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Review

Pharmacodynamic of cyclooxygenase inhibitors in humans

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Abstract

We provide comprehensive knowledge on the differential regulation of expression and catalysis of cyclooxygenase (COX)-1 and COX-2 in health and disease which represents an essential requirement to read out the clinical consequences of selective and nonselective inhibition of COX-isozymes in humans. Furthermore, we describe the pharmacodynamic and pharmacokinetic characteristics of major traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) and coxibs (selective COX-2 inhibitors) which play a prime role in their efficacy and toxicity. Important information derived from our pharmacological studies has clarified that nonselective COX inhibitors should be considered the tNSAIDs with a balanced inhibitory effect on both COX-isozymes (exemplified by ibuprofen and naproxen). In contrast, the tNSAIDs meloxicam, nimesulide and diclofenac (which are from 18- to 29-fold more potent towards COX-2 in vitro) and coxibs (i.e. celecoxib, valdecoxib, rofecoxib, etoricoxib and lumiracoxib, which are from 30- to 433-fold more potent towards COX-2 in vitro) should be comprised into the cluster of COX-2 inhibitors. However, the dose and frequency of administration together with individual responses will drive the degree of COX-2 inhibition and selectivity achieved in vivo. The results of clinical pharmacology of COX inhibitors support the concept that the inhibition of platelet COX-1 may translate into an increased incidence of serious upper gastrointestinal bleeding but this effect on platelet COX-1 may mitigate the cardiovascular hazard associated with the profound inhibition of COX-2-dependent prostacyclin (PGI_2).

Keywords: Cyclooxygenase-1; Cyclooxygenase-2; tNSAIDs; Coxibs; Prostacyclin; Thromboxane

Contents

Abbreviations: COX, cyclooxygenase; GI, gastrointestinal; LPS, lipopolysaccharide; PG, prostaglandin; PGI_2, prostacyclin; tNSAIDs, traditional nonsteroidal anti-inflammatory drugs; TX, thromboxane

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Prostanoids are a cluster of bioactive lipids [i.e. prostaglandin (PG) E_2, $PGF_{2\alpha}$, PGD_2, prostacyclin (PGI_2) and thromboxane (TX) A_2], which interact with specific cell-membrane receptors of the superfamily of G-protein-coupled, playing 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, gastrointestinal (GI) cytoprotection and ulceration, angiogenesis and cancer, haemostasis and thrombosis, renal hemodynamics and progression of kidney disease, atheroprotection and progression of atherosclerosis [1,2]. They are generated through the cyclooxygenase (COX) and peroxidase activity of PGG/H synthase-1 and -2 (known as COX-1 and COX-2) which catalyze the conversion of free arachidonic acid (AA) to PGG_2, and then to PGH_2. The different prostanoids are generated from the intermediate PGH_2 through the activity of tissue-specific isomerases and synthases [3].

Aspirin and other nonsteroidal anti-inflammatory drugs [collectively known as traditional (t)NSAIDs] and selective COX-2 inhibitors (coxibs) cause antipyretic, analgesic and anti-inflammatory actions, through their competitive inhibition of COX active site of COX-2—apart from aspirin which modifies irreversibly the catalytic activity of COX-2 [1,3,4]. tNSAIDs and coxibs result clinically equivalent for the relief of acute pain and symptoms of arthropathies at doses which cause a comparable profound suppression of COX-2 activity [3,5].

Coxibs (i.e. celecoxib, etoricoxib, lumiracoxib, rofecoxib and valdecoxib) were developed with the aim to reduce the incidence of serious upper GI adverse events associated with the administration of tNSAIDs, as a consequence of the inhibition of COX-1-derived prostanoids [1–3]. However, the reduced incidence of serious GI adverse effects compared to tNSAIDs demonstrated for two selective COX-2 inhibitors (i.e. rofecoxib and lumiracoxib) has been countered by an increased incidence of myocardial infarction and stroke detected in five placebo controlled trials involving celecoxib, rofecoxib and valdecoxib [6,8–11]. The results of a recent large nested case-control study using data from the UK General Practice Research Database have shown that an increased risk of acute myocardial infarction is attached to the first generation (celecoxib and rofecoxib) but also second generation (etoricoxib and valdecoxib) of selective COX-2 inhibitors [12]. Suppression of COX-2-derived PGI_2, leaving unconstrained prothrombotic and atherogenic stimuli, such as TXA_2, is a plausible mechanism involved in the increased cardiovascular risk attached to coxibs [2]. However, the results of numerous observational studies with tNSAIDs, despite being conflicting, have led to consider a possible cardiovascular hazard associated also with tNSAIDs [2,13]. However, misleading knowledge may be achieved when combined analyses of vascular events, recorded for different tNSAIDs in population-based observational studies or meta-analysis of randomised trials, are performed. In fact, tNSAIDs are a heterogeneous cluster of compounds in respect of pharmacodynamic (i.e. COX-1/COX-2 selectivity) and pharmacokinetic features [14], thus, each drug should be evaluated separately for its cardiovascular risk.

This review aims to provide comprehensive knowledge on the differential regulation of expression and catalysis of COX-1 and COX-2 in health and disease which represents an essential requirement to read out the clinical consequences of selective and nonselective inhibition of COX-isozymes in humans. Secondly, we describe the pharmacodynamic and pharmacokinetic characteristics of the major tNSAIDs and coxibs which play a prime role in efficacy and toxicity outcomes evidenced in clinical trials.

1. Regulation of COX-1 and COX-2 expression and activity

Despite COX-1 and COX-2 share the same catalytic activities, i.e. cyclooxygenase and peroxidase [15], they are differently regulated. In fact, it has been shown that COX-2 requires considerably lower levels of hydroperoxides to initiate cyclooxygenase catalysis than those required by COX-1 [16]. Moreover, the COX-2 activity occurs at lower levels of free AA than COX-1 activity [17]. Another important difference between the two pathways of prostanoid biosynthesis is related on the regulation of the expression of COX-1 and COX-2 genes. In fact, COX-1 has the structural features of an “housekeeping” gene while COX-2 those of an immediate early gene [3,18–20]. Moreover, both mRNA and protein of COX-1 are more stable than those of COX-2 [21].

These important differences in the regulation of catalysis and expression of COX-1 and COX-2 have led to the development of tissue-specific pathways of prostanoid biosynthesis dominated by one or the other enzyme in vivo in health and disease. We will describe some examples of cell-specific prostanoid biosynthesis driven by COX-2 or COX-1.