Dexamethasone-mediated Regulation of 3-Methylcholanthrene-induced Cytochrome P-450d mRNA Accumulation in Primary Rat Hepatocyte Cultures*

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We have previously demonstrated that cytochrome P-450c and P-450d mRNAs can be induced by 3-methylcholanthrene (MCA) in primary cultures of rat hepatocytes grown in serum-free hormonally defined medium (HDM) plus minimal salts (Silver, G., and Krautter, K. S. (1988) J. Biol. Chem. 263; 11802–11807). Such cultures were used to investigate the role of the individual hormonal components present in the medium in the hydrocarbon-mediated induction process. Replacing HDM with minimal salts plus 10% fetal bovine serum (FBS) resulted in a 4-fold reduction in the accumulation of P-450d mRNA in response to MCA. In contrast, no effect was seen on induced levels of P-450c mRNA. Mixing experiments, in which primary cultures of hepatocytes were grown in medium containing HDM plus 10% FBS, indicated that there was no negative acting component present in FBS, but rather there was a positive acting component present in the mixture of hormones in HDM which permitted P-450d induction by MCA. Testing the effects of singly deleting each of the 10 components in HDM on MCA-induced P-450d expression demonstrated that dexamethasone was the only factor which affected the induction of P-450d. Deletion of this component from HDM resulted in a 4-fold decrease in the maximum MCA induced expression of P-450d mRNA. Moreover, supplementation of minimal salts plus 10% FBS with dexamethasone restored full P-450d inducibility by MCA. Deletion of the other components from HDM had no effects on P-450d mRNA accumulation. Although substratum clearly contributed to the quality of primary hepatocyte cultures, we were unable to demonstrate any role of the substratum on MCA induction of P-450d. In vitro nuclear run-on experiments revealed that dexamethasone had little effect on the rate of transcription of the P-450d genes. Therefore, the effect of dexamethasone on induction must be at the post-transcriptional level.

The primary response of most organisms to exposure to aryl hydrocarbons, including 3-methylcholanthrene (MCA), 1β-naphthoflavone, and 2,3,7,8-tetrachlorodibenzo-p-dioxin, is the induction of a set of genes whose products act to metabolize these xenobiotics (1, 2). In rat liver, cytochromes P-450c and P-450d are the major MCA-induced proteins. Although both genes are expressed after carcinogen administration in vivo, in cultured cell lines, only P-450c and not P-450d is induced by MCA (1, 3–6). The failure to observe induction of P-450d in vitro has been postulated to be due to hypermethylation of the gene in cultured cells or the absence of required trans-acting factors in the cell types tested (1, 7).

Recently, we were among the first to report the MCA-induced expression of rat cytochrome P-450d mRNA in a cultured hepatocyte cell system (8, 9). Accumulation of P-450d mRNA in response to the hydrocarbon was rapid, and reached levels of expression similar to those seen in rat liver in vivo. In addition, we showed that P-450d induction was regulated at a post-transcriptional level both in rat liver and in the cultured hepatocyte system (8). In our studies, we had utilized culture conditions which included hormonally defined medium, collagen substratum, and the absence of serum. Work by others had demonstrated that components of fetal bovine serum can extinguish expression of certain liver-specific genes in culture (10). We wished to explore the relationship between the cell growth conditions and the induction of P-450d by MCA. In this report, we investigated the contributions of each component in the defined medium with respect to MCA induction, and found that induction of P-450d mRNA by MCA was dependent on the presence of only one component of HDM, dexamethasone, in the culture medium. We further showed that serum, a component of the growth medium used by many other investigators, has no effect on the ability of primary cultured cells to induce P-450d in response to MCA. Finally, using in vitro nuclear run-on experiments, we demonstrated that the dexamethasone effect is entirely post-transcriptionally mediated.

MATERIALS AND METHODS

All hormones were obtained from Sigma. Fetal bovine serum was obtained from Gibco. All radiotopes were obtained from Amersham Corp.

