A REVIEW ON NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

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ABSTRACT

NSAIDs constitute an important class of drugs with therapeutic applications that have spanned several centuries. Treatment f inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA) starting from the classic drug aspirin to the recent rise and fall of selective COX-2 inhibitors has provided an enthralling evolution. This review traces the origins of NSAIDs, their mechanism of action at the molecular level such as cyclooxygenase (COX) inhibition, inflammatory Process, biosynthesis of prostanoids, COX isoforms, their structure, function and comparision, development of selective COX-2 inhibitors, adverse gastrointestinal effects of NSAIDs. The presence of COX-3 is discussed. A little history of the market withdrawal of selective COX-2 inhibitors is explained. The last section describes briefly some of the recent advances toward developing effective anti-inflammatory agents such as nitric oxide donor NO-NSAIDs, dual COX/LOX inhibitors and Hydrogen sulfide (H_2S) Containing NSAIDs. In spite of the tremendous advances in the last decade, the design and development of a safe, effective and economical therapy for treating inflammatory conditions still presents a major challenge.

Keywords: Nonsteroidal, Inflammation, Prostaglandin Cyclooxygenase, Lipoxygenases.

INTRODUCTION

The fascinating ability to treat fever and inflammation dates back about 3500 (400 B.C.) years ago to a time when the Greek physician Hippocrates prescribed an extract from willow bark and leaves. Later in the 17th century, the active ingredient of willow bark salicin was identified in Europe. The Kolbe company in Germany started mass producing salicylic acid in 1860. Acetylsalicyclic acid (aspirin) [1] the more palatable form of salicyclic acid was introduced into the market by Bayer in 1899. However, the mechanism of action of anti-inflammatory and analgesic agents such as aspirin and indomethacin [2] remained elusive until the early 1960's. This all changed in the seventies, when John Vane discovered the mechanism of action of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) thereby increasing our ability to develop novel anti-inflammatory therapies. The success of NSAIDs in treating various inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA) validated inhibition of the enzyme prostaglandin H synthase (PGHS) or cyclooxygenase (COX) as a highly suitable target in anti-inflammatory therapies. However, the gastrointestinal (GI) toxicities associated with widespread NSAID use proved to be a major drawback during long term therapy [2].

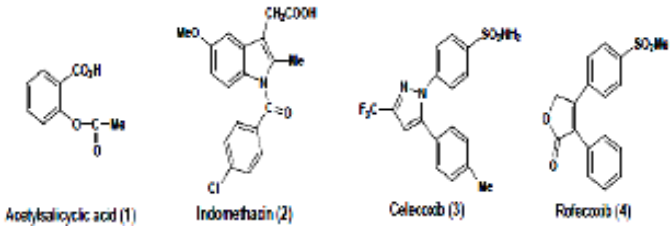


Figure 1: Some representative examples of NSAIDs

In the early 90's, Needleman, Simmons and Herschman's group reported the presence of an inducible isoform of the enzyme COX later identified as COX-2. This discovery led to the hypothesis that anti-inflammatory prostaglandins (PGs) were produced through constitutive expression of COX-1, whereas the proinflammatory PGs were produced via induction of the COX-2 isoform. In 1999, G.D. Searle and Pfizer (now Pfizer Inc) launched the first selective COX-2 inhibitor celecoxib **3** (Celebrex®). This was followed by the launch of Merck's selective COX-2 inhibitor rofecoxib **4** (Vioxx®). In spite of this initial success after the launch of selective COX-2 inhibitors, concerns were raised regarding their adverse cardiovascular demonstrated that selective COX-2 inhibitors may tip the natural balance between prothrombotic thromboxane A2 (TxA2) and antithrombotic prostacyclin (PGI2) potentially increasing the possibility of a thrombotic cardiovascular event [3, 4]. In April of 2005, the US FDA advisory committee overwhelmingly concluded that coxibs increase the risk of cardiovascular events and recommended the suspension of Pfizer's Bextra® (valdecoxib). Celecoxib was allowed to remain in the market place, but with a black box warning indicating a risk of adverse cardiovascular events [5]. Health Canada recently decided to withdraw Novartis Pharmaceuticals selective COX- 2 inhibitor lumiracoxib (Prexige®) due to concern regarding its liver toxicity [2]. Recently, the American Heart Association issued a statement advising prescribing clinicians pertaining to the use of NSAIDs [6].

INFLAMMATORY PROCESS

Inflammation is a biochemical and cellular response that occurs in all vascularized tissue whose health and vitality is threatened by either an internal or an external source. Most of the essential components of the inflammatory response can be found in the blood, and most of the early mediators (facilitators) of inflammation function to increase the movement of plasma and infection fighting blood cells from the capillary bed into or around the injured tissue. Collectively known as exudate, usually a clear serous fluid, these substances defend the host against infection and facilitate tissue repair and healing [7]. The superficial hallmarks of inflammation have been described since antiquity. They are: • Redness (rubor) • Heat (calor) • Pain (dolor) • Swelling (tumor) • Loss of function (functio laesa).

