Principles, Mechanisms of Action, and Future Prospects of Anti-inflammatory Drugs

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Bibiana Rius and Joan Clària

Introduction

Bioactive lipid mediators are major regulators of inflammatory response. Seminal discoveries in the field of lipid mediators generated from the omega-6 polyunsaturated fatty acid, arachidonic acid, have identified prostaglandins (PGs) as essential constituents of inflammation in response to injury. Later on, the identification of cyclooxygenase (COX) as the enzyme responsible for the formation of PGs offered a novel paradigm in the therapeutic modulation of inflammation. Indeed, this enzyme evolved to become the primary target for nonsteroidal anti-inflammatory drugs (NSAIDs), which block the formation of PGs by inhibiting COX activity. Subsequent investigations defined other enzymes belonging to the COX pathway that participate in the formation of PGs, the identification of which offered novel opportunities for blocking/inhibiting this inflammatory pathway. Among these, the discovery of COX-2 in the early 1990s, the enzyme involved in the production of PGs during the inflammatory process, revolutionized the field and provided novel avenues for the design and development of safer anti-inflammatory drugs collectively known as COXIBs. The main advantage of these anti-inflammatory compounds was that they were able to reduce inflammation while sparing the formation of PGs from COX-1, which is the main COX isoform involved in the production of PGs responsible for housekeeping functions such as the maintenance of gastric mucosa and the integrity of renal function. Unfortunately, COXIBs fell into disgrace when their use was associated with a higher incidence of thrombotic events. Luckily, alternative scenarios including the design of compounds selectively inhibiting microsomal PGE synthase 1 (mPGES-1) have emerged as a means to reduce PGE_2 formation without affecting other COX products. Other promising strategies are the use of PG agonists and antagonists acting on specific prostanoid receptors. The latter approach offers more advantages in terms of safety and specificity as compared to the traditional upstream COX inhibitors, although the ten types and subtypes of membrane prostanoid receptors are hamper-ing progress in this area. Other therapeutic opportunities that have been considered are dualCOX-lipoxygenase (LOX) inhibitors, cyclo-pentenone PGs, NSAIDs coupled to nitric oxide (NO) donors, and NSAIDs coupled to H_2S-releasing compounds. Finally, the so-called aspirin-triggered lipoxins, a new genus of lipid mediators that promote the resolution of inflammation, have attracted special interest.

B. Rius, Ph.D. • J. Clària, Ph.D. (✉)
Biochemistry and Molecular Genetics Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERehd, and Department of Biomedical Sciences, Barcelona University School of Medicine, Villarroel 170, Barcelona 08036, Spain
e-mail: jclaria@clinic.ub.es

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Eicosanoids

Eicosanoids comprise a large family of biologically active lipid mediators originating from arachidonic acid, an essential long-chain omega-6 polyunsaturated (4 double bonds) fatty acid with a backbone of 20-carbon atoms. The term eicosanoids derives from the Greek term *eicosa* (20) which refers to the peculiarity that all these arachidonic acid derivatives retain the parent 20-carbon structure. In resting cells, arachidonic acid is stored within the cell membrane and esterified to glycerol in the phospholipids, which are the most abundant structural lipid components in mammalian cells [1, 2]. Phospholipids are amphipathic molecules composed of a glycerol backbone with two fatty acids esterified to the sn (stereospecific numbering) 1 and 2 positions (sn1 and sn2) and a phosphate group bound to the third hydroxyl group. This phosphate group is esterified to another hydroxyl group on another hydrophilic compound, such as choline, ethanolamine, serine, or inositol, forming different phospholipids with unique properties [1, 2]. Upon stimulation, the enzyme phospholipase A_2 (PLA_2) catalyzes the hydrolysis of phospholipids at the sn2 position in a single-step reaction, releasing arachidonic acid into the intracellular space [1, 2]. Other phospholipases such as phospholipase C (PLC) or phospholipase D (PLD) do not release free arachidonic acid directly. Rather, they generate arachidonate-containing diacylglycerol and phosphatidic acid, from which arachidonic acid is subsequently released by diacylglycerol and monoacylglycerol lipases, respectively [1, 2].

Once released to the cytoplasm, free arachidonic acid is highly toxic to the cell and therefore is either rapidly converted into biologically active lipid mediators (i.e., eicosanoids), reincorporated into phospholipids, or diffused outside the cell. There are two major routes of eicosanoid biosynthesis in mammalian cells: the COX and LOX pathways, which are complemented by a third distinct enzymatic pathway, the cytochrome P450 epoxygenase or CYP pathway [3]. The COX pathway results in the formation of prostaglandins (PGs) and thromboxane (TXA_2), which are known for their powerful physiological properties and their critical role in inflammation [4–6]. On the other hand, the LOX pathway comprises three major LOXs, designated 5-LOX, 12-LOX, and 15-LOX. 5-LOX converts arachidonic acid into 5(*S*)-hydroxyeicosatetraenoic acid (5-HETE) and leukotrienes (LTs), which also represent another consolidated pharmacological target in inflammation, whereas 12-LOX and 15-LOX generate the corresponding 12- and 15-HETEs, respectively [4–7]. Alternatively, arachidonic acid can be converted into epoxyeicosatrienoic acids (EETs) through the CYP pathway [8]. These CYP metabolites are subsequently converted by the enzyme soluble epoxide hydrolase into inactive compounds designated diHETEs [9]. Since to date no cognate receptors or second messengers have been identified for these eicosanoids, they will not be discussed in this review.

In recent years, new families of eicosanoids generated by sequential interaction between individual LOX or between COX and LOX interactions have been described. The first mediators of this novel class ever described were the lipoxins (LXs), which are conjugated trihydroxytetraene-containing eicosanoids generated from arachidonic acid [10]. These mediators are the result of transcellular biosynthesis initiated by 15-LOX/5-LOX, 5-LOX/12-LOX, or aspirin-acetylated COX-2/5-LOX interactions [10]. In contrast to the majority of eicosanoids, which have consolidated proinflammatory properties, LXs are anti-inflammatory and not only act as "stop signals" for inflammation but also promote its active resolution [11]. More information on these mediators is given later on of this chapter.

