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Expert Review

Elucidating the 'Jekyll and Hyde' Nature of PXR: The Case for Discovering Antagonists or Allosteric Antagonists

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Abstract. The pregnane X receptor belongs to the nuclear hormone receptor superfamily and is involved in the transcriptional control of numerous genes. It was originally thought that it was a xenobiotic sensor controlling detoxification pathways. Recent studies have shown an increasingly important role in inflammation and cancer, supporting its function in abrogating tissue damage. PXR orthologs and PXR-like pathways have been identified in several non-mammalian species which corroborate a conserved role for PXR in cellular detoxification. In summary, PXR has a multiplicity of roles *in vivo* and is being revealed as behaving like a "Jekyll and Hyde" nuclear hormone receptor. The importance of this review is to elucidate the need for discovery of antagonists of PXR to further probe its biology and therapeutic applications. Although several PXR agonists are already reported, virtually nothing is known about PXR antagonists. Here, we propose the development of PXR antagonists through chemical, genetic and molecular modeling approaches. Based on this review it will be clear that antagonists of PXR and PXR-like pathways will have widespread utility in PXR biology and therapeutics.

KEY WORDS: agonists; antagonists; machine learning; pharmacophore; pregnane X receptor.

PXR BIOLOGY

The pregnane X receptor (PXR) or NR1I2 (1–5) belongs to the nuclear hormone receptor (NHR) superfamily of transcription factors containing ligand- and DNA-binding domains. PXR was initially described as a xenobiotic sensor critical for the transcriptional regulation of genes central to detoxification pathways [reviewed in (5,6)]. The first PXR targets to be elucidated were transporters and drug- and steroid hormone-metabolizing enzymes (7). It is now known that the physiological importance of PXR extends far beyond xenobiotic protection (PXR and the related former orphan receptor, constitutive androstane receptor (CAR, NR1I3) which have both been implicated in ameliorating cholestatic injury to the liver, inhibiting rodent liver fibrogenesis, increasing cholesterol metabolism, enhancing bone homeostasis, improving gut mucosal defense, and preventing osteoporosis (8–12). In long lived "*little*" mice, up-regulation of genes involved in xenobiotic detoxification are largely through bile-acid mediated activation of FXR and not through PXR and CAR activation (13). These data suggest that loss of PXR function, at least in mice, does not play a role in curtailing longevity. More recently, PXR has been shown to have a significant effect on ablating the inflammatory response mediated by exogenous toxins (*e.g.*, bacteria) and to have an important role in modulating inflammatory diseases of the bowel (14–16). A list of commonly known important genes targeted by PXR (as observed by qPCR, microarray analysis and other studies) can be found in Supplementary Table I. While there has been consequently less research into antagonists of PXR, this may also have clinical implications as described later.

Ongoing research has revealed the biology of PXR is more complex and subtle than first appreciated. Several investigators have demonstrated that PXR plays a central role in mediating blood–brain barrier efflux of drugs through the modulation (upregulation) of efflux transporters like P-glycoprotein (MDR1, ABCB1) and multidrug resistance-related protein 2 (MRP2, ABCC2). PXR agonists can therefore decrease delivery and retention of central nervous system directed drugs such as anti-epileptics and analgesics, thereby reducing therapeutic efficacy (17–24).

