

Review

Regulation of Drug-metabolizing Human Cytochrome P450s

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Abstract

Drug-metabolizing enzymes, primarily cytochrome P450 (P450) enzymes, play central role in biotransformation, detoxication and elimination of various, structurally diverse xenobiotics. The expression of P450s is controlled by specific receptors capable of sensing xenobiotics, including notably aryl hydrocarbon receptor, a member of the Per/Arnt/Sim family of transcription factors, pregnane X receptor, constitutive androstane receptor, and peroxisome proliferators activated receptor, members of the nuclear receptor superfamily, as well as classical steroid receptors such as glucocorticoid receptor and vitamin D receptor. Because these receptors can interact with and be activated by xenobiotics, they are often designated as xenosensors. The xenobiotic signaling pathways appear to be embedded within a tangle of regulatory networks and the expression of P450s is regulated not only by xenobiotics, but also by numerous endogenous compounds (corticoids, hormones, cytokines, bile salts) frequently increased in pathophysiological conditions. Conversely, xenobiotics appear to affect the expression of genes controlling endogenous signaling pathways. The ability of nuclear receptors to control the transcription of several distinct genes suggests the existence of a complex regulatory network of metabolism of xenobiotics and endogenous compounds. This sophisticated network providing adaptive responses to many exogenous stimuli, e.g. drug treatment or exposure to chemical pollutants is discussed in this review.

Keywords: Drug metabolism, P450 regulation, nuclear receptors, xenoreceptors

1. Introduction

Cytochrome P450 (P450) enzymes are the major players in oxidative metabolism of a wide range of structurally diverse xenobiotics, including drugs, pesticides, food additives or chemical pollutants. Members of P450 superfamily, CYP1-4 families are responsible for the metabolism and disposition of more than 90% of therapeutics on the market.^{1,2} The metabolites of a drug can be inactive or less active than the parent compound, although some biotransformation products show enhanced pharmacological or toxicological activity.³ P450 enzymes are also involved in biotransformation of endogenous substrates (fatty acids, cholesterol, bile acids, prostaglandins, steroid hormones and retinoids), not only in elimination of these endogenous compounds, but also in their production.⁴

The activities and the levels of P450 enzymes in human liver display substantial interindividual variation, leading to differences in drug metabolism in the population.⁵ The

activity of P450 enzymes can determine the patient's response to a drug. Any change in the activity of P450 isoforms influences the rate of activation or inactivation of drugs. Individual drug-metabolizing capacity is determined mainly by genetic factors. Some P450 genes (*CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*) are highly polymorphic, resulting in enzyme variants with reduced or even no activity.⁶ The genetically determined variance in metabolic capacity of P450 system is further modulated by internal (age, gender, starvation, diseases) and environmental factors (nutrition, smoking, alcohol consumption, co-medication), resulting in different drug-metabolism phenotypes. Drugs or other xenobiotics often interfere with P450 enzymes by inhibition or induction, leading to significant drug interactions.⁷ Metabolic drug interactions are responsible for approximately 20% of adverse drug reactions and are therefore of great clinical interest. The inhibition of P450 function resulting in increased blood levels of drugs in patients can cause unexpected toxic side effects, whereas the increased elimination of a drug in

consequence of P450 induction leads to the loss of the pharmacological effect.⁸ P450-mediated biotransformation processes primarily lead to detoxication; however, certain substrates are bioactivated, resulting in the formation of reactive metabolites with increased toxicity or mutagenicity.³ Metabolic drug interaction as a side effect of drug therapy may produce a deleterious imbalance between detoxication and toxication.⁹

The induction of P450s *via* the adaptive increase of P450 enzyme levels of the cells is governed by various mechanisms, including transcriptional regulation of P450 gene expression, stabilization of corresponding mRNA and enzyme protein, and post-translational modification. Nuclear receptors play great role in the transcriptional mechanism of P450 induction.^{10–13} Receptor-mediated P450 gene expression follows the sequence of events: i) the presence of the ligand or inducer activates the nuclear receptor directly or *via* signal transduction pathway; ii) the active receptor forms hetero- or homodimer in the nucleus; iii) the dimer complex binds to DNA-responsive elements in the regulatory region of P450 gene; iv) activation of the P450 gene occurs. Transcriptional regulation of P450 gene expression is modified by several co-activators or co-repressors. The enzymes of CYP1 family, CYP2B, CYP2C, CYP3A and CYP4A subfamilies are regulated *via* the mediation of nuclear receptors, whereas prevention of P450 mRNA or enzyme protein from degradation is involved in up-regulation of CYP2E1.¹⁴ The present review focuses on the regulation of P450 gene expression and the functional cross-talk between nuclear receptors and transcription factors with respect to pharmacological and toxicological consequences.

2. Nuclear Receptors and Their Action

Receptor-mediated regulation involves transformation of extracellular and intracellular signals into cellular responses by triggering the transcription of nuclear receptor target genes. Nuclear receptors display some similarities in their structure and function.^{15–17} Their modular structure consists of a ligand-binding domain, a highly conserved DNA-binding domain with dimerization regions and transactivation domains (AF-1 and AF-2) (Figure 1A).^{18,19} Ligand binding or ligand-induced receptor activation leads to significant structural changes in the ligand-binding domain and consequently to the reposition of AF-2.^{20,21} AF-1 is a ligand-independent activation domain, which can interact with AF-2. Nuclear receptors recruit co-regulators: co-activators and co-repressors.²² Co-activators possessing intrinsic histone acetyltransferase (or methyltransferase) activity, or recruiting additional acetyltransferases, eventually result in chromatin relaxation and association with the basic transcriptional machinery.²³ Ligand-free nuclear receptors primarily interact with co-repressors,

and recruit various histone deacetylases, leading to chromatin condensation and suppression of gene transcription.²⁴

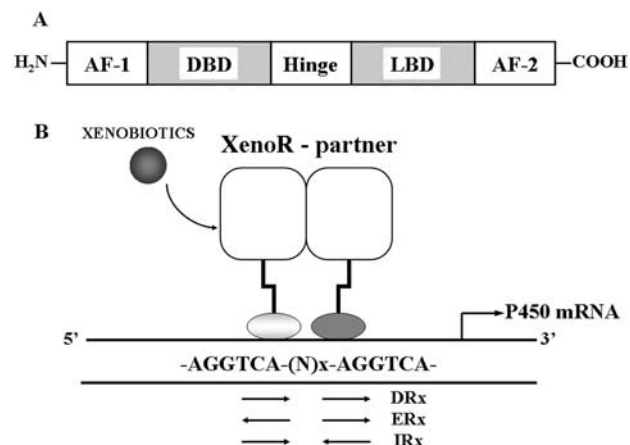


Figure 1: The structure (A) and DNA-binding (B) of nuclear receptors involved in regulation of P450 expression.

AF: activation function; DBD: DNA-binding domain; LBD: ligand-binding domain; DR: direct repeat; ER: everted repeat; IR: inverted repeat; XenoR – partner: xenobiotic receptor – dimerization partner

The DNA-binding domain consisting of two zinc finger subdomains is responsible for the recognition of the response element in the promoter region of target genes. This domain contains eight cysteins forming a pair of tetra coordinate binding sites for zinc atoms. The zinc atoms allow folding of the receptor protein, and an α -helix is placed into the major groove of the DNA, which enables the receptor to recognise the DNA in a sequence specific way. DNA-responsive elements are generally constituted of two half-sites of 5'-AGGTCA-3'. The hexamer sequences are arranged as direct (DR), everted (ER) or inverted repeats (IR) spaced by 1–7 nucleotides (Figure 1B).^{25,26} The nuclear receptor dimer (hetero- or homodimer) formation is evolved by overlapping in ligand-binding domains and DNA-binding domains.¹⁹ Regulation of *CYP2B*, *CYP2C* and *CYP3A* genes involves several nuclear receptors, including constitutive androstane receptor (CAR), pregnane X receptor (PXR), glucocorticoid receptor (GR), and vitamin D receptor (VDR).²⁷ Liver X receptor (LXR) and farnesoid X receptor (FXR) with their structures close to that of CAR, PXR or VDR are responsible for the maintenance of cholesterol and bile acid homeostasis. Some structural differences are displayed for aromatic hydrocarbon receptor (AhR) implicated in the regulation of *CYP1* genes. (see 2. 1.) Peroxisome proliferators-activated receptors (PPARs) play critical role in the regulation of lipid metabolism and of several genes involved in maintenance of lipid homeostasis. In spite of the basic structural differen-

ces, the general functions of these nuclear receptors show similarities regarding ligand activated signaling and signal transductional regulation of P450 and other target genes. The same nuclear receptor is able to control the expression of various genes, even if the target genes contain different response elements in their promoters. Nuclear receptor-mediated regulation is a complex process, including ligand-binding, selective dimerization, DNA-binding site selection and modification by tissue-, sex- or development-dependent co-regulators.

