Inhibition of the Transcription of CYP1A1 Gene by the Upstream Stimulatory Factor 1 in Rabbits

COMPETITIVE BINDING OF USF1 WITH AhR-Arnt COMPLEX

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A xenobiotic-responsive element (XRE)-binding factor(s) other than the AhR-Arnt complex was found to inhibit the transcription of CYP1A1 gene in the liver from adult rabbits, known to be nonresponsive to CYP1A1 inducers. The constitutive factor(s) in liver nuclear extracts bound to the core sequence of XRE. The binding was eliminated by the presence of an excess amount of the AhR-Arnt complex synthesized in vitro. To identify the constitutive factor(s), a sequence similar to rabbit XRE was sought. It was found that the sequence of rabbit XRE overlapped with that of the upstream stimulatory factor 1 (USF1)-binding site in the mouse metallothionein I promoter. In fact, a super shift assay using a specific antibody against human USF1 indicated that USF1 was capable of binding to rabbit XRE. Additionally, the AhR-Arnt-mediated activation of XRE-TK/Luc reporter gene in RK13 cells was blocked by the transfection with a USF1 expression vector with the amounts of the expression vector transfected. These results indicate that the XRE of the rabbit CYP1A1 gene is recognized by the basic helix-loop-helix proteins to regulate the expression of CYP1A1 in both an agonistic (AhR-Arnt) and an antagonistic (USF1) manner.

CYP1A1 is the microsomal enzyme responsible for the bioactivation of carcinoogenic compounds such as benzo(a)pyrene (1) and is known to be induced by halogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polycyclic aromatic hydrocarbons including MC (2, 3). However, the induction of CYP1A1 by MC occurs only in neonatal but not in adult rabbits (4–7). To date, this mechanism seen in rabbits has not been clarified despite its significance in toxicology.

The activation of CYP1A1 gene by aryl hydrocarbons is mediated by a soluble protein designated as AhR (8). Prior to the binding with such an inducer, AhR exists in the cytoplasm as part of a complex that has a molecular mass of about 280 kDa. This complex is comprised of AhR, two molecules of the 90-kDa heat shock protein (Hsp90), and possibly other proteins (9–12). After binding with a ligand, AhR dissociates from the above complex and translocates to the nucleus where it heterodimerizes with Arnt (13, 14). The heterodimer AhR-Arnt complex binds to several copies of short sequences, termed XREs, located within the 5′-flanking region of CYP1A1 gene to stimulate the synthesis of CYP1A1 protein and several other proteins involved in xenobiotic metabolism (15–18). Thus, the induction of CYP1A1 is regulated exclusively at the transcriptional level (19, 20).

AhR and Arnt proteins have two domains necessary for the TCDD-induced activation of CYP1A1 gene. One of the two domains is the Per-Arnt-Sim region composed of approximately 300 amino acids that mediates the ligand binding and interaction with Hsp90. This region is also found in the Drosophila regulatory proteins Per and Sim (21) and the mammalian hypoxia-inducible factor 1α (22). The other is a bHLH motif essential to the DNA binding and the dimerization of AhR and Arnt toward their amino termini (23, 24).

The bHLH motif has been seen in common in a number of transcriptional factors. Most transcriptional factors such as Max, USF1, MyoD, and E47 contain bHLH motif and bind as dimers to the specific DNA sequence (CACGTG), termed E-box (25–28). Recently, it has been reported that Arnt constitutively binds as a homodimer to the E-box motif of AdMLP (29, 30). On the other hand, the AhR-Arnt heterodimer recognizes an asymmetrical XRE sequence that only partially resembles the E-box. The consensus sequence of XRE has been identified as 5′-G/GNGCGTG(A/C)(G/C)(A/T)-3′ (31–33). Four core nucleotides (5′-CGTG-3′) within XRE are absolutely required for the binding with AhR-Arnt heterodimer. Arnt binds to the thymidine in the 5′-CGTG-3′ core identical to an E-box half site (GTG), whereas AhR binds to 5′ proximal to the 5′-CGTG-3′ core in the XRE (34). In the present study, we found USF1 to be an additional factor capable of binding to the rabbit XRE to inhibit the interaction of the AhR-Arnt complex with XRE in rabbits.