COX Pathway

COX is the key enzyme in the biosynthesis of PGs and TXB_2 from arachidonic acid [5, 6, 12]. There are two distinct COX isoforms,

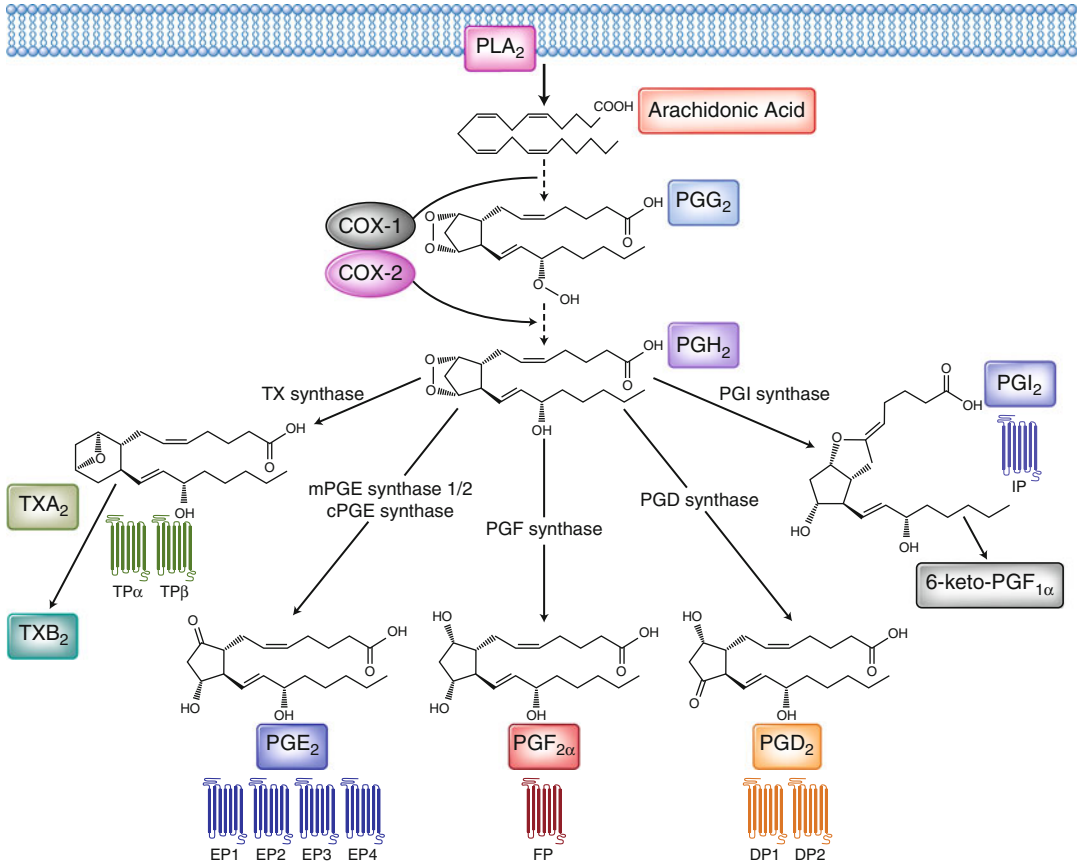

Fig. 2.1 Schematic diagram of the cyclooxygenase (COX) pathway. Once released from membrane phospholipids by phospholipase A_2, arachidonic acid is transformed by COX isoforms (COX-1 and COX-2) into prostaglandin (PG) G_2, which is subsequently reduced to PGH_2. PGH_2 is a highly unstable endoperoxide that is rapidly converted by specific synthases into PGs of the E, D, F, and I series as well as into thromboxane (TX) A_2. Both PGI_2 (prostacyclin) and TXA_2 have a very short half-life and are rapidly hydrolyzed to the inactive compounds 6-keto-$PGF_{1\alpha}$ and TXB_2, respectively. Each COX product interacts with its specific receptor(s) on target cells and tissues. Ten different receptors have been described: four for PGE_2, two for PGD_2, two for TXA_2, and one each for $PGF_{2\alpha}$ and PGI_2

designated COX-1 and COX-2, that generate the same structural products (i.e., PGs). However, COX-1 is a constitutive enzyme expressed in virtually all cells, whereas COX-2 has limited expression in most tissues but is induced by inflammatory mediators. Induction of COX-2 is seen in response to interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interferon (IFN) γ, and lipopolysaccharide (LPS), and therefore, it is generally accepted as the COX isoform involved in inflammatory response [13, 14]. In any event, both COX isoforms sequentially transform arachidonic acid into PGG_2 and, subsequently, into PGH_2, which is finally converted into PGs of the D, E, F, and I series as well as into TXA_2 by specific terminal synthases (Fig. 2.1). The biosynthesis of each of these products is cell specific and depends on which synthase is predominant in a particular cell type. Consequently, any given cell type tends to specialize in the formation of one of these eicosanoids as its major product. For example, endothelial cells mainly produce PGI_2 (prostacyclin) from PGH_2 by means of PGI synthase, and platelets release TXA_2 from PGH_2 through the action of TX synthase. Both PGI_2 and TXA_2 have a very short half-life and

are rapidly hydrolyzed to the inactive compounds 6-keto-$PGF_{1\alpha}$ and TXB_2, respectively [12]. PGH_2 can be alternatively converted into $PGF_{2\alpha}$ by PGF synthase, which is mainly expressed in the uterus. PGH_2 is also converted into PGD_2 by the action of PGD synthase, of which two distinct types have been identified: lipocalin-type PGD synthase and hematopoietic-type PGD synthase [5]. PGD_2 is readily dehydrated to the cyclopentenone PGs of the J_2 series (PGJ_2 and 15-deoxy-Δ (delta)^{12,14}-PGJ_2 (15d-PGJ_2)) (see below). PGE_2 is formed by the enzyme PGE synthase (PGES) present in virtually every cell type. There are three different PGES isoforms (mPGES-1, cPGES-1, and mPGES-2), of which mPGES-1 was the first to be identified and characterized [15]. Owing to their instability, PGs and TXA_2 exert their functions mainly in the proximity of their sites of synthesis. Thus, they typically act as autocrine or paracrine hormones, maintaining homeostasis within their cells of origin or in neighboring cells in the tissue. Ten different types and subtypes of receptors, which belong to the G protein-coupled rhodopsin-type receptor superfamily of seven transmembrane domains, mediate the biological effects of PGs [16] (Fig. 2.1). Four of the receptor subtypes bind PGE_2 (EP1, EP2, EP3, and EP4), two bind PGD_2 (DP1 and DP2), two bind TXA_2 (TPα and TPβ), and the rest are single receptors for $PGF_{2\alpha}$ and PGI_2 (FP and IP, respectively) [16]. In addition to these classical membrane receptors, PGs and especially cyclopentenone PGs such as the PGD_2 final metabolite 15d-PGJ_2 can also transduce signals upon direct ligand binding to nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) [17]. These receptors are found in three different isoforms (i.e., PPARα, PPARδ, and PPARγ) and act as ligand-activated transcription factors with a DNA-binding domain that recognizes response elements in the promoter region of specific target genes linked to inflammation, cell proliferation, apoptosis, and differentiation [18].

