The Constitutive Androstane Receptor and Pregnane X Receptor Function Coordinate to Prevent Bile Acid-induced Hepatotoxicity*

Received for publication, August 6, 2004, and in revised form, September 8, 2004
Published, JBC Papers in Press, September 8, 2004, DOI 10.1074/jbc.M409041200

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A double null mouse line (2XENKO) lacking the xenobiotic receptors CAR (constitutive androstane receptor) (NR1I3) and PXR (pregnan X receptor) (NR1I2) was generated to study their functions in response to potentially toxic xenobiotic and endobiotic stimuli. Like the single knockouts, the 2XENKO mice are viable and fertile and show no overt phenotypes under normal conditions. As expected, they are completely insensitive to broad range xenobiotic inducers able to activate both receptors, such as clotrimazole and dieldrin. Comparisons of the single and double knockouts reveal specific roles for the two receptors. Thus, PXR does not contribute to the process of acetaminophen hepatotoxicity mediated by CAR, but both receptors contribute to the protective response to the hydrophobic bile acid lithocholic acid (LCA). As previously observed with PXR (Xie, W., Radominska-Pandya, A., Shi, Y., Simon, C. M., Nelson, M. C., Ong, E. S., Waxman, D. J., and Evans, R. M. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 3375–3380), pharmacologic activation of CAR induces multiple LCA detoxifying enzymes and provides strong protection against LCA toxicity. Comparison of their responses to LCA treatment demonstrates that CAR predominantly mediates induction of the cytochrome p450 CYP3A11 and the multidrug resistance-associated protein 3 transporter, whereas PXR is the major regulator of the Na+ -dependent organic anion transporter 2. These differential responses may account for the significant sensitivity of the CAR knockout, but not the PXR knockout, to an acute LCA dose. Because this sensitivity is not further increased in the 2XENKO mice, CAR may play a primary role in acute responses to this toxic endobiotic. These results define a central role for CAR in LCA detoxification and show that CAR and PXR function coordinate to regulate both xenobiotic and bile acid metabolism.

Metabolism and detoxification of both foreign compounds, termed xenobiotics, and endogenous substrates, termed endobiotics, is a major function of the liver. Two members of the nuclear hormone receptor superfamily, constitutive androstane receptor (CAR)1 and pregnane X receptor (PXR), are key regulators of xenobiotic metabolism (3–5). Both receptors heterodimerize with retinoid X receptor and activate expression of xenobiotic metabolizing enzymes. Disruption of either PXR or CAR in mice results in severe defects in such responses, including the induction of cytochrome P450 3A (CYP3A) and cytochrome P450 2B (CYP2B) expression in response to xenobiotic stimuli (6, 7). Several recent studies indicate that CAR and PXR can recognize each other’s response elements and coordinate to induce CYP2B, CYP3A, and other targets in response to both specific and overlapping xenobiotic stimuli (8–11).

The more recently identified functions of these receptors in response to potentially toxic endobiotics (1, 2, 12) may also overlap. Thus, recent results suggest that CAR plays a major role in bilirubin clearance (12), but PXR regulates expression of the major bilirubin-metabolizing enzyme UGT1A1 and may significantly contribute to the balance of bilirubin metabolism (13). The specific and overlapping functions of CAR and PXR broaden our view of the complexity of liver metabolism and suggest the existence of both specific and functionally redundant defenses against exogenous and endogenous insults.

Fourteen enzymes in hepatocytes function to convert cholesterol to the two primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA) (14). In the gut, CA and CDCA can be converted into the secondary bile acids deoxycholic acid and lithocholic acid (LCA) by bacterial 7α-hydroxylases. Both primary and secondary bile acids are reabsorbed in the gut and transported back to the liver, where LCA, the most hydrophobic and toxic bile acid, can cause intrahepatic cholestasis (15). This toxic effect is counteracted by an intrahepatic detoxification process that includes hydroxylation by CYP3A, sulfation by dehydroepiandrosterone sulfotransferase (STD), and glucuronidation by UDP-glucuronosyltransferase (UGT) (16–18).

