Chemistry, Pharmacodynamics, and Pharmacokinetics of NSAIDs

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a heterogeneous group of drugs used to treat inflammation, pain, and fever. Despite substantial differences in their chemical structure, they present a common mechanism of action consisting of the inhibition of the enzymes responsible for prostanoid synthesis, namely, cyclooxygenases (COX). However, since they are so heterogeneous, they exert other actions that can condition their therapeutic value.

Chemistry

NSAIDs are organized in subgroups according to their parental chemical structure (Table 1.1, Fig. 1.1). Most are organic acids with relatively low p*K*a (Table 1.2), and this acidic nature influences their pharmacodynamic and pharmacokinetic profiles (see below). The exceptions to this rule are paracetamol and pyrazolic derivatives (metamizole, propyphenazone), which are often excluded from the NSAID group because of their low anti-inflammatory activity, and also the diaryl heterocyclic compounds (coxibs).

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Pharmacodynamics

The therapeutic effects of NSAIDs are mediated chiefly through the inhibition of prostaglandin synthesis. Prostanoids are formed enzymatically through prostaglandin–endoperoxide synthases 1 and 2 (PGHS-1 and PGHS-2), which are also known as cyclooxygenases 1 and 2 (COX-1 and COX-2). PGHSs catalyze two different reactions at two sites that are physically distinct but functionally linked. The cyclooxygenase reaction provokes a bisoxygenation of arachidonic acid to generate prostaglandin G2 (PGG2), which is then transformed into PGH2 through a peroxidase reaction. These unstable intermediates are quickly transformed into different prostaglandins, prostacyclins, and thromboxanes by specific synthases. A major limiting factor of prostanoid formation is the availability of the substrate arachidonic acid, and this constraint usually determines a low rate of basal prostanoid formation. However, this synthetic pathway is greatly enhanced when phospholipase A2 is activated to release arachidonic acid from phospholipids (Fig. 1.2).

This arachidonic acid cascade is of great importance in inflammation, pain, and fever. Prostanoid synthesis is significantly elevated in inflamed tissues, where PGE2 and prostacyclin (PGI2) contribute to this response by increasing local blood flow, vascular permeability, and leukocyte infiltration [1–3]. These prostanoids also

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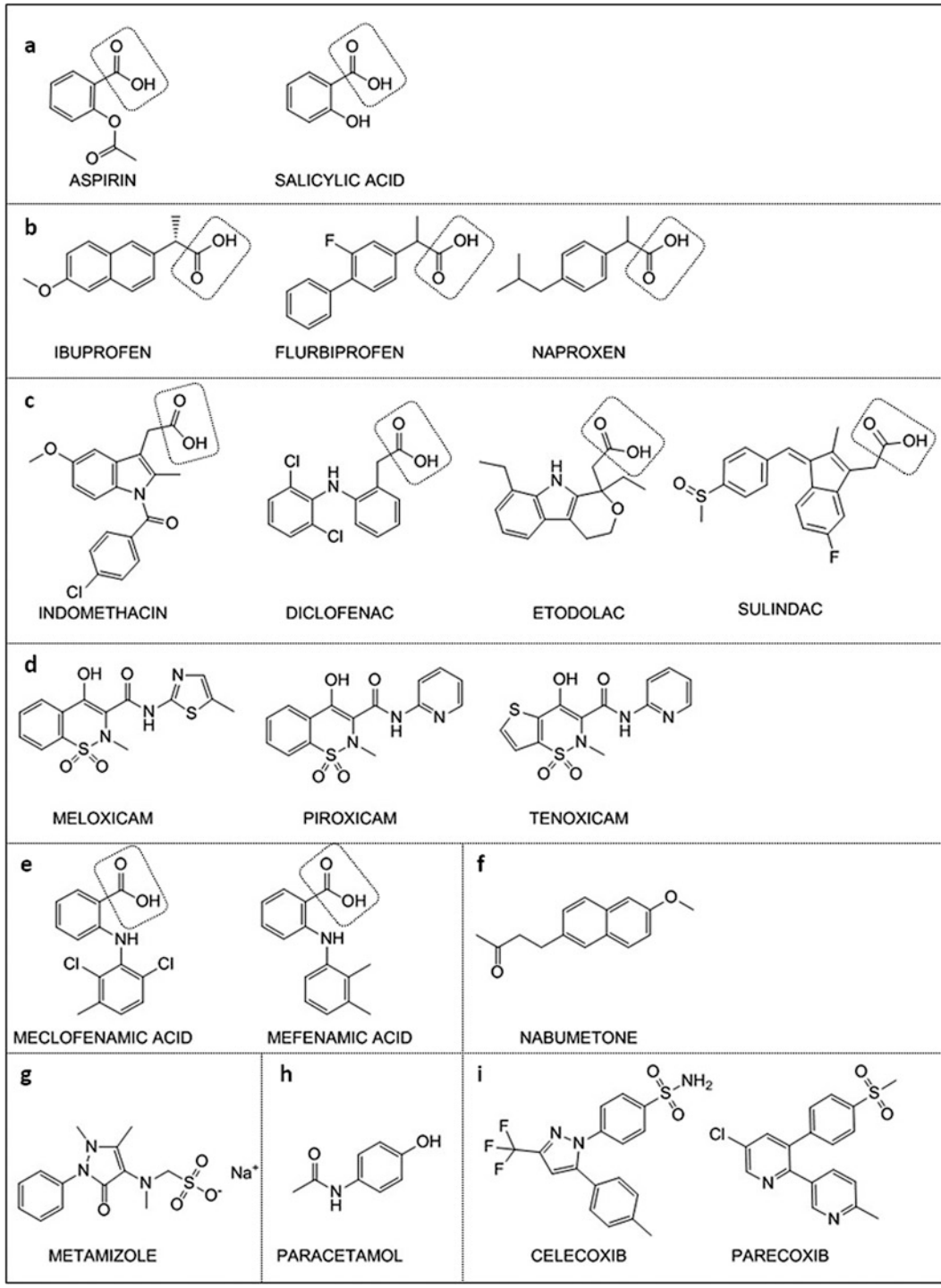