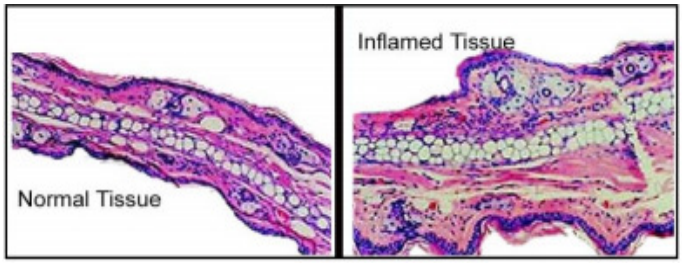


Figure 2: Histological sections through a normal and an inflamed retina.(age-related macular degeneration)

On a microscopic level, three characteristic changes in the microcirculation occur near the site of tissue injury. i) Increased blood flow to the area. ii) Increased vascular permeability which allows leakage of plasma into the damaged area. iii) An increased number of white blood cells immigrating through vessel walls to the site of injury. Histological sections through a normal and an inflamed retina shown in (Figure 2).

BIOSYNTHESIS OF PROSTANOIDS

PGs and thromboxane A_2 (TXA_2), collectively termed prostanoids, are formed when arachidonic acid (AA), a 20-carbon unsaturated fatty acid, is released from the plasma membrane by phospholipases (PLA_2) and metabolized by the sequential actions of PGG/H synthase or by cyclooxygenase (COX) and their respective synthases. There are 4 principal bioactive PGs generated in vivo: prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), prostaglandin D_2 (PGD_2), and prostaglandin $F_{2á}$ ($PGF_{2á}$). PG production (Figure 3) depends on the activity of PGG/H synthases, colloquially known as COXs , bifunctional enzymes that contain both COX and peroxidase activity and that exist as distinct isoforms referred to as COX-1 and COX-2 [8, 9].

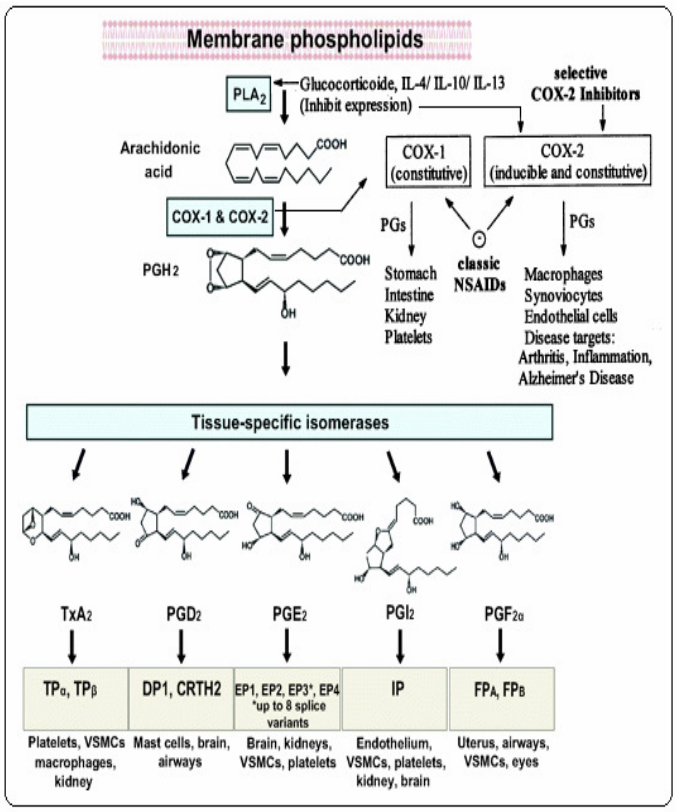


Figure 3: Biosynthesis of Prostanoids and site of action of anti-inflammatory drugs

PGH_2 is produced by both COX isoforms, and it is the common substrate for a series of specific isomerase and synthase enzymes that produce PGE_2, PGI_2, PGD_2, $PGF_{2á}$, and TXA_2. COX-1 couples preferentially, but not exclusively, with thromboxane synthase, PGF synthase, and the cytosol (c) PGE synthase (PGES) isozymes.COX-2 prefers prostaglandin I synthase (PGIS) and the microsomal (m) PGES isozymes, both of which are often coinduced along with COX-2 by cytokines and tumor promoters. Prostanoids exert their actions on other cells through various G-protein coupled receptors.

CYCLOOXYGENASES

The COX isoforms are heme containing enzymes that exhibit distinct expression profiles and roles in several physiological processes. The first crystal structure of ovine COX-1 complexed with the NSAID flurbiprofen was reported in 1994. The structures of human and murineCOX-2 are virtually super imposable on ovine COX-1. Comparison of the COX-1 and COX-2 isoforms given in Table1.The COX isoforms are homodimers, with each monomer comprised of three structural domains; a *N*-terminal epidermal growth factor (EGF) domain, a membrane binding domain (MBD) and a large Cterminal catalytic domain (Figure 4). The COX catalytic reaction occurs in a hydrophobic channel in the core of the enzyme while the peroxidase site is located in the heme containing region near the protein surface. The MBD is made up of four alpha helices with helix D merging into the catalytic domain. These helices surround an opening through which fatty acid substrates and NSAIDs are believed to enter the COX active site. *N*-glycosylation of the COX isoforms is required for enzyme folding and activity [2].