Two nuclear hormone receptors, Farnesoid X receptor (FXR) (NR1H4) and PXR, have been identified as important regulators of bile acid metabolism in the liver. FXR can be activated by many bile acids and regulates the expression of metabolizing enzymes and transporters in the bile acid homeostasis pathway (19–21). The numerous target genes of FXR include cholesterol 7α-hydroxylase (CYP7A) and sterol 12-α-hydroxylase (CYP8B1), the membrane transporters bile salt export pump (ABCB11) Na+-dependent taurocholate cotransporting polypeptide, multidrug resistance-associated protein 2 (MRP2) (ABCC2), and the sulfotransferase STD (22–26). The import-

* This work was supported by National Institutes of Health Grants R01 DK65466 (to D. M.) and U19 DK62434 (to D. M. and R. M. E.) and National Research Service Award Fellowship F32 DK63780 (to W. H.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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† The abbreviations used are: CAR, constitutive androstane receptor; PXR, pregnane X receptor; CARKO, CAR knockout; PXKRO, PXR knockout, 2XENKO, CAR and PXR knockout; LCA, lithocholic acid; TCP0B0, 1,4-bis-[2-(3,5-dichloropyridyloxy)]benzene; MRP, multidrug resistance-associated protein; CYP3A, cytochrome P450 3A; STD, dehydroepiandrosterone sulfotransferase; OATP2, Na+-dependent organic anion transporter 2; UGT, UDP-glucuronosyltransferase; FXR, Farnesoid X receptor; ALT, alanine aminotransferase.
tance of FXR in bile acid homeostasis is confirmed by the observation that disruption of the FXR gene in mice results in increased serum levels of bile acids, cholesterol, and triglycerides under basal conditions and severe liver toxicity in animals fed a cholic acid-containing diet (23). When fed an LCA-containing diet, the FXR null mice showed a sexually dimorphic phenotype, with decreased toxicity in females that may be because of the higher basal expression of SRE (27).

PXR also functions in bile acid homeostasis (1, 2). Activation of PXR by pregnane-16α-carbonitrile induces CYP3A4, SRE, and Na\(^{+}\)-dependent organic anion transporter 2 (OATP2), which are important for LCA detoxification and transport (1, 2). LCA is a PXR agonist ligand, and in vivo administration of LCA induces expression of CYP3A4 and other target genes. However, this response is not lost in PXR\(^{-/-}\) null mice, suggesting other nuclear receptors may be involved (1, 2, 28). When fed a cholic acid-containing diet, PXR\(^{-/-}\) and PXR\(^{-/-}\) double null mice show significantly increased expression of CAR and CYP2B10, indicating a possible role of CAR in compensating for the loss of FXR and PXR function in bile acid detoxification (29). This was recently supported by the demonstration that transgenic mice expressing an active VP16-CAR fusion protein in the liver are resistant to LCA toxicity (30). Here we have shown that CAR is activated by LCA treatment in vivo. The importance of this response is confirmed by the observation that CAR null mice are markedly more sensitive to LCA-induced hepatotoxicity than either wild type or PXR\(^{-/-}\) null mice. Comparisons of single null and 2XENKO double xenobiotic receptor knockouts suggest that this increased sensitivity may be a consequence of the primary role of CAR in response to the LCA-detoxifying enzymes CYP3A4 and MRP3.

**EXPERIMENTAL PROCEDURES**

**Generation of PXR and CAR Double Null Mice—**CARKO and PXRKO mice were crossed to generated double null mice (2XENKO) and genotyped as previously described (7, 6). The wild type, single knockout, and double knockout mice used in these studies were all maintained in an equivalent 129/Sv and C57BL/6 mixed background. This mixed background did not result in any apparent variations in responses to the various treatments.

**Animals and Treatments—**Mice were housed in a pathogen-free animal facility under a standard 12-h light/dark cycle. Age-matched groups of 8–10-week-old animals were used for all experiments. Mice were treated intraperitoneally for indicated time periods with dieldrin (50 mg/kg), clotrimazole (90 mg/kg), tepobradar (100 mg/kg), TCPOBOP (5 mg/kg), or LCA (125 or 250 mg/kg). For the feeding experiment, mice were fed with 0.5 or 1% LCA in powdered diet for 2 weeks. All the drugs were purchased from Sigma.

