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Mini review:

BIOLOGY OF PXR: ROLE IN DRUG-HORMONE INTERACTIONS

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ABSTRACT

Hormonal homeostasis is essential for a variety of physiological and pathological processes. Elimination and detoxification of xenobiotics, such as drugs introduced into the human body, could disrupt the balance of hormones due to the induction of drug metabolizing enzymes (DMEs) and transporters. Pregnane X receptor (PXR, NR1I2) functions as a master xenobiotic receptor involved in drug metabolism and drug-drug interactions by its coordinated transcriptional regulation of phase I and phase II DMEs and transporters. Recently, increasing evidences indicate that PXR can also mediate the endocrine disruptor function and thus impact the integrity of the endocrine system. This review focuses primarily on the recent advances in our understanding of the function of PXR in glucocorticoid, mineralocorticoid, androgen and estrogen homeostasis. The elucidation of PXR-mediated drug-hormone interactions might have important therapeutic implications in dealing with hormone-dependent diseases and safety assessment of drugs.

Keywords: PXR, hormone homeostasis, xenobiotic receptor, drug-hormone interactions

INTRODUCTION

Hormones, especially steroid hormones, act as chemical messengers to regulate a variety of physiological processes (Norman et al., 2004), such as metabolism, development and growth. Disruption of hormone balance contributes to the pathogenesis of sexual dysfunction, cardiovascular diseases, metabolic syndrome, and a multitude of cancers. It has been recognized that variations in the expression and/or activity levels of drug metabolizing enzymes and transporters can affect the biotransformation, excretion and function of hormones, therefore influence the susceptibility of individuals to certain hormone-dependent diseases (Lakhani et al., 2003; Secky et al., 2013). In this regard, drug-hormone interactions should be considered for safety assessment of drugs.

There is now compelling evidence that several orphan nuclear receptors can function as "steroid receptors" by impacting steroid hormone homeostasis (Falkenstein et al., 2000). Orphan nuclear receptors belong to nuclear receptor (NR) superfamily, whose endogenous and/or exogenous ligands have not yet been identified at the time the receptors were discovered (Chawla et al., 2001;

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Mangelsdorf and Evans, 1995). Recently, endogenous and/or synthetic ligands for many of the orphan receptors have been discovered. These receptors were subsequently re-classified as "adopted" orphan NRs (Chai et al., 2013; Mukherjee and Mani, 2010). Examples of the "adopted" orphan NRs include pregnane X receptor (PXR; NR1I2), constitutive androstane receptor (CAR; NR1I3), liver X receptors α and β (LXRs; NR1H3 and NR1H2), retinoid X receptors (RXRs; NR2B1, NR2B2 and NR2B3), peroxisome proliferator-activated receptors (PPARs; NR1C1, NR1C2 and NR1C3), farnesoid X receptor (FXR; NR1H4) and hepatocyte nuclear factor-4 α (HNF4α; NR2A1, NR2A2 and NR3A3).

Some NRs, such as CAR, LXR, PXR and GR, have been reported to affect the hormone regulation (Gong et al., 2007, 2008; Qatanani et al., 2005), among which PXR has been increasingly recognized for its function in mediating the endocrine disrupting effect and affecting steroid homeostasis. This is because PXR is a master xenosensor involved in drug metabolism and drug-drug interactions by its coordinated transcriptional regulation of phase I/II drug metabolizing enzymes (DMEs) and transporters (Chai et al., 2013; Chen et al., 2012; De Mattia et al., 2013). The same enzyme and transporter systems are also responsible for the metabolism of many of the steroid hormones. Therefore, drugs that activate PXR can potentially impact hormonal homeostasis, leading to the so-called drug-hormone interactions. In this review, we aim to summarize the most recent findings and further understand the potential mechanisms by which PXR mediates drug-hormone interactions.

