Cyclooxygenase-2 Inhibitors as a Therapeutic Target in Inflammatory Diseases

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Abstract: Inflammation plays a crucial role in the development of many complex diseases and disorders including autoimmune diseases, metabolic syndrome, neurodegenerative dis-eases, and cardiovascular pathologies. Prostaglandins play a regulatory role in inflammation. Cyclooxygenases are the main mediators of inflammation by catalyzing the initial step of arachidonic acid metabolism and prostaglandin synthesis. The differential expression of the constitutive isoform COX-1 and the inducible isoform COX-2, and the finding that COX-1 is the major form expressed in the gastrointestinal tract, lead to the search for COX-2-selective inhibitors as anti-inflammatory agents that might diminish the gastrointestinal side effects of traditional nonsteroidal anti-inflammatory drugs (NSAIDs). COX-2 isoform is expressed predominantly in inflammatory cells and decidedly upregulated in chronic and acute inflam-mations, becoming a critical target for many pharmacological inhibitors. COX-2 selective in-hibitors happen to show equivalent efficacy with that of conventional NSAIDs, but they have reduced gastrointestinal side effects. This review would elucidate the most recent findings on selective COX-2 inhibition and their relevance to human pathology, concretely in inflamma-tory pathologies characterized by a prolonged pro-inflammatory status, including autoimmune diseases, metabolic syndrome, obesity, atherosclerosis, neurodegenerative diseases, chronic obstructive pulmonary disease, arthritis, chronic inflammatory bowel disease and cardiovas-cular pathologies.

Keywords: Cyclooxygenase, COX inhibitors, inflammation, interleukin, natural compound. prostaglandin.

1. INTRODUCTION

Inflammatory diseases are a kind of illnesses char-acterized by a prolonged pro-inflammatory state mainly marked by a new connective tissue formation [1]. A large number of diseases are included in this category, such as autoimmune diseases, metabolic syndrome, neurodegenerative diseases, chronic obstructive pulmonary diseases, chronic inflammatory bowel disease and cardiovascular diseases.

Nowadays, it is considered that inflammation is a tissue process which consists of a set of molecular, cellular and vascular defensive phenomena against physical, chemical or biological attacks. It is also established that inflammation is the initial response to restore homeostasis and tissue function [2]. The acute inflammatory response is characterized by an increase in blood flow, changes in vascular permeability, accumulation of leukocytes and inflammatory mediators production, such as interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α), IL-6, IL-1, IL-8, γ interferon (IFNγ) and other chemokines [3, 4]. Some of these cytokines can activate nuclear factor κB (NFκB) expression, a transcription factor that can mediate the inflammatory response

[5] by regulating the transcription of many acute phase proteins and a large variety of stress response genes, such as inducible nitric oxide synthase (iNOS) and cy-clooxygenase-2 (COX-2) [5]. In fact, COX-2 plays an important role during inflammatory response [6].

Cyclooxygenases (COXs) are a family of oxidorreductase enzymes that catalyze eicosanoids bio-synthesis through arachidonic acid (AA) oxidation. Three isoforms of COXs have been described to date, COX-1, COX-2 and COX-3 [7, 8]. COXs are consid-ered bifunctional enzymes due to their both cyclooxy-genase and peroxidase activities [9]. COXs are con-served enzymes and can be found in all vertebrates and even in some invertebrates as Porifera or Cnidaria [10]. However, in unicellular organisms and plants, a kind of oxygenases called pathogen inducible oxygenases has been found. They are able to oxidize polyunsaturated fatty acids and they have 30% of homology with COXs [11].

COX-1, the first discovered COX isoform, is consti-tutively expressed in almost all tissues, although it is mainly located in quiescent cells of platelets, kidneys and the gastrointestinal (GI) tract, and its metabolites play an important role in maintaining the physiological conditions of the organism [12]. COX-2, the inducible isoform, is only expressed in some stages of cell differ-entiation or during replication. Besides, COX-2 expres-sion has been observed in pathological processes such as inflammation and angiogenesis, among others [6]. COX-1 and COX-2 catalyze AA conversion in prosta-glandins trough a two-steps reaction [13]. Firstly, two molecules of oxygen are added to AA generating pros-taglandin G2 (PGG2); after this reaction, PGG2 is re-duced generating PGH2, which is the origin of the rest of prostaglandins, tromboxan A2 and prostacyclins [14]. COX-3 has similar structural and catalytic fea-tures to COX-1 and COX-2, but it exhibits 20% of the activity of COX-1 and COX-2. Anyhow, this isoform has not been isolated in humans yet [7]. COX-2 is a suitable drug target against inflammatory diseases and tumorigenesis, because it is the major contributor en-zyme to prostanoid synthesis in inflammatory proc-esses and its expression is upregulated by inflammatory mediators, and also under hypoxic conditions and in many cancers.

