Anti-inflammatory drugs with therapeutic effects and drug regulators

REVIEW ARTICLE

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ABSTRACT

For prostaglandin production, the enzyme cyclooxygenase (COX) is required. The two COX isoforms are constitutive COX-1 (which is responsible for physiological functions) and inducible COX-2 (involved in inflammation). COX inhibition explains both the medicinal (inhibition of COX-2) and negative effects (inhibition of COX-1) effects of non-steroidal anti-inflammatory medicines (NSAIDs). Nonsteroidal anti-inflammatory medicines (NSAIDs) act by blocking the enzyme cyclooxygenase (COX), which produces prostaglandins (PGs). To a greater or lesser extent, they share similar side effects, such as stomach and renal toxicity. According to a recent study, there are at least two COX isoenzymes. COX-1 is a naturally occurring enzyme that creates prostaglandins (PGs), which protect the stomach and kidneys. Aspirin's well-known anti-cancer impact could also be related to its influence on COX-2, which is expressed in this condition. As a result, selective COX-2 inhibitors may have new therapeutic potential as anticancer drugs, as well as in preventing premature labor and maybe reducing the progression of Alzheimer's disease.

Keywords: cyclooxygenase. NSAIDs, inflammation, colon cancer, anticancer agent.

1. Introduction

The Ebers papyrus, written some 3,500 years ago in ancient Egypt, advocated applying a decoction of dried myrtle leaves to the abdomen and back to relieve rheumatic pains in the womb. Hippocrates advised the juices of the poplar tree to cure eye disorders and the juices of willow bark to relieve childbirth pain and lower fever a thousand years later. Salicylates are present in all of these therapeutic treatments.

The use of extracts of salicylate-containing plants, particularly the bark of the willow tree (Salix alba and other members of the Salix species), in the treatment of fever, pain, and inflammation, gave rise to anti-inflammatory analgesic medications. Inflammation is the body's natural response to harm. Enzyme activation, mediator release, fluid extravasation, cell migration, tissue disintegration, and repair are all part of the process. This paper will focus on the aspects of anti-inflammatory medicines that are affected, with a particular focus on the prostaglandin (PG) system. Phospholipase A2 activates this, releasing arachidonic acid, the cyclooxygenase substrate (COX or prostaglandin H2 [PGH2] synthase). Prostaglandin production rises as a result of this. COX is a dual-function enzyme that performs both cyclooxygenase and peroxidase functions.

Following the publishing of what were possibly the first clinical trials of willow bark extract for the treatment of agues or fever by the Reverend Edward Stone in the 17th century, the popularity of these plant extracts grew during the 17th–19th centuries. In the early 19th century, the main active salicylate components were isolated, and in the mid-late 19th century,

advances in chemistry in Europe and developments in the German chemical industry led to the synthesis of salicylic and acetylsalicylic acids, the latter of which was highly successful commercialised by Bayer AG as AspirinTM over 100 years ago.

In inflammatory circumstances ranging from experimental acute edema and sunburn to chronic arthritis, PGE2 is the most common eicosanoid found in humans. Because inflammation is one of the few settings in which PGE2 is a prominent product of COX, it's probable that the enzymatic route is directed towards this product by the inflammation process. A second enzyme, 5-lipoxygenase, transforms arachidonic acid to leukotrienes, which are important asthma mediators. (1) PGE2 is a powerful dilator of vascular smooth muscle, which explains why acute inflammation causes vasodilation and erythema (redness). (2) Vasodilation increases blood flow through inflamed tissues, which exacerbates the edema induced by vascular permeability-increasing substances such bradykinin and histamine. (3) Inflammatory pain is also caused by PGE2, which works in concert with other mediators. PGE2 sensitizes receptors on afferent nerve endings to the effects of bradykinin and histamine without directly causing pain. (4) Furthermore, PGE2 is a potent pyretic agent, and its production in bacterial and viral infections, which is driven by the release of interleukin-1 (IL-l), adds to the associated fever. (5)

Inflammatory lesions have been found to contain a variety of COX products. PGFm, PGD2, prostacyclin (PGI2 as 6-oxo-PGF1 alpha) and thromboxane A2 (TXA2 [as TXB2]) are among them, but their concentrations are usually less than a fifth of those of PGE2. Prostacyclin, which is likewise a powerful vasodilator and a more potent hyperalgesic agent than PG2, is arguably the most important of these compounds in terms of inflammatory symptoms. Both PGEz and prostacyclin are believed to play a role in the development of inflammatory erythema and discomfort. (6)

Discovery of NSAIDs

Phenylbutazone (by JR Geigy, Basel, Switzerland) and later indomethacin (by Merck & Co, Rahway, NJ, USA) were the earliest of the nonsteroidal anti-inflammatory medications (NSAIDs), of which aspirin is now recognized as the progenitor. Initially, phenylbutazone was used in conjunction with antipyrine in the hopes of enhancing the latter's effects. However, it was discovered to have greater anti-inflammatory/analgesic activity than antipyrine and was successfully used for the treatment of arthritic and other painful inflammatory conditions for the better part of 30 years until its popularity waned after associations with life-threatening agranulocytosis and bone marrow suppression (still largely unproven today), upper respiratory infections, and other side effects.

