PPARγ, NF-κB and the UPR pathway as new molecular targets in the anti-inflammatory actions of NSAIDs: Novel applications in cancers and central nervous system diseases?

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac, ibuprofen, or celecoxib have a well-established and unquestionable role in the human therapeutic arsenal, but still new perspectives are being discovered. This review presents new anti-inflammatory mechanisms of NSAIDs action, other than the classical one, i.e., the inhibition of cyclooxygenase (COX) isoforms leading to the prostanoids synthesis blockage. Literature data show that this group of drugs can activate anti-inflammatory peroxisome proliferator-activated receptor gamma (PPARγ), inhibit pro-inflammatory nuclear factor-κB (NF-κB) activation or modulate the components of the unfolded protein response (UPR) pathway. These alternative pathways induced by NSAIDs may not only enhance their basic anti-inflammatory mechanism of action but also promote other effects of the drugs such as anti-cancer. It was also proved that neuroinflammation, with the involvement of NF-κB, PPARγ and the components of the UPR pathway has an essential impact on the development of central nervous system (CNS) diseases. Thus, it seems possible that these new molecular targets may expand the use of NSAIDs, e.g., in the treatment of cancers and/or CNS disorders.

Key words: NF-κB, PPARγ, NSAIDs, UPR pathway, cancers, CNS diseases

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac, ibuprofen, or celecoxib are popular drugs available both with and without prescription and are commonly used by patients with various ailments/diseases. For these reasons, questions arise as to how NSAIDs affect comorbidities such as neurodegenerative diseases, depression disorders, cardiovascular diseases, diabetes, cancers, and others. Moreover, the scientific interest may also result from the fact that NSAIDs are a heterogeneous group of drugs (chemical structure of NSAIDs is presented in Table 1), which means that each of them may show additional properties, related not only to their effects on cyclooxygenase (COX) isoforms.

Table 1. Division of non-steroidal anti-inflammatory drugs (NSAIDs) based on their chemical structure and the effect on COX isoforms

Chemical group	Mechanism of action	
	non-selective COX-1 & COX-2	selective COX-2
Salicylates	acetylsalicylic acid (aspirin), sodium salicylate	–
Acetic acid derivatives	indomethacin, diclofenac, sulindac sulfide	–
Heteroaryl acetic acid derivatives	ibuprofen, naproxen	–
Enolic acid (oxicams)	piroxicam, meloxicam	–
Diaryl heterocycles (coxibs)	–	celecoxib, rofecoxib, parecoxib

COX-1 – cyclooxygenase-1; COX-2 – cyclooxygenase-2.

Objectives

While NSAIDs have been used for many years, their mechanisms of action are still being explored, and other anti-inflammatory molecular targets that may expand their use or explain adverse effects are being investigated. Anti-inflammatory effects of NSAIDs, in addition to the basic mechanism of action, i.e., COX inhibition, may also result from their impact on other pathways, such as oxidative stress[1] or kynurenine,[2] but they have been widely discussed elsewhere.[1,2] This work offers a complex overview of selected but mutually related mechanisms of action of NSAIDs, namely peroxisome proliferator-activated receptor gamma (PPARγ), nuclear factor-κB (NF-κB) and the unfolded protein response (UPR) pathways. There is a growing interest in these signaling molecules

Table 2. Effects of NSAIDs on PPARγ, NF-κB and UPR pathways. Within the mechanisms of action of NSAIDs, the literature is arranged alphabetically in relation to the drug under investigation.

Experimental model	Dose/concentration of NSAIDs and scheme of administration	Effects of NSAIDs on the signaling pathways	Role of NSAIDs action	Ref.
NSAIDs – the anti-inflammatory mechanism of action through the PPARγ receptor				
Carrageenan-induced paw edema in rats – an acute inflammation model	celecoxib (0.3–30 mg/kg; ip.)	Activation of PPARγ receptor and anti-inflammatory IL-10. Decrease in inflammatory cytokines.	anti-inflammatory	3
Lewis lung carcinoma cells	celecoxib (50–200 μM for 24 h)	Increased AA level and decreased PGE_2 production through upregulation and downregulation of cPLA2 and COX-2 proteins, respectively. Increased expression of PPARγ protein.	pro-apoptotic	4
3T3-L1 preadipocytes	indomethacin (10 μm) ibuprofen (75 μm) sodium diclofenac (25 μM)	Stimulation of PPARγ activity. Regulation of PPARγ-dependent target genes.	adipocyte differentiation	5
C3H10T1/2 clone 8 murine fibroblasts	indomethacin (10^{-4} M)	Inhibition of COX activity and activation of PPARγ.	adipocyte differentiation	6
Rat hepatoma cell line H4-II-E-C3 and CV-1 cells co-transfected with rat PPARα and PPARγ	ibuprofen, indomethacin and naproxen (10^{-8}–10^{-3}M)	Activation of PPARα and PPARγ isoforms at concentrations of 10^{-4}–10^{-3} M.	potential angiostatic and anti-cancer effect	7
Preadipocytes (3T3-L1) and prostate cancer cells (DU-145)	diclofenac (25 μM)	Activation of PPAR (partial agonist) and inhibition of PPAR trans-activation by rosiglitazone (competitive antagonist).	Antagonism of PPAR signaling by diclofenac resulted in the inhibition of adipocyte differentiation and increased proliferation of prostate cancer cells.	8
In vitro: hemangioma-derived mesenchymal stem cells (Hem-MSCs) obtained from patients. In vivo: 6-week-old, male, mice with xenograft tumors from Hem-MSCs	celecoxib (0.1–1000 μg/mL for 24 h) celecoxib (0.1 mg/g/day) administered to the mice via oral intake for 4 weeks	Increased expression levels of genes involved in adipogenic differentiation: COX-2, human-CCAAT-enhancer-binding protein (CEBPα) and PPAR-γ.	Inhibition of the proliferation and stimulation of the adipogenic differentiation of Hem MSCs in vitro and in the xenograft tumors.	9

Table 2. Effects of NSAIDs on PPARγ, NF-κB and UPR pathways – cont.