PXR AS A XENOBIOTIC RECEPTOR

PXR was originally identified as a xenobiotic nuclear receptor highly expressed in the liver and intestine. PXR is involved in drug metabolism, bile acid transport, cancer, cholesterol metabolism and inflammation (Biswas et al., 2009; Kliewer et al., 1998; Lehmann et al., 1998). PXR has similar structure with other NRs, but a larger and flexible ligand-binding pocket, which enables it to accommodate a more diverse array of ligands (Watkins et al., 2001), including prescription drugs, herbal medicines, dietary supplements, environmental pollutants, and endobiotics (Ma et al., 2008; Poso and Honkakoski, 2006). When ligand bind to ligand binding domain (LBD) of PXR, it translocates from the cytoplasm to the nucleus (Squires et al., 2004) and then binds to DNA binding domain (DBD) in xenobiotic response element (XRE) as a heterodimer or heterotetramer with the retinoid X receptor (RXR) (Teotico et al., 2008). PXR can recruit multiple co-activators, such as the steroid receptor co-activators 1 (SRC-1), TIF/GRIP (SRC-2) and PPARγ co-activator 1α (PGC-1α) (Li and Chiang, 2005; Mangelsdorf and Evans, 1995; McKenna et al., 1999), and also with nuclear receptor HNF4α (Guengerich, 2003; Tirona et al., 2003), leading to PXR-mediated transcriptional activation of target genes.

Among PXR domains, the LBD amino acid sequence of PXR are more diverse among species (Maglich et al., 2001), which is responsible for the species-specific PXR activation and target gene induction. For instance, the antibiotic rifampicin (RIF) and SR12813 are effective PXR agonists for hPXR, but they have little effect on the mouse or rat PXR (Jones et al., 2000; Lehmann et al., 1998). Another case is that, the synthetic antiglucocorticoid pregnenolone-16a-carbonitrile (PCN) can potently activate the rodent PXR but has little effect on hPXR (Kliewer et al., 2002; Lehmann et al., 1998). Therefore, PXR humanized transgenic mice were developed and emerged as an important model to overcome the species specificity when testing compound efficacy in vivo and exhibited a humanized hepatic xenobiotic response profile (Ma et al., 2007; Xie et al., 2000).

Drug-metabolizing enzymes and drug transporters regulated by PXR

PXR is a well-established xenobiotic sensor that regulates various phase I/II

DMEs and transporters. Phase-I oxidative metabolism is primarily catalyzed by several members of the cytochrome P450 (CYP) family of haem-containing monooxygenase (Nelson et al., 1996), which are abundance in the liver and intestine. They play pivotal roles in the first stage of xenobiotic (e.g. drugs, environmental chemicals) and endogenous (e.g. lipophilic substrates, fatty acid) metabolism. Among these CYPs, members of the CYP3A family are predominantly responsible for more than 60 % metabolic substrates (Rendic, 2002). The CYP3A induction by xenobiotics is now thought to be largely due to xenobiotic binding and transcriptional activation of PXR. For example, PXR/RXR heterodimers bind DR3 element in the human CYP3A4 gene enhancer and an ER6 element located in the proximal promoter of the CYP3A4 gene (Bertilsson et al., 1998; Goodwin et al., 1999; Lehmann et al., 1998) .

Phase II enzyme genes up-regulated by PXR ligands include glutathione S-transferase (GST), UDP glucuronosyltransferase (UDPGT) , Sulfotransferase (SULT) and carboxylesterase families (Falkner et al., 2001; Hosokawa et al., 1993; Madhu and Klaassen, 1991). Besides the function in drug metabolism, SULTs have been widely studied due to their important role in steroid homeostasis and neurotransmitters (Hellriegel et al., 1996; Hempel et al., 2004). Therefore, it is not surprising that the investigation of the effects of NR (including PXR)-mediated regulation of SULTs on physiological and pathophysiological processes is becoming active (Gamage et al., 2006; Runge-Morris, 1998; Runge-Morris et al., 2013).

