutic and side effects of NSAIDs are dependent on cyclooxygenase (COX) inhibition [101]. It has been suggested that COX-2 inhibition is responsible for the therapeutic effects of NSAIDs, while COX-1 inhibition causes the gastrointestinal and renal side effects [60, 106, 107].

In this review, the anti-inflammatory and side effects of nonselective COX inhibitors and selective COX-2 inhibitors will be discussed and compared. COX isoenzymes, which form the basis of the mechanism of action of NSAIDs, will be described in order to make an understanding of the subject easier.

COX isoenzymes

Until the beginning of the 1990s, it had been thought that there was only one COX enzyme. In 1990, rapid development of the studies in this field revealed that COX enzyme had two distinct isoforms with different genetic coding [42, 75]. Although both isoforms had similar amino acid sequence and catalytic activity, they were demonstrated to have different functions [49, 106]. These isoforms were named 'constitutive' COX-1 and 'inducible' COX-2. COX-1 catalyzes the formation of cytoprotective prostaglandins (PGs) in thrombocytes, vascular endothelium, stomach mucosa, kidneys, pancreas, Langerhans islets, seminal vesicles, and brain [36, 57, 90]. Figure 1 gives a summary of the biosynthesis of PGs: the first step in the biosynthesis of prostanoids catalyzed by phospholipase A_2 is arachidonic acid (AA) release from the membrane phospholipids. The second step is AA conversion by cyclooxygenase. First, the unstable PGG_2 is produced in the COX reaction, which is then immediately converted into PGH_2 by the same enzyme in a peroxidase reaction. The end products of the AA metabolism are PGs, thromboxanes and prostacyclin [18]. Induction of COX-2 by various growth factors, proinflammatory agents, endotoxins, mitogens, tumor agents [21, 54, 56] indicates that this isoform may have a role in formation of pathological processes, such as inflammation [73, 96]. COX-1 products, prostaglandins (PGI_2 and PGE_2), maintain integrity of gastrointestinal system (GIS) by reducing gastric acid

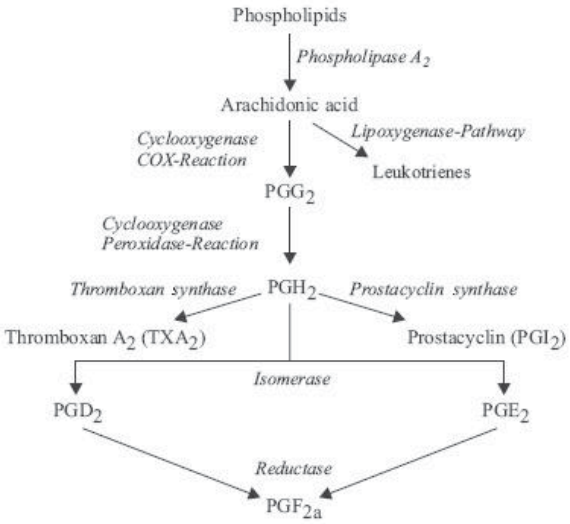

Fig. 1. Arachidonic acid cascade (Reprinted with permission of Elsevier Ltd., [18])

