Protein Kinase C Modulates Regulation of the CYP1A1 Gene by the Aryl Hydrocarbon Receiver*

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Transcriptional activation of the human CYP1A1 gene by halogenated and polycyclic aromatic hydrocarbons is mediated by the aryl hydrocarbon receptor (AhR) complex, a ligand-dependent transcription factor. A competent AhR comprises at least two components following nuclear translocation and DNA binding, the AhR and the AhR nuclear translocator (Arnt) protein, whose combined action on human CYP1A1 gene transcription is shown to be dependent upon a functional protein kinase C (PKC). In the present study, we examined the effects of phorbol 12-myristate 13-acetate, a potent PKC activator, on the ligand-induced transcriptional activation of the CYP1A1 gene and cellular function of the AhR in human HepG2 101L cells. The 101L cells carry a stable transgene consisting of 1800 bases of 5′-flanking DNA and the promoter of the human CYP1A1 gene linked to the firefly luciferase structural gene (Postlind, H., Vu, T. P., Tukey, R. H. & Quattrrochi, L. C. (1993) Toxicol. Appl. Pharmacol. 118, 255–262). Pretreatment of cells with 12-myristate 13-acetate enhanced ligand-induced CYP1A1 gene expression 2–3-fold. Inhibition of PKC activity blocked directly the transcriptional activation and the transactivation of these cytochromes is felt to proceed in large part through a signaling process involving ligand-dependent activation of the aryl hydrocarbon receptor (AhR). The current thinking regarding properties of the ligand and AhR-directed gene transcription is based upon both cellular and molecular studies that have focused primarily on the inducible expression of the CYP1A1 gene. The cytosolic AhR belongs to the family of basic helix-loop-helix (bHLH) proteins and is occupied in the cytoplasm of the cell with hsp90, which is uncoupled from the receptor in the presence of ligand (3–5). The ligand-activated AhR migrates rapidly to the nucleus, where it associates with the bHLH AhR nuclear translocator (Arnt) protein and then binds to specific enhancer sequences flanking the CYP1A1 gene, dioxin responsive elements (DREs). DNA binding of the dimeric AhR-Arnt to the DREs initiates the recruitment of transcriptional factors followed by induction of the CYP1A1 gene.

It was originally believed that the movement of the ligand-activated AhR to the nucleus was a process dependent upon the Arnt protein (6). However, recent observations demonstrate that Arnt is a nuclear protein and most likely participates only in the nucleus to facilitate ligand-dependent AhR binding to DNA (7). The release of hsp90 from the cytosolic AhR is initiated by ligand binding (8), a process that is then followed by rapid transport of the AhR to the nucleus. Yet little is known regarding the cellular characteristics of the AhR that initiate transcriptional activation of target genes. It is known that the AhR is a phosphoprotein, and in the vitro treatment of cytosol or of induced nuclear extract with either acid or alkaline phosphatase abolishes the specific binding of the AhR to its responsive DNA element (9–12). Our laboratory has recently demonstrated that the acute treatment of mice with phorbol esters dramatically reduces the ligand-induced nuclear accumulation of the AhR, an event that was concordant with lowered Cyp1a-1 and Cyp1a-2 transcription rates (13). In addition, prolonged treatment of tissue culture cells with phorbol esters and the down-regulation of PKC activities inhibits ligand induced accumulation of CYP1A1 mRNA (9). While it has been suggested that ligand binding does not directly influence the phosphorylation state of the AhR (12, 15), PKC activity may play a central role in additional cellular processes that coordinate the AhR-Arnt complex in facilitating gene regulation. Since the AhR is a heterodimer complex that is composed of both cytosolic and nuclear proteins, the actions of PKC could be targeting cellular events that facilitate its activity both in the cytosol as well as in the nucleus.