Experimental model	Dose/concentration of NSAIDs and scheme of administration	Effects of NSAIDs on the signaling pathways	Role of NSAIDs action	Ref.
Breast cancer MCF7cells	celecoxib (0.02 mM) diclofenac (0.375 mM) ibuprofen (0.75 mm) indomethacin (0.5 mm) sulindac (0.06 mM) for 24 h	Upregulation of the PPARγ expression and its translocation to the nucleus.	proapoptotic activity	10
NSAIDs – the anti-inflammatory mechanism of action through the NF-κB pathway				
Human non-small cell lung carcinoma (H1299)	celecoxib (100 μM) with TNF (0.1 nM) for 24 h	Inhibited activation of IKK and NF-κB as well as related signaling kinases, i.e., JNK, p38 MAPK and ERK in cancer cells.	anti-inflammatory antiproliferative	11
Murine fibroblast cell line (NIH-3T3)	celecoxib – 25 μM for 1 h with TNF-α (10 ng/mL)	Inhibition of the TNF-α-induced nuclear accumulation of the NF-κB p65 subunit.	anti-inflammatory	12
Osteoclasts derived from mouse hematopoietic stem cells	diclofenac (10–500 nM) for 30 min	Inhibition of the IκB degradation, which maintained inactive NF-κB in the cytosol.	regulation of the osteoclast differentiation	13
Model of cystic fibrosis using respiratory epithelium cells	ibuprofen (480 μM) for 30 min before stimulating cells with 10 ng/mL TNF-α	Modest suppression of TNF-α-induced NFκB activation.	anti-inflammatory	14
RAW 264.7 mouse macrophages	etoricoxib and lumiracoxib (1/10/100 μM) for 30 min and then stimulated for 30 min with 10 μg/mL LPS	Inhibition of the LPS-induced NF-κB activation by etoricoxib and lumiracoxib at highest concentration of 100 μM. Etoricoxib additionally inhibited CREB activation, which contributed to a reduced expression of iNOS and COX-2 expression.	anti-inflammatory	15
Human leukemic cell line KBM-5	aspirin (1–10 mm) ibuprofen (1–5 mm) indomethacin (0.1–1 mm) diclofenac (0.2–1 mm) celecoxib (10–50 mM) for 4 h or 8 h and before stimulating cells with 0.1 nM TNF for 30 min	Tested NSAIDs suppressed activation of NF-kB by inhibiting IKK activation and IkBα degradation.	anti-inflammatory and antiproliferative	16
Human vulvar squamous cell carcinoma (A431 cells)	ibuprofen and diclofenac combined with cannabidiol equimolar to 20 μM	Decreased level of NF-κB p50 and p65 proteins and their ability to bind to DNA by combinations of cannabidiol with NSAIDs.	anti-inflammatory and antiproliferative	17
Rats with collagen-induced arthritis (CIA)	ibuprofen (30 mg/kg) given twice daily to CIA rats for 2 weeks	Attenuation of elevated levels of phosphorylated p38, JNK and NF-κB p65 in the hippocampus of CIA rats. In addition, normalization of the decreased excitatory amino acid transporter 2 (EAAT2) level, the increased extracellular glutamate, and the upregulated hippocampal NMDA receptor 2B of CIA rats.	inhibition of neuroinflammation memory improvement	18
Human ovarian cancer cell lines SKOV3 and OVCAR3 In vivo: mice inoculated subcutaneously with cells SKOV3	celecoxib (100 mM)	diminished NF-κB p65 expression	Celecoxib and chemotherapy drugs can enhance the inhibition of ovarian cancer cells in vivo.	19
NSAIDs – the anti-inflammatory mechanism of action through the UPR pathway				
Primary human coronary artery endothelial cells (HCAEC) Human umbilical vein endothelial cells (HUVEC) Human pulmonary artery endothelial cells (HPAEC)	In the presence of tunicamycin (1.0 μM) or high-dextrose (27.5 mM) the cells were treated with different concentrations of celecoxib and rofecoxib (0–10,000 nM)	Celecoxib, but not rofecoxib inhibited ER stress in endothelial cells. It downregulated the ATF6 and GRP78 expression and phosphorylation of IRE1α and PERK.	ER stress involved in unfavorable effects of rofecoxib on cardiovascular outcomes.	20

Table 2. Effects of NSAIDs on PPARγ, NF-κB and UPR pathways – cont.

Experimental model	Dose/concentration of NSAIDs and scheme of administration	Effects of NSAIDs on the signaling pathways	Role of NSAIDs action	Ref.
Human colorectal cancer cell lines: HCT-8, HT-29, HCT-116	celecoxib (20 μM) in sequential treatment followed by bortezomib (20 nM)	Enhanced activation of apoptotic markers (i.e., caspase-9, caspase-3 and PARP, Bax, p53, and PUMA) through the ER stress-mediated mitochondrial dysfunction and increased cytosolic and mitochondrial $Ca2^+$ and increased induction of CHOP. Additionally, celecoxib followed by bortezomib enhanced the ER stress-mediated autophagy-associated cell death (induced expression of Beclin-1 and autophagosome-associated LC3-I/II proteins).	pro-apoptotic induction of autophagy-associated cell death	21
Hepatoma HepG2 cells	celecoxib (80 μM) for 24 h and 48 h	Increased the mRNA and protein levels of ATF4, ATF6, sXBP-1, unspliced XBP1 (uXBP1), and CHOP.	pro-apoptotic	22
Human neuroblastoma SH-SY5Y cells	diclofenac (100–300 μM) added 2 h before the stimulation by 100 nM thapsigargin or by 3 mg/mL tunicamycin for 24 h	Inhibition of caspase-2, caspase-9 and caspase-3 activation and prevention from a decrease in mitochondrial membrane potential caused by ER stress.	anti-apoptotic	23
Endothelial EA.hy926 cells	diclofenac (75 μM) concomitantly with tunicamycin 0.5 μg/mL for 24 h	Inhibition of ER stress-responsive genes, i.e., CHOP/DITT3, GRP78/HSPA5 and DNAJB9. Additionally, the drug diminished the significant upregulation and release of the GRP78 protein.	anti-apoptotic	24
In vitro: gastric carcinoma cells In vivo: mice were inoculated subcutaneously with MKN-45 cells	celecoxib (10–100 μM) celecoxib orally (100 or 200 mg/kg/day)	Activation of PERK and eIF2α leading to ATF4 expression. The overexpression of GRP78. GRP78 upregulation.	pro-apoptotic inhibition of xenograft tumor growth	25
Human hepatoma Huh-7 cells	diclofenac (300 μM) indomethacin (500 nM)	Activation of the PERK pathway followed by enhanced expression of the proapoptotic GADD153/CHOP protein.	pro-apoptotic	26
In vitro: glioblastoma, breast carcinoma, pancreatic carcinoma, Burkitt's lymphoma, multiple myeloma cell lines In vivo: 6-week-old male athymic nu/nu mice implanted with U87 glioblastoma cells	celecoxib (40–80 μM) 2,5-dimethyl-celecoxib (20–60 μM) 2,5-dimethyl-celecoxib (150 mg/kg, orally for 50 h)	Activation of ER stress-associated proteins GRP78, CHOP, and caspase-4 in cancer cell lines. Increase in CHOP protein expression in the tumor tissue.	pro-apoptotic reduced tumor growth	27
In vivo: Sprague Dawley male rats after middle cerebral artery occlusion	parecoxib (10 or 30 mg/kg, IP)	Inhibition of translocation of CHOP and Foxo1 and increase in GRP78 and ORP150 (oxygen-regulated protein 150) expression.	suppressed cerebral ischemic injury	28

AA – arachidonic acid; ATF4 – activating transcription factor 4; ATF6 – activating transcription factor 6; CEBPα – human-CCAAT-enhancer-binding protein; CHOP – C/EBP homologous protein; CIA – collagen-induced arthritis; COX – cyclooxygenase; PLA2 – cytosolic phospholipase A2; CREB – cAMP response element-binding protein; DITT3 – DNA damage inducible transcript 3; DNAJB9 – DnaJ heat shock protein family (Hsp40) member B9; EAAT2 – excitatory amino acid transporter 2; eIF2α – eukaryotic translation initiation factor 2α; ER – endoplasmic reticulum; ERK – extracellular signal-regulated kinases; Foxo1 – Forkhead box protein O1; *GADD153* – DNA damage-inducible gene 153; GRP78 – 78-kDa glucose-regulated protein; HSPA5 – heat shock protein family A; IKK – IκB kinase; IL-10 – interleukin 10; iNOS – inducible nitric oxide synthase; IRE1 – inositol-requiring enzyme 1; IκB – inhibitor of nuclear factor kappa B; JNK – c-Jun N-terminal kinase; LPS – lipopolysaccharide; NF-κB – nuclear factor-κB; NMDA – N-methyl-D-aspartate receptor; NSAIDs – non-steroidal anti-inflammatory drugs; ORP – oxygen-regulated protein; p38 MAPK – p38 mitogen-activated protein kinases; PARP – poly (ADP-ribose) polymerase; PERK – protein kinase R-like ER kinase; PGE_2 – prostaglandin E_2; PPARα – peroxisome proliferators–activated receptor α; PPARγ – peroxisome proliferators–activated receptor γ; PUMA – p53-upregulated modulator of apoptosis; sXBP-1 – spliced X-box binding protein 1; TNF-α – tumor necrosis factor alpha; uXBP1 – unspliced X-box binding protein 1.