Fig. 1.1 Chemical structures of some NSAIDs including representative salicylates (**a**), propionates (**b**), acetic acid derivatives (**c**), enolic acid derivatives (oxicams) (**d**), fenamates (**e**), nabumetone (**f**), metamizole (or dipyrone) (**g**), paracetamol (or acetaminophen) (**h**), and diaryl heterocyclic compounds (coxibs) (I). Note the general presence of a carboxylic acid moiety in groups (**a–c**, **e**; *dashed rectangle*). It is also present in the nabumetone active metabolite (not represented)

Table 1.1 Classification of NSAIDs according to their parental chemical structure

Derivatives of	
Salicylic acid	Aspirin
	Diflunisal
Propionic acid	Ibuprofen
	Flurbiprofen
	Ketoprofen
	Naproxen
Acetic acid	Indomethacin
	Diclofenac
	Aceclofenac
	Etodolac
	Ketorolac
Enolic acid	Piroxicam
	Tenoxicam
	Meloxicam
	Lornoxicam
	Phenylbutazone
Fenamic acid	Mefenamic acid
	Meclofenamic acid
Alkanones	Nabumetone
Para-aminophenol	Acetaminophen or paracetamol
Pyrazole	Metamizole or dipyrone
	Propyphenazone
Diaryl heterocyclic compounds	Celecoxib
	Valdecoxib
	Rofecoxib
	Etoricoxib

Table 1.2 Values of p*K*a and logP of several NSAIDs

Drug	p*K*a	logP
Aspirin	3.49	1.19
Meloxicam	4.08	3.43
Diclofenac	4.15	4.51
Naproxen	4.15	3.18
Mefenamic acid	4.20	5.12
Parecoxib	4.24	3.51
Flurbiprofen	4.42	4.16
Indomethacin	4.50	4.27
Ketoprofen	4.45	3.12
Etodolac	4.65	2.50
Sulindac	4.70	3.42
Ibuprofen	4.91	3.97
Piroxicam	6.30	3.06
Paracetamol	9.38	0.46
Valdecoxib	10.06	2.82
Celecoxib	10.70	4.01

p*K*a: acid dissociation constant (values $\underline{1/\alpha}$ acidity); logP: octanol–water partition coefficient (values $\underline{\alpha}$ hydrophobicity) (Data obtained from PubChem and DrugBank)

cause peripheral sensitization by reducing the threshold of peripheral nociceptors, while PGE2 and other prostaglandins induce central nociceptive sensitization at the spinal dorsal horn neurons [4, 5]. Finally, PGE2 acts at the hypothalamus to increase body temperature by increasing heat production and reducing heat loss [1, 6]. Likewise, inhibition of prostanoid synthesis by NSAIDs is responsible for undesired side effects such as gastrointestinal and renal toxicities, since prostanoids are physiological regulators of gastrointestinal mucosal defense and renal homeostasis.

A key event in the evolution of this pharmacological group was the discovery and characterization of COX-2 [7–9] (Fig. 1.3). Unlike COX-1, which is constitutively expressed in most cells and responsible for many of the housekeeping functions mediated by prostanoids, COX-2 is expressed constitutively in a small number of tissues. However, it is induced in response to an extremely wide range of agonists that include cytokines and tumor promoters, which endows this isoenzyme with a significant role in inflammation and perhaps also in cancer. This paradigm has motivated an avid search for drugs capable of inhibiting "pathological" COX-2 activity while preserving the "physiological" COX-1 function [10]. However, later evidence has argued in favor of a mixed pattern in which both isoenzymes are involved in homeostasis and also in inflammatory processes. It seems that COX-1 activity contributes to inflammation in the early phases, until COX-2 is upregulated and takes up its role as a motor of the synthesis of pro-inflammatory prostanoids [1, 2, 11]. Both isoenzymes are also expressed in the spinal cord and mediate nociceptive stimuli [1, 12], while hyperthermia seems to depend mainly on COX-2 activity [1, 6]. On the other hand, besides the clear role of COX-1-derived prostanoids in the digestive mucosal barrier, renal homeostasis, and platelet aggregation, accumulating evidence indicates that