2. CYCLOOXYGENASES CHARACTERISTICS

COXs (EC 1.14.99.1) are also known as prostaglan-din-endoperoxide synthase, fatty acid cyclooxygenases, prostaglandin synthetases, prostaglandin G/H syn-thases, prostaglandin synthases, and prostaglandin syn-thetase. COXs are hemoproteins acting as both dioxy-genases and peroxidases that are able to catalyze the synthesis of prostaglandin H2 (PGH2) from AA. Two COX isoforms (COX-1 and COX-2), with 60% amino acid sequence homology encoded by distinct genes but expressing different profiles, have been described [15, 16]. COX-3 is a third isoform derived from the COX-1 gene that maintains the intron 1 in its mRNA [7, 17]. Prostaglandins produced by the COX enzymes are ubiquitous in human physiology and regulate numerous processes [18, 19] mediating basic housekeeping func-tions in the body [20, 21] (Fig. 1). COX-1 and COX-2 isoforms are bifunctional, they are membrane-bound located on the lumenal surfaces of the endoplasmic re-ticulum, and on the inner and outer membranes of the nuclear envelope [22]. COX-1 is expressed in most tissues whereas COX-2 is also expressed in both brain and kidney but it is primarily an inducible enzyme, whose expression is activated in response to cytokines, mitogens, endotoxin, and tumor promoters in a variety of cell types [9]. The structure and mechanism of COX isoenzymes and the structure-function relationships of COX inhibitors have been excellently reviewed [9, 23¬26]. In addition, the structural details and the interac-tion between the substrate, inhibitors and the catalytic and regulatory sites of COXs are published in several reviews [25-28] and also in the protein data bank struc-ture [29].

AA oxygenation occurs in two sequential reactions (Fig. 1); the first cyclooxygenase reaction is a dioxy-genase reaction in the cyclooxygenase active site gen-erating PGG2, and the second one is the posterior PGG2 reduction until PGH2 in the peroxidase active site. Di-oxygenase reaction of COXs begins with abstraction of the 13-pro-S-hydrogen from AA by a tyrosyl radical centred on Tyr-385 of the enzyme in the rate-determining step to generate an arachidonoyl radical [30, 31]. Then, two oxygens are sequentially added to the arachidonyl chain with concomitant rearrangements to form the bicyclic hydroperoxide PGG2 that diffuses to the peroxidase active site. The peroxidase activity of COXs reduces the 15-hydroperoxyl of group of PGG2 to generate PGH2, the final product of COXs from AA. It has been described that both COX-1 and COX-2 iso-forms have similar efficiency catalyzing the conversion of AA to PGH2 [30, 32]. In fact, both isoforms are quite similar structurally [33] and mechanistically [9, 26], with only subtle kinetic differences in substrate [34] and inhibitor specificities [24, 35], and hydroper-oxide activator requirements [36, 37].

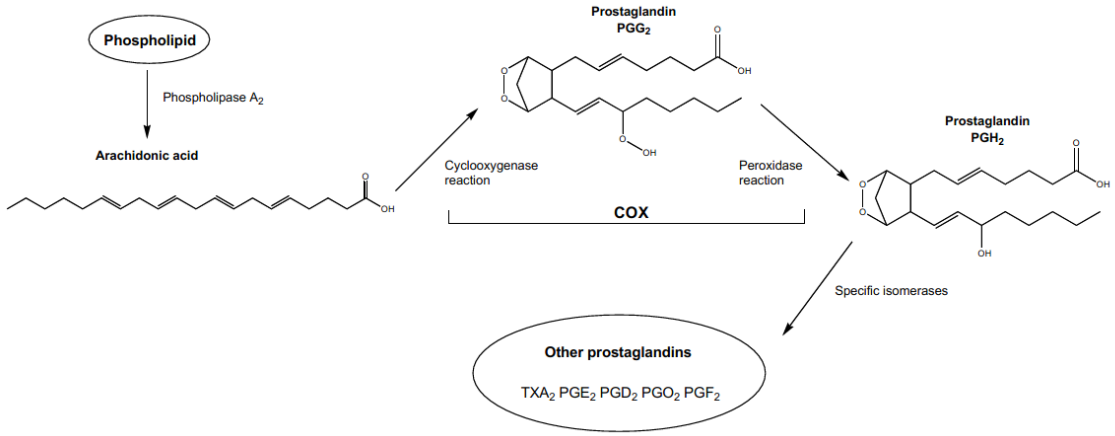

Fig. (1). Main biosynthesis steps of the arachidonic acid to prostaglandin H2 (PGH2) via the prostaglandin-endoperoxide syn-thase or COX pathway. PGH2 is an important precursor of eicosanoids such as prostaglandins, thromboxanes, leukotrienes and resolvins, among others.