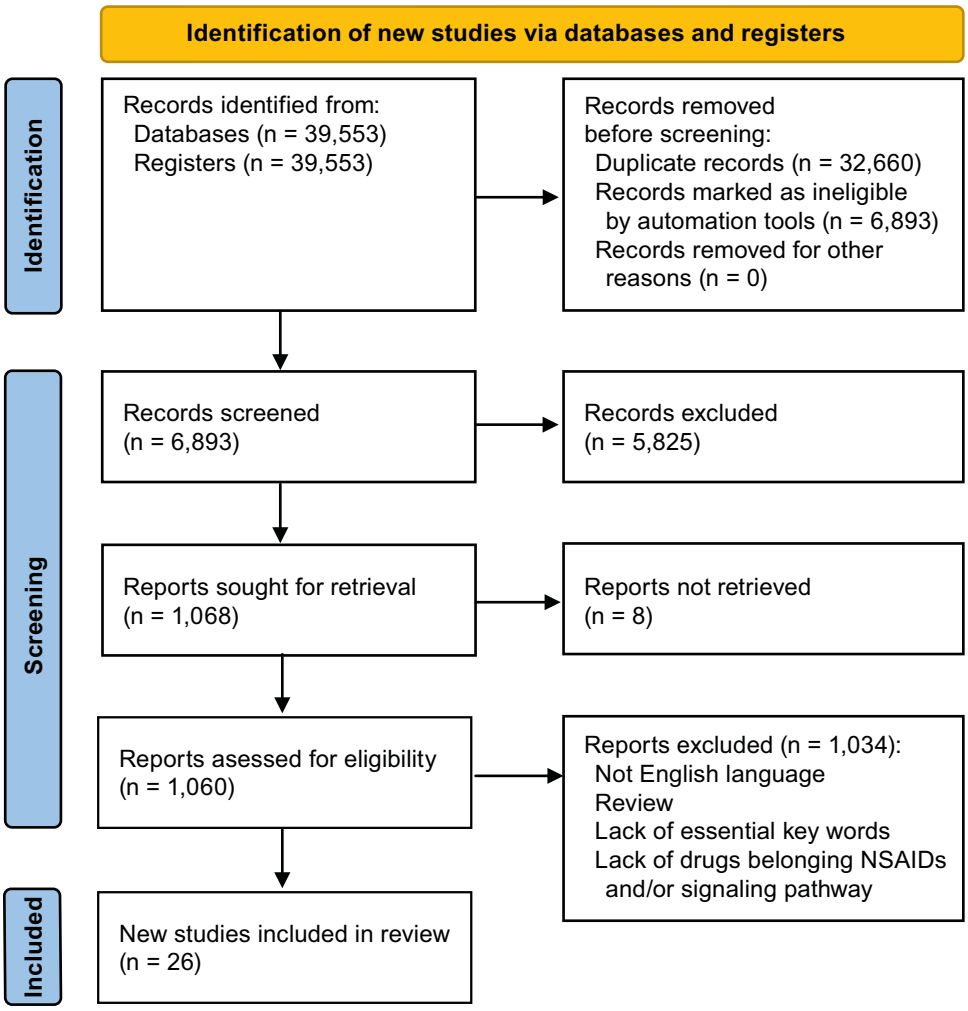

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart

as mediators of the anti-inflammatory effects of NSAIDs in many diseases, i.e., cancer, neurodegenerative disorders and depression. Interestingly, these pathways may also underlie the mechanisms of action of NSAIDs on pathological processes other than inflammation, such as uncontrolled cancer cell proliferation or neuronal dysfunction. Herein, we will attempt to answer the question of how these new molecular targets may affect the therapeutic actions of NSAIDs pharmaceuticals.

Methodology

A literature search was carried out in the PubMed and Google Scholar databases on September 15, 2022, using the queries: "NSAIDs "and" mechanism of action"; "NSAIDs "and" PPARγ"; "NSAIDs "and" NF-κB"; "NSAIDs "and" ER stress (endoplasmic reticulum stress)". We then selected key studies that examined both diverse cell lines and in vivo models. Their results are discussed in the text and presented in Table 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is presented as Fig. 1.

Classical mechanism of action of NSAIDs

Non-steroidal anti-inflammatory drugs are among the most widely administered medications worldwide.[29] This is attributed to their variety of applications, including anti-inflammatory, antipyretic, analgesic, and antithrombotic effects for aspirin, along with their limited side effects. The inflammatory response is triggered by external stimuli, where membrane phospholipids activate phospholipase A_2 to release arachidonic acid, which is then converted to the precursor prostaglandin (PG)H_2 by COX isoforms. Following PGH_2 production, prostacyclin (PGI_2), prostaglandins, e.g., PGE_2, and thromboxane (TX) A_2 are formed.[30] TXA_2 causes vasoconstriction and platelet aggregation, while PGE_2 causes hyperalgesia, and both prostacyclin and prostaglandins (prostaglandin E_2 – PGE_2, prostaglandin I_2 – PGI_2, prostaglandin D_2 – PGD_2) cause vasodilation. These prostanoids mediate inflammation by contributing to pain, redness, and swelling.[31] The main mechanism of NSAIDs, first discovered by Sir John Vane in 1971, works by inhibiting the synthesis of prostaglandins, specifically by blocking the COX enzymes COX-1

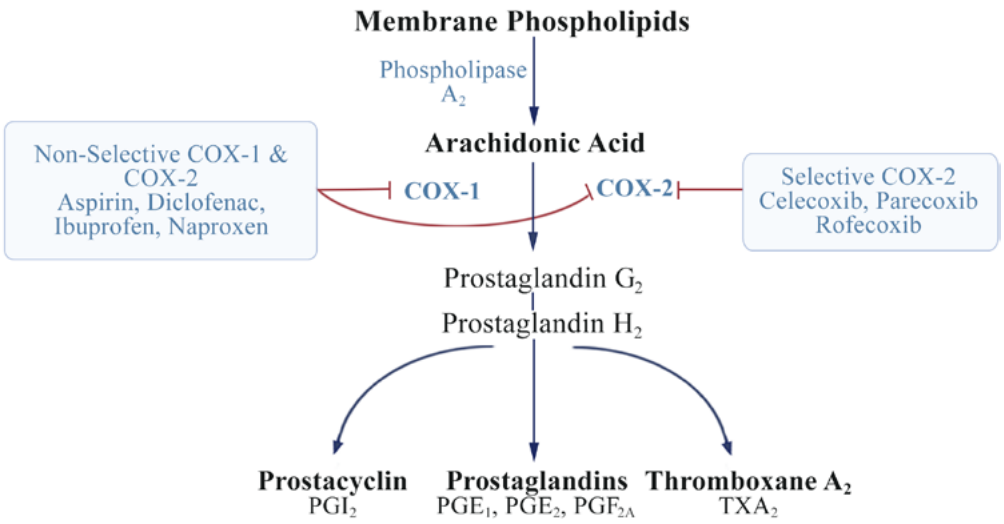

Fig. 2. Mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs). Membrane phospholipids produce arachidonic acid by phospholipase A_2. Arachidonic acid produces the first precursor prostaglandin G_2 by cyclooxygenase (COX)-1 and COX-2. Then, prostaglandin H_2 is produced from prostaglandin G_2, which by various enzymes produces prostacyclin (PGI_2), prostaglandins, e.g., PGE_1, PGE_2, and thromboxane A_2 (TXA_2). NSAIDs act as COX-1 and COX-2 inhibitors. Diclofenac, ibuprofen and naproxen reversibly inhibit COX-1 and COX-2, and aspirin irreversibly inhibits COX-1 and COX-2. Celecoxib is a COX-2 selective and reversible blocker

