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Inhibition of LXRα signaling by vitamin D receptor: Possible role of VDR in bile acid synthesis

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Abstract

The expression of cholesterol 7α-hydroxylase (CYP7α), the rate-limiting enzyme in the catabolism of cholesterol to bile acid, is stimulated by oxysterol receptor, liver X receptor α (LXRα) and negatively regulated by a bile acid receptor, farnesoid X receptor. In the current study, we demonstrated that 1,25-$(OH)_2$D3 blunted the LXRα-mediated induction of CYP7α mRNA in H4IIE rat hepatoma cells. In co-transfection experiments in HepG2 cells, VDR repressed the activity of rat CYP7α promoter in a ligand-dependent manner through inhibition of LXRα signaling. We also confirmed the ability of VDR to repress LXRα transcriptional activation using a synthetic LXRα responsive reporter. Deletion analyses revealed that the ligand-binding domain of VDR was required for the suppression and the DNA-binding domain was dispensable. Given the fact that VDR can be activated by the secondary bile acid as well as 1,25-$(OH)_2$D3, the crosstalk between LXRα and VDR signaling in regulation of bile acid metabolism provides a possible contribution of VDR to modulate bile acid and cholesterol homeostasis, and highlights a physiological function of VDR beyond calcium metabolism in the body.

Keywords: Vitamin D receptor; Liver X receptor; Cholesterol 7α-hydroxylase; 1,25-$(OH)_2$D3; Bile acid

Bile acids, the products of the catabolism of cholesterol, are synthesized in the liver and excreted into the intestine. Most of excreted bile acids are circulated back to the liver. The amounts of returning bile acids tightly control bile acid synthesis through a complicated regulatory loop involving multiple enzymatic activities [1,2]. Disruption of bile acid homeostasis might induce aberrant accumulation of bile acids, such as the secondary bile acid, lithocholic acid (LCA) that is known to cause diseases in the liver and intestine [3].

Cholesterol 7α-hydroxylase (CYP7α) is a key enzyme that catalyzes the first rate-limiting step in bile acid synthesis pathway. The expression of CYP7α is regulated by a variety of transcriptional factors including nuclear receptors [2,4]. The liver X receptor α (LXRα) functions as an oxysterol-activated transcriptional factor that modulates cholesterol absorption, transport, and elimination [5,6]. Recent studies showed that LXRα-null mice lost cholesterol-induced transcription of CYP7α gene and dramatically increased accumulation of cholesterol in the liver [7]. The LXR response element (LXRE) has been identified in the proximal CYP7α promoter, suggesting that LXRα directly mediates the induction of CYP7α gene [5]. On the other hand, farnesoid X receptor (FXR) is identified as a bile acid receptor that represses CYP7α expression coordinately with two nuclear receptors, short heterodimer partner (SHP) and the liver receptor homolog-1 (LRH-1) [8,9]. SHP is known as a nuclear receptor lacking a DNA-binding domain

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(DBD), which is capable of inhibiting the activities of other transcriptional factors [10]. LRH-1 is an orphan nuclear receptor that binds as a monomer to response element located within CYP7α promoter for inducing the expression of CYP7α [11]. It has been reported that bile acid-activated FXR induces the expression of SHP, which interacts with LRH-1 to decrease CYP7α expression [8,9,12]. Thus, FXR-SHP pathway is involved in a negative regulation of CYP7α transcription. However, the evidence from human and SHP-null mice showed the existence of alternative pathways for down-regulation of bile acid biosynthesis [13–15].

The vitamin D receptor (VDR) is also a member of nuclear receptor superfamily. Binding of 1,25-$(OH)_2$D3 promotes VDR to form heterodimer with retinoid X receptor (RXR) and transactivate the VDR responsive elements present in its target genes mainly involved in regulation of calcium and phosphorus absorption in the intestine and kidney [16]. In addition, recent studies showed that a cytochrome P450 enzyme, CYP3A, which catalyzes the metabolic conversion of LCA and xenobiotics is a target gene of VDR [17], indicating that VDR has additional physiological functions beyond calcium homeostasis. The secondary bile acids, LCA, and its metabolites have been identified as novel agonists for VDR [17,18], which raises a possibility of VDR to mediate bile acid metabolism.

In this paper, we demonstrated that VDR is able to target LXRα and antagonize its transcriptional activity on rat CYP7α gene. Moreover, the induction of antagonistic SHP is not required for the inhibition of CYP7α expression by VDR. These results outline a role of VDR and its agonists in the control of bile acid and cholesterol metabolism.

Materials and methods

Materials. Chenodeoxycholic acid and lithocholic acid were acquired from Sigma Chemical Co. (St. Louis, MO). TO-901317 was purchased from CAYMAN Chemical Company. 1,25-$(OH)_2$D3 was a kind gift by ChuGai Pharmaceutical Co. (Japan).