2. 1. AhR

The AhR is expressed in every tissue, and within the cytosol of the cell, the inactive AhR exists as a complex with the chaperone Hsp90, the co-chaperone p23, and an immunophilin-like protein termed XAP2 (hepatitis B virus X-associated protein 2).^{28,29} The AhR ligands include hydrophobic environmental pollutants of polyhalogenated aromatic hydrocarbons, such as polychlorinated dibenzodioxins, dibenzofurans and coplanar biphenyls, or polycyclic aromatic hydrocarbons (responsible for the name of the receptor), e.g. benzo(a)pyrene, 3-methylcholanthrene, benzoflavones and omeprazole.³⁰ Exposure to AhR ligands triggers the AhR signaling pathway and the AhR action co-ordinately regulates the expression of the genes of AhR gene battery including *CYP1s*, UDP-glucuronyl transferase 1A1 (*UGT1A1*) and 1A6 (*UGT1A6*), glutathione S-transferase A2 (*GSTA2*), aldehyde dehydrogenase (*ALDH3*), or NADPH:quinone oxidoreductase (NQOR).^{31–33} By binding of AhR ligand, AhR is activated by a conformational change, which exposes a nuclear localization signal, and AhR with the inducer translocates to the nucleus.³⁴ AhR signaling leads to the dissociation of basic cytosolic complex, to the interaction with its dimerization partner AhR-nuclear translocator (Arnt), and activation of the xenobiotic response elements (XREs) in the regulatory region of target genes.^{35–38}

Both AhR and Arnt belong to the bHLH/PAS family (basic helix-loop-helix / Per-Arnt-Sim family) of transcription factors (Figure 2). The bHLH domain at the N-terminal region consists of two α -helices separated by a non-helical loop. Heterodimer formation involves interactions between the HLH domains of AhR and Arnt, whereas DNA binding occurs over their basic regions. The interaction of the PAS domains is also required for the heterodimer formation. PAS domain of AhR is involved in binding of the chaperone Hsp90 or the ligand. The carboxy-terminal domains of both AhR and Arnt contain transcriptional activation domains (TADs). The TAD of Arnt is somewhat simpler than that of AhR.^{39–42}

In the nucleus, the AhR/Arnt heterodimer binds to the XRE region with a canonic sequence of 5'-CACGCNA-3', and stimulates the transcriptional expression of target genes.^{43,44} The proteolytic degradation pathway is induced by the nuclear export signal of AhR, which plays role in

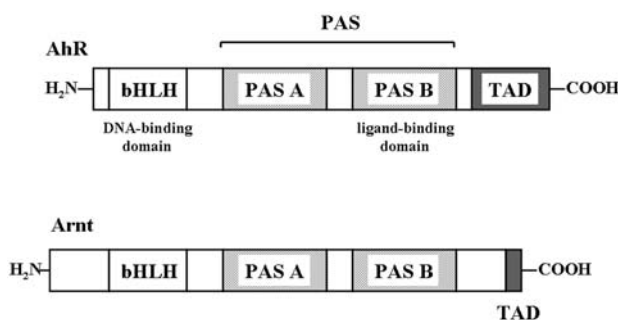


Figure 2: Functional domains of AhR and Arnt.

AhR: aromatic hydrocarbon receptor; Arnt: AhR nuclear translocator; bHLH: basic helix-loop-helix; PAS: Per-Arnt-Sim; TAD: transcriptional activation domain

removal of the receptor from the nucleus. In the cytosol, AhR is rapidly degraded by the ubiquitin-proteasome dependent mechanism. In the absence of ligand, AhR is masked by Hsp90 and immunophilin-like proteins, which prevent AhR degradation. These proteins also participate in masking of nuclear localization signal and retain the inactive receptor in the cytosol.^{45–48}

2. 2. CAR

CAR (NR1I3) was originally characterized as a transactivator of retinoic acid response elements in the absence of ligand.^{49,50} CAR is predominantly expressed in the liver and to a lesser extent in the intestine and the stomach.^{48,51} In contrast to most nuclear receptors, which contain five domains, the human CAR protein contains three: a highly conserved DNA-binding domain; a hinge region; and a divergent ligand-binding/dimerization/transcriptional activation domain. CAR possesses neither an A/B (AF-1) domain that typically confers a ligand-independent transactivation response, nor the less well-characterized hypervariable F domain. In CAR, the ligand-binding AF-2 domain of the protein interacts with the co-activator SRC-1 (steroid hormone receptor co-activator 1) in a ligand-independent manner. However, some ligands, which are inverse agonists, affect the protein by binding in such a way that an inactive conformation is induced.⁵² CAR is located in the cytosol under normal conditions.^{53,54} In response to the activators such as phenobarbital (PB), CAR translocates to the nucleus where it forms functional heterodimers with retinoid X receptor α (RXR α). The molecular mechanism responsible for this translocation is still unclear, but seems to involve specific phosphorylation-sensitive steps, as suggested by the interfering effect of okadaic acid, an inhibitor of protein phosphatases 1 and 2A or the possible implication of AMPK (AMP-activated protein kinase) and LKB1 (serine/threonine protein kinase) in its activation.^{53,55–57} In support of this observation, the importance of phosphoryla-

tion in CYP2B induction has been reported previously.^{58,59} In addition, the PB-inducible translocation activity of the receptor has been mapped to a xenochemical response signal corresponding to a leucin-rich peptide near the carboxy-terminus of the CAR protein (L³¹³GLLAEL³¹⁹); however, the molecular and cellular mechanism, which regulates the nuclear translocation of CAR in response to PB-type inducers, remains an enigma.^{60,61} Nuclear translocation appears to be a general process by which CAR regulates gene induction, since various PB-type inducers (e.g., chlorpromazine, chlorinated biphenyls, and methoxychlor) are also capable of inducing the translocation of CAR into the nucleus in the liver. In addition, ligand binding to CAR alone is not sufficient to induce CAR translocation into the nucleus and induction of CAR target genes.⁶² Because CAR exhibits an intrinsically high transcriptional activity, its nuclear localization provokes the activation of target gene expression in the absence of ligand binding.⁶³

Very little is known about the mechanism of CAR activation by chemicals or its transcriptional regulation. The mouse *CAR* gene has two identified mRNA isoforms (mCAR1 and mCAR2). mCAR1 is closely related to human CAR. In contrast, mCAR2 is truncated, lacking a carboxy-terminal region of the ligand-binding domain, resulting from alternative exon splicing, and leading to the loss of exon 8.⁶⁴ In man, CAR is expressed predominantly in hepatocytes, and the most prominent mRNA band migrates as a rather broad band spanning approximately 1.3–1.7 kb.⁴⁹ It is curious that certain CAR activators have not been identified as ligands of the reference CAR isoform.^{65,66} Thus, it is possible that certain inducing compounds, such as PB or PB-like compounds may interact with the ligand-binding domain of other CAR isoforms, as recently hypothesized.⁶⁷ These CAR isoforms could be part of a range to enlarge the number of xenobiotics recognized by the body.

The production of CAR knockout mouse confirms that this orphan nuclear receptor mediates the induction of CYP2Bs and CYP3As, as well as the increase of both liver weight and DNA synthesis in response to TCPOBOP (3,3',5,5'-tetrachloro-1,4-bis(pyridyloxy)benzene) or PB.⁵¹ CAR exhibits a pronounced species-specificity of ligands, activators and inverse agonists. Some of the CAR activators like TCPOBOP and estrogens are able to reverse the inhibition induced by the presence of inverse agonists. Interestingly, some CAR activators are not ligands *in vitro*. This is notably the case for PB, which does not influence CAR–SRC-1 binding. Only a few molecules among P450 inducers have been shown to bind directly to human CAR. These include clotrimazole, 5- β -pregnane-3,20-dione, 6-(4-chlorophenyl)-imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO), and dehydroepiandrosterone (DHEA).^{62,66–68} In man, recent data show that CAR mediates the PB induction of UGT1A1, CYP2A6, CYP2B6, CYP3A4 and CYP2C8–

9.^{69–72} Several groups have identified a CAR-response element, which consists of two nuclear receptor-binding sites (termed NR1 and NR2) and one NF1-binding site.^{53,69,73} NR1 and NR2 are both imperfect DR4 motifs essential for the PB induction of *CYP2B* genes.