and COX-2, which prevents the formation of PGI_2, PGs and TXA_2[29] (Fig. 2). Blocking the effects of these prostaglandins results in the therapeutics and side effects of NSAIDs.[32] As the use of NSAIDs has risen drastically over the years, the caution about their adverse effects has increased as well, including concerns regarding increased formation of gastrointestinal tract ulcers.[33] This, in turn, has halted NSAIDs as a medication for chronic pain, even though this was once a major indication for their use.[30]

As the years progressed and scientific research advanced, the classification of NSAIDs has progressed from initially being based on their chemical structure to being differentiated according to their selectivity to cyclooxygenase inhibition.[33] Research has proven the presence of at least 2 COX isoforms until now. The 1st isoform of COX (COX-1) is constitutively expressed and carries out homeostatic functions in the body. It is regulated by development and highly expressed in platelets, renal collecting tubules, monocytes, and endothelial cells.[30] When COX-1 is activated, it promotes the protection of the gastric mucosa and platelet activation, and preserves kidney function.[32] The 2nd isoform of COX (COX-2) is activated mostly by mediators of inflammation, such as tumor necrosis factor alpha (TNF-α), lipopolysaccharides (LPS) and interleukin-1 (IL-1). It acts on a vast range of cells and tissues, including rheumatoid synovial endothelial cells, vascular endothelial cells, macrophages, and monocytes.[30] Conversely, COX-2 has also been shown to express low-level physiological actions in tissues such as the uterus, brain and kidney.[34]

There are also other isoforms of COX, such as COX-3, which is a splice variant of COX-1. It was identified in mice, rats and dogs. However, it remains controversial whether a COX-3 and 2 shorter variants without cyclooxygenase activity, i.e., PCOX-1a and PCOX-1b[35,36] proteins, exist in humans, and their biological role is unknown.

Traditional NSAIDs non-selectively bind and inhibit COX-1 and COX-2 to varying degrees. However, due to the critical side effects of nonselective inhibition, the difference in size between both COX isoform active sites was used to develop COX-2-specific inhibitors to gain the therapeutic uses of NSAIDs without their COX-1 inhibiting side effects. These side effects include small bowel and gastric mucosal injuries, renal injury, hepatotoxicity, and pulmonary complications.[33,37] COX-2 selective inhibitors include meloxicam, rofecoxib and celecoxib,[32] which demonstrate fewer gastrointestinal symptoms and complications compared to nonselective COX inhibitors, such as ibuprofen and diclofenac.[38] However, this is not to say that COX-2 selective inhibitors are void of concerning side effects. The most dangerous is the increase in cardiovascular risk.[39]

Based on their chemical structure (Table 1), NSAIDs can be broadly classified into salicylates (e.g., sodium salicylate, acetylsalicylic acid), aryl, and heteroaryl acetic acid derivatives (e.g., ibuprofen, naproxen), indole/indene acetic acid derivatives (e.g., indomethacin, sulindac), anthranilates (e.g., diclofenac), and enolic acid derivatives (e.g., piroxicam, meloxicam).[40] However, a more common classification of NSAIDs is based on the type of COX interaction and selectivity, i.e., both COX enzymes can be inhibited equally (e.g., indomethacin, aspirin, diclofenac, naproxen, and ibuprofen), COX-2 can be inhibited with 5-50-fold selectivity (e.g., celecoxib, rofecoxib, parecoxib), COX-2 can be inhibited with greater than 50-fold selectivity (NS-398), and finally, some NSAIDs show poor selectivity for COX enzymes (e.g., sulfasalazine, sodium salicylate).[33,41]

However, the mechanism of action of NSAIDs described above, which is based on the cascade of AA metabolite conversions, is only a small fragment of the myriad processes that occur within the organism during an inflammatory event.

At the onset of inflammation, different signaling pathways are activated by proinflammatory factors, and these may work to either reinforce or diminish their actions. During this process, proinflammatory and other factors are formed due to tissue damage and induce a cascade

of AA conversions, as well as COX and LOX activation. As a result of these conversions, reactive oxygen species (ROS) are being formed, leading to the activation of NF-κB, a factor responsible for the promotion of proinflammatory signaling pathways. Conversely, AA, other polyunsaturated fatty acids (PUFA), and prostanoid conversion products, e.g., 15d-PGJ2, activate the anti-inflammatory factor PPARγ.[42–44] Thus, endogenous proinflammatory and anti-inflammatory systems can be activated and modulated by these pathways.

The anti-inflammatory mechanism of NSAIDs action through the PPARγ receptor

The peroxisome proliferator-activated receptor (PPAR) belongs to the family of ligand-inducible nuclear receptors acting as transcription factors. The family of PPARs comprise 3 isoforms, namely PPARα, PPARδ/β and PPARγ. The latter isoform is present in adipose tissue, the liver, the kidney, and the immune system, including bone marrow, lymphocytes, monocytes, and macrophages,[45–47] and also in the central nervous system (CNS) cells, namely neurons, microglia, astrocytes, and oligodendrocytes.[48,49] Peroxisome proliferator-activated receptor gamma plays an important role in lipid and glucose metabolism, and insulin sensitivity. Therefore, agonists of this receptor are called insulin-sensitizing medications, and they are used in the treatment of type 2 diabetes (e.g., pioglitazone). Previous studies indicate that PPARγ agonists[43] stimulate the differentiation of monocytes to macrophages in peripheral tissue, control brain inflammation through inhibition of the proinflammatory function of microglia, and suppress the expression of inducible nitric oxide synthase (iNOS), matrix metalloproteinase (MMP-9) and proinflammatory cytokines, IL-1β, IL-6 and TNF-α.[47,50,51] Therefore, PPARγ is the most intensively studied of the 3 isoforms. Stimulation of PPARγ antagonizes the activity of NF-κB and consequently inhibits the formation of proinflammatory cytokines.[50,51] There are numerous natural PPARγ ligands, including polyunsaturated fatty acids, e.g., linoleic acid, docosahexaenoic acid, exogenous agonists such as flavonoids[52] (e.g., curcumin) and drugs such as glitazones,[53,54] and NSAIDs[43] that are responsible for an anti-inflammatory effect. Several members of the heterogenous nonsteroidal anti-inflammatory family of drugs have been described as ligands for PPARγ according to their affinities and activity for PPARγ. These anti-inflammatory drugs were divided into 3 groups: 1. Those with high affinity (indomethacin and diclofenac); 2. Those with moderate affinity (ibuprofen, fenoprofen, flufenamic acid); and 3. Those without agonistic effect (aspirin, piroxicam).[47,55] The studies mentioned above[47,55] were conducted in vitro and determined the affinity of NSAIDs to the PPARγ receptor without formulating a conclusion about possible therapeutic properties of the effects.[55] Puhl et al.[5] found that NSAIDs bind to PPARγ with a range of affinities as follows: sulindac sulfide > diclofenac > indomethacin > ibuprofen. Additionally, it was demonstrated that diclofenac is a weak partial agonist of PPARγ, ibuprofen shows an intermediate agonistic activity, and indomethacin is a strong agonist of the receptor. Moreover, full agonists include thiazolidinediones, such as rosiglitazone, and stimulation of PPARγ activity by NSAIDs has been shown to contribute to adipocyte differentiation. However, other studies indicate that activation of PPARγ follows a different order, namely S-naproxen > indomethacin > S-ibuprofen > R-ibuprofen.[7] The work of Adamson et al.[8] has demonstrated that diclofenac shows an affinity for PPARγ 50 times greater than other NSAIDs and 10 times lower than full agonist rosiglitazone, but similar to pioglitazone. Diclofenac is a partial agonist; therefore, it may function as a competitive antagonist in the presence of a full agonist, and consequently can displace other drugs, e.g., rosiglitazone, from the binding site of the receptor. Therefore, diabetic patients whose blood glucose is controlled using thiazolidinedione drugs may experience poorer glycemic control in the presence of diclofenac. Table 2 summarizes the effects of selected anti-inflammatory drugs on the PPARγ receptor and the significance of these actions.