Plasmids. pCMX hLXRα, pCMX GaL4-LXRα-LBD, and TK-(LXRE)x3-Luc plasmids were kindly provided by Dr. D.J. Mangelsdorf.

VDR cDNA was generously provided by Dr. B.W. O'Malley and expressed under the control of CMV promoter. To create a DNA-binding defective mutant VDR, one base coding for a cysteine residue in P box of the DBD was substituted to phenylalanine (C66F) using QuikChange Multi Site-directed mutagenesis Kit (Stratagene, La Jolla, CA) [19]. The CYP7α luciferase reporter harbors 650 bp gene sequences of the proximal rat CYP7α promoter [12]. Correct sequences were confirmed by using ABI 310 Genetic Analyzer (Applied Biosystems).

Cell cultures and transient transfection assays. COS7 cells were cultured in DMEM containing 10% fetal bovine serum (FBS). Transfections were performed in 24-well plates by calcium phosphate co-precipitation method. Eight hours later, ligands were delivered to the cells. Cells were harvested after incubation for 24 h and analyzed for luciferase and β-galactosidase activities, respectively. HepG2 cells were grown in DMEM supplemented with 10% FBS. Plasmid DNA was introduced into HepG2 cells by using the FuGENE 6 (Roche Diagnostics, Indianapolis, IN). Cells were transfected overnight and then treated with corresponding ligands. After incubation for 24 h, luciferase activities were measured.

RNA isolation and real-time quantitative PCR. The H4IIE Cells were maintained for 24 h in DMEM containing 10% FBS in the absence or presence of corresponding ligands. Total RNA was extracted from cells by using RNeasy kit (Qiagen). First-strand cDNA was synthesized by MuLV reverse transcriptase with oligo(dT) primer using GeneAmp RNA PCR Core Kit (Roche, New Jersey).

A real-time PCR (SYBR Green) was applied to determine the mRNA expression by using ABI 7000 Sequence Detection system (Applied Biosystems). cDNA (10–20 ng) was used per reaction. The forward and reverse primers used for PCR were listed below. 5′-TGCCGGTACTA GACAGCATCA-3′ and 5′-TAGCTGTGCGGATATTCAAGGA-3′ for CYP7α (Accession No. J05460), 5′-GGAGTCTTTCTGGAGCCTT GAG-3′ and 5′-CCCAGTGAGCCTCCTGTTG-3′ for SHP (Accession No. NM-057133), 5′-TCACATTTACCGGCAAGTAGCA-3′ and 5′-GCGACTTCTGTGTTTGAGATG-3′ for LRH-1 (Accession No. NM-021742), and 5′-TGCCAAGTATGATGACATCAAGAAG-3′ and 5′-AGCCCAGGATGCCCTTTAGT-3′ for GAPDH (Accession No. NM-017008). Each reaction was carried out in triplicate samples. Data represent means ± SD. GAPDH was used for internal normalization.

Pull-down assays. The pull-down assays were performed as described previously [20]. The LBD coding regions of hVDR were cloned into pGEX-2TK vector to produce GST-VDR LBD in *Escherichia coli*. ^{35}S-labeled RXRα and LXRα were generated using TNT Quick Coupled Reticulocyte lysate system (Promega). The ^{35}S-labeled proteins were incubated with GST or GST-VDR LBD fusion proteins, which bound to glutathione–Sepharose beads, in the binding buffer [20 mM Tris–CI, pH 7.8, 0.1% Triton X-100, 100 mM NaCI, 10% glycerol, 1 mM dithiothreitol, 1 mM EDTA, 1 mM PMSF, and 0.1% protease inhibitor mixture (Roche)]. After incubation for 2 h at 4 °C in the absence or presence of 10^{-7}M 1,25-$(OH)_2$D3, the beads were extensively washed and the co-precipitated proteins were analyzed by SDS–PAGE and autoradiography.

Results

1,25-$(OH)_2$D3 decreased LXRα-dependent gene expression of CYP7α

To examine whether VDR could modulate bile acid metabolism, H4IIE cells were treated with 1,25-$(OH)_2$D3 in the absence or presence of LXRα agonist and tested for the ability of VDR on rat CYP7α gene expression. As shown in Fig. 1A, analysis of gene expression by quantitative PCR revealed robust activation of rat CYP7α gene by a LXRα agonist, TO-901317. The increment of CYP7α expression by TO-901317 was decreased in response to co-incubation with 1,25-$(OH)_2$D3 (Fig. 1A). Consistent with the previous reports, addition of FXR agonist, chenodeoxycholic acid (CDCA), resulted in a dramatic reduction of CYP7α expression (Fig. 1A) [9,21].