In human *CYP2B6*, the PB-responsive enhancer element is located between –1,684 and –1,733.⁷⁴ The CAR–RXR heterodimer can bind to an array of prototypic nuclear receptor-binding sites, including DR5, DR4, DR3, ER6 and IR8 motifs.^{65,75} Such elements have been found in the promoter of several major hepatic P450s involved in drug metabolism in human beings. These include *CYP2B6*, *CYP2C9* and *CYP3A4*.^{69,70} CAR also seems to regulate the expression of cytochrome P450 reductase, an essential component of P450-dependent metabolic activity.⁷⁶

2. 3. PXR

In 1998, Kliewer and co-workers identified a new member of the nuclear hormone receptor family and designated PXR (NR1I2) for the pregnane X receptor, because it was activated primarily by natural pregnanes.⁷⁷ Interestingly, this receptor also appeared to be activated by both synthetic glucocorticoids and antiglucocorticoids, including dexamethasone and pregnenolone 16 α -carbonitrile, two well-known inducers of CYP3As. Simultaneously, two other groups isolated and characterized the same receptor designated by them as SXR (steroid and xenobiotic receptor) and PAR (pregnane activated receptor), respectively.^{78,79} Collectively, these observations established for the first time consistent mechanistic links relating to CYP3A induction and a nuclear receptor activated by xenobiotics. Various orthologous forms of PXR have now been isolated from different organisms including man, monkey, pig, dog, rabbit, rodents, fish, chicken and *Xenopus laevis*, indicating that the signaling pathway mediated by this xenobiotic-sensing receptor has been preserved during species evolution.^{78,80–83} Interestingly, the chicken receptor CXR displays almost equal primary sequence identity to both human PXR and CAR (64 and 67% in the DNA binding domain and 50 and 48% in the ligand binding domain, respectively).⁸³

PXR is expressed mainly in the liver, small intestine and colon as well as in the kidney.^{77,80} In rodents, PXR has been shown to be retained in the hepatocyte cytosol of untreated mice, whereas it translocates into the nucleus after ligand (pregnenolone 16 α -carbonitrile) administration.⁸⁴ A nuclear localization signal at the amino acid residues 66–92 within the DNA-binding domain of the protein was identified, which regulates the translocation process. PXR nuclear localization signal appears to be a bipartite motif (similar to the one found in the AhR and other receptors) consisting of two clusters of positively charged amino acids, 17 amino acid residues apart from each other. In contrast to classical nuclear receptors for which the li-

gands exhibit very high affinity (K_s in the nanomolar range), PXR binds generally with low affinity (EC_{50} in the micromolar range) a wide variety of structurally diverse exogenous and endogenous compounds, including drugs such as rifampicin, PB, nifedipine and other calcium channel blockers, clotrimazole, mifepristone, metyrapone, steroid hormones and metabolites such as progesterone, estrogens, corticosterone, androstenediol and DHEA, and dietary compounds such as coumestrol and hyperforin, and pesticides including metolachlor, pretilachlor, bupirimate, or oxadiazon.^{68,79–81, 85–89} After some controversial studies of PXR activation by dexamethasone, this compound has also been shown to be a real ligand of the human PXR, but only at supramicromolar concentrations.^{77,79,81,90} This is consistent with CYP3A4 induction.

Interestingly, the species-specificity observed in CYP3A inducibility correlates with the species-specificity characterizing the xenobiotic-mediated activation of PXR.^{91,92} In addition, some agonists of rodent PXR are also antagonists of human PXR, notably polychlorinated biphenyls (PCBs). PCBs constitute a family of persistent organic contaminants suspected to cause adverse effects in wild life and man. In rodents, PCBs bind to AhR and PXR, and induce the expression of the CYP1A and 3A subfamilies. Certain highly chlorinated PCBs can antagonize the human PXR, so that exposure to such compounds blunts the human xenobiotic response and thus inhibits the detoxication of steroids, bioactive dietary compounds and xenobiotics normally mediated by PXR.⁹³ Crystal structure analyses revealed that the ligand-binding domain of human PXR is highly hydrophobic and flexible, allowing lipophilic molecules of different size to bind in multiple orientations.^{94,95} PXR appears to be responsible for the xenobiotic-mediated induction of a battery of genes including *CYP3A4*, *CYP3A7*, *CYP2B6*, *CYP2C9*, *UGT1As*, *MDR1*, *BSEP*, *MRP2* and other genes involved in detoxication, including notably murine 5-aminolevulinic acid synthase *ALAS-1*.^{69,70,74,75,79–81,96–102}

It can be hypothesized that PXR polymorphisms contribute to the variability of CYP3A4 and other P450s. Single nucleotide polymorphisms (SNPs) and 9 variations including amino acid changes have been identified in the human *PXR* gene. Zhang et al. have reported an hPXR variant, R122Q, which reduces DNA binding activity and results in a slight attenuation of the rifampicin-induced CYP3A4 promoter activity.¹⁰³ Hustert et al. have reported V140M, D163G, and A370T in the hPXR ligand-binding domain.¹⁰⁴ Among those, D163G reduces the basal and rifampicin-induced activities toward a reporter gene construct containing the *CYP3A4* proximal and distal promoter. In addition, four non-synonymous SNPs have been identified in 205 Japanese subjects, i.e. 292C > T, R98C; 443G > A, R148Q; 1141C > T, R381W; 1207G > A, I403V.¹⁰⁵ Basal and drug-induced transactivation of the *CYP3A4* enhancer/promoter were determined and were found to be reduced compared to the wild type hPXR.

These observations are consistent with the idea that polymorphisms in the ligand binding domain could directly contribute to individual differences in drug response profile.

On the other hand, it has been reported that the 5' region of PXR transcripts is more complex than it was initially proposed, with the identification of five types of transcripts in human liver cDNA libraries. Type-a transcript, namely exon 1a/exon 2 splice form, was the most abundant transcript in human PXR mRNA expression in normal liver. Notably, two variants resulting from alternative splicing were identified, which exhibit 39-amino acid N-terminal extension and an internal 37-amino acid deletion, respectively.^{79,106} The wild-type PXR and both variants are expressed in human liver and intestine as well as in HepG2 cells, whereas none of the variants is detectable in the colic carcinoma Caco-2 cells. In transfection assays, these isoforms displayed different properties in transactivating *CYP3A7*, *UGT1A1* and *UGT1A3* promoters.¹⁰⁷ In addition, several variants of PXR proteins have been identified and their role in CYP3A4 expression was analyzed by the expression in cell lines by transfection assays.^{104,108} Some of them exhibited altered basal and/or induced transactivation of the *CYP3A* promoter reporter gene, including altered DNA binding.

2. 4. VDR

The biologically active form of vitamin D3, 1,25-dihydroxy vitamin D3, is an important regulator of cell growth, differentiation, and death. The cellular action of 1,25-dihydroxy vitamin D3 is known to be mediated *via* an intracellular receptor, the VDR (NR1I1), a member of the superfamily of steroid receptors. Ligand-activated VDR provokes partial arrest in G0/G1 of the cell cycle, the induction of differentiation and the control of calcium homeostasis.¹⁰⁹ Although the liver is the site of the 25-hydroxylation of vitamin D, it has been shown to have a very low proportion of VDR and, consequently, has not been considered as a target site of vitamin D action. However, further studies have demonstrated that calcium and/or vitamin D deficiency has a significant effect on liver cell physiology.¹¹⁰ After ligand binding, VDR forms a heterodimer with RXR α , which transactivates vitamin D response elements (VDREs) present in the regulatory region of the target genes.^{111,112} Although the consensus VDRE is an imperfect direct repeat of 5'-(G/A)GGT (G/C)A-3' with a three-nucleotide spacer (DR3), previous investigations identified other VDRE motives including a DR4 and an inverted palindrome IP9.¹¹¹ VDR has been shown to bind to and transactivate response elements previously characterized as PXR and CAR response elements in *CYP2* and *CYP3A* genes. This is likely to generate functional cross-talk between vitamin D homeostasis and xenobiotic detoxication pathways. (see 4. 2.) Several reports have revealed that 1 α ,25-dihydroxy vitamin D3 be-

has as a transcriptional inducer of *CYP3A4* in the Caco-2 cell line and the human intestinal LS180 cell line.¹¹³ In addition, it has been shown that $1\alpha,25$ -dihydroxy vitamin D3 induces the expression of *CYP3A4* and to a lesser extent that of *CYP2B6* and *CYP2C9* genes in normal differentiated primary human hepatocytes.¹¹⁴ Electrophoretic mobility shift assays and co-transfection in HepG2 cells using wild-type and mutated oligonucleotides revealed that the VDR binds and transactivates those xenobiotic-responsive elements (ER6, DR3 and DR4) previously identified in *CYP3A4*, *CYP2B6* and *CYP2C9* promoters and shown to be targeted by PXR and/or CAR. Co-transfection of a *CYP3A4* homologous promoter-reporter construct (including distal and proximal PXR-binding motives) and of PXR or CAR expression vectors in HepG2 cells revealed the ability of these receptors to compete with VDR for transcriptional regulation of *CYP3A4*.^{114,115} In addition, VDR also functions as a receptor for the secondary bile acid, lithocholic acid, which is hepatotoxic and a potential carcinogen.