COX-1 and COX-2 are homodimers composed of strong association of two 70 kDa monomers with iden-tical sequences that can be dissociated into their monomers only under denaturation [38]; dimerization is required for structural integrity and catalytic activity [38]. Briefly, each COX monomer consists of three structural domains [23]: a short N-terminal epidermal growth factor domain, a membrane binding domain, and a large, globular C-terminal catalytic domain [39]. The cyclooxygenase and peroxidase active sites are located on opposite sides of the catalytic domain; this domain constitutes the main catalytic monomer with the heme prosthetic group located at the base of the peroxidase site. The epidermal growth factor domain and the catalytic domain create the dimer interface, being the two membrane binding domains on the same side of the homodimer. However, although COX en-zymes are homodimers, they act as conformational het-erodimers during both catalysis and inhibition [39-42].

The maximal COX activity is attained with one heme per dimer [43] and, similarly, the stoichiometry of some inhibitors (such as flurbiprofen and other non-specific nonsteroidal anti-inflammatory drugs) is one inhibitory molecule per dimer [44]. COX enzymes op-erate like an allosteric/catalytic couple, in which one COX active site has a catalytic activity with heme bound

(modulated by the ligand occupying the COX site of the partner monomer), and an allosteric mono-mer without heme [39, 42]. In this sense, COXs acquire a stable, asymmetric allosteric and catalytic form dur-ing folding and processing, working as a conforma-tional heterodimer [45]. The only heme is bound to the peroxidase active site of the catalytic subunit, which binds to the substrate fatty acids and also a subset of COX inhibitors. Moreover, both substrate and non-substrate fatty acids and a second subset of COX in-hibitors can also bind to the COX site of the allosteric monomer [46]. To sum up, the COXs are allosteric en-zymes that may bind substrates, activators, or inhibitors to the allosteric subunit, and this can influence the binding in the catalytic subunit via the dimer interface communication [47]. Kinetically, COX-2 inhibition can occur in rapid-reversible or slow-tight ways. Com-pounds that are rapid-reversible COX-2 inhibitors are named as “substrate-selective”. They bind the allosteric subunit at very low concentrations and induce a con-formational change that blocks the catalytic activity of the other subunit. Binding of a second inhibitor mole-cule in the catalytic subunit blocks AA oxygenation, although this typically needs high inhibitor concentra-tions [40]. In fact, the oxygenation of all substrates can be blocked by slow, tight-binding inhibitors bind in the catalytic monomer at equal concentrations [44, 48].

The substrates of COXs can be n-3 and n-6 18-22 carbon polyunsaturated fatty acids, although with vary-ing efficiencies and, generally, with higher Km values than AA [34, 49-52]. COXs also can be an endocan-nabinoid metabolizing enzyme due their role oxygenat-ing arachidonate-containing lipids [27]. The fatty acid binding COXs is interpreted as a mode of production, leading to the inhibition of prostaglandins from the AA oxidation [53-55]. In fact, different fatty acids could compete with AA for binding to the allosteric or cata-lytic sites of COXs and regulating eicosanoid synthesis [56]. Although saturated and monounsaturated fatty acids are not COX substrates, they can bind to the allosteric subunit regulating COX activities; palmitic acid binds allosteric subunit stimulating COX-2 but inhibiting COX-1 [56]. C-22 n-3 polyunsaturated fatty acids, such as docosahexaenoic (DHA), have higher affinities for catalytic than for allosteric COX subunits; whereas C-20 n-3 polyunsaturated fatty acids, such as eicosapentaenoate (EPA), preferentially bind the COX-1catalytic subunit and the COX-2 allosteric one [56]. Fish oil containing both EPA and DHA reduces about 50% prostaglandin, suggesting that fatty acids alter the rate of prostaglandin production [56]. However, the products of n-3 polyunsaturated fatty acid oxidation by COXs are relevant for the inflammation resolution [57]. Synthetic inhibitors, such as aspirin, produce a highly conserved Ser-530 COX form by acetylation of the catalytic subunit [30, 41, 58]. The Acetylated-COXs transform AA into 15R-hydroxyeico-sapentaenoic acid (15R-HETE) [59, 60], which is a precursor of potent anti-inflammatory molecules [61¬63]; and transforms EPA and DHA in bioactive trihydroxylated compounds named resolvin E1 (RvE1) and 17R-resolvin D1 (17R-RvD1) [57, 64]. Resolvins play an active role in the resolution of inflammation processes [64].

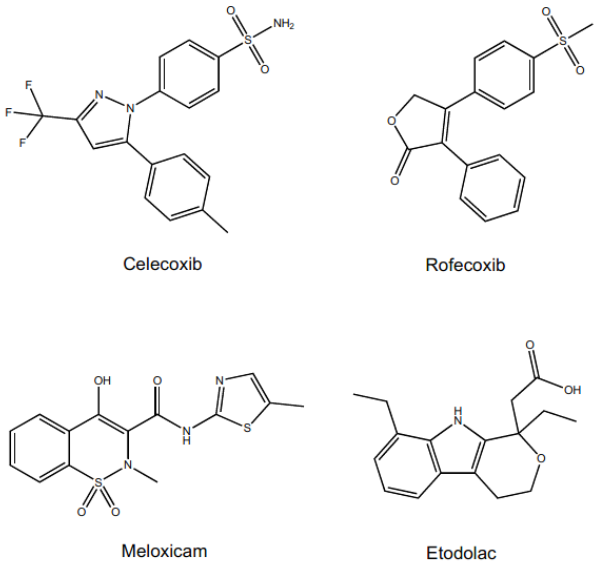

Fig. (2). Chemical structure of cyclooxygenase 2 inhibitors celecoxib, rofecoxib, meloxicam and etodolac.