We have recently developed a sensitive tissue culture cell line that can be used to study the intracellular events in the AhR-mediated expression of the human CYP1A1 gene (16). The 101L cells are derived from the human hepatoma cell line, HepG2, and carry a stably integrated human CYP1A1 pro-
PKC and CYP1A1 Gene Transcription

The AhR, a member of the nuclear receptor superfamily, is activated by a variety of ligands. In this study, we examined the effects of various AhR agonists on CYP1A1 gene induction in 101L cells. The cells were transiently transfected with a luciferase reporter construct containing the CYP1A1 promoter and 5′-flanking sequences. Following treatment with various AhR agonists, luciferase activity was assessed.

**Materials and Methods**

Chemicals and Biochemicals—TCDD was obtained from Chemexin Science Laboratories (Lexena, KS). PCBs were kindly supplied by Dr. Steven Safe (Texas A & M University). 3-Methylcholanthrene (3MC), DMH, and staurosporine were purchased from Sigma. Chelerythrine chloride, H89, and 4,4′-phorbol 12,13-didecanoate were from LC Laboratories (Woburn, MA). Luciferin was obtained from Analytical Luminescence Laboratory (Ann Arbor, MI). [γ-32P]ATP (3000 Ci/μmol) was purchased from Amersham Life Science. All tissue culture media supplies and Geneticin (G-418) were purchased from Life Technologies, Inc.

Cell Culture and Transient Transfections—The human 101L cells were stably transfected with the AhR and the 5′-flanking sequences, fused to the luciferase gene. The 101L cells were grown as monolayers at 37 °C in 95% air and 5% CO2 in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum and 0.4 mg/ml G-418. The 101L cells were grown under the same conditions with or without 4,4′-phorbol 12,13-didecanoate (PMA). After the addition of the media, the Me2SO concentration never exceeded 0.3% (v/v). The remaining laboratory chemicals were of the highest quality available.

**Results**

Effects of Various AhR Agonists on CYP1A1 Gene Induction in 101L Cells—It has previously been demonstrated that the treatment of 101L cells with AhR ligands such as TCDD, 3MC, and omeprazole leads to a rapid and dose-dependent induction of the CYP1A1-luciferase activity (16, 23). However, when the cells were pretreated with 4,4′-phorbol 12,13-didecanoate (PMA) for 3 h followed by an 18-h exposure to the TCDD or 3MC, the cells were a sensitive biological tool to examine the actions of AhR ligands such as other halogenated aromatic hydrocarbons (29), a series of PCBs were examined for their ability to induce CYP1A1 gene transcription. The levels of induction were compared with those of TCDD and 3MC. Consistent with previous studies, TCDD is the most potent inducer of the CYP1A1 gene transcription as shown in Fig. 1. The PCBs induce transcription in a dose-dependent fashion, and the order of potency from most active to weakest was 3,3′,4,4′,5-pentachlorobiphenyl > 3,3′,4,4′,5,5′-hexachlorobiphenyl > 2,3,4,4′,5-pentachlorobiphenyl > 3,3′,4,4′-tetrachlorobiphenyl > 2,3,3′,4,4′-pentachlorobiphenyl. At a concentration of 10 μM, 3,3′,4,4′,5,5′-hexachlorobiphenyl was the weakest inducer, displaying approximately a 40-fold induction of luciferase activity, while 3,3′,4,4′,5-pentachlorobiphenyl generated a 130-fold increase.

Electrophoretic Mobility Shift Assay (EMSA)—A complementary pair of synthetic oligonucleotides containing the sequence 5′-GATC-CGGCGCTTGGTACCACTCGAGCTAC-3′ and 5′-GATCTGGCAT-CAGGTTCTGAGAAGAGGGCCG-3′ (the 27-base pair AhR binding site of DRE, designated here as “DRE oligonucleotide”) (27) were synthesized, annealed, and labeled at their 5′ ends by T4 polynucleotide kinase and [γ-32P]ATP. DNA binding was measured using an EMSA, which was performed as described by Denison et al. (28). The binding reactions contained nuclear protein (10 μg) or activated cytosolic protein (40 μg), 2.4 μg of poly(dI-dC), 1 μg of salmon sperm DNA, and 1 × 10^10 cpm of 32P-labeled double-stranded DRE in a final volume of 0.3 μl of binding buffer (25 mM HEPES, pH 7.5, 1.5 mM EDTA, 1 mM DTT, and 10% glycerol). To determine the specificity of binding to DRE, a 200-fold molar excess of unlabeled DRE oligonucleotide was used. DNA-protein complexes were separated under non-denaturing conditions on a 6% polyacrylamide gel using 1 TBE (89 mM Tris borate, 89 mM boric acid, 2 mM EDTA) as a running buffer. The gels were then dried, and protein-DNA complexes were visualized by autoradiography.

