Orphan Receptor Promiscuity in the Induction of Cytochromes P450 by Xenobiotics*

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The mechanisms by which different classes of chemicals induce the same cytochrome P450 (CYP) or the same chemical differentially induces more than one CYP are not well understood. We show that in primary hepatocytes and in vivo in liver (transfected by particle-mediated delivery) two orphan nuclear receptors, constitutive androstane receptor and pregnane X receptor (PXR1), transactivate a CYP gene via the same response element in a xenobiotic-specific manner. The constitutive androstane receptor mediates the barbiturate activation of expression of CYP2B1 and CYP3A1. PXR1 activates both genes in response to synthetic steroids. To exert their effect the receptors bind to the same direct repeat site (DR4) within the phenobarbital response element of the CYP2B1 promoter and to the same DR3 site in the pregnane X response element of CYP3A1. The receptors are therefore promiscuous with respect to DNA binding but not ligand binding. Differences in enhancer half-site spacing may influence the efficiency of interactions between the receptor and the transcription machinery and hence form the basis for the differential induction of CYP2B1 and CYP3A1 in response to barbiturates and synthetic steroids.

Cytochromes P450 (CYPs)† are a superfamily of proteins, members of which catalyze the metabolism of a wide range of endogenous and exogenous chemicals (1). CYP-mediated detoxification is a key defense mechanism whereby organisms protect themselves from the potentially harmful effects of foreign hydrophobic chemicals to which they are exposed. The xenobiotics are converted to more hydrophilic compounds, which are then more easily excreted (2). Many of these xenobiotics serve as inducers of the particular CYP required for their metabolism. Induction of CYPs is mediated primarily at the transcriptional level by the interaction of ligand-nuclear receptor complexes with enhancer sequences that lie upstream of CYP gene promoters (reviewed in Refs. 3 and 4). A single CYP can be induced to different extents by different classes of chemicals, and a single chemical can differentially induce more than one CYP. For instance, CYP2B1 and CYP3A1, members of two different CYP subfamilies, can both be induced in the liver by the barbiturate phenobarbital (PB) and by the structurally unrelated synthetic pregnane pregnenolone 16α-carbonitrile (PCN). CYP2B1 is induced to a greater extent by PB than by PCN (5), whereas CYP3A1 is induced more highly by PCN than by PB (6). Induction of CYP2B1 in response to PB is mediated by the interaction of the constitutive androstane receptor (CAR) (7) with a phenobarbital response element (PBRE) (8, 9), and that of CYP3A1 in response to PCN by binding of the pregnane X receptor (PXR1) to a pregnane X response element (PXRE) (10–13). However, no PBRE has been identified in the flanking regions of the CYP3A1 gene, and a PXRE has not been identified in the CYP2B1 gene. The mechanisms of induction of CYP2B1 by PB and of CYP3A1 by PB are not known.

Here we show that CAR and PXR1 can transactivate the CYP2B1 gene by interacting with the same direct repeat 4 (DR4) element of the PBRE. Similarly, the receptors transactivate the CYP3A1 gene by binding to the same DR3 element of the PXRE. In each case, the receptors transactivate gene expression in a xenobiotic-specific manner; PXR1 is activated by PCN (but not by PB) and CAR by PB (but not by PCN). The two orphan nuclear receptors thus exhibit promiscuity with respect to DNA binding but not ligand binding. The significance of the results for our understanding of the mechanisms that mediate differential induction of CYPs by xenobiotics is discussed.

EXPERIMENTAL PROCEDURES

Plasmids—The reporter plasmid (CYP2B1 PBRE)-SV40-luc was constructed by inserting the CYP2B1 PBRE sequence (−2301 to −2142 of the CYP2B1 gene) into the Bgl II site of the plasmid pG3SV40 promoter (Promega). The plasmid pRL-TK (Promega), which encodes the Renilla luciferase gene under the control of the thymidine kinase promoter, was used as a control vector to normalize the results of transient transfection assays. The reporter plasmid (CYP3A1)_2-tk-CAT, containing four copies of the CYP3A1 PXRE, was kindly provided by Dr. S. Kliewer. When cells were transfected with the chloramphenicol acetyltransferase reporter plasmid, (CYP3A1)_2-tk-CAT, the psV-blue-galactosidase control vector (Promega) was used to normalize the results of transient transfection assays. Nuclear receptor expression plasmids for mouse CAR (cDM8-mCAR-β), mouse retinoid X receptor (RXR) (pSg5-mRXRα), mouse PXR1 (pSg5-mPXR1), and newt retinoic acid receptor

