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Review

Cyclooxygenase inhibitors: From pharmacology to clinical read-outs ☆

Paola Patrignani [a], Carlo Patrono [b,*]

[a] Center of Excellence on Aging and Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University, Chieti, Italy
[b] Department of Pharmacology, Catholic University School of Medicine, Rome, Italy

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ABSTRACT

Acetylsalicylic acid (aspirin) is a prototypic cyclooxygenase (COX) inhibitor. It was synthesized serendipitously from a natural compound, *i.e.*, salicylic acid, with known analgesic activity. This chemical modification, obtained for the first time in an industrial environment in 1897, endowed aspirin with the unique capacity of acetylating and inactivating permanently COX-isozymes. Traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) were developed to mimic the pharmacological effects of aspirin, using aspirin-sensitive experimental models of pain and inflammation as the template for screening new chemical entities. Among the tNSAIDs, some were endowed with moderate COX- selectivity (*e.g.*, diclofenac), but no studies of sufficient size and duration were performed to show any clinically relevant difference between different members of the class. Similarly, no serious attempts were made to unravel the mechanisms involved in the shared therapeutic and toxic effects of tNSAIDs until the discovery of COX-2. This led to characterizing their main therapeutic effects as being COX-2-dependent and their gastrointestinal (GI) toxicity as being COX-1-dependent, and provided a rationale for developing a new class of selective COX-2 inhibitors, the coxibs. This review will discuss the clinical pharmacology of tNSAIDs and coxibs, and the clinical read-outs of COX-isozyme inhibition. This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance."

1. Introduction

Acetylsalicylic acid (aspirin) (Fig. 1) is a prototypic cyclooxygenase (COX) inhibitor. It was synthesized serendipitously from a natural compound, *i.e.*, salicylic acid, with known analgesic activity. This chemical modification, obtained for the first time in an industrial environment in 1897, endowed aspirin with the unique capacity of acetylating and inactivating permanently COX-isozymes [1]. Traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) were developed to mimic the pharmacological effects of aspirin, using aspirin-sensitive experimental models of pain and inflammation as the template for screening new chemical entities. The chemical structures of major NSAIDs are shown in Fig. 1. Among the tNSAIDs, some were endowed with moderate COX-2 selectivity (*e.g.*, diclofenac), but no studies of sufficient size and duration were performed to show any clinically relevant difference between different members of the class [2]. Similarly, no serious attempts were made to unravel the mechanisms involved in the shared therapeutic and toxic effects of tNSAIDs until the discovery of COX-2 [3]. This led to characterizing their main therapeutic effects as being COX-2-dependent and their gastrointestinal (GI) toxicity as being COX-1-dependent, and provided a rationale for developing a new class of selective COX-2 inhibitors, the coxibs [3].

Except for a well known effect of NSAIDs (including coxibs) on blood pressure control, no cardiovascular safety issue had been raised until 1999, when the COX-2-dependence of prostacyclin (PGI_2) biosynthesis in humans was first reported [4]. Until then, practicing physicians had not been concerned about any potential increase in cardiovascular risk associated with tNSAIDs because it was widely assumed that these drugs would mimic the antithrombotic effect of aspirin [5] through a COX-1-dependent antiplatelet effect.

At the same time, there was some interesting observational evidence that both aspirin and tNSAIDs might protect against some cancers, particularly of the lower GI tract [6].

All we knew about the safety of tNSAIDs was largely derived from observational studies that perhaps overemphasized the burden of GI toxicity of these agents [7]. The real turning point of our understanding of NSAID safety was represented by: i) the large GI outcome trials of coxibs in the post-marketing phase of their development [8,9]; ii) the

Abbreviations: 2-AG, 2-arachidonoyl-glycerol; 5′UTR, untranslated region; AP-1, activator protein 1; AA, arachidonic acid; AEA, arachidonoyl-ethanolamide; ARE, AU-rich element; C/EBP, CCAAT-enhancer-binding protein; CRC, colorectal cancer; CREs, cAMP-response elements; COX, cyclooxygenase; c, cytosolic; PGES, PGE synthase; GI, gastrointestinal; GPCRs, G-protein coupled receptors; HuR, human antigen R; KD, knock-down; KO, knock-out; miRNAs, microRNAs; NF-IL6, nuclear factor for interleukin-6; NF-κB, nuclear factor κB; OA, osteoarthritis; OTC, over-the-counter; PD, pharmacodynamic; PK, pharmacokinetic; PL, phospholipases; PGI2, prostacyclin; PG, prostaglandin; RCTs, randomized clinical trials; RA, rheumatoid arthritis; TCF4, transcription factor 4; TX, thromboxane; tNSAIDs, traditional nonsteroidal anti-inflammatory drugs; UGIB, upper GI bleeding

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* Corresponding author at: Istituto di Farmacologia, Università Cattolica del S. Cuore, Largo Francesco Vito, 1, 00168 Rome, Italy. Tel.: +39 06 30154253; fax: +39 06 3050159.
E-mail address: carlo.patrono@rm.unicatt.it (C. Patrono).

