Chapter 2

Mechanism of Action of Nonsteroidal Anti-Inflammatory Drugs

Newman Osafo, Christian Agyare,
David Darko Obiri and Aaron Opoku Antwi

Additional information is available at the end of the chapter

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Abstract

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) dates back to thousands of years when man used natural sources of these agents in a lot of pain and inflammatory conditions. The tone for modern day discovery and use of NSAIDs was set with the discovery of aspirin. Today in addition to aspirin, a host of other NSAIDs of varying potency and efficacy is employed in the management of pain and inflammatory conditions. This chapter looks with key interest in the existing and evolving role of NSAIDs in therapeutics with emphasis on the current insights into their mechanism of action and side effect profiles associated with its use in pain and inflammation as well as its potential therapeutic benefits in cancer chemotherapy.

Keywords: nonsteroidal anti-inflammatory drugs, inflammation, cyclooxygenase, pain, fever

1. Introduction

The history of nonsteroidal anti-inflammatory drugs (NSAIDs) dates as far back as thousands of years with Hippocrates and other physicians prescribing the willow bark for a wide range of conditions [1]. The tone for the modern era of NSAIDs was, however, set by identifying salicin as the willow plant's active ingredient and the subsequent introduction of acetylsalicylic acid by the Bayer Company about two centuries later [2]. Today in addition to aspirin, nonselective NSAIDs, such as piroxicam, mefenamic acid, diclofenac, naproxen, and selective cyclooxygenase-2 (COX-2) inhibiting NSAIDs, such as celecoxib and rofecoxib, remain mainstays of pain and inflammatory disorder therapy.

NSAIDs remain one of the most consumed drugs either by prescription or over-the-counter [3]. Their fever relieving effect has been well documented since their discovery and they have proven effective over the years in controlling pain and inflammatory conditions. It is particularly effective in acute and chronic orthopedic pain (osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis) and postsurgical pain [4]. While these represent the traditional uses of NSAIDs, studies have pointed to their potential in Alzheimer's [5], cancer [6], and Parkinson's disease [7]. Most of these studies exploit the benefits of controlling the underlying inflammatory mechanisms of these diseases.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of therapeutic agents with diverse structural and pharmacodynamics profiles but similar mode of action. Broadly, NSAIDs are grouped into aspirin and nonaspirin NSAIDs. Despite similarities in their mechanism of action and toxicity profiles, they differ slightly in the manner they each interact with the cyclooxygenase enzyme [8]. A more popular classification, however, is based on structural differences and similarities [9]. They are grouped as follows: salicylates (aspirin), aryl alkanoic acids (diclofenac, indomethacin, nabumetone, sulindac), 2-arylpropionic acids or profens (ibuprofen, flurbiprofen, ketoprofen, and naproxen), n-arylanthranilic acids or fenamic acids (mefenamic acids, meclofenamic acid, pyrazolidine derivatives, e.g., phenylbutazone), oxicams (piroxicam, meloxicam), and sulfonamides (nimesulide).

2. Mechanism(s) of NSAIDs action

2.1. COX and COX inhibition

There is overwhelming evidence pointing to the inhibition of cyclooxygenase enzyme as the main mechanism of NSAIDs' analgesic, antipyretic, and anti-inflammatory properties. Since the characterization of this mechanism by Vane for aspirin [10], other drugs in this class have proven consistent this mechanism. This is surprising considering the differences in structures of the individual drugs as described above. Cyclooxygenase (COX) inhibition and the resulting inhibition of prostaglandin and other eicosanoid synthesis mitigate pain, fever, and inflammation. The cyclooxygenase (COX) enzyme also known as prostaglandin endoperoxide H synthase (PGHS) exists in two isoforms: PGHS-1 or COX-1 and PGHS-2 or COX-2. There is a significant structural distinction between the two, with only 60% homology [11]. Although encoded by different genes, both isoforms are membrane-bound glycoproteins that catalyze the formation of prostanoid from arachidonic acid [12].