2. 5. GR

GR (NR3C1) is a classical hormone receptor activated by natural and synthetic glucocorticoids such as cortisone, hydrocortisone, deoxycorticosterone or dexamethasone. GR regulates the transcription of GR-responsive genes, which contain glucocorticoid responsive elements (GREs) in their promoters. Several of P450 genes, *CYP2C9* or *CYP3A4/5* are shown to be glucocorticoid responsive. Dexamethasone at submicromolar concentrations results in the induction of *CYP2C9*. A functional GRE at the position of -1,648/-1,684 was displayed in the promoter of human *CYP2C9*.⁷⁰ *CYP2C9* appears to be a primarily glucocorticoid responsive gene, which in addition, is induced by xenobiotics through CAR and PXR activation. Other functional GREs were detected in *CYP3A* genes. Two GREs were identified with two half-sites (5'-TGTTCT-3') separated by 160 nucleotides at -891/-1109 in the human *CYP3A5*.¹¹⁶

Dexamethasone produces a biphasic induction of *CYP3A4* expression consisting of a low-dexamethasone component of low amplitude, followed by a high-dexamethasone component of high amplitude.²⁷ Low concentration of dexamethasone (<0.1 μ M) activates GR, which forms a homodimer and binds to GREs. Submicromolar concentrations of dexamethasone stimulate GRE response of *CYP3A*, whereas higher concentrations induce *CYP3A* through PXR-RXR heterodimer. The expression of nuclear receptors, CAR and PXR, is under glucocorticoid control, which results in an additional indirect regulation of *CYP2B*, *CYP2C* and *CYP3A* genes by supramicromolar concentrations of dexamethasone.^{54,117} (see 4.2.) The response of glucocorticoids may be divided into two phases: i) involving GR for physiological doses and ii) PXR for stress-induced or pharmacological doses.

The first intron of both rat and human *CYP1A1* also contains three GRE sequences. Although glucocorticoids alone are not able to trigger transcriptional activation of *CYP1A1*, they can modify *CYP1A1* induction by dioxin or polyaromatic hydrocarbons in rats. The function of GREs in the human *CYP1A1* gene is not completely understood. (see 3.1. and 4.1.)

2. 6. PPAR α

PPAR α (also called NR1C1) is a nuclear receptor that controls lipid metabolism, thus is expressed preferentially in tissues, where fatty acids are catabolized.^{118,119} Peroxisome proliferators and fatty acids are able to activate rodent PPAR α , which mediates the induction of CYP4As and peroxisomal enzymes catalyzing β -oxidation of fatty acids.^{120–123} (see also 3.5.) Exposure of rodents to peroxisome proliferators, such as clofibrate, fenofibrate or ciprofibrate, stimulates the proliferation of peroxisomes and produces hepatocellular carcinomas. Peroxisome proliferators are not considered to be genotoxic carcinogens; however, several of them have tumor promoting activity in susceptible animal models.^{124,125} Hydrogen peroxide and related oxidants are assumed to be involved in liver injury and hepatocellular carcinogenesis.^{126,127} In contrast to mice, peroxisome proliferation has not been observed, and induction of CYP4As has not been demonstrated in human liver in consequence of hypolipidemic drug treatment. The fact that PPAR α is expressed at more than 10-fold lower levels in human than in mouse may account for lacking CYP4A induction. In addition to low amount of receptor, species differences in susceptibility to peroxisome proliferation may also explain the human resistance to peroxisome proliferators.^{120,127–130}

The structure of PPAR α contains functional domains similar to other nuclear receptors: a ligand-independent transcriptional activation domain, a DNA-binding domain, a ligand-binding domain and an additional domain involved in dimerization, nuclear localization and association with co-activators and co-repressors. Our knowledge about regulation of the expression of human PPAR α is poor. Human *PPAR α* gene contains eight exons in which exons 1 and 2, 5'-end of exon 3 and 3'-end of exon 8 are not translated.¹³¹ A regulatory element has been identified at -1,483/-1,492 of the *PPAR α* promoter region. Transcription factors, HNF-4 (hepatocyte nuclear factor 4), COUP-TFII (chicken ovalbumin upstream promoter – transcription factor II), and the nuclear receptor, PPAR α , are able to bind this regulatory element with different activities. HNF-4 and PPAR α stimulate transcription of *PPAR α* gene, whereas COUP-TFII down-regulates promoter activity.¹³² Additionally, the promoter of human *PPAR α* gene (at -536/-648) contains an FXR-responsive regulatory element (FXRE), which mediates regulation of PPAR α expression by bile acids (e.g., chenodeoxycholic acid). Bile acid activated FXR binds FXRE and increases

transcription of *hPPAR α* gene. In contrast to human, murine *PPAR α* promoter is not responsive to chenodeoxycholic acid treatment.^{129,133} Bile acids, directly *via* FXR and/or *via* FXR-mediated *PPAR α* induction, increase the expression of carnitine palmitoyltransferase I (CPT-I) involved in mitochondrial fatty acid uptake. CPT-I is the rate limiting factor of mitochondrial oxidation of fatty acids; thus bile acids eventually lead to an increase of fatty acid metabolism.¹³³ Treatment of patients with gallstone with chenodeoxycholic acid results in reduced plasma triglyceride levels.¹³⁴

3. Regulation of Drug-metabolizing P450 Enzymes

The expression of P450 genes is regulated by endogenous factors (hormones, cytokines and bile acids) or by structurally diverse chemicals. P450 induction resulting in an increase in detoxication is generally an adaptive response to xenobiotics; however, it can also have toxicological consequences. The elevation of P450 expression may lead to increased production of reactive intermediates and metabolites or to higher metabolic activation of precarcinogenic and premutagenic compounds.

3. 1. Regulation of the Expression of CYP1 Genes

CYP1A1, CYP1A2 and CYP1B1 belong to the human CYP1 family. Although CYP1B1 evolved from the common ancestral gene as CYP1A1 and CYP1A2, CYP1B1 is located on human chromosome 2, whereas CYP1As on chromosome 15.^{135–137} Human CYP1A1 gene contains several enhancer and silencer regions: BTE – basic transcription element, XRE (or DRE) – xenobiotic (or dioxin) response element, NRE – negative regulatory element, GRE – glucocorticoid response element.¹³⁸

BTE is a GC-rich region, which mediates the basal transcription of the gene.¹³⁹ Sp-1-like transcription factors up- or down-regulate genes containing BTE in their promoter. Sp-1 is involved in the expression of CYP1A1 at both basal and induced levels. Other Sp-1-like proteins, BTEB3 and 4 (BTE binding proteins) have been reported to down-regulate CYP1A1 expression. By binding of BTEB3/4 to CYP1A1 promoter, a co-repressor with histone deacetylase activity is recruited, which generally decreases gene transcription.^{140–143}

The members of CYP1 family are target genes of AhR, and are induced by polycyclic aromatic hydrocarbons and polyhalogenated aromatic hydrocarbons.³⁰ Xenobiotic signal transduction is achieved by AhR/Arnt-binding to XREs in the 5' upstream region (Figure 3).^{35,36,144–146} The heterodimer associates with co-activators (including CBP/p300 and the members of NcoA/SRC-1/pCIP family) having histone acetyltransferase activity and with

other transcription factors (NF-1, TBP, TFIIF, PolII).^{147,148} The AhR/Arnt dimer functions as a transcriptional enhancer of CYP1A1 and other genes belonging to the AhR gene battery (see 2. 1.). AhR also induces the expression of AhRR (AhR repressor), which is the member of bHLH/PAS family with the structure similar to that of AhR or Arnt.^{149,150} AhRR is located in the nucleus and interacts with Arnt. Although the AhRR/Arnt heterodimer binds to XREs, this heterodimer is transcriptionally not active and inhibits AhR function. AhRR induction by AhR results in a negative feedback loop. The expression of AhRR is also induced by NF κ B which is activated by various cytokines such as IL-1 or TNF. NF κ B has also been proposed to exhibit physical interaction and mutual functional repression with AhR. The action of cytokines eventually leads to the suppression of CYP1A1 or CYP1A2 expression.^{150–154}

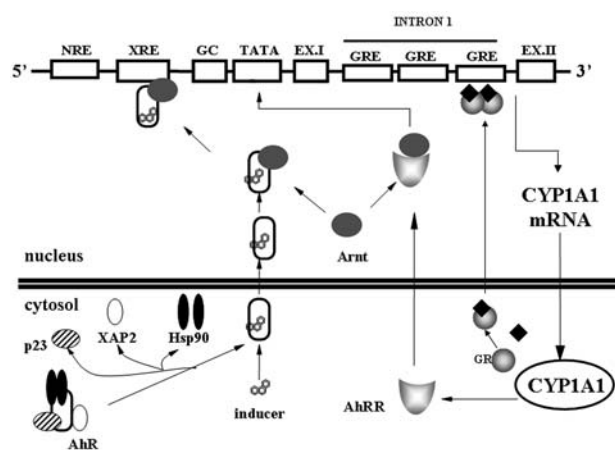


Figure 3: Induction of CYP1A1.