MATERIALS AND METHODS

Isolation of the 5′-Flanking Region of Rabbit CYP1A1 Gene—To isolate the 5′-flanking region of rabbit CYP1A1 gene (35), a gene library prepared from the rabbit DNA cleaved by EcoRI and cloned into λZAPII vector (Stratagene, La Jolla, CA) was screened with a 32P-labeled CYP1A1 cDNA as a probe (36). By screening about 1.1 × 105 plaques, we obtained a genomic clone (pBK4.5k) containing the 5′-flanking region of rabbit CYP1A1 gene and mapped for further studies.

Construction of Reporter and Expression Plasmids—Fusion genes with various external deletions were constructed as follows. The pBK4.5k was treated with exonuclease III after cleavage with SauI and

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BamHI. The digested plasmids were treated with T4 DNA ligase and then introduced into Escherichia coli TG1 to yield intermediate plasmids. These intermediate plasmids were cleaved with KpnI and HindIII to shorten them and to obtain the various lengths of 5′-flanking sequences. The fragments were inserted into the unique KpnI-HindIII site of pSH-2 (Stratagene), a rabbit nuclear extract plasmid described above, antibodies were added to the reaction mixtures and incubated for 1 h at 4 °C. The products were then analyzed by a gel shift assay.

Cell Culture and Transient Transfection—Rabbit kidney RK13 cells were grown in a minimal essential medium containing fetal calf serum (10%) and nonessential amino acids (42). Reporter and expression construct were introduced into the cultured cells by a modification of the calcium phosphate coprecipitation procedure (43). After exposure for 16 h, the DNA-containing culture medium was removed. The cells were washed with a minimal essential medium and then exposed to a culture medium with either 1 μM MC or the equivalent volume of Me2SO (0.1% (v/v) at final concentration as a control). After another 38 h, the cells were washed with phosphate-buffered saline (0.15 μM NaCl) and then lysed. Insoluble materials were removed by centrifugation. A luciferase activity was determined using Lumat LB9501 luminometer (Berthold, Tokyo, Japan). β-Galactosidase activity was determined as described (43). Each luciferase activity was corrected by β-galactosidase activity.

RESULTS

Analysis of Sequences in an Upstream Region Responsible for the Induction of Rabbit CYP1A1 in RK13 Cells—To identify possible regions responsible for the MC-induced expression of rabbit CYP1A1 gene, 5′ deletion mutants were constructed as shown in Fig. 1A. These plasmids were transfected into rabbit kidney RK13 cells to show the inducibility of CYP1A1 by some inducers (data not shown). The cells were then exposed to MC. The maximal MC-induced activity was seen in the cells transfected with LucI.6. The activity decreased with progressive deletions starting from −1.6 kb of rabbit CYP1A1 gene. The luciferase activity was significantly decreased by the deletion of the sequences between nucleotides −1.06 and −0.95 kb, −0.95 and −0.83 kb, and −0.68 and −0.45 kb from the transcription start sites. These results indicate that at least three regions containing essential XREs are responsible for the induction of rabbit CYP1A1 gene. Deletions to −1.28 kb resulted in an approximately 55% decrease in a constitutive expression, whereas further deletions to −0.18 kb decreased to about 5%. Comparing the sequences of possible XREs in the 5′-flanking region of rabbit CYP1A1 gene up to −1.4 kb with the consensus sequence (Fig. 1B) reported so far, XRE3, XRE4, and XRE5 were found to be identical with the reported consensus sequence (31–33). However, other XREs possessed the replacement of some nucleotides from the consensus sequence. To analyze the specificity of AhR-Arnt to bind to the XREs, a competition analysis was carried out (Fig. 1C). The specific binding of AhR-Arnt disappeared when a 150-fold molar excess of an unlabeled probe (XRE3, XRE4, or XRE5) was added. Thus, we focused on the XREs that possibly regulate the CYP1A1 induction by MC in RK13 cells.

Constitutive Binding to Functional XRE—We found a constitutive factor(s) in rabbit liver nuclear extracts that bound to XRE3 and XRE5. Thus, the amounts of the constitutive factor(s) present in the nuclear extracts from neonatal livers were compared with those from adult livers (Fig. 2). The binding of a liver-specific transcriptional factor HNF4 (44) was monitored as a control. The amount of the constitutive factor(s) bound to XRE3 and XRE5 was greater in the nuclear extracts from adult rabbit livers than neonatal rabbit livers. No shifted bands were observed when the nuclear extracts from neonatal and adult livers were added to XRE4 used as a probe.

