Pergamon

Biochemical Pharmacology, Vol. 50, No. 10, pp. 1535–1542, 1995.

0006-2952/95 $9.50 + 0.00

0006-2952(95)00212-X

COMMENTARY

CYCLOOXYGENASE-2: REGULATION AND RELEVANCE IN INFLAMMATION

JANE A. MITCHELL,* SIMON LARKIN and TIMOTHY J. WILLIAMS

Department of Applied Pharmacology, The National Heart and Lung Institute, London SW3 6LY, U.K.

Key words: cyclooxygenase; inflammation; nitric oxide; cytokines; prostaglandins; aspirin

Accumulating evidence suggests that some enzymes exist as distinct constitutive and inducible isoforms. The inducible isoforms are often expressed in pathophysiological conditions, particularly those regulated by cytokines. These enzymes can be important in the protective functions of inflammation. However, the inappropriate induction of such enzymes can lead to an over-production of mediators that augment inflammatory conditions. One such enzyme that is particularly important in inflammation is COX.† COX is the first enzyme in the pathway by which arachidonic acid is converted to prostaglandins and thromboxanes. COX was first purified and characterized using sheep vesicular gland preparations [1]. We now know that COX exists in at least two isoforms, a constitutive, "house keeping" isoform (COX-1), which probably represented most of the activity in the original preparations, and a cytokine-inducible isoform (COX-2). COX-1 is thought to be responsible for the acute production of prostaglandins, such as prostacyclin, from the gastric mucosa, thromboxane from platelets, and prostaglandins during acute inflammatory episodes. However, COX-2 appears to be the predominant isoform present in more chronic inflammatory conditions. NSAIDs, such as aspirin, inhibit both isoforms of COX, explaining their beneficial (inhibition of COX-2) and potentially deleterious (inhibition of COX-1) effects. The recent identification of COX-1 and COX-2, together with the demonstration that COX-2 predominates in inflammatory conditions, has led to new approaches for the development of anti-inflammatory therapies. Considering that NSAIDs constitute one of the largest groups of prescribed drugs worldwide, the search for selective inhibitors of COX-2 may well provide extensive benefits. This commentary will focus on the key events that have provided the impetus for the development of second generation NSAIDs (COX-2 specific inhibitors).

Biosynthesis of prostaglandins and thromboxanes

In the 1930s, studies showed that seminal fluid contracted strips of uterus and relaxed vascular smooth muscle. The active material from seminal fluid was then shown to be lipid soluble and termed prostaglandin. Prostaglandins were shown subsequently to constitute a family of 20 carbon atom fatty acid compounds [1], which are synthesized in most tissues in the body. The three phases of prostaglandin production can be simplified as: (i) mobilization of arachidonic acid from cellular phospholipids, (ii) conversion of arachidonic acid to the prostaglandin endoperoxides, prostaglandin G_2 and then prostaglandin H_2, and (iii) either isomerization or reduction of prostaglandin H_2 to biologically active derivatives. Mobilization of arachidonic acid is achieved mainly by the actions of phospholipase A_2 on phosphatidylethanolamine and phosphatidylcholine (for other routes by which arachidonic acid production is regulated, see Irvine [2]). Arachidonic acid can then be metabolized by several enzymes including COX. COX exhibits both *bis*-oxygenase (cyclooxygenase) activity catalysing the formation of prostaglandin G_2, and peroxidase activity, catalysing a two-electron reduction of prostaglandin G_2 to prostaglandin H_2. Prostaglandin H_2 is then further metabolized by specific isomerases or synthetases to various derivatives including prostaglandin E_2, prostacyclin, thromboxane A_2 and prostaglandin $F_{2\alpha}$ [1].