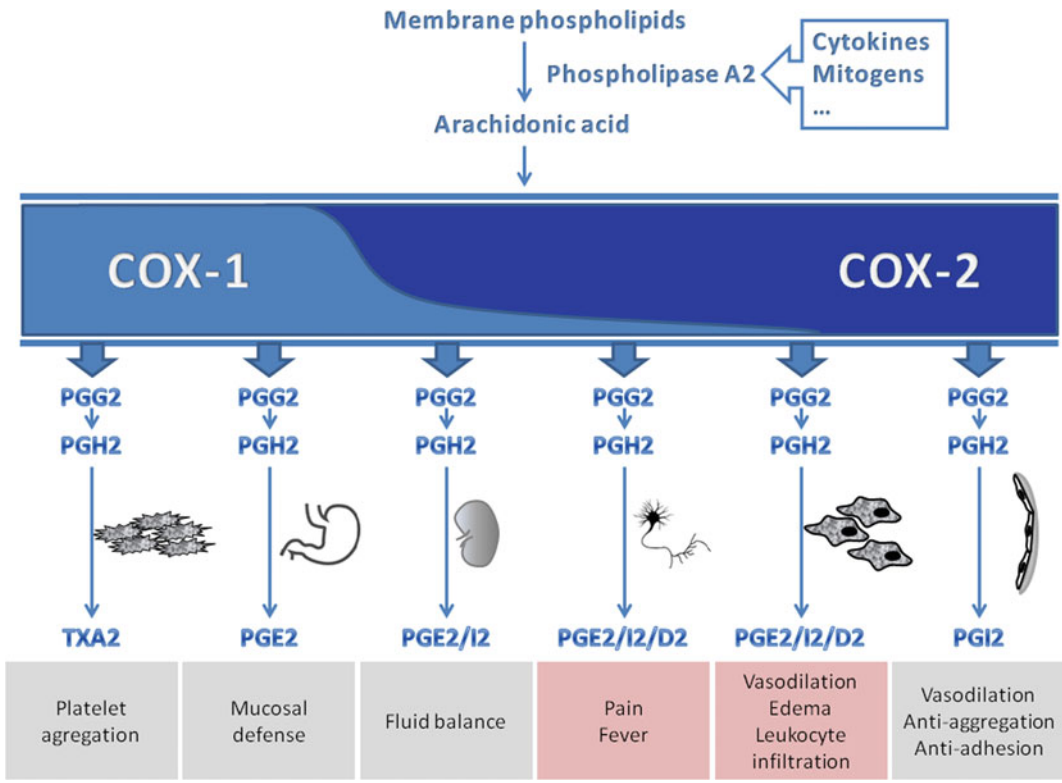

Fig. 1.2 Overview of the prostaglandin synthetic pathways with the relative contribution of COX-1 and COX-2 to different physiological and pathological functions

COX-2-dependent prostanoids formed in endothelial cells and the kidney counteract the effects of prothrombotic and atherogenic stimuli and contribute to arterial pressure homeostasis [13]. In addition to specific new COX-2 drugs, the selectivity for COX-1/COX-2 of the older NSAIDs has been reevaluated in order to understand differences in pharmacodynamic profiles and side effects.

Nonselective vs. Isoform-Specific COX Inhibitors

As previously explained, NSAIDs are usually subdivided into two classes:

- Classic or "nonselective" NSAIDs: inhibit both COX-1 and COX-2, with varied potencies on each isoenzyme
- COX-2-selective or "isoform-specific" NSAID inhibitors: designed to be more selective against COX-2

However, this classification is questionable, since COX-2 selectivity is a continuous variable rather than an absolute category, and all NSAIDs can inhibit both isoenzymes to some extent.

COX-1/COX-2 selectivity in vivo is predicted according to ex vivo assays performed in human whole blood (platelet COX-1 and macrophage COX-2) or in a combination of human whole blood and human lung cancer cells (as a consistent source of COX-2). These assays provide an estimate of potency and selectivity of inhibition of the two COX enzymes in a setting that takes into account the binding of NSAIDs to plasma proteins. Table 1.3 lists some IC80 values for several NSAIDs obtained in a broad comparative analysis using the aforementioned assay