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The role of PXR in cholesterol metabolism is controversial. PXR activation was initially thought to have a beneficial effect on cholesterol metabolism, based on a murine model showing inhibition of the cholic-acid mediated decrease in plasma high-density lipoprotein (HDL) levels (25). Furthermore, PXR regulates the expression of several key enzymes controlling the bile acid synthesis pathway, lipid metabolism and glucose homeostasis (26–28). These and other investigations indicated that activation of PXR was likely to be beneficial in the treatment of atherogenesis. Earlier studies had also shown in rodents that PXR agonists (*e.g.*, clotrimazole analogs) increase hepatic apoA1 mRNA (apolipoprotein A1 or apoA1 being a major protein component of HDL), and plasma HDL-C mRNA (29). More recent data, however, point towards the complicated but deleterious atherogenic effects of PXR activation *in vivo*. First, PXR agonism decreases plasma HDL levels *in vivo* in atherogenic prone ApoE3-Leiden.CETP mice (30). Second, while the PXR agonist PCN (pregnenolone carbonitrile) decreases plasma LDL-cholesterol by 66% in homozygous LDL receptor knock out mice (an established mouse model of atherogenesis), and also in apolipoprotein E knock out mice, there is a significant decrease in lipid lipolysis, an increase in VLDL-triglycerides and the development of hepatic steatosis (marked by increased triglyceride and phospholipid levels in liver) (31). In another study in mice, PXR mRNA is significantly elevated in non-alcoholic steatohepatitis (NASH)-induced livers, implicating a role for PXR (32). Furthermore, in humans, the PXR agonist rifampicin induces significant increases in blood cholesterol and fasting triglycerides (33). Since HDL-cholesterol and triglycerides are independent prognosticators of cardiovascular disease and mortality (34), PXR agonism in the context of atherogenesis would appear detrimental based on the most recent studies. In a healthy individual, the dual and opposite roles of PXR with respect to cholesterol metabolism (decreasing LDL-cholesterol, but increasing triglycerides) may neutralise each other. But in people with 'metabolic syndrome' (high risk of cardiovascular disease and diabetes) triglyceride accumulation may be extremely damaging. Thus, a PXR antagonist may help to prevent accumulation of triglyceride and phospholipids in the liver (a hallmark of hepatic steatosis and NASH), which may be especially effective in people with "metabolic syndrome".

In cancer growth and carcinogenesis, there is a preponderance of evidence to suggest that PXR induces cell growth and is pro-carcinogenic (10,11,35–72) [Table I, Supplementary Table 2], thereby acting as a possible oncogene. Several mechanisms have been proposed and include activation of the reactive oxygen species (ROS) system, down-regulation of pro-apoptotic genes with up-regulation of inhibitors of apoptosis, and cytochrome P450 (CYP)-mediated activation of pro-carcinogens (52,60,61,68). One report provides contrary evidence that PXR induces apoptosis in breast cancer cells through nitric oxide (NO)-dependent stabilization of p53 and up-regulation of cell cycle regulatory and pro-apoptotic genes such as p21, PUMA and BAX (75). However, other reports show that PXR can induce cell proliferation in breast cancer through mechanisms involving the organic anion transporter 1A2 (OATP1A2) mediated import of estrogen sulphate and/or by altering co-repressor (SMRT) binding to estrogen receptor-α (ERα) (76). The effects of PXR on ERα-mediated transcription, is cancer cell type specific and dependent on the estrogen response element. Indeed, estrogen binds and activates human PXR, which could also contribute estrogenic effects in breast cancer (77). In this context, there is an inverse correlation between PXR mRNA expression in breast tumors compared with ERα (78,79). Together, these data suggest that estrogen could act through PXR in ER-positive tumors, thereby, inducing growth. Notably, in an MMTVneu mouse model of breast cancer, 4-nonyphenol (an environmental estrogen that also activates PXR and CYP enzymes that produce estriol) induces a marked increase in estriol-induced mammary tumors. All these data support the role for PXR in inducing breast tumors through multiple cancer specific pathways (80).

In 60 human breast carcinoma specimens, PXR was detected in carcinoma tissues but not in non-neoplastic and stromal cells of breast tumors. A significant positive correlation was detected between PXR and both the histologic grade and the lymph node status of the carcinoma cases. In the same report, in ER-positive cases, PXR expression was also positively correlated with expression of the cell proliferation marker Ki-67. The overall implications of these data are that PXR may play a significant anti-apoptotic role in breast cancer (73). Indeed, these results support PXR's role as a protector against tissue damage, a role that may be pathophysiologic in neoplastic cells. In addition, perhaps more widely known is that PXR has been shown to induce cancer drug resistance by regulating expression of enzymes and transporters that can affect chemotherapy metabolism and efflux (36,69–72,74).

