REVIEW

Role of the nuclear pregnane X receptor in drug metabolism and the clinical response

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The pregnane X receptor (PXR) is an orphan nuclear receptor that regulates the expression of phase I and phase II drug metabolizing enzymes and transporters involved in the absorption, distribution, metabolism, and elimination of xenobiotics. PXR is expressed predominantly in the liver and intestine and resembles cytochrome P450s (CYPs), which is a phase I drug metabolizing enzyme. It is estimated that CYP 3As and CYP2Cs metabolize > 50% of all prescription drugs. PXR upregulates gene expression of these CYPs. Therefore, PXR plays a crucial role detoxifying xenobiotics and could potentially have effects on drug-drug interactions. PXR is reportedly responsible for activating a variety of target genes through cross-talk with other nuclear receptors and coactivators at transcriptional and translation levels. Recent findings have demonstrated the regulatory role of PXR and show the potential use of a PXR antagonist during drug therapy. In addition, genetic variations in the PXR gene are associated with the pharmacological effects of several drugs, and inter-individual differences in the clinical response are likely to be understood through these PXR polymorphisms. Many approaches have been used to explain the PXR regulatory mechanisms, such as microRNA-mediated PXR post-translational regulation and diverse PXR haplotype analysis. Understanding these PXR polymorphisms may lead to improving personalized therapeutic treatments.

Keywords: pregnane X receptor; drug metabolizing enzyme; polymorphism; personalized therapeutic treatment

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Introduction

The pregnane X receptor (PXR) is a member of the nuclear receptor (NR) superfamily of ligand-activated transcription factors and regulates the expression of phase I and phase II drug/xenobiotic metabolizing enzymes and transporters responsible for the absorption, distribution, metabolism, and elimination of xenobiotics and endogenous substrates [1-3]. PXR was first isolated from mouse liver in 1998. Its orthologs in rats, rabbits, and humans have been identified and cloned. PXR is NR subfamily 1 group I member 2 in the standard nomenclature, along with the pregnane-activated receptor (PAR) and the steroid and xenobiotic receptor [1, 4-6]. Similar to other orphan NRs, PXR possesses a common structural organization with a conserved N-terminal DNA-binding domain (DBD) and a ligand-binding domain (LBD). The DBD is characterized by two zinc fingers, which link the receptor to the specific promoter regions of its target genes [7].

However, compared with other NRs, PXR contains a bulky and flexible ligand-binding cavity that accommodates molecules of various shapes and sizes, including drugs, natural products, dietary supplements, environmental pollutants, endogenous hormones, and bile acids [8]. PXR is expressed in a wide range of human tissues, including liver, intestine, colon, kidney, ovary, breast, prostate, mononuclear blood cells, placenta, bone marrow, spinal cord, stomach and heart as well as numerous types of carcinoma tissues, including breast cancer, ovarian cancer, endometrial cancer, colon cancer, prostate cancer, and osteosarcoma [9, 10] The orphan NRs have emerged as transcriptonal regulators of target genes through co-activator recruitment [11].

Increasing evidence suggests that PXR regulates not only drug metabolism and disposition but also physiological and pathophysiological processes, such as glucose metabolism, lipid metabolism, bile acid homeostasis, cancer, diabetes, inflammatory diseases, metabolic diseases and liver diseases [12-15]. Therefore, any genetic variations in PXR that play a role detoxifying xenobiotics could potentially have widespread effects on endocrine signaling pathways and could explain interindivdual variations in response [16]. The purpose of this review is to highlight recent findings on the functions of PXR regulating drug metabolizing enzymes (DMEs) and transporters and the implications of these functions under both physiological and pathological conditions.

Regulation of drug-metabolizing enzymes

PXR regulates phase I DMEs

Phase I DMEs are responsible for catalyzing the oxidation, reduction, and hydrolysis, which are the first step in the detoxification of xenobiotics by converting lipophilic compounds into more soluble derivatives suitable for excretion [17, 18]. Among phase I DMEs, the cytochrome P450 (CYPs; P450s) superfamily, which is abundant in the liver, gastrointestinal tract, lung, and kidney, is the most important family of enzymes mono-oxygenating lipophilic compounds. In fact, CYP2B6 and CYP2C metabolize approximately 25% and 20% of all xenobiotics, respectively [19]. CYP3A4 alone has been estimated to metabolize 50–60% of all prescription drugs [20, 21]. PXR is the predominant up-regulator of CYP3A4 gene expression by binding to several specific elements in the 5' upstream regulatory region of the gene. Many CYP3A4 substrates are also human PXR activators [22]. In addition, PXR regulates the expression of genes encoding phase I enzymes, such as CYP2B6, CYP2B9, CYP2C8, CYP2C9, and CYP2C19, as well as CYP3A family members in various species [23-26].