Finally the removal of toxicant from body is accomplished by phase III transporters, among the hepatic transporters, PXR has been shown to stimulate the expression of Oatp1a4, Oatp21 (Oatp1b1), MDR1, MRP2 and MRP3 differently in rodents and human (Chai et al., 2013).

Taken together, PXR coordinately regulates multistep system consisting of three groups of proteins in the liver and intestine that are involved in all aspects of the detoxification and elimination of xenobiotics from the body (Xu et al., 2005).

PXR in drug metabolism and drug-drug interactions

Our body is confronted daily with a wide array of environmental chemicals, including prescription drugs, over-the-counter medications and herbal medicines, which may exert toxic effects through various mechanisms, especially when there's excess accumulation (Zhang et al., 2008). PXR mediated induction of DMEs and transporters can recognize a large spectrum of pharmaceutical substrates, relevant gene-inducing drugs and thus potentially be capable of affecting the metabolism and clearance of co-consumed drugs.

Recent studies have suggested that in anticancer chemotherapy where drug combination therapies are typically employed, activation of PXR may compromise the effectiveness of antineoplastic drugs and contribute to drug resistance (Chen, 2010). For example, paclitaxel is one of the most commonly used antineoplastic agents in human breast cancer (Chen et al., 2009; Choi et al., 2007), ovarian cancer (Gupta et al., 2008) and prostate cancer cell lines (Chen et al., 2007). Several in vitro studies demonstrated that the activity of paclitaxel is significantly reduced by paclitaxel induced activation of PXR and hence the induction of metabolic drug inactivation (i.e., CYP3A4) and drug efflux transporters (i.e., MDR1). Additionally, a study of breast cancer patients treated with tamoxifen-based adjuvant therapy demonstrated an association between higher PXR expression in tumor tissue and resistance to tamoxifen, which resulted in a higher probability of relapse (Conde et al., 2008). The identification of rifampicin as a potent hPXR agonist has also provided an explanation as to why this drug is an efficient inducer of drug-metabolizing enzymes compromising the effectiveness of other drugs. Other than rifampicin and paclitaxel, Sinz and colleagues summarized a more comprehensive analysis

of the effect of commonly used clinical drugs on PXR activation(Sinz et al., 2006).

The regulation of drug-metabolizing enzymes by PXR is also implicated in clinical drug–drug interactions, in which one drug accelerates the metabolism of a second co-administered medication and consequently affecting the efficiency of other drugs or cause possible adverse results. It was reported that a significant high incidence of unwanted pregnancies occurred in female patients using oral contraceptives and antituberculosis drug rifampicin simultaneously in the early 1970s for rifampicin activated PXR accelerated the metabolism of contraceptives (Reimers and Jezek, 1971). As expected, co-administration of the CYP3A4 inducing St. John's Wort (SJW), a popular herbal antidepressant, together with cyclosporine leads to enhanced metabolism and clearance of cyclosporine due to the similar pharmacokinetic interactions (Gibson et al., 2002). In an investigation of several traditional Chinese medicines (TCMs), two TCM herbs, Wu Wei Zi and Gan Cao were shown to be capable of activating PXR and administration of both two herbs in rats increased the metabolism of coadministered warfarin (Mu et al., 2006), reinforcing concerns involving the safe use of herbal medicines to avoid PXR-mediated drug-drug interactions.

Moreover, accelerated metabolism might be harmful for some drugs because of the production and accumulation of toxic metabolites. For example, co-administration of rifampicin with acetaminophen can increase toxic responses to drugs via up-regulation of CYP3A4 (Crippin, 1993). Likewise, SJW (another PXR agonists) has been reported to trigger severe adverse interactions with a number of clinical drugs, such as anticancer agents (imatinib and irinotecan), anti-HIV agents (e.g. indinavir, lamivudine and nevirapine), anti-inflammatory agents (e.g. ibuprofen and fexofenadine) (Di et al., 2008). Taken together, cautions should be taken when these PXR activators are used in combination with prescribed drugs.