The formation of PGs has been reported in almost every tissue and body fluid. With the exception of seminal fluid, PGs are not stored in tissues or cells. Instead, once synthesized, they are released and/or exported to the extracellular space. Owing to instability, PGs and TXA_2 exert their functions mainly in the proximity of their sites of synthesis. Thus, they typically act as autocrine or paracrine hormones, maintaining homeostasis within their cells of origin or in neighboring cells in the tissue. In general terms, COX products play a major role in inflammation and participate in the regulation of smooth muscle tone, hemostasis, thrombosis, parturition, and protection of gastrointestinal and renal integrity as well as in the progression of cancer.

Among the different PGs, PGE_2 plays a crucial role in the development of the five cardinal signs of inflammation: *edema*, *erythema*, *pain*, *fever*, and *loss of function*. In this regard, PGE_2 increases vascular permeability contributing to fluid extravasation and the appearance of *edema* (*swelling*), in a synergistic fashion with other soluble factors such as complement, bradykinin, histamine, and LTs [5]. In addition, PGE_2 is a potent vasodilator that increases tissue blood flow, contributing to the appearance of the characteristic *erythema* (*redness*) [19]. PGE_2 also sensitizes peripheral sensory nerve endings located at the site of inflammation and acts in the spinal cord to evoke hyperalgesia *pain* [20, 21]. Finally, PGE_2 is crucial in the appearance of *fever* [22]. *Pyresis* is the consequence of increased levels of PGE_2 in the central nervous system secondary to the actions of the proinflammatory cytokines IL-1β and TNF-α produced by activated immune cells in the systemic circulation [23]. It is of note that PGs are able to potentiate and prolong the action of other mediators of inflammation such as bradykinin, histamine, neurokinins, and complement [5].

PGI_2 (prostacyclin) is the chief COX product of the vascular endothelium [5]. It is mostly produced by endothelial cells and has vasodilatory properties and works as an inhibitor of platelet aggregation [5]. In contrast, TXA_2 is produced by platelets and is a potent vasoconstrictor and pro-thrombotic agent [5]. There is a fine balance between TXA_2 and PGI_2 in the regulation of systemic blood pressure and thrombogenesis. $PGF_{2\alpha}$ is also a prostanoid

with vasoconstrictor properties mainly produced by vascular and uterine smooth muscle [5]. $PGF_{2\alpha}$ induces the contraction of the uterus during labor and reproduction and induces bronchoconstriction in the lungs [5]. Finally, PGD_2 is a major product of mast cells and is actively involved in allergy and asthma [5].

COX-2

COX-2 was identified as a second COX isoform, which, unlike the constitutive isoform COX-1, is inducible and belongs to the category of immediate-early genes [24–26]. The COX-2 gene is localized on chromosome 1, is about 8 kb long, has 10 exons, and is transcribed as 4.6, 4.0, and 2.8 kb mRNA variants [27, 28]. The cDNA for COX-2 encodes a polypeptide, which, before cleavage of the signal sequence, contains 604 amino acids with an apparent molecular mass of 70 kDa [27, 29]. Sequence analysis of the COX-2 5′-flanking region has revealed several potential transcription regulatory elements including a TATA box, a NF-IL-6 motif, two AP-2 sites, three Sp1 sites, two NF-kB sites, a *Cre* motif, and an E-box [28]. COX-2 was originally identified as a unique, inducible gene product in studies addressing cell growth signaling pathways as well as in investigations on COX activity in response to cytokines and other inflammatory factors (reviewed in references [4, 13, 14, 30]). In fact, COX-2 is markedly induced by IL-1α, IL-1β, TNF−α, IFNγ, LPS, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and oncogenes such as v-src and v-ras [13, 14, 30]. Induction of COX-2 has been reported in many cell types including fibroblasts, monocytes and macrophages, epithelial, endothelial, smooth muscle, mesangial and mast cells, synoviocytes, osteoblasts, and central nervous system neurons [13, 14, 30].

The amino acid sequences of COX-1 and COX-2 from a single species are about 60 % identical and catalyze identical reactions and exhibit the same kinetic constants for the conversion of arachidonic acid to PGs [24, 25, 29]. However, the two COX isoforms have distinct tissue distribution and regulation. COX-1 is a constitutive isoform widely distributed throughout the gastrointestinal system, the kidneys, the vascular smooth muscle, and platelets and is presumably involved in the *housekeeping* functions of PGs such as cytoprotection of the gastric mucosa and the integrity of platelet and renal functions [31]. On the contrary, COX-2, which is not commonly found in differentiated cells in the absence of stimulation, has been referred to as the *inducible* isoform because, like other immediate-early genes, it can be rapidly upregulated in response to growth factors and cytokines [31]. This led to the dogma that the inducible COX-2 isoform was responsible for the synthesis of PGs involved in inflammatory response, whereas COX-1-derived PGs were involved in preserving the physiological functions of these prostanoids. This dogma is not entirely accurate, since COX-1 can be induced or upregulated under certain conditions, whereas COX-2 can be constitutively expressed in organs such as the brain and the kidneys [30, 31]