COX-1 is expressed constitutively in most mammalian cells and tissues such as seminal vesicle, platelets, and endothelium. In quiescent conditions, it performs ongoing regulatory functions referred to as "housekeeping duties." Prostaglandins produced by COX-1 activity perform functions such as gastro and renal protection, macrophage differentiation, platelet aggregation, and mucus production [3, 13]. In inflammatory conditions, molecular studies have demonstrated that COX-1 mRNA and protein expression do not change, confirming their limited role in the inflammatory process [14]. COX-1, however, remains both experimentally and clinically relevant due to the adverse effects triggered by the nonselective inhibition of cyclooxygenase enzymes by some NSAIDs.

COX-2 is an inducible enzyme called upon by tissue injury and other stimuli such as lipopolysaccharide (LPS), interleukin-1, and tumor necrosis factor alpha (TNFα) [15, 16]. It is active at injury sites and in a variety of tissues such as the vascular endothelium, and rheumatoid synovial endothelial cells mediating inflammatory, pain, fever, and carcinogenic responses [17, 18]. A manifold increase in COX-2 levels occurs in inflammatory processes triggering an increased synthesis of pro-inflammatory prostaglandins. Initially thought of as exclusively inducible in nature, studies have shown COX-2 has some constitutive or regulatory roles. Housekeeping duties in reproduction, renal physiology, bone resorption, and neurotransmission have been documented [19, 20].

Indeed studies have shown that both isotypes are constitutive and inducible depending on the physiological conditions [21, 22]. COX-3, a third isotype, has been identified [23]. Its function, distribution, and role in NSAIDs mechanisms are still uncertain and subject of debate [24].

2.2. Pain, fever, and inflammation

The arachidonic acid pathway is central to inflammatory responses and consequently the mechanism of action of NSAIDs. Prostanoids, the end product of this pathway, performs a wide range of physiological functions.

NSAIDs are largely thought of as inhibitors of peripheral pain though several works in literature point to a potential and significant central analgesic activity. At the periphery, a host of mediators occurs to trigger nociception in response to physical, chemical, or electrical stimuli. Prostaglandins act synergistically with other mediators to sensitize nociceptors [10, 25]. Some NSAIDs have exhibited central analgesic effects in several animal models of pain. This is attributed to disruption of synthesis of central prostaglandins and other modulators in the nociceptive pathway. Arguments in favor of central activity stem from studies showing the inhibitory effect of NSAIDs on N-methyl-D-aspartate (NMDA) receptor activation-induced prostaglandin expression in cerebrospinal fluid [26] and antinociceptive effect of spinally administered ibuprofen [27] among others. A classic study by Hunskaar [28] showed overlapping time-effect relationship for aspirin and morphine in the first phase of formalin-induced pain response; a feature highly indicative of central activity.

NSAIDs have proven effective in inflammatory conditions such as arthritis, acute trauma, and pain associated with inflammation. Inflammatory mediators at injury site mediate vasodilation extravasation of protein exudates and nociception. Here, prostaglandins that are key players in this process are inhibited. Though COX inhibition is maintained as the main mechanism for the anti-inflammatory activity of NSAIDs, other mechanisms loosely referred to as non-COX mechanisms have been reported in the literature. NSAIDs are documented to have the suppressive effect in nuclear factor (NF)-κB, a transcription factor for pro-inflammatory proteins such as chemokines, adhesion molecules, and cytokines. NSAIDs also exhibit some suppression of activator protein 1, membrane stabilizing, and inhibition of reactive oxygen species (ROS) production [29–31]. Although these are believed to contribute at a molecular level, it is unclear how they directly aid in the clinical benefits of NSAIDs.

NSAIDs relieve fever by inhibiting COX-mediated prostaglandin synthesis. Upon exposure to external pyrogens, mostly pathogen-associated molecular patterns (lipopolysaccharide, peptidoglycan, viral RNA, etc.), cells of the innate immune system respond by releasing

endogenous pyrogens to induce pyrexia. Circulating interleukin-1, interleukin-6, and TNFα gets to the brain and induced the synthesis of prostaglandin via the cyclooxygenase in the preoptic hypothalamic region of the brain. Prostaglandin E_2 (PGE_2) binds to an EP-3 receptor of the endothelium of the hypothalamus to reset the body's thermoregulation. An ensuing physiological process occurs to attain this set temperature. NSAIDs disrupt this process by COX inhibition and therefore have proven useful in curbing the harmful effects of high and persistent temperatures. It is important to note that they have no effect on normal body temperature or atypical rise in temperature such as malignant hyperthermia and heat stroke. Mechanisms in these cases are independent of the COX/prostaglandin inflammatory pathway.