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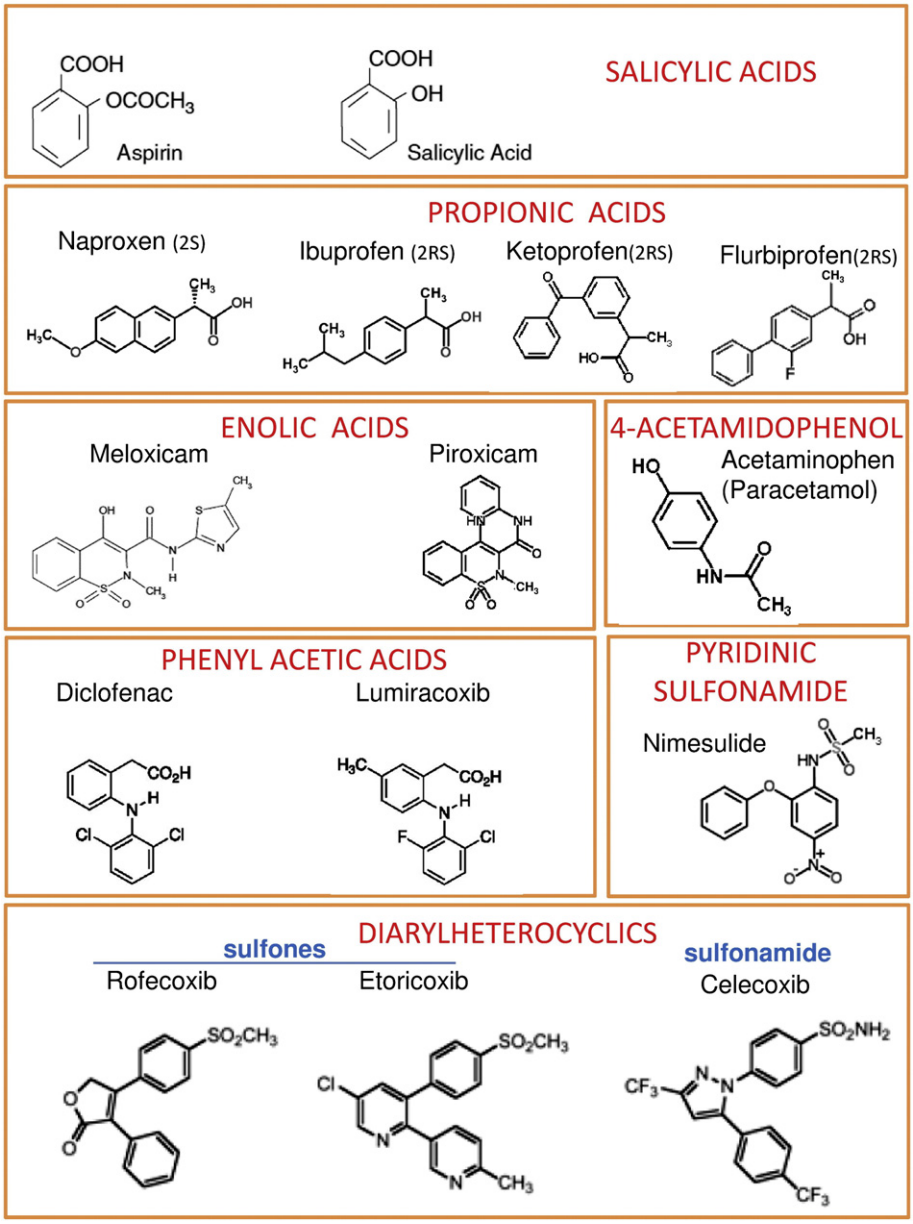

Fig. 1. Chemical structures of NSAIDs. The drugs are grouped on the basis of their chemical features. Ibuprofen, like other 2-arylpropionate derivatives (including ketoprofen, flurbiprofen, naproxen), contains a chiral carbon in the α-position of the propionate moiety. As such, there are two possible enantiomers (R) and (S). Except naproxen clinically used as (S) enantiomer, the other propionic acid-derivatives are used clinically as racemic agents.

long-term, placebo-controlled trials of celecoxib [10] and rofecoxib [11] for chemoprevention of sporadic colorectal adenoma recurrence; and iii) meta-analyses of all the randomized coxib and tNSAID trials [12,13].

2. Mechanism of action

NSAIDs act by inhibiting the biosynthesis of prostanoids [14], a family of bioactive lipids [*i.e.* prostaglandin (PG)E_2, $PGF_{2\alpha}$, PGD_2, PGI_2 and thromboxane (TX)A_2], which interact with specific cell-membrane receptors of the superfamily of G-protein coupled receptors (GPCRs), and play important roles in many cellular responses and pathophysiologic processes, such as modulation of the inflammatory reaction and its resolution, erosion of cartilage and juxtaarticular bone, GI cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics and progression of kidney disease, atheroprotection and progression of atherosclerosis [15,16].

Prostanoids are autacoids which act in an autocrine and paracrine manner [15]. Their functional responses are orchestrated by the level and type of the specific prostanoid receptor(s) expressed on cells/tissues [17–19]. The prostanoid receptor family consists of eight rhodopsin-like (class A) GPCRs each being the product of an individual gene: DP1 (for PGD_2), EP1, EP2, EP3 and EP4 (for PGE_2), FP (for $PGF_{2\alpha}$), IP (for PGI_2) and TP (for TXA_2). DP1, EP2, EP4 and IP receptors are classically associated with elevation of intracellular cyclic adenosine monophosphate (cAMP) levels through activation of Gs proteins; EP1, FP and TP receptors induce elevation of intracellular calcium through Gq, and EP3 causes the reduction of intracellular cAMP levels through Gi. Moreover, splice variants have been identified for EP1, EP3 and TP which couple with different G proteins [17,20]. A ninth prostanoid receptor named CRTH2 or DP2, belonging to the GPCR family A, was also identified [21]. PGD_2 is its natural ligand but the receptor shows higher sequence homology with other leukocyte chemoattractant receptors than prostanoid receptors [22]. It is coupled *via* pertussis-toxin sensitive