Preparation of Cultures—Primary rat hepatocytes were prepared from collagenase-perfused Sprague-Dawley liver, according to the methods of Jefferson et al. (11). The cells were plated on 10-cm dishes coated with type I collagen at a density of 6 X 106 cells/dish. After cell attachment was attained in RPMI 1640 plus 10% FBS, the medium was replaced with a serum-free hormonally defined medium (HDM), consisting of RPMI 1640 (GIBCO) supplemented with: 10

1 The abbreviations used are: MCA, 3-methylcholanthrene; HDM, hormonally defined medium; FBS, fetal bovine serum.

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µg/ml insulin, 10 µg/ml linoleic acid complexed with bovine serum albumin, 20 milliunits/ml prolactin, 10 microunits/ml growth hormone, 10^{-6} M T_{3}, 10^{-6} M transferrin, 10^{-6} M dexamethasone, 10^{-10} M ZnSO_{4}, 10^{-7} M CuSO_{4}, 10^{-7} M selenium acid, 100 µg/ml penicillin, 100 µg/ml streptomycin.

These cultures were fed with fresh medium every 24 h. At various times after plating, MCA dissolved in dimethyl sulfoxide was added to a final concentration of 1 µg/ml. The final concentration of dimethyl sulfoxide in the culture medium was 0.1%. Control plates received dimethyl sulfoxide alone at the same concentration.

Preparation of RNA and Hybridization Conditions—Culture dishes were washed twice with ice-cold phosphate-buffered saline (140 mM NaCl, 3 mM KCl, 8 mM Na_{2}HPO_{4}, 1.5 mM KH_{2}PO_{4} and scraped with a Teflon-coated razor blade into GTC lysis buffer (4 M guanidine isothiocyanate, 50 mM EDTA, 100 mM Tris-HCl, pH 7.4, and 1 M β-mercaptoethanol). Cells were homogenized through a 20-gauge needle and highly purified RNA was collected after centrifugation (150,000 × g, 18 h) through a CsCl₂ cushion (5.7 M CsCl₂, 50 mM EDTA). Sprague-Dawley rats were injected intraperitoneally with MCA (400 µg/ml) dissolved in corn oil or corn oil alone. Liver RNA was prepared according to the methods of Derman et al. (12).

Total RNA was resolved and analyzed by formaldehyde denaturing gel electrophoresis and blotting as previously described (8). Hybridization and washes were performed at 65 °C in 5 × SSPE (1 × SSPE = 150 mM NaCl, 10 mM Na_{2}HPO_{4}, 1 mM EDTA), 80% formamide, 0.2% Carnation nonfat dried milk (BLOTTO), 0.5% sodium dodecyl sulfate, and 200 µg/ml denatured salmon sperm DNA. Filters were washed and exposed to x-ray film as previously described (8). Labeled riboprobes were prepared according to Melton et al. (13).

Probes Used in Filter Hybridizations—The cDNA probe used to detect rat P-450d mRNA in these experiments was a mouse P-450 cDNA clone which was isolated from a Agt10 library constructed in our laboratory. The library contained cDNA clones of poly(A)+ mRNA isolated from C57BL/6 male mice treated 20 h with MCA (250 mg/kg, intraperitoneally). Clones were identified by hybridization to a probe enriched for MCA-induced sequences by subtractive hybridization (14). Each clone used was identified by complete DNA sequence analysis. The P-450 cDNA probe used was a partial cDNA clone of the P-450 mRNA which includes bases 780-1880 of the mRNA. Of the 1080 bases in the fragment, 910 (84%) are identical to the rat P-450 mRNA sequence (15,16) with most of the mismatch in the alignment. The P-450 fragment cross-hybridizes weakly with rat P-450 due to its 60% homology over the length of the clone. Thus, the probe detects both P-450d and P-450d mRNAs on Northern blots. Probe, and thus the cross-hybridization can be used to estimate the probe's ability to obtain gene induction in cultured cells.

Results

In Vitro Nuclear Run-on Analysis—1-day-old primary hepatocyte cultures were grown for 1 day in culture on type I collagen substratum, in the medium indicated over each panel, either in the presence (+) or absence (—) of MCA or a,-antitrypsin (α₁-AT) mRNA (12, 17). The level of expression of a₁-antitrypsin is not affected by MCA treatment in primary hepatocyte culture or in rat liver (8). Additional cloned DNA fragments used include full-length human γ-actin and a 1.1-kilobase fragment of a human skeletal myosin heavy chain cDNA clone (8).