COX-1 is mainly expressed in the gastrointestinal tract, and its activity inhibition displays side effects. For that reason, research is centered on COX-2-selective inhibitors as potential anti-inflammatory agents [65].

3. CLASSICAL CYCLOOXYGENASE INHIBITORS

Non-steroidal anti-inflammatory drugs (NSAIDs) are a type of drugs with large range of applications in clinic, although their indications are limited due to various adverse effects and interactions which may be potentially severe, so they should be prescribed in se-lected patients [66]. Concretely, traditional NSAIDs can exert nonselective inhibition effects on COX-1/COX-2, and thereby they inhibit the synthesis of prostaglandins and thromboxanes. Nonetheless, the tissue location of COX-1 underlines GI side effects such as stomach irritation, GI bleeding and even ulcers provoked by traditional NSAIDs that inhibit both COX-1 and COX-2, particularly the aspirin. These drugs exert their therapeutic effects by inhibiting COX-2-dependent prostanoid biosynthesis and COX-1 de-pendent gastroprotective prostaglandins production, which in turn cause gastrointestinal damage [65, 66]. Therefore, this fact led to the search for a new genera-tion COX-2-selective inhibitors (known as Coxibs) as anti-inflammatory agents that might attenuate the GI side effects and diminish tissue toxicity of traditional non-steroidal anti-inflammatory drugs (NSAIDs). The use of Coxibs in humans not only provided the oppor-tunity for obtaining anti-inflammatory, analgesic and antipyretic effects with equivalent efficacy as the rest of NSAIDs and a better adverse effect profile, but also unraveled a cardiovascular protective role of COX-2 by generation of prostacyclin [67, 68].

COX-1 and COX-2 isoforms present a high degree of homology, but a substitution at position 523 (iso-leucine in COX-1 and valine in COX-2) makes the dif-ference in terms of selectivity. The single methyl group provides extra space in the active site, creating a COX-2 side pocket with larger solvent accessible surface, suitable for bulky drugs as coxibs [69]. Another substi-tution of phenylalanine in COX-1 for leucine in COX-2 leads to a more flexible active site that let chemically dissimilar drugs as meloxicam to inhibit COX-2. An-other remarkable dissimilarity between COX-

1 and COX-2 is the type of inhibition they experiment. While NSAIDs bind to COX-1 through reversible hydrogen-bonding and the inhibition is carried out by stearic hin-drance, COX-2 traps the inhibitors owing to an active closure of the lower enzyme site. This fact results in a meta-stable transitional state with the ligand irreversi-bly bind [70].

Traditionally, NSAIDs have been classified by chemical structure, although most recent drugs can be bibliographically found according to its mechanism of action. Then, NSAIDS can be separated into two groups: non-selective cyclooxygenase inhibitors and selective COX-2 inhibitors. Most NSAIDs act inhibit-ing non-selectively both COX-1 and COX-2 isoen-zymes in a competitively reversible way (except aspi-rin, in which the inhibition is irreversible). COX-2 se-lective inhibitors represent a noteworthy therapeutic development because of their ability to circumvent side effects associated with COX-1 inhibition. The first group of non-selective inhibitors is generally organized as follows: salicylates, where aspirin stands out; propi-onic acid derivatives, with ibuprofen as an archetypal drug; acetic acid derivatives, such as diclofenac; enolic acid derivatives, such as piroxicam, and sulfonanilides. The second group embraces selective COX-2 inhibi-tors, also called Coxibs [71]. Essentially two groups of drugs have been shown to inhibit COX-2 selectively. The first group is called Coxibs, and include celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumira-coxib and etoricoxib, tri-cyclic drugs that access the COX-2 side-pocket [69, 70]. Coxibs were discovered to be COX-2 selective since their finding and were de-veloped and exposed as improved GI safety com-pounds compared to traditional NSAIDs. The second group includes previously described NSAIDS that were retrospectively found to show COX-2 selective inhibi-tory activity, such as meloxicam, nimesulide or etodolac.