It has been known that SHP mediates the FXR-dependent down-regulation of CYP7α gene [12]. To evaluate the role of SHP in the repression of CYP7α transcription by 1,25-$(OH)_2$D3, the mRNA expression of SHP and LRH-1 was analyzed. As shown in Fig. 1B, treatment with 1,25-$(OH)_2$D3 did not stimulate the expression of SHP in H4IIE cells. While CDCA repressed the CYP7α expression, concomitant induction of SHP expression was observed in the CDCA treated cells (Fig. 1B), as reported [8,9,21]. Additionally, Fig. 1C shows that the expression of LRH-1 was unaffected by 1,25-$(OH)_2$D3. Thus, it is likely that induction of antagonistic SHP or alteration of LRH-1 expression is not involved in the inhibition of CYP7α gene by VDR.

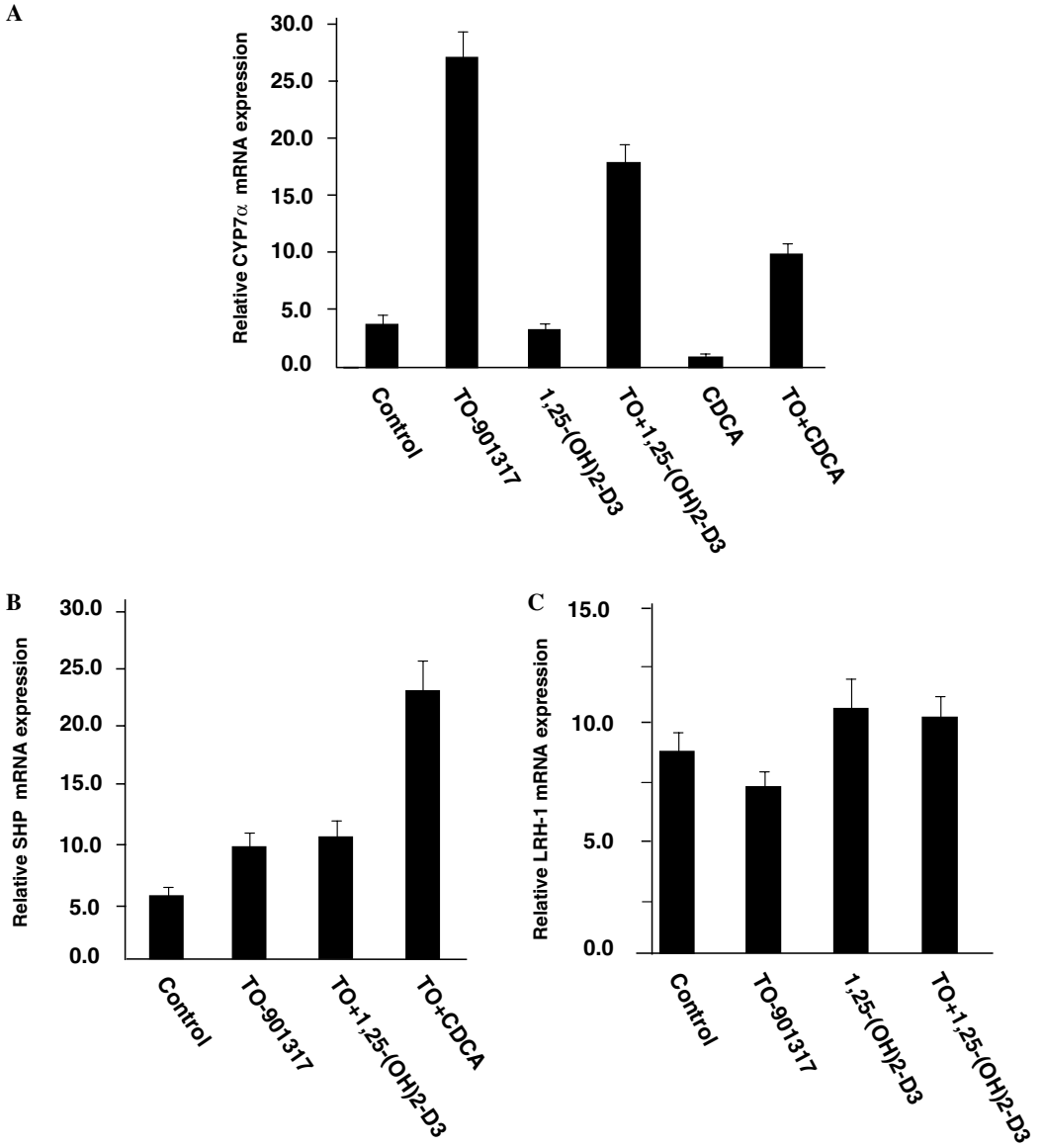

Fig. 1. 1,25-$(OH)_2$D3 decreased LXRα-induced gene expression of CYP7α. Total RNA was extracted from H4IIE cells treated with indicated ligands, 1.5×10^{-6} M TO-901317, 10^{-7} M 1,25-$(OH)_2$D3, and 5.0×10^{-5} M CDCA for 24 h. The expression levels of CYP7α (A), SHP (B), and LRH-1 (C) were analyzed by quantitative PCR and normalized with GAPDH. Results are given as means ± SD from two independent experiments with triplicate samples.