Role of prostaglandins in inflammation

Inflammation is a complex set of events modulated by various chemical mediators released by both resident and infiltrating cells. The processes of arterial dilation, plasma protein leakage, and leukocyte extravasation are key events in all inflammatory responses. Experimental models in animals have shown that the early vascular responses of vasodilatation and edema formation involve the local release of low molecular weight mediators including histamine, serotonin, bradykinin as well as prostaglandins. Prostaglandins exert their potent biological effects by binding to specific cell-surface receptors, which results in the transfer of a signal via G-proteins to signal transduction pathways, usually cAMP [3]. Although there are similarities in the signal transduction pathways through which these receptors are linked, prostanoids have remarkably varied biological actions. In the cardiovascular system, for instance, prostacyclin is a vasodilator and a potent inhibitor of platelet aggregation, whilst thromboxane is a vasoconstrictor and causes the aggregation of platelets. In most vascular beds, prostaglandin E_2 is also a vasodilator, and together with prostacyclin it is a cytoprotective agent in the stomach [4]. However, it has become evident that the vasodilator prostaglandins have an important regulatory role in both

* Corresponding author: Dr. Jane A. Mitchell, Department of Applied Pharmacology, The National Heart and Lung Institute, Dovehouse St., London SW3 6LY, U.K. Tel. 44-171-351-8170; FAX 44-171-351-8270.

† Abbreviations: COX, cyclooxygenase; cAMP, adenosine 3′,5′-cyclic monophosphate; IL-1, interleukin-1; NO, nitric oxide; NOS, nitric oxide synthase; LPS, lipopolysaccharide; TGFβ, transforming growth factor-β; NSAIDs, nonsteroidal anti-inflammatory drugs; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; and CEF, chicken embryo fibroblasts.

acute and prolonged inflammatory responses. Although inflammation is a symptom of many diseases, such as arthritis, asthma and ulcerative colitis, the role of prostaglandins in inflammation has been characterized the best in the skin.

Intravenous infusion of prostaglandin E_1 or prostaglandin E_2 in animals and prostaglandin E_1 in human forearm showed them to be potent vasodilators of the peripheral vasculature [5, 6]. Prostaglandin $F_{1\alpha}$ and prostaglandin $F_{2\alpha}$ are less active than the E-type prostaglandins at producing erythema [7–9]. Originally, the microvascular protein leakage induced in animal skin by prostaglandins was attributed to the release of mast cell amines. However, prostaglandins alone were shown to be relatively weak edema-inducing agents, prostaglandin E_1 being 1,000–10,000 less potent than bradykinin [10]. Indeed, the synergistic effects of prostaglandins with other inflammatory mediators are thought to be more important. In the guinea pig and rat, for example, edema induced by histamine and bradykinin is potentiated markedly by the co-administration of E-type prostaglandins, an effect that correlates with their potency as vasodilators [10–13]. In addition, the combined generation of prostaglandins and chemoattractants, such as the complement fragment C5a, leads to synergistic potentiation of inflammatory responses. In the presence of circulating leukocytes [14], C5a increases venular permeability, while the prostaglandins cause arterial dilatation and increase intravenular hydrostatic pressure downstream, thus promoting plasma protein leakage from the venule [15, 16]. Through their effects on blood flow, prostaglandins can also increase the delivery of pro-inflammatory cells to sites of inflammation [17]. Accordingly, prostaglandins have important pro-inflammatory actions in some allergic and non-allergic responses, as illustrated by experimental forms of passive cutaneous anaphylaxis [18], immune complex-mediated reactions, and responses to microbes [13, 14, 19]. Similarly, exudates extracted from human skin affected by allergic and irritant dermatitis contain elevated levels of arachidonic acid and prostaglandin E_2 [20, 21], and release of these mediators parallels the erythema that occurs after exposure to ultraviolet light or heat [22, 23].

In addition to their effects on plasma leakage, there is evidence that prostaglandins sensitize pain receptors in both central and peripheral neurones. Studies in the human skin show that injections of prostaglandin E_1 are not painful *per se* but cause hyperalgesia [7, 8, 24], possibly through the facilitation of sensory neuropeptide release from local sensory neurones [24–26].

In the conditions described above, NSAIDs have proven anti-inflammatory activity. However, the blockade of prostaglandin synthesis in conditions such as gastric ulceration and asthma can exacerbate the disease. Thus, in certain inflammatory states prostaglandins have important *anti*-inflammatory activities. This has been demonstrated using exogenous prostaglandins *in vivo* [27] and may be dependent on the precise site of generation [28].