4. CYCLOOXYGENASE-2 INHIBITORS AND INFLAMMATORY DISEASES

There is a lot of available data about the therapeutic use of COX-2 inhibitors in diverse inflammatory dis-eases including inflammatory bowel diseases which include ulcerative colitis and Crohn's disease, os-teoarthritis and neurological diseases especially epi-lepsy. It is well established that COX-2 plays an impor-tant role in the development of ulcerative colitis be-cause prostaglandins are involved in the inflammatory process, enhancing the activity of 5-lipooxygenase and the release of inflammatory leukotrienes [72]. Cele-coxib treatment has been reported to reduce the damage and neutrophil infiltration in the mucous membrane of the large intestine, and also reduce the levels of IL-1 β in a mouse model of experimentally-induced colonic lesions [72]. Similar effects of rofecoxib were observed in a mouse model of induced colitis. Rofecoxib in-creased the amount of intestinal mucus that acts as a protective barrier. It is also observed that rofecoxib decreased myeloperoxidase levels in the intestinal mu¬cosa and reduced colonic inflammation due to suppres-sion in neutrophils infiltration [73]. However, it is not clear if Coxibs have more beneficial effects than side effects since diverse studies have reported that Coxibs can exacerbate inflammatory bowel diseases and Crohn’s disease signs [74-76].

Osteoarthritis is the most common joint disorder in western countries, affecting over 70% of adults aged 55 to 70 years [77]. COX-2 inhibitors are often used in arthritis treatment. It has been observed that celecoxib was able to reduce cartilage damage; furthermore, a reduced loss of chondrocytes and an increase in pro-teoglycan synthesis were also observed [78]. However, the underlying mechanisms of celecoxib treatment on the disease progression remain still unclear [79-81]. Pro-inflammatory cytokines play an important role in osteoarthritis pathogenesis due to an inhibitory activity on proteoglycan synthesis and on chondrocyte apopto-sis induction. It has been observed that treatment with celecoxib reduced IL-6 levels in synovial fluid, and TNF-α and IL-1β expression in the synovial membrane [78, 81, 82]. In vitro, it

was also demonstrated that chondrocytes' pro-inflammatory cytokine secretion was reduced after celecoxib treatment, which could slow down the progression of the disease [83]. In addition, celecoxib treatment also influences bone structure. Some studies have demonstrated that celecoxib admini-stration can reduce the mineral bone loss and enhance trabecular bone volume but without affecting bone formation [84-86]. Finally, it has been observed that rofecoxib is able to reduce joint pain and improve life quality in arthritic patients after three weeks of treat-ment [87-89].

Epilepsy is a condition of the brain characterized by recurrent epileptic seizures. It has been observed that prostaglandin brain levels together with a high COX-2 expression increase dramatically in seizures produced by an epileptic status suggesting that COX-2 plays an important role in epilepsy [90]. It has been observed that oral administration of celecoxib has an anticonvulsant action, but these effects were reversed by PGE2 intracerebroventricular administration in ani¬mal murine models [91]. It has been demonstrated that intraperitoneal injection of rofecoxib also reduced con-vulsions induced by pentylenetetrazol (PTZ) [92]; however, other studies using oral administration of rofecoxib for 5 days previous PTZ induction did not show any effect on the severity of seizures [93]. COX-2 inhibitors could be great strategies to fight against a migraine as it has been observed that doses of 25 and 50 mg of rofecoxib significantly reduced headaches two hours after administration [94]. Coxibs are also used in Alzheimer's disease treatment although their beneficial effects are not clear [95]. Several studies have demonstrated that rofecoxib slows down the dis-ease progression and could reduce the reactive oxygen species' production in rat's brain [96-99]. However, other studies have shown no effects of rofecoxib ad-ministration on disease progression [95, 100]. The administration of Celecoxib as a treatment against Alz-heimer's disease was studied, but no significant effects on the disease were observed [101, 102].

5. SIDE EFFECTS OF CYCLOOXYGENASE-2 INHIBITORS

Not long after the development and introduction of the first NSAIDs in the late seventies, the first reports on side effects in the cardiovascular and renal systems started to appear. Relationships between the inhibition of COX and platelet thrombus formation [103] and occasional decreases in glomerular filtration rate and re¬nal function [104] were reported as early as 1980s. Al-though some contradictory results have been obtained throughout the years, the evidence point out to a certain increase of the risk of cardiovascular incidences, espe-cially when high doses are administered on a long-time basis. The mechanisms by which the Coxibs exert their effects on the vasculature seem to be multifactorial. On one hand, these inhibitors can activate platelet produc-tion and function, thus promptingan increase in blood viscosity and the formation of thrombi, which can fur-ther lead to the development of a cardiovascular event. As prostaglandins are involved in the inhibition of platelet aggregation [105] and thromboxane A induces pro-aggregative processes [106], the selective inhibi-tion of COX-2 without inhibiting COX-1 disposes to the activation of platelet aggregation. On the other hand, these compounds can increase the blood pres-sure, especially in hypertensive subjects [107, 108] through a decrease in renal blood flow and subsequent sodium and water retention [67, 109, 110].

