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PharmGKB summary: ibuprofen pathways

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Introduction

Ibuprofen is a traditional nonsteroidal anti-inflammatory drug (NSAID) widely used for its analgesic, anti-inflammatory, and antipyretic properties [1,2]. At low over-the-counter doses (800–1200 mg/day), ibuprofen is indicated to relieve minor pain and inflammation, including headache, muscular aches, toothache, fever, backache, and dysmenorrhea. At prescription doses (1800–2400 mg/day), it is used for the long-term treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and other chronic conditions [2]. Ibuprofen has also been used off-label to promote closure of patent ductus arteriosus (PDA) in preterm neonates [3]. It is commonly used in pediatric patients for the treatment of acute pain and fever (5–10 mg/kg every 6–8 h) due to its relative safety compared with aspirin and its high efficacy compared with acetaminophen [2]. Prescription doses of ibuprofen (adult: 200–800 mg every 6–8 h; pediatric: 5–10 mg/kg every 6–8 h) have greater antipyretic and analgesic effects in both children and adults compared with commonly used doses of acetaminophen (adult: 500–1000 mg every 6–8 h; pediatric: 10–15 mg/kg every 4–6 h) [4].

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Conflicts of interest

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Pharmacokinetics

Ibuprofen is most commonly administered orally, but an intravenous formulation is also approved for use in the USA. Other formulations, most notably topical and rectal, can be prepared by compounding pharmacies in the USA and may be commercially available in other countries. Ibuprofen is rapidly and completely absorbed following oral administration (t_{max}, ~ 1–2 h depending on the specific oral formulation), and unbound concentrations show linear pharmacokinetics at commonly used doses [1,5]. It is extensively (>98%) bound to plasma proteins at therapeutic concentrations [1]. Although ibuprofen may displace other highly protein-bound drugs, this is unlikely to result in clinically relevant drug–drug interactions for agents with a low extraction ratio, such as warfarin [6] and phenytoin [7]. Consistent with the high degree of plasma protein binding, ibuprofen exhibits a low apparent volume of distribution that approximates plasma volume (~0.1–0.2 l/kg), but it is able to penetrate into the central nervous system (CNS) and accumulate at peripheral sites where its analgesic and anti-inflammatory effects are required. Ibuprofen is present in a free, unbound form in cerebrospinal fluid and is retained in the synovial fluid in the inflamed joints of arthritic patients [2]. Ibuprofen has a wide therapeutic concentration range for its analgesic, antipyretic, and anti-inflammatory effects (~10–50 mg/l) and a relatively short plasma half-life ($t_{1/2}$, ~ 1–3 h), necessitating frequent administration to maintain therapeutic plasma concentrations [1,2].

The pharmacokinetic profile of ibuprofen in the pediatric population (age > 0.5 years) appears to be similar to that observed in adults in general, although some studies have indicated that young children (0.5–5 years) have higher rates of ibuprofen clearance [2]. In contrast, the half-life of ibuprofen in premature neonates is in the order of 30–45 h following intravenous administration, which may be due to several factors including developmental effects on cytochrome P450 (CYP) enzyme activity and lower glomerular filtration rates in neonates compared with adults [2,3].

Metabolism

Like most NSAIDs, ibuprofen is administered as a racemic mixture of *R* and *S* enantiomers, with *S*-ibuprofen being largely responsible for its pharmacologic activity [1]. Following administration, an estimated 50–65% of *R*-ibuprofen undergoes inversion to the *S* enantiomer through an acyl-CoA thioester by the enzyme α-methylacyl-coenzyme A racemase (encoded by gene *AMACR*) [1,8,9]. This appears to occur predominantly systemically in the liver [1,10], but may occur pre-systemically in the gut as well [11].

Ibuprofen is almost completely metabolized, with little to no unchanged drug found in the urine [1,9,12]. The primary route of elimination is oxidative metabolism by CYP enzymes to inactive metabolites (Fig. 1). Urinary excretion of the two major metabolites, carboxy-ibuprofen and 2-hydroxy-ibuprofen (and their corresponding acyl glucuronides), accounts for ~37 and 25% of an administered dose, respectively [1,9]. Small amounts of other hydroxylated metabolites (3-hydroxy-ibuprofen and 1-hydroxy-ibuprofen) have also been detected in urine [12].

CYP2C9 is the primary CYP isoform responsible for ibuprofen clearance, catalyzing the formation of 3-hydroxy-ibuprofen (most of which is subsequently converted to carboxy-ibuprofen by cytosolic dehydrogenases [12,13]) and 2-hydroxy-ibuprofen [13,14]. Consequently, coadministration of ibuprofen with CYP2C9 inhibitors (i.e. selective serotonin-reuptake inhibitors) or other CYP2C9 substrates (i.e. warfarin) may precipitate a pharmacokinetic drug–drug interaction, thereby increasing the risk for an adverse drug event (for a broader discussion, refer to the Drug–drug interactions section) [6,15,16]. Whereas CYP2C9 can readily metabolize both enantiomers of ibuprofen *in vitro*, CYP2C8, which plays a minor role in ibuprofen clearance, exhibits stereoselectivity, preferentially catalyzing the 2-hydroxylation of *R*-ibuprofen [13,14,17]. CYP3A4 also contributes to ibuprofen clearance at high concentrations through 2-hydroxylation, whereas CYP2C19 appears to play a minor role [14].