**RNA Preparation and Northern Blot Analysis—**Total RNA was extracted from mouse liver using Trizol reagent (Invitrogen). Equivalent RNA from CARKO and PXRKO mice was retained in both CARKO and PXRKO single null mice. Comparisons of single null and 2XENKO double xenobiotic receptor knockouts suggest that this increased sensitivity may be a consequence of the primary role of CAR in response to the LCA-detoxifying enzymes CYP3A4 and MRP3.

- **ALT and Bilirubin Measurement—**Blood was collected 24 h after the last treatment and transferred to T-MGA tubes (Terumo Medical Corporation, Elkton, MD). Serum was separated by centrifugation at 1,200 \( \times g \) for 10 min. Alkaline aminotransferase (ALT) levels and total bilirubin levels were measured as previously reported (12, 31). At least five mice were used for each treatment group.

- **Histological Examination—**The left lobe of the livers was fixed in formaldehyde and immediately fixed in 4% formaldehyde-phosphate-buffered saline solution, embedded in paraffin, sectioned at 5 \( \mu m \), and stained with hematoxylin and eosin as described previously (31). Samples were examined under a light microscope.

**Statistics—**Student’s t test was performed to examine the statistical significance of variations between groups. Data presented denote the mean ± S.E. of the results from separate groups.

**RESULTS**

**Characterization of the CAR and PXR Double Null Mice in Response to Xenobiotic Stimuli—**CAR and PXR have been suggested to play specific and overlapping roles in mediating both xenobiotic and endobiotic responses. Thus, we generated CAR\(^{-/-}\) and PXR\(^{-/-}\) double null mice, termed 2XENKO, to further delineate their functions in xenobiotic and endobiotic responses. The 2XENKO mice were generated by breeding previously described CAR and PXR single null mice (6, 7). As expected, they did not express either FXR or CAR transcripts (Fig. 1A). CAR expression was increased 2–3-fold in PXR single null mice, whereas there was no significant change of PXR mRNA levels in the CAR null mice.

The 2XENKO mice did not show any obvious developmental defects or other overt phenotypes and were fertile. As expected, however, they were completely defective in responses to certain broad spectrum xenobiotic inducers. The antifungal agent clotrimazole and the pesticide dieldrin have been shown to induce both CYP2B10 and CYP3A11 in several studies conducted in wild type and CAR\(^{-/-}\) and PXR\(^{-/-}\) single null mice (8, 10). As demonstrated in Fig. 1, B and C, 2XENKO mice showed no increase in CYP2B10 or CYP3A11 expression in response to either clotrimazole or dieldrin. However, the responses of CYP3A11 were retained in both CARKO and PXRKO single null mice.
knockouts, confirming that both receptors are capable of up-regulating CYP3A11 in response to either inducer, as previously suggested. In contrast, the responses of CYP2B10 were retained only in PXRKO mice, suggesting that CAR is responsible for CYP2B10 induction in response to clotrimazole or dieldrin.

Although CAR and PXR share both inducers (clotrimazole, dieldrin) and target genes (CYP2B10, CYP3A11), it is likely that they also have distinct functions. CAR has been found to mediate hepatotoxicity induced by acetaminophen (APAP), a widely used painkiller that can cause acute liver failure at high doses (31). To investigate whether PXR also contributes to APAP-induced toxicity, we administrated a single dose of 500 mg/kg APAP to wild type, CARKO, PXRKO, and 2XENKO mice. Serum ALT levels were measured as an index of liver toxicity. The CARKO mice showed significantly lower ALT levels than the wild type or PXRKO mice, and this decreased sensitivity was not affected by the additional loss of PXR in the 2XENKO animals (Fig. 1D). Thus, PXR does not contribute to the acetaminophen response mediated by CAR.