Several clinical trials carried out in the recent years have evidenced this relationship between NSAIDs use and increased risk of cardiovascular events. The VIGOR study revealed an increase of the risk of myo-cardial infarction associated to the use of rofecoxib, but only in a subgroup of patients with high risk of infarc-tion and without affecting overall mortality [111]. Similar results with the same rofecoxib were obtained in subsequent clinical trials such as the APPROVE study, in which the use of rofecoxib was related to an increased incidence of thrombotic and

cerebrovascular events and myocardial infarctions [112] but without affecting overall cardiovascular mortality. The CLASS study performed on 8059 patients with osteoarthritis or rheumatoid arthritis revealed no differences in the inci-dence of cardiovascular events between celecoxib and ibuprofen or diclofenac [113]. This lack of effect was supported by the results of the ADAPT study in pa-tients over 70 years with a family history of Alz-heimer's disease in which the rate of cardiovascular events in patients receiving celecoxib did not differ from receiving placebo [114]. However, another study published in the same year on the effect of celecoxib in the prevention of adenomas showed a nearly 2-fold-increased cardiovascular risk and a trend for a dose-related increase in cardiovascular events and blood pressure [115].

The results of different meta-analyzes point alto-gether to a moderate increase in the risk of vascular events associated to the use of these NSAIDs [116] but this risk is highly dependent on the concrete inhibitor used and some inhibitors such as celecoxib and meloxicam seem to be safer than others such as ro-fecoxib [117-119].

These results evidence that the use of certain selec-tive COX-2 inhibitors can increase the risk of suffering cardiovascular events, especially in predisposed high-risk patients. This is why the American Heart Associa-tion guidelines published in 2007 stated that in these patients, the use of COX-2 inhibitors should be limited to patients, for whom there are no appropriate alterna-tives, and then, only in the lowest dose and for the shortest duration necessary [120] and the FDA raised warnings in 2005 and 2015 on the increase in myocar-dial infarction and cerebrovascular accidents associated to NSAIDs. This fact and the recent market removal of some coxibs such due to their undesirable cardiovascu-lar side effects clearly encourage focusing on future research to investigate and assess alternative templates with COX-2 inhibitory activity such as natural com-pounds.

6. NATURAL COMPOUNDS AS CYCLOOXYGENASE-2 INHIBITORS

Taking into account that most COX inhibitors ex-hibit deleterious effects which can lead to gastrointesti¬nal, renal and cardiovascular toxicity, much attention has been focused on natural compounds. Although these natural compounds are not specific COX inhibi-tors, they are able to reduce inflammation by inhibition of the expression of pro-inflammatory mediators in-cluding COX-2. In this way, diverse authors reported that plant extracts or plant secondary metabolites such as phenolic compounds exert anti-inflammatory activ ity by ameliorating the levels and/or expression of various inflammatory mediators.

A number of studies performed in vitro investigated the anti-inflammatory effects of specific compounds mainly in LPS-stimulated murine macrophage cell lines (RAW 264.7 and THP-1). In these studies, the inhibi-tory effects of phenolic compounds such as naringenin, quercetin, procyanidin C1, monotropein, 3,4-dihydroxytoluene, gamma-irradiated genistein and res-veratrol and chromone isoeugenol against COX-2 ex-pression were clearly evidenced [121-127]. Resveratrol and its related compounds, orcinol and 4-allylphenol were also effective in COX-2 expression when RAW264.7 cells were stimulated with Porphyromonas gingivalis fimbriae [128]. Phenolic compounds also exerted COX-2 inhibitory activity in other cell types including HaCaT keratinocytes and Caco-2 intestinal cells [129, 130]. However, it is important to note that other compounds than polyphenols have the capability to inhibit COX-2. In a research done by Cam and de Mejia [131], lunasin, a 43–amino-acid bioactive pep-tide derived from soybean, inhibited proinflammatory markers by downregulating the activation of Akt-mediated NFκ13 pathways through interaction with αV□3 integrins.

Isolated compounds were also reported to be effec-tive in inhibiting COX-2 and inflammatory processes in diverse animal models. Berberine hydrochloride, a natural extract from Rhizoma coptidis (Ranunculaceae), improved intestinal mucosa inflammation and reduced COX-2 expression in a rat model of acute endotoxemia induced by LPS administration [132]. In another study, chelidonic acid, a constituent of Chelidonium majus (Papaveraceae), was also effective against dextran sul-fate sodium (DSS)-induced ulcerative colitis in the mouse. Chelidonic acid administration attenuated PGE2 production levels and COX-2 and hypoxia induced fac-tor-1α (HIF-1α) expression in colonic tissues [133]. 4-vinyl-2,6-dimethoxyphenol (canolol) were also investi-gated in DSS-induced colitis in the mouse. Inflamma-tory mediators, such as COX-2 and cytokines, and oxi-dative injury of DNA were ameliorated by canolol treatment [134]. In the same animal model, the treat-ment with fraxinellone, a natural occurring lactone, significantly alleviated the main signs of colitis in mice [135]. Moreover, the expression of macrophage-related molecules in the colon, including adhesion molecules, iNOS and COX-2 were markedly inhibited. Rhodo-dendron, isolated from Rhododendron brachycarpum (Ericaceae) leaves, was also found to be effective as an anti-inflammatory agent in trinitrochlorobenzene (TNCB)-treated mouse ear skins [136]. Isofraxidin, a coumarin compound, significantly lowered LPS-induced mortality and the levels of inflammatory me-diators in serum and bronchoalveolar lavage fluid and COX-2 protein expression in lung tissues [137].