2. Mechanism of Action of Steroids in Inflammation

Anti-inflammatory drugs known as corticosteroids are commonly used to treat rheumatologic disorders such as rheumatoid arthritis, lupus, and vasculitis (inflammation of the blood vessels). The drugs cortisone and prednisone are examples of specific corticosteroids. Corticosteroids diminish arachidonic acid release via inhibiting the activity of phospholipase A2. As a result, corticosteroids stop prostaglandins, thromboxane, and leukotrienes from forming. Anti-inflammatory hormones inhibit phospholipase A2 indirectly by releasing lipocortin 1, an inhibitory protein. (7)

Inhibiting phospholipase-induced edema in the rat paw, recombinant lipocortin 1 inhibits the release of eicosanoids from human tissues (8) and is a strong anti-inflammatory drug. (9) In reaction to

glucocorticoids, not all types of cells make lipocortin l. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor, which is found in nearly every vertebrate animal cell. (10) The word "glucocorticoid" alludes to its role in glucose metabolism, adrenal cortex synthesis, and steroidal structure. Glucocorticoids have an effect on cells by binding to the glucocorticoid receptor. The activated glucocorticoid receptor-glucocorticoid complex upregulates anti-inflammatory protein expression in the nucleus (transactivation), while repressing proinflammatory protein expression in the cytosol (trans-repression) by preventing other transcription factors from the cytosol from entering the nucleus. (11)
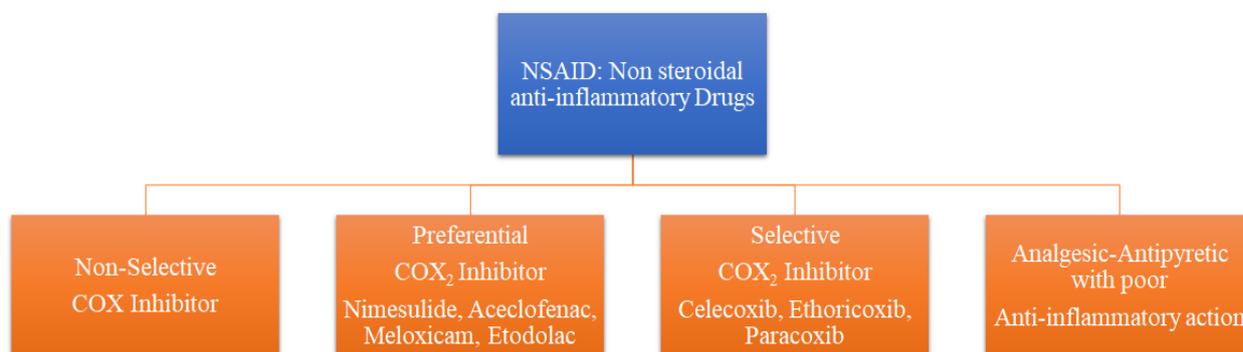

Figure 1. Chemical Classification of the NSAIDs

Another component of glucocorticoids' anti-inflammatory effect is their suppression of inducible cyclooxygenase-2 (COX-2) synthesis. They bind to and activate cytoplasmic glucocorticoid receptors, which regulate the transcription of numerous key response genes such as COX-2 and nitric oxide synthase.

3. Mechanism of Action of Non-Steroidal Anti-Inflammatory Agents

It's hard to believe, but before 1971, no one knew how aspirin, the world's most widely used nonprescription medicine, worked. Since the active principle of willow bark was identified in 1876, the pharmacologic effects of aspirin and other nonsteroidal anti-inflammatory medicines (NSAIDs) have been known. (12) Aspirin inhibits COX by causing irreversible acetylation of the cyclooxygenase component, leaving the enzyme's peroxidase activity unchanged (13) NSAIDs such as indomethacin and ibuprofen, in contrast to aspirin's irreversible action, generate reversible COX inhibition by competing with the enzyme's substrate, arachidonic acid, for the active site. (14)

All of the activities of aspirin-like medications can be explained by inhibiting prostaglandin production. They inhibit the pathological overproduction of prostaglandins, which lead to inflammation (therapeutic actions) and the physiological creation of prostanoids (which results in the characteristic side effects). Aspirin's ulcerogenic potential stems from its reduction of prostacyclin synthesis, which is a key cytoprotective component of the gastric mucosa. (15) Experimental stomach ulcers can be reversed or prevented with the administration of several prostaglandins

(16), and some of the recently produced prostaglandin derivatives are now available for clinical usage. Furthermore, NSAIDs' ability to erode the stomach mucosa is linked to their ability to suppress COX.