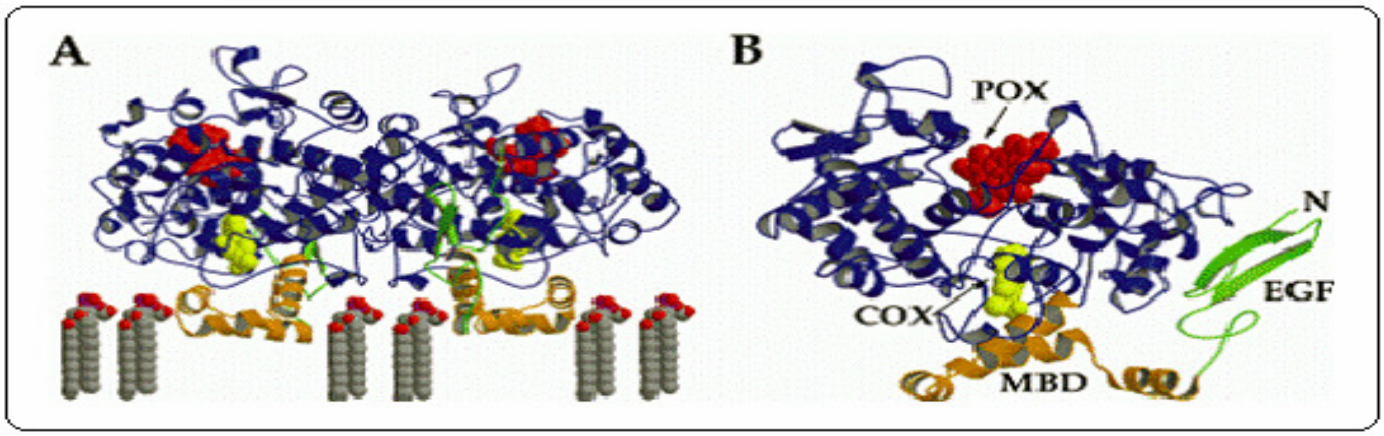


Figure 4: **A.** diagram of the ovine COX-1 homodimer with flurbiprofen bound within the COX active site. **B.** diagram of ovine COX-1 monomer with flurbiprofen bound indicating the locations of the COX and peroxidase (POX) active sites and the EGF and MBD domains. Flurbiprofen is represented as a yellow space filling model.

Table 1: Comparison of the COX-1 and COX-2 isoforms [10]

Parameter	COX-1	COX-2
Regulation	Usually Constitutive	Inducible
Range of Induced Gene Expression	2 to 4-fold	10 to 80-fold
Rate of Gene Activation	24 hours	0.5 to 4 hours
Effect of Glucocorticosteroids	Little or None	Inhibits Expression
Relative Size of Active Site	Smaller	Larger
Rate of Arachidonic Acid Consumption	34 nmol/min/mg	39 nmol/min/mg
Effect of aspirin on COX activity	Inhibited	Not Affected

PRESENCE OF COX-3?

A new twist was added to the COX story in 2002 with the discovery of a third isoform COX-3 by Simmons and coworkers. Their study in dogs showed that COX-3 was present as an alternative splice variant of COX-1 [11, 12]. The Simmons group showed that indeed COX-3 was the target of acetaminophen. However, the initial excitement surrounding the discovery of COX-3 as a potential drug target received a reality check when it was discovered that one can not generalize the presence of canine COX-3 to humans. It is now known that COX-3 encodes proteins with completely different amino acid sequences than COX-1 or COX-2 in rodents and humans and moreover lacks COX activity. This negates its role in causing pain and fever. Therefore, the clinical relevance of COX-3 as a drug target is questionable. However the final jury on this question is not out yet [13, 14].

MECHANISM OF ACTION OF NSAIDS

A simplified explanation of the effect of inhibitors of the COX enzymes is as follows. The carboxyl moiety of acidic NSAIDs interacts with Arg120 in both COX isoforms, via hydrogen bonding or electrostatic interactions. The remaining ligand-protein interaction is hydrophobic. Most NSAIDs act reversibly, mainly by excluding arachidonate, but aspirin binds to and acetylates the serine at position 530 causing irreversible inactivation of the enzymes.

The crucial differences between the two COX enzymes (Figure 5) are at position 523: here COX-1 has bulky isoleucine while COX-2 has valine smaller molecule that leaves a gap, which gives access to a side pocket. It is this side pocket that is believed to be the binding site for COX-2 selective agents, which in general have a rigid side-extension that can reach across the channel and interact with the pocket. This aspect of their structure appears to be the basis of their selectivity for COX-2: they may be too bulky to fit into the COX-1 channel [15].

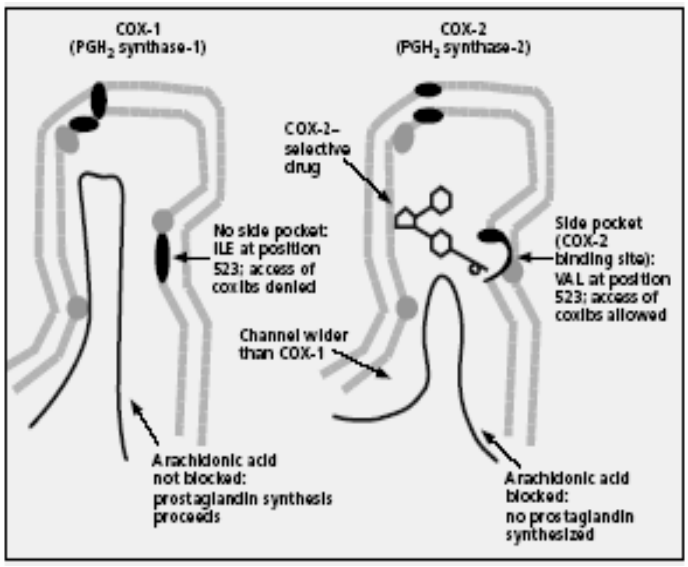


Figure 5: Structure of the COX-1 and COX-2 enzymes. Schematic showing active site similarities and differences.(ILE = isoleucine; VAL = valine.)