AhR: aromatic hydrocarbon receptor; Arnt: AhR nuclear translocator; AhRR: AhR repressor; NRE: negative regulatory element; XRE: xenobiotic response element; GRE: glucocorticoid response element; GR: glucocorticoid receptor

Two NREs have been described in the 5'-flanking region of the human and rat CYP1A1 genes. NRE consists of a 21-bp palindrome with a point-symmetry at -784 and two GC-rich elements, which flank the palindrome. A member of NF-Y transcription factor family seems to be implicated in negative gene regulation *via* NRE.^{155,156}

The exon 1 of both rat and human CYP1A1 is a non-coding region and the transcriptional starting site is located at exon 2. Intron 1 contains regulatory elements, three GRE sequences of 5'-TGTCCT-3'.¹⁵⁷ The inducibility of CYP1A1 by planar aromatic compounds is potentiated by the action of glucocorticoid receptor.¹⁵⁸ The activated GR as a homodimer stimulates GRE sequences, interacts with the initiation complex in the promoter of CYP1A1 gene and enhances the degree of CYP1A1 induction by polycyclic aromatic hydrocarbons at the transcriptional level (Figure 3). Although glucocorticoids alone do not influence the

expression of CYP1A1, they potentiate the rat CYP1A1 induction, if they are surrounded by activated XRE.^{157,159} However, the effect of glucocorticoids on CYP1A1 induction is species dependent. Potentiation of CYP1A1 transcription occurs in rat, but not in human. In human hepatocytes, glucocorticoids reduce CYP1A1 induction by 50 to 60% at enzyme protein level, whereas do not have an effect on CYP1A1 mRNA amount.¹⁶⁰

3. 2. Regulation of CYP2 and CYP3A Genes

Several P450 genes from the CYP2 and CYP3 families are inducible by many xenobiotics, notably including barbiturates and rifampicin. Two nuclear receptors, the PXR (NR1I2; see 2. 3.) and the CAR (NR1I3; see 2. 2.), have recently been shown to mediate *CYP2* and *CYP3* gene induction in animals and man.

In the CYP2B subfamily, CYP2B6 has long been thought to play a minor role in human drug metabolism and has therefore received little attention. However, several recent findings have generated an increased interest in this isoenzyme: identification of ethnic differences in its expression, the identification of new substrates for CYP2B6 and perhaps a shared specificity with CYP3A4, and the suggestion that its transcriptional activation is regulated by mechanisms similar to those affecting CYP3A4.^{72,74,161–164} The human CYP2B subfamily contains two active genes, *CYP2B6* and *CYP2B7*, located on chromosome 19 close to *CYP2A* and *CYP2F* genes.¹⁶⁵ CYP2B6 is expressed primarily in the liver, while CYP2B7 is a lung specific P450 enzyme. The transcriptional regulation of CYP2B6 expression involves at least five steps: i) activation of CAR, ii) nuclear translocation of CAR, iii) heterodimer formation with RXR, iv) CAR-RXR binding to PB-responsive element module (PBREM) in the promoter of *CYP2B6* gene (at –1,683/–1,733), v) transcriptional activation of CYP2B6 gene. (see 2. 2.)

The CYP2C subfamily includes in humans at least four functional members: CYP2C8, CYP2C9, CYP2C18 and CYP2C19. They are involved in the metabolism of nume-

rous substrates, such as phenytoin, tolbutamide, torsemide, S-warfarin, S-mephenytoin and numerous non-steroidal anti-inflammatory drugs (diclofenac).¹⁶⁶ CYP2C8 and CYP2C9 are the most strongly inducible members of the CYP2C subfamily in human hepatocytes. PXR/CAR-binding sites in the *CYP2C8* and *CYP2C9* promoter have been delineated, in addition to a glucocorticoid-responsive element within these promoters.^{167,168} Xenobiotics known to be CYP2B6 and CYP3A4 inducers (PB, dexamethasone, rifampicin) also have induction potential for CYP2C8/9. GRE is determined as an imperfect palindrome at –1,662/–1,676, whereas CAR-responsive element is a DR4 motif at –1,808/–1,818 recognized and transactivated by GR and by CAR and PXR, respectively. The presence of these two responsive elements suggests a complex regulation in response to glucocorticoids and xenobiotics.^{70,169} However, *CYP2C9* appears to be primarily a glucocorticoid-responsive gene, which in addition, may be induced by xenobiotics through CAR and/or PXR activation.

The CYP3A subfamily includes the most abundant P450 present in the adult human liver, comprising approximately 30% of the total content. The human CYP3A family consists of four enzymes (CYP3A4, CYP3A43, CYP3A5 and CYP3A7), which show variable levels of expression in the population. Among them, the CYP3A4 isoform is the most prevalent in adults. It has been estimated that about 50% of currently marketed drugs are metabolized by CYP3A4.¹⁷⁰ The substrates for this enzyme include drugs such as quinidine, nifedipine, diltiazem, lidocaine, lovastatin, erythromycin, cyclosporin, triazolam and midazolam, and several endogenous substances, including testosterone, progesterone, androstenediol and bile acids. CYP3A4 also activates procarcinogens, including aflatoxin B1, polyaromatic hydrocarbons, NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and 6-aminochrysene.^{91,171} CYP3A4, CYP2B6 and CYP2C9 are induced in human hepatocytes by rifampicin, dexamethasone, PB, calcium channel modulators such as nifedipine and its derivatives, and vitamin D.^{54,90,113,172–179} PXR controls CYP3A4 and CYP3A7 induction by target-

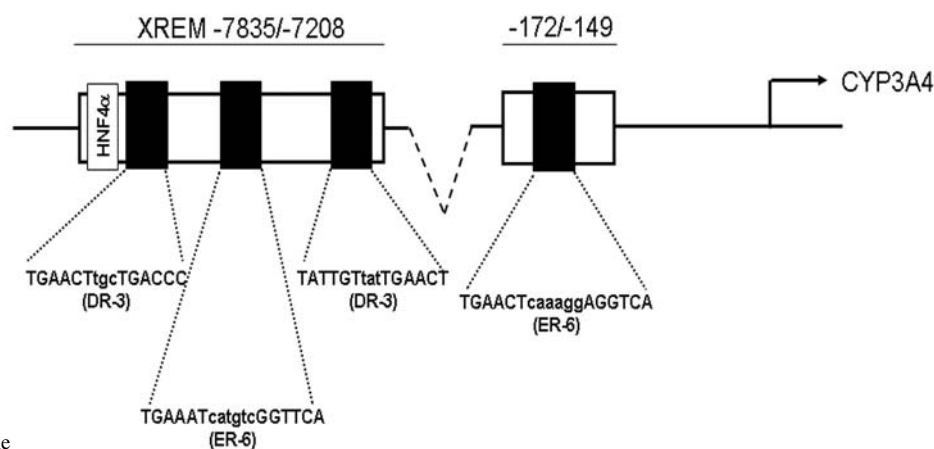


Figure 4: The structure of *CYP3A4* promoter. XREM: xenobiotic response element module

ting two specific responsive elements present in the regulatory region of these genes.^{96,180,181} One of these regulatory regions is the proximal PXR-responsive element located at -160. It consists of an everted repeat of the nuclear receptor half-site 5'-AGGTCA-3' separated by 6 nucleotides (ER6). This element is essential, but not sufficient for full transactivation of the *CYP3A4* promoter. Indeed, full PXR-mediated induction requires the presence of a second distal xenobiotic-responsive element (dPXRE), located between -7,200 and -7,800.¹⁸⁰ This element is a composite and consists of two direct repeats separated by 3 nucleotides (DR3), encompassing an ER6 motif (Figure 4). In human *CYP2B6*, the rifampicin and PB-responsive element module (PBREM) is located between -1,684 and -1,733 and has been shown to bind to and be transactivated by CAR and by PXR.⁷⁴ Similarly to *CYP3A4*, the full CAR and PXR-mediated *CYP2B6* gene induction by xenobiotics requires the cooperation between a distal DR4 motifs (-8.5 kilobases upstream from the *CYP2B6* encoding region) and the -1,684/-1,733 NR1 motif.¹⁸²

3. 3. Regulation of CYP2D6

CYP2D6 is the only functional gene of CYP2D subfamily in human. It is involved in metabolism of great number of drugs such as β -adrenergic blocking agents (bufuralol, propranolol, metoprolol), antiarrhythmics (propafenone), analgetics (codeine, dextromethorphan), tricyclic antidepressants (clomipramine, imipramine, nortriptyline), and other antidepressants (fluoxetine, paroxetine) or antipsychotics (haloperidol, thioridazine).¹⁸³ Great differences between individuals exist in drug-metabolizing capacity of *CYP2D6*; however, it does not derive from the inducibility of *CYP2D6*. In contrast to the other P450 enzymes discussed in this review, *CYP2D6* is not inducible and the expression of *CYP2D6* gene is not regulated by xenobiotics. The high degree of interindividual variability is primarily due to the extensive genetic polymorphism.^{184–186} Poor metabolizers inheriting two non-functional alleles are unable to metabolize *CYP2D6* substrates leading to an increased risk of adverse drug reactions or lack of therapeutic response. At the other extreme, the ultrarapid metabolizers inherit multiple copies (2 or even 13 arranged tandem) of *CYP2D6* gene.¹⁸⁷ The mechanism of endogenous regulation of *CYP2D6* is not completely understood and the factors that play role in transcription of the gene have not been revealed.