The primary role of COX-2 in gastrointestinal cancer deserves specific mention. Normal gastric mucosa scarcely expresses COX-2, but COX-2 expression and PGE_2 levels are upregulated through the multistep process of gastric carcinogenesis [32]. Since Ristimäki et al. described an elevated expression of COX-2 in gastric cancer for the first time [33], a number of studies has evaluated the relationship between COX-2 and cancer. The increased production of PGs observed in tumors likely reflects enhanced COX-2 activity since nearly 85 % of adenocarcinomas show between a two- and a fifty-fold increase in COX-2 expression at both mRNA and protein levels compared with matched, macroscopically normal, colonic mucosa from the same patient [34, 35]. Thus, COX-2 likely plays a role in early gastric carcinogenesis, although the precise mechanisms leading to the elevated expression of COX-2 are still not fully elucidated. Nevertheless, evidence suggests that proinflammatory cytokines, gastrin, mitogen, and growth factors could be involved in this process [36]. On the other hand, COX-2-overexpressing cells produce large amounts of vascular endothelial growth factor (VEGF), a

key pro-angiogenic factor that stimulates endothelial cell migration, proliferation of cancer cells, and angiogenesis [37]. Moreover, several mechanisms may concur to enhance COX-2 gene expression in cancer: in particular, mutations of APC and *ras*, activation of EGF receptor and IGF-I receptor pathways and the heregulin/HER-2 receptor pathway, and direct COX-2 induction by the Epstein-Barr virus oncoprotein and latent membrane protein 1 [38–40].

COX Inhibitors

The COX pathway offers unprecedented therapeutic opportunities in the arena of anti-inflammation. Seminal discoveries by Vane, Ferreira et al. and Smith et al. [41–43] were published in 1971 linking the ability of NSAIDs to suppress inflammation to the inhibition of COX and PG biosynthesis. At present, NSAIDs are among the most widely prescribed class of over-the-counter medications showing proven clinical utility in treating pain, fever, and inflammation [5]. A list of currently marketed NSAIDs is provided in Table 2.1. Among these NSAIDs, aspirin (acetylsalicylic acid) plays an undisputed central role in inflammation therapy. In fact, aspirin is the most widely consumed NSAID worldwide and the standard against which all new anti-inflammatory agents are compared. Aspirin has a long history of use and availability without prescription, and because of its low cost and safety, aspirin is the drug of choice for relieving inflammation and mild to moderate pain and fever. In addition to the well-known anti-inflammatory, analgesic, and antipyretic properties, aspirin also inhibits platelet aggregation and therefore is useful in preventing myocardial infarction and stroke [44]. Moreover, numerous epidemiological studies have also shown that the long-term use of low doses of aspirin represents a potentially viable option in the prevention of sporadic colon cancer [45] (see below).

The pharmacological properties of aspirin are related to its ability to acetylate COX, leading to the irreversible inhibition of the biosynthesis of

Table 2.1 List of the most common drugs marketed (brand names given in brackets) targeting the COX pathway

NSAIDS
Acetylsalicylic acid (Aspirin)
Choline salicylate (Arthropan)
Diclofenac potassium (Cataflam)
Diclofenac sodium (Voltaren)
Diclofenac sodium with misoprostol (Arthrotec)
Diflunisal (Dolobid)
Etodolac (Lodine)
Fenoprofen calcium (Nalfon)
Flurbiprofen (Ansaid)
Ibuprofen (Advil, Motrin)
Indomethacin (Indocin)
Ketoprofen (Actron, Orudis, Orudis KT, Oruvail)
Magnesium salicylate (Arthritab, Bayer Select, Doan's Pills, Magan, and others)
Meclofenamate sodium (Meclomen)
Mefenamic acid (Ponstel)
Meloxicam (Mobic)
Nabumetone (Relafen)
Choline and Magnesium salicylates (CMT, Tricosal, Trilisate)
Naproxen (Aleve, Naprosyn)
Oxaprozin (Daypro)
Piroxicam (Feldene)
Salsalate (Amigesic, Anaflex 750, Disalcid, Marthritic, Mono-Gesic, and others)
Sodium salicylate (various generics)
Sulindac (Clinoril)
Tolmetin sodium (Tolectin)
COXIBS
Celecoxib (Celebrex)
Etoricoxib (Arcoxia)
Lumiracoxib (Prexige)
NS-389 (Piroxicam)
Parecoxib (Dynastat)
Valdecoxib (Bextra, Dynastat)
RECEPTOR AGONISTS AND ANTAGONISTS
AA-2114 (Seratrodast)
Alprostadil (Edex)
BAY-U-3405 (Baynas)
Bimatoprost (Allergan, Lumigan)
Carboprost tromethamine (Hemabate)
Dinoprostone (Prepidil)
Iloprost (Ventavis)
Latanoprost (Xalatan)
Misoprostol (Cytotec)
Travoprost (Travatan)
Treprostinil (Remodulin, Tyvaso, Orenitram)
Tromethamine (Hebamate)

the eicosanoids (i.e., PGs and TXA_2). However, there are properties of aspirin that are independent of COX and PG inhibition. For example, aspirin-like drugs are able to either activate the heat shock transcriptional factor and the p38 mitogen-activated protein kinase or to inhibit the mitogen-activated protein kinases p44Erk1 and p42Erk2 and the activity of transcriptional factors such as nuclear factor-kB and activator protein 1 [46–48]. Therefore, complete knowledge of the mechanisms of action underlying the pleiotropic effects of aspirin is still a subject of interest and debate.

Unfortunately, apart from the beneficial anti-inflammatory, antipyretic, and analgesic effects, NSAIDs also exert unwanted side effects, particularly in the gastrointestinal tract [49]. This is due to the fact that traditional or conventional NSAIDs nonspecifically inhibit both COX-1 and COX-2 isoforms. In other words, COX-1-derived PGs are mainly involved in housekeeping functions including gastrointestinal cytoprotection, whereas COX-2-derived PGs are mostly responsible for inflammation, and consequently inhibition of both COX-1 and COX-2 by traditional NSAIDs (i.e., aspirin, indomethacin, ibuprofen, and meclofenamate) produces gastrotoxicity. That is, at concentrations required to inhibit PG biosynthesis at sites of inflammation (COX-2 activity), they also elicit a marked suppression of PG production in the gastrointestinal and renal systems (COX-1 activity).

