20 Pharmacologic Effects of NSAIDs and Implications for the Risks and Benefits of Long-Term Prophylactic Use of Aspirin to Prevent Cancer

Michael J. Thun and Bonny Blackard

Abstract This paper briefly reviews the pharmacologic effects of nonsteroidal antiinflammatory drugs (NSAIDs) that influence the risks and benefits of using these drugs prophylactically for cancer. It describes the metabolism of arachidonic acid through the cyclooxygenase (COX) pathway, the physiologic functions of prostanoids (prostaglandins, prostacyclin, and thromboxane A_2) produced by this pathway, and the pharmacologic consequences of blocking the enzymatic activity of the two COX isoforms. We mention other proposed mechanisms by which NSAIDs may directly or indirectly affect non-COX pathways. The diverse pharmacologic effects of NSAIDs, when combined with the relatively low probability that an individual with average risk will develop any single type of cancer over a lifetime, severely limit the tolerance for toxicity if aspirin or related drugs are to be administered prophylactically to large numbers of otherwise healthy people. Further research is needed to identify a drug, dose, treatment regimen, and patient population(s) where the benefits of prophy- lactic treatment will exceed the risks. A singular advantage of aspirin over all other NSAIDs is the potential to combine reduced risk of certain cancers with cardiovascular benefit. However, many elements that are needed to achieve this remain unresolved.

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20.1 Introduction

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are a chemically diverse group of compounds that share the ability to block the metabolism of arachidonic acid through the cyclooxygenase (COX) pathway. Their pharmacologic effects are thought to derive principally from decreased formation of downstream tissue-specific signaling lipids produced by this pathway. These compounds, collectively called prostanoids, include prostaglandins, prostacyclin, and thromboxane A_2 (Fig. 20.1) [1]. They differ from systemic hormones in that they are not stored in tissues but are produced on demand, act locally in the tissue of origin (autocrine)

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and/or adjoining tissues (paracrine), and are then rapidly inactivated in the systemic circulation.

Biosynthesis of prostanoids begins with arachidonic acid (AA), which is normally bound to phospholipids in the cell membrane but is released by phospholipases (principally A_2) in response to inflammatory or other stimuli (Fig. 20.1) [1]. Free AA can be metabolized by several pathways (Fig. 20.1). Only metabolism through the COX pathway leads to the production of prostanoids, and only the inhibition of COX activity has unequivocally been proved to result from therapeutic concentrations of NSAIDs. Alternative pathways for AA metabolism include the lipoxygenase (LOX) pathway [which generates leukotrienes, lipoxins, and hydroxyeicosatetraenoic acid (HETE) compounds], metabolism by various cytochrome P450 enzymes, and nonenzymatic degradation by free radicals to isoprostanes (Fig. 20.1). Even though NSAIDs may not affect these alternative pathways directly, they do increase the availabil-