2.3. Structure and mechanisms

Current studies have made it possible to understand the structural basis of both nonselective cyclooxygenase inhibition and COX-2 selective inhibition and the variations in individual NSAID's interactions with COX. The catalytic site of COX-1 is long narrow hydrophobic channel spanning from the membrane-binding domain to the enzyme core. The threshold of the channel is made up of polar groups such as Arg120 and Glu524. NSAIDs bind at the upper portion of this channel specifically at a region near TYR385 and ARG120. Acidic NSAIDs, for instance, interact with ARG120 via hydrophobic and electrostatic forces [32].

While aspirin for instance irreversibly inhibits the COX enzyme by covalently modifying it active Ser529 [10], other NSAIDs such as ibuprofen and naproxen bind reversibly [33]. Studies by Kurumbail et al. [34] revealed a COX-2 3D structure closely resembling COX-1. An extra pocket in the COX-2 catalytic site, however, is created by the valine replacements at positions 523 and 434 (occupied by isoleucine in COX-1). This alteration in structure, among others, is exploited in the design of COX-2 selective drugs.

2.4. H_2S-releasing derivatives of anti-inflammatory drugs

NSAIDs, including selective COX-2 inhibitors, are able to stimulate adherence of leukocytes to the vascular endothelium in the mesenteric circulations [35–38] and that has been strongly associated with NSAID-induced gastric damage [37–39]. With studies pointing to the ability of H_2S donors to suppress leukocyte adherence, it would have been expected that an H_2S-releasing NSAID would not induce leukocyte adherence and will be devoid of the gastric damaging property of NSAIDs. This is actually the case and was realized with studies conducted employing H_2S-releasing derivative of diclofenac (ATB-337) on leukocyte adherence and gastric mucosal integrity in rat [40]. The diclofenac derivative did not stimulate leukocyte adherence and also not elevate lymphocyte function-associated antigen 1 (LFA-1) or intercellular adhesion molecule 1 (ICAM-1), as was observed in diclofenac; also, it did not cause gastric damage [41]. The H_2S-releasing diclofenac, however, did not significantly inhibit gastric prostaglandin synthesis and systemic COX-1 activity [40]. Similar profile in activity was also observed in the H_2S-releasing derivative of indomethacin (ATB-343).

H_2S-releasing derivatives of NSAIDs have also been established to reduce infiltration of leukocytes in models of inflammation. A diclofenac derivative has been shown to reduce

LPS-induced infiltration of neutrophils into the lung and liver [41]; also an H_2S-releasing derivative of mesalamine profoundly reduced granulocyte infiltration in a mouse model of colitis [42] with effect significantly greater than that observed in the parent molecules in each case. H_2S-releasing diclofenac was also realized to be more potent than diclofenac in reducing paw edema in the carrageenan-induced paw edema model in rat.

The upregulation in TNF-α and COX-2 expression in the rat stomach [43, 44] by NSAIDs is not observed in the H_2S-releasing derivatives of NSAIDs despite their ability to cause marked suppression of gastric prostaglandin synthesis [40]. Moreover, these derivatives inhibit endotoxin-induced NF-κB activation and the associated increase in plasma TNF-α, nitrate, and nitrite [41].

2.5. Antitumor action of NSAIDs

NSAIDs have many effects that might contribute to chemoprevention of cancers such as colorectal cancer (CRC). This mode of prevention can be either COX-dependent or COX-independent which can be synergistic at different steps of this multistep process [45] with evidence for replacement of adenomatous polyposis coli (APC) function by NSAIDs. In this direction, sulindac and indomethacin have been shown to inhibit tumorigenesis through inhibition of peroxisome proliferator-activated receptor delta (PPARδ), a gene that is normally regulated by APC [46]. Currently, alterations of the COX-2-related pathways are in primary focus [47].