The identification and development of PXR antagonists have their implications in drug metabolism and may be useful to prevent harmful drug–drug interactions and thus improve the therapeutic efficacy of therapeutics. There is a growing list of large- and small-molecule PXR antagonists that includes anticancer compound ET-743 (Synold et al., 2001), Rand A-792611 (Healan-Greenberg et al., 2008), polychlorinated biphenyls (Tabb et al., 2004) and ketoconazole (Huang et al., 2007), fluconazole and eniconazole (Wang et al., 2007), sulforaphane (Zhou et al., 2007) and coumestrol (Wang et al., 2008). PXR antagonist pharmacophore models were developed using computational approaches based on the three azoleantagonists and biphenyls (Ekins et al., 2008). By using this approach, Ekins et al. discovered several new PXR antagonists with in vitro activity and their data suggested that most of the known PXR antagonists interact on the outer surface of PXR at the AF-2 domain and disrupt the recruitment of co-activators (Ekins et al., 2008). More recently, Li et al. (2013) developed a novel yeast-based two-hybrid assay and molecular docking analysis to define an antagonist, ketoconazole's, unique binding residues such as Ser-208, which is on the opposite side of the protein from the AF-2 region critical for receptor regulation. Further investigation is needed to develop potent, tissue-selective PXR antagonists that may be useful in clinical application. For example, selectively target neoplastic cells or disrupt undesirable PXR-mediated up-regulation of drug metabolism in the liver or elsewhere (Biswas et al., 2009). This can be achieved by modification and optimization of the functional groups of our recently discovered antagonists, thus generate new analogs with improved potency and selectivity against hPXR.

However, it should be pointed out that some drug–drug interactions may be beneficial by reducing the adverse reactions of an anti-cancer agent. Recently, a randomized clinical trial has demonstrated that Chinese herbal medicine reduces chemotherapy-inducedside effects in vivo (Lam et al., 2010; Lee et al., 1999; Mehendale et al., 2004).

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Although PXR is a master regulator of xenobiotic metabolism, evolving evidence has pointed to an equally important role of PXR as an 'endobiotic receptor' that responds to a wide array of endogenous chemicals (endobiotics). Moreover, the activation of PXR by endogenous or xenobiotic ligands demonstrated that PXR has been implicated in a number of physiological and pathophysiological processes. For example, PXR signaling contributes to bile acid (Staudinger et al., 2001; Xie et al., 2001), lipid (Zhou et al., 2006a), bone (Tabb et al., 2003; Xu et al., 2006), inflammatory responses (Păunescu, 1970; Gu et al., 2006; Zhou et al., 2006b) and glucose homeostasis and energy metabolism (Gao and Xie, 2010; Spruiell et al., 2014).

Steroid hormones are important endobiotics, the formation and elimination of which involve many drug-metabolizing enzymes and transporters. As expected, emerging evidence has indicated that PXR might have broad implications in steroid hormone homeostasis and drug-hormone interactions.

PXR IN GLUCOCORTICOID AND MINERALOCORTICOID HOMEOSTASIS

Glucocorticoids (cortisol in human, corticosterone in rodents) and mineralocorticoids (aldosterone, deoxycorticosterone) are essential endocrine hormones, whose homeostasis is essential for the appropriate function of many cell types and for various physiological processes.

Altered glucocorticoid levels due to stress or upon medication (dexamethasone, synthetic glucocorticoid) can activate PXR and thus may significantly influence the detoxification of many endogenous and exogenous chemicals (Kliewer et al., 1998; Pascussi et al., 2000).Another study indicates that CYP3A4 induction by phthalates is dependent on glucocorticoid induced PXR expression (Cooper et al., 2008).