Approximately 10–15% of an ibuprofen dose is directly glucuronidated to ibuprofen-acyl glucuronide [1,9]. In-vitro experiments indicate that multiple uridine 5′diphosphoglucuronosyltransferases (UGTs) are capable of metabolizing ibuprofen, including UGT1A3, UGT1A9, UGT2B4, UGT2B7, and UGT2B17 [18–20]. UGT1A10, which is predominantly expressed in the gut, can also generate ibuprofen-acyl glucuronide [21]. CYP-derived hydroxy and carboxy metabolites are metabolized to the corresponding acyl glucuronides, but the UGTs that catalyze this reaction have not been investigated. Further studies are necessary to characterize the relative contributions of individual UGTs to ibuprofen metabolism *in vivo*.

Although glucuronidation is generally considered a detoxification pathway, acyl glucuronides are potentially reactive metabolites. They can undergo intramolecular rearrangement and are capable of binding covalently to macromolecules and contributing to toxicity [22]. Consistent with this, covalent binding of ibuprofen-acyl glucuronide to plasma proteins has been detected *in vitro* and in elderly individuals chronically treated with ibuprofen *in vivo* [23]. However, ibuprofen-acyl glucuronide was relatively less reactive than other compounds investigated, and the degree of covalent binding to plasma proteins was low, suggesting that ibuprofen-acyl glucuronide is not a key contributor to toxicity in most individuals [23]. Conjugation to thiols has also been reported, although these conjugates account for less than 1% of urinary metabolites [24]. Like acyl glucuronides, these metabolites are considered reactive and may contribute to adverse drug events; however, evidence demonstrating the toxicity of these metabolites in humans *in vivo* is lacking [25].

Transport

NSAIDs interact with various classes of transporters. It is still unclear which, if any, transporters facilitate the uptake or efflux of ibuprofen *in vivo* or whether this influences the distribution or clearance. Ibuprofen is a weak acid and is lipid soluble; hence, it is feasible that it may be able to cross membranes without the need for specific transporters [1]. However, the interaction of ibuprofen with various transporters may result in clinically relevant drug–drug interactions.

In-vitro studies have demonstrated that ibuprofen is a substrate for SLC22A6 and SLC22A8 [26] and can inhibit various transporters, including SLC22A6 (hOAT1), SLC22A7 (hOAT2), SLC22A8 (hOAT3), SLC22A9 (hOAT4), SLC22A1 (OCT1), SLC15A1 (hPEPT1), SLC5A8 (hSMCT1), and SLC16A1 (MCT1) [26–31]. Stereoselectivity in transporter inhibition has been observed in some cases, with *S*-ibuprofen being a more potent inhibitor of SLC22A6 than *R*-ibuprofen, whereas both enantiomers inhibited SLC22A8 equipotently [32]. Although ibuprofen is not a substrate for the organic anion-transporting polypeptides, it does interact with SLCO1B1 (hOATP1B1) and SLCO1B3 (hOATP1B3) to increase the uptake of pravastatin and inhibit the uptake of bromosulfophthalein [33]. Additional studies are necessary to determine whether these transporter interactions observed *in vitro* lead to clinically relevant drug–drug interactions *in vivo*.

One drug–drug interaction in which transporters may play a role is the well-recognized interaction between methotrexate and ibuprofen. Coadministration of NSAIDs with methotrexate reduces methotrexate clearance, resulting in elevated systemic concentrations [1,6]. Ibuprofen inhibited methotrexate uptake by SLC22A6, SLC22A8, and SLC22A9 *in vitro* [32,34,35], suggesting that inhibition of these transporters in the kidney may contribute to the reduction in renal clearance of methotrexate upon coadministration with ibuprofen. Another possible mechanism is through the inhibition of ABCC2 (MRP2)-mediated and ABCC4 (MRP4)-mediated transport of methotrexate, which would also be hypothesized to decrease the renal clearance of methotrexate *in vivo* [36].

Although the interaction between methotrexate and ibuprofen is potentially fatal, some transporter-mediated interactions with ibuprofen may enhance the efficacy or limit the toxicity of the interacting drug. For example, ibuprofen was shown to modulate the activity of ABCB1 (P-glycoprotein) such that treatment of human sarcoma cells with ibuprofen reversed ABCB1-mediated efflux of doxorubicin and led to increased drug accumulation, cytotoxicity, and apoptosis [37]. Ibuprofen may increase intracellular concentrations and potentiate the antiviral efficacy of nucleoside reverse transcriptase inhibitors, including zidovudine, lamivudine, tenofovir, and abacavir, through the inhibition of ABCC4, which mediates the export of these drugs out of T cells [38]. Through the inhibition of SLC22A6, ibuprofen may limit the nephrotoxicity of the antiviral drug adefovir, known for its cytotoxicity in the renal proximal tubules [39].