Induction of COX-2 in vitro

Under physiological conditions, the synthesis of prostaglandins is limited by the availability of arachidonic acid. However, when certain cytokines, such as IL-1, are elevated, phospholipase A_2 is expressed in high levels [29] and is present in both the intra- and extracellular space. Consequently, the levels of arachidonic acid are elevated, and, together with the induction of COX enzyme, this results in the release of large amounts of prostaglandins. The effects of various cytokines, mitogens and hormones on *de novo* COX synthesis have been noted since the late 1970s [30].

Subsequently, many cell types *in vitro* have been shown to synthesize increased amounts of COX under experimental inflammatory conditions [30]. Stimulation of cell division by mitogens activates a variety of intracellular events, including the protein synthesis-independent transcription of "primary response" [31] or "immediate-early" [32] genes. In 1990, the identification of COX as an immediate-early gene, induced by phorbol esters, led to the important realization that COX exists in at least two discrete isoforms (see Table 1). These are a constitutive isoform present in, for example, endothelial cells [33] named COX-1, and a cytokine/mitogen/inflammation-induced isoform named COX-2 (Fig. 1). The identification of COX-2 began when several groups working in parallel used differential hybridization procedures to identify cDNAs rapidly elevated in response to mitogenic or viral stimulation of cells. Independent studies on the cDNA of the immediate-early genes, TIS-10 (TPA-induced sequence 10; [34]) and CEF-147 (chicken embryo fibroblast gene-147; [35]), proved to be the starting point of a new aspect to the field of prostaglandin research. Rous sarcoma virus was shown to induce in CEF a 4.1-kb mRNA (CEF-147) encoding a 603-amino acid protein. Analysis of the CEF-147 protein sequence showed 59% homology with sheep COX [35]. Significant differences were found at both the protein and mRNA levels, suggesting that CEF-147 was a novel isoform of COX. Similarly, TPA was shown to induce a 3.9-kb mRNA encoding a predicted protein of 604 amino acids with striking similarity to COX [36]. The similarities in CEF-147 and TIS-10 products, together with a comprehensive review of how these genes are regulated, is given by Xie and co-workers [37]. Since then the sequences described for COX-2 primers and specific COX-2 antibodies have been used by several laboratories to investigate how COX-2 is regulated in a variety of cells including endothelial [38, 39], macrophage [33, 40–42], monocyte [41], and ovine [43] and human [44] pulmonary epithelial cells (see Table 1).

In each cell type, the induction of COX-2 requires protein synthesis and, where tested, it is inhibited by dexamethasone [39, 40, 44–46]. The inhibitory effects of dexamethasone on COX-2 induction support previous observations showing that steroids inhibit the *de novo* synthesis of COX enzyme in murine macrophages *ex vivo* following LPS administration *in vivo* [47]. Thus, the anti-inflammatory corticosteroids can now be considered to act, at least in part, by the inhibition of COX-2 expression.

Many of the agents that cause the induction of COX-2 act on receptors that have an intracellular tyrosine kinase domain, activation of which results in the phosphorylation of proteins [48]. Indeed, activation of tyrosine kinase by cytokines may be a key event in the signal transduction pathways that mediate some of the late cellular events stimulated by cytokines [48]. Recently, we used two tyrosine kinase inhibitors, erbstatin and genistein, to demonstrate that tyrosine kinase activity is a crucial step in the induction of COX-2 protein and