On the other hand, PXR can also regulate glucocorticoid and mineralocorticoid homeostasis. The PXR target gene, CYP3A4 exhibits a significant role in cortisol metabolism (Buters et al., 1994). And cortisol activities were also used as biomarkers for CYP3A4 induction or inhibition (Fayer et al., 2001; Konishi et al., 2004).

Our study showed that genetic (VP-hPXR transgene) and pharmacological (ligand, RIF) activation of hPXR in mice markedly increased plasma concentrations of corticosterone and aldosterone, glucocorticoid and mineralocorticoid respectively (Zhai et al., 2007). The increased levels of corticosterone and aldosterone were associated with elevated expression of adrenal steroidogenic enzymes, including Cyp11a1, Cyp11b1, Cyp11b2 and 3β-hydroxysteroid dehydrogenase. The PXR-activating transgenic mice also exhibited hypertrophy of the adrenal cortex, loss of glucocorticoid circadian rhythm as well as impaired stress responses. However the function of HPA axis of the VP-hPXR transgenic mice was intact despite a severe disruption of adrenal steroid homeostasis (Zhai et al., 2007).

Hypercortisolism is the clinical hallmark of the pseudo-Cushing's syndrome in patients. This syndrome is most seen in people who are alcohol abuse, depressed or obese. However, Zhang suggested that these susceptible patients might be associated with increased expression and/or activity of PXR (Zhang et al., 2008). As a proof, PXR-activating transgenic mice and rifampicin treated tuberculosis patients can also show hypercortisolism (Zawawi et al., 1996). The glucocorticoid elevation effect appeared to be PXR-specific, as the activation of CAR in transgenic mice had little effect on the homeostasis of the glucocorticoids. We propose that PXR is a potential endocrine disrupting factor that may have broad implications in steroid homeostasis and drug-hormone interactions (Zhai et al., 2007).

PXR IN ANDROGEN HOMEOSTASIS

Chen et al. first detected the differential expression of PXR in normal and cancerous prostate tissues (Chen et al., 2007). In PC3 human prostate carcinoma cells, activation of PXR with SR12813 enhanced the expression of both CYP3A4 and MDR1 that accelerate

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the metabolism and the elimination of anticancer drugs, contributing to the resistance of PC3 cells to these drugs, such as paclitaxel and vinblastine. On the other hand, the targeted knockdown of PXR using shRNA decreased the activity of PXR towards the promoter of CYP3A4 and increased the sensitivity of PC3 cells to paclitaxel and vinblastine, suggesting that down-regulation of PXR sensitizes prostate cancer cells toward chemotherapy. The results indicated that PXR may be important in prostate cancer resistance to chemotherapeutic agents. Additionally, another study suggested that PXR may be a strong prognostic indicator of favorable outcomes, for clinical results indicated that higher PXR expression was correlated with increased survival rate of prostate cancer patients (Fujimura et al., 2012).

Recently, a novel PXR-mediated and metabolism-based mechanism to reduce androgen activity was reported. CYP3As and SULT2A1 are enzymes important for the metabolic deactivation of androgens. CYP3A is the key enzyme in catalyzing hydroxylation of testosterone and progesterone, leading to inactivation of hormones (Buters et al., 1994; Niwa et al., 1998). SULT2A1 is the primary SULT isoform responsible for the sulfonation and deactivation of androgen (Strott, 2002). The study showed that genetic or pharmacological activation of PXR reduced the androgenic activity and inhibited androgen-responsive prostate regeneration in castrated male mice receiving daily injections of testosterone propionate by inducing the expression of CYP3As and hydroxysteroid SULT2A1.