NSAIDs have been shown to decrease prostaglandin synthesis in a range of cell types and tissues, ranging from whole animals and humans to microsomal enzyme preparations. The concentration of a PGEz-like molecule in the synovial fluid of rheumatoid arthritis patients, for example, is around 20 ng/ml. This falls to zero in patients on aspirin, providing clinical evidence of the drug's influence on prostaglandin synthesis. (17) Several inhibitor classes have been found (18), with at least 12 key chemical series known to have direct effects on prostaglandin synthesis. (19)
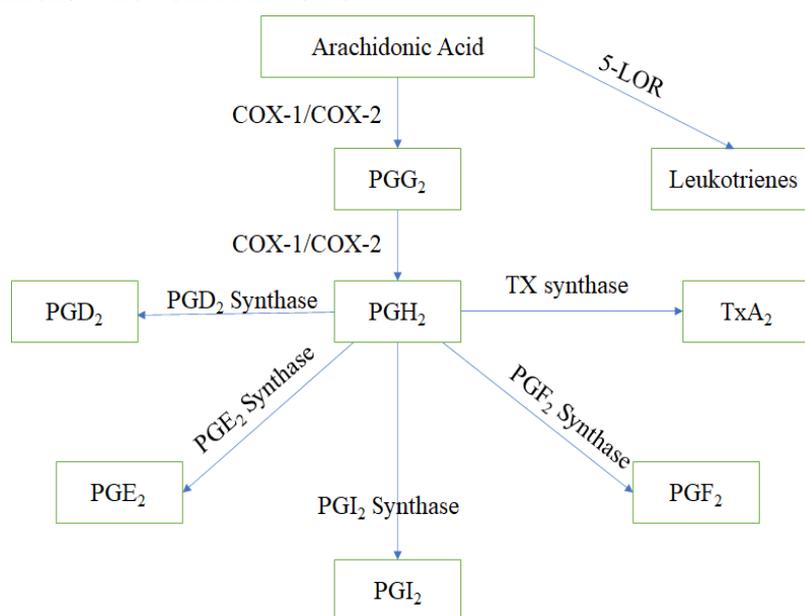

Figure 2. Process involved in production of prostaglandins and leukotrienes

4. A Second Cyclooxygenase Enzyme has Been Found

Needleman and colleagues discovered that bacterial endotoxin significantly boosted COX activity in human monocytes in vitro (20) and mice peritoneal macrophages in vivo. (21, 22) Dexamethasone inhibited this rise, which was linked to the creation of new COX protein. An inducible synthase was discovered a year or so later as an unique isoform of cyclooxygenase (COX-2) encoded by a different gene than the constitutive enzyme (COX-1). (23)

Cyclooxygenase-1

Cyclooxygenase-1 is an enzyme that speeds up the creation of chemical messengers known as prostaglandins in several parts of the body, including the stomach, kidneys, and inflammatory sites. Prostaglandins encourage the formation of a protective natural mucus lining in the stomach. They also interact within specific cells that control inflammation and other processes. The activity of cyclooxygenase has long been examined in ram seminal vesicles, and a homogenous, enzymatically active COX was isolated in 1976. (24)