**Discussion**

The results indicate that 101L cells are a sensitive biological tool to examine the actions of AhR ligands on the stimulation of gene transcription. In turn, events that might impact on AhR function can now be accurately correlated with the biological role of the AhR.
PKC and CYP1A1 Gene Transcription

Fig. 1. CYP1A1 gene transcription induced by AhR ligands. Several structurally related PCBs were evaluated for their ability to induce CYP1A1 gene transcription in 101L cells, and the levels were compared with the induction by 3MC and TCDD. Each reagent was added to a growing monolayer of 101L cells in Me2SO, and the cells were harvested for luciferase activity 18 h later. Luciferase activity is expressed as RLU/µg of protein. The results reported at each dose represent the average of three separate determinations, with each enzyme assayed in duplicate. The fold induction is indicated above each bar graph. PCB, polychlorinated biphenyl; HCB, hexachlorobiphenyl; TCB, tetrachlorobiphenyl.

Fig. 2. Effects of PMA on CYP1A1 gene transcription in 101L cells. For these experiments, 101L cells were pretreated with 125 nM PMA for 3 h followed by an 18-h treatment of TCDD (10 nM) and several structurally related PCBs (10 µM). Luciferase activity was measured, and the activity was expressed as RLU/µg of protein. The values represent the average of three individual determinations. DMSO, Me2SO.

We tested. Depending on the ligand tested, PMA facilitated up to a 2–2.5-fold increase in transcriptional activity. Therefore, the actions of PMA appear to affect the functional properties of the AhR. In addition, 4α-phorbol 12,13-didecanoate, an inactive phorbol ester derivative, at concentrations between 50 nM and 1 µM showed no effect on the TCDD-induced transcriptional activation of the CYP1A1 gene (data not shown). Since one of the principal actions of active phorbol esters leads to modulation of PKC activity, this result suggests that the actions of PMA on AhR-mediated gene transcription in tissue culture may be modulated through a PKC-directed mechanism.

To examine the direct actions of PKC activity on CYP1A1 gene transcription, inhibitions of cellular protein kinase activities were examined. Protein kinase inhibitors were added to 101L cells for 1 h followed by TCDD treatment for 3 h. As in other experiments, a 3-h exposure to TCDD induced gene transcription 50-fold. The specific PKA inhibitor H89 (30), showed no effect on the TCDD-induced or PMA-enhanced CYP1A1 gene transcription at the concentration up to 1 µM (Fig. 3). However, the PKC inhibitors, staurosporine and chelerythrine chloride, at concentrations that have been reported to inhibit general PKC activity (18, 19, 31), completely blocked AhR ligand-induced CYP1A1 gene transcription (Fig. 4, A and B). Similar results were also observed with the PKC inhibitor calphostin C (data not shown).