It is important to note that studies to date have been performed *in vitro*, largely with cells transfected with the transporter of interest. Although the majority of these studies used concentrations of ibuprofen in the range of the total drug concentrations observed in plasma, it is unclear how well these conditions approximate the unbound concentrations that would be available to inhibit transport *in vivo.* Thus, additional studies are necessary to clarify the clinical relevance of these transporter-mediated drug–drug interactions *in vivo*.

Pharmacodynamics

The main mechanism of action of ibuprofen is the non-selective, reversible inhibition of the cyclooxygenase enzymes COX-1 and COX-2 (coded for by *PTGS1* and *PTGS2*,

respectively; Fig. 2) [1]. In-vitro studies have indicated that, of the two enantiomers, *S*-ibuprofen is a more potent inhibitor of COX enzymes compared with *R*-ibuprofen [40,41]. In an in-vitro human whole-blood assay, *S*-ibuprofen was seen to have comparable inhibitory activities toward COX-1 and COX-2 (IC_{50} 2.1 and 1.6 μmol/l, respectively). In contrast, *R*-ibuprofen was ~ 15-fold less potent than *S*-ibuprofen as a COX-1 inhibitor (IC_{50} 34.9 μmol/l) and did not inhibit COX-2 at concentrations of up to 250 μmol/l [42]. COX-1 and COX-2 catalyze the first committed step in the synthesis of prostanoids – prostaglandin (PG) E_2, PGD_2, $PGF_{2\alpha}$, PGI_2 (also known as prostacyclin), and thromboxane (Tx) A_2 – from arachidonic acid. Prostanoids produce a diverse array of biologic effects through the activation of prostanoid receptors, and play important roles in a variety of homeostatic and pathologic processes [43].

Many of the pharmacodynamic effects of ibuprofen can be directly linked to the inhibition of prostanoid synthesis. Single and repeated oral doses of ibuprofen inhibited the production of COX-1-derived TxB_2 (a stable metabolite of TxA_2) *ex vivo* by ~ 96 and ~ 90%, respectively, whereas COX-2-derived PGE_2 production *ex vivo* was inhibited by ~ 84 and ~ 76%, respectively [44]. PGE_2 and PGI_2 are proinflammatory prostanoids that enhance edema formation, increase vascular permeability, and promote leukocyte infiltration. They also reduce the threshold of nociceptor sensory neurons to stimulation [43]. Ibuprofen exerts its anti-inflammatory and analgesic effects largely by inhibiting the formation of these prostanoids. PGE_2 is also a primary mediator of pyresis, and its synthesis is triggered in the hypothalamus by pyrogens such as cytokines, endotoxin, and products from activated leukocytes [45]. Thus, the antipyretic effects of ibuprofen can be attributed to inhibition of PGE_2 synthesis. Inhibition of both $PGF_{2\alpha}$ and PGE_2, which trigger spasm of the uterine smooth muscles and inflammatory pain, is responsible for the therapeutic efficacy of ibuprofen in primary dysmenorrhea [46]. TxA_2, a major product of COX-1 in platelets, causes vasoconstriction and promotes platelet activation and aggregation, thereby leading to thrombus formation [43,47]. Consequently, ibuprofen exhibits a mild, transient antiplatelet effect through reversible inhibition of platelet COX-1, as evidenced by its ability to inhibit stimulus-triggered platelet aggregation *in vitro* [48].

In addition to the direct inhibition of prostanoid synthesis, ibuprofen exerts other biologic effects that may contribute to its anti-inflammatory action and might be consequent to the suppression of prostaglandin synthesis. Several studies have suggested that ibuprofen can inhibit neutrophil aggregation and degranulation as well as proinflammatory cytokine production by immune cells *in vitro* and *in vivo* [49–53]. During inflammation, immune cells, such as macrophages, mast cells, eosinophils, and neutrophils, robustly produce reactive oxygen species (e.g. superoxide anion, $O_2^{\bullet -}$, hydroxyl radical, $HO^{\bullet}$, and other unstable molecules) and reactive nitrogen species (e.g. nitric oxide, $^{\bullet}NO$, and peroxynitrite anion, $ONOO^-$) that contribute to the pathophysiology of the inflammatory processes [54]. Using noncellular in-vitro screening systems, ibuprofen was reported to scavenge $HO^{\bullet}$, $^{\bullet}NO$, and $ONOO^-$ radicals at concentrations comparable to the high doses prescribed for chronic inflammatory conditions [55]. Cell-based in-vitro studies have indicated that ibuprofen can activate or inhibit nitric oxide production through constitutive nitric oxide synthases (cNOS) (neuronal NOS, encoded by *NOS1*, and endothelial NOS, encoded by *NOS3*) or

inflammation-induced nitric oxide synthase (iNOS, encoded by *NOS2*) depending on the type of the enzyme and the cellular system used [48,56]. In healthy human individuals, therapeutic doses of ibuprofen triggered a reduction in exhaled NO and urinary excretion of nitrite and nitrate, consistent with an inhibitory effect of the drug on nitric oxide production [57]. Taken together, these findings suggest that ibuprofen exhibits pleiotropic anti-inflammatory effects by inhibiting prostanoid synthesis, interfering with immune cell function, scavenging reactive oxygen and nitrogen species, and altering nitric oxide synthesis. However, further studies are required to determine whether the effects of ibuprofen on immune cells and reactive oxygen and nitrogen species result from the inhibition of prostaglandin production.