Zoxazolamine is both a muscle relaxant and a substrate of a number of cytochrome P450 enzymes (CYPs), and the duration of paralysis in response to a fixed dose of zoxazolamine is used as an indicator of CYP activity. After administration of 250 mg/kg zoxazolamine to wild type, CARKO, PXRKO, and 2XENKO mice, the CARKO animals showed a 3-fold increase in time paralyzed compared with wild type animals, which is consistent with previous results (7). Because CAR is inactive under basal circumstances, this suggests that zoxazolamine may activate CAR and thereby increase its own clearance. As expected, CAR target genes were specifically induced in zoxazolamine-treated wild type mice (data not shown). In contrast, PXRKO animals showed more than a 2-fold decrease in paralysis time, which is also similar to a previous report (2). This decrease is consistent with the increased expression of CAR in the PXRKO mice and indicates that PXR does not augment the protective role of CAR in response to zoxazolamine. The paralysis time in the 2XENKO animals was comparable with, but somewhat less than, that observed with the CARKO mice.

**CAR Activation Protects the Liver against LCA Toxicity**—PXR has been shown to act as an LCA sensor and accelerate LCA detoxification (1, 2), and we have recently found that expression of a VP16-CAR fusion confers resistance to LCA toxicity (30). To define the function of wild type CAR in protection against LCA-induced liver toxicity, we pretreated the wild type and CAR KO mice with or without the stable mouse CAR agonist TCPOBOP, which produces long-term CAR activation, followed by 5 days of treatment with a relatively high dose of LCA (250 mg/kg). The liver samples from LCA-treated wild type mice showed severe necrosis and highly elevated ALT levels, but this toxicity was essentially absent in TCPOBOP-treated wild type mice (Fig. 2, A and B). In contrast, the CAR KO mice all had severe liver toxicity and did not survive this treatment.

The known CAR target genes include a variety of Phase I- and Phase II-modifying enzymes and transporters. Some of the genes associated with LCA detoxification and transport, for example CYP3A11, MRP2 and MRP3, have been reported to be up-regulated by phenobarbital and TCPOBOP treatments (10–12, 31, 32). As expected, induction of these genes and also the recently identified CAR target STD (30) was lost in the CARKO mice. These data indicate that CAR activation can protect the liver against the toxic LCA via up-regulation of LCA detoxification enzymes and transporters.

**CARKO Mice Have Severe Defects in LCA Detoxification**—To define the relative roles of CAR and PXR in the toxicity of hydrophobic bile acids, CARKO, PXRKO, and 2XENKO mice were treated with LCA. Because the CARKO mice cannot survive the treatment used for the TCPOBOP protection assay, the LCA dose was decreased to 125 mg/kg. This resulted in only mild toxicity in the wild type mice, as demonstrated by liver histology and ALT levels (Fig. 3B). The CAR-KO and 2XENKO mice showed more severe toxicity than the PXRKO animals, as demonstrated by 2–3-fold higher ALT levels. Serum samples from CAR null and double null mice also showed highly elevated total bilirubin levels (Fig. 3C), which is consistent with the role of CAR in promoting bilirubin clearance.
showed only minor toxicity and no bilirubin elevation (data not shown). We therefore isolated total liver RNA from these mice for Northern blot analysis. As shown in Fig. 4A, CYP2B10 was induced in wild type and PXRKO mice, but not CAR mice, indicating CAR is activated upon LCA treatment. Among the genes associated with LCA detoxification, CYP3A11, MRP3, and OATP2 were all induced by LCA treatment in the wild type mice. OATP2 up-regulation was retained in CARKO and 2XENKO mice were also significantly higher than those in PXRKO (p<0.05). C, total serum bilirubin levels from the same treatment groups were measured. CARKO and 2XENKO had significantly higher total bilirubin levels compared with WT and PXRKO (p<0.01).