Activation of VDR blocks transcriptional activity of LXRα on rat CYP7α promoter

In order to clarify whether 1,25-$(OH)_2$D3 suppressed CYP7α expression at the transcriptional level, we tested the effect of 1,25-$(OH)_2$D3 on CYP7α promoter. The rat CYP7α promoter contains a functional LXRE and is activated by TO-901317 in HepG2 cells. Co-transfection of VDR expression plasmid slightly stimulated the CYP7α promoter activity induced by LXRα (Fig. 2A). However, treatment of the cells with 1,25-$(OH)_2$D3 in the presence of VDR efficiently repressed rat CYP7α promoter activity induced by LXRα and TO-901317 (Fig. 2A). We then treated HepG2 cells with LCA that has been reported to stimulate VDR. As observed in Fig. 2B, in the absence of VDR, LCA had a little effect on CYP7α reporter activity. While in the presence of VDR, LCA repressed the LXRα stimulated reporter activity (Fig. 2B), which was similar to that shown in Fig. 2A. Taken together, these results suggest that VDR could down-regulate rat CYP7α promoter in the presence of VDR agonists.

Specific DNA-binding of VDR is not required to inhibit LXRα signaling

To understand the mechanism underlying the inhibition of CYP7α promoter by VDR, we examined the effect of VDR on a synthetic LXRα responsive reporter, TK-(LXRE)x3-Luc, that contains three tandem repeats of LXRE derived from the mouse mammary tumor virus LTR [22]. As shown in Fig. 3A, co-transfection with increasing amounts of VDR plasmid resulted in a dose-