Importantly, in human prostate cancer cells, treatment with the PXR agonist rifampicin inhibited androgen-dependent proliferation of LAPC-4 cells, but had little effect on the growth of the androgen-independent isogenic LA99 cells. Down-regulation of PXR or SULT2A1 in LAPC-4 cells by shRNA or siRNA abolished the rifampicin effect, indicating that the inhibitory effect of rifampicinon androgens was PXR- and SULT2A1-dependent. Based on these data, PXR and its target androgen metabolizing enzymes may represent novel therapeutic target for hormone-dependent prostate cancer (Zhang et al., 2010).

A POTENTIAL ROLE OF PXR IN ESTROGEN HOMEOSTASIS

Estrogens play an important role in various of physiological or pathophysiological processes, which are including development (Nilsson and Gustafsson, 2002), cardiovascular diseases and metabolic disorders such as obesity and type 2 diabetes (Mauvais-Jarvis et al., 2013). Most, if not all, hormone replacement therapy regimens containing estrogens either alone or in combination with progestins have been widely used to treat menopause related syndromes (Warren, 2004). In addition, endocrine-based therapies against ER+ breast cancers including antagonize ER function with synthetic selective estrogen receptor modulators (SERMs) (e.g. tamoxifen) or down-regulate estrogen activities (antiestrogens and aromatase inhibitors) (Patel et al., 2007), have been proven effective to treat breast cancers. However, subsequently side effects such as resistance to aromatase inhibition and risk for endometrial cancer are frequent during these treatments. So it is rewarding to develop novel and effective estrogen deprivation strategies.

Among the major PXR induced human hepatic P450s, CYP3A4, which can be activated by PXR as we previously mentioned, most efficiently catalyzes 6β- and 16α-hydroxylation of progesterone (Niwa et al., 1998). It also catalyzes 2-,4-, and 16-hydroxylation of estradiol, leading to estrogen deactivation (Badawi et al., 2001; Lee et al., 2001). In a CYP3A4-transgenic mouse line, females were found to be deficient in lactation, leading to a markedly lower pup survival. This impaired lactation phenotype was associated with significantly reduced serum estradiol levels in CYP3A4, suggesting that CYP3A4 may play an important role in estrogen homeostasis (Yu et al., 2005). This may be of relevance in administrating drugs that are PXR activators to pregnant and lactating women. Notably, rifampicin, a PXR agonist, is contraindicated in pregnancy ex-

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cept in the presence of a severe disease untreatable with other drugs, such as tuberculosis. Teratogenicity was found in animals administered with rifampicin and also there were case reports of malformation, death and hemorrhagic disorders in infants whose mothers were undergoing rifampicin therapy due to estrogen homeostasis disorder caused by rifampicin triggered PXR activation (Ma and Lu, 2008).

Another critical metabolic pathway to deactivate estrogens is through the estrogen sulfotransferase (EST, or SULT1E1)-mediated sulfation, because sulfonated estrogens cannot bind to and activate ER, thus losing their estrogenic activities (Song, 2001). In 2012, a study conducted by Gao et al. showed that loss of SULT1E1 in female mice improved metabolic function in ob/ob, dexamethasone- and high-fat diet-induced mouse models of type 2 diabetes, which might result from decreased estrogen deprivation and increased estrogenic activity in the liver (Gao et al., 2012).

Recently Kodama et al. (2011) revealed a novel function of PXR in estrogen homeostasis related to SULT1E1. The study found that, upon activation by rifampicin, PXR, via its interactions with HNF4α, prevents the promoter from forming the active chromatin structure, thereby repressing the transcription of SULT1E1 in human primary hepatocytes and hepatocellular carcinoma Huh7 cells. Therefore hPXR activation would tip the hepatocellular androgen/estrogen balance toward greater estrogenicity by attenuating the inactivation of estrogen (Kodama et al., 2011), thereby affecting the physiology and/or pathophysiology of liver.