MANAGEMENT OF NSAIDS RELATED GASTROINTESTINAL TOXICITY

Current hypotheses for roles of COX-1 and COX-2 in the pathogenic mechanism of NSAID-induced gastric damage. The motility hypothesis suggests that gastric motility plays an important role in NSAID damage. NSAIDs induce vagal-dependent gastric hypermotility via inhibition in COX-1-mediated prostaglandin (PG) production and CNS actions. Subsequent microvascular disturbances lead sequentially to neutrophil-endothelial interaction and oxyradical production. Inhibition of COX-1 leads to up-regulation of COX-2 expression [16]. PG production mediated by COX-2, which may suppress the neutrophil-endothelial interaction, is also decreased by COX-2 selective or nonselective NSAIDs (Figure 6). The neutrophil-endothelial interaction plays a major role in the neutrophil hypothesis, which suggests that NSAIDs activate the neutrophil through alteration of arachidonic acid metabolites (eg, PGs), enhancing neutrophil-endothelial cell adhesion.

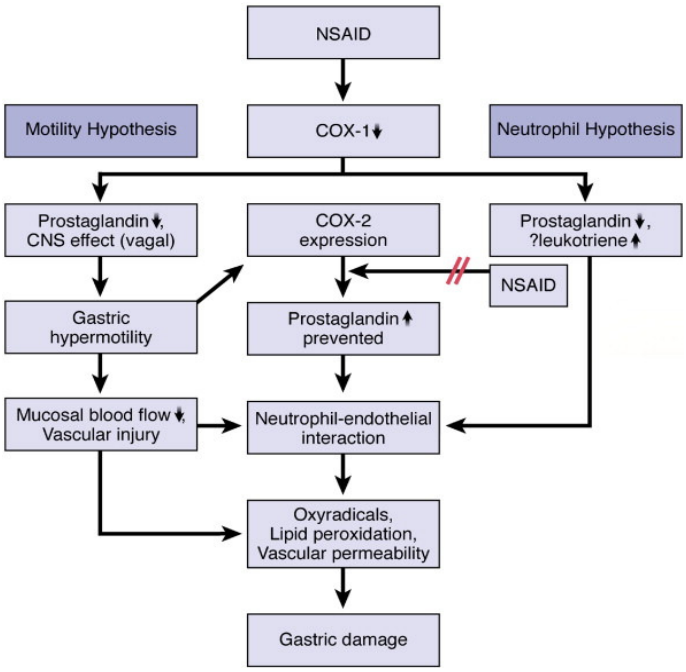
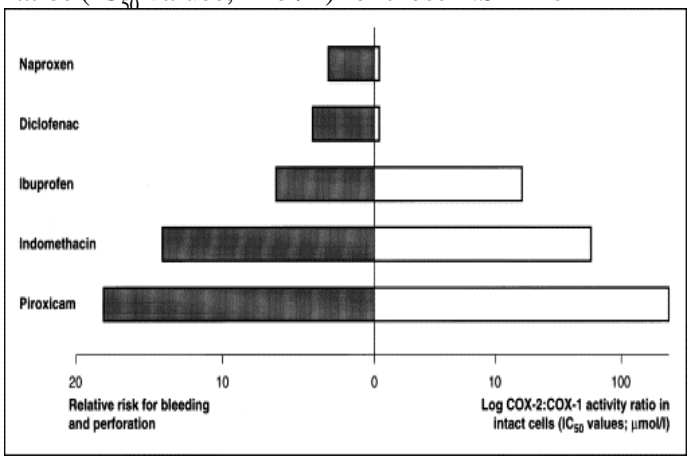


Figure 6: Roles of COX-1 and COX-2 in the pathogenic mechanism of NSAID-induced gastric damage

Comparisons of gastric damage and cyclo-oxygenase (COX) selectivity of nonsteroidal anti-inflammatory drugs (NSAIDs). The left-hand side of the (Figure 7) represents the adjusted relative risk for bleeding and perforation of the upper gastrointestinal tract. Values for anti-inflammatory doses of NSAIDs are shown [17]. The right-hand side of the figure represents log COX-2 : COX-1 activity ratios (IC_{50} values; ìmol/L) for these NSAIDs



Figue 7: Comparisons of gastric damage and COX selectivity NSAIDs

CONVERSION OF NONSELECTIVE COX INHIBITORS TO COX-2-SELECTIVE INHIBITORS [18, 19]

Modifying well known NSAIDs into selective COX-2 inhibitors represents an interesting strategy. Indomethacin, zomepirac, aspirin and flurbiprofen have been successfully elaborated into selective COX-2 inhibitors (Figure 8). However, the methodology utilized in NSAID modification does not follow a general scheme. Classic NSAIDs such as indomethacin possess both COX-1 and COX-2 inhibiting activity. Various attempts have been made to shift the enzyme selectivity of indomethacin from COX-1 to COX-2 while keeping the potency on the same level and reducing the unwanted side-effects at the same time. In principle, the strategy consisted of introducing larger substituents to fit into the active site volume of COX-2 (L-748780). Introducing a larger trichlorobenzoyl analogue instead of the chlorobenzoyl analogue optimized COX-2 selectivity. A similar strategy was used for the modification of zomepirac, basically a COX-1 selective drug. The desired COX-2 selectivity was achieved by replacing the acetic acid group by other moieties such as the pyridazinone ring or an *N*-acyl aminosulfonyl phenyl group to yield RS-57067 and RS-1048934, respectively. In contrast exchanging the carboxylate moiety of the aspirin with alkyl sulfide functionalities afford specific COX-2 inhibitors.