Competition between the Constitutive Factor(s) and the AhR-Arnt Complex to Bind to the XRE—As a first step to prove our idea that the unknown XRE-binding factor(s) in the nuclear extracts from adult rabbit livers bound to XRE to compete with
the AhR-Arnt complex, we examined the possibility that the constitutive factor(s) recognized the core sequence of XRE. As shown in Fig. 3A, the factor(s) did not bind to a XRE possessing a mutation, indicating that the core sequence of XRE was specifically recognized by the constitutive factor(s). Additionally, the shifted band disappeared when a 300-fold molar excess of a nucleotide with a consensus sequence (CANNTG) was added, supporting the idea that this constitutive factor(s) be-

**Fig. 1. Regulatory DNA elements in the 5′-flanking region of rabbit CYP1A1 gene.** A, structure and transcriptional activity of 5′ deletion mutants in the 5′-flanking region of CYP1A1 gene. The construction of deletion mutants is described under “Materials and Methods.” The numbers given to deletion plasmids indicate the 5′-ends of the 5′-flanking sequence of rabbit CYP1A1 gene counted negatively from the transcriptional start site. The XRE most distant from the mRNA start site was defined as XRE1. The extent of induction by MC is shown as the ratio of the induced to the uninduced activity. The position of the XRE most distant from XRE6 is shown by a vertical arrow. All values represent the means ± S.D. with the number of independent experiments shown in parentheses. The data are expressed as a percentage of the basal activity obtained with Luc4.5. B, alignment of possible XREs found in the 5′-flanking region of rabbit CYP1A1 gene. The sequence of the rabbit XRE was compared with that of consensus sequences identified in the CYP1A1 gene reported so far (31–33). The numbers given to XREs indicate the position of the nucleotide counted negatively from the transcriptional initiation site. C, competition analysis with various XREs. A synthetic XRE4 was used as a labeled probe. Rabbit AhR and Arnt proteins produced by in vitro translation were incubated in the presence of 1 μM MC, followed by gel shift assay as described under “Materials and Methods.” The arrow indicates the AhR-Arnt XRE4 complex. A competitor DNA was added at 75- or 150-fold molar excess of the probe XRE4 DNA. The elimination of the shifted band by the addition of a 150-fold molar excess of XRE3, XRE4, or XRE5 demonstrates the specificity of the complex. Mutant XRE used as a competitor is as follows: XRE4 mu, 5′-CGCCCAGGTTGAGAAGGGCTTGGA-3′ and 3′-GCGGGTCCTCAACTAACTCTTCCCGAACCT-5′. To prove the specificity of AhR-Arnt heterodimer, a 150-fold molar excess of XRE4 mutant was added.
rabbit AhR and Arnt proteins were incubated in the presence of 1 mM menadione, the binding activity of HNF4 was determined in neonatal and adult rabbit livers by competition with the AhR-Arnt complex and the constitutive factor(s) bound to rabbit XREs. As a control experiment, the binding activity of HNF4 was determined in neonatal and adult rabbit livers by competition with the AhR-Arnt complex. The DNA binding of the AhR-Arnt heterodimer to bind to XRE3 was decreased by the addition of the constitutive factor(s). When nuclear extracts from adult rabbit livers were added, the super shifted band corresponding to the constitutive factor(s) appeared, indicating that a factor(s) other than the AhR-Arnt complex recognized the core sequence of XRE. The binding of AhR-Arnt heterodimer to XRE disappeared when the antibodies against human AhR were added. Although antibodies to human AhR inhibited the heterodimerization of AhR with Arnt, antibodies to human Arnt did not inhibit the formation of the AhR-Arnt complex (30). Thus, a super shifted band was detected by the presence of the antibodies against human Arnt.

Similarity of the Recognition Sites of AhR-Arnt Complex and USF1—We found that the sequence of rabbit XRE3 was similar to that of the USF1-binding site (Fig. 6). The USF1-binding site was originally identified as the E-box motif (CAGCTG) of AdMLP (45). This site was also found in human growth hormone (46), mouse metallothionein I (47), rat γ-fibrinogen (48), and Xenopus TFIIA genes (49), although some nucleotides in the binding site of USF1 identified in a variety of cellular and viral promoters differed from those in the E-box motif (50). It is of particular interest to note that the sequence of rabbit XRE3 is identical to that of the USF1-binding site (CGCGTGAC) in the mouse metallothionein I promoter.