Selective COX-2 Inhibitors (COXIBs)

The discovery of COX-2 and the characterization of its role in inflammation were crucial for understanding why some existing NSAIDs including etodolac (*Lodine*®), meloxicam (*Mobic*®), and nimesulide (*Mesulid*® and others, currently withdrawn from the market) were associated with a lower range of deleterious effects. The most plausible explanation for this phenomenon was that these NSAIDs have a higher selectivity for COX-2 in comparison with COX-1. In any event, the most important advance in the field of inflammation occurred when drug companies took up the search for a new class of compounds specifically designed to selectively inhibit COX-2 without affecting COX-1-dependent PG biosynthesis. These new series of compounds were generically designated as COXIBs. The first generation of selective COX-2 inhibitors displayed high selectivity for blocking COX-2 activity in vitro and proved to be as efficacious as standard NSAIDs in a number of in vivo models of inflammation (rat carrageenan-induced foot-pad edema and rat adjuvant-induced arthritis) and hyperalgesia (rat carrageenan-induced hyperalgesia) [50–52]. These preclinical results led to the rational design of the first clinical trials for selective COX-2 inhibitors, which were sufficient to prove that these compounds were useful for relieving the signs and symptoms of osteoarthritis and rheumatoid arthritis and for alleviating pain following dental extraction, while reducing the incidence of gastrointestinal ulcers and erosions seen with standard NSAID therapy [53–57]. This novel class of compounds aroused particular interest for combating inflammation in diseases such as liver cirrhosis, in which renal function is critically dependent on COX-1-derived PGs [58–61]. The two first selective COX-2 inhibitors approved and marketed were celecoxib (*Celebrex*®) and rofecoxib (*Vioxx*®). A second generation of selective COX-2 inhibitors including valdecoxib (*Bextra*®), etoricoxib (*Arcoxia*®), parecoxib, an injectable prodrug of valdecoxib (*Dynastat*®), and lumiracoxib (*Prexige*®) (Table 2.1) was also approved for the treatment of osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, and postoperative pain. Since their introduction into the market in 1999, selective COX-2 inhibitors have become hugely popular and one of the world's best selling drug class. Unfortunately, rofecoxib (*Vioxx*) was withdrawn from the market in 2004 based on the findings from the prospective, randomized, placebo-controlled clinical trial, adenomatous polyp prevention on *Vioxx* (APPROVe), which demonstrated an increased relative risk for confirmed cardiovascular events, such as heart attacks and strokes, in patients taking *Vioxx*

compared to those taking placebo [62]. It has been postulated that the increased cardiovascular risk associated with COX-2 inhibitors may be secondary to prostacyclin/TXB_2 imbalance, since prostacyclin inhibits platelet aggregation and causes vasodilatation and is derived mainly from COX-2, whereas TXB_2 causes platelet aggregation and vasoconstriction and is mainly a COX-1 product.

An interesting aspect of COX-2 is that this isoform plays a crucial role in cell growth, angiogenesis, and cancer progression [37–39]. Consequently, COXIBs were also envisioned from the very first moment as promising anticancer agents. The use of these compounds in clinical and experimental studies has provided clear proof that COX-2 is indeed involved in the cancer preventive actions of NSAIDs. In a randomized clinical trial, the COX-2 inhibitor celecoxib effectively inhibited the growth of adenomatous polyps and caused regression of existing polyps in patients with hereditary familial adenomatous polyposis [63]. Studies in rodents have also demonstrated that pharmacological inhibition of COX-2 activity prevents chemically induced carcinogenesis and intestinal polyp formation in an experimental model of FAP [40]. Interestingly, animal studies have shown that celecoxib is able to potentiate the antitumor activity of conventional chemotherapy and radiation [64, 65], an effect that could be related to the recently uncovered COX-2 capability of blocking p53- or genotoxic stress-induced apoptosis [66]. Cell growth and angiogenesis can be blocked in vitro by selective COX-2 inhibitors, highlighting the role of COX-2 in cancer progression [67, 68]. Nevertheless, a significant antiproliferative effect following selective COX-2 inhibition has been observed in colon cancer cells that do not express COX-2 [69]. It has been suggested that the therapeutic activity of COX-2 inhibitors might also be related to their ability to inhibit IkB kinase (IKK) activity [70]. This finding together with the observation that sulindac sulfone, a sulindac metabolite devoid of COX inhibitory activity, is able to reduce colon cancer cell growth [71] suggests that COX-2-independent pathways and/or pathways unrelated to PGs are also involved in the antineoplastic effects of NSAIDs and selective COX-2 inhibitors.

mPGES-1 Inhibitors

Given the controversy surrounding the COXIBS, increased interest emerged regarding the pharmacological modulation of PG production through inhibition of specific PG synthases. Among the different PG synthases, PGE synthase was of particular interest because this enzyme is responsible for PGE_2 biosynthesis. In theory, pharmacologic inhibition of PGE synthase activity could decrease the formation of the proinflammatory prostanoid PGE_2 while sparing the production of other prostanoids with vascular protective effects such as prostacyclin. In 1999, Jakobsson and coworkers [15] reported the cloning and characterization of human PGE synthase, now designated mPGES-1, which is a member of the membrane-associated proteins involved in the eicosanoid and glutathione metabolism superfamily with the ability to catalyze the conversion of PGH_2 into PGE_2. Following this discovery, a cytosolic form of PGE synthase, termed cPGES-1, which also isomerizes PGH_2 to PGE_2 rather specifically in the presence of glutathione, was also cloned [72]. cPGES is ubiquitously expressed and identical to p23 [73]. In addition, a second isoform of membrane-associated PGE synthase, designated mPGES-2, was identified in 2002 [74]. Among the three different PGE synthases, mPGES-1 has received much attention because it is an inducible enzyme functionally coupled with COX-2 [15, 72–75]. Indeed, protein expression for mPGES-1 and COX-2 is concomitantly induced by IL-1β [15, 76]. Moreover, in a series of elegant experiments, Murakami et al. demonstrated that cotransfection of human mPGES-1 and COX-2 into HEK 293 cells results in a higher PGE_2 production when cells are subsequently stimulated with ionophore or IL-1β than cotransfection of mPGES-1 with COX-1, thus providing evidence that mPGES-1 preferentially couples with COX-2 activity [77]. The fact that

mice lacking the mPGES-1 gene have impaired inflammatory, pain, and fever responses clearly highlights the role of this enzyme in inflammation [78, 79]. At the moment, a number of compounds specifically targeting mPGES-1 are under development, although they are not yet available for clinical use.