Additional analgesic effects of ibuprofen may be attributable to elevated levels of the endocannabinoid anandamide (also known as arachidonoylethanolamide), which activates the antinociceptive axis through the cannabinoid receptors (CB_1 and CB_2) in the CNS. Animal studies have suggested that, at therapeutic concentrations, ibuprofen inhibits anandamide metabolism [58,59] and, together with anandamide, exerts a synergistic antinociceptive effect in a model of inflammatory pain [60]. In in-vitro studies, ibuprofen was shown to inhibit the binding of a potent synthetic agonist to the human CB_2 cannabinoid receptor, indicating that it may compete with endogenous ligands for receptor binding and activation of the analgesic pathway [61]. However, the clinical relevance of these findings is still to be investigated in human participants.

Adverse events

The short plasma half-life, a wide therapeutic window, and the lack of prolonged retention in specific body compartments make ibuprofen a relatively safe drug. There is no evidence of ibuprofen accumulation in the elderly and relatively little impact of chronic disease states (arthritis) or mild renal/hepatic impairments on the pharmacokinetics of ibuprofen [1,2]. Although serious skin diseases, such as the Stevens–Johnson syndrome and toxic epidermal necrolysis, have been reported in patients with ibuprofen use, these are exceedingly rare, at a rate of less than 1 per 1 million users per week for most NSAIDs [62].

Like other NSAIDs, ibuprofen can cause serious gastrointestinal and possibly cardiovascular adverse events, especially at high doses [1,2,63–66]. Most observational studies with ibuprofen have reported no increased risk for cardiovascular events, such as myocardial infarction and sudden cardiac death [67–69]. However, the risk for cardiovascular events might increase with prolonged exposure to ibuprofen (i.e. greater than 1 year) [70]. It still remains to be determined how ibuprofen compares with COX-2-selective inhibitors, known to pose a cardiovascular risk [66]. In the Therapeutic Arthritis Research and Gastrointestinal Event Trial, gastrointestinal safety and cardiovascular safety were compared between a COX-2 inhibitor lumiracoxib and traditional NSAIDs ibuprofen and naproxen [64,65]. Despite a higher incidence of cardiovascular events in the lumiracoxib group, the Therapeutic Arthritis Research and Gastrointestinal Event Trial involved patients at low risk, was under-powered, and used an intention-to-treat analysis [65]. A recent meta-analysis of 280 randomized trials of NSAIDs versus placebo and 474 trials of one NSAID versus another NSAID focused on the cardiovascular and gastrointestinal risks of this class of drugs

among different patient populations, especially those at increased risk for vascular disease [63]. Compared with placebo, high-dose ibuprofen significantly increased the risk for major coronary events (nonfatal myocardial infarction or coronary death), although the number of events was low and, similarly to other NSAIDs, was associated with increased upper gastrointestinal complications. All NSAIDs, including ibuprofen, doubled the risk for heart failure causing hospital admission, and none of the NSAIDs studied was associated with an increased risk for stroke. Although high-dose ibuprofen significantly increased the risk for major coronary events, further studies are required to verify whether the cardiovascular risks associated with ibuprofen are comparable to those associated with COX-2-selective inhibitors [63]. Moreover, the cardiovascular risk associated with short-term, low-dose ibuprofen use is a topic of some debate, as prospective studies defining this risk are lacking. Overall, relative to other NSAIDs, especially COX-2-selective inhibitors, ibuprofen might have lower gastrointestinal and cardiovascular risks, especially when used over a short term at over-the-counter doses [1,2,63,66]. However, resolving the issue of cardiovascular risk from ibuprofen alone or relative to COX-2 inhibitors would require a large-scale, long-term, adequately powered, randomized, controlled outcome trial.

Drug–drug interactions

Ibuprofen exhibits pharmacodynamic interactions with a variety of drugs. Ibuprofen antagonizes the cardioprotective effect of low-dose aspirin (acetylsalicylic acid) through competition for the NSAID binding site of COX-1 in platelets [71]. Low-dose aspirin is recommended as an effective antiplatelet therapy for secondary prevention of myocardial infarction and stroke [72,73]. Consumption of low-dose aspirin results in maximum inhibition of TxA_2 synthesis by platelets, with subsequent inhibition of platelet aggregation. Under chronic dosing conditions, when ibuprofen is administered three times a day, this interaction undermines aspirin-induced inhibition of platelet aggregation irrespective of which of the drugs precedes the other in the morning [71]. The follow-up studies on ibuprofen–aspirin interactions range from confirming ibuprofen antagonistic effect on aspirin antiplatelet action [64,74,75] to reporting no change after the concurrent administration of the two drugs [69,76], although a well-powered, clinical end-point study has never been conducted.