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† The abbreviations used are: CYP, cytochrome P450; PB, phenobarbital; PCN, pregnenolone 16α-carbonitrile; CAR, constitutive androstane receptor; CAT, chloramphenicol acetyltransferase; PBRE, phenobarbital response element; PXR1, pregnane X receptor; PXRE, pregnane X response element; DR, direct repeat; RXRα, retinoid X receptor α; RAR, retinoic acid receptor; NR, nuclear receptor; TCPOBOP, 1,4-bis(2,5-dichloropyridyloxy)benzene.
Cell Culture and Transfection—Primary rat hepatocytes cultured on Matrigel (1 mg/ml) (Becton Dickinson) (5 × 10^5 cells/60-mm plate) were transfected using Tfx50 reagent (Promega) according to the supplier’s recommendations. Transfection mixture (6 ml) contained 2.5 μg of reporter plasmid, 0.25 μg of control plasmid, and 0.25 μg of an expression plasmid. Cell extracts were assayed for luciferase (Dual-Luciferase reporter assay system), chlamydomoncal acetyltransferase (CAT enzyme assay system), or β-galactosidase (β-galactosidase enzyme assay system) (all from Promega) activities according to the supplier’s recommendations.

In Vivo Transfection of Liver by Biolistic Particle Delivery—Gold particles, 25 mg (1 micron, Bio-Rad), were coated with 100 μg of DNA. The ratios of (CYP2B1 PBRE)-SV40-luc, pRL-TK and the expression plasmid (either dCMV-mCAR-β or pSG5-mRXRβ) were 10:1:1. The amount of total DNA/cartridge was 2 μg. Male Harlan Sprague-Dawley rats (200–250 g) were anesthetized and the liver shot at two different positions in a single lobe. A single dose of PB (100 mg/kg) or PCN (100 mg/kg) was given intraperitoneally as soon as suturing was complete. 24 h later the liver was removed and assayed for luciferase activity as described above.

GeM Mobility Shift Assays—Nuclear proteins were prepared from the livers of untreated and PB-treated rats as described previously (14, 15). CAR, PXR1, and RXRα were synthesized in vitro using a TNT transcription/translation-coupled reticulocyte lysate system (Promega) according to the supplier's recommendations. GeM mobility shift assays contained 10 mM HEPES (pH 7.6), 0.5 mM dithiothreitol, 15% (v/v) glycerol, 2.5 μg poly(dI-dC) (Amersham Pharmacia Biotech) or 50 mM NaCl, 1.5 μl of in vitro translated products or 5 μg of liver nuclear protein extract, and 3 × 10^6 cpm of a 32P-labeled double-stranded oligonucleotide. The binding reaction was performed at room temperature for 20 min. For competition assays, various amounts of unlabeled double-stranded oligonucleotide were included as indicated. The following oligonucleotides, synthesized by Amersham Pharmacia Biotech, were used as probes or competitors: the CYP2B1 nuclear receptor half-site NR1 (DR4), 5'-TGTACGTATCTGGACCTT-3', the CYP3A1 PXRE (DR3), 5'-AGAGCAGAATACCTGTTGCTTAT-3', for supershift assays, rabbit polyclonal antibodies against RXRα (SC-7737x) (2 μg) or PXR1 (SC-7737x) (2 μg) (Santa Cruz Biotechnology, Inc.) were added 15 min after the start of the binding reaction. Incubation was continued for another 20 min.

To assess binding of nuclear receptor/RXRα heterodimers to DNA response elements, in vitro transcription/translation reaction master mixes were prepared, one containing 35S-labeled methionine (Redivue™ [L-35S]methionine, Amersham Pharmacia Biotech) and the other, unlabeled methionine. Each master mix was split into equal batches and the translated products or 5 μg of in vitro translated products or 5 μg of liver nuclear protein extract, and 3 × 10^6 cpm of a 32P-labeled double-stranded oligonucleotide. The binding reaction was performed at room temperature for 20 min. For competition assays, various amounts of unlabeled double-stranded oligonucleotide were included as indicated. The following oligonucleotides, synthesized by Amersham Pharmacia Biotech, were used as probes or competitors: the CYP2B1 nuclear receptor half-site NR1 (DR4), 5'-TGTACGTATCTGGACCTT-3', the CYP3A1 PXRE (DR3), 5'-AGAGCAGAATACCTGTTGCTTAT-3'. For supershift assays, rabbit polyclonal antibodies against RXRα (Santa Cruz Biotechnology, Inc.) were added 15 min after the start of the binding reaction. Incubation was continued for another 20 min.