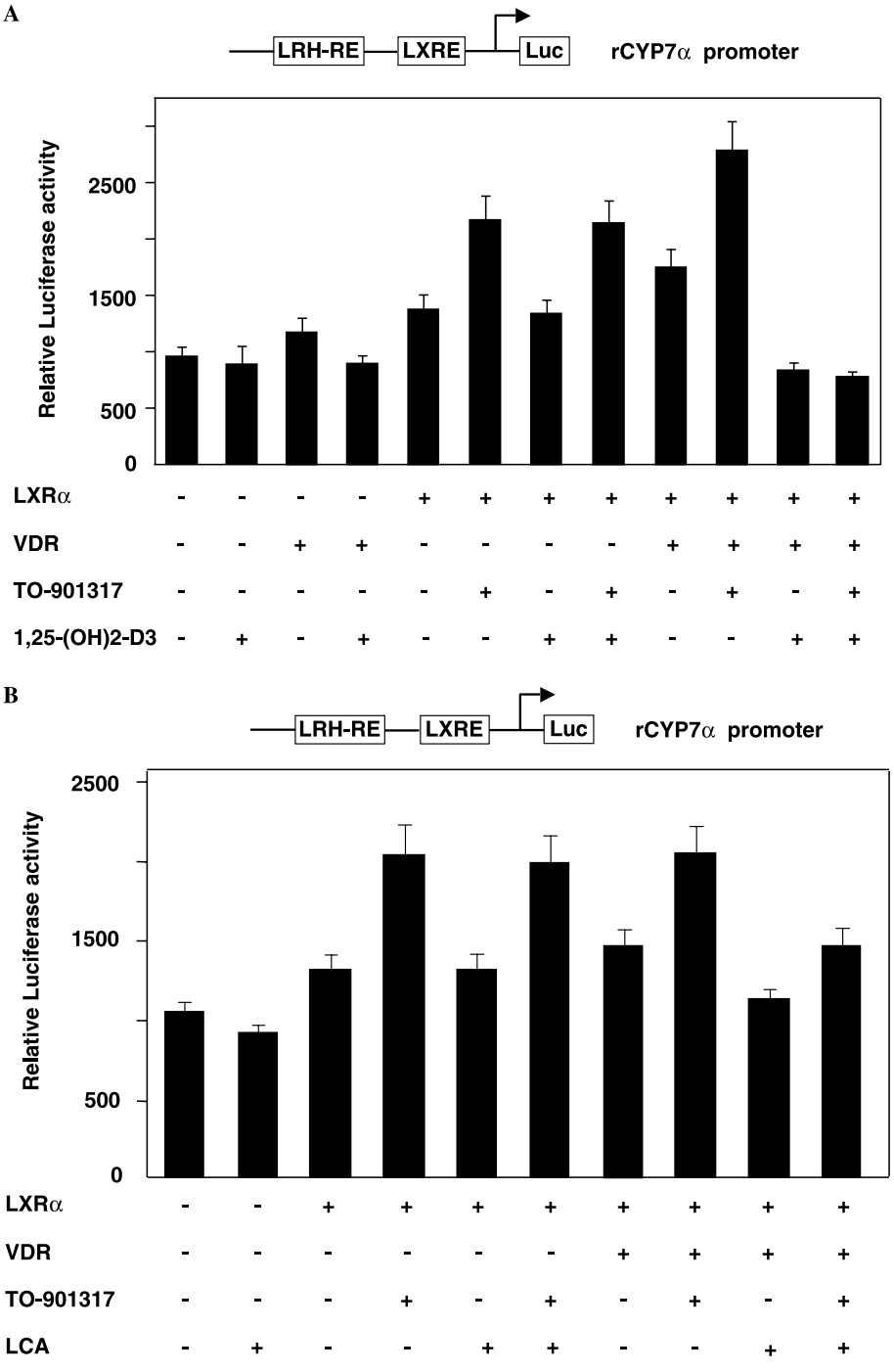

Fig. 2. VDR inhibited the LXRα transactivation on rat CYP7α promoter. (A) VDR repressed LXRα-mediated transactivation in the presence of 1,25-$(OH)_2$D3. HepG2 cells were transfected with 50 ng/well pCMX LXRα, 25 ng/well pCMV VDR, and 100 ng/well rCYP7α-luc gene. Cells were treated with DMSO vehicle, or 10^{-7} M 1,25-$(OH)_2$D3 and/or 1.5×10^{-6} M TO-901317 for 24 h. (B) VDR repressed LXRα-mediated transactivation in the presence of LCA. The transfections were performed using the similar protocol as (A). VDR was activated by 5.0×10^{-5} M LCA instead of 1,25-$(OH)_2$D3. The results are given as means ± SD of three independent experiments.

dependent inhibition of TO-901317-induced LXRα activity on TK-(LXRE)x3-Luc reporter (Fig. 3A). The inhibition of LXRα transcription by VDR was also observed when LXRα was activated by naturally occurring LXRα agonists, 22(*S*)-hydroxycholesterol or 25-hydroxycholesterol (data not shown). In a manner similar to that observed in 1,25-$(OH)_2$D3, LCA dose-dependently suppressed the TK-(LXRE)x3-Luc activity stimulated by TO-901317, despite its weaker response than 1,25-$(OH)_2$D3 (Fig. 3B). In control experiments, VDR and 1,25-$(OH)_2$D3 did not alter the transcriptional activity of TK promoter in the absence of LXRE (data not shown). These observations