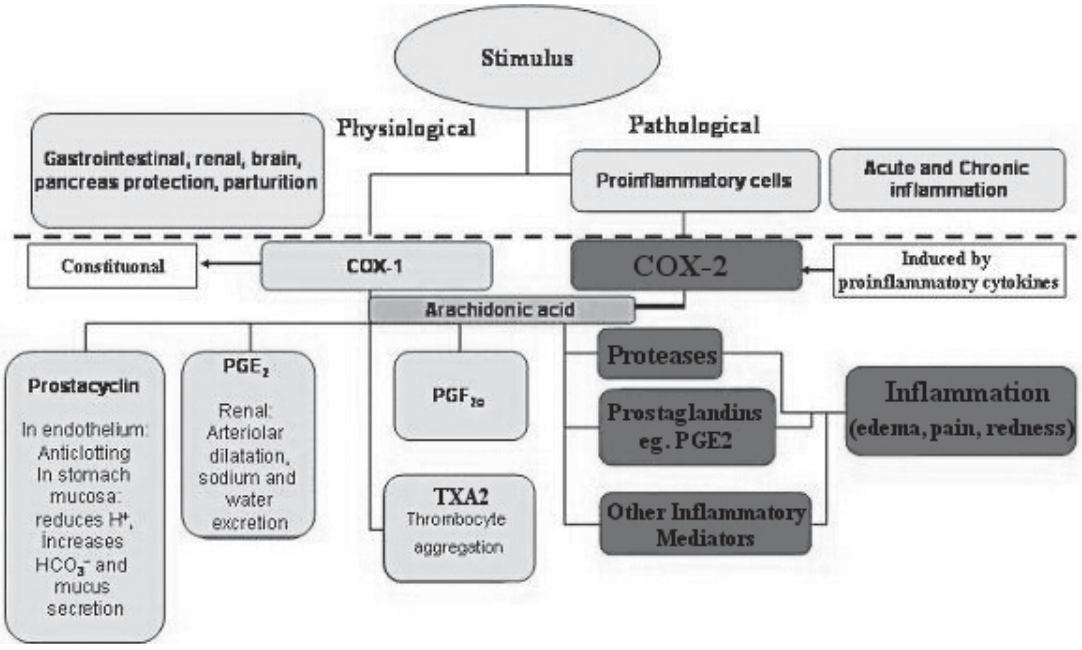

Fig. 2. Roles of COX-1 and COX-2 [18]

secretion, increasing the thickness of mucus layer, stimulating bicarbonate secretion and enhancing mucosal blood flow [26, 32, 86, 90]. PGE_2 enhances mucus secretion by activating cAMP in gastric epithelial cells (Fig. 2) [87]. Glucocorticoids and endogenous steroids can suppress the gene responsible for COX-2 synthesis [50, 56]. Drugs, which inhibit COX-1 more than COX-2, such as indomethacin, naproxen, ibuprofen, cause more severe damage to the gastric tissues [43]. As a result of studies focused on reduction of the adverse effects of NSAIDs, selective COX-2 inhibitors, such as celecoxib and rofecoxib, have been developed. Today, it is a well-known hypothesis in medicine that COX-1 is constitutive and cytoprotective, while COX-2 is an inducible enzyme in the inflamed tissues (Fig. 2). However, recent studies [59, 100] have questioned this hypothesis. Continuing research on COX isoforms has indicated that paracetamol has a more potent effect on COX preparations from the brain than on COX preparations from the spleen. It has been proposed that the third isoform of the enzyme, COX-3, may exist in the brain [23, 94].

Classification of NSAIDs

NSAIDs can be grouped in four categories:

1. Selective COX-1 inhibitors, such as aspirin;
2. Non-selective COX inhibitors: a number of the NSAIDs examined exhibit COX-1/COX-2 IC_{50} ratios between 0.5 and 3.0;
3. Relatively selective COX-2 inhibitors, such as meloxicam, nimesulide, diclofenac with COX-1/COX-2 IC_{50} ratios of 10–20;
4. Highly selective COX-2 inhibitors comprising three experimental compounds (NS-398, L-745, 337 and SC-58125, the prototype of celecoxib) with COX-1/COX-2 IC_{50} ratios from 140 to 250 and rofecoxib with the ratio > 400 (Tab. 1) [60].

General information about NSAIDs

These drugs are named NSAIDs because they are structurally different from steroidal anti-inflammatory drugs [95]. As NSAIDs possess analgesic, antipyretic and anti-inflammatory effects, they have certain advantages in the treatment of diseases with pain, fever and inflammation, when compared to steroidal anti-inflammatory and narcotic analgesic drugs [2]. Although NSAIDs have distinct chemical structures, they have similar therapeutic and side effects [64].

Tab. 1. COX isoform selectivity assessed in the whole blood assays *in vitro* by cyclooxygenase inhibitors (Reprinted with permission of Elsevier Ltd., [60])

Inhibitor	COX-1/COX-2 IC_{50} ratio	
Aspirin	0.01	Selective COX-1 inhibitors
S-Indobufen	0.043	
Valeryl Salicylate	< 0.24	
Ibuprofen	0.50	Non-selective COX inhibitors
Naproxen	0.56	
S-Ketoprofen	0.61	
Flurbiprofen	1.00	
Sodium Salicylate	1.03	
6-MNA[a]	1.49	
Indomethacin	1.90	
Piroxicam	3.12	
Meloxicam	11.16	Relatively selective COX-2 inhibitors
Nimesulide	17.69	
Diclofenac	18.90	
SC-58125	143.30	Highly selective COX-2 inhibitors
NS-398	168.00	
L-745,337	246.00	
Rofecoxib	410.00	