Because it reversibly inhibits COX-1 in platelets, ibuprofen has a transient antiplatelet effect for 1 h during the 8 h dosing interval, which may increase bleeding risk when administered with other anticoagulant or antiplatelet agents. Concomitant administration of warfarin with ibuprofen was reported to prolong the bleeding time [77] and increase the international normalized ratio, a measure of the clotting tendency of blood [78]. An increased risk for gastrointestinal bleeding has been reported after coadministration of NSAIDs with selective serotonin-reuptake inhibitors (SSRIs). SSRIs block serotonin reuptake by platelets and downregulate serotonin receptors, leading to the inhibition of platelet function and increased bleeding risk [15]. SSRI use alone increases the risk for bleeding by 30% as compared with non-NSAID/non-SSRI use, and the risk for gastrointestinal events increases to 50–60% when SSRIs are coadministered with NSAIDs [6]. These effects may be compounded by a concomitant pharmacokinetic drug–drug interaction through CYP2C9 (see the Pharmacokinetics section). Individuals with *CYP2C9*2* and *CYP2C9*3* variants, who

comprise about 20% of the white population, may be especially susceptible to the bleeding events [6].

In patients with a bipolar affective disorder, the concomitant use of lithium with NSAIDs has been reported to increase the serum lithium level and reduce lithium clearance, thus causing acute lithium intoxication [79]. Mechanistically this might be due to inhibition of prostaglandin-mediated excretion of lithium in the distal tubule. However, the degree of elevation in serum lithium concentrations with concomitant ibuprofen treatment has been inconsistent across studies [80–83]. In a geropsychiatric population, coadministration of lithium with ibuprofen for 6 days was found to increase the serum lithium level and decreased lithium clearance, with pronounced interindividual variability [82]. The magnitude of increase in the serum lithium level ranged from 12 to 66.5%, with an average increase of 34%, suggesting that there is substantial interindividual variability in the clinical significance of this drug–drug interaction. Thus, frequent monitoring of serum lithium levels upon initiation of concomitant therapy with ibuprofen is recommended to identify those individuals in whom a reduction in lithium dosage is necessary. The effect of long-term ibuprofen therapy in lithium-treated patients needs to be further investigated [82].

Finally, NSAIDs, including ibuprofen, interfere with the efficacy of many antihypertensive agents, including β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics [84–87]. This is mediated through the inhibition of the production of vasodilatory prostanoids in the kidneys, thereby inducing vasoconstriction of afferent renal arterioles, fluid retention, and reduction in renal blood flow, promoting activation of the rennin–angiotensin system [2]. Although a well-designed trial, adjusting for drug exposure and comparing the hypertensive effects of NSAIDs, has not been conducted to date, a retrospective study reported that ibuprofen appears to be less likely than diclofenac and piroxicam to necessitate an intensification of antihypertensive treatment [86].

Pharmacogenomics

Pharmacogenomic studies on ibuprofen have examined the effects of genetic polymorphisms on pharmacokinetics (clearance, half-life, area under the curve) [88–92], pharmacodynamics (inhibition of COX-1 and COX-2) [88,90], the safety profile (gastrointestinal adverse events) [88,93–97], and therapeutic efficacy (analgesia, PDA closure, cancer chemoprevention) [3,98–107].

Several studies have investigated the effect of genetic variations in *CYP2C8* and *CYP2C9* on ibuprofen pharmacokinetics because of the key role of these enzymes in ibuprofen clearance. Ibuprofen clearance is significantly reduced in carriers of the *CYP2C9*3* variant allele compared with individuals with the *CYP2C9*1/*1* genotype, whereas the *CYP2C9*2* variant appears to have no significant impact on the pharmacokinetics of ibuprofen [88–90]. One study reported that the reduction in ibuprofen clearance in *CYP2C9*3* variant allele carriers was accompanied by an increased pharmacodynamic effect, namely, prolonged inhibition of TxB_2 and PGE_2 synthesis, indices of COX-1 and COX-2 inhibition, respectively [90], but another study found no differences in the degree of COX-1 or COX-2

inhibition in variant allele carriers [88]. Similarly, conflicting data have been reported on the relationship between the *CYP2C8*3* variant and interindividual variability in ibuprofen pharmacokinetics [88,89,91,92]. To date, most studies have suggested that ibuprofen clearance is reduced by the *CYP2C8*3* allele [89,91,92], but one study reported 20% higher ibuprofen clearance in *CYP2C8*3* variant allele carriers compared with *CYP2C8*1/*1* individuals [88].