Agonists and Antagonists of Prostanoid Receptors

The modulation of the COX pathway by compounds acting on specific prostanoid receptors provides advantages over upstream COX, COXIBs, and mPGES-1 inhibitors, because they can offer more specificity to their actions. Unfortunately, progress in this field has been slow and difficult, mainly because of the existence of such a large number of prostanoid receptors and their function similarity. Nevertheless, the cloning and characterization of specific prostanoid receptors have facilitated the development of synthetic agonists and antagonists for some of these receptors. Most of these compounds have proven to be very useful in the identification of the biological role of a given prostanoid receptor, and some have shown therapeutic potential (Table 2.1). Some examples are misoprostol (*Cytotec*®), an EP3/EP2 agonist used as an adjunct to COX inhibitor therapy to reduce gastric irritation and bleeding [80]; alprostadil (*Edex*®), an EP4/EP2 agonist used for erectile dysfunction [81]; travoprost (*Travatan*®), latanoprost (*Xalatan*®), and bimatroprost (*Allergan*® *or Lumigan*®), which are FP agonists marketed for the treatment of glaucoma and ocular hypertension [82]; carbaprost tromethamine (*Hebamate*®), a 15-methyl analogue of naturally occurring prostaglandin F2α prescribed for termination of pregnancy and also used for postpartum hemorrhage [83]; iloprost (*Ventavis*®), an IP agonist used in pulmonary hypertension; treprostinil (*Remodulin*®, *Tyvaso*®, and *Orenitram*® among others), a PGI_2 analogue used to treat pulmonary arterial hypertension [84]; beraprost sodium, the first chemically stable orally active prostacyclin analogue currently only approved in Japan [85]; dinoprostone (*Prepidil*®), natural occurring PGE_2 which is a pharmacologic agent administered intravaginally or intracervically for ripening the cervix [86]; and AA-2114 (*Seratrodast*®) and BAY-U-3405 (*Baynas*®), which are orally active TX receptor antagonists available for the treatment of asthma [87, 88].

Cyclopentenone PGs

Cyclopentenone PGs (cyPGs) are products of the nonenzymatic dehydration of PGs. CyPGs are structurally defined by the presence of a highly reactive α,β-unsaturated carbonyl moiety in the cyclopentenone ring [89]. From a biological point of view, the most relevant cyPGs are those derived from the dehydration of PGD_2, including the PGs of the J_2 series: PGJ_2, Δ^{12}-PGJ_2, and 15d-PGJ_2. Unlike other PGs, no specific transmembrane receptors for cyPGs have been identified to date. Instead, 15d-PGJ_2 is a natural ligand of PPARγ and appears to exert its effects through binding and activation of this member of the nuclear receptor superfamily of ligand-activated transcription factors [90]. Other actions independent of PPARγ have been reported for cyPGs, including downregulation of NF-kB transcriptional activity [91], inhibition of cytokine production by monocytes [92], and direct inhibition of key enzymes of the eicosanoid cascade, namely, cytosolic phospholipase A_2, COX-2, and mPGES-1 [93, 94].

CyPGs have a broad spectrum of biological effects and, unlike conventional PGs, display powerful immunomodulatory and anti-inflammatory properties [95]. CyPGs have been shown to suppress chronic inflammation and pannus formation in rats with adjuvant-induced arthritis [96] and to have a protective role in models of renal ischemia-reperfusion injury [97] and inflammatory bowel disease [98]. Interestingly, in rats with carrageenan-induced pleurisy, in which the generation of 15d-PGJ_2 takes place during the resolution phase, administration of cyPGs brings about acute inflammatory

resolution, whereas inhibition of 15d-PGJ_2 synthesis is associated with an exacerbation of inflammation [99, 100]. In addition, cyPGs suppress viral replication, stimulate osteogenesis, exhibit antiproliferative effects on cancer cells, and attenuate the tumorigenic potential of cancer cells in nude mice [89, 95, 101]. Unfortunately, these compounds have not progressed toward clinical development.

Other Approaches

Drugs Acting on the 5-LOX Pathway

Arachidonate 5-LOX is the key enzyme in the biosynthesis of LTs. It initially transforms free arachidonic acid to 5-HPETE through the stereospecific abstraction of the pro-*S* hydrogen at carbon-7, followed by insertion of molecular O_2 at carbon-5 [102]. 5-HPETE is either reduced to 5-HETE or subjected to the stereospecific removal of the pro-*R* hydrogen at carbon-10 to generate the highly unstable allylic epoxide LTA_4 [103]. Once formed, LTA_4 is rapidly transformed to either LTB_4 via stereoselective hydration by LTA_4 hydrolase [104] or to LTC_4 through glutathione conjugation catalyzed by LTC_4 synthase [105]. Sequential metabolic reactions catalyzed by γ-glutamyl transferase and a specific membrane-bound dipeptidase convert LTC_4 into LTD_4 and LTE_4, respectively. Together LTC_4, D_4, and E_4 are termed cysteinyl-leukotrienes (Cys-LTs) and in the past were referred to as the slow-reacting substances of anaphylaxis.

Over the past 25 years, a number of pharmacological agents that modify the 5-LOX pathway and the biosynthesis of LTs have been developed to treat inflammatory diseases such as asthma, ulcerative colitis, arthritis, and psoriasis. These agents, which are generically known as LT-modifying drugs, include 5-LOX and FLAP inhibitors and Cys-LT receptor antagonists. Drugs that directly block 5-LOX activity were the first pharmacological compounds considered as LT-modifying drugs. Many of the molecules originally developed were discarded because of severe side effects and never entered the market, although some are currently used for in vitro research [106]. Caffeic acid, AA-861 and BW-775C, fall within this category. Nordihydroguaretic acid (NDGA) also known as masoprocol (*Actinex*®) was a potent 5-LO inhibitor used to treat actinic keratoses, although it was withdrawn from the USA and Canada in 1996. Other molecules designed to chelate the active iron, such as the N-hydroxyurea derivative Zileuton, have been developed. Zileuton (*Zyflo*®) has been marketed as therapy for the prevention and chronic treatment of asthma in adults and children 12 years of age or older. A different approach to inhibit 5-LOX activity is by means of FLAP inhibitors. The indole-based compound AM803 underwent clinical investigation and passed phase II trials with asthma patients [107]. A similar compound named AM103 underwent phase II clinical trials for treatment of respiratory disorders [108]. A very potent and selective FLAP inhibitor BAYX1005 was developed by Bayer and passed a phase II clinical trial for myocardial infarction as the compound DG-031 (*Veliflapon*®) from the company deCODE genetics [109]. However, while entering phase III for the prevention of heart attacks and stroke, participant recruitment was suspended.