[a] 6-MNA is the active metabolite of nabumetone

Mechanisms of action of NSAIDs

These mechanisms comprise inhibition of synthesis of COX and leukotriene (LO) products, prevention of release of toxic oxygen radicals and lysosomal enzymes, prevention of neutrophil aggregation, adhesion and chemotaxis, and uncoupling of oxidative phosphorylation [4, 10, 14, 29, 33, 48]. Recently, it

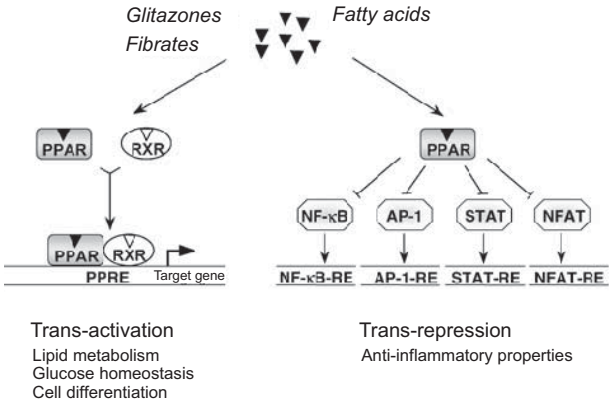

Fig. 3. Regulation of gene expression by PPARs. PPARs influence gene expression either by 'transactivation' through direct binding to PPREs or through indirect interference with other transcription factor pathways (AP-1, NF-κB, STAT and NFAT) leading in most cases to transcription inhibition ('transrepression'); (Reprinted with permission from Nature Publishing Group, [16])

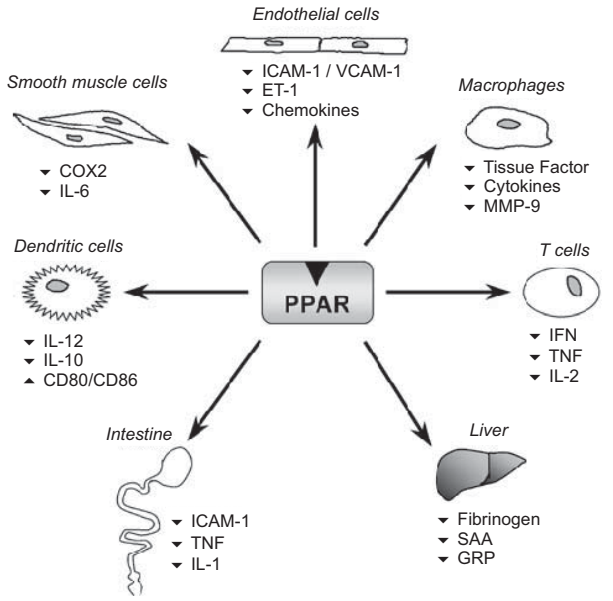

Fig. 4. Control of inflammation by PPARs. PPARs are modulators of the inflammatory response in different cell types and tissues (Reprinted with permission from Nature Publishing Group, [16])

has been suggested that stimulation of peroxisome proliferator-activated receptors (PPARs) and inhibition of nuclear factor kappa B (NF-κB) and other transcription factors play an important role in the mechanism of actions of NSAIDs.

PPARs are members of the nuclear receptor family. Three genes encode the peroxisome proliferator-activated receptor (PPAR) family members, PPAR-α, PPAR-β/δ and PPAR-γ. All three PPARs are widely expressed in different tissues. Their relative levels, however, differ between tissues reflecting their different biological functions. PPAR-α is highly expressed in the liver, skeletal muscle and heart. PPAR-γ is detected in adipose tissue, but is also present at high levels in the intestine, breast tissue, etc. PPAR-β/δ is ubiquitously expressed with the highest levels in the skin and skeletal muscle. Cells of the vascular wall and the immune system express all three PPARs. PPARs are activated by natural ligands such as fatty acids, eicosanoids and oxidized fatty acids and by pharmacological drugs. The lipid-lowering fibrates and the antidiabetic glitazones are synthetic ligands for PPAR-α and PPAR-γ, respectively. Influence of PPARs on gene expression may occur directly through promoter-binding and transcriptional modulation of target genes or through indirect interference with other transcription factor pathways leading in most cases to transcription inhibition (Fig. 3). PPARs regulate transcription of target genes involved in lipid and lipoprotein metabolism, glucose homeostasis and cell differentiation (particularly adipogenesis). PPARs inhibit the activation of certain inflammatory response genes acting as transrepressors.