It is worth mentioning that NSAIDs bind to the PPARγ at micromolar concentrations, and this is a higher concentration than what is needed to inhibit COXs.[6,7] However, such a concentration can be achieved during rheumatoid disease when NSAIDs are used at high doses to obtain therapeutic effect.[8]

NSAIDs anti-inflammatory mechanism of action through the NF-κB

Nuclear factor-κB consists of a family of transcription factors that play essential roles in inflammation, immunity, cell proliferation, differentiation, and survival.[56–58] Under normal conditions, NF-κB as the heterodimer p50/p65 interacts with IκB to remain in an inactive state in the cytosol. However, proinflammatory cytokines (e.g., TNF-α and Il-1), bacterial and viral products, and cellular stress (oxygen and ER stress) lead to the phosphorylation of IκB protein by the activated IKK (IκB kinase) complex.[56–58] Interestingly, the IκB protein acts as the natural inhibitor of NF-κB. Thus, phosphorylation of IκB results in its degradation, leading to the release of NF-κB (p50/p65) that is then able to translocate into the nucleus and regulate multiple target genes encoding proinflammatory cytokines, chemokines, cell adhesion molecules, and enzymes that produce proinflammatory factors, such as nitric oxide and prostaglandins.[56–58]

The impact of NSAIDs on NF-κB was confirmed in studies on different cell lines and animal models (Table 2).[11–16] All NSAIDs inhibit NF-κB signaling, but the mechanisms of their actions and the potency of inhibition can differ between drugs. For example, a study by Takada et al.[16] showed a comparison indicating that the most potent inhibitor of NF-κB is celecoxib, followed by diclofenac > indomethacin > naproxen > ibuprofen > aspirin. There are also studies on the development of diclofenac[59] and ibuprofen[60] derivatives that demonstrate better effectiveness than reference drugs.

Non-steroidal anti-inflammatory drugs suppress the transcription factor NF-κB, which controls the gene expression of proinflammatory factors, including COX-2, which is not only responsible for inflammation but is also implicated in tumor cell proliferation. This effect is obtained by the inhibition of IKK and the subsequent inhibition of IκB degradation.[11–14,16] Interestingly, diclofenac appeared to regulate osteoclast differentiation by stabilizing the inactive form of NF-κB,[13] whereas ibuprofen given to rats with collagen-induced arthritis inhibited neuroinflammation in the hippocampus by attenuating the NF-κB cascade, and contributed to the memory improvement.[18] This latter example shows that the presence of inflammatory processes and activation of the immune system may affect the CNS and trigger or exacerbate neuroinflammation. It was further demonstrated that inflammatory mediators are implicated in depressive symptoms by directly affecting brain tissue, modulating the monoaminergic system and initiating neurotoxic processes in brain areas responsible for emotions and emotional memories.[61]

PPARγ compared to NF-κB

As mentioned above, PPARγ shows an anti-inflammatory effect in contrast to the proinflammatory NF-κB. Previous studies demonstrate that PPARγ modulates the inflammatory response initiated by activation of NF-κB-dependent Toll-like receptors (TLRs). The activation of PPARγ stimulates the expression of the genes and proteins that negatively regulate NF-κB, such as IκB.[44,62] Moreover, potent exogenous agonists of PPARγ, such as pioglitazone or rosiglitazone, used alone or in the presence of LPS (an inflammatory stimulator), significantly reduced the activation of NF-kB in a mouse cystic fibrosis biliary epithelium.[62] This effect results from the upregulation of IκB, a negative regulator of NF-κB.[62] Peroxisome proliferator-activated receptor gamma also has enzymatic properties, being an E3 ubiquitin ligase. Therefore, the effect of PPARγ on NF-κB is also a result of the ubiquitination and degradation of p65, which appears to be critical to the NF-κB signaling pathway.[63]

Thus, NSAIDs stimulate PPARγ-mediated inhibition of the proinflammatory transcription factor NF-κB, while also potentially directly inhibiting NF-κB. Further research is required in this regard to define whether the inhibitory effects of NSAIDs on NF-κB are indirect, direct, or if both mechanisms are interrelated.

NSAIDs anti-inflammatory mechanism of action through the UPR pathway

Endoplasmic reticulum (ER) is involved in many different cellular functions, such as regulating the synthesis, folding, maturation, and transport of proteins, the synthesis and storage of lipids, acting as the main cellular storage for Ca^{2+}, contributing to glucose metabolism, and serving as a platform for signaling and communication between organelles. Endoplasmic reticulum stress homeostasis is constantly challenged by physiological demands or pathological factors that affect its multiple functions. Physiological and/or pathological processes that disturb proper protein folding resulting in the accumulation of unfolded or misfolded proteins, cause a cellular state known as ER stress. The UPR involves the reduction of new protein synthesis, and the elimination of misfolded proteins through the ER-associated protein degradation (ERAD) pathways and autophagy. Another possibility to restore ER homeostasis can be by enhancing the capacity of the ER to fold proteins. Depending on the strength or duration of the factor triggering ER stress, the UPR can have contrasting effects, being either cell-protective or cell-destructive. When attempts to restore proper homeostasis fail, and ER stress cannot be arrested, the signaling pathways switch from pro-survival to pro-apoptotic.[64–70] The accumulation of unfolded/misfolded proteins is sensed by 3 ER transmembrane effector proteins, namely inositol requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK) and the activating transcription factor 6 (ATF6). Under physiological conditions, these 3 proteins are stored in inactive forms by binding to reticular chaperones 78-kDa glucose-regulated protein (GRP78) and 94-kDa glucose-regulated protein (GRP94). When ER stress is induced, GRP78 and GRP94 disassociate from PERK, IRE1 and ATF6, thereby activating their intracellular pro-survival and/or pro-apoptotic functions.[64–70]

Protein kinase R-like ER kinase inhibits protein translation in the cell by phosphorylation of eukaryotic initiation factor 2α (eIF2α), leading to the transient attenuation of protein synthesis and the reduced influx of newly synthesized proteins into the ER. This marks one of the first responses of the cell to ER stress. Inhibition of protein synthesis supports cell survival by blocking the accumulation of unfolded nascent proteins. However, sustained stress again changes the pro-survival response to pro-apoptotic. This is accomplished by the promotion of increased activating transcription factor 4 (ATF4) expression, which is responsible for the transcription of different pro-apoptotic factors such as 1) growth arrest and