COX-1 is expressed ubiquitously in most tissues and serves as a "housekeeper" by synthesizing prostaglandins that regulate normal cell activity (in the given figure 3). The enzyme's concentration is largely steady, however minor increases in expression of two to fourfold can occur in response to hormone or growth factor stimulation. (25)
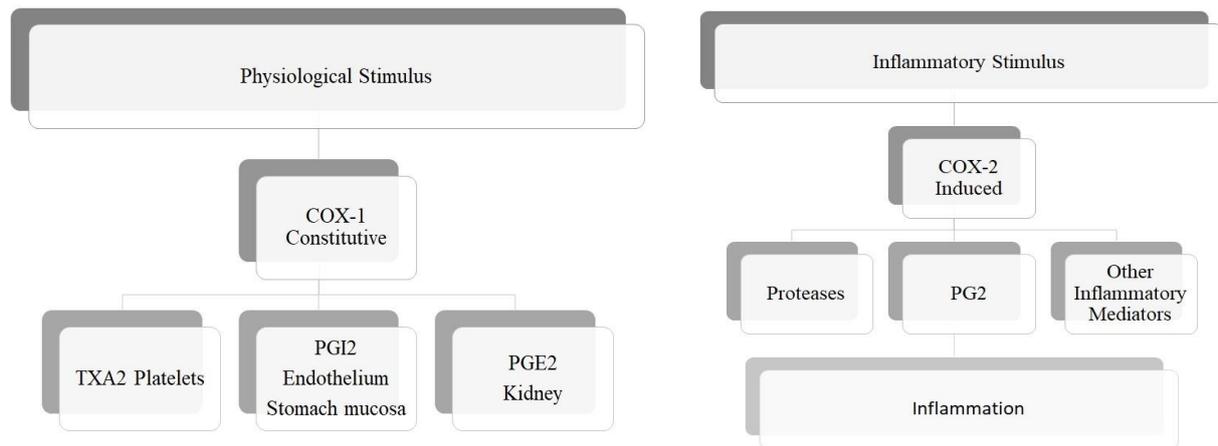
Figure 3. Relationship between the pathways leading to the generation of prostaglandins by COX-1 and COX-2.

Cyclooxygenase-2

COX-2 protein levels rise along with the overproduction of prostaglandins in numerous cells and tissues during chronic inflammation. The COX-2 gene is part of a group of main response genes that includes the inducible nitric oxide synthase gene, which is triggered during inflammation and cell proliferation. (26) Cox-2 catalyzes the conversion of arachidonic acid to prostaglandins and is an inducible type of cyclo-oxygenase. TNF and EGF can activate Cox-2, which is produced by inflammatory cells like macrophages.

Cyclooxygenase-2 Selective Inhibition

NSAIDs differ in the severity of their adverse effects at anti-inflammatory doses, although having equivalent degrees of anti-inflammatory efficacy in the clinic. When only one COX was known, this was impossible to explain. The discrepancies in anti-inflammatory activity of aspirin and salicylate, as well as the mechanism of action of acetaminophen, were other aspects that remained unsolved until the discovery of COX-2 (paracetamol).

In certain cell lines, salicylate has only about half the effectiveness of aspirin in suppressing COX-2. This profile is consistent with salicylate's lack of stomach irritation (27) and its lack of platelet activity (COX-1). (28) Salicylate appears to be active exclusively in whole cells, therefore the reduction of COX activity could be attributable to a metabolite.

Acetaminophen is an antipyretic and analgesic drug with limited anti-inflammatory properties. Furthermore, it shows only sporadic efficacy against most COX preparations, but is much more effective at reducing prostaglandin synthesis in the brain. (29) Perhaps the brain enzyme is a third isoform of cyclooxygenase, COX-3, for which no specific inhibitors have been discovered.

COX-1 and COX-2 have different functions.

GI Tract (Gastrointestinal Tract)

Endogenously generated prostacyclin and prostaglandin E2 (PGE2), which inhibit gastric acid output and exert a direct vasodilator action on the arteries of the gastric mucosa, are primarily responsible for prostaglandins' "cytoprotective" function in preventing stomach erosions and ulceration.

COX-I produces protective prostaglandins in most species, including humans, while (30) discovered modest amounts of COX-2 in the normal rat stomach. COX-2 is expressed in Helicobacter pylori-infected human stomach mucosa and ulcerative

colitis. (31) In mice and rats, COX-2 is also expressed in the periphery of stomach ulcers.

Kidney

Vasodilator prostaglandins are required for the maintenance of kidney function in both animal models of disease and individuals with congestive heart failure, liver cirrhosis, or renal insufficiency. When prostaglandin synthesis is lowered by NSAIDs, these patients are at risk of renal ischemia. PGE2 and prostacyclin are mostly synthesized by COX-I, albeit low quantities of COX-2 mRNA have been detected. (32) Following salt shortage, COX-2 expression in the macula densa is also upregulated. The renin-angiotensin system may be driven by COX-2 expression.