PPARs and inflammation control

The first evidence for the role of PPARs in inflammation was obtained in PPAR-α-deficient mice which displayed a prolonged inflammation in response to the proinflammatory leukotriene B4 (LTB4). Recent studies aimed to delineate the cellular and molecular mechanisms by which PPAR-α modulates the inflammatory response. Activated PPAR-α blocks the production of inflammatory response markers, such as endothelin-1, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells and tissue factor, matrix metalloproteinase (MMP)-9 and tumor necrosis factor alpha (TNF-α) in macrophages. In human aortic smooth muscle cells (SMC), PPAR-α activation by fibrates inhibits interleukin-1 (IL-1)-stimulated IL-6 secretion and 6-keto platelet growth factor (PGF)1 production by de-

creasing IL-6 and COX-2 gene transcription. Furthermore, aortic explants from PPAR-α-deficient mice showed an intensified response to inflammatory stimuli such as lipopolysaccharide (LPS), as indicated by increased IL-6 secretion. Taken together, these observations provide evidence that PPAR-α plays a role in the inflammatory response in different cell types (Fig. 4). Studies addressing the molecular mechanisms of the anti-inflammatory actions of PPARs suggest that many of the effects of PPARs are mediated by an inhibition of proinflammatory transcription pathways, such as NF-κB, AP-1, NFAT, C/EBP or Smad3, *via* protein-protein interaction and competition for cofactor recruitment [16].

The NF-κB family of transcription factors plays a major role in the regulation of the expression of a number of genes implicated in cell growth, inflammation, and apoptosis. The NF-κB/Rel family is composed of five members, c-Rel, p65, Rel B, p50, and p52. In most non-activated cells, NF-κB is in a cytoplasmic inactive complex through its association with the inhibitory proteins IκBs. Inducers of NF-κB, which include inflammatory cytokines, reactive oxygen species, and viral products, activate a dimeric IκB kinase (IKK) complex, which phosphorylates IκBα on Ser-32 and Ser-36 leading to subsequent ubiquitination and degradation of IκBα and release of NF-κB proteins. Free NF-κB dimers translocate to the nucleus where they regulate target gene transcription [19].

Use of NSAIDs

NSAIDs are used in the following diseases: rheumatoid arthritis, juvenile arthritis, ankylosing spondilitis, psoriatic arthritis, systemic lupus, crystal arthritis, posttraumatic pain, headache, toothache, upper respiratory tract infections, early stage cancer pain, urologic diseases, and tendency to thrombotic events [20, 76, 91, 104].

Side effects of NSAIDs

It is well-known that therapy with COX inhibitors is associated with a number of side effects including gastrointestinal erosions, and renal and hepatic insufficiency. Such critical adverse reactions are highly dependent on COX-1 inhibition [12]. The most common side effect of NSAIDs is gastrointestinal (GI) toxicity. GI toxicity has been attributed to the inhibition of the COX-1-mediated generation of the cytoprotective prostanoids, such as prostaglandin PGE_2 and PGI_2 [52]. GI system damage may vary from hidden blood loss to ulcer perforations [7, 98]. NSAIDs may also cause a rise of serum creatine levels and induce hypercalemia, interstitial nephritis, proteinuria, and acute renal dysfunction (renal toxicity) [66, 72, 76, 99]. Due to a reduced production of PGs, such as PGI_2, PGE_2 involved in the regulation of renal blood circulation, the rate of glomeruleral filtration is reduced. Especially in patients with reduced renal function, this results in retention of water, hypertension and, in some cases, to renal failure.