DNA damage-inducible 34 (GADD34), and 2) transcription factor C/EBP homologous protein (CHOP), as well as 3) the pro-apoptotic BCL-2 family proteins. The *CHOP* is one of the most potently upregulated genes during prolonged ER stress, and the interplay of GADD34, ATF4 and CHOP results in the activation of genes involved in cell death, cell-cycle arrest and senescence.[64–70]

Inositol requiring enzyme 1, having an endoribonuclease activity, is responsible for the splicing of X-box binding protein 1 (XBP1) mRNA, resulting in the generation of an active (spliced) transcription factor XBP1s. Once generated, XBP1s induce expression of ER stress-responsive genes involved in the increased protein folding capacity and degradation of misfolded proteins to restore homeostasis and increase cell survival following stress.[64–71]

Upon ER stress, ATF6 is transported to the Golgi apparatus, where it is cleaved by site-1 and site-2 proteases to release a fragment containing a basic leucine zipper (bZIP) transcription factor, termed "ATF6p50". This 50 kDa ATF6 fragment translocates to the nucleus where it increases transcription of UPR-responsive genes, i.e., gene expression of ER chaperones, and ERAD components.[64–71]

It is important to note that there is extensive crosstalk between PERK, IRE1 and ATF6 signaling pathways. For example, ATF4, which is regulated via the PERK pathway, increases the transcription of IRE1, whereas ATF6 can also induce the expression of XBP1 and CHOP to enhance UPR signaling. All 3 UPR pathways contribute to inducing cell apoptosis when the cell protective measures mediated by the UPR fail to restore folding capacity.[64–71]

The ER stress-induced UPR not only maintains cellular homeostasis but can also directly regulate the inflammatory pathways.[71] The principal inflammatory signaling proteins whose expression is directly initiated during the UPR are 1) NF-κB and 2) mitogen-activated protein kinase (MAPK) family proteins consisting of A) stress-inducible kinases including JNK and p38 MAPK, and B) extracellular signal-regulated kinase (ERK). During ER stress, the IRE1-TRAF2 pathway has been shown to promote the NF-κB-mediated inflammatory response by triggering the recruitment of IKK, the phosphorylation and subsequent degradation of IκB, resulting in the activation of NF-κB (the IKK-IκB pathway). Additionally, PERK and ATF6 have been reported to promote NF-κB activation. In response to ER stress, activation of the PERK-eIF2α signaling pathway results in the attenuation of global mRNA translation and decreased translation of both IκB and NF-κB. Due to a shorter half-life of IκB compared to NF-κB, the higher proportion of NF-κB to IκB favors NF-κB-mediated inflammatory responses.[71,72] Moreover, the ATF6-mediated arm of the UPR has been demonstrated to activate NF-κB.[71] Therefore, this data highlights that ATF6 directly participates in regulating the inflammatory response as a transcription factor.

The effect of NSAIDs on UPR signaling was first described in a search for mechanisms underlying the adverse effects of these drugs. For example, studies carried out by Tsutsumi et al.[73] showed that cultured guinea pig gastric mucosal cells treated with NSAIDs (indomethacin, diclofenac, ibuprofen, and celecoxib) decreased cell viability, increased DNA fragmentation, and displayed elevated CHOP mRNA and protein. Additionally, indomethacin was shown to induce the expression of other components of the UPR pathway, such as GRP78, ATF6, ATF4, and XBP1. In those studies, NSAIDs elicited ER stress-dependent apoptosis of cultured gastric mucosal cells, which was particularly related to the expression of CHOP.[73]

NSAIDs effect on UPR signaling and cancer

Other studies have shown that the UPR-dependent induction of apoptosis by NSAIDs has important anti-cancer actions[27]; therefore, the anti-neoplastic effect of NSAIDs has been widely studied in various types of cancer and was found to be associated with COX-dependent mechanisms, as well as with anti-apoptotic properties resulting from ER stress stimulation (Table 2).

Endoplasmic reticulum (ER) stress is an important factor in cancer development as increased expression of the main components of UPR pathways was observed in tissue sections from a variety of human tumors. In different cancer cell types, such as glioblastoma, breast and pancreatic carcinoma, Burkitt's lymphoma, and multiple myeloma, celecoxib was shown to induce activation of ER stress-associated proteins GRP78, CHOP and caspase-4, resulting in cancer cell death.[27,74] In gastric carcinoma cells, the pro-apoptotic action of celecoxib was demonstrated to be related to PERK and eIF2α phosphorylation, leading to ATF4 expression. However, silencing of ATF4 partially reversed the overexpression of GRP78, which was also induced by celecoxib, suggesting that ATF4 was one of the UPR arms responsible for GRP78 upregulation after celecoxib treatment.[25] A recent meta-analysis of studies focusing on the molecular mechanisms of celecoxib in tumor development further highlighted its various anti-cancer actions.[75] It was shown that celecoxib mainly regulates the proliferation, migration and invasion of tumor cells by inhibiting the COX-2/prostaglandin E2 signal axis, thereby inhibiting the phosphorylation of NF-κB gene binding Akt, a signal transducer and activator of transcription, and the expression of MMP-2 and MMP-9. Likewise, diclofenac and indomethacin also efficiently activated the PERK pathway of the UPR, which enhanced the expression of the pro-apoptotic GADD153/CHOP protein in Huh7 hepatoma cells.[26]

However, NSAIDs do not always cause ER stress-dependent apoptosis in cancer cells. Yamazaki et al.[23] were the first to demonstrate that diclofenac, indomethacin, ibuprofen, aspirin, and ketoprofen have protective effects against ER-stress-induced apoptosis of human neuroblastoma SH-SY5Y cells, and this is independent of its COX-inhibitory activity.

NSAIDs and the UPR signaling in other experimental models

The role of UPR signaling in the mechanism of action of NSAIDs has been widely studied in cancer cells. However, limited data are available for other experimental models (Table 2). For example, in endothelial cells, diclofenac significantly inhibited the activation of ER stress-responsive genes, i.e., *CHOP*/*DITT3*, *GRP78*/*HSPA5* and *DNAJB9*. Additionally, the drug diminished the significant upregulation and release of the GRP78 protein in endothelial cells.[24] Similar effects in endothelial cells (e.g., HCAEC, HPAEC and HUVECs) were obtained after the application of meloxicam, ibuprofen and acetylsalicylic acid, although notably not for celecoxib. Celecoxib downregulated ATF6 and GRP78 expression, as well as IRE1α and PERK phosphorylation stimulated by ER-stress inducer tunicamycin.[20] There is also a study on a model of cerebral ischemic injury, in which parecoxib significantly suppressed cerebral ischemic injury-induced nuclear translocation of CHOP and Foxo1, and attenuated the immunoreactivity of caspase-12 in ischemic penumbra. Furthermore, the protective effect of parecoxib was accompanied by an increased GRP78 and 150-kDa oxygen-regulated protein (ORP150) expression. This study suggested that elevated GRP78 and ORP150, and suppression of CHOP and Foxo1 nuclear translocation may contribute to parecoxib-mediated neuroprotection during ER stress responses.[28] The effects of NSAIDs on components of the UPR pathway in different experimental models are summarized in Table 2.