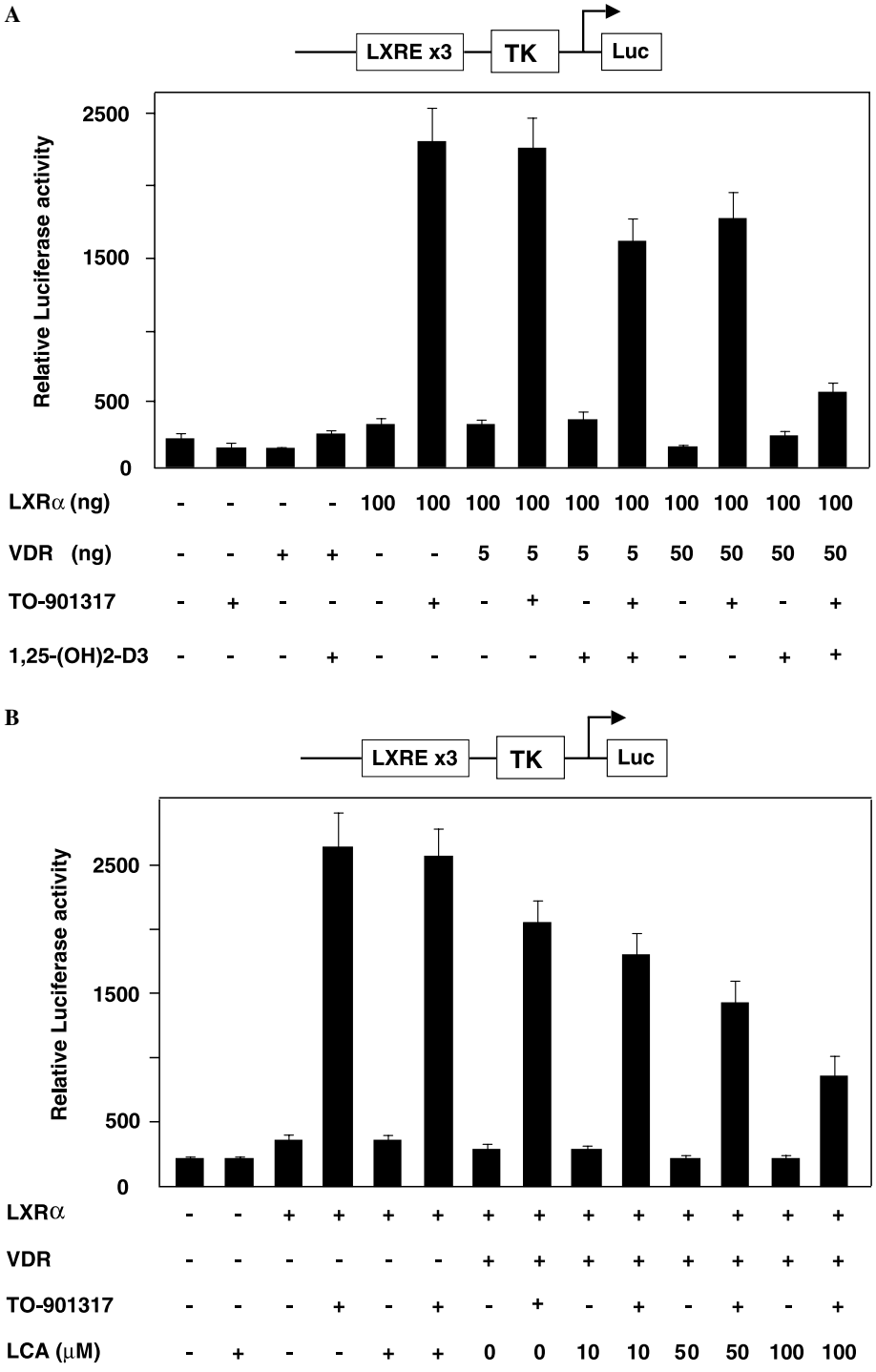

Fig. 3. VDR repressed the LXRα activity on a synthetic LXR responsive reporter. (A) Increasing amounts of VDR plasmid suppressed the ability of LXRα on TK-(LXRE)x3-Luc reporter. COS7 cells were transfected with 100 ng/well pCMX LXRα, 5–50 ng/well pCMV VDR plasmids. The reporter activities were measured after incubation with indicated ligands for 24 h. (B) VDR repressed the transcriptional activity of LXRα in a LCA dose-dependent manner. Cells were transfected with 150 ng/well TK-(LXRE)x3-Luc gene, 100 ng/well pCMX LXRα, 50 ng/well pCMV VDR expression plasmids. Cells were treated with various concentrations of LCA (1.0×10^{-5} to 1.0×10^{-4} M). The data shown as means ± SD are from three independent experiments.

suggest that VDR inhibits CYP7α promoter by antagonizing the action of LXRα.

To further investigate the repression by VDR, we introduced the mutation at the first zinc-finger of DBD to destroy the DNA-binding ability of VDR and performed the transient transfection assays. As shown in Fig. 4A, co-transfection of VDR-DBD mutant still suppressed the transcriptional activity of LXRα on TK-(LXRE)x3-Luc reporter in COS cells. The similar results were also seen with rat CYP7α promoter in the presence of VDR-DBD