The Central Nervous System (CNS)

COX-l is located in neurons throughout the brain, but it is most numerous in the forebrain, where prostaglandins are thought to play a role in complex integrative activities like autonomic nervous system control and sensory processing. Pyogenic chemicals like LPS, interleukin I (IL-I), or tumor necrosis factor (TNF) activate COX-2 mRNA in brain tissue and cultured glial cells. (33) However, without prior stimulation by pro-inflammatory stimuli, low quantities of COX-2 protein and COX-2 mRNA have been found in forebrain neurons. COX-2 mRNA is also found in the spinal cord of normal rats, suggesting that it is involved in the processing of nociceptive stimuli. (34)

System of Reproduction

In fetal hearts, kidneys, lungs, and brains, as well as the decidual lining of the uterus, COX-1 expression is substantially higher than COX-2 expression. (35, 36) COX-I-produced prostaglandins appear to be critical for fetuses' survival during parturition, as the majority of children born to homozygous COX-l knockout mice do not survive. (37) COX-2 induction is involved in ovulation and is a definite trigger for parturition (38), resulting in PGF2a release and uterine smooth muscle contractions.

Endothelium

Prostacyclin is an anti-aggregatory and vasodilator produced by endothelial cells. They certainly contain COX-I, but (39), employing the particular COX-2 inhibitor celecoxib, reported that celecoxib significantly reduced urine excretion of the prostacyclin metabolite at doses up to 800 mg in volunteers. They came to the conclusion that COX-2 is increased in circulating endothelial cells, most likely as a result of laminar shear stress. (40)

Ratios of COX-2 to COX-1

The differences in pharmacology of the two enzymes underline the significance of discovering the inducible COX-2. (41) COX-2 inhibitors such as aspirin, indomethacin, and ibuprofen are substantially less effective than COX-1 inhibitors. (42) Indeed, the NSAIDs that cause the most stomach damage are those that inhibit COX-I the most, such as aspirin, indomethacin, and piroxicam. (43) Because NSAIDs suppress COX-2, they are used to treat inflammation. The differences in the adverse effects of NSAIDs at their anti-inflammatory levels are explained by the range of actions of NSAIDs against COX-I compared to COX-2. Anti-inflammatory drugs with a high potency against COX-2 and a low COX-2/COX-l activity ratio have substantial anti-inflammatory activity with little stomach and kidney adverse effects. In anti-inflammatory doses, piroxicam and indomethacin showed substantial gastrointestinal toxicity. These medications are substantially more effective against COX-l than COX-2. (44)

5. Selective COX-2 Inhibitors' Potential Therapeutic Applications

Premature Birth

During labor, prostaglandins cause uterine contractions. NSAIDs, such as indomethacin, postpone premature labor by reducing prostaglandin production, but they also cause the ductus arteriosus to close early and limit urine output by the fetal kidneys (Sawdy et al. 1997). Because mRNA for COX-2 increases dramatically in the amnion and placenta shortly before and after the commencement of labor (Gibb and Sun, 1996), the delay in the delivery process is most likely due to inhibition of COX-2, whereas the side effects on the fetus are attributable to inhibition of COX-1.

Colon Cancer

Epidemiological studies have found a substantial association between aspirin consumption and a lower risk of colon cancer. (45, 46) Sulindac also reduced prostaglandin synthesis and adenomatous polyp regression in 11 of 15 patients with familial adenomatous polyposis (FAP), a syndrome in which many colorectal polyps form spontaneously and proceed to malignancies. COX-2 (but not COX-I) is significantly expressed in human and animal colon cancer cells, as well as in human colorectal adenocarcinomas, indicating that COX activity is involved in the process leading to colon cancer. (47, 48)

Alzheimer's disease is a type of dementia that affects people.

Because there is no animal model of Alzheimer's disease, the link between COX and the disease has been established primarily in epidemiology. A number of studies have found that those who take NSAIDs as anti-inflammatory medication had a lower risk of Alzheimer's disease. (49-51). It's likely that the aspirin dose was too low to have an anti-inflammatory impact. The protective effect of NSAIDs is in line with findings of inflammatory activity in Alzheimer's disease pathogenesis. COX-2 has a lot of interest in Alzheimer's disease, and (52) found COX-2 expression in the frontal cortex of Alzheimer's patients' brains.

6. Conclusions

Industrial screening programs discovered selective COX-2 inhibitors as strong NSAIDs with low toxicity in the stomach and kidneys even before the COX-2 enzyme was identified, employing models of chronic inflammation in conjunction with models of gastric injury. The evidence that selective COX-2 inhibitors will have considerably decreased side effects is strong, both in animal experiments and in clinics. Anti-inflammatory therapy will benefit greatly from selective COX2 inhibitors. They are unlikely to be more effective anti-inflammatory medicines than traditional NSAIDs, but they will have the significant benefit of being safer and more well tolerated. Meloxicam's clinical findings already suggest that it has enhanced safety and tolerability, despite the fact that it still has some COX-I action. In the future, these medications may be used to prevent colon cancer, Alzheimer's disease, and premature labor, in addition to their positive effects in inflammatory illnesses.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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