Table 1. Identification of COX-2 as a novel isoform of COX

Cell type	Inducer	COX activity	Parameters determined	Reference
CEF	RSV	ND	COX-2 gene (CEF-147) cloned; 4.1-kb mRNA for COX-2; encoded protein size, 603 amino acids; 59% amino acid identity with COX-1	37
Mouse fibroblasts (3T3)	TPA	ND	COX-2 gene (TIS-10) cloned; 3.9-kb mRNA for COX-2; encoded protein size, 604 amino acids	36
Mouse fibroblasts (3T3)	TPA, serum	↑	Structure of COX-2 gene; expression of functional COX-2 in transfected cells	91
Mouse fibroblasts	Serum, IL-1, PDGF	↑	COX-2 gene cloned; 4.1-kb mRNA for COX-2; expression of functional COX-2 in transfected cells	46
Rat granulosa cells	Trophic hormones	ND	Characterization of the expression of COX-2 gene	92
Rabbit alveolar Mac	LPS	ND	COX-2 protein confirmed using specific anti-COX-2 antibody	42
Rat alveolar Mac	LPS	↑	Comparison of COX-2 activity, mRNA and protein	40
Human UVEC	IL-1	↑	Human COX-2 gene cloned; 4.5-kb mRNA encoding a protein of 604 amino acids	38
Human lung Ep	IL-1	↑	Comparison of COX-2 activity and protein	44
Bovine AEC	LPS	↑	Comparison of COX-2 activity and protein	39
Murine Mac (J774)	LPS	↑	Comparison of COX-2 activity and protein	33
Human alveolar Mac and blood monocytes	LPS	↑	Comparison of COX-2 activity, mRNA and protein	41
Rat intestinal Ep	TGFα, TPA	↑	Comparison of COX-2 activity, mRNA and protein	45

Abbreviations not defined in text: Mac, macrophage; UVEC, umbilical vein endothelial cells; Ep, epithelial cells; AEC, aortic endothelial cells; RSV, Rous sarcoma virus; PDGF, platelet-derived growth factor; TGFα, transforming growth factor-α; and ND, not determined. For an extensive review of agents that will induce isolated cells to synthesize *de novo* COX protein, see De Witt [30].

activity in both murine macrophages and bovine aortic endothelial cells [39]. Clearly, the continued study of events involved in the regulation of COX-1 and COX-2 isoforms will provide an improved understanding of some inflammatory conditions.

Comparison and interaction of the COX and NOS pathways

NO is released from many cells by constitutive isoforms of NOS present in central [49, 50] and peripheral [51] neurones (nNOS) and in vascular endothelial cells (eNOS; [52, 53]). In analogy to COX-2, there is also a distinct cytokine-inducible isoform of NOS (iNOS; [54]). As NO has a role as an endogenous signalling molecule that synergizes with prostaglandins in some conditions [55], it is worth reviewing some of the recent literature describing parallel induction of iNOS and COX-2. Co-induction of iNOS and COX-2 has been shown recently to occur in several cell types, stimulated with either LPS or cytokines. These include rat vascular smooth muscle [56, 57], murine macrophages [58, 59], rabbit chondrocytes [60] and rabbit hepatocytes [61] but not human fetal fibroblasts [59] or bovine aortic endothelial cells [39]. Such studies raise the question of possible cross talk between NO and COX-2, or prostaglandins and iNOS. Interestingly, endogenously released NO has been shown to both inhibit and activate COX-2, e.g. NO or sodium nitroprusside (a compound that spontaneously releases NO) inhibits the release of prostacyclin from endothelial cells (COX-1; [62–64]) and in the same cells the coupled release of NO inhibits both COX-2 activity and induction [60, 61]. The mechanism by which NO inhibits COX activity has been explained by the ability of NO to reduce the ferric-active form of COX to the ferrous-inactive form [65]. In contrast, both endogenously released and exogenously applied NO have been shown to stimulate COX activity in LPS-activated murine macrophages [59] and vascular smooth muscle cells [57]. These contradictory observations may possibly be explained by the different amounts of NO present in the various assay systems used and the subsequent production of different quantities of radicals [60]. For instance, COX activity is modulated by hydroperoxides that can enhance activity in trace amounts and inhibit activity in exaggerated amounts [1].