PXR regulates phase II DMEs

In addition to phase I enzymes, PXR transcriptionally activates a variety of target genes, such as phase II conjugative enzymes and drug transporters [27]. Phase II enzymes add charged species onto xenobiotics or their phase I metabolites, primarily through methylation, esteration, acetylation, glucuronidation, sulfation, and conjugation with glutathione or amino acid. Phase II products are usually highly water-soluble; therefore, they are more readily excreted through biliary and urinary pathways. These enzymes include quinone reductases, NAD(P)H:menadione reductases, methyltransferases, epoxide hydrolases, N-acetyltransferases, glutathione S-transferases, uridine-5'-diphosphate glucuronosyl transferase, and sulfotransferases [28].

PXR is also involved in regulating drug transporters responsible for both efflux and uptake of endogenous and exogenous chemicals. Activated PXR regulates phase III drug transporter gene products, including numerous ATP-binding cassette (ABC) membrane pumps of the multidrug resistant family [MDR1] (also known as P-glycoprotein [P-gp] or ABCB1), multidrug resistant-associated protein (MRP), organic anion transporting protein 1A4 (OATP1A4), and OATP2 [29-32]. Phase I DMEs, phase II DMEs, and drug transporters together mediate the metabolism and elimination of various endobiotics and xenobiotics including drugs and toxicants, sometimes leading drug-drug interactions (DDI).

PXR coordinately regulates a large number of genes encoding drug metabolizing enzymes and transporters in the liver and intestine that are involved in all aspects of detoxification and elimination of xenobiotics and lead to undesirable DDI by increasing drug toxicity and decreasing therapeutic efficacy [33]. In summary, PXR induces key enzymes, such as CYP 2B6, CYP3A4, and UGT1A1, which are involved in the metabolism of over 80% of clinically used drugs [34]. Therefore, induction of these enzymes contributes to increased enzyme expression, followed by DDI. Thus, elucidating the mechanisms underlying gene expression of key enzymes is important for developing safer medicines [35].

Implications of PXR in DDIs

It is now known that many clinically relevant DDIs and herb-drug interactions involving the regulation of DMEs are mediated through the actions of PXR. The clinical response of PXR interactions with many xenobiotics have been demonstrated in a number of reports. Hyperporin is an active constituent found in St. John's Wort (SJW), which is derived

from the flowering plant *Hypericum perforatum*, a popular herbal remedy used to treat a variety of conditions, including depression and inflammation [36, 37]. Hyperporin is a potent PXR agonist [38]. Although hyperporin inhibits CYP3A4 and P-gp *in vitro* [39], chronic use of hyperporin induces CYP3A by activating PXR [36]. Studies show that SJW induces CYP3A4 expression in the intestine [40] and in primary cultures of human hepatocytes [36]. A number of clinically important drug interactions have been reported in patients taking SJW. Induction of CYP3A4 enhances the metabolism of many therapeutic drugs, such as amitriptyline, cyclosporine, digoxin, indinavir, irinotecan, warfarin, phenprocoumon, alprazolam, dextrometorphane, simvastatin, and oral contraceptives [41-45]. Pregnenolone 16α-carbonitrile (PCN), which is a synthetic antiglucocorticoid, induces the CYP3A family [46, 47]. Rifampin is an inducer of CYP3A4 and activates PXR. The features that numerous PXR ligands present across species permit species-specific activation of PXR. Rifampin and PCN induce CYP3A differently in rodents and humans [48]. For example, rifampin is a strong activator of PXR in humans and rabbits, whereas it is a weak activator of PXR in the mouse or rat. In contrast, PCN activate the mouse and rat PXR but has no effect on human PXR (hPXR) [49, 50].

Inducing expression of CYP3A4 could make one drug accelerate the metabolism of a second medicine. Rifampin increases the metabolism of antihypertensive drugs, such as verapamil, by inducing CYP3A4 and reduces the therapeutic effect of verapamil by reducing the oral bioavailability of (S)-verapamil by 90% during long-term treatment [51, 52]. In addition, rifampin decreases the level of digoxin by inducing P-gp protein expression [53]. Similar to CYP3A4, PXR-dependent activation of P-gp by rifampin has been demonstrated [32].

PXR can also be activated by several chemotherapeutic agents, including paclitaxel [23] and cisplatin [54]. Synold *et al*. showed that paclitaxel-activated hPXR induced hepatic expression of CYP3A4 and CYP2C8, as well as MDR1 expression in intestinal tumor cells resulting in enhanced metabolism of paclitaxel by CYP3A4 and CYP2C8, and excretion from the intestine via P-gp. The hPXR-mediated paclitaxel clearance pathway may lead to increased intestinal excretion and resistance to paclitaxel. In contrast, docetaxel, a taxane analog, does not activate PXR or PXR-mediated drug clearance. This difference demonstrates that docetaxel has superior pharmacokinetic properties to those of paclitaxel, although both drugs have similar antineoplastic activity [23].