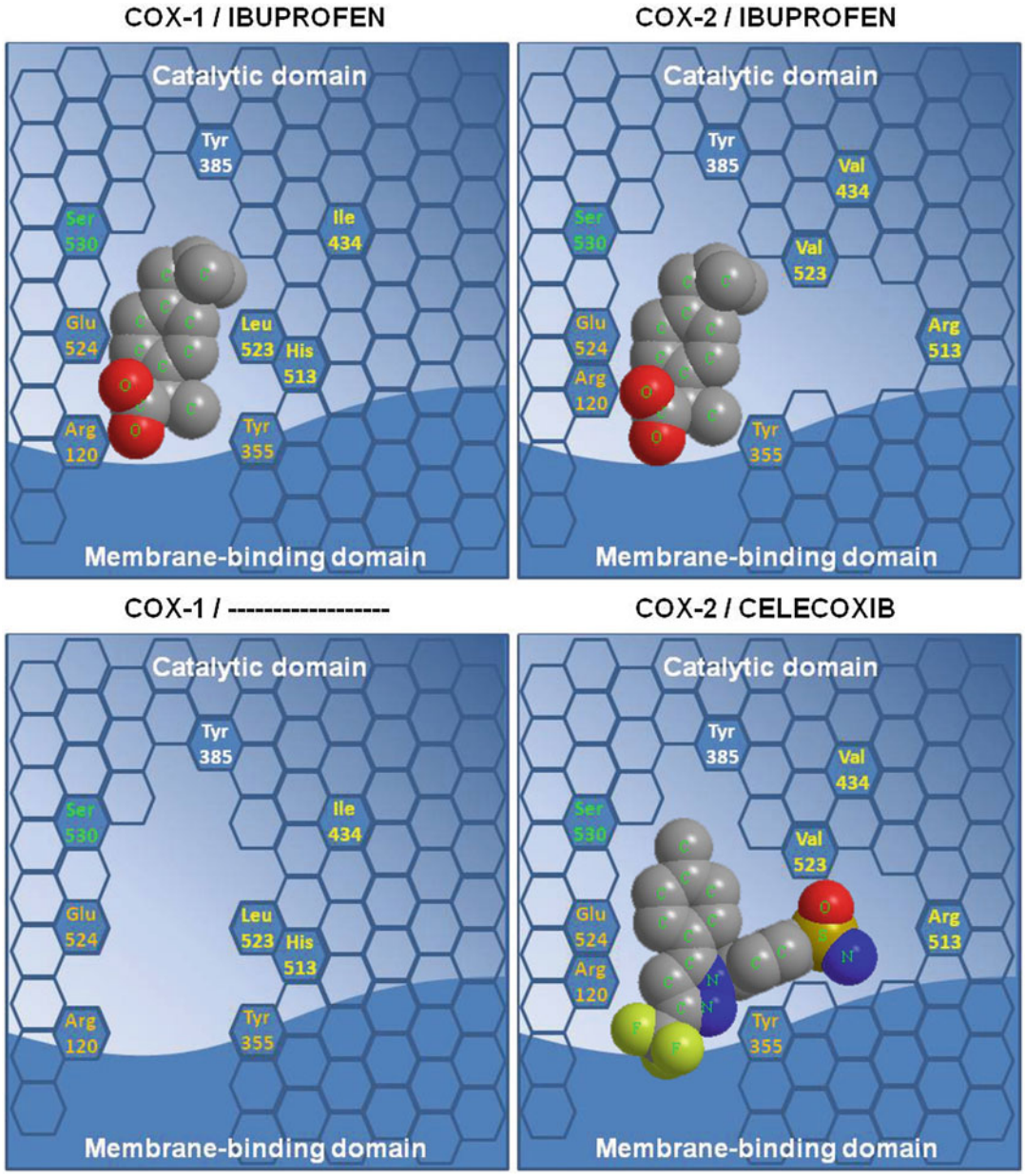

Fig. 1.3 Schematic diagram of the active site in COX-1 and COX-2 isoenzymes and the interaction with a nonselective (ibuprofen, *upper panel*) and a COX-2-selective (celecoxib, *bottom panel*) NSAID. Some key residues are shown: Arg120 stabilizes the carboxylate group that is present in most NSAIDs; Tyr385 is a highly conserved residue situated in the upper part of the largely hydrophobic binding channel that accommodates the aromatic ring structures; Leu523 in COX-1 is changed to Val523 in COX2, which allows the opening of a side pocket and accommodation of the bulkier diaryl heterocyclic compounds; His513 is changed to Arg513 in COX-2, which stabilizes the sulfonamide or methyl sulfone group of these COX-2 inhibitors by hydrogen bonding; Ile434 in COX-1 is changed to Val434 in COX-2, which allows a more stable binding of COX-2-selective inhibitors; and Ser530 is the residue that is acetylated by aspirin

Table 1.3 Ratio between the concentrations of drug inhibiting 80 % of COX-2 and COX-1 activities (IC80) determined in vitro for several NSAIDs (values >1 indicate a higher selectivity for COX-1; values <1 indicate a higher selectivity for COX-2)

Compound	IC80 ratio COX-2/COX-1
Ketorolac	294.00
Flurbiprofen	51.00
Ketoprofen	6.00
Indomethacin	4.30
Aspirin	3.80
Naproxen	3.00
Ibuprofen	2.60
Fenoprofen	1.00
Sodium salicylate	0.92
Diflunisal	0.75
Piroxicam	0.47
Meclofenamate	0.30
Sulindac sulfide	0.29
Diclofenac	0.23
Celecoxib	0.11
Meloxicam	0.09
Rofecoxib	0.05
Etodolac	0.04

Data from Warner et al. (1999) [14]

combining whole blood and cancer cells. IC80 was considered more appropriate than IC50 for comparisons, because normal plasma levels of NSAIDs are in the range of concentrations that produce 80 % inhibition of COX enzymes in this assay [14]. These numbers illustrate that some of the so-called traditional NSAIDs exert a COX-2-selective inhibition similar to that of coxibs, which are the prototypical COX-2-selective drugs. Although in vitro data varies from one study to another, a global analysis combined with information regarding therapeutic plasma levels and half-lives of the individual agents provides an estimable predictor of the pharmacodynamic and toxicodynamic effects of specific compounds.

A special case is that of paracetamol. This drug induces a redox-sensitive blockade of COX activities that is inhibited by the high extracellular concentrations of arachidonic acid and peroxide at the sites of inflammation [15, 16]. This pharmacodynamic particularity, together with the low concentrations of paracetamol observed in inflamed tissues (see below), justify its lack of anti-inflammatory activity.

Combination of structural, functional, and kinetic investigations outlines different patterns of interaction and expands the concept of COX-2 selectivity as a direct consequence of particular structural features (just a matter of size). By considering other influencing factors, such as kinetics and allosterism, the mechanisms of binding to COX-1 and COX-2 by different NSAIDs have been shown to be as impressively diverse as is explained in the following sections.

Structural Factors

COX-1 and COX-2 are dimers of 70 kDa subunits. The homodimer is membrane-bound and localized in the lumen of the endoplasmic reticulum and in the nuclear envelope. Although the global identity between COX-1 and COX-2 in a particular species involves around 60 % of the protein, cyclooxygenase active sites present a higher homology (>85 %), which limits the options available for obtaining selective interactions.