PPARγ compared to NF-κB compared to the UPR pathway

This paper presents a certain outline of anti- and proinflammatory processes that might be modified by NSAIDs that involve 3 different pathways related to PPARγ, NF-κB and UPR signaling. While they appear closely related, there are currently only limited data on their interrelation (Fig. 3). For example, it was demonstrated that inflammatory stimuli can induce NF-κB, and early activation of NF-κB stimulates 3 branches of the UPR, being PERK, ATF and IRE1. Conversely, prolonged ER stress results in CHOP expression, that is responsible for the low level of PPARγ. In the absence of CHOP, PPARγ was strongly upregulated in epithelial cells.[70] Okamura et al.[76] showed that the anti-inflammatory potential of the UPR may be mediated, at least in part, by the induction of GRP78, leading to diminished activation of NF-κB. The ER chaperone GRP78 also has anti-inflammatory and immunomodulatory properties when present in the extracellular environment.[72] However, in some cell types, e.g., in human prostate cancer cells, GRP78 may be involved in the activation of NF-κB by suppressing the activation of IKK.[77] Thus, the role of GRP78 and other factors of the UPR pathway in the regulation of NF-κB is complex and is likely to be cell type-dependent.

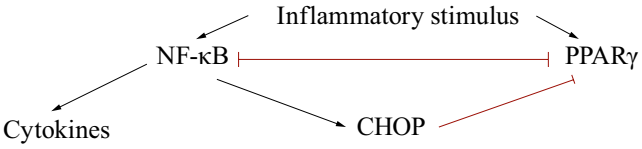

Fig. 3. Relations between peroxisome proliferator-activated receptor gamma (PPARγ), nuclear factor-κB (NF-κB) and unfolded protein response (UPR) pathways. Inflammatory stimulus induces pro-inflammatory pathways such as NF-κB and anti-inflammatory mechanism of action through the PPARγ. These transcription factors can inhibit each other. NF-κB induces the UPR pathway and the release of cytokines. During chronic inflammation and prolonged endoplasmic reticulum (ER) stress, the expression of CHOP is stimulated. CHOP inhibits PPARγ

Potential new therapeutic applications of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer

As shown in Table 2, many studies on the impact of NSAIDs on PPAR, NF-κB and UPR pathways have been conducted on cancer cells or in xenograft tumors. The reason for this is that the classical mechanism of action of NSAIDs, responsible for their anti-inflammatory effects, i.e., inhibition of COX-1 and COX-2 enzymes, also contributes to cancer development. Particularly, COX-2 expressed in response to inflammation seems to play a leading role in most cancers. This discovery has led to the investigation of further mechanisms underlying the involvement of COX enzymes in cancer development, aiming to clarify this phenomenon. For example, it has been shown that PGE_2, which is a product of COX action, is involved in cancer cell proliferation, invasion, migration, and angiogenesis. For these reasons, NSAIDs, by inhibiting COX-2, may show anti-cancer action, and this new property of the drugs has become the subject of intensive research.[19] In this review, it was demonstrated that alternative pathways induced by NSAIDs, i.e., PPARγ stimulation, inhibition of NF-κB activation, or modulatory effects on different components of the UPR pathway, on the one hand, may enhance the basic anti-inflammatory mechanism of action of the drugs, and on the other hand, may be directly involved in different, e.g., anti-cancer effects of NSAIDs.

Promising results of the in vitro studies contributed to the administration of NSAIDs to cancer patients, leading to the analysis of the relationship between taking these drugs and the incidence of cancer. The use of NSAIDs in patients showed different effects, not always as spectacular as in experiments in vitro. Therefore, in most of the studies (Table 3), the need for further research and analysis regarding dosage, treatment duration, and, most importantly, the selection of the drug from the group

Table 3. Examples of potential new therapeutic applications of NSAIDs. The order of research presented is arranged alphabetically by disease, i.e., tissue origin of cancer, next: degree of advancement, next: neurodegenerative diseases, next: neurological disorder

Disease	Type of study	Methodology	Results	Ref.
Cancer				
Bladder cancer	epidemiological study	1,514 cases of incident bladder cancer	All classes of NSAIDs, except pyrazolon derivatives, were negatively associated with bladder cancer risk. Protective effect varied in strength by subcategories of formulation: the strongest for acetic acids and the weakest for aspirin/other salicylic acids and oxicam.	79
Breast cancer	meta-analysis	16 studies with 23,813 participants	The use of NSAIDs may be associated with a small decrease in the risk of breast cancer. However, the available data are insufficient to estimate the dose–response effect for duration and frequency of use of any particular types of NSAID.	80
Colorectal cancer	systematic reviews and meta-analyses	986 participants with low dose of aspirin (81–325 mg/day) 2,289 participants with celecoxib (400–800 mg/day) 1,277 participants with rofecoxib (25 mg/day)	The beneficial effect of low-dose aspirin on recurrence of any adenomas. The effect on advanced adenomas was inconclusive. Possible increased risk of recurrence of adenomas observed after discontinuing regular use of NSAIDs.	81
Ovarian cancer	systematic review and meta-analysis of observational studies	380,277 participants	The use of aspirin significantly reduced the risk of invasive ovarian cancer. A similar tendency was observed for non-aspirin NSAIDs, but the results were not significant.	82
Prostate cancer	systematic review and meta-analysis	108,136 cases from 39 observational studies (20 case-control and 19 cohort studies)	No association with the use of non-aspirin NSAIDs and the development of prostate cancer. Aspirin provided potential benefits in the reduction of prostate cancer incidence.	83
Advanced cancer	meta-analysis of 11 randomized clinical trials	11 randomized clinical trials consisting of 2,570 patients with advanced cancer	Celecoxib showed a benefit in the treatment of advanced cancers but with increased risk of cardiovascular events. Benefit compared to harm needs to be carefully considered when celecoxib is recommended in patients with advanced cancers.	84
Neurodegenerative diseases				
Alzheimer's disease (AD)	systematic review and meta-analysis of observational studies	14,654 participants	NSAIDs offered some protection against the AD development. The appropriate dosage and duration of drug use and the ratio of risk to benefit are unclear.	85
	systematic review prospective and non-prospective studies	7 non-prospectives studies with 1,500 AD cases and 3 prospectives studies with 475 AD cases	NSAIDs exposure was associated with decreased risk of AD.	86
	meta-analysis based on the preferred reporting items for systematic reviews and meta-analysis checklist	236,022 participants	NSAIDs exposure might be significantly associated with reduced risk of AD.	87
Parkinson's disease (PD)	systemic review meta-analysis of observational studies random-effects meta-analyses	301,420 participants	Protective effect of non-aspirin, non-steroidal anti-inflammatory drugs on the risk of PD possibly by influencing a neuroinflammatory pathways in the pathogenesis of PD.	89
	meta-analysis, cohort, case-control	17 articles with 14,713 patients with PD	No association between NSAIDs and the risk of PD.	89
	systematic review and meta-analysis of observational studies	11 studies with 1,020,379 participants	NSAIDs as a class did not seem to modify the risk of PD. Ibuprofen may have a slight protective effect in lowering the risk of PD.	91
	meta-analyses of prospective studies	136,197 participants	Ibuprofen but not other NSAIDs lowered the risk of PD.	91

Table 3. Examples of potential new therapeutic applications of NSAIDs – cont.