The inhibition of COX in thrombocytes leads to decreased production of thromboxane A_2. This phenomenon prolongs bleeding time and leads to inhibition of platelet aggregation [18]. In addition, NSAIDs may increase liver enzyme levels, and may cause agranulocytosis, aplastic anemia, toxic epidermal necrosis, cartilage metabolism dysfunction (NSAIDs block glucosaminoglucan synthesis), Reye's syndrome, vertigo [2, 8, 30, 31, 63, 65, 105]. Bronchoconstriction with asthmatic events is also a severe side effect of NSAIDs. The reduced amount of bronchodilatating PGE_2 and a shift in the metabolic pathway from the COX pathway to the 5-lipooxygenase pathway are responsible for the bronchoconstricting effect of NSAIDs. The latter pathway metabolizes 'overflow' AA, which cannot be transformed by the blocked COX pathway. The final leukotrienes act as bronchoconstrictors [18].

Selective COX-1 and non-selective COX Inhibitors

These inhibitors include many groups (Tab. 1). We will discuss two groups of these inhibitory drugs in this review:

1. Salicylates (selective COX-1 inhibitors);
2. Phenylpropionic acid derivatives (non-selective COX inhibitors).

Salicylates

Acetylsalicylic acid (ASA), also known as aspirin, is the most commonly used drug amongst salicylates. It is an anti-inflammatory, analgesic, and antipyretic drug, which is not COX-2 specific and inhibits prostaglandin and thromboxane synthesis [53, 82]. ASA inhibits COX-1 more than COX-2 and the inhibition is irreversible [24]. ASA is effective in the treatment of inflammatory diseases, especially arthritis and carditis, and in acute rheumatoid fever [31, 92]. It is also administered in acute coronary heart diseases and chronic treatment of cerebral sinovenous thrombosis [3, 34]. ASA may induce epithelial damage in stomach mucosa, ulcer, and bleeding [37, 41, 71]. The bleeding arises from a reduction in synthesis of coagulation factors in the liver and inhibition of thrombocyte aggregation [51]. Allergic reactions, such as bronchospam, vasomotor thinitis, and angioedema may occur after ASA administration [2]. Salicylates have been found to have nephrotoxic and hepatotoxic effects [66]. Sodium salicylate has weaker analgesic, antipyretic, and anti-inflammatory effects in comparison with ASA. In addition, its antiaggregatory effect is not obvious, since it inhibits thromboxane synthase [31]. It is known to be as effective as ASA in rheumatoid diseases, although it is a weaker COX inhibitor than ASA. The fact that sodium salicylate does not cause gastric damage is in accordance with its ineffectiveness as COX-1 inhibitor [93]. Difluorophenyl derivative of salicylic acid, diflunisal, has anti-inflammatory, analgesic, and antipyretic effects. It weakly inhibits COX-1 and COX-2. Duration of diflunisal effect is longer than other salicylates. It is mainly used as an analgesic in muscle-skeleton system diseases and has side effects similar to salicylates [45]. Other salicylate derivatives are not used to produce systemic effects.

Phenylpropionic acid derivatives

This group contains analgesic, antipyretic and anti-inflammatory drugs, such as ibuprofen, naproxen, ketoprofen, fenbufen, tiaprofenic acid, fenprofen. These drugs inhibit both COX isoforms [11, 15, 35, 93]. Ibuprofen is effective in the treatment of rheumatoid arthritis, osteoarthritis, gout arthritis, and diseases with pain (headache, toothache, and dysmenorrhea) and reduces fever by inhibiting prostaglandin synthesis [1, 36, 45, 74]. It may cause GI side effects, renal dysfunction, meningeal syndrome, and bone marrow depression [13, 39, 41, 43, 61, 77, 107]. Naproxen is an anti-inflammatory, analgesic and antipyretic drug with a long-term effect. It inhibits both COX isoforms [43]. It strongly inhibits functions of leukocytes at the inflammatory site [31, 45, 77] and it is frequently used in rheumatoid arthritis, ankylosing spondilitis, and traumatic damage to joints and surrounding tissues [69]. Most common side effects of naproxen are GI irritation [78], headache, vertigo, and depression [77, 97]. Ketoprofen effects are similar to naproxen. It has both central and peripheral analgesic effects [28]. Fenbufen and tiaprofen are anti-inflammatory, analgesic and antipyretic drugs. The former has fewer gastropathic effects, and the latter does not inhibit proteoglycan synthesis in cartilage tissues [46, 47].

Selective COX-2 inhibitors

Selective inhibitors of COX-2 are drugs whose therapeutic effects are as strong as conventional NSAIDs but which lead to fewer side effects [77].