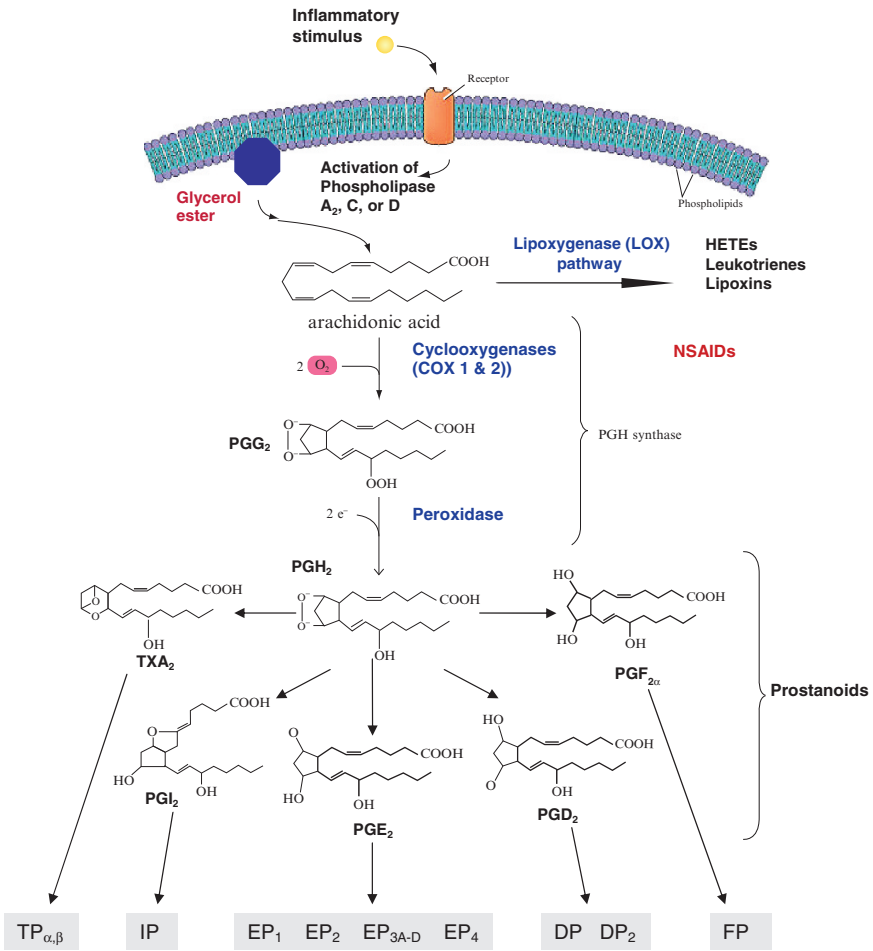

Fig. 20.1 Metabolism of arachidonic acid through the COX pathway (modified from [1]). Membrane-bound receptors shown in *gray boxes at bottom* transduce different effects in different tissues

ity of AA substrate by blocking its metabolism through the COX pathway.

The biologic effects of prostanoids differ markedly in different tissues, both because tissue-specific isomerases affect the end product, and because there are multiple membrane-bound receptors that transduce different effects [1]. For example: thromboxane A_2 (TXA_2) promotes the aggregation of platelets, vasoconstriction, and other factors involved in hemostasis; prostacyclin (PGI_2) in vascular endothelial cells causes vasodilatation and inhibits platelet aggregation; prostaglandin E_2 (PGE_2) in gastric epithelium helps to protect the gastric mucosa against acid, whereas PGE_2 in inflammatory tissues depresses the humoral immune response and can promote inflammation, wound healing, and neoplasia. Given these diverse physiologic functions, it is not surprising that blockade of the COX pathway by NSAIDs results in complex and often conflicting pharmacologic effects that can be can be therapeutic, toxic, or both depending upon the treatment regimen and patient characteristics.

The defining pharmacologic effect of NSAIDs is their ability to inhibit the first step of the COX pathway by blocking the activity of the prostaglandin G/H synthases, commonly known as cyclooxygenases [2]. There are at least two isoforms of this enzyme. COX-1 is expressed constitutively in most cells of the body where its products maintain many of the housekeeping functions described above. A second isoform, COX-2, discovered in 1992, is induced in many tissues in response to inflammation, wound healing, and neoplasia. The functions of COX-2 can be perceived as detrimental in the context of chronic inflammation, but beneficial in vascular endothelium where the isoform is expressed constitutively and is the major source of PGI_2.

The diverse chemical structures of NSAIDs are shown in Figs. 20.2 and 20.3. The so-called traditional NSAIDs (tNSAIDs), depicted in Fig. 20.2, nonselectively block both COX-1 and COX-2, especially at high doses. Aspirin is the oldest and best known of the tNSAIDs. At low doses (<100 mg), aspirin selectively inhibits COX-1 in platelets, whereas at higher, antiinflammatory doses, aspirin and other tNSAIDs inhibit both COX-1 and COX-2. Aspirin is the only NSAID that binds covalently (irreversibly) to COX-1 and permanently inhibits platelet aggregation for the life of the platelet. The widely used analgesic acetaminophen is not classified as an NSAID because it has not been demonstrated to inhibit COX-1 or COX-2.

The structures of a number of newer drugs, collectively called coxibs, are shown in Fig. 20.3. These compounds were developed to be selective inhibitors of COX-2, with the goal of sparing COX-1 and thereby minimizing gastrointestinal toxicity. Rofecoxib proved to be the most potent and selective inhibitor of COX-2 among the currently available Coxibs. It was withdrawn from the market because of unanticipated cardiovascular toxicity.

The pharmacologic consequences of blocking the COX pathway are complex and depend on the dose and treatment regimen as well as on the specific NSAID. For example, low-dose aspirin (<100 mg daily) has no antiinflammatory effects but irreversibly inhibits COX-1 production of thromboxane A_2 in platelets, thereby decreasing the risk of thrombotic cardiovascular events but increasing the risk of bleeding. Antiinflammatory doses of nearly all NSAIDs reduce the pain, swelling, redness and fever that are hallmarks of inflammation, but also cause gastrointestinal irritation, bleeding, and, particularly at older ages, renal dysfunction.