RESULTS

CAR and PXR1 Transactivate CYP2B1 Expression via the PBRE in Response to PB and PCN, Respectively—In primary rat hepatocytes, both PB and PCN increase the expression of a reporter gene under the control of the CYP2B1 PBRE (Fig. 1A), suggesting that induction of CYP2B1 by PCN is mediated by the interaction of either CAR or the ligand's cognate receptor, PXR1, with the PBRE. To investigate this possibility, we tested the effect of the xenobiotics on the expression of the CYP2B1 PBRE-reporter construct in hepatocytes transfected with expression plasmid for either CAR or PXR1 (Fig. 1A). Reporter gene expression was constitutively increased almost 5-fold by CAR but not by PXR1. In cells cotransfected with a PXR1 expression vector, reporter gene expression was increased 6-fold by PCN but not by PB. In cells cotransfected with a CAR expression vector, PB expression gene increased more than 3-fold above the level meditated constitutively by CAR, whereas PCN had no effect. Therefore induction of CYP2B1 gene expression in response to PB and PCN is mediated, respectively, by the interaction of CAR and PXR1 with the PBRE.

We next determined whether CAR and PXR1 bind to the same or different sites within the PBRE. CYP2B PBREs contain two DR4 nuclear receptor half-sites, NR1 (5'-TGTACGTATCTGGACCTT-3') and NR2 (5'-TCAACTTGACCT-3'), separated by a NF-1 (nuclear factor-1) site (8, 9, 16). PXR1, produced by in vitro transcription/translation, was found to bind, as a heterodimer with RXRs, to the NR1 element (Fig. 1B), the same site within the PBRE to which CAR binds as a RXRα heterodimer (Fig. 1B) (9). Neither CAR nor PXR1 binds to the rat CYP2B1 NR2 site when heterodimerized with mouse RXRs (17). However, when heterodimerized with human RXRα, CAR can bind to the NR2 site of the mouse Cyp2b10 gene (18).

Complexes formed between the NR1 site and liver nuclear proteins were competed by the PXRE of CYP3A1 and were supershifted by antibodies against PXR1 and RXRα (Fig. 1C). These results are similar to those obtained using the CYP3A1 PXRE as probe (Fig. 1C) and confirm the interaction of PXR1/RXRα heterodimers with the NR1 site of the PBRE.

To determine the effect of the receptors on CYP2B1 expression in vivo we performed transfection experiments in liver (Fig. 1D). A CYP2B1 PBRE-reporter plasmid, together with
expression vectors for either PXR1 or CAR, was introduced into rat liver by bioisotopic particle-mediated DNA transfer. Reporter gene expression was increased constitutively by CAR but not by PXR1. The CAR-mediated transactivation of reporter gene expression was increased further in response to PB but not to PCN. Conversely, the presence of PXR1 stimulated the induction of gene expression by PCN, whereas it decreased the effect of PB, presumably by competition with endogenous CAR for binding to the PBRE (see Fig. 2F). The results are qualitatively similar to those obtained in hepatocyte cultures (see Fig. 1A) and confirm that in vivo both PXR1 and CAR are able to transactivate gene expression via interaction with the same CYP2B1 enhancer element (the NR1 of the PBRE) in response to PCN and PB, respectively. Hence, the regulation of CYP2B1 expression by xenobiotics involves cross-talk between ligand-receptor complexes.