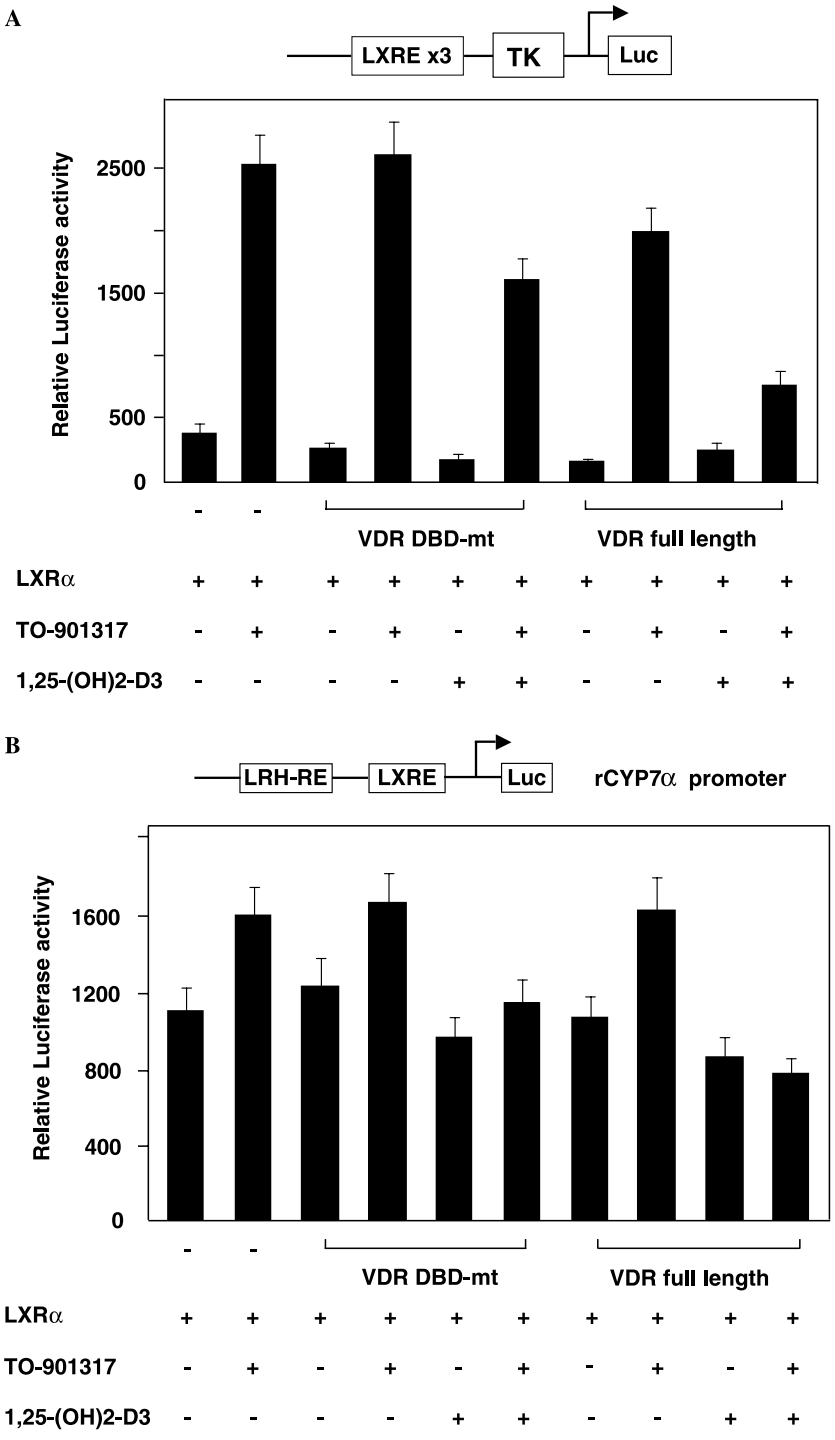

Fig. 4. The DNA-binding of VDR is not required to repress LXRα activity. (A) The DBD mutant of VDR repressed the TK-(LXRE)x3-Luc activity. COS7 cells were transfected with 100 ng/well pCMX LXRα and 50 ng/well VDR plasmids. (B) HepG2 cells were transfected with rat CYP7α promoter reporter and VDR expression plasmid. Cells were treated with vehicle or 10^{-7} M 1,25-$(OH)_2$D3. (C) COS7 cells were transfected with TK-(UASx3)-Luc gene, 100 ng/well GaL4-LXRα-LBD, and 100 ng/well pCMV VDR expression plasmids. Cells were treated with 1.5×10^{-6} M TO-901317 or/and 10^{-7} M 1,25-$(OH)_2$D3 for 24 h. The data represent means ± SD from two independent studies with triplicate samples. (D) VDR directly interacted with LXRα in pulldown assays. Radiolabeled LXRα and RXRα were produced by in vitro transcription/translation system and incubated with GST-VDR LBD or GST in the absence or presence of 10^{-7} M 1,25-$(OH)_2$D3.

mutant and 1,25-$(OH)_2$D3 in HepG2 cells (Fig. 4B). It is likely that the DNA-binding ability of VDR is not necessary for VDR-dependent inhibition of LXRα signaling. We next tested whether VDR could suppress the activity of GaL4-LXRα-LBD. Fig. 4C shows that GaL4-LXRα-LBD-activated UAS-luciferase reporter in the presence of TO-901317. This activation was suppressed by overexpression of VDR, and the suppression was enhanced by