Each monomer of COX consists of three structural domains:

- A short N-terminal epidermal growth factor domain
- A membrane-binding domain
- A large, globular C-terminal catalytic domain that constitutes the major part of the COX monomer and is the site of arachidonic acid binding and transformation

As explained previously, arachidonic acid is transformed in two sequential reactions: double dioxygenation, to generate PGG2 in the cyclooxygenase active site, and the reduction of PGG2 to PGH2 at the peroxidase active site. For this reaction, the entrance to the COX active site occurs at the base of the membrane-binding domain and leads to a long hydrophobic channel that extends deep into the interior of the catalytic domain. This hydrophobic channel can be divided into the lobby and the binding site by a constriction of three residues (Arg120, Glu524, and Tyr355)

at the interface between the membrane-binding domain and the catalytic domain [17]. Most inhibitors bind in the COX active site above the constriction residues between the highly conserved residues Arg120 and Tyr385. Arg120 provides a positive charge that binds the negative charges of carboxylic acid substrates and inhibitors, serving in both isoenzymes as an anchor for acidic NSAIDs [10, 18, 19] (Fig. 1.3).

Some differences between COX-1 and COX-2 have been shown to be responsible for the selectivity of some NSAIDs for COX-2 (reviewed in [9, 10, 17]):

- The membrane-binding domain changes the last helix position and the location of Arg120 at the constriction site in COX-2. This change increases the space at the interface between the membrane-binding and catalytic domains, reduces steric and ionic crowding by Arg120, and, as a consequence, enhances the binding of nonacidic NSAIDs to COX-2.
- Above the constriction, the COX-2 active site presents spatial changes that result from changes in some amino acids (Ile523, His513, and Ile434 in COX-1 become Val523, Arg513, and Val434 in COX-2, respectively):
  - Val523 in COX-2 vs. Ile523 in COX-1 → this substitution makes accessible a small side pocket in the catalytic center of COX-2 that accommodates the sulfonamide or sulfone group of the diarylheterocycles celecoxib and rofecoxib. Mutating Val523 to an isoleucine restricts access to this side pocket, and COX-2 is no longer differentially sensitive to these inhibitors. Conversely, when Ile523 is substituted by Val523 in COX-1, this isoenzyme increases its affinity for COX-2-selective inhibitors.
  - Arg513 in COX-2 vs. His513 in COX-1 → alters the chemical environment of the side pocket by endowing it with a stable positive charge at its center. This arginine apparently interacts with polar moieties entering the pocket and contributes somewhat to the COX-2 selectivity of diarylheterocycles. In combination with the change of Ile523 to Val523, mutating His513 to an arginine in COX-1 makes this isoenzyme much more sensitive to COX-2 inhibitors.
  - Val434 in COX-2 vs. Ile434 in COX-1 → this modification in the surroundings of the COX active site allows a more stable binding of selective inhibitors to the COX-2 isoform.

Thus, despite the considerable homology between the two enzymes, this side pocket off the main active site channel, which is more accessible in COX-2 than in COX-1, makes the COX-2 active site approximately 27 % larger and allows the accommodation of bulkier NSAIDs such as diarylheterocycle derivatives. The fundamental structural factors responsible for the potent and selective inhibition of COX-2 of these drugs include (1) two adjacent aromatic rings as a central scaffold and (2) the presence of a sulfonamide or methyl sulfone group on one of the phenyl rings [10, 18].

Kinetic Factors

While all NSAIDs compete with arachidonate for the COX active site, each NSAID can inhibit COX in a time-dependent or time-independent manner, and this may be relevant for drug potency and COX-1/COX-2 selectivity. Time dependency is deduced from experiments which show that (1) the degree of COX inhibition induced by a drug depends on the period of time elapsed between addition of the inhibitor and addition of the substrate and (2) after reducing the concentration of the inhibitor, the recovery of COX activity occurs at a slow, sometimes almost undetectable, rate [20, 21]. According to this, different kinetic patterns have been observed [17, 18]:

i. Rapid and reversible binding followed by covalent modification (time-dependent)
ii. Rapid and reversible competitive inhibition (time-independent)

iii. Rapid and low-affinity competitive inhibition followed by a time-dependent transition to a high-affinity, slowly reversible, inhibitory mode
iv. A mixed pattern involving (ii) and (iii)

Among traditional NSAIDs, we can find prototypes of all kinetic patterns. The only example of the first type of inhibition is **aspirin**. This unique NSAID covalently modifies both COX-1 and COX-2 through acetylation of Ser-530 to inhibit these enzymes in a time-dependent fashion (i) [22]. Aspirin is significantly more potent against COX-1 than against COX-2, but the reason for this difference is unclear. **Ibuprofen and mefenamic acid** are examples of the second pattern (ii), causing a competitive and rapidly reversible COX inhibition through a single-step kinetic mechanism [22, 23].