Unlike the effects of endogenously released NO on the activity of COX-2, the accompanying release of prostanoids does not affect the activity of NOS [57, 59]. However, exogenously applied prostaglandin E_2 or iloprost (a stable analogue of prostacyclin) inhibits nitrite accumulation in LPS-treated J774.2 cells [66]. On the other hand, prostaglandin E_2 enhances the formation of nitrite by LPS-treated Kupffer cells [67]. Therefore, it

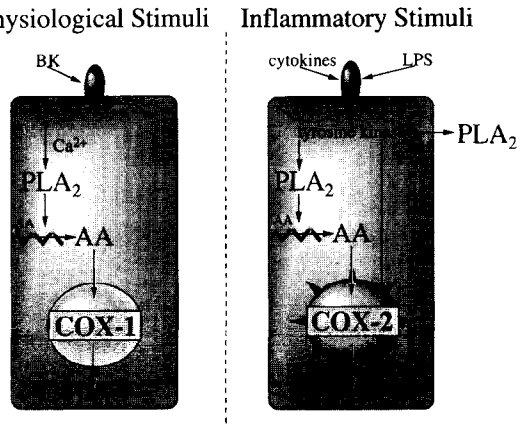

Fig. 1. Release of prostaglandins by cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) activation. Left panel: under physiological conditions, cells contain predominately COX-1. Under these conditions, the activation of cell surface receptors by ligands, such as bradykinin (BK), causes liberation of inositol phosphates (IP_3) and an elevation in intracellular calcium (Ca^{2+}) concentration. Increased Ca^{2+} directly activates phospholipase A_2 (PLA_2) enzymes, which liberate arachidonic acid (AA) from membrane phospholipids. Intracellular AA is then metabolized by COX-1, ultimately leading to the production of prostaglandins (PGs). Right panel: in inflammatory conditions, cytokines are elevated and act on cell surface or soluble receptors, causing the induction of both COX-2 and PLA_2 via the activation of tyrosine kinase. Under these conditions, the parallel induction of COX-2 and PLA_2 results in the release of exaggerated amounts of PGs.

seems that the amounts of prostanoids released by individual cell types and the distribution of their receptors may determine the effect of COX inhibition on NOS activity.

Thus, NO appears to have a bell-shaped response curve for its effects on COX activity, causing stimulation in some conditions and inhibition in others. This feedback mechanism may be particularly important *in vivo* where iNOS and COX-2 are co-induced in sepsis [56] and at sites of inflammation [68, 69].

Induction of COX-2 in vitro

Following the demonstration that COX-2 is induced *in vitro* by pro-inflammatory agents, it became clear that COX-2 may be the isoform that predominates at sites of inflammation *in vivo*. Thus, COX-2 would represent a new target for drug development in the search for a second generation aspirin-like drug. Interestingly, probably the first demonstration of COX-2 induction *in vivo* was part of a physiological process, ovulation. COX-2, or a related isoform of COX, is induced in rat ovarian follicle cells during ovulation and facilitates the burst of prostaglandins necessary for ovulation to occur [70]. Furthermore, immunohistochemical studies using a specific COX-2 antibody showed that COX-2 is the predominant isoform in fallopian tube epithelial cells throughout all stages of the estrous cycle [71].

Some of us have used an air pouch model of granulomatous inflammation in the mouse to demonstrate that COX-2 predominates over COX-1 in acute, chronic and resolving phases of inflammation [68]. An early peak in COX-2 protein and activity (24–48 hr) correlated with IL-1 expression and a later and larger peak (14–21 days) correlated with TGFβ expression [72]. More recently, a similar study confirmed the predominance of the COX-2 isoform in the air pouch model of inflammation and demonstrated potent actions of a selective COX-2 inhibitor on prostaglandin production in the granulomatous tissue [73]. COX-2 protein and activity are also expressed in the rat carrageenin-induced pleurisy model of acute inflammation where there is a peak in COX-2 activity at 2–6 hr after the injection of carrageenin, primarily within polymorphonuclear neutrophils [69].