Meloxicam, a relatively selective COX-2 inhibitor, has a more potent inhibitory effect on COX-2 than on COX-1 (Tab. 1) [44, 67]. However, COX-2 selectivity of meloxicam at high doses decreases and inhibition on COX-1 increases. Meloxicam is well tolerated by patients [27]. It has been as effective as other NSAIDs in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondilitis and was shown to have a better safety profile [40].

Nimesulide is a relatively selective COX-2 inhibitor and an analgesic, antipyretic and anti-inflammatory drug (Tab. 1) [35]. Studies have shown that nimesulide inhibits COX-2 *in vitro* up to five-fold more potently than COX-1 [17].

Nimesulide inhibits COX-2 more potently at lower doses, but at higher doses its COX-2 selectivity is abolished and it inhibits COX-1 more strongly than COX-2 [25]. Antipyretic effect of nimesulide is based on inhibition of prostaglandin synthesis [15].

Pain reducing effect of nimesulide has been found to arise, in part, from inhibition of cytokines [22], which are known to have a role in inflammatory process [85]. Nimesulide induces less damage to the gastric tissue. It did not induce gastric damage, even when given with steroidal anti-inflammatory drug, prednisolone [35]. Nimesulide also has antioxidant

properties [38]. It is used in the treatment of inflammatory pain [6]. Highly selective COX-2 inhibitory drugs such as celecoxib and rofecoxib have been developed since they have less adverse effects. They possess analgesic, antipyretic and anti-inflammatory effects as potent as traditional anti-inflammatory drugs [70]. Celecoxib and rofecoxib inhibit COX-2 375 and 800 times more strongly than COX-1, respectively [36]. It has been reported that these drugs do not induce damage to the stomach tissue [13]. Rofecoxib and celecoxib are as effective as other NSAIDs in inflammatory diseases [76], but recent studies have demonstrated that these drugs may result in thrombotic cardiovascular problems [58]. Therefore, the use of their (particularly rofecoxib and celecoxib) is controversial in recent days.

Recently some new coxibs (i.e. etoricoxib, valdecoxib, parecoxib and lumiracoxib) with increased biochemical COX-2 selectivity over that of rofecoxib and celecoxib have been developed. Valdecoxib has *in vitro* evidenced higher biochemical selectivity than celecoxib. This may be relevant to the improved gastrointestinal safety. Parecoxib, a prodrug of valdecoxib, is the only injectable selective COX-2 inhibitor. Etoricoxib displays slightly improved COX-2 selectivity than rofecoxib. Lumiracoxib, the most selective COX-2 inhibitor *in vitro*, is the only acidic coxib. These new molecules are suggested to have comparable effect to nonselective NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis and acute pain, but they have similar renal adverse-effects, in several randomized clinical studies. The apparent dose-dependence of renal toxicity may limit the use of higher doses of the novel coxibs for improved effect [88].

As selective COX-2 inhibitors do not inhibit thromboxane A_2, incidence of bleeding is reduced. It has been hypothesized that these drugs cannot be used instead of aspirin [25]. The COX-2 isoform produces PGs at inflammatory sites as well as PGI_2, which is a vasodilator and inhibitor of platelet aggregation. Selective COX-2 inhibitors would have no effect on thromboxane A_2 production, but by decreasing PGI_2 production may disturb the natural balance between prothrombotic thromboxane A_2 and antithrombotic PGI_2, and may lead to an increase in thrombotic cardiovascular events [58]. Although these drugs are used in the treatment of rheumatoid arthritis, osteoarthritis, and inflammatory diseases [5, 6, 70, 79], they may cause blood pressure impairments and other cardiorenal events in patients with hypertension. Some studies have shown that edema development and high diastolic blood pressure were observed in patients with hypertension taking rofecoxib and celecoxib. In celecoxib-administered patients, edema and blood pressure impairments were less frequent than in patients administered rofecoxib [102]. In another study, it was seen that rofecoxib enhanced markedly systolic blood pressure, while celecoxib did not increase it [103]. In addition, rofecoxib had a higher renal toxicity when compared to celecoxib and traditional NSAIDs [107].