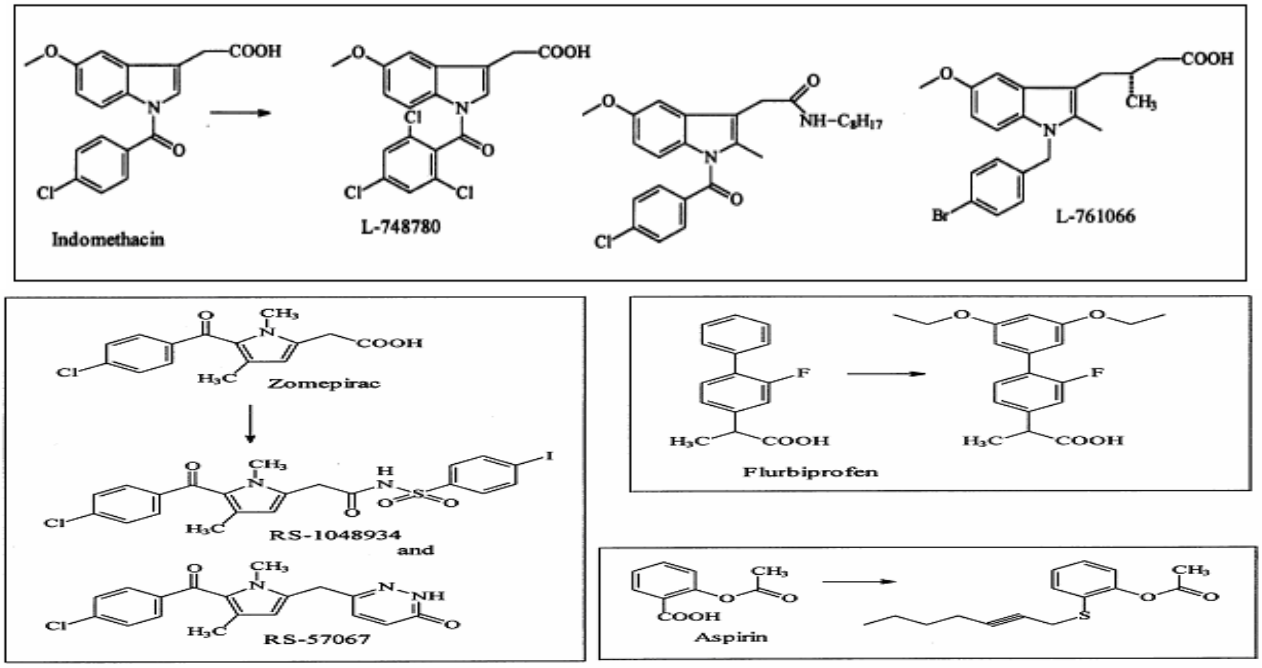
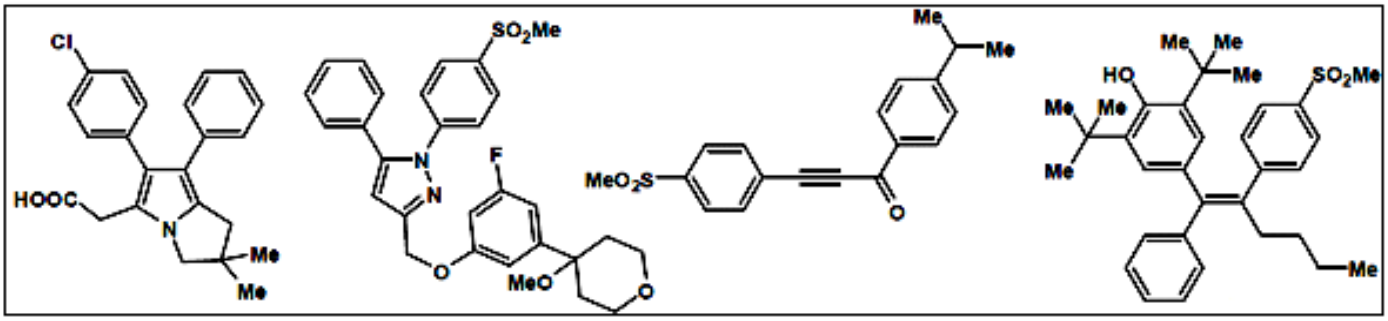


Figure 8: Conversion of nonselective COX inhibitors to COX-2-selective inhibitors[15]