Several different NSAIDs follow the third kinetic pattern (iii), although their interaction with the active site presents particularities in each case. **Indomethacin** exerts a time-dependent and functionally irreversible inhibition of COX through a two-step binding to COX enzymes. Indomethacin is recovered intact after prolonged incubation with either enzyme, suggesting that the time-dependent inhibition of COX is not caused by a covalent interaction [20, 23]. **Diclofenac's** kinetics are similar to those of indomethacin; however, it binds to the active site of COX-2 in a unique inverted binding mode different to that described for all the other NSAIDs analyzed [24]. A similar slow, tightly binding, time-dependent, functionally irreversible COX inhibition through a two-step mode is observed with **flurbiprofen** and **meclofenamic acid**, despite being structural analogues of ibuprofen and mefenamic acid, respectively [21]. With regard to COX-2-selective diarylheterocycle inhibitors, such as **rofecoxib** and **celecoxib**, a competitive, reversible kinetic with COX-1 is observed. However, with COX-2, these drugs exert an initial two-step competitive and reversible interaction that is followed by a third pseudoirreversible step leading to a tightly bound complex. This process causes a time-dependent inhibition that depends on the penetration of the sulfonamide or methylsulfonyl groups into the abovementioned side pocket. The significant differences between their kinetics on COX-1 and COX-2 seem critical to the selectivity for this isoenzyme [23, 25].

Finally, **naproxen** and some **oxicams** exhibit a "mixed" pattern of inhibition of COX (iv) that combines a quick and reversible blockade with a slow and functionally irreversible inhibition of the enzyme. This "mixed" pattern is observed with COX-2, while COX-1 blockade only presents the time-independent component [23].

A global analysis of these data suggests that tight binding/time dependency usually confers higher potency (with the exception of aspirin, which causes a covalent modification). When kinetics were analyzed in both isoenzymes, drugs exhibiting similar (e.g., ibuprofen and indomethacin) and different (naproxen, oxicams, coxibs) patterns of inactivation of COX-1 and COX-2 were identified, and in some cases this difference has an impact on their selectivity. Finally, the structural basis for time-dependent inhibition is not yet well defined and may vary for different drugs.

Allosteric Factors

Different studies suggest that cyclooxygenases exhibit enzymatic activity at a single COX active site at a given time [20, 26] and function as conformational heterodimers with an allosteric and a catalytic monomer [19]. Thus, the allosteric monomer regulates its catalytic partner by establishing a ligand-dependent cross talk between both monomers.

It was subsequently found that different fatty acids, which may or may not be COX substrates, are allosteric regulators of PGHSs and that a given fatty acid can elicit a stimulatory or inhibitory effect on arachidonic acid oxygenation depending on the COX isoform. Since nonsubstrate fatty acids such as palmitic acid bind preferentially to the allosteric subunit, they are used to determine the monomer targeted by different NSAIDs. These fatty acids interfere

with inhibitors that bind to the allosteric subunit, but have no effect on or even potentiate the actions of inhibitors that bind to the catalytic partner. By means of this kind of analysis, different patterns of NSAID binding to COX-2 heterodimers have again been observed (reviewed in Smith et al. [19]):

- Inhibitors that bind to the catalytic monomer (e.g., celecoxib, rofecoxib, indomethacin, diclofenac, or aspirin). These drugs can cause a complete inhibition by competing with the substrate for the active site in the enzyme (aspirin causes a covalent modification of this subunit).
- Inhibitors that bind to the allosteric monomer (e.g., flurbiprofen, naproxen). They induce an incomplete inhibition of COX.
- Inhibitors that bind to both monomers (e.g., ibuprofen and mefanamate). They can induce a mixed inhibition depending on the dose.

Most of these studies have been performed on COX-2; therefore, whether or not the pattern of interaction described for a particular inhibitor also applies to COX-1 is largely unknown at present.

The significance of COX allosterism remains unresolved, but, apart from its relevance in the mechanism of action of particular NSAIDs, the allosteric regulation of COX activity by common endogenous and dietary fatty acids raises the possibility that both the pathological role of COX and the pharmacological/therapeutic effects of NSAIDs are affected by circumstances that modulate the levels of these lipids (e.g., pathology, diet, etc.).

Thus, NSAIDs inhibit PG synthesis by binding to COX enzymes in many different ways, which is comprehensible considering the structural heterogeneity of this pharmacological group. However, there are still many unanswered questions regarding the mechanism of action of these drugs, even though some of them have been used for several decades (almost 120 years in the case of aspirin). This knowledge is important, as a better understanding of how both, explained and currently unknown factors, affect NSAID activity on COX isoenzymes may help in the future to develop drugs with more specific anti-inflammatory actions with less alteration of the housekeeping roles of prostanoids.

COX-Independent Actions

The significant varieties of molecular structures and pharmacological profiles observed in the NSAID group have driven the search for alternative mechanisms of action that could complement their common inhibitory activity on COX (Table 1.4). One field of research has analyzed the ability of NSAIDs to insert themselves inside the lipid bilayers of biological membranes, describing a range of actions mediated through this mechanism, including putative anti-inflammatory effects such as antioxidant activity or inhibition of phospholipase A2, or side effects like disruption of gastric mucosal barrier or mitochondrial toxicity [27]. Other investigations have focused on the ability of some NSAIDs to modulate transcription factors that control the inducible expression of many genes involved in inflammation, such as nuclear factor-kappa B (NF-kappa B) or AP-1, while other studies describe the ability of some NSAIDs to modulate signaling pathways involved in inflammatory responses, such as the MAPK or PI3k/Akt pathways, or to interact with nuclear receptors that regulate inflammation [28, 29]. Additionally, a variety of NSAIDs seem to inhibit the function of the adhesion molecules responsible for the leukocyte–endothelial cell interactions that initiate the inflammatory focus [30]. Although these alternative mechanisms have been implicated in many particular effects induced by different NSAIDs and observed in varying experimental conditions, there is no consensus with regard to their relative contribution to the anti-inflammatory activity of NSAIDs observed at the concentrations attained with clinically used doses.