We next investigated the relative affinity with which CAR and PXR bind to the DR4 CYP2B1 NR1 and DR3 CYP3A1 PXRE sites. Competitive gel shift assays were performed in which constant amounts of in vitro transcribed and translated CAR and RXRα or PXR and RXRα were incubated in the presence of unlabeled NR1 or PXRE with radiolabeled oligonucleotides specifying either the NR1 or PXRE sites. The CAR-RXRα-NR1 complex was competed more effectively by NR1 than by PXRE (Fig. 2A), whereas the PXR-RXRα-PXRE complex was competed more effectively by the PXRE than by NR1 (Fig. 2B). When increasing amounts of in vitro synthesized CAR/RXRα proteins were incubated with NR1 or PXRE probes, radiolabeled to the same specific activity, the protein-DNA complex formed on the NR1 site was more abundant than on the PXRE site (Fig. 2C). Conversely, PXR/RXRα bound more effectively to the PXRE than to the NR1 site (Fig. 2C). A comparison of relative binding affinities showed that CAR/RXRα bound to PXRE was about three times that for NR1 (Fig. 2E).

The ability of CAR and PXR1 to bind to the same response element, albeit with different affinities, suggests that the receptors will compete with each other for binding to this site in vitro and thus exhibit functional cross-talk. This theory was supported by the finding that CAR-mediated transactivation of a CYP2B1 PBRE-reporter construct in response to PB was inhibited by PXR1 in a dose-dependent manner (Fig. 2F). Reporter gene activity was decreased by about 60% when PXR and CAR expression plasmids were present in equimolar amounts and by as much as 80% by a 5-fold molar excess of PXR over CAR plasmid. As a control for squelching, hepatocytes were cotransfected with expression vectors for CAR and RAR, another nuclear receptor that heterodimerizes with RXRα, and whose cDNA was cloned into the same type of expression vector as that used for PXR, namely pSG5. RAR decreased reporter gene expression by −25% (Fig. 2F). Therefore, although some of the inhibitory effects of PXR may be due to competition with CAR for binding to RXRα, the majority most likely is due to competition with CAR for binding to the NR1 site of the PBRE.

CAR and PXR1 Transactivate CYP3A1 Expression via the PXRE in Response to PB and PCN, Respectively—in response to PCN, PXR1 stimulates CYP3A1 gene expression by binding to a DR3 PXRE (5′-TGAAGCTCA TGAACT-3′) (10, 13). The PXRE of CYP3A1 and the NR1 of the CYP2B1 PBRE were found to compete in gel mobility shift assays for binding to rat liver nuclear proteins (Fig. 1C). Furthermore, in vitro synthesized CAR bound as a heterodimer with RXRα to the PXRE (Fig. 2A and C), suggesting that PXR1 and CAR may transactivate CYP3A1 by binding to the same site within the gene’s promoter. To determine whether CAR can mediate PB-induced transactivation via the PXRE, hepatocytes were cotransfected with CYP3A1 PXRE-reporter plasmid and an expression vector for either CAR or PXR1 (Fig. 3). In cells cotransfected with CAR, reporter gene expression was induced 10-fold in response to PB, whereas PCN had little effect. In contrast, in cells cotransfected with PXR1, gene expression was increased 11-fold by PB but not by PCN. Thus, as is the case for the CYP2B1 gene, PXR1 and CAR bind to the same enhancer element within the CYP3A1 promoter (the PXRE) to activate gene expression in response to two different xenobiotics, PCN and PB, respectively. Each receptor can therefore mediate the xenobiotic induction of members of two different CYP subfamilies by interacting with a different response element within each of
Fig. 3. CAR and PXR1 transactivate via the same CYP3A1 DNA element. Primary hepatocytes were transfected with the reporter plasmid (CYP3A1)tk-CAT and the control vector pSV-β-galactosidase with or without (No E.P.) expression plasmids for CAR or PXR1. Cells were treated with vehicle (DMSO) alone or with PB or PCN and then assayed for chloramphenicol acetyltransferase and β-galactosidase activities. *, p < 0.01; **, p < 0.05, compared with the corresponding control value (two-tail paired Student’s t test).

the corresponding genes. The receptors are therefore promiscuous with respect to DNA binding. However, they are specific with respect to their xenobiotic activator; PXR1 is activated by PCN (but not by PB) and CAR by PB (but not PCN).

DISCUSSION

The mechanisms by which different classes of chemicals induce the same CYP or the same chemical differentially induces more than one CYP are not well understood. Here we show that in primary hepatocytes and in vivo in the liver two orphan nuclear receptors, CAR and PXR1, transactivate a CYP gene via the same response element in a xenobiotic-specific manner. CAR mediates barbiturate activation of expression of CYP2B1 and CYP3A1. PXR1 activates both genes in response to synthetic steroids. To exert their effect the receptors bind to the same DR4 site within the PBRE of the CYP2B1 promoter and to the same DR3 site in the PXRE of CYP3A1. The receptors are therefore promiscuous with respect to DNA binding.