Table I. Possible Therapeutic Applications of PXR Antagonists or Allosteric Antagonists

Therapeutic application	Effects of PXR antagonist
Cancer	Decrease cell proliferation anti-apoptotic role in breast cancer (73), Interfere with cancer drug resistance/induction of enzymes and transporters affecting chemotherapy(36,69–72,74)
Drug–drug interactions	Prevent failure of ethinyl estradiol
Osteomalacia	Prevent increased clearance of 1,25-dihydroxyvitamin D_3
Acetaminophen hepatotoxicity	Prevent the conversion of acetaminophen to a hepatotoxic metabolite
Immunology	Does PXR have a role?
Blood brain barrier (BBB)	Could antagonists of PXR be used to make the BBB more permeable by block increased expression of transporters that normally efflux compounds and maintain a tight BBB?
Intestine	Could antagonists of PXR be used to turn off expression of enzymes and transporters in the gut to increase bioavailability?

PXR AGONIST AND ANTAGONIST PHARMACOLOGY

There have been many studies that characterize endogenous and exogenous agonists that activate PXR (81,82). Subsequently we now know that PXR has the broadest ligand specificity of the NHR superfamily, with a structurally diverse array of compounds able to activate PXR (83–87). PXR agonists include prescription medications (anticonvulsants, HIV protease inhibitors, rifampicin), herbal drugs (St. John's wort), steroid hormones, bile salts, and fat-soluble vitamins. Multiple crystal structures of human PXR, unliganded and bound to different agonists, revealed a large, spherical, and flexible ligand-binding pocket (LBP) (88–92). These properties of the human PXR LBP make computational prediction of PXR–ligand interactions difficult, for example docking a small molecule into a large binding site.

PXR activation has been implicated in a number of clinically significant adverse drug–drug interactions. In many of these cases, PXR activation by a drug such as rifampicin or the St. John's wort component, hyperforin leads to the up-regulation of drug-metabolizing enzymes such as the CYP3A isoforms that can metabolize concomitant medications. Hyperforin, is a potent PXR agonist (EC_{50} of 23 nM) and significantly affects serum concentrations of the chemotherapeutic agent irinotecan (CPT-11). Co-administration of irinotecan and St. John's wort reduces the gastrointestinal toxicity of irinotecan but also its anti-neoplastic efficacy. In this context, activation of PXR is a double edge sword (89,93–98). Hence, development of oral PXR antagonists with rapid absorption within the stomach [so that intestinal PXR antagonism is spared in all cases, as PXR protects the intestine against inflammatory bowel disease (14)] and high hepatic extraction may control such drug interactions. PXR activation may also affect the metabolism of steroid hormones and fat-soluble vitamins. Chronic administration of a PXR activator can lead to therapeutic failure of estrogen-containing oral contraceptives by metabolism of ethinyl estradiol or osteomalacia by increased clearance of 1,25-dihydroxyvitamin D_3. Antagonism of hepatic PXR may therefore be beneficial in preventing undesirable side effects in patients who must chronically take medications that are PXR activators. Another example where the antagonism of hepatic PXR would be clinically beneficial is acetaminophen hepatotoxicity, where PXR activation increases the conversion of acetaminophen to a hepatotoxic metabolite. As such, there would appear to be a market for successful PXR antagonists (58,99,100) (Table I).

There have been relatively few attempts to understand or develop *in silico* models of antagonism of PXR (85). One computational approach focused on the ligand binding domain (LBD) using the crystal structure of PXR bound to T-0901317 (92), but this proved difficult (101). The list of PXR antagonists is however steadily growing and even includes some compounds first characterized as weak PXR agonists (Table II). For example, the azole antagonists ketoconazole (104), fluconazole and enilconazole (105) have all been shown to inhibit the activation of PXR in the presence of paclitaxel, while behaving as weak agonists on their own. The azole anti-fungals should more appropriately be called non-competitive allosteric antagonists as they do not directly bind to the LBD. Competitive antagonists reversibly bind to receptors at the same binding site (active site) as the endogenous ligand or agonist, but without activating the receptor, and block agonist binding. Agonists and competitive antagonists "compete" for the same binding site on the receptor. The level of activity of the receptor will be determined by the relative affinity of each molecule for the site and their relative concentrations. The effects of a competitive antagonist may be overcome by increasing the concentration of agonist. But, non-competitive or allosteric antagonists bind to a distinctly separate binding site from the agonist, exerting their action at that receptor via another binding site. Thus, they do not compete with the agonist for binding. The bound allosteric antagonists may result in a decreased affinity of an agonist for that receptor, or alternatively may prevent conformational changes in the receptor required for receptor activation after the agonist binds. No amount of agonist can completely overcome the inhibition once it has been established and thus allosteric non-competitive antagonists can be potentially more effective than competitive antagonists. Ketoconazole does not bind to the LBD of PXR, but it was shown to inhibit the interaction of PXR with the co-activator SRC-1 (steroid receptor coactivator-1) suggesting binding to the AF-2 (Activation Function 2) site (104). This hypothesis was further confirmed with site-directed mutagenesis data (105), indicating ketoconazole behaved like the histidine residue of SRC-1 (105). Pharmacophore modeling of the three azole antagonists and docking with human PXR additionally confirmed these molecules were likely interacting outside the LBD (86) as allosteric antagonists. Ketoconazole was docked into the exterior site, and the piperazine ring was predicted as solvent exposed. The pharmacophore model also indicated the minimum requirements of these azoles, suggesting the complimentary nature of different computer-aided antagonist design methods (86). These computational approaches have also been used to search databases of commercially available and FDA approved molecules for novel non-azole PXR