Binding of USF1 to XRE3 in the Rabbit CYP1A1 Gene—To determine if USF1 could bind to XRE3, we performed a competition assay using an E-box motif of AdMLP as a competitor. When nuclear extracts from adult rabbit livers were added, the formation of the complex with XRE3 was abolished by the presence of a 50-fold molar excess of the unlabeled AdMLP (Fig. 7A). Super shift bands were detectable with antibodies against USF1, although the amounts of super shift bands varied depending on the probe (Fig. 7B). To further prove the specific binding of USF1 with XRE3, USF1 was expressed in RK13 cells by transfection of the expression plasmid USF-SRα into the cells. Nuclear extracts prepared from the cells were applied to a gel shift assay. Consequently, a specific band appeared only when nuclear extracts from USF1-transfected cells were applied. Antibodies against USF1 recognized the super shifted band. This antibody-bound band exhibited a further retarded mobility in the polyacrylamide gel (Fig. 7C).

Suppression of the MC-induced Expression of CYP1A1 by USF1—To determine the functional consequences of the interaction of USF1 with XRE3 of rabbit CYP1A1 gene, the expression plasmid carrying USF1 was cotransfected to RK13 cells with the expression vectors for AhR and Arnt in addition to the XRE-TK/Luc or TK/Luc. Relative to pUC-SRα-transfected or nontransfected cells, the transfection of AhR- and Arnt-SRα together with XRE-TK/Luc resulted in a 2-fold increase in...
basal expression in the absence of MC. USF1 inhibited the transactivation of XRE-TK/Luc reporter gene by the AhR complex and MC (Fig. 8B). Relative to the maximum induction observed with the absence of USF-SRα (16 ± 1-fold), the down-regulation observed with USF-SRα (2 µg) (9.5 ± 0.3-fold) and USF-SRα (4 µg) (6.1 ± 0.2-fold) was significant with p values all equal to <0.0001 but not with USF-SRα (1 µg) (14 ± 1-fold) with p value of >0.05. The increasing amounts of the USF-SRα expression vector did not affect basal expression. However, the transfection of USF-SRα (>5 µg) enhanced the basal activity of XRE-TK/Luc gene (data not shown). The co-transfection of RK13 cells with the USF1 expression vector together with Luc 1.28 reporter plasmid inhibited the induction by MC by 39% (data not shown). These results indicate that USF1 depresses the induction of CYP1A1 by MC in rabbit livers by competing XRE3 with the AhR-Arnt complex.

**DISCUSSION**

The induction of CYP1A1 by MC occurs only in neonatal and not in adult rabbits, probably resulting in low susceptibility to carcinogens (4–7). However, the mechanism(s) involved in the nonresponsive nature of rabbits to such an inducer in rabbits has not been clarified despite its significance in toxicology. Our hypothesis to account for this phenomenon is that bHLH proteins in addition to the AhR complex are capable of recognizing the core sequence of XRE and that a factor(s) that binds to XRE inhibits the induction of CYP1A1 by MC in adult rabbits. To examine this idea, we performed a gel shift assay using nuclear extracts from adult rabbit livers as a competitor to the binding of the AhR-Arnt complex with XRE3 and found a constitutive factor(s) that inhibited the binding as expected.

Scatchard plots showed that the binding affinity of the factor(s) for XRE3 was similar to that of the AhR-Arnt complex (Fig. 4). In fact, the binding of the AhR-Arnt complex to XRE3 was not observed even after treatment of adult rabbits with
Fig. 7. Binding of USF1 to XRE3. A, competition between a constitutive factor(s) and AdMLP to bind to XRE3. A 32P-labeled double-stranded XRE3 fragment was incubated with 10 μg of nuclear extracts from adult rabbit livers in the presence of a 50-, 100-, and 150-fold molar excess amount of AdMLP at 25 °C for 1 h. The arrow indicates the complex of a constitutive factor(s) with XRE3. B, super shift assay using antibodies to USF1. A 32P-labeled double-stranded XRE3 or AdMLP was incubated with nuclear extracts from adult rabbit livers in the absence or the presence of antibody against human USF1 as described under “Materials and Methods.” The arrow indicates the super shifted band of USF1. C, binding of human USF1 expressed in RK13 cells to XRE3. Nuclear extracts from RK13 cells transfected with USF1-SRα were prepared essentially as described by Dignam et al. (41). A 32P-labeled double-stranded XRE3 was incubated with 10 μg of the nuclear extracts from RK13 cells at 25 °C for 1 h. The specificity of the binding of USF1 was determined by super shift assay as described under “Materials and Methods.” The arrow indicates the complex of human USF1 with XRE3.