A few studies have suggested that a decrease in clearance, leading to sustained ibuprofen levels, may increase the risk for gastrointestinal bleeding in *CYP2C8* and *CYP2C9* variant allele carriers. In a small study of Italian NSAID users who experienced gastroduodenal bleeding after short-term NSAID use (< 1 month; all NSAIDs: $n = 26$; ibuprofen: $n = 3$), significantly higher frequencies of *CYP2C9*1/*2* and *CYP2C9*1/*3* genotypes were reported in cases versus controls [94]. A French study representing nonaspirin NSAID users of various ethnicities (all NSAIDs: $n = 57$; ibuprofen: $n = 11$) similarly found a greater risk for acute gastrointestinal bleeding in patients heterozygous [odds ratio (OR) (95% confidence interval (CI)): 4.0 (1.7–9.5)] and homozygous [OR (95% CI): 15.7 (1.8–138.0)] for the *CYP2C9*3* variant allele, but did not replicate the association for *CYP2C9*2* [95]. A study in Spanish NSAID users (all NSAIDs: $n = 94$; ibuprofen: $n = 9$) reported an increased risk for acute gastrointestinal bleeding in *CYP2C9*2* variant allele carriers [OR (95% CI): 1.92 (1.14–3.25), $P = 0.009$], but found no association with *CYP2C9*3* [96]. A subsequent study by the same group repeated this analysis and investigated the effect of the *CYP2C8*3* variant allele in an expanded population (all NSAIDs: $n = 134$; ibuprofen: $n = 14$) [93]. The greatest risk for NSAID-related gastrointestinal bleeding was observed in individuals who carried both the *CYP2C8*3* and *CYP2C9*2* variant alleles [OR (95% CI): 3.73 (1.57–8.88), $P = 0.003$], whereas there was no elevation in risk among individuals who carried only the *CYP2C8*3* [OR (95% CI): 1.36 (0.39–4.66), $P = 0.646$] or *CYP2C9*2* [OR (95% CI): 0.73 (0.22–2.51), $P = 0.637$] variant allele in isolation [93]. In contrast to these findings, no significant differences in the frequency of *CYP2C9*2* and *CYP2C9*3* variant alleles were observed between patients with NSAID-induced gastric ulceration and controls (all NSAIDs: $n = 54$; ibuprofen: $n = 5$) in a predominantly Caucasian cohort from New Zealand [97]. Notably, all studies to date have enrolled patients taking a variety of NSAIDs; thus, it is unclear to what degree the potentially increased risk for gastrointestinal bleeding in *CYP2C8* and *CYP2C9* variant allele carriers is specifically related to ibuprofen use.

To date few studies have evaluated the effect of genetic variation on the therapeutic efficacy of ibuprofen [3,98]. One study has investigated the effect of polymorphisms in COX-1 (*PTGS1*) and COX-2 (*PTGS2*) on pain perception with either ibuprofen or rofecoxib after third molar (i.e. wisdom tooth) extraction [98]. The authors also quantified the mRNA expression level of COX-1, COX-2, and other related genes in mucosal biopsies before and 2–4 h after the oral surgery. No significant associations were observed with regard to variants in *PTGS1*. However, one variant located in the *PTGS2* promoter, rs20417 (-765G > C), was associated with both lower *PTGS2* mRNA expression in mucosal tissue and greater analgesic response to ibuprofen in variant allele carriers. At 48 h after surgery, patients who carried the minor allele for rs20417 (CC +CG) reported significantly lower pain scores on a visual analog scale (100 mm) following treatment with ibuprofen compared with rofecoxib

(ibuprofen: 7.0 ± 1.9 mm vs. rofecoxib: 37.0 ± 6.8 mm, P <0.01), whereas patients homozygous for the major allele (GG) had a better response to rofecoxib than to ibuprofen (ibuprofen: 31.3 ± 6.7 mm vs. rofecoxib: 7.2 ± 2.5 mm, P <0.01; note: this gene is on the minus chromosomal strand, complemented on PharmGKB to the plus strand; in the paper this is reported on the minus strand) [98]. These results suggest that the *PTGS2* rs20417 variant may have utility in guiding the selection of COX-2-selective versus traditional NSAID therapy following third molar extraction, but additional studies are necessary to validate these findings. Another study evaluated the relationship between *CYP2C8* and *CYP2C9* variants and the response to ibuprofen for PDA closure in preterm neonates because higher ibuprofen serum concentrations had been previously associated with higher response rates. No significant associations between the *CYP2C8* or *CYP2C9* genotype and ibuprofen response were observed after multivariate adjustment, which may reflect the substantial clinical heterogeneity in this patient population, as well as the potential influence of development on the expression and catalytic activity of CYP2C enzymes [3].