CYP2C9 is the second most abundantly expressed CYP in the liver and metabolizes approximately 16% of clinically prescribed drugs, such as phenytoin, tolbutamide, warfarin, torsemide, losartan, and several nonsteroidal anti-inflammatory agents [55]. Gerbal-Chaloin *et al*. showed that CYP2C8, CYP2C9, and CYP2C19 respond to the same inducers as CYP3A4 and CYP2B6 mediated by PXR. CYP2C8 and CYP2C9 mRNAs are coregulated in response to rifampin and phenobarbital as PXR is upregulated by glucocorticoids. CYP2C9 is induced by exposure to the same agents as CYP3A4 and CYP2B6, including dexamethasone, rifampin, and phenobarbital. Dexamethasone, which upregulates PXR expression, potentiates CYP2C8 and CYP2C9 mRNA induction in response to rifampicin and phenobarbital [26, 56]. Chen *et al*. showed that PXR mediates induction of CYP2C9 in the presence of rifampin, PCN, phenobarbital [55]. Rifampin is a potent hPXR ligand [57].

The scope has widened to include many natural products after it was demonstrated that gugulipid, kava kava, Coleus forskolii, *Hypoxis*, *Sutherlandia*, Sweet Wormwood, *Schisandra chinensis*, and *Glycyrrhiza* are activators of PXR-mediated target gene expression [58]. PXR is also activated by vitamins E (tocopherol) and K2 [59, 60] .

In addition to CYP2C9, PXR plays an important role regulating CYP2C19 expression. Lopinavir/ritonavir induces CYP2C19, CYP2C9 and CYP1A activities, and it is likely that PXR plays an important role regulating these DMEs [61]. Rifampin, which activates PXR, also induces CYP2C19 mRNA and protein [26].

Intestinal P-gp and the 5'-upstream region of human MDR1 have been examined for the presence of potential PXR response elements, and PXR-mediated induction of MDR1 by rifampin has been investigated [32]. Concomitant use of rifampin and digoxin reduces plasma digoxin levels, which affects the actions of digoxin by inducing P-gp [53].

MRP2 (ABCC2), which is expressed in liver, intestines and kidneys, is an efflux transporter of endogeneous substrates, such as bilirubin glucuronide, estrogens, glutathione conjugates, bile salts, and anthracycline chemotherapeutic agents. Kast *et al*. showed that hepatic MRP2 expression is induced by the PXR ligands rifampin and hyperforin [62].

Clinical implications of a PXR antagonist

Taken together, PXR contributes to DDIs, which can cause undesired results. Recent studies show that hPXR is a key modulator of the hepatotoxicity produced by rifampin and isoniazide co-therapy [63]. PXR activated by several antineoplastic drugs may contribute to drug resistance during anticancer chemotherapy [64]. PXR antagonists also have effects on drug metabolism and may be useful to prevent

DDIs and improve therapeutic efficacy. Further studies are necessary to determine whether PXR antagonists have clinical implications. Several PXR antagonists, such as ET-743, ketoconazole, fluconazole, eniconazole, FLB-12, sulforaphane, A-792611, polychlorinated biphenyls, coumestrol, aryl sulfonamides allyl isothiocyanate, and coumestrol, have been reported [23, 63, 65-74] and can improve drug effects and tolerance.

Cross-talk between PXR and the constitutive androstane receptor (CAR)

A variety of studies have shown that NRs cross-talk among themselves, demonstrating that the signaling pathways controlling drug metabolism are involved within a tangle of regulatory networks. Hepatocyte nuclear factor-4α (HNF-4α) and glucocorticoid receptor (GR) have an important role regulating the expression of other ligand-activated transcription factors, such as PXR, CAR, and farnesoid X receptor. For example, GR modulates PXR- and CAR-mediated induction of CYP2B, CYP2C, CYP3A, and GST genes [75-80]. HNF4α, GR, and CAR, crosstalk with PXR and co-activators to control target gene expression [81]. Unlike other NRs, PAR and CAR share some unique features, such as ligand promiscuity, species differences, and some of the response elements to regulate the many overlapping sets of target genes. Some studies have suggested that the mechanism of cross-regulation is through shared response elements between receptors [82, 83].