Table 1.4 COX-independent direct cellular targets of different NSAIDs

Target	Effect	NSAIDs
Transcription factors	Inhibition of NF-κB	Aspirin
		Salicylate
		Ibuprofen
		Flurbiprofen
		Sulindac sulfide
		Indomethacin
	Inhibition of AP-1	Aspirin
Kinases	Inhibition of MAPK cascade	Aspirin
		Salicylate
		Sulindac sulfide
		Ibuprofen
		Celecoxib
	Inhibition of PI3k/Akt	Naproxen
		Oxaprozin
Nuclear receptors	Stimulation of PPAR-γ	Ibuprofen
		Indomethacin
	Inhibition of PPAR-δ	Indomethacin
		Sulindac sulfide
Leukocyte-adhesion molecules	Inhibition of L-selectin shedding	Aspirin
		Salicylate
		Ketoprofen
		Diclofenac
		Indomethacin
		Aceclofenac
		Meclofenamic acid
		Mefenamic acid
	Inhibition of ß2-integrin activation	Piroxicam
		Meloxicam
	Inhibition of VLA-4 activation	Diclofenac
		Indomethacin
		Aceclofenac

Pharmacokinetics

Absorption

NSAIDs are generally well absorbed following oral ingestion and present a high bioavailability (80–100 %), although there are some exceptions (e.g., diclofenac, celecoxib). Their absorption is generally quick, and peak plasma concentrations are usually observed within 2–3 h, except for some derivatives of the enolic acid (piroxicam, meloxicam, nabumetone) and certain diaryl heterocyclic compounds (e.g., celecoxib, rofecoxib). Food intake may delay absorption, but rarely decreases systemic availability. Some compounds, such as diclofenac or aspirin, undergo a significant first-pass effect that significantly reduces their bioavailability, while a first-pass metabolism generates the active drug in the case of others, like dipyrone, nabumetone, sulindac or etoricoxib (Table 1.5). When applied topically, NSAIDs' penetration of inflamed tissues and joints appears to be minimal, and detectable concentrations in synovial fluid observed after some topical treatments (i.e., with diclofenac) seem to depend on dermal absorption and systemic circulation.

Distribution

Most NSAIDs are extensively bound to plasma proteins (95–99 %), and this binding may be saturable with a potential for interaction with drugs that compete for the same binding sites. The distribution pattern has a significant impact on the pharmacological actions and side effects of NSAIDs. Most compounds achieve sufficient concentrations in the central nervous system to exert a central analgesic effect, while their kinetics in inflammatory foci seem to be affected by particular physicochemical characteristics, like acidity. Acidic drugs (p*K*a 4–5), including diclofenac, ibuprofen, ketoprofen, or lumiracoxib, seem to accumulate and persist in inflamed tissue, such as in the synovial fluid of inflamed joints (reviewed in Brune and Patrignani [31]). This accumulation may be the consequence of several factors:

- The local acidic microenvironment caused by inflammation facilitates nonionic diffusion of these drugs into the cell interior; once there, the higher intracellular pH causes drug ionization. This process, termed ion trapping, increases the intracellular concentration of the drug.

Table 1.5 Pharmacokinetic data of common NSAIDs

Drug	Bioavailability (oral, %)	First-pass	Peak C_p (*h*)	Protein binding	$t_{1/2}$ (*h*)	Active metabolites	Urinary excretion (%)
Salicylates							
Aspirin	>80	+++	0.4	80–90	0.25–0.3	Salicylic acid	
Salicylic acid	100	–	1–2	95	2–3[a]		2–30
Diflunisal	90		2–3	99	8–12		
Para-aminophenol derivative							
Paracetamol	75–90	+	0.5–1	20–50	2[b]		
Pyrazolones							
Dipyrone	>90[c]	+++	0.5–1	15	2–4[c]	4-Methyl-amino-antipyrine	5
				58[c]		Amino-antipyrine	
Propyphenazone	>90		1–3	10–20	1–1.5		0.6
Acetic acid derivatives							
Indomethacin	90–100	±	1–2	99	1–6		20
Diclofenac	54	+++	2–3	99	1–2		<1
Aceclofenac	100	–	1.25–3	99	4–5		
Etodolac			1	99	7		
Ketorolac	80–100	±	0.5–1	99	4–6[d]		5–10
Sulindac	90		1–2	90	7	Sulindac sulfide	
			8[e]		18[e]		
Propionic acid derivatives							
Ibuprofen	>80	–	0.25–0.5	99	2–4		<1
Naproxen	99	±	1	99[f]	14		10
Fenoprofen	85		2	99	2		
Flurbiprofen	92	–	1–2	99	6		2
Ketoprofen	100	±	1–2	98	2		
Fenamates							
Mefenamic acid	>90	–	2–4	high	3–4		<6
Meclofenamate			0.5–2	99	2–3		
Enolic acid derivatives							
Meloxicam	89	11	5–10	90	15–20		<1
Piroxicam	100	–	3–5	99	45–50		<5
Alcanones							
Nabumetone	35[g]		2–8[g]	99[g]	24[g]	6-Methoxy-2-naphthylacetic acid (6MNA)[h]	
Diaryl heterocyclic derivatives							
Celecoxib	22–40		2–3	97	8–12[i]		<1
Etoricoxib	100		1	92	22		<2
Parecoxib				98[h]	0.3	Valdecoxib	<5[h]
					8–11[h]		