LT receptor antagonists are another important class of LT-modifying drugs. Orally active receptor antagonists directed against the Cys-LT1 receptor have been marketed [110–112]. The Cys-LT1 receptor antagonists montelukast (*Singulair*®), pranlukast (*Ultair*®), and zafirlukast (*Accolate*®) were tested in a number of clinical trials which demonstrated improvement of pulmonary function and reduction of asthma exacerbations, especially in exercise-induced asthma [113]. On the other hand, LTB_4 receptor antagonists such as SC-41,930 are CP-105,696 were shown to be efficacious in reducing the arthritis index and ankle bone destruction in IL-1-accelerated collagen-induced arthritis and to reduce atherosclerosis lesion progression in mice [114, 115].

Dual COX-2/5-LO Inhibitors

Considering the proinflammatory properties of COX-2- and 5-LO-derived eicosanoids, dual COX-2/5-LO inhibitors should, in theory, have a superior anti-inflammatory profile than individual selective COX-2 and 5-LO inhibitors. Although no human data are available analyzing the superiority of the anti-inflammatory efficacy of inhibiting two pathways versus inhibition of a single pathway, experimental and cellular studies indicate that dual inhibitors may have some disease-modifying activity and may stop disease progression by reducing the expression of matrix metalloproteinase-13 and IL-1β as well as chondrocyte death [116, 117].

While in theory it is quite easy to design drugs acting on one enzyme, it is more daunting to design a drug that selectively inhibits two different enzymes, especially if these are not structurally related. One of the first compounds with dual COX/5-LO inhibitory activity was tepoxalin, a pyrazole-containing hydroxamic acid able to chelate the nonheme iron atom of 5-LO [118]. Tepoxalin underwent clinical evaluation for psoriasis and rheumatoid arthritis but unfortunately was discontinued in phase II [119]. This drug received animal healthcare approval later on for reduction of inflammation and relief of pain caused by acute and chronic musculoskeletal disorders such as arthritis. A COX/5-LO inhibitor also evaluated in clinical trials for arthritis was S-2474, which displayed excellent anti-inflammatory and analgesic activities associated with remarkable gastric safety [120, 121]. RWJ-63556, a compound structurally related to the selective COX-2 inhibitor nimesulide, was another potent orally active COX-2/5-LO inhibitor with remarkable anti-inflammatory activity in experimental carrageenan-induced inflammation [122]. An interesting activity profile was also noted for ER-34122, which suppressed progression of PMN infiltration, subsynovial soft tissue edema, and multiplication of synovial lining cells in the early stages of arthritis in a mouse model of systemic lupus erythematosus [123, 124].

Licofelone, also known as ML-3000, deserves special mention. Licofelone is a pyrrolizine derivative and an arachidonic acid substrate analogue that inhibits both COX and 5-LO. Unlike most of the previously described dual inhibitors, licofelone is neither an antioxidant nor an iron chelator [125, 126]. Licofelone was shown to inhibit COX in bovine and human platelets and 5-LO in bovine and human granulocytes [126]. Moreover, licofelone exhibits not only anti-inflammatory but also potent analgesic, antipyretic, and antithrombotic activities with little or no gastrointestinal damage in experimental animals [125–127]. In addition, in guinea pigs challenged with arachidonic acid or antigen and in sheep challenged with antigen, licofelone displayed potent antiasthmatic activity [128]. Licofelone showed an excellent gastrointestinal profile, much better than conventional NSAIDs and equivalent to selective COX-2 inhibitors in phase III trials [129, 130]. Furthermore, in healthy subjects, licofelone is well tolerated with no hepatotoxicity and has a good pattern of tissue distribution, with the highest levels being reached in the lung, liver, kidneys, heart, and large and small intestine [127, 129, 130].

NSAIDs Releasing Nitric Oxide (NO) or Hydrogen Sulfide (H_2S)

A new class of NSAIDs that offers new perspectives is the COX-inhibiting NO donators (CINODs) which are generated by adding a NO-generating moiety to a parent NSAID via an ester linkage [131]. CINODs are designed to reduce the potential toxicity of the parent drug, while maintaining its analgesic and anti-inflammatory effects. In this regard, NO cooperates with endogenous PGs in the maintenance of gastric integrity and microcirculation by potentiating gastric alkaline mucus secretion and inhibiting gastric acid secretion [132, 133]. NO also modulates leukocyte-endothelial interactions as demonstrated in in vivo microscopy experiments in single venules [134]. All these findings raised the possibility that NO could be

GI protective in NSAID-induced gastric damage, which is characterized by increased leukocyte adherence, reduced gastric blood flow, and impaired mucosal repair [135]. Naproxcinod®, Nicox's lead drug, was the first CINOD ever evaluated in preclinical and clinical studies. It is metabolized to naproxen and has been shown to donate NO in vitro and in vivo [135]. Phase III clinical trials of Naproxcinod® are currently underway, with the aim of reducing potential toxicity while maintaining its analgesic and anti-inflammatory effects.

More recently, H_2S-releasing derivatives of NSAIDs have been developed. H_2S is a normal component of our bodies where it is present in very low concentrations. This gas is produced through a number of pathways, the most common being related to the metabolism of L-cysteine, cystine, and homocysteine [136]. As with NO, H_2S seems to play an important role in a variety of physiologic processes and diseases. Among others, H_2S plays an important role in neuromodulation, hypertension, inflammation, gastric mucosal integrity, and vascular tone [137–140]. H_2S, which is also produced by the gastric mucosa like NO, contributes to the ability of this tissue to counteract the damage induced by several luminal substances. The production of H_2S was found to be reduced following NSAID administration, supposedly through the inhibition of the expression of a key enzyme for conversion of L-cysteine into H_2S, the enzyme cystathionine γ-lyase [141]. The provision of H_2S donors could avoid the decrease in gastric blood flow induced by current NSAIDs as well as prevent NSAID-induced leukocyte adherence. Thus, as with the CINODs and dual LOX/COX inhibitors, the existing preclinical data appear to indicate a potential for H_2S-releasing NSAIDs to provide similar anti-inflammatory efficacy as traditional NSAIDS without the burden of gastric toxicity.