SUMMARY AND PERSPECTIVE

Based on this review, it will be clear that novel molecular targets of PXR-mediated hormone regulation may have implications in the prevention and treatment of hormone-related endocrine disorders and other metabolic diseases (Figure 1), such as diabetes and obesity. What's more, PXR activities are not limited to regulating glucocorticoid, mineralocorticoid, androgen, and estrogen homeostasis. For example, PXR agonist DMP 904 (Wong et al., 2005) was demonstrated to have effects on thyroid hormone homeostasis in rats.

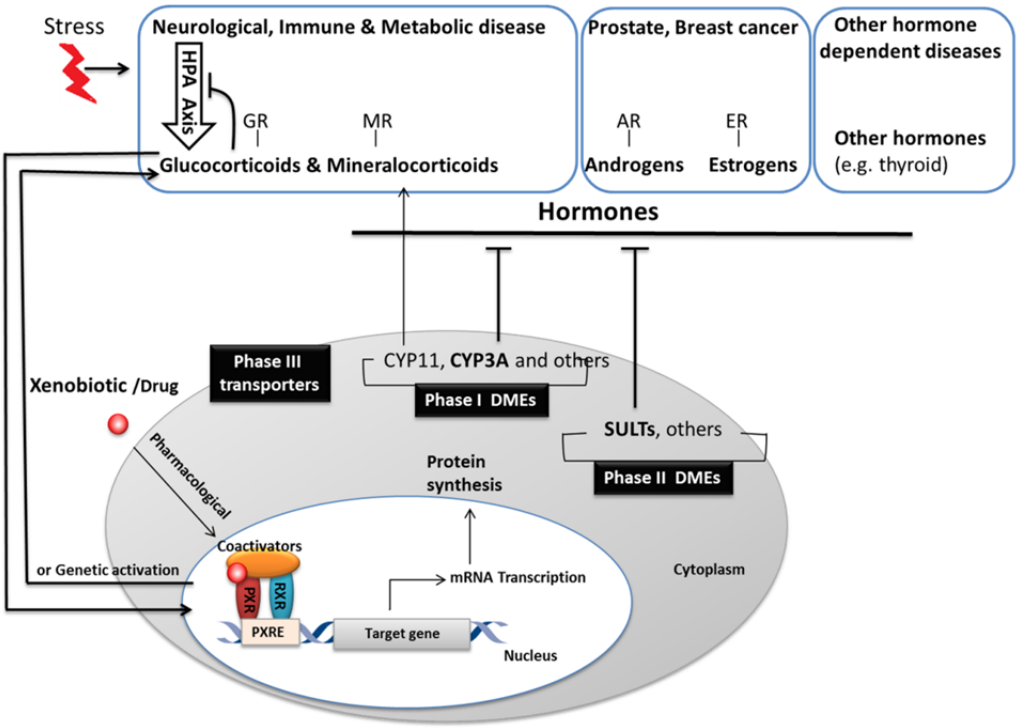

Figure 1: Schematic representation of the role of PXR in hormone metabolism

However using PXR manipulation as a strategy to alter hormone activity generates many challenges and sparks concerns regarding the PXR-induced harmful drug-drug interactions. On one hand, PXR is promiscuous and unique in that it is activated by a diverse group of xenobiotics, including therapeutic anticancer drugs and naturally-occurring endocrine disruptors. On the other hand, drugs mediated PXR activation inclined to interfere with endocrine hormone system and alter the metabolic changes. Therefore, the PXR-mediated drug-drug and drug-hormone interactions further prompt the development of antagonists of PXR to avoid undesirable PXR activation in patients undergoing combination or hormone therapies. We face the challenge of making appropriate drug management by balancing the beneficial effects against potential risks of drugs.

Taken together, the role of PXR in drug-hormone interactions may provide an important clue as to the mechanism by which PXR agonist/antagonists disrupting the endocrine system of body. However, this review of evidences regarding PXR mediated drug-hormone interactions is still far from comprehension. A more complete understanding of mechanism underlying PXR as a potential endocrine disruptor is necessary to interrogate the physiological and/or pathophysiological roles of PXR.

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