Peak C_p: time to peak plasma drug concentration; urinary excretion: as unaltered drug
[a]Dose-dependent half-life
[b]Half-life increases in liver disease, elderly, and children
[c]As 4-methyl-amino-antipyrine
[d]Half-life increases in elderly, liver, and renal disease
[e]As sulindac sulfide
[f]Increased free fraction and half-life in elderly
[g]As 6-methoxy-2-naphthylacetic acid
[h]Reduced in liver disease
[i]Increased in cases of P450-2C9 genetic polymorphisms, co-treatment with P450-2C9 inhibitors or liver disease
[h]As valdecoxib

- Changes in the hemodynamics of tissue during inflammation, including increased localized blood flow and edema, allows protein-bound and protein-unbound drugs to escape into the tissue.
- The high concentration of albumin in inflamed tissues and synovial fluid retains drugs that present a high affinity for this protein.
- The mildly acidic extracellular pH may reduce their binding to plasma proteins and increase the free fraction of the drug.

These factors would modulate the kinetics in the inflammatory focus, thereby prolonging the therapeutic action of the drug beyond that expected based on analysis of plasma pharmacokinetics. However, ion trapping also results in acidic compounds achieving high concentrations in the stomach wall and kidney, in which blockade of prostanoid synthesis causes the typical organ toxicity elicited by these compounds. Due to their lack of acidic structure, other COX inhibitors, such as dipyrone and paracetamol, are distributed homogenously throughout the body at therapeutic doses and induce analgesia, but induce no or very slight anti-inflammatory effects. This is partly due to their low concentration in inflamed tissues [31].

Elimination

The majority of NSAIDs are cleared from plasma by hepatic biotransformation followed by renal excretion of their metabolites. Renal excretion of active drugs is negligible in most cases (except indomethacin or salicylic acid) (Table 1.5). Some have active metabolites (e.g., nabumetone, sulindac) and nearly all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation), a process that seems to contribute to NSAID enteropathy. Some NSAIDs are metabolized by phase I (oxidation, hydroxylation, demethylation) followed by phase II (glucuronidation, other conjugations) mechanisms, while others suffer only phase II reactions. The family of NSAIDs includes drugs with very different half-lives, from 1 to 4 h in the

Table 1.6 Particularities of some NSAIDs

Specific characteristics of individual NSAIDs
Aspirin
• Most widely consumed NSAID
• Used as antiplatelet agent
• Only NSAID that causes irreversible inhibition of COX
• After absorption, quickly hydrolyzed to salicylic acid
• Excretion of salicylates extremely variable: dose- and pH-dependent elimination; reduced in renal disease
Celecoxib
• COX-2 selectivity
• Fewer gastrointestinal side effects
• Increased risk of cardiovascular events
• Metabolism reduced in hepatic impairment
• Inhibitor of CYP2D6
Diclofenac
• Potent NSAID
• Selectivity for COX-2 similar to that of celecoxib
• Short half-life, substantial first-pass effect, accumulation in synovial fluid
Dipyrone
• Prodrug
• Analgesic and antipyretic activity
• Weak anti-inflammatory action
• Some antispasmodic activity
Etodolac
• Some degree of COX-2 selectivity
Etoricoxib
• Long half-life
• Metabolism reduced in hepatic impairment
Ibuprofen
• Most commonly used NSAID (besides aspirin)
• Interferes with the antiplatelet effects of aspirin
Indomethacin
• Potent nonselective COX inhibitor
• Limited use due to its toxicity
• Undergoes enterohepatic cycling
Nabumetone
• Prodrug of 6-methoxy-2-naphthylacetic acid (6MNA)
Oxicams
• Long half-life, allowing once daily dosing
Paracetamol
• Analgesic and antipyretic
• Very weak anti-inflammatory action: probably related to the inhibitory effect of peroxides on its blocking effect on COX and to low levels of paracetamol in the inflammatory focus due to its lack of acidity

(continued)

Table 1.6 (continued)

Specific characteristics of individual NSAIDs
• Low incidence of gastrointestinal side effects
• Severe hepatic damage when overdose
Parecoxib
• Prodrug of valdecoxib
• Inhibitor of CYP2C9 and CYP2C19
• Metabolism reduced in elderly and hepatic impairment
Sulindac
• Prodrug of sulindac sulfide
• Complex pharmacokinetics: metabolized to active drug; extensive enterohepatic circulation

case of ibuprofen, diclofenac, or acetaminophen to 20–60 h in the case of oxicams. COX-2-selective drugs present an intermediate half-life (Table 1.5).

Some authors have hypothesized that the short half-life of acidic compounds confers an advantage in that their rapid disappearance from the central compartment allows the recovery of COX-2 activity in endothelial cells at the end of each dosing interval, while analgesia resulting from COX blockade in the inflamed tissue is continuously inhibited by the accumulated drug. This rationale could also be applied to other tissues and organs in which prostaglandin synthesis exerts a homeostatic action [31, 32].

The clearance of many NSAIDs is reduced in the elderly due to changes in hepatic metabolism. Additionally, older patients may present lower levels of plasma albumin and, consequently, higher concentrations of unbound NSAIDs. These elevated NSAID concentrations, in addition to impaired gastric mucosal defenses, explain the higher susceptibility to gastrointestinal complications observed in older patients.

Some clinically relevant characteristics of specific NSAIDs are summarized in Table 1.6.

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