Effects of PMA and PKC Activity on Cytosolic AhR Function—CYP1A1-induced gene transcription by AhR ligands is entirely dependent upon binding of the ligand-activated AhR complex to enhancer sequences flanking the promoter. To determine if the changes in DNA binding of the AhR complex paralleled the changes we have observed in transcriptional activity, EMSAs were performed to measure the direct binding of the activated AhR to DRE. The cytosolic AhR, which is coupled with hsp90, can be activated in vitro to a DNA binding species by incubating cytosol with ligand. To determine whether the actions of PMA and PKC on 101L cells influence the ability of the cytosolic AhR to bind ligand and then to associate with DNA, 101L cells were treated with PMA for 3 h or staurosporine for 4 h followed by the preparation of cytosolic extracts. Cytosolic preparations were then incubated with TCDD, and the ability of the ligand-activated cytosolic AhR to bind to DNA was analyzed by EMSA. As shown in Fig. 5, PMA treatment of 101L cells did not significantly increase the activated DNA binding of the cytosolic AhR (lane 7 versus lane 3). Similar results were obtained with staurosporine treatment. At concentrations of staurosporine that completely blocked TCDD-directed CYP1A1 gene transcription, there was no effect on the ability of the activated cytosolic AhR to associate with DNA (lane 5 versus lane 3). The treatment of cells with both staurosporine and PMA did not impact on the ability of the cytosolic AhR to associate with DNA. These results indicate that the actions of PKC has a limited impact on the ability of ligand to activate the cytosolic AhR to a functional DNA binding species. Similar conclusions have been made in experiments designed to inhibit PKC activity in vitro, followed by analysis of AhR activation and DNA binding to enhancer sequence (15).
The Actions of PMA and PKC on Nuclear DNA Binding to Enhancer Sequences—EMSAs were also used to measure the accumulation of TCDD-induced nuclear AhR complex as measured by direct binding to DRE. In this experiment, 101L cells were pretreated with either 200 nM staurosporine (St) for 1 h, 125 nM PMA for 3 h, or staurosporine for 1 h followed by PMA for 3 h. At the end of the treatments, cytosol extracts were prepared and incubated with 32P-labeled DRE and 20 nM TCDD (lanes 3, 5, 7, and 10) or Me2SO (lanes 2, 4, 6, and 8) at room temperature for 3 h. The activated AhR and the binding profiles were then analyzed by EMSAs. Lane 1 is probe alone, and the position of the activated AhR is indicated on the left.

Effects of Staurosporine on the Transactivation of AhR and Arnt—The AhR and Arnt proteins have been shown independently to transactivate reporter gene constructs (20, 32). To examine the actions of staurosporine on the components of the AhR complex, chimeric constructs were used for the transactivation experiments. Both the AhR and Arnt cDNAs lacking the coding region of the N-terminal bHLH domains were fused to a functional human glucocorticoid receptor (GRDBD) containing the DNA-binding domains. These chimerics, upon transfection, bind to the GRE element flanking a GRE-driven luciferase reporter plasmid. Similar to previous studies (20, 32), the pGRDBD-Arnt is constitutively expressed at high levels and is not responsive to TCDD treatment, whereas the expression of pGRDBD-AhR is dependent upon ligand treatment (Fig. 7). Both TCDD-induced transactivation by the pGRDBD-AhR and the constitutive transactivation by the pGRDBD-Arnt chimeric proteins were blocked by staurosporine treatment, indicating that the nuclear transactivation event is dependent upon PKC activity. This result supports previous experiments that indicate a role for PKC in the transcriptional activation of the CYP1A1 gene. In addition, these results also suggest that both components of the AhR complex are dependent upon PKC, which supports previous studies indicating that phosphorylation of both AhR and Arnt is critical for DNA binding activity (10).

DISCUSSION

AhR mediates the biological actions of ligands such as polychlorinated dibenzo-p-dioxins, polycyclic aromatic hydrocarbons, benzo(a)pyrene, and bioflavonoids. The cellular events that underlie AhR-mediated gene transcription involve a series of dynamic steps that bring together several cellular and nuclear proteins, one of which appears to be PKC. In the cytosol of the cell, the AhR is coupled with the 90-kDa heat shock protein.
treatment of 1 nM TCDD and/or 125 nM PMA. As outlined under "Materials and Methods," nuclear extracts were prepared, 10 no detectable cell toxicity.

CYP1A1 and activates promoter-specific transcription. In 101L cells, we can directly monitor AhR function by its ability to stimulate CYP1A1 gene transcription as measured by firefly luciferase activity (16), and we can also quantitate AhR concentration in the nucleus by its ability to bind to specific enhancer sequences. In addition, the activated form of the AhR can also be quantitated in vitro using cytosol, and it is possible to examine the cellular influences on the ability of ligand to stimulate hsp90 release and transform the AhR-Arnt complex into a species that binds DNA. By studying a series of AhR-mediated events, such as gene transcription, nuclear DNA binding, and ligand activation of the receptor, it has been possible to conclude that ligand-induced gene transcription, and not cytosolic AhR activation, is dependent upon PKC activity.