DUAL COX AND LIPOXYGENASE (LOX) INHIBITORS

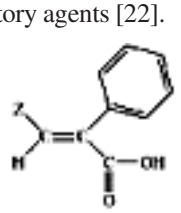
It is well known that arachidonic acid (AA) primarily undergoes biotransformation to proinflammatory and anti-inflammatory PGs via COX mediated isoform catalysis. Lipoxygenases (LOXs), which belong to a class of non-heme ironcontaining enzymes, catalyze dioxygen incorporation into AA, to form hydroperoxide products. For example, AA metabolism catalyzed by 5-LOX affords proinflammatory leukotrienes (LTs) that may play a role in cardiovascular diseases since they are potent vasoconstrictors . In addition, other LOX mediated metabolites such as cysteinyl-LTs are known to cause GI mucosal damage. ML-3000 (licofelone)(**1**)exhibits dual COX and 5-LOX inhibitory activities. Licofelone exhibited effective

anti-inflammatory activities with reduced GI toxicities in animal models. Preliminary data in humans have shown that licofelone could be an alternative to NSAIDs in treating OA. In this regard, compound-**(2)** possesses the pyrazole ring system present in the selective COX-2 inhibitor celecoxib in conjunction with the 5-LOX pharmacophore present in the marketed drug ZD-2138. This dual inhibitor exhibited excellent COX-2 inhibitory potency and selectivity along with potent 5-LOX inhibition [20]. The propynone **(3)** exhibited selective COX-2 inhibition and 5-LOX inhibition along with in vivo anti-inflammatory activity in animal models. In another study compound-**(4)** evaluated in this study exhibited dual COX/LOX inhibition. Related studies targeted to the design of novel COX/LOX inhibitors as effective anti-inflammatory agents with reduced side effects have been reported. The molecular structures of few potent dual inhibitors are given in (Figure 9)

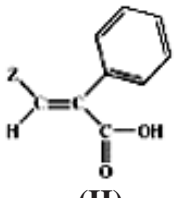


(1) (2) (3) (4)

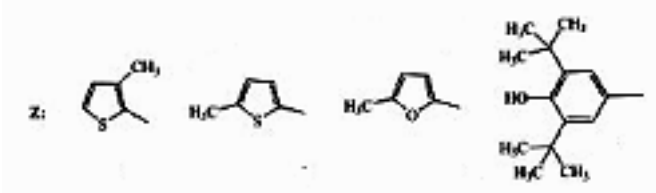
Figure 9: Molecular structures of dual inhibitors licofelone (2-[6-(4-chlorophenyl)-2, 2-dimethyl-7-phenyl-2, 3-dihydro-1H-pyrrolizin-5-yl] acetic acid) have been found to be significantly effective in Phase III clinical trials conducted on patients of osteoarthritis [21]. A series of novel acrylic acid derivatives (I, II) were designed and synthesized bearing at the 3 position thienyl, furfuryl and 3,5-ditert-butyl-4-hydroxyphenyl substituents and tested as potential dual lipoxygenase/cyclooxygenase-1 (LOX/COX-1) inhibitors and as anti-inflammatory agents [22].



(I)



(II)



NITRIC OXIDE (NO) CONTAINING NSAIDS

The first reports describing NO-NSAIDs began to appear in the literature during the 1990's. NO-NSAIDs were investigated with the objective of abolishing the GI toxicity associated with traditional NSAID therapy since NO was known to protect the GI mucosa. These studies showed that hybrid NO-NSAIDs exhibited efficient anti-inflammatory activities without causing GI side effects. The recent adverse cardiovascular events associated with selective COX-2 inhibitor therapy has provided a strong stimulus for the development of NO-NSAIDs since NO exhibits beneficial cardiovascular effects such as vasodilation, and inhibition of platelet aggregation [23]. In this regard, a novel class of pyrazole analogs developed as selective COX-2 inhibitors containing nitrate groups as hybrid-NO donors. Compound **(a)** (Figure 10) exhibited potent COX-2 inhibition and selectivity in conjunction with good GI tolerance (safety). An alternate approach also described wherein the central furanone ring system of rofecoxib was replaced by a furoxan ring. This concept was based on the observation that a furoxan ring system can act as a

NO-donor. Therefore, 3,4-diphenylfuroxans were designed for evaluation as hybrid COX-inhibitor/NO donors. Within this class of compound, the furoxan **(d)** exhibited selective COX-2 inhibition in conjunction with NO-donor properties. NO-NSAIDs such as aspirin, naproxen, and diclofenac have been investigated the most. In the majority of these studies, organic nitrates or nitrosothiols have been employed as the NO-donor group [2]. However, long term treatment with organic nitrates can cause "nitrate tolerance" leading to lack of GI and cardiovascular benefits. To counter this problem NO-NSAIDs containing novel diazonium-diolate groups developed that have the potential to theoretically release two molecules of NO with half-lives that correlate well with their pharmacological durations of action . The aspirin **(b)** and ibuprofen **(c)** hybrid NO-donors exhibited effective anti-inflammatory activity with reduced or no GI toxicities. Compounds **(e)** and **(f)** exhibited COX-2 selectivity as well as vasodilator properties.