Several studies have investigated the anti-inflammatory effects of plant extracts or diverse com-positions mainly from traditional Asian medicine. In a study, primary human chondrocytes were isolated from patients with osteoarthritis, SW1353 chondrocytes and THP-1 macrophages pretreated with an extract from the heartwood of Caesalpinia sappan (Leguminosae) prior to stimulation with interleukin-1beta (IL-1 13) or LPS evidenced a significant inhibition of COX-2 tran-scription [138]. Another study using LPS-stimulated RAW 264.7 macrophages evidenced that Schizonepeta tenuifolia (Lamiaceae) ethanolic extract significantly decreased COX-2 and prostaglandin PGE2 levels, and NO production [139]. Korean Red Ginseng (Panax ginseng) water extract was also reported to suppress acrolein-induced COX-2 expression and to reduce apoptosis in HUVECs [140]. Oldenlandia diffusa (Ru-biaceae) extract, a traditional oriental medicine for in-flammation, protected mice against DSS-induced coli¬tis by suppressing the plasma levels of IL-6, IL-113 and expression of COX-2 in colon tissues [141]. In the same animal model, inhibitory effects on COX-2 and iNOS expression were also reported after the treatment with a fungus Phellinus linteus extract germinated on brown rice [142]. Similar results were obtained when the extract was used in LPS-stimulated RAW 264.7 macrophages. Using trinitrobenzene sulfonic acid (TNBS)-induced rat model of inflammatory bowel dis-ease, diverse authors investigated the protective effects of several compounds. In this way, Pogostemon cablin (Lamiaceae), a traditional Korean medicine, suppressed clinical signs of colitis and reduced COX-2 expression in a dose-dependent manner [143]. Similarly, Gegen-qinlian decoction, an oral Chinese medicine compound, assayed in rats with TNBS-induced colitis resulted in reduced colonic injury, inflammatory mediators levels, and iNOS, COX-2, macrophage inflammatory protein-2 (MIP-2), intercellular adhesion molecule-1 (ICAM-1) and toll-like receptor (TLR)-2 and -4 expressions [144]. The anti-inflammatory effects of Caragana tangutica (Fabaceae: Papilionoideae) were studied in diverse mouse models of inflammation including ear and paw oedema and lung inflammation. The C. tangutica ethyl acetate extract significantly reduced the release of PGE2 and COX-2 expression [145]. In addi-tion, the treatment with a composition based on the ex-tracts from the leaf of Uncaria gambir (Rubiaceae) and the root bark of Morus alba (Moraceae) suppressed paw edema and ear thickness in animal models by in-hibiting COX-2 and lipoxygenase (5-LOX) enzyme activities [146].

In addition, synthesized phenolic compounds were newly designed and tested as potential COX-2 inhibi-tors. For example, the novel 2-{6-fluoro-2-[(4-methyl-2-pridinyl)carbonyl]-1H-indol-3-yl}acetic acid com-pound was an effective and selective COX-2 inhibitor in vitro using human umbilical vein endothelial cells (HUVECs) and with anti-inflammatory capability against carrageenan-induced foot in Sprague-Dawley rats [147]. The synthetic pyranochalcone-derived compound,(E)-3-(3,4-Dimethoxyphenyl)-1-(5-hydroxy-2,2-dimethyl-2H-chromen-6-yl)prop-2-en-1-one was also effective in ameliorating inflammation in a mouse model of collagen-induced arthritis [148]. In another assay, the synthetic flavonoid, (E)-1 -(4-ethoxyphenyl)-3-(4-nitrophenyl)-prop-2-en-1-one (ETH) inhibited LPS-induced inflammation in LPS-stimulated RAW 264.7 macrophages via suppressing NFκβ signalling pathway [149]. Finally, an interesting study by Srinivas et al., [150] reported that new synthesized 1,2-oxazine-based derivatives exerted a high degree of selectivity in inhibition towards COX-2 over COX-1. Molecular docking analyzes evidenced that the presence of an iso-leucine residue in the active site of COX-1 was respon-sible for the lower affinity to COX-1.