3. 4. Regulation of CYP2E1

CYP2E1 catalyzes the metabolism of endogenous compounds such as acetone, linoleic acid or arachidonic acid. Several exogenous chemicals with low molecular weight including organic solvents (chloroform, ethanol, or dimethylsulfoxide), halogenated anesthetics (halothane, enflurane), drugs (chlorzoxazone, acetaminophen) and

carcinogenic nitrosamines (N,N-dimethylnitrosamine) can also be metabolized by *CYP2E1*.¹⁸⁸ During ethanol oxidation, *CYP2E1* generates reactive oxygen species (superoxide anion radical, hydrogen peroxide and hydroxyl radicals) and also displays efficient NADPH-dependent lipid peroxidation.^{189–191}

Regulation of *CYP2E1* is somewhat different from other drug-metabolizing P450s mentioned above. The expression of human *CYP2E1* gene is under tight developmental control. It is not expressed in the foetal liver; however, the gene is activated immediately after birth. The first exon and intron of *CYP2E1* gene contains several methylation sites. In foetal tissues, the transcription of the gene is blocked by hypermethylation of the 5'-region, which is released postnatally.¹⁹² In contrast to other P450 enzymes such as *CYP1A1/2*, *CYP2B6*, *CYP2C9* or *CYP3A4*, which are induced by receptor-mediated transcriptional activation, *CYP2E1* is primarily regulated at post-transcriptional and post-translational levels by physiological and pathophysiological processes, and by xenobiotics (Figure 5A). Increased half-lives of the enzyme protein or *CYP2E1* mRNA lead to higher steady-state enzyme levels.¹⁹³ Xenobiotics such as acetone, ethanol or isoniazid induce *CYP2E1* by stabilization of enzyme pro-

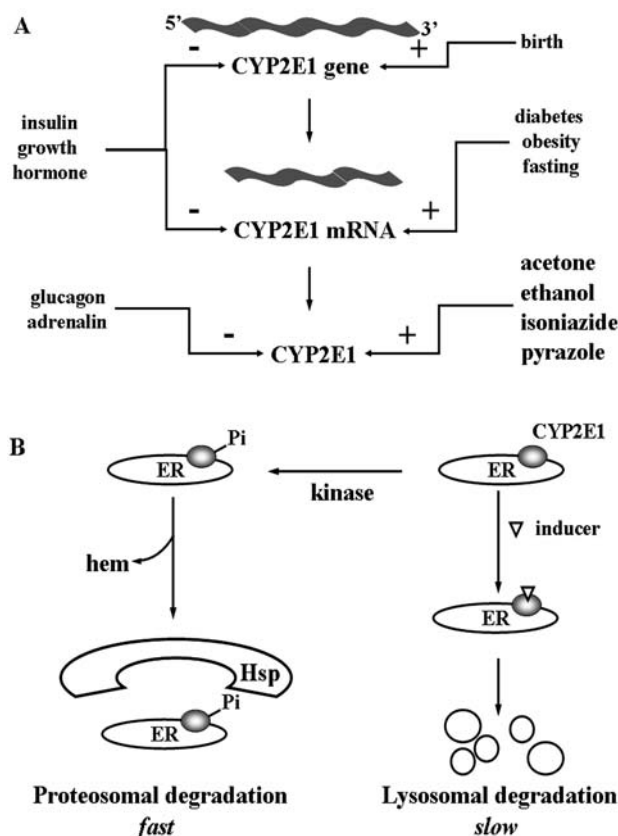


Figure 5. Regulation of *CYP2E1* expression (A) and mechanism of *CYP2E1* degradation (B). Hsp90: heat shock protein 90; ER: endoplasmic reticulum

tein and decrease the rate of enzyme degradation without an increase in CYP2E1 mRNA level.¹⁹⁴ CYP2E1 exhibits biphasic turnover with a short half-life of approximately 7 h and a longer half-life of 37 h.¹⁹⁵ The rapid proteosomal degradation is assisted by Hsp90 and mediated by proteases.^{196,197} The slower pathway is the lysosomal degradation through fusion of endoplasmic reticulum with lysosomal membranes. Ethanol or acetone has been proved to abolish the rapid phase of degradation, whereas the slower pathway is not influenced resulting in the increase in CYP2E1 content (Figure 5B).¹⁹⁰

Fasting and insulin-dependent diabetes highly induce CYP2E1 mRNA and enzyme protein; however, transcription of *CYP2E1* gene is not enhanced suggesting mRNA stabilization. Insulin treatment is able to reverse CYP2E1 mRNA stabilization by activation of a cytosolic protein, which binds to a 16-nucleotide sequence in 5'-region of CYP2E1 mRNA. In diabetic patients, high serum levels of ketone bodies (CYP2E1 inducers) are detected suggesting additional mechanism of induction by stabilization of enzyme protein. Glucagon also influences the level of CYP2E1 protein enhancing its turnover by cAMP-dependent mechanism.^{198,199}

The function of CYP2E1 is controlled by phosphorylation at Ser129 of the enzyme, by a reaction, which denatures the protein. cAMP-dependent protein kinase A catalyzes phosphoryl transfer from ATP to CYP2E1 resulting in the inactivation of P450 enzyme. The chemical inducers may prevent CYP2E1 from phosphorylation by kinases and consequently from degradation.^{200–203}

3. 5. Regulation of CYP4A Expression

CYP4A subfamily contains two human enzymes: CYP4A11 and CYP4A20.¹²⁸ Previously reported human CYP4A9 has been proved to be identical with CYP4A11 and is no longer considered as a separate entity in the P450 database. CYP4A enzymes play role principally in the metabolism of endogenous substrates, such as saturated and unsaturated fatty acids with medium and long chains, arachidonic acid and prostaglandins. Fatty acids are hydroxylated primarily at their ω -carbon atom, but some CYP4As (rat CYP4A1/2/3, human CYP4A11) are able to catalyze hydroxylation the ($\omega - 1$)-carbon atom depending on the chain length of the fatty acid. The ω -hydroxylation of fatty acids by CYP4As, their subsequent oxidation to dicarboxylic acids by cytosolic dehydrogenases and peroxisomal β -oxidation of dicarboxylic acids provide an important secondary pathway for fatty acid metabolism when the availability of free fatty acids increases during fasting and uncontrolled diabetes or when mitochondrial β -oxidation of fatty acids is disrupted by inhibition or genetic deficiencies.^{119,121,204} Formation of epoxyeicosatrienoic and 20-hydroxy-eicosatetraenoic acids from arachidonic acid by CYP4As is also of significant interest, because they play role in constriction of vas-

cular smooth muscle by activating protein kinase C (PKC) and mitogen activated protein kinase (MAPK).^{205,206}

Regulation of CYP4A expression is mediated by PPAR α in a manner similar to other nuclear receptors. In the absence of ligands, PPAR α exists as monomer. Xenobiotics including hypolipidemic drugs (clofibrate, fenofibrate, ciprofibrate, gemfibrozil), phthalate plasticizers (diethylhexyl phthalate), solvents (trichloroethylene), or non-steroidal anti-inflammatory drugs (ibuprofen, indomethacin) and endogenous compounds such as fatty acids and eicosanoids were found to preferentially activate PPAR α .^{123,130,207} Binding of peroxisome proliferators activates the receptor; whereas there are PPAR α activators such as dehydroepiandrosterone, which can activate the receptor without direct binding. Receptor activation by dehydroepiandrosterone is possibly the result of an effect of phosphorylation status of PPAR α .²⁰⁸ The activated receptor forms heterodimer with RXR recruiting co-activators such as PGC-1 (PPAR γ co-activator 1).²⁰⁹ The PPAR α -RXR dimer binds to PPAR α responsive element (PPRE) of *CYP4A* genes. PPRE is an imperfect DR1 preceded by a conserved A/T rich sequence that is required for function. The number of the responsive elements is different in the promoter of *CYP4A* genes, but each contains two or three 5'-AGGTCA-3' motives, characteristic of nuclear receptor binding sites.²¹⁰ DR1 motif recognized by PPAR α also binds other transcription factors, ARP-1 (apolipoprotein regulatory protein 1) and COUP-TFI, which compete with PPAR α for binding to PPRE and suppress PPAR α -mediated transcription.¹³²