Chen *et al*. provided supporting evidence that there is cross-talk between distal CAR/PXR sites and HNF-4α binding sites in the CYP2C9 promoter, and that proximal HNF-4α binding sites are required for optimal activation of the CYP2C9 promoter by both CAR and PXR. Two HNF-4α binding sites, located −185 and −152 bp from the translation start site, mediate transactivation of the CYP2C9 promoter and synergize with CAR/PXR [81]. HNF-4α is also an important determinant of PXR- and CAR-mediated induction of CYP3A4 by binding upstream of the PXR and CAR response elements in the CYP3A4 gene enhancer [2, 84].

PXR pharmacogenetic effects

Several studies have described genetic variations in the PXR gene, including other NRs, encoding for transporters and DMEs, and some of these have been associated with the pharmacological effects of several drugs [85-88], which is due to functional changes in NR expression. Therefore, it is likely that inter-individual variability in the clinical responses to several drugs will be understood through PXR genetic polymorphisms [89]. The hPXR gene is located on chromosome 3q12q13.3. The coding region consists of exons 2–9, spanning 434 amino acids. Zhang *et al*. provided the first evidence linking variant PXR alleles to altered drug clearance. That study provided 38 single nucleotide polymorphisms (SNPs) and showed that several genetic variations within the PXR non-coding region were associated with either enhanced or reduced expression of PXR target genes, such as CYP3A4 and MDR1[90]. To date, more than 300 hPXR SNPs have been deposited in the dbSNP database [91, 92]. Some of these are well investigated and their functional significance has been elucidated. These SNPs could affect protein expression, the ability to bind target DNA, or activation of PXR by ligands [85, 93].

Many studies have been performed to identify whether genetic polymorphisms in regulatory NRs (CAR, HNF-4α, and PXR) can affect specific drug responses through changes in expression and/or activity of DMEs or drug transport genes. A study of 101 patients with breast cancer from three Asian ethnic groups showed genotypic variations in the PXR transcriptional regulator rs1523127 (A>C). CAR and HNF4α have not been associated with docetaxel or doxorubicin pharmacokinetics or pharmacodynamics [86]. However, PXR rs2276707 in combination with rs3814058 (T>C) in the 3′ untranslated region (UTR) lowered doxorubicin clearance in 311 patients with breast cancer undergoing adjuvant treatment with doxorubicin and cyclophosphamide [94].

Moon *et al*. suggested that the rs2472682 (A>C) intronic PXR SNP is significantly associated with stable warfarin doses in patients with prosthetic cardiac valves and that the combination of the rs2501873/rs3212198/rs2472682 CAR/HNF-4α/PXR SNPs resulted in differences in the warfarin dose between grouped genotypes [95]. Other as yet undiscovered genetic drug disposition and toxicity factors should be studied further. These results suggest that PXR may have a pharmacogenetic effect and that it selectively affects activation of some drug but not others.

Much of the recent research progress has explained the role of PXR. MicroRNAs are short (about 22 nucleotides in length) non-coding regulatory RNAs that control target genes by binding to complementary regions of transcripts, resulting in repression of their translation or mRNA degradation [96]. The possibility of miRNA-mediated PXR post-transcriptional regulation has emerged. Takagi *et al*. reported that miR-148a recognizes the complementary sequence in the 3′ UTR of hPXR mRNA, which leads to downregulation of the PXR protein and those of its target genes [97]. A haplotype analysis is more comprehensive and persuasive than single SNP studies. Oleson *et al*. identified an association between a haplotype of 10 SNPs located in the PXR 3′ UTR and clearance of midazolam by CYP3A [98]. Another study reported that doxorubicin clearance in patients

with breast cancer harboring the PXR*1B haplotype is significantly lower than clearance in patients with other haplotypes and that it is associated with reduced hepatic CYP3A4 mRNA expression by PXR [94].

Conclusions and Perspectives

NRs have important roles regulating the expression of genes encoding DMEs and drug transporters resulting in altered clinical drug responses. Recent evidence has revealed that PXR may significantly contribute to the coordinated regulation of phase I, II, and III drug metabolism and transporters with other receptors, such as CAR and HNF4-α and/or transcription factors as well as coactivators. Various PXR regulated genes, such as CYP3As, CYP2Cs, and UGT1As, have been investigated for their possible roles influencing drug efficacy or toxicity.

Many studies suggest that PXR polymorphisms and their specific haplotype clusters exist and that some affect individual variations in drug responses or DDIs. A better understanding and the relevance of NR pharmacogenetics may result in more effective and safer personalized therapeutic treatments. Further studies are necessary to identify the genetic mechanism by which PXR influences the pharmacological profiles of various drugs at the transcription and translation levels. These studies will highlight the way to improve personalized medicine.

Conflicting interests

The authors have declared that no competing interests exist.

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