The exaggerated release of prostaglandins by synovial tissues is considered to be a key event in the erosion of joint tissue in rheumatoid arthritis. Indeed, the expression of "COX" immunoreactivity in synovial tissue from patients with rheumatoid arthritis parallels the severity of the inflammatory response [74] and COX-2 protein is present in rheumatoid synovia, particularly in infiltrating mononuclear cells, vascular endothelial cells and subsynovial fibroblast-like cells [75]. However, there is currently no quantitative evidence as to which isoform of COX predominates in these tissues, although increasing evidence suggests that COX-2 rather than COX-1 is responsible for the production of prostaglandins in protracted inflammatory conditions. Taken together, these findings suggest that any inflammatory response where cytokines or growth factors are unregulated ultimately results in COX-2 induction. For this reason, intense efforts have been made to develop specific inhibitors of the COX-2 isoform.

Effects of NSAIDS on COX-1 and COX-2

NSAIDs, including aspirin and indomethacin, are amongst the most widely prescribed group of drugs worldwide. NSAIDs constitute the drugs of choice in the treatment of rheumatic disorders and other degenerative and inflammatory joint diseases, and as multi-purpose analgesics. Although NSAIDs are a group of drugs with diverse structures, inhibition of COX, and therefore prostaglandin production, is the common basis for their therapeutic benefits [76]. NSAIDs also cause side-effects, including gastric ulceration and renal failure, which limit their use in some patients. These side-effects can also be attributed to inhibition of COX, as the formation of prostaglandins such as prostacyclin and prostaglandin E_2 can be cytoprotective [4]. It is therefore tempting to speculate that inhibition of COX-2 accounts for the therapeutic benefits of NSAIDs whereas inhibition of COX-1 accounts for their shared side-effects.

Some of us [33, 77] and others [78, 79] have shown recently that COX-1 and COX-2 are differentially inhibited by a selection of commonly used NSAIDs (Fig. 2). We used endothelial cells, which contain exclusively COX-1, and LPS-activated macrophages, which contain exclusively COX-2 [33], as a basic screen to assess the relative potency of many of the presently prescribed NSAIDs. Others have used semi-purified preparations of recombinant COX-1 and COX-2 obtained from transfected cells [78, 79]. Interestingly, most of the NSAIDs tested were selective inhibitors of COX-1, with the exception of 6-methoxy-2-naphthylacetic acid (the active metabolite of nabumetone; [78]), meclofenamic acid [79], diclofenac, naproxen and BF 389 [33]. Thus, drugs such as piroxicam, tolmetin, aspirin, sulindac and indomethacin were found to be highly selective inhibitors of COX-1. This subgroup of NSAIDs is notorious for their

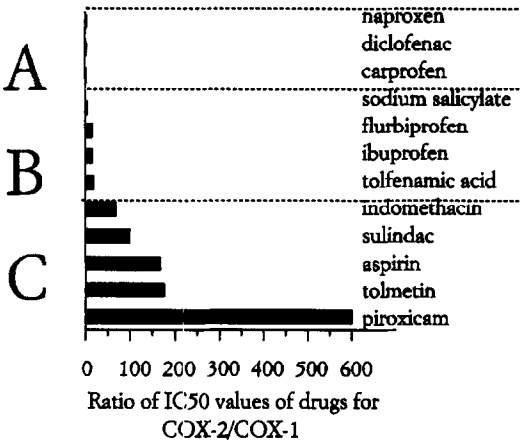

Fig. 2. Relative potency of typical nonsteroidal anti-inflammatory drugs as inhibitors of cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) in intact cells. The figure shows the approximate ratio of the IC_{50} values (μg/mL) of drugs as inhibitors of COX-2/COX-1 (adapted from Mitchell *et al.* [33] and Akarasereenont *et al.* [39]). A high value, therefore, represents a drug that is COX-1 selective. Group C represents drugs with a greater than 50-fold selectivity as inhibitors of COX-1, group B contains drugs that have ratios of between 50 and 10, whilst group A contains drugs that are approximately equipotent inhibitors of COX-1 and COX-2.