The anticancer effects of NSAIDs appear to be mediated in experimental models by the restoration of apoptosis, induction of cell cycle arrest, inhibition of proliferation, and inhibition of angiogenesis. There is no scientific consensus about the underlying mechanism(s), however, and it remains unclear whether these effects are caused predominantly by modulation of prostanoids, by factors outside the COX pathway, or by some combination of the two. Supra-physiologic concentrations of aspirin have been reported to

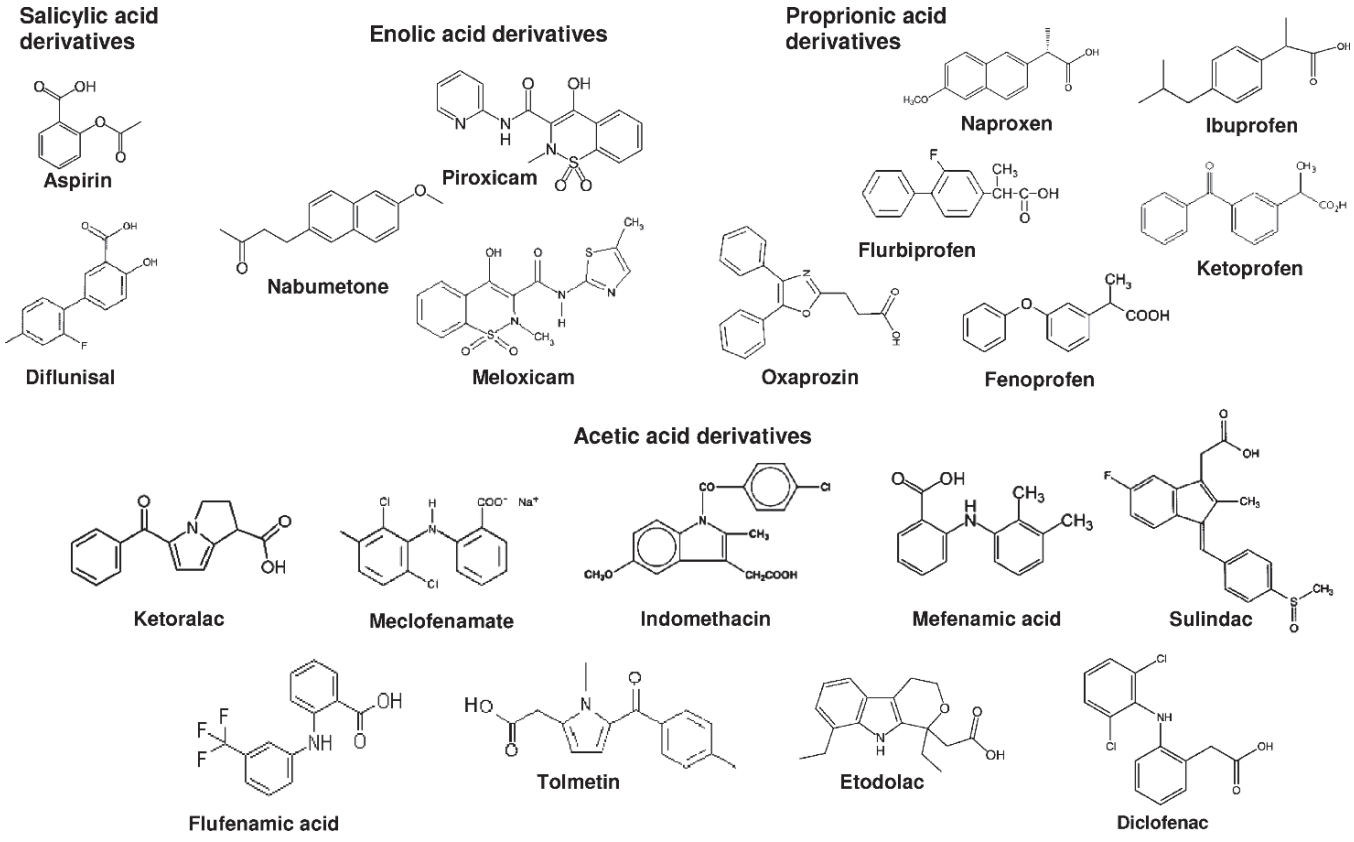

Fig. 20.2 Chemical structures of traditional NSAIDs (tNSAIDs)