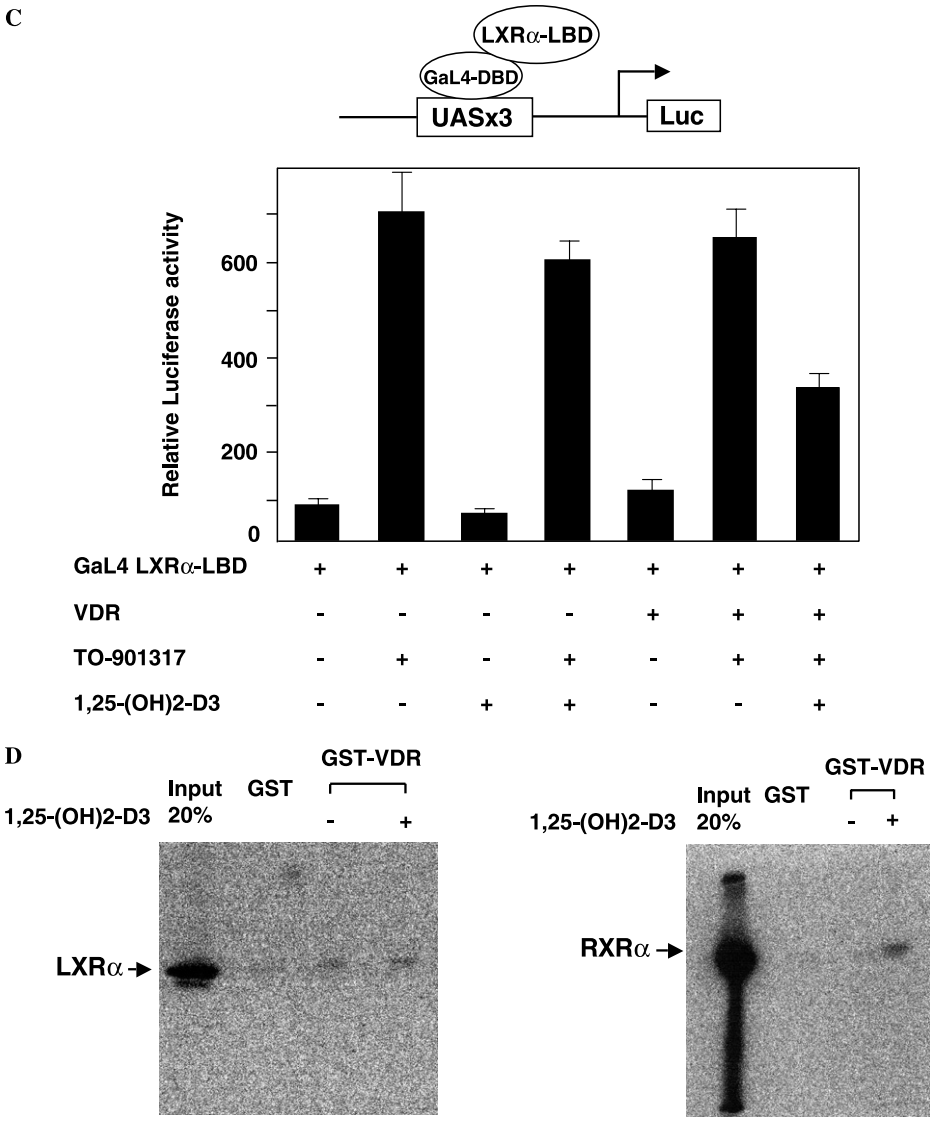

Fig. 4 (*continued*)

addition of 1,25-$(OH)_2$D3 (Fig. 4C). Collectively, these data indicated that the competitive binding to a response element by VDR is not involved in the crosstalk between VDR and LXRα signaling.

Discussion

Multiple genetic transcriptional factors have been linked to cholesterol and bile acid homeostasis through regulating CYP7α gene transcription [2,8,23]. In this paper, we demonstrate that VDR could repress rat CYP7α expression through inhibiting the LXRα transcriptional activity. One possible mechanism underlying down-regulation of CYP7α gene by VDR may account for the crosstalk between LXRα and VDR. In this study, we showed that VDR possesses the ability to repress LXRα transactivation on the LXRE reporter in the presence of 1,25-$(OH)_2$D3 or LCA, suggesting that the inhibition of CYP7α promoter by VDR is mediated at least in part through crosstalk between LXRα and VDR signaling pathways. Interestingly, introduction of mutation at the DBD of VDR does not impair the repressive effect of VDR, indicating that specific DNA-binding to a response element is not required for this transrepression. It has been reported that the crosstalk between nuclear receptors may occur via sequestration of common nuclear receptor partner RXR [24]. Like other nuclear receptors that include thyroid hormone receptor, peroxisome proliferator-activated receptor, both VDR and LXRα form heterodimer with RXR to recognize the receptor response elements within target genes. However, we found that co-transfection of increasing amounts of RXRα did not restore the inhibition by VDR (data not shown), suggesting the repression by VDR might not be due to the titration of limited amounts of RXR. We examined a possible interaction between VDR and LXRα. The direct interaction between LXRα and the LBD of VDR was observed in pulldown assays (Fig. 4D). Physical interaction between VDR and LXRα might be involved in the

repression by VDR. Collectively, these observations point out a possibility for controlling intracellular signaling pathways by VDR, which is different from classical transactivation by nuclear receptors [25].

The feed-back control of bile acid production has been reported to be through FXR-SHP-LRH-1 nuclear receptor cascade. Nevertheless, disruption of SHP gene in mice showed the existence of SHP-independent regulation of CYP7α expression by bile acids. To date, the SHP-independent regulatory pathways that involved pregnane X receptor (PXR), constitutive androstane receptor (CAR), and the c-Jun-N-terminal kinase (JNK) mitogen-activated protein kinase were confirmed [13,14,26]. In the present study, we demonstrate that VDR could down-regulate the transcription of rat CYP7α gene. The suppression is mediated through a pathway, in which neither SHP nor LRH-1 is involved. It has been shown that the expression of CYP3A4, CYP2B6, and CYP2C9 is mediated by VDR in primary hepatocytes, in a manner similar to that observed in PXR and CAR [17,27]. PXR and CAR were recently identified as bile acid receptors with specificity relative to LCA and provided the hepatic defense to maintain bile acid and cholesterol homeostasis [13,26]. Moreover, it is known that the structure of VDR is similar to those of PXR and CAR with a high degree [28]. These results suggest that like PXR and CAR, VDR might have a protective function from bile acid toxicity in vivo.

In this paper, we demonstrated the negative regulation of LXRE by VDR. The crosstalk between VDR and LXR signaling pathways might provide the potential of VDR to mediate cholesterol and bile acid metabolism. Continued evaluation of role of VDR in bile acid homeostasis awaits further investigation.

Acknowledgments

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