Numerous studies have investigated the effect of genetic variants on the efficacy of NSAIDs for cancer chemoprevention, but have yielded conflicting information [99 –107]. One study observed no significant role of interactions between NSAID use and polymorphisms in *CYP2C8*, *CYP2C9*, *PPARD*, *PPARG*, and *UGT1A6* in modifying the risk for colorectal cancer, but it did report a nonsignificant trend (P for interaction = 0.24) toward a greater protective effect of nonaspirin NSAIDs, including ibuprofen, in carriers of the *PPARG* Ala12 variant allele [103]. A subsequent study in a larger population validated this potential interaction between ibuprofen use and the *PPARG* Pro12Ala variant in modifying rectal cancer risk (P for interaction =0.03) [107]. Other studies in colorectal cancer patients have reported significant interactions between ibuprofen use and genetic variants of *CYP2C9* (*CYP2C9*2* and **3*) [105], *SMAD7* (rs4939827 and rs4464148) [104], and *UGT2B4* (rs1131878, rs1966151, and rs13119049) [106], but not *PTGS2* (rs68946, rs20432, and rs5275) [99]. Studies in men with advanced prostate cancer have suggested that the protective effect of ibuprofen may be modified by the *LTA* C +80A (P for interaction =0.008) [102] and *PTGS2* rs2745557 (P for interaction =0.12) [101] variants, but the numbers of ibuprofen users in these studies were relatively small. In contrast, no significant interactions between ibuprofen use and genetic variation in *PTGS2* were observed in women with breast cancer [100].

An interesting area for future research with respect to ibuprofen is how the drug may interact with *AMACR* variants and modulate cancer risk [8]. Elevated protein levels of AMACR, which converts *R*-ibuprofen to *S*-ibuprofen, have been detected in prostate cancer cells and a number of other cancers, and variants and alternative splice forms of *AMACR* have been associated with cancer risk. However, the potential for ibuprofen to modify these relationships has not been explored to date [8].

Conclusion

To date, the most robust finding with regard to the pharmacogenomics of ibuprofen has been the relationship between the *CYP2C9*3* variant and decreased ibuprofen clearance. Given ibuprofen's wide therapeutic window, the clinical significance of this relationship is unclear,

but *CYP2C9*3* variant allele carriers may be at a greater risk for adverse events or drug–drug interactions, particularly with concomitant use of other CYP2C9 substrates (i.e. warfarin). Although some associations between genetic variation and therapeutic efficacy of ibuprofen have been reported, further study is necessary to validate these findings, as well as to define the role of pharmacogenomics in guiding ibuprofen therapy.

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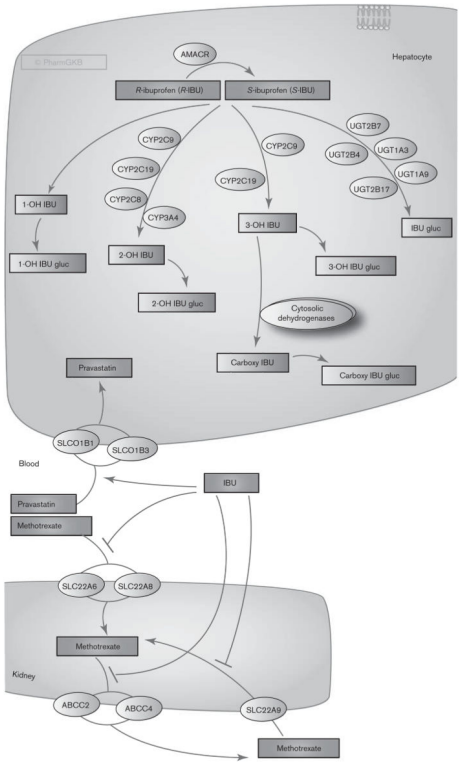

Fig. 1.

Metabolism and transport of ibuprofen in the liver and kidney. IBU, ibuprofen; IBU gluc, ibuprofen glucuronide. A fully interactive version is available online at http://www.pharmgkb.org/pathway/PA166041114.