There is apparent evidence that both COX-1 and COX-2 are present in the kidney in constitutive and inducible forms, which suggests that selective COX-2 inhibitors will have the same effects on renal prostaglandins as nonselective NSAIDs. The PGs that are most important in the kidney are PGE_2 and PGI_2, or prostacyclin. PGE_2 decreases sodium reabsorption at the thick ascending limb of the loop of Henle and PGI_2 stimulates renin release, which in turn increases aldosterone. Aldosterone increases sodium reabsorption and potassium secretion at the distal nephron. Prostacyclin is also a strong vasodilator that maintains glomerular filtration rate (GFR) and renal blood flow in patients with decreased actual or effective circulating volume. In healthy individuals, the vasodilatory role of PGI_2 is not operative and has little importance in renal hemodynamics. By understanding the physiological effects of renal PGs and their function, the consequences of inhibiting them can be predicted. Inhibiting PGE_2 will cause sodium retention, which can be manifested as weight gain, peripheral edema, or rarely, congestive heart failure. Blood pressure may also increase because of sodium retention. This occurs most often in patients with hypertension who are being treated with antihypertensive medications. In addition, inhibition of PGI_2 can cause hyperkalemia or, in patients at risk for adverse renal effects, acute renal failure [9]. Effects of selective COX-2 inhibitors on delayed wound healing (in gastric tissue) have been discussed in the following section.

Effects of some NSAIDs on gastric tissue

Effects of indomethacin, naproxen, ibuprofen, nimesulide, and diclofenac on rat stomach tissue have been

investigated. Indomethacin was observed to induce the largest damage to the gastric tissue. On the other hand, diclofenac induced the smallest lesions, naproxen and ibuprofen induced moderate damage to the gastric tissue, while nimesulide did not provoke ulcer [83]. The studies of Mitchell et al. [55] indicated that indomethacin and ibuprofen inhibited COX-1 more strongly than COX-2, while diclofenac inhibited COX-2 more than COX-1. These data show that the results are in accordance with the hypothesis of COX-1 and COX-2. In addition, ranitidine and nimesulide have been shown to completely prevent indomethacin-induced ulcers in rats [80]. Rofecoxib and celecoxib could not prevent indomethacin-induced ulcers [84]. In addition, both drugs enhanced stress-induced ulcers [68] while nimesulide, at a dose of 500 mg/kg, reduced stress-induced ulcers [83]. These data suggest that either COX hypothesis is not true or mechanisms of action of rofecoxib and celecoxib are not sufficiently defined. Prevention of indomethacin-induced ulcers by nimesulide suggested that there might be a chemical antagonism between indomethacin and nimesulide. Studies have emphasized that nimesulide and ranitidine do not chemically react with indomethacin [81], and there is no chemical antagonism between indomethacin and nimesulide. In a recent study by Kataoka et al. [35], it has been reported that indomethacin causes inhibition of COX-1 in gastric tissue, lowers PGE_2 levels, and increases acid secretion, myeloperoxidase (MPO) activity, stomach movement, while nimesulide relatively inhibits COX-2, does not affect PGE_2 and MPO levels and reduces gastric acid secretion. In another study, indomethacin increased hydrochloric acid (HCl) secretion and lowered bicarbonate (HCO_3) and PGE_2 synthesis [86].

There are several more issues that need to be addressed. May nimesulide be preventing indomethacin-induced ulcers by inhibiting H_2 receptors? Is COX-2 selectivity of nimesulide abolished at high doses? May ranitidine have anti-inflammatory effect?

Nimesulide and famotidine, when given together, inhibited HCl secretion more than when given alone, and this indicates that nimesulide does not affect histamine H_2 receptors [89]. Nimesulide, at a dose of 500 mg/kg, prevented stress-induced ulcers better than H_2 receptor blockers [83]. Both COX isoforms must be inhibited to provoke ulcer [62]. Should both enzymes be activated to induce gastroprotective effect?

These data demonstrate that mechanisms of action of drugs under discussion are multidirectional and complex. These drugs or their derivatives, which belong to the same group, have distinct pharmacological effects, side effects and potencies which imply that there may be more than two, five, or even tens of COX isoforms. The drugs that are well tolerated by some patients may cause serious adverse effects in other patients. Do effects of this kind arise from insufficiency of COX isoforms rather than from any organ pathology? Such questions and others will remain unanswered until new reports elucidate the unknown aspects of the relationship between COX isoforms and their physiological functions. Especially, the suggestion that COX may have a third isoform in the brain will be the focus of forthcoming studies. Until satisfactory data become available, clinicians must use NSAIDs cautiously.

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