In vivo CYP3A1 is less inducible (3-fold) by PB than is CYP2B1 (50-to 100-fold) (6, 19). Similarly, PCN is a less potent inducer of CYP2B1 (3-fold) than of CYP3A1 (10-to 20-fold) (6). The deletion of a single base pair from a nuclear receptor half-site spacer region will alter the displacement (by 3.4 Å) in the interface between an orphan receptor and its heterodimerization partner, RXRα (and between PXR1 and RXRα) when bound to the DR4 (23). It is not surprising, therefore, that CAR is able to bind to the DR4 CYP3A4 PXRE. In agreement with our results, Moore et al. (24) found that the mouse isoform of PXR transactivates a CYP3A4-reporter gene in response to PCN but not to PB. These workers also found that neither human nor mouse CAR was able to transactivate a CYP3A4-reporter gene in response to PB. However, these experiments were performed in CV-1 cells, which, unlike primary hepatocytes, do not support PB-induced CAR-mediated transactivation of gene expression (17).

Several models can be proposed to explain how a single CYP can be induced by different classes of chemicals and how a single chemical can differentially induce more than one CYP. For instance, CYP genes may contain multiple xenobiotic response elements, each of which binds a distinct nuclear receptor. In this model, structurally related compounds may bind to the same receptor, but different classes of chemical would interact with different receptors. For example, many polycyclic aromatic hydrocarbons are able to interact with the aryl hydrocarbon receptor, whereas several steroids can bind to the PXR1. Differential induction of CYP genes by the same xenobiotic may be the result of differences in the sequence or environment of a particular response element in different genes. In a second model, a receptor can bind structurally unrelated xenobiotics before interacting with its cognate response element. For example, chlorotrimazole and TCPOBOP have been shown to bind to human PXR and transactivate gene expression via a CYP3A4 PXRE (24). Differences in receptor conformation, as a result of binding different chemicals, may account for differential induction responses. In this model, differential induction of CYP genes by the same chemical would result from binding of the chemical to different receptors, each of which then binds to its cognate response element and transactivates with a different efficiency. The results presented in this paper support a third model in which different receptors interact with the same response element, i.e., the receptors are promiscuous with respect to DNA binding but not ligand binding. Differences in the interface between an orphan receptor and its dimerization partner, RXRα, because of differences in the half-site spacing of responsive elements may influence the efficiency with which the heterodimer interacts with the transcriptional machinery and hence provide the basis for the differential induction of CYP genes by the same chemical. These models are not mutually exclusive, and all three could be involved in regulating the expression of a particular CYP gene.

CAR was originally shown to bind to and transactivate gene expression via DR2 and DR5 retinoic acid response elements (7, 25, 26). Subsequently, it was found that the receptor could transactivate via a DR4 element in CYP2B genes (9) and a DR1 peroxisome proliferator response element in the enoyl-CoA hydratase/3-hydroxy acyl-CoA dehydrogenase gene (27). Here we show that CAR can transactivate CYP gene expression in response to PB via DR4 and DR3 elements. CAR is thus extremely promiscuous with respect to DNA binding and must therefore have a great flexibility in its interactions with its heterodimerization partner, RXRα, and with components of the transcriptional machinery.
PB regulates the transcription of 30 or more genes in the liver (28). The recent production of a CAR knock-out mouse confirms that this orphan nuclear receptor mediates the induction of CYP2B by phenobarbital (29). It will be of interest to determine whether all PB-inducible genes are activated by CAR and to identify the enhancer site permutations to which this receptor and others, such as PXR1, can bind in the promoters of xenobiotic-regulated genes.

The detoxification of xenobiotics is necessary for survival. The evolution of orphan receptors that exhibit versatility with respect to the regulatory elements to which they bind in response to xenobiotics has clear advantages for the ability of organisms to protect themselves against potentially harmful foreign chemicals by enabling selective induction of the enzymes required to metabolize such compounds. However, competition of receptors for the same response element may lead to adverse drug-drug or xenobiotic-drug interactions.

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