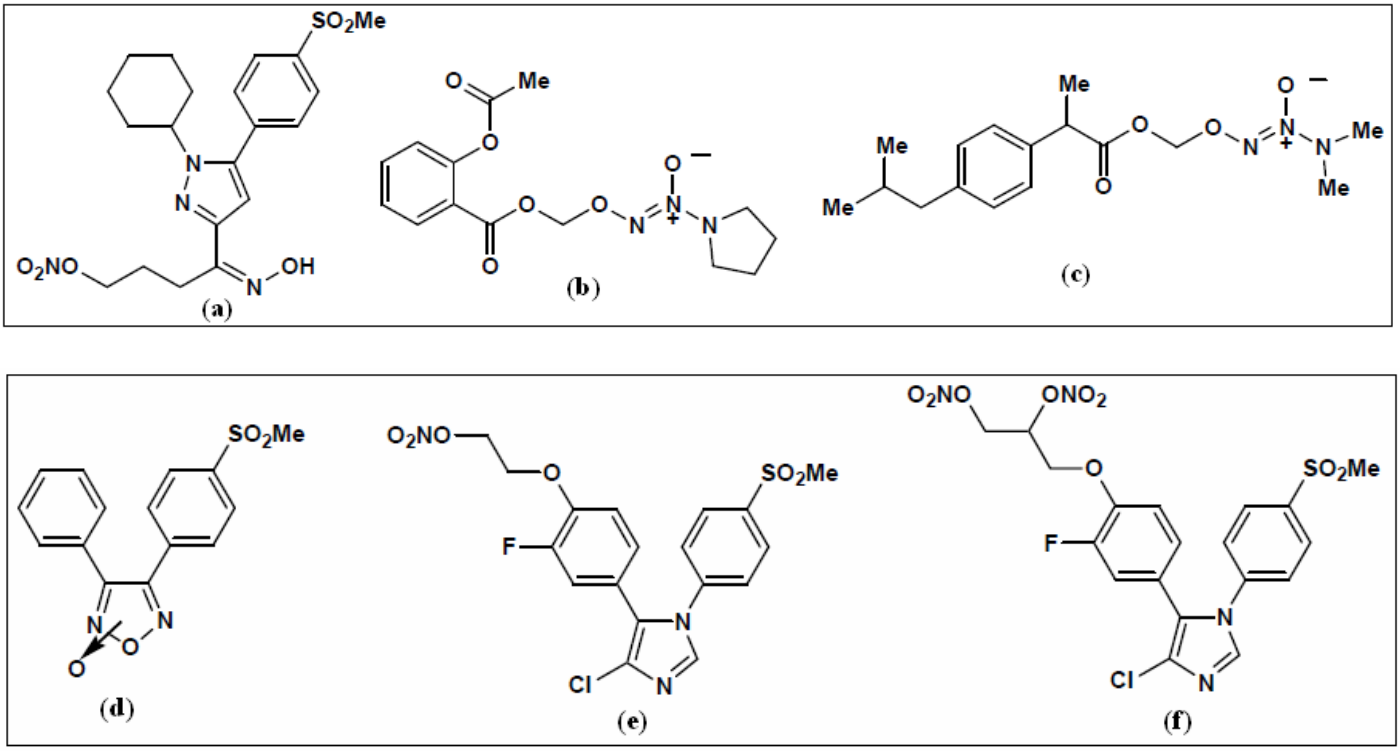
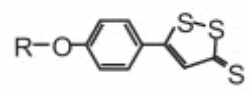


Figure 10: Examples of hybrid NO-NSAIDs.

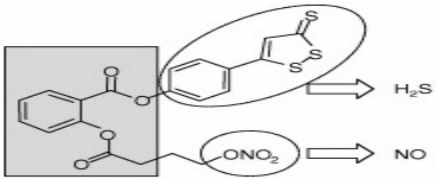
HYDROGEN SULFIDE (H2S) CONTAINING NSAIDS

Hydrogen sulfide, H_2S, is a colorless gas with a strong odor that until recently was only considered to be a toxic environmental pollutant with little or no physiological significance. However, the past few years have demonstrated its role in many biological systems and it is becoming increasingly clear that H_2S is likely to join nitric oxide (NO) and carbon monoxide (CO) as a major player in mammalian biology. An overview of the chemistry and biology of H_2S and have summarized the chemistry and biological activity of some synthetic H_2S-donating compounds have provided (III). The synthetic H_2S donating NSAIDs of aspirin, sulindac, diclofenac, indomethacin, and ibuprofen have been reviewed in detail [24]. The newly reported NOSH-aspirin (IV) that releases both NO and H_2S has also been discussed.



R= asprin, Sulindac
Diclofenac
Indomethacin
Ibuprofen

(III)



(IV) NOSH - aspirin

A study said that a molecule, which releases hydrogen sulphide - the gas that gives rotten eggs their characteristic smell- have an anti-inflammatory effect. The team hopes that using H_2S donating molecules to control H_2S delivery in the body could pave the way for the development of novel approaches to the treatment of inflammatory. He discovered that when H_2S is delivered in a slow and sustained manner, a potent anti-inflammatory effect is produced. The cell signalling molecules that drive inflammation, such as TNFa, IL-1, IL-6 and prostaglandins, were reduced while levels of the body''s own anti-inflammatory molecules (i. e. IL-10) were increased [25].

When hydrolyzed, H_2S-releasing NSAIDs produce the parent NSAID and the H2S-releasing moiety from which H_2S is released (Figure 11).The NSAID component inhibits COX-1 and COX-2 resulting in compromised mucosal defense mechanisms, which may lead to ulcers. NSAIDs can reduce renal perfusion, which can lead to increases in blood pressure (BP) leading to cardiovascular (CV) damage. The released H_2S counteracts many of the detrimental effects of NSAIDs. These protective effects appear to be mediated through activation of KATP channels. H_2S enhances the mucosal defense mechanisms; causes vasodilation thus reducing BP leading to cardioprotective effects. Both the NSAID and H_2S have anti-inflammatory effects, the former through inhibition of COX and latter through inhibition of nuclear transcription factor êB (NF-êB).