**DISCUSSION**

CAR and PXR direct overlapping responses to a wide range of potentially toxic xenobiotics and several toxic endobiotics. This functional overlap is due to the regulation of a number of common target genes in the liver, including cytochrome P450s such as CYP3A11 and CYP2B10 (in mouse), phase II enzymes such as UGT1A1, GSTs, and STD, and membrane transporters such as MDR1 and MRP2. This redundancy could allow each receptor to compensate for the loss of the other. Thus, it is essential to compare the single null mice not only to the wild type but also to the double knockouts to fully characterize the specific functional roles of the two xenosensors. It was anticipated that this might reveal shared basal functions not evident in the single knockouts. For example, because steroids are substrates for the CYP target genes, the 2XENKO mice might have shown infertility or other phenotypes as a consequence of defects in steroid homeostasis. However, no major changes were observed in basal expression of CYPs or other CAR and PXR target genes, and the 2XENKO mice showed no obvious reproductive, developmental, or metabolic phenotype. Although it is possible that more subtle phenotypes will emerge, these results indicate that CAR and PXR do not have critical roles in basal conditions but instead function primarily to mediate responses to both exogenous and endogenous chemical stresses.

The loss of both CAR and PXR has significant effects on responses to xenobiotics, particularly those that can activate both receptors. As expected, the residual responses to clotrima-
zole and dieldrin observed in the single CAR and PXR knockouts were completely absent in the double null mice. Comparisons of the single and double knockouts also provide insights into more physiologic functions. Thus, although potential effects of the loss of PXR on acetaminophen toxicity could have been masked by the presence of CAR in the PXRKO animals, the lack of a significant effect in the 2XENKO relative to the CARKO mice suggests that PXR does not have an important role in hepatotoxicity due to high doses of acetaminophen.

Previous results show that prior activation of either CAR or PXR strongly increases the rate of zoxazolamine clearance (6, 7). Interestingly, however, the two single knockouts show divergent responses to treatment with zoxazolamine alone. Based on the increased paralysis time in the CARKO animals, it is likely that CAR is required for induced expression of drug-metabolizing enzymes in response to zoxazolamine and that the increased basal expression of CAR contributes to the decreased paralysis time in the PXR null mice.

Prior activation of either PXR or CAR results in resistance to hepatotoxic effects of the hydrophobic bile acid LCA (1, 2, 30). The results described here confirm these conclusions and show that CAR also has an important protective role in the direct response to LCA alone. As previously reported (34), we have obtained no evidence that LCA or other bile acids are agonists ligands for CAR. Thus, the CAR-dependent responses of target genes such as CYP2B10, CYP3A11, and MRP3 to LCA must be because of the indirect translocation mechanism that accounts for CAR activation by a number of other compounds, including phenobarbital, acetaminophen, and bilirubin (12, 31, 35, 36).

It is remarkable that the addition of CAR increases to four the number of nuclear hormone receptors that respond to bile acids (1, 2, 19–21, 37). Thus, a class of compounds that until quite recently had no clearly defined signaling function is now second only to steroids in targeting nuclear hormone receptors. Particularly because recent results indicate that bile acids can also activate a variety of membrane-based signaling pathways (38–41), it is evident that their well known role in promoting absorption of dietary lipids is complemented by an unexpectedly broad range of important regulatory functions.

The functions of the four bile acid-activated nuclear receptors are distinct. FXR controls the production of bile acids in the liver and the flux of the primary and secondary bile acids through the liver and intestine (26). Vitamin D receptor appears to function mainly to protect the intestine against toxic bile acid metabolites such as LCA (37). Within the hepatocyte, CAR and PXR protect against hepatotoxic effects of toxic bile acids. This is consistent with the fact that both phenobarbital, an activator of both human CAR and PXR, and the human PXR agonist rifampicin have been used for decades to treat pruritis, which is a consequence of the elevated serum bile acids associated with intrahepatic cholestasis (42). However, the results described here suggest that CAR and PXR induce distinct responses to LCA. The CARKO mice are much more sensitive to the more chronic stress of 2 weeks of dietary LCA. The functions of the four bile acid-activated nuclear receptors result not only in distinct roles in specific responses but also provide a safe network to coordinately maintain liver function and metabolic homeostasis.

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J. Biol. Chem. 2004, 279:49517-49522.
doi: 10.1074/jbc.M409041200 originally published online September 8, 2004

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