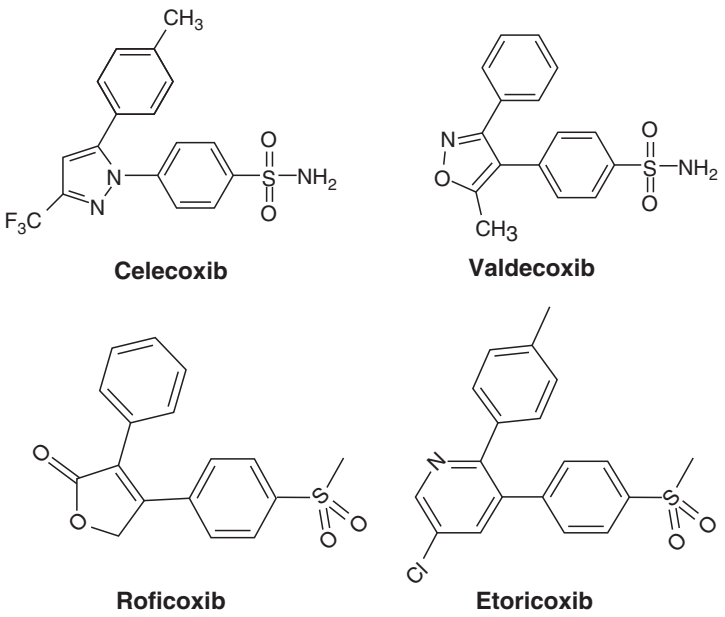

Fig. 20.3 Chemical structures of selective COX-2 inhibitors

induce apoptosis through COX-independent mechanisms that involve 15-LOX-1 [3] and genes that are both pro- and antiapoptotic (*PAR-4* and *Bcl-XL* respectively) [4, 5]. Chan and others have proposed that the tumor-suppressive effects of NSAIDs are attributable not to the reduction in prostaglandins but to increased levels of arachidonic acid stimulating apoptosis through production of ceramide [6]. Others propose that NSAIDs may induce apoptosis by the activation of caspases [7], p38 MAP kinase [8], or the release of mitochondrial cytochrome c [9].

20.2 Risk–Benefit Considerations

Drug toxicity poses a serious challenge to the development of "safe" and effective interventions to prevent cancer. "Safety" in this context signifies that the net benefits exceed the net risks, not that the intervention is without risk. Constraints from toxicity are greatest when interventions to prevent a specific type of cancer are applied to the general population, and large numbers of otherwise healthy people must be treated for many years to prevent this endpoint from occurring in a small fraction of those treated. For example, only 6% of the United States population, on average, will be diagnosed with colorectal cancer over a lifetime. The benefits of aspirin to prevent colon cancer are offset by the increase in side effects due to bleeding. However, several strategies can be pursued to shift the balance of risks and benefits from prophylactic treatment with aspirin. These include finding the least toxic treatment regimen, documenting other common cancers besides colon cancer that can be prevented, and selecting patient populations for whom the benefits of treatment will outweigh the risks.

Aspirin has a singular advantage over other NSAIDs in that it is the only COX inhibitor that

has been shown to be highly effective at reducing the risk of thrombotic cardiovascular events, even at very low doses. The development of low-dose aspirin as the optimal antiplatelet therapy takes advantage of several unique characteristics of aspirin and platelets. Aspirin is the only NSAID that binds irreversibly to COX-1 in platelets; platelets migrate through the portal circulation where the concentration of salicylic acid is higher than in the systemic circulation; and platelets lack a nucleus and cannot regenerate active enzyme. In contrast to aspirin, rofecoxib and other potent selective COX-2 inhibitors increase cardiovascular risk, effectively precluding their use for cancer prevention.

It is admittedly more difficult to determine the lowest effective dose of aspirin for cancer prevention without a better understanding of the specific target tissue(s) and mechanisms that mediate these effects. However, it would be possible to conduct longer-term clinical trials to determine whether aspirin at various doses (80 mg or 325 mg) inhibit the development of common cancers (particularly colorectal, breast, and prostate). Future trials should test daily administration of aspirin, rather than every other day, since daily treatment is optimal to inhibit platelet aggregation and matches the current clinical recommendation for the prevention of heart disease.

It may also be possible to broaden the potential benefits of long-term prophylactic treatment with aspirin if intervention can be shown to decrease the risk of breast and prostate cancer as well as colorectal cancer. Whereas the benefits of preventing colorectal cancer with aspirin treatment are counterbalanced by the side effects of gastrointestinal bleeding and hemorrhagic stroke, this would not be the case if other common cancers were also inhibited. Even if a higher dose of aspirin were needed to accomplish this, the net effect might be favorable, since the absolute risk of bleeding increases only slightly across the range from a baby aspirin (80 mg) daily to an adult aspirin (325 mg) daily.

20.3 Conclusions

Prophylactic treatment with aspirin continues to have promise for the prevention of colorectal and perhaps other cancers. Major gaps in the evidence, however, currently preclude any clinical recommendation. Additional research is needed to identify the specific dose, treatment regimen, and patient population(s) where the benefits of prophylactic treatment will exceed the risks.

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