Aspirin-Triggered 15-Epi-lipoxins

Aspirin-triggered lipoxins (ATL) have received the most attention as a novel anti-inflammatory approach [10, 142, 143]. The acetylation capacity of aspirin is a critical aspect in the ATL biosynthetic pathway, and this property is not shared but any other NSAID. Indeed, this biosynthetic pathway triggered by aspirin is initiated by acetylation of COX-2, which switches the enzyme catalytic activity from a PG synthase to 15-LOX [142]. Thus, PG biosynthesis by aspirin-acetylated COX-2 is inhibited, and arachidonic acid is transformed to 15R-HETE. The further conversion of 15R-HETE to 15-epi-LXA_4 (ATL) by a 5-LOX present in immune cells is the result of a process called transcellular biosynthesis. This process involves cell-cell interaction and processing of a metabolic intermediate generated by one cell (donor cell) by a vicinal cell (acceptor cell) for the production of an active eicosanoid that neither cell can generate alone [144]. ATLs are 15-epimers of LXs, which have a unique spectrum of bioactions indicative of anti-inflammatory and pro-resolution properties. The most relevant biological action of these aspirin-triggered eicosanoids (i.e., ATLs) is that they work as putative endogenous "breaking signals" for leukocyte recruitment and therefore play a key role in the resolution of inflammation [10]. For example, these eicosanoids inhibit chemotaxis, selectin- and integrin-mediated adhesion to and transmigration across endothelial monolayers in response to LTB_4 and formylmethionyl-leucyl-phenylalanine, TNF-α-stimulated superoxide generation, and degranulation and interleukin-1 release by neutrophils [10]. In vivo, LX stable analogues inhibit LTB_4-induced leukocyte rolling and adherence and neutrophil margination and extravasation [10]. LX analogues inhibit TNFα-stimulated leukocyte trafficking and chemokine secretion in murine air pouches and when applied topically to mouse ears dramatically inhibit leukocyte infiltration and vascular permeability [10]. In addition, ATL analogues protect mice from renal ischemia-reperfusion injury and glomerulonephritis [10]. In an animal model of periodontal disease, LX and ATL analogues attenuate gingivitis and leukocyte recruitment [10]. Intravenous delivery of LXs and ATL inhibits acute dermal inflammation and neutrophil infiltration

of skin microabcesses and lungs in LTB_4 receptor transgenic mice [10]. In a murine model of asthma, stable LX and ATL analogues attenuate airway hyperreactivity and inflammation and accelerate resolution of pulmonary edema [10]. Administration of a metabolically stable LXA_4 analogue in a mouse model of chronic airway inflammation and infection associated with cystic fibrosis suppresses neutrophilic inflammation, decreases pulmonary bacterial burden, and attenuates disease severity [10]. Finally, a randomized clinical trial in healthy subjects demonstrated that low-dose aspirin (81 mg daily), used for long-term antithrombotic prophylaxis, initiates the production of anti-inflammatory ATL contrary to the inhibition of the pro-thrombotic TXA_2 [145]. Overall, LXs and ATL are anti-inflammatory and pro-resolution eicosanoids that work efficiently in reducing the signs and symptoms of inflammation in a wide range of disease models. Consequently, this property may effectively mediate, at least in part, the beneficial actions of aspirin.

More recently, aspirin was shown to trigger the conversion of omega-3-PUFA (i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to another group of anti-inflammatory and pro-resolution lipid mediators termed ASA-triggered resolvins and ASA-triggered-protectins [146, 147]. Similar to what has been described for the biosynthesis of ATL, endothelial cells expressing COX-2 acetylated by aspirin transform DHA into 17R-HDHA which is further converted by 5-LOX into the corresponding 17R-RvD1, 17R-RvD2, and other 17R-D resolvins, which are collectively known as aspirin-triggered (AT) resolvins [11, 148]. ASA-triggered protectin D1 (AT-PD1) is biosynthesized in a similar process. Finally, biosynthesis of resolvins of the E-series from EPA is initiated with the formation of 18R-hydroperoxy-EPE (18R-HEPE) by endothelial cells expressing aspirin-acetylated COX-2 [147]. 18R-HEPE is transformed by transcellular biosynthesis in neighboring 5-LOX-containing leukocytes into RvE1 (5S,12R,18R-trihydroxy-EPA) via a 5S,6-epoxide intermediate [147]. Collectively, these omega-3-derived lipid mediators also exert anti-inflammatory and pro-resolution actions both in vitro and in vivo and contribute to the understanding of the preventive actions observed with both aspirin and dietary omega-3PUFA.

Conclusions

For the last 40 years, COX-derived PGs have evolved as the best consolidated inflammatory mediators among the plethora of bioactive lipid mediators generated from arachidonic acid. A large number of over-the-counter medications based on the inhibition of these lipid mediators (i.e., NSAIDs) are still the most currently available class of drugs to fight inflammation, pain, and fever. Despite numerous efforts to improve the safety, the use of drugs targeting PG biosynthesis is still the front line of inflammation therapy. COX-2 inhibitors, for example, were safer than NSAIDs and exhibited a better gastric tolerance, but fail because of unexpected thrombotic events. At present much hope has been raised over the use of compounds that specifically target PG receptors hat inhibit the activity of specific terminal synthases, and the outcome of this effort will be the subject of discussion in the coming years. Finally, the use of drugs that modulate the PG cascade in combination with the modulation of other pathways of lipid mediator biosynthesis is a subject that will receive much attention in the next years. For example, the interaction of NSAIDs, which target the omega-6 arachidonic acid-derived products, with the omega-3 family of polyunsaturated fatty acids, which also function as substrates for the same COX enzymes, is a matter of interest in the search for novel strategies to harness unremitting inflammation.

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