In human, peroxisome proliferators have not been reported to produce significant effects on the expression of *CYP4A* genes. Species differences in the expression of PPAR α and in susceptibility to peroxisome proliferation may provide explanation of the human resistance.²¹¹ Epidemiological studies of patients who received gemfibrozil or clofibrate for 5 to 8 years did not display statistically significant increase in liver cancer. The fact that serum triglyceride levels decrease after the treatment provides evidence for functional PPAR, which is pharmacologically active, but cannot induce CYP4A expression.¹²⁷

4. Some Aspects of Cross-Talk Between Nuclear Receptors and Other Transcriptional Factors

4. 1. Cross-talk Between AhR and Other Receptors or Transcription Factors

Some possibilities for cross-talk between AhR and other transcription factors have been discussed in 3.1. i) AhR/Arnt-mediated CYP1A1 induction is negatively modulated by AhRR serving as negative feedback loop.^{149,150} ii) Glucocorticoids activate GRE sequences in the first intron of *CYP1A1* gene and act synergistically with polyaro-

matic hydrocarbons in CYP1A1 induction in rat.^{157–159} Human *CYP1A1* gene also contains GREs; however, glucocorticoids do not seem to potentiate CYP1A1 transcription. Even more, CYP1A1 protein level decreases in the presence of glucocorticoids.¹⁶⁰

Another example of a cross-talk between AhR and other factors is the one involving AhR and hypoxia-inducible factor 1 α (HIF-1 α).²¹² Under hypoxia conditions, the decrease of AhR-Arnt complex with DNA was observed. Both AhR and HIF-1 α are bHLH/PAS proteins and are able to form dimers with Arnt. These facts suggest the interference of AhR and HIF-1 α signaling pathways. The amount of HIF-1 α is regulated by O₂-tension; normoxia results in hydroxylation of the key amino acid residues and rapid degradation of HIF-1 α . Low O₂-tension inhibits hydroxylation and stabilizes HIF-1 α protein resulting in increased translocation into the nucleus, interaction with Arnt and in parallel activation of HIF-1 α target genes (erythropoietin, vascular endothelial growth factor, glycolytic enzymes).²¹³ However, it has to be clarified whether the interference of AhR and HIF-1 α derives from the competition for Arnt, and whether AhR activation by polycyclic aromatic hydrocarbons results in inhibition of the expression of HIF-1 α target genes under hypoxia conditions. It should be mentioned that the affinity of HIF-1 α for Arnt is higher than the affinity of AhR.²¹⁴

4. 2. Cross-talk Between PXR-CAR-VDR-GR

Previous work from the group of Guzelian suggested that induction of the rat CYP3A by glucocorticoids, and paradoxically also by antiglucocorticoids, is dependent on a nonclassical glucocorticoid-mediated induction process.¹⁷⁶ These studies revealed an atypical profile of CYP3A23 induction, compared to the classical glucocorticoid-mediated induction of known GR-dependent genes.^{174,215} For example, the induction of CYP3A23 by dexamethasone requires a concentration 100 times higher than that necessary for the maximal induction of the *TAT* gene (tyrosine aminotransferase). Furthermore, the potency of various glucocorticoids for inducing CYP3A23 does not correlate with their potency for inducing TAT. On the other hand, it had previously been reported that GR binds to a glucocorticoid response element present in the rat *CYP3A1* gene, and it has been suggested that cooperation of the upstream GRE and downstream elements (e.g., PXR-responsive element) may be required for the maximal response of CYP3A to glucocorticoids.^{216,217} Schuetz et al. proposed that the GR is not required for the induction of CYP3A by glucocorticoids in mouse, while its expression is essential for the induction of CYP2B.¹⁷⁴ However, extrapolating data from rodents to man is hazardous because of the species-specificity in the response of P450s and nuclear receptors to xenobiotics.^{92,216–218} Although computer analysis of approximately 1 kb of the hu-

man *CYP3A4* proximal promoter revealed the presence of putative binding sites for the estrogen receptor, COUP-TF, HNF4, HNF5 and Oct-1 (octamer protein), no consensus binding site for the GR was identified within this region.²¹⁹ However, the human *CYP3A5* gene promoter contains two GREs separated by 160 bp, which confer glucocorticoid response to reporter genes in HepG2 cells.¹⁷⁴ Interestingly, the *CYP3A5* promoter has no functional PXR-binding site in its proximal region, but is still inducible by glucocorticoids.^{78,220} In contrast, a functional GRE in the *CYP2C9* gene promoter has been reported to trigger the GR-mediated *CYP2C9* gene induction by glucocorticoids, while PXR failed to transactivate this element.⁷⁰ Several lines of evidence suggest that CAR and PXR may not totally account for the steroid induction of CYP2s and CYP3A, and the possibility exists that the GR is involved indirectly in this process: i) induction of human CYP2B6, CYP2C8/9 and CYP3A4 in cultured hepatocytes is potentiated by pretreatment of cells with dexamethasone; ii) the response of a *CYP3A4* promoter-dependent gene reporter to glucocorticoids increased in the presence of co-transfected hGR; iii) transcriptional activation of rat *CYP3A1* and human *CYP3A4* promoters by dexamethasone is blocked by the antiglucocorticoid mifepristone (RU486), a mouse and human PXR activator; iv) induction of CYP3A4 and CYP2C9 expression by dexamethasone in cultured human hepatocytes is inhibited by submicromolar concentrations of RU486, while this compound induces CYP3A4 mRNA only at micromolar concentrations, suggesting the involvement of at least two distinct pathways in the response of this gene to agonist and antagonist glucocorticoids.^{54,63,70,81,85,87,90,215}

In addition, we have shown that the expression of CAR and PXR in human hepatocytes is regulated by glucocorticoid hormones, and made the hypothesis that GR controls the expression of PXR and CAR on the basis of the following arguments: i) dexamethasone does not affect the degradation of CAR and PXR mRNA; ii) the induction of CAR and PXR mRNA is blocked by the glucocorticoid antagonist RU486; iii) the induction is not suppressed by cycloheximide treatment, indicating that it is mediated by preexisting GR; and iv) the RNA synthesis inhibitor, actinomycin D, abolishes the stimulatory effect of dexamethasone.^{54,117} This hypothesis was confirmed after the cloning and the analysis of 4.7 kb of the human CAR regulatory region.²²¹ The results revealed the existence of a functional GRE between –4,432 and –4,447. This element has a classical GRE structure, i.e., two half-sites separated by three nucleotides. Mutations of this GRE in either half-site drastically decreased both binding and transactivation by hGR. These *in vitro* experiments were confirmed by a chromatin immunoprecipitation assay revealing that dexamethasone treatment of cultured human hepatocytes causes binding of GR to this DNA region of the *CAR* promoter in intact cells. Of particular significance is that the homologous region of the murine *CAR* promoter gene pre-

sely matches to the human GRE (starting at chromosome 1 position 172,485,157), suggesting that similar glucocorticoid-dependent regulation should be observed in these species. Whether PXR is a primary glucocorticoid responsive gene as well remains to be confirmed. Interaction of this GR regulatory pathway with the PXR and CAR-mediated xenobiotic signaling pathway suggests the existence of an activation cascade of signal transmission: GR-CAR/PXR-CYP2/3. According to this model, both glucocorticoids and PXR and CAR activators have to be present for the cascade to work. Hence, it may explain the cooperative effect observed between glucocorticoids and PB or rifampicin on the expression of several PXR or CAR target genes, as well as the inhibitory effect of RU486 on rifampicin or PB-mediated P450 induction.^{54,63,77,79,81,117,222}