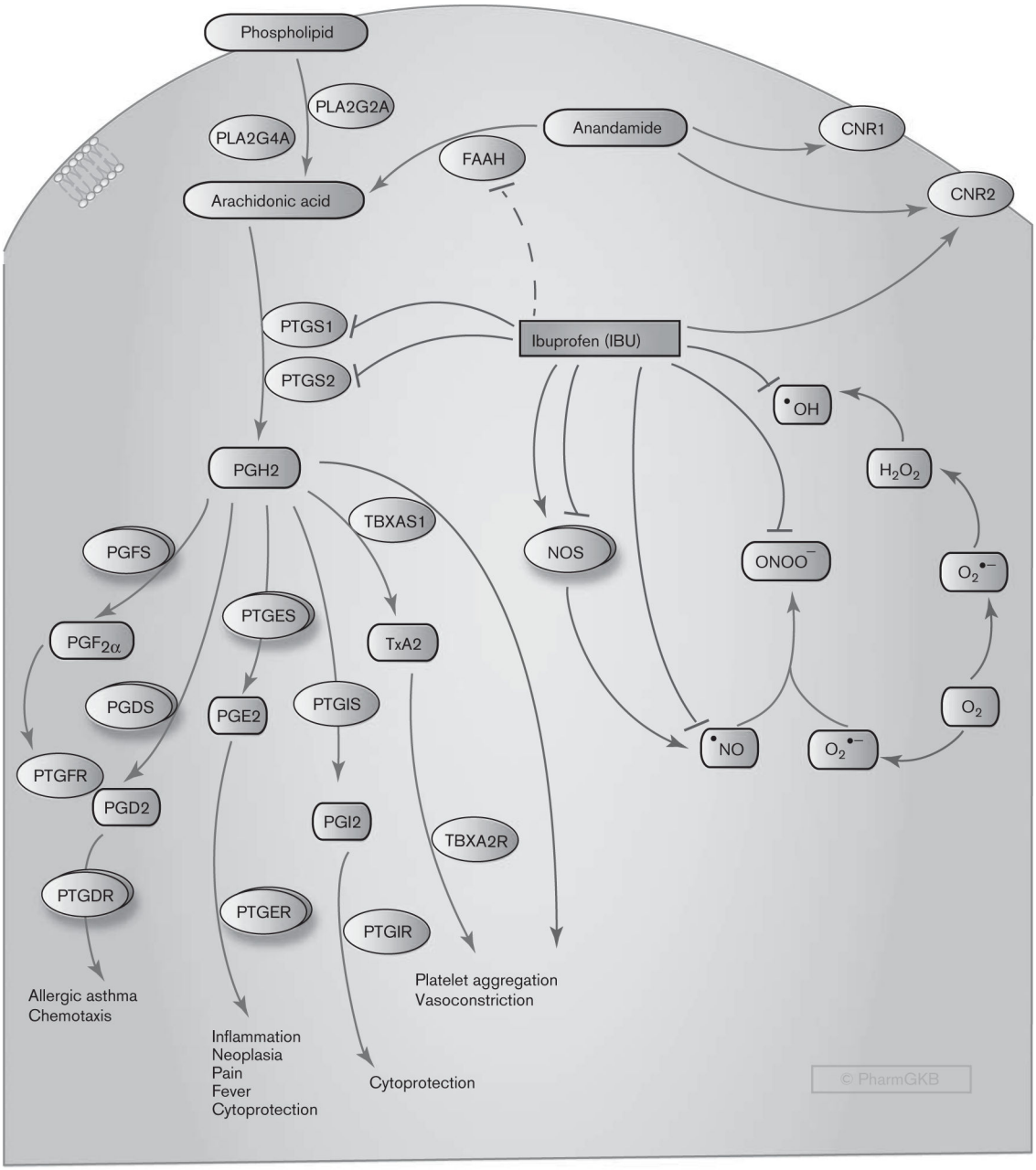

Fig. 2.

Stylized cell depicting the mechanism of action of ibuprofen (IBU). Arachidonic acid is released from the cell membrane phospholipids by phospholipase A_2 (PLA_2), encoded by *PLA2G4A* (cytosolic, calcium-dependent) and *PLA2G2A* (in platelets and synovial fluid). Arachidonic acid is converted to the unstable intermediate prostaglandin (PG) H_2 by cytosolic prostaglandin G/H synthases, termed cyclooxygenases (COX), that exist in two forms, COX-1 and COX-2, and are encoded by *PTGS1* and *PTGS2*, respectively. PGH_2 is converted by tissue-specific synthases to various prostanoids – that is, PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and TxA_2. These bioactive lipids act through their corresponding receptors to trigger a series of biological effects. Ibuprofen exerts its anti-inflammatory and analgesic effects

through inhibition of both COX isoforms. In addition, ibuprofen scavenges $HO^{\bullet}$, $^{\bullet}NO$, and $ONOO^{-}$ radicals and can potentiate or inhibit nitric oxide formation through its effects on nitric oxide synthase (NOS) isoforms. Ibuprofen may activate the antinociceptive axis through binding to the cannabinoid receptors and through inhibition of fatty acid amide hydrolase (FAAH), which metabolizes the endocannabinoid anandamide. CNR1 and CNR2, cannabinoid receptors 1 and 2; H_2O_2, hydrogen peroxide; FAAH, fatty acid amide hydrolase; $^{\bullet}NO$, nitric oxide; NOS, nitric oxide synthase; $ONOO^{-}$, peroxynitrite anion; $O_2^{\bullet-}$, superoxide anion; PGD_2, prostaglandin D_2; PGDS, prostaglandin D synthase; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGFS, prostaglandin F synthase; PGH_2, prostaglandin H_2; PGI_2, prostacyclin; PTGDR, prostaglandin D receptors; PTGER, prostaglandin E receptors; PTGES, prostaglandin E synthase; PTGFR, prostaglandin F receptors; PTGIR, prostacyclin receptor; PTGIS, prostacyclin synthase; TBXA2R, TxA_2 receptor; TBXAS1, thromboxane A synthase 1; TxA_2, thromboxane A_2. A fully interactive version is available online at http://www.pharmgkb.org/pathway/PA166121942.