Table II. PXR Antagonists or Allosteric Antagonists Identified *In Vitro*

Compound	Antagonist data	Reference
ET-743	IC_{50} 2 nM	(102)
Polychlorinated biphenyls	K_i 0.6–24.5 μM	(103)
Ketoconazole[a]	IC_{50} ~20 μM	(104)
Fluconazole	IC_{50} ~20 μM	(105)
Enilconazole	IC_{50} ~20 μM	(105)
Sulforaphane[b]	IC_{50} 12 μM	(106)
Coumestrol	IC_{50} 12 μM	(107)
HIV protease inhibitor A-792611	IC_{50} ~2 μM	(108)
SPB03255	IC_{50} 6.3 μM	(86)
SPB00574	IC_{50} 24.8 μM	(86)
Leflunamide	IC_{50} 6.8 μM	(86)
Itraconazole	IC_{50} 8.96 μM	(86)
SPB3256	IC_{50} 6.21 μM	(86)
SPB6061	IC_{50} 5.22 μM	(86)
SPB06257	IC_{50} 16.42 μM	(86)
SPB02372	IC_{50} 5.82 μM	(86)

[a] (+)-2R,4S-Ketoconazole 16.4 μM, (−)-2S,4R-Ketoconazole 16.6 μM (86)

[b] (S)-Sulforaphane 5.64 μM, (R)-Sulforaphane 5.58 μM (86)

antagonists followed by *in vitro* testing. Several new PXR antagonists were discovered in this way (Table II) which we suggest may also be binding similarly as allosteric antagonists.

PXR IN NON-MAMMALIAN SPECIES

So far, this review has focused primarily on PXRs of humans and rodents. With only a few exceptions, the physiologic functions of PXRs of non-mammalian species are not well-understood. Studies of zebrafish PXR have suggested a role in regulating organogenesis during stressful environments and xenobiotic detoxification (109,110; http://zfin.org/cgi-bin/webdriver?MIval=aa-fxfigureview.apg&OID=ZDB-FIG-080410-3), The ligand specificities of non-mammalian PXRs differ significantly from that of human and other mammalian PXRs, leading to speculation that cross-species differences in exogenous and/or endogenous toxic compounds provide evolutionary selective pressure for PXR ligand diversity (84,111). Pharmacophore analysis performed on 16 agonists for mammalian (human, mouse, rat), chicken, frog and zebrafish PXRs highlighted the effect of evolution on ligand specificity (112), with mammals possessing similar pharmacophores while the other species were very different. Non-mammalian PXRs generally have narrower selectivity for ligands, with homology models of frog and zebrafish PXRs, predicting ligand binding pockets substantially smaller than that for human PXR (112). Pharmaceutical compounds or environmental contaminants that are activators of non-mammalian PXRs could therefore have deleterious effects on wildlife and the ecosystem.