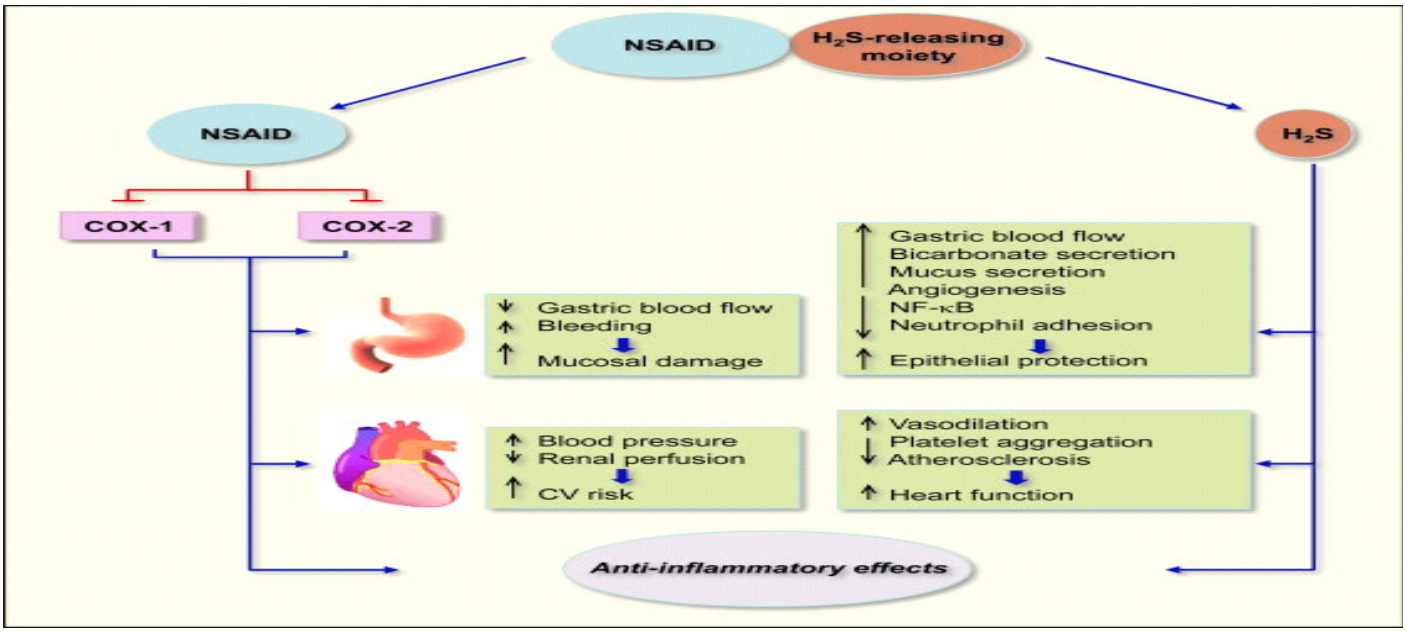


Figure 11: Mechanisms of action of H2S-releasing NSAIDs

FUTURE PROSPECTS

Various epidemiological and laboratory studies have indicated that NSAIDs may be able to reduce the risk of cancer (colorectal cancer in particular), Angiogenesis and Alzheimer's disease due to their inhibitory activity on COXs, especially COX-2 [22].

A constitutive overexpression of COX-2 seems to be important in colon carcinogenesis. In cultured human colonic fibroblasts it was shown that growth factors such as hepatocyte growth factor are involved in the progression of tumors. COX-2 inhibitors are now assumed to inhibit COX-2-mediated PG synthesis which is responsible for hepatocyte growth factor expression.

It is hypothesized that tumor-derived growth factor promotes angiogenesis by inducing the production of COX-2-derived PGE_2. PGs are known to be pro-angiogenic molecules and contribute to tumor growth by inducing the newly formed blood vessels (neoangiogenesis) that sustain tumor cell viability and growth.

Recent results indicate an important role of COX-2 in the central nervous system (CNS). COX-2 expression is markedly induced in CNS neurons by excitatory stimuli such as ischemia and seizures so that a role of COX-2 derived PGs in certain forms of neurodegeneration can be assumed. The fact that COX-2 mRNA is elevated in areas related to memory (hippocampus, cortex) and that the amount of COX-2 correlates with the deposition of beta-amyloid protein represents a possible therapeutic benefit and a hopeful new strategy in the prevention or treatment of Alzheimer's Disease (AD). It has also been shown that celecoxib maximally inhibits COX-2 in the CNS at anti-inflammatory doses.

CONCLUSIONS

NSAIDs represent an important class of compounds. The rapid discovery of selective COX-2 inhibitors can be attributed to the rational drug design approach. However, the gastrointestinal adverse effects of traditional NSAIDs and the cardiovascular adverse effects associated with selective COX-2 inhibitors highlights the pitfalls that may be encountered in the drug discovery paradigm. NO-NSAIDs, H_2S-releasing NSAIDs and dual COX/LOX inhibitors represent novel approaches directed toward the development of effective anti-inflammatory therapy. In spite of the unprecedented advances in drug discovery, developing a safe, effective and economical therapy for treating inflammatory conditions still presents a major challenge [2].

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