Neurodegenerative diseases seem to be linked to in-flammation in microglia and other neuronal cells, rep-resenting a target for studying new treatments. Unfor-tunately, current COX inhibitors used as possible treatments have failed to obtain positive results in this kind of illnesses, despite the fact that some studies have revealed hopeful findings [151]. However, other stud-ies related to neuroinflammation and natural com-pounds as COX inhibitors have already been performed on the cells. The sesquiterpene torilin, isolated from Ulmus davidiana var. Japonica, has been used in tradi-tional medicine for inflammation. Torilin was able to reduce the extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, the cyclic AMP-responsive element (CRE)-binding protein (CREB) and NFκβ in lipopolysaccharide (LPS)-stimulated microglial BV2 cells. This resulted in a decrease of the inducible nitric oxide synthase (iNOS), COX-2 and IL-1β expressions, and also a decrease in the following release of nitric oxide, prostaglandin E2 and IL-1β [152]. Similar results were found in other study using the same cell model, observing the suppression of NFκβ and TLR2 or TLR4 signalling pathways, and without affecting cell viability by Ganoderma lucidum extract [153], and by a multi-herb mixture (PMC-12) [154]. In a model rat of cerebral ischemia, Eleutherococcus senticosus (eleutheroside E, eleutheroside B and chlorogenic acid) extract was used as a treatment. The authors reported a task memory improvement and a reduction of the death of hippocampal neurons, and also an inhibition of the expression of COX-2, glial fibrillary acid protein (GFAP, astrocytes marker) and CD11b antibody (OX-42, microglia marker) in that region in a dose-dependent manner [155]. In the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydro pyridine (MPTP)-induced mouse model of Parkinson's disease, inflammatory and oxida-tive responses were observed in astrocyte and micro-glia, this was reflected by a rise of the expressions of the NFκβ, iNOS and COX-2, and an upregulation of the tumor necrosis factor alpha (TNF-α) and IL-1β ex-pression in the strata. The flavonoid procyanidin (pycnogenol®), an extract of the maritime pine bark, reversed these effects; however, the used compound was a mixture of procyanidin and polyphenols [156]. More recently, the flavonoid hesperidin given to mice with cognitive impairment induced by streptozotocin showed similar results, as it improved the memory per¬formance and inhibited the overexpression of several markers, including COX-2, iNOS, NFκβ and GFAP [157] The use of ethanol extracts of Ophiocordyceps sinensis displayed similar results in a rat model of focal cerebral ischemia/reperfusion [158]. Although some clinical assays have been performed to study the effects of natural compounds in neurological diseases [159¬161], the results are not conclusive and do not aim to research the role of COXs. More research is needed to deepen the knowledge of the effects of natural products as COX inhibitors in order to ameliorate the neurologi-cal diseases driven by inflammation processes.

7. MECHANISM OF ACTION OF NATURAL COMPOUNDS

The inflammatory response is a complex network that involves multiple signalling cascades. However, when analysing the mechanism of action of these com-pounds or extracts, the underlying pathways are mostly the same. The final target of the different assayed com-pounds is the inhibition of the NFκβ signalling pathway which is an inflammatory situation that up-regulates the expression of diverse pro-inflammatory genes in-cluding COX-2 [162]. Cytokines, such as TNF-α and IL-1β, and pathogen-associated molecular patterns, such as LPS via TLR4, mediate inflammation and im-mune responses by activating NFκβ, MAPKs and PI3K/Akt signalling pathways [130, 136, 138]. In addi tion, NFκβ signalling is also closely associated to MAPK, and PI3K/Akt signalling. Most of the compounds have been reported to suppress the activa-tion of MAPKs and PI3K/Akt pathways via reducing the phosphorylation of ERK1/2, p38 and/or Akt [121, 132, 163]. Moreover, the treatment with natural com-pounds is associated to a reduced degradation and phosphorylation of IκBα and/or NFκβ subunit p65, and reduced phosphorylation of the upstream signalling protein IKKα/β [127, 136]. These compounds also pre-vented the nuclear translocation of NFκβ and can di-rectly interfere with the DNA binding activity of NFκβ subunits [136, 138].

CONCLUSION

COXs, and specifically COX-2, are considered the main regulators of inflammatory processes since they catalyze the initial step of arachidonic acid metabolism and prostaglandin biosynthesis, central messenger molecules in the process of inflammation.

Therapeutic interventions aiming to reduce the de-gree of inflammation in chronic inflammatory diseases may need to be focused on the inhibition of some of the enzymes directly involved in the synthesis of inflam-matory mediators such as COX-2. The use of NSAIDs that inhibit non-selectively both COX-1 and COX-2 isoenzymes or COX-2 selective inhibitors have been reported as a promising approach to counteracting the higher inflammatory mediators production induced by over-expressed COX-2 in inflammatory diseases. However, the classical COX inhibitors have been re-ported to exert some degree of undesirable side effects including cardiovascular or gastrointestinal effects. Al-together, it clearly encourages developing new thera-peutic drugs for the treatment of mental diseases that overcome the side effects of currently known COX in-hibitors. Natural compounds, mainly polyphenols and derivates, are a new and interesting approach as they have been reported to act as potent anti-inflammatory molecules with a promising future in the therapeutic management of inflammatory diseases. Although the underlying mechanisms of action of the natural com-pounds are becoming well known, the absence of clini-cal trials makes strongly necessary additional studies to determine adequate dosages, combinations, safety and efficacy in order to establish the therapeutic uses of these compounds for the pharmacological treatment of inflammatory diseases.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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