It should be noted, however, that the implications for the therapeutic alteration of xenobiotic signaling and drug resistance is far more important in non-mammals. Interestingly, PXR-like pathways appear to exist in invertebrate species. In the fruit fly *Drosophila*, the ortholog of PXR, DHR96, induces decreased sensitivity to the pesticide DDT (113,114). DHR96 controls metabolic and stress-response genes, thus acting as a xenosensor for toxin resistance and could therefore decrease sensitivity of flies to pesticides. In the Chordate *Ciona intestinalis*, there is a vitamin D receptor (VDR)/PXR ortholog that has a low sequence identity to vertebrate PXR and VDR which is activated by a small set of planar molecules (109,115). There are also other PXR-like pathways which may not be orthologous to PXR. For example, in yeast cells, there is a pathway regulating multidrug resistance in which the receptor, Pdr1p, (functionally similar to PXR) reveals an unexpected analogy between fungal and metazoan regulators of multidrug resistance. Activation of Pdr1p induces the MDR phenotype in *S. cerevisiae* and *C. glabrata* (116). In the worm *C. elegans*, a PXR-like receptor, daf12 (or nhr8, nhr48) also induces toxin resistance. In favorable environments, Daf12 induces reproductive growth and inhibits the dauer diapause [which also affects developmental age, adult longevity (117) and is directly implicated in cell survival in the mid-larval stage]. In unfavorable environments, it has the opposite effect, inhibiting reproductive growth and initiating the dauer diapause. Daf12 antagonists could therefore reverse this process in both environments (117,118). A final example of a PXR-like pathway is the steroid hormone ecdysone, acting through the orphan nuclear receptor DHR78, which is

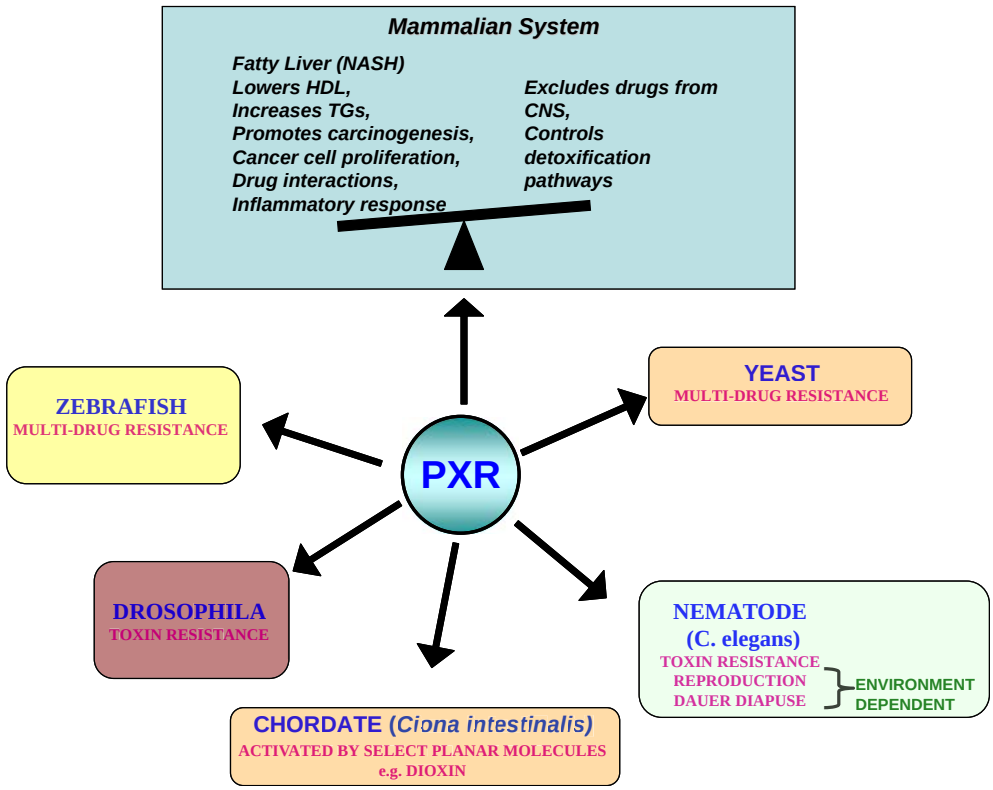

Fig. 1. PXR roles in different species.

required for growth and viability during *Drosophila* larval stages (119). Thus, from the above discussion it seems that a broad range of non-mammalian species have PXR-like pathways that regulate toxin/drug resistance. Thus an antagonist (or allosteric antagonist) to PXR in these species may help in developing effective anti-fungal or anti-nematode agents.