With NSAIDs being transcriptional inhibitors of COX-2 expression [48], these agents might selectively inhibit the induction of apoptosis in human intestinal stem cells with aberrant Wnt signaling [49]. The most compelling evidence of the possible chemopreventive action of some NSAIDs was the finding that aspirin reduces the risk of CRC in individuals with elevated COX-2 expression but not in those without [50] with associated reduced mortality [51], in an observational study. This was however experimentally confirmed when data affirmed the involvement of prostaglandins and nonprostaglandin COX-2 products were central to the development of CRC [52].

Measurable levels of NSAID-activated gene-1 (NAG-1) were detected in an NSAID-treated human CRC cell line. NAG-1 belongs to the transforming growth factor beta (TGFβ)-superfamily of growth factors and plays a significant role in apoptosis and tumorigenesis. In the CRC cells, NAG-1 expression positively correlates apoptosis and inversely correlates with COX-2 expression, with NAG-1 upregulation linked with NSAID administration in a Prostaglandin-independent manner [53]. Overexpression of NAG-1 in APC-mutated Min/+ mice results in reduced tumorigenesis. Interestingly, however, high COX-2 expression in colorectal tumors is associated with decreased expression of NAG-1, suggesting a reciprocal relationship [54]. It is henceforth being speculated that high levels of COX-2 in colorectal tumors suppress the expression of NAG-1; hence induction of NAG-1 by NSAIDs might contribute to the chemopreventive action of these agents [55].

Aspirin has a unique property of acetylating COX-2, which is not seen in other NSAIDs. This switches COX-2 from synthesizing prostaglandins (PGE_2) (tumor promotion) to antitumorigenic 15-epi-lipoxin-A_4 (LXA_4), a 5-lipoxygenase catalyzed reaction. 15-epi-lipoxin-A_4 is

anti-inflammatory as well as anti-proliferative on carcinoma cells [56]. This effect of aspirin is seen at low antiplatelet doses with one study with 75 mg/day for 10 days not only reducing PGE_2 formation and white cell accumulation in inflamed tissues but also significantly increasing local lipoxin production [57]. This establishes that the anticancer potential of aspirin may be due to lipoxin production.

Several studies also point to COX-2 independent actions may also play a role in apoptosis and such pathways have been realized to be sensitive to NSAIDs. Not all human CRCs express COX-2 and produce prostaglandins [58, 59]. However, the potency of NSAIDs to inhibit proliferation is similar to COX-2 producing CRC [60]. This is suggestive of the fact that the antitumor actions of NSAIDs are not necessarily via inhibition of COX-2 or prostaglandin formation [45, 59]. Sulindac reduces the number of aberrant crypt foci and adenomas in patients under conditions when etodolac, COX-2 inhibitor, was ineffective [61]. Moreover, sulindac was also found to significantly increase NAG-1 even in COX-2-deficient tumor cell lines [53].

The potential COX-2-independent mechanism of NSAIDs' antineoplastic action includes downregulation of proto-oncogenes, such as *c-myc*, and transcriptional factors such as PPARδ, NF-κB, prostate apoptosis response-4 (PAR-4), and *Bcl-2*. The most recent therapeutic approach therefore entails combining NSAIDs and epidermal growth factor (EGF) receptor inhibitors in chemoprevention of CRC [62].

3. Conclusion

The therapeutic importance of NSAIDs in the management of acute and chronic pain and inflammation cannot be overemphasized. Also with the emergence of their therapeutic benefits in cancers, it is worth chronicling its pharmacological profile, specifically their established and expected mechanistic pathways of eliciting their activity. With promising outcomes in the experimental studies with improved gastrointestinal effects associated with modified NSAIDs and potential anticancer activity of NSAIDs, we strongly believe there is more to NSAIDs than we currently know. This chapter will henceforth give an insight into what is known and what could be possibly done in advancing the therapeutic potentials of NSAIDs beyond the management of pain and inflammation as we know.

Author details

Newman Osafo[1]*, Christian Agyare[2], David Darko Obiri[1] and Aaron Opoku Antwi[1]

*Address all correspondence to: nosafo.pharm@knust.edu.gh

1 Department of Pharmacology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

2 Department of Pharmaceutics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

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