Prolonged therapy with rifampicin causes vitamin D deficiency.^{223,224} In eight healthy subjects, rifampicin treatment reduced circulating levels of 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D by 34% and 23%, respectively. In addition, rifampicin and PB are two of the drugs most commonly associated with osteomalacia, a metabolic bone disease characterized by a defect in bone mineralization frequently due to an alteration of vitamin D metabolism. Owing to the fact that VDR is able to activate PXR- and CAR-responsive genes including *CYP3A4*, *CYP2C9* and *CYP2B6*, the clinical observations above suggest the hypothesis that the reciprocal proposition is true, that is, PXR and CAR are able to activate VDR-responsive genes.¹¹⁴ In particular, this suggests that CAR and/or PXR might be involved in the control of the genes responsible for the synthesis or catabolism of vitamin D. The major route of degradation of vitamin D is oxidation of the side chain of the molecule, catalyzed by vitamin D-24 hydroxylase (*CYP24*), an enzyme, which is induced by 1,25-dihydroxy vitamin D and its other derivatives.²²⁵ It is therefore possible that xenobiotics stimulate the expression of VDR target genes, notably *CYP24* through CAR and PXR activation. Indeed, we reported that CAR and PXR bind to and transactivate VDRE-1 and VDRE-2 of the *CYP24* gene.²²⁶ These findings suggest that the VDR-PXR cross-talk resulting from the recognition of same response elements is reciprocal. Interestingly, it was reported recently that *CYP2D25*, the porcine microsomal vitamin D 25-hydroxylase, is down-regulated at the transcriptional level by VDR in the presence of vitamin D metabolites and by both CAR and PXR in the presence of PB.^{226–228} These observations are in favor of another aspect of the cross-talk between CAR, PXR and VDR. However, induction of *CYP24* by xenobiotics *via* CAR or PXR is certainly not the only molecular mechanism by which xenobiotics might induce bone disorders. Indeed, Xu et al. demonstrated that, in addition to *CYP24*, *CYP3A4* may efficiently contribute to the catabolism of 1,25-dihydroxy-vitamin D and other vitamin D metabolites by generating 23R- and 24S-hydroxy metabolites in liver and intestine under xenobiotic treatment.²²⁹ Such

cross-talk provides, at least in part, an objective explanation to the observation that long-term treatment of patients with drugs, which are CAR or PXR agonists, results in low 1,25-dihydroxy-vitamin D levels and osteomalacia.^{224,230,231}

4. 3. Nuclear Receptor Cross-talk Preventing Bile Acid Toxicity

Bile acids are biological detergents with a series of important functions including hepatic generation of bile flow and excretion of biliary cholesterol, lipid emulsification in the intestine and uptake of lipid-soluble vitamins. However, bile acids are highly cytotoxic and imbalance of their synthesis results in various pathological processes. PXR has an important role in cholesterol and bile acid homeostasis serving as a physiological sensor of bile acids. Bile acids such as cholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid or 3-ketolithocholic acid are able to activate PXR. The activated PXR induces the expression of both *Oatp1a4* (organic anion transporting polypeptide 1a4, previously known as *Oatp2*) and *CYP3A* involved in the transport and the metabolism of the highly toxic lithocholic acid. Up-regulation of *Oatp1a4* by PXR agonists may function as an enhanced hepatic extraction of bile acids from blood. Then the hepatic *CYP3A4* can metabolize toxic bile acids into less toxic and more polar hydroxyl-derivatives (6 α - and 6 β -hydroxy-lithocholic acids). PXR also represses *CYP7A1* (cholesterol 7 α -hydroxylase) that catalyzes the first step in cholesterol-bile acids pathway.^{232–235}

Besides microsomal *CYP7A1*-catalyzed cholesterol 7 α -hydroxylation, an alternate pathway of bile acid synthesis exists in mitochondria, the *CYP27*-mediated cholesterol side chain hydroxylation. The pathway initiated by *CYP27* preferentially produces chenodeoxycholic acid, whereas *CYP7A1* pathway produces equivalent amounts of cholic acid and chenodeoxycholic acid, the relative levels of which are regulated by *CYP8B1* (12 α -hydroxylase). *PPAR α* has been reported to regulate bile acid synthesis. *PPAR α* activation by hypolipidemic agents leads to a decrease in bile acid synthesis by suppression of *CYP7A1* and *CYP27*.^{236–238} Due to reduction of chenodeoxycholic acid formation, the production of highly toxic lithocholic acid also decreases, which is considered to be a protective mechanism to reduce bile acid toxicity.^{239,240} In human, *PPAR α* activation increases the expression of *UGT2B4*, which is responsible for conjugation of hyodeoxycholic acid, the monohydroxylated metabolite of lithocholic acid.²⁴¹ By inducing *UGT2B4*, *PPAR α* contributes to reducing the toxicity of bile acids. Additionally, the activation of *FXR* by bile acids increases the expression of human *PPAR α* . Increased transcription of *PPAR α* eventually leads to a decrease in bile acid production and an increase in bile acid metabolism. Thus PXR, *FXR* and *PPAR α* -mediated gene regulation co-ordi-

nately prevents the accumulation of the potentially harmful bile acids by increasing their metabolism and blocking their synthesis.

5. Conclusion

From the first report on AhR-mediated CYP1A induction, our knowledge on regulation of nuclear receptors controlling P450 expression has been increasing; however, several points of the mechanism of P450 induction require clarification. The ability of nuclear receptors to control the transcription of several distinct genes suggests the existence of a complex regulatory network of metabolism of xenobiotics and endogenous compounds. This sophisticated network provides adaptive responses to many exogenous stimuli, e.g. drug treatment or exposure to chemical pollutants. Many physiological and pathophysiological factors influence the process of P450 induction *via* cross-talk between the nuclear receptors and other transcription factors. Pathophysiological changes may alter the organism's ability to metabolize xenobiotics and may generate imbalance of toxication and detoxication processes. On the other hand, drugs, which are shown to be activators of nuclear receptors, may also affect homeostasis of endogenous compounds.

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7. Abbreviations

AF	activation function
AhR	aromatic hydrocarbon receptor
AhRR	AhR repressor
Arnt	AhR-nuclear translocator
bHLH	basic helix-loop-helix
BTE	basic transcription element
CAR	constitutive androstane receptor
CPT	carnitine palmitoyltransferase
COUP-TF	chicken ovalbumin upstream promoter – transcription factor
DBD	DNA-binding domain
DHEA	dehydroepiandrosterone

DR	direct repeat
ER	everted repeat
FXR	farnesoid X receptor
FXRE	FXR-responsive regulatory element
GR	glucocorticoid receptor
GRE	glucocorticoid responsive element
HIF	hypoxia inducible factor
HNF	hepatocyte nuclear factor
Hsp	heat shock protein
IR	inverted repeat
LBD	ligand-binding domain
LXR	liver X receptor
NRE	negative regulatory element
Oatp	organic anion transporting polypeptide
P450	cytochrome P450
PAS	Per-Arnt-Sim
PB	Phenobarbital
PBREM	PB responsive element module
PCB	polychlorinated biphenyl
PGC-1	PPAR γ co-activator 1
PPAR	peroxisome proliferators activated receptor
PPRE	PPAR responsive element
PXR	pregnane X receptor
RXR	retinoid X receptor
SNP	single nucleotide polymorphism
SRC-1	steroid hormone receptor co-activator
TAD	transcriptional activation domain
TAT	tyrosine aminotransferase
TCPOBOP	3,3',5,5'-tetrachloro-1,4-bis(pyridyloxy) benzene
UGT	UDP-glucuronyltransferase
VDR	vitamin D receptor
VDRE	vitamin D response element
XRE	xenobiotic response element

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Povzetek

Citokromi P450 (P450) in drugi encimi, ki presnavljajo zdravila, igrajo glavno vlogo v biotransformaciji, detoksifikaciji in izločanju strukturno različnih ksenobiotikov. Izražanje citokromov P450 uravnavajo posebni receptorji, ki zaznavajo ksenobiotike. To so aril-hidrokarbonski receptor, član družine Per/Arnt/Sim transkripcijskih faktorjev; pregnanski X receptor, stalni androstanski receptor in receptor peroksisomske proliferacije. Vsi so člani naddružine jedrnih receptorjev, kamor spadajo tudi klasični steroidni receptorji, kot sta glukokortikoidni receptor in receptor vitamina D. Ker vsi ti receptorji vežejo ksenobiotike in se z njimi tudi aktivirajo, jih imenujemo tudi ksenosenzorji. Ksenobiotska signalna pot je vpletena v vozlišča regulatornih mrež, saj izražanje citokromov P450 ni uravnava le s ksenobiotiki, temveč tudi s številnimi endogenimi molekulami (kortikoidi, hormoni, citokini, žolčne kisline), ki so pogosto povišane v patofizioloških pogojih. Kaže, da ksenobiotiki vplivajo tudi na izražanje genov, ki uravnavajo endogene signalne poti. Sposobnost jedrnih receptorjev, da uravnavajo prepisovanje različnih genov, kaže na obstoj kompleksnih regulatornih mrež presnove ksenobiotikov in endogenih spojin. Revijiški članek predstavlja, kako ta kompleksna mreža omogoča prilagoditve na zunanje dražljaje, kot so tretma z zdravili ali izpostavljenost kemijskim onesnaževalcem.