SUMMARY AND FUTURE DIRECTIONS

How might we find new molecules that could interfere with PXR and enable a more complete understanding of its functional role in different species? We have already described some early success using pharmacophores for allosteric antagonists and this work followed their earlier use in identification of PXR agonists alongside other computational methods (81,120,121). Different PXR agonist pharmacophores built with unique datasets (86) have also been used with *in vitro* data to predict antibiotics that activate PXR and induce CYP3A4 (122). Machine learning (support vector machines, K-nearest neighbors, recursive partitioning and random forest) methods for predicting PXR agonists have been used most recently (120,123,124) with large sets of binary data. Their results with increasingly larger external test sets of molecules indicate that the support vector machine (SVM) method performs well and generally outperforms docking methods (123,124) with test set accuracies between 72% and 81% (124). Studies evaluating different molecular descriptors, algorithms and larger quantitative datasets will be the likely trend in the future. Docking and protein-based modeling methods have been less widely used, although a recent study has compared the splice variant PXR.2 with PXR.1, using a homology model lacking the 37 amino acids that make up helix 2, to suggest why agonists do not appear to activate it (125). One could imagine homology models of various site directed mutants to narrow the ligand binding domain or the antagonist site and engineer specific interactions between ligand and protein. The search for further PXR antagonists (or allosteric antagonists) could be dramatically expanded to search many more diverse libraries than the few analyzed to date (86). In addition, one could also try developing tissue-selective PXR antagonists. These could be used to selectively target neoplastic cells or disrupt undesirable PXR-mediated up-regulation of drug metabolism in the liver or elsewhere. It may also be possible to search for additional antagonist or allosteric sites on PXR that could modulate activity, and then apply computational approaches to find molecules that could fit into these sites selectively. For some purposes, having more than one antagonist might be preferable. As the literature continues to grow around PXR we will increasingly require systems biology analysis software to track the complex interactions that have already been used to visualize PXR and downstream genes (122,126).

Where might we look for additional important roles for PXR in the future? NHRs seem to have a developing role in resisting infection from mycobacteria such as tuberculosis (127–129). VDR gene variants have been suggested to regulate the cytotoxic T-cell response via 1,25(OH)2D3 mediated suppression of granzyme A (a serine protease that induces apoptosis) expression in tuberculosis infection (129). FXR regulates the tryptophan-aspartate containing coat protein (TACO) which plays a key role in the entry/survival of tuberculosis. To date we are not aware of similar roles for PXR. But, it may be worth looking into whether rifampicin (130) and other antibiotics (122) binding to PXR can make this a drug target that could be exploited with downstream signaling effects that impact on infection in macrophages. It would be interesting to observe the effect of antagonists or allosteric antagonists in this scenario. They could improve the drug–drug interactions that occur upon treatment with HIV therapies concomitantly, impacting therapeutic response. Alternatively, there could be distant PXR orthologs or PXR-like pathways in bacteria or parasites that could be targeted by antibiotics. To our mind this deserves further study especially as the search for new therapies for tuberculosis and other pandemic diseases is urgently needed (131) and recent reviews have pointed to the severe shortage of compounds in the pipeline for infectious diseases overall (132).

In summary, PXR has a multiplicity of roles *in vivo* and behaves like a "Jekyll and Hyde" NHR. Some of these roles are conserved (*e.g.*, regulation of xenobiotic metabolism) but others are divergent and tissue dependent (*e.g.*, cell proliferation, differentiation, *etc*). In some tissues and conditions, PXR activation may seem beneficial while in other cases it may be deleterious, making a significant argument in favor of the continued development of PXR-directed antagonists and allosteric antagonists (Fig. 1). These compounds could have wide-reaching implications from human patho-physiology to the development of antimicrobials (*e.g.,* anti-fungal, anti-bacterial and anti-parasitic drugs) and anticancer compounds. PXR antagonists or allosteric antagonists do not appear to be currently actively pursued by biotechnology or pharmaceutical companies, perhaps because of the complexity of the biology and the lack of understanding of its role. However, development of potent PXR allosteric antagonists suitable for animal studies could provide key proof-of-concept for human drug design.

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