Exposure of 101L cells to PMA, a potent PKC activator, dramatically enhances transcriptional activation of the CYP1A1 gene induced by various AhR ligands (Figs. 1 and 2). This experiment indicates that the actions of PMA affect either the functional properties of the AhR or participate in modulating the actions of the AhR. When 101L cells were pretreated with PKC inhibitors for 1 h, transcriptional activation of TCDD-inducible as well as the PMA-enhanced CYP1A1 gene transcription was completely blocked (Fig. 4). Since PKA inhibition did not affect transcriptional activation (Fig. 3), phosphorylation events carried out through PKC are assumed to underlie the induction process. Transcriptional inhibition was not reflective of AhR binding to enhancer sequences, either with activated cytosol or with DNA binding of ligand-stimulated nuclear receptor. It has been proposed that actions of PKC may participate in the events that lead to nuclear uptake of the AhR (34). This theory is based upon observations that the treatment of mouse hepatoma Hepa-1 cells with staurosporine blocks the appearance of TCDD-stimulated induction of the AhR to the nucleus, as measured by EMSA. Other studies have shown that staurosporine treatment of Hepa-1 cells does lead to a decrease in ligand binding to cytosolic AhR as well as affect total cellular AhR levels (35), all of which may impact on nuclear receptor levels of the AhR complex. However, using human HepG2 cells, staurosporine has no effect on inhibiting the nuclear accumulation of the AhR within the very rapid time period that it blocks transcription (Fig. 6). These results indicate that the actions of PKC in modulating CYP1A1 gene transcription are occurring independently from cellular and molecular events that modulate cellular activation of the AhR, nuclear transport and DNA binding to enhancer sequences.

The accelerated rate of CYP1A1 transcription by phorbol esters and the linkage to PKC activity could involve signal transduction processes. Interestingly, AhR ligands are known to induce PKC activity (34, 36) as well as AP-1 activity (37), and the latter is a cellular event controlled by PKC signaling mechanisms in the cell. The activation of PKC leads to the recruitment the Jun/Fos, the AP-1 family of transcription factors (38). The AP-1 family of proteins belong to the class of basic leucine zipper proteins that bind DNA as dimers. These dimers may be homodimers, but they can also be heterodimers formed between two members of the Jun family or between Jun and Fos. Formation of AP-1 complexes, in response to the activation of PKC, could act to bind to specific DNA sequences and, in conjunction with the AhR, promote transcriptional activation. In addition, these proteins can participate in cross-talk between different regulatory pathways and can act independently via mechanisms that do not require binding to DNA consensus sequences (39, 40). In light of observations that PKC has little immediate impact on the biochemical properties of the AhR, it could be imagined that the activation of AP-1 activity by AhR ligands serves a central role in facilitating the inducible expression of the CYP1A1 gene by the AhR.

An alternative explanation for the actions of PKC could be that it modulates the phosphorylation patterns of complexes that make up the transcriptional initiation complex. A common
response to extracellular signals is the rapid programmed changes in the rates of gene expression, a process that is brought about by the activation of transcription factors through changes in phosphorylation states. Interestingly, it has recently been demonstrated that the interactions of AhR-Arnt with enhancer sequences are associated with binding of other constitutively expressed transcription factors to the enhancer as well as the promoter (41, 42). These changes lead to alterations in chromatin structure, an event that precedes transcription. Since phosphorylation is believed to modulate the activity of many transcriptional factors (43), cellular signaling events carried out following activation of PKC may be essential in promoting gene responses initiated by the actions of the AhR. It is possible that phosphorylation may facilitate protein-protein interactions between the nuclear AhR and other transcription factors to promote transcriptional initiation. Since there are several AhR enhancer sequences that exist upstream of the CYP1A1 gene, the AhR may work cooperatively with other activated transcriptional factors to produce the synergistic effect on gene expression (41, 44, 45).

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