MC. Alternatively, the constitutive factor(s) bound to XRE3 (data not shown). Recently, we reported that there was a lesser amount of Arnt mRNA in rabbit livers than in extrahepatic tissues (7). Thus, it is possible that the amount of Arnt limits the amount of the AhR-Arnt complex, leading to the low level of induction of CYP1A1. These results indicate that the interaction of a constitutive factor(s) with XRE3 occurs predominantly in the livers from MC-treated rabbits, accounting for the known fact that the induction by MC does not occur in adult rabbits.

A computer search was performed to find a sequence(s) similar to XRE3 in the rabbit CYP1A1 gene. The sequence of rabbit XRE3 was highly homologous to that of USF1-binding sites (Fig. 6). The presence of the conserved sequences has been reported in AdMLP (45), human growth hormone (46), mouse metallothionein I (47), rat γ-fibrinogen (48), and Xenopus TFIIBA genes (49). Particularly, the sequences of XRE3 and XRE5 were identical to the USF1-binding site of mouse metallothionein I promoter (CCCGTG) (Fig. 6). The existence of the XRE core sequence (CCCGTG) allowed us to predict that rabbit CYP1A1 gene is regulated in a positive (AhR-Arnt) and a negative (USF1) manner through the overlapped XRE sequence. Interestingly, the portion of XRE sequence identical with that of USF1 sequence was conserved in humans but not in rats and mice known to be highly responsive to aromatic hydrocarbons (34, 51, 52). Unlike the rabbit CYP1A1 gene, the binding site of USF1 was not found in the possible XRE sequences in the 5′-flanking region of rabbit CYP1A2 gene (35). CYP1A2 is known to be induced by TCDD in both neonatal and adult rabbit livers (35).

Our super shift assay indicated that one of the constitutive factor(s) was USF1, a bHLH protein (Fig. 5). However, the E-box motif is reported to be recognized by a number of bHLH proteins such as USF2, Max, MyoD, and E47 (25–28, 53, 54). This suggests that a factor(s) in addition to USF1 also binds to the core sequence of XRE3. In fact, only some of the bands were super shifted by antibodies to USF1 when XRE3 and AdMLP were used as probes. Similar to the binding shown in the present study, the factor(s) constitutively bound to XRE has been found in human keratinocytes (55) and human fibroblasts (56). It has also been reported that an additional XRE-binding factor was detectable only in the presence of TCDD (17). Because these findings were obtained with XREs that did not contain the binding site of USF1 within the core sequence, the constitutive factor (USF1) found in the present study was distinct from the above factors. Recently, it has been reported that AhR2 negatively regulates the MC-induced expression of CYP1A1 gene by blocking the heterodimerization of AhR with Arnt or competing with the AhR-Arnt complex on the same binding site (57). Thus, a factor such as AhR2 may also contribute to the negative regulation of the induction of CYP1A1 in rabbits.

To date, the mechanism responsible for the suppression of the induction of CYP1A1 has been widely discussed. A negative regulatory element has been found in the 5′-flanking region of human CYP1A1 gene (58–61). An unknown factor(s) in HepG2 cells bound to a 21-base pair palindrome in the human CYP1A1 gene, resulting in the negative regulation of the enhancement of the transcription of CYP1A1 gene by TCDD. Because the negative regulatory element was not present in the upstream region of rabbit CYP1A1 gene, the incapability of adult rabbits to induce CYP1A1 must be caused by the negative regulatory element-binding factor(s).

In the present study, we showed that USF1 bound to XRE3 to compete with the AhR-Arnt complex in the rabbit CYP1A1 gene. Because the sequence of XRE3 in the rabbit, to which USF1 bound, was not present in the 5′-upstream region of rat and mouse CYP1A1 gene, the inhibition of the induction by
USF1 may not occur in the rat and mouse. This regulation of CYP1A1 expression may account, at least in part, for the species differences in chemical carcinogenesis and cytotoxicity.

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