Disease	Type of study	Methodology	Results	Ref.
Neurological disorders				
Depression	randomized double-blind placebo-controlled study	40 patients with MDD received celecoxib (200 mg twice daily) or placebo in addition to sertraline (200 mg/day) for 6 weeks.	Reduction of interleukin-6 by celecoxib. Celecoxib can be effective as an adjunctive antidepressant.	92
	double-blind randomized placebo control	40 patients with psychotic depression receiving reboxetine (4–10 mg/day) with celecoxib (400 mg/day) or reboxetine with placebo for 6 weeks	Additional treatment with celecoxib had significant positive effects on the therapeutic action of reboxetine with regard to depressive symptomatology.	93
	double-blind randomized placebo control	40 patients with depression received celecoxib (400 mg/day) or placebo with fluoxetine (40 mg)	The combination of fluoxetine and celecoxib showed a significant superiority effect over fluoxetine alone in the treatment of symptoms of major depression.	94
	review and meta-analysis randomized placebo-control trials	14 trials (6,262 participants) with subanalyses with celecoxib (200–400 mg/day)	Celecoxib decreased depressive symptoms without increased risks of adverse effects.	95
	review and meta-analysis randomized controlled trials	312 participants with bipolar depression, 53 patients received NSAIDs	A moderate antidepressant effect for adjunctive NSAIDs compared with conventional therapy alone in the treatment of bipolar depression.	96

NSAIDs – non-steroidal anti-inflammatory drugs; MDD – major depressive disorder.

is emphasized. Examples of epidemiologic studies have shown a diminished incidence of adenomatous polyps and lower colorectal cancer death rates in persons regularly taking NSAIDs. It suggests a possible protective effect of NSAIDs on the general population. Some recent randomized clinical trials showed that aspirin suppressed the recurrence of adenomatous polyps in patients with a previous polyp.[78] In turn, the use of all classes of NSAIDs, except pyrazolone derivatives, suppressed the bladder cancer risk; however, the protective effects varied in strength depending on the subcategories of the formulation.[79] More examples can be found in Table 3.

Potential new therapeutic applications of NSAIDs in CNS disorders

Central nervous system disorders, including those of a psychiatric or neurological nature, are a major challenge for medicine and public health worldwide. They are multifaceted disorders with diverse and ill-defined pathophysiological mechanisms, e.g., the development of inflammatory processes, ER stress and disturbance of neuronal–glial communication. The pathological processes are associated with specific signaling pathways, and their elements can become strategic points of development for new drugs and for new applications of those already approved. Therefore, NSAIDs have been used in epidemiological studies analyzing their therapeutic effectiveness as protective factors in CNS disorders.

Neuroinflammation with the involvement of NF-κB, PPARγ and the UPR pathways also has an impact on the development of CNS disorders. Neuroinflammation is a defense mechanism that initially protects the brain by removing or inhibiting diverse pathogens, but persistent inflammation can induce microglia and astrocytes toward a proinflammatory phenotype, which causes the neurotoxic effect. The UPR dysfunction, which is characterized by the accumulation and aggregation of misfolded proteins, mediates neuronal death in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and psychiatric disorders such as schizophrenia, depression and post-traumatic stress disorder (PTSD).[97,98] Considering all 3 trans-ER membrane stress sensors (IRE1, PERK and ATF6) are present in astrocytes, it is clear that the PERK-mediated arm of the UPR is most linked to the induction of inflammatory responses in astrocytes and may be a target to attenuate immune responses in neurological diseases. However, other signaling molecules may also contribute to the pathogenic activities of astrocytes.

Currently, there are several neuroprotective mechanisms of NSAIDs being investigated, including those resulting from the stimulation of the PPARγ receptor and the reduction of microglia activation. It is believed that activation of these anti-inflammatory effects may contribute to the anti-amyloidogenic action of NSAID.[85,99,100]

Various clinical trials have already revealed promising results using PPARγ agonists and, therefore, may represent an attractive therapeutic target for the treatment of AD.[100] Many clinical trials and meta-analyses have shown that NSAID exposure may be significantly associated with a reduced risk of AD.[85,86] However, this evidence was only based on observational studies, while other types of investigations did not find this association.[85]

According to the analysis of prospective and retrospective studies, NSAID exposure was associated with a decreased risk of AD, slower progression and reduced severity of dementia.[86] Similar neuroprotective effects, although still controversial, were obtained in other neurodegenerative disorders such as PD. A meta-analysis presented by Gagne and Power[88] indicated that the use of non-aspirin NSAIDs, particularly ibuprofen, reduced the risk of PD by 15%, while the use of aspirin did not show any effect. The NSAIDs have demonstrated neuroprotective potential, but a meta-analysis by Poly et al.[89] showed that there is no association between NSAIDs and the risk of PD at the population level. Other research suggested that ibuprofen may have a slight protective effect in lowering the risk of PD, whereas NSAIDs as a class of drugs do not seem to modify the risk of PD.[90,91]

Neuroinflammation is implicated in a variety of neurologic and somatic illnesses, including depression. It has been reported that a significant proportion of major depressive disorder (MDD) patients exhibit increased levels of TNF-α and IL-6 in plasma.[101,102] Neuroinflammation also contributes to non-responsiveness to current antidepressant therapies. It has been shown that the response to conventional antidepressant medications is associated with a decrease in inflammatory biomarkers, whereas resistance to treatment is accompanied by increased inflammation.[103] For these reasons, there have been few successful trials investigating whether treatment with NSAIDs may show beneficial effects on MDD. Meta-analyses of randomized controlled trials (RCTs) of NSAIDs, given in monotherapy or as add-on therapy, indicated that these medications may be beneficial in treating depression.[93,95] For example, a combination of celecoxib with sertraline or fluoxetine could exhibit a more efficacious antidepressant effect than sertraline or fluoxetine treatment alone.[92,94] However, another meta-analysis of adjunctive use of NSAIDs in the treatment of bipolar depression showed only moderate antidepressant effects of the drugs compared with conventional therapy alone.[96] In a retrospective analysis of the association between NSAID use by adults with chronic inflammatory conditions and the presence of depression among them, no statistically significant results were observed.[104]

Several studies have provided evidence that PPARγ receptor expression or the levels of its endogenously produced modulators are downregulated in several neurological and psychiatric disorders such as depression,[105] schizophrenia[106] and PD.[107] Therefore, synthetic agonists should be investigated in the context of these disorders.[108]

Conclusions

Non-steroidal anti-inflammatory drugs have a well-established role in the human therapeutic arsenal, but still, new perspectives are being discovered. This review presents new anti-inflammatory molecular targets of NSAIDs involving actions on PPARγ, NF-κB and the components of the UPR pathway. More importantly, the effects of NSAIDs on these signaling molecules are observed in higher concentrations than those required for COX inhibition. However, it should be emphasized that it is difficult to compare concentrations used in laboratory studies, i.e., on cell lines, with effective doses necessary to obtain the effect in humans. Additionally, some literature shows derivatives of individual drugs from the anti-inflammatory group, which more potently affect the above-mentioned molecular targets, and thus they may become a valuable alternative to classic NSAIDs in the future.

Another aspect is the search for new drug targets for the therapy of neurological and neurodegenerative disorders or cancers. Many epidemiological prospective and retrospective studies show the beneficial contribution of NSAIDs in the prevention or treatment of these diseases, but the mechanisms of the observed effects remain mostly unknown. Nevertheless, searching for new applications and molecular targets of already approved drugs represents an important avenue of exploration and may contribute to the development of more effective therapies. However, the question of whether NSAIDs or other drugs affecting PPARγ, NF-κB or UPR pathways will be applied in the future in the treatment of cancers or neurodegenerative disorders still needs answering.

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