high risk of side-effects, including gastrointestinal ulceration and haemorrhage, when given at anti-inflammatory doses [80–82]. For example, aspirin, indomethacin and tolmetin produce the highest incidence of ulcers in patients taking NSAIDs for arthritis [80]. Moreover, in a recent report using a "toxicity index" to standardize the severity of different side-effects in patients taking NSAIDs, indomethacin, tolmetin, piroxicam and sulindac proved to be among the most toxic drugs analysed [81]. Tolfenamic acid, ibuprofen and sodium salicylate are moderately selective inhibitors of COX-1, and tolfenamic acid and ibuprofen produce less gastric side-effects than indomethacin or aspirin. In addition, ibuprofen is less ulcerogenic than sulindac, piroxicam and tolmetin [80]. However, in normal volunteers receiving the highest recommended doses, ibuprofen was found to cause gastric and duodenal mucosal injury equal to that of aspirin [83]. Thus, despite a clear general trend, there are discrepancies between the relative degree of side-effects induced by different NSAIDs. These may reflect large variations in the dosage, duration of therapy, underlying disease or age of patients, or the relative contribution of COX-1 or COX-2 isoforms.

Carprofen, diclofenac, naproxen or ticlopidine are approximately equipotent inhibitors of COX-1 and COX-2, making them the least COX-1 selective agents tested. To substantiate the hypothesis that the ability of drugs to inhibit COX-1 is indeed responsible for their side-effects, the therapeutic use of these agents should be associated with the lowest incidence of gastrointestinal damage in humans. This is the case for carprofen, which produces less side-effects (e.g. gastric irritation) than piroxicam, aspirin and indomethacin [84–86]. Similarly, diclofenac and naproxen produce a lower incidence of gastrointestinal damage than aspirin, tolmetin and indomethacin [80, 87–90].

Ticlopidine [77] and paracetamol [33] are very weak inhibitors of COX-2. However, the therapeutic applications of both ticlopidine and paracetamol are mainly independent of their anti-inflammatory effects. For example, paracetamol is a weak anti-inflammatory and is chiefly used as an analgesic. Ticlopidine is commonly used as an anti-platelet agent, which inhibits COX activity in platelets (COX-1). Clearly, in some cases (aspirin, indomethacin, sulindac, tolmetin and piroxicam), the ability of NSAIDs to inhibit COX-1 selectively correlates with the ulcerogenic side-effects and, hence, substantiates the hypothesis that COX-1 is responsible for the production of cytoprotective prostaglandins from the endothelium and the gastric mucosa.

Potential benefits from second generation aspirin-type drugs (COX-2 specific)

The primary screen in the search for NSAIDs has thus far been the ability of compounds to inhibit COX activity. As most of the COX preparations (e.g. sheep vesicular glands) used presumably consisted of COX-1, it is not surprising that the currently available NSAIDs are mainly active against COX-1. However, increasing evidence suggests that in many inflammatory states the production of prostaglandins is regulated by COX-2 induction. The use of COX-2 activity in different forms has already led to the identification of COX-2 NSAIDs specific for COX-2. These drugs may well prove to be effective anti-inflammatory agents with fewer side-effects. Nevertheless, the use of this new class of drugs may be limited. The predicted induction of COX-2 at the site of gastric inflammation may result in the production of cytoprotective prostaglandins, inhibition of which would exacerbate the inflammatory process. Furthermore, the effects of NSAIDs on COX may be more complicated than inhibition of prostaglandin production. For example, aspirin blocks all metabolites of COX-1, while it modifies the enzymic actions of COX-2, causing the synthesis of 15-hydroxyeicosatetraenoic acid (15-HETE, typically a lipoxygenase product). The aspirin-induced synthesis of 15-HETE by COX-2 is blocked by co-incubation with indomethacin [43, 78, 79]. Phenomena such as these may well contribute to arachidonic acid shunting from COX metabolites to other derivatives, resulting in complications like aspirin-sensitive asthma. Consequently, the effects of novel NSAIDs on the production of other arachidonic acid derivatives should also be studied.

Acknowledgements—The authors would like to thank the British Heart Foundation, the National Asthma Campaign, and Wellcome Trust for financial support. The authors are also indebted to Dr. Maria Belvisi, Dr. Timothy D. Warner, Dr. Y. S. Bakhle and Professor Peter Barnes for their helpful discussions.

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