In Vitro Nuclear Run-on Analysis—1-day-old primary hepatocyte cultures were grown in the presence or absence of dexamethasone and then harvested in the presence of MCA for 0, 12, or 24 h. Nuclei were prepared as previously described (8). Nascent chain labeling was performed at 31 °C for 20 min utilizing [³²P]UTP (3000 Ci/mmol). Labeled RNA was purified by phenolchlorform (1:1) extraction, followed by ethanol precipitation. Approximately 1–2 × 10^{6} cpm of [³²P]-labeled RNA was hybridized to 5 µg of either purified insert DNA or to single-stranded M13 DNA containing the sense or antisense strand of the P-450 cDNA (see Probes, above), immobilized on nylon membranes with a slot blotting apparatus (Bethesda Research Laboratories). Hybridization and washing of filters were carried out as previously described (8).

\textbf{RESULTS}

Fetal Bovine Serum Does Not Contain an Inhibitor of P-450 mRNA Induction—The study of the molecular basis of gene induction by aryl hydrocarbons has been greatly facilitated by the ability to obtain gene induction in cultured cells.

Thus, a considerable body of information has been obtained describing the regulation of mouse P-450 and rat P-450 genes, which are induced by hydrocarbons in many cell types tested (18–25). On the other hand, very little is known about the molecular basis of the hydrocarbon induction of rat P-450d or mouse P-450 genes, mainly because induction of P-450d in cultured cells has only recently been attained (8, 9). We have previously shown that P-450d could be induced in primary hepatocyte cultures when cells were grown in hormonally defined medium on collagen substratum (8). However, it was not clear from those experiments whether or not defined medium was required to obtain MCA induction. It was important to determine if our success at obtaining MCA-induced expression of P-450d was the result of the growth conditions employed or rather was related to a less tangible part of the cell preparation protocol we used. In the studies described below, we determine the precise culture components which are required to permit P-450d induction in primary hepatocytes, and by simple mixing experiments demonstrate that negative effectors of P-450d inducibility are not present in serum.

One hypothesis to explain the failure of others to obtain MCA induction of P-450d in cultured hepatocytes is that serum used in the medium inhibits the expression of P-450d by an unknown mechanism. To address this issue, we compared the induction by MCA of both P-450c and P-450d mRNAs in cells cultured in HDM (RPMI 1640 minimal salts plus hormones) to cells cultured in RPMI minimal salts supplemented with 10% FBS, both grown on type I collagen substrata. As shown in Fig. 1, cells grown in HDM and treated with MCA for 24 h produce ~35-fold more P-450d than do cells which are not exposed to MCA (see Table I for quantitation). In contrast, cells cultured in the presence of RPMI plus serum showed only an ~8-fold induction of P-450d by MCA (see Fig. 1). This represented a 4-fold reduction in the response to MCA. Surprisingly, P-450c mRNA, which is inducible in many cell types, showed essentially no difference (1.2-fold) in its level of induction in the presence or absence of serum. The difference in P-450c and P-450d response to the growth medium are no doubt related to their different mechanisms of induction by MCA (8). Nevertheless, the levels of induction of P-450d in the presence and absence of serum suggested that either MCA contained positive acting signals A. Hepatocytes

| HDM | RPMI | MCA: + + + + + - + |
|-----|-----|-------------------|
| - | + | - | + | + | + | | |

B. Liver

| HDM | RPMI | MCA | serum |
|-----|-----|-----|-------|
| - | + | - | + |

![Fig. 1. Regulation of P-450d mRNA accumulation by serum factors. Northern analysis was used to quantitate total RNA (25 µg/lane) extracted from rat liver or from primary rat hepatocytes grown for 1 day in culture on type I collagen substratum, in the medium indicated over each panel, either in the presence (+) or absence (−) of MCA (1 µg/ml). Identically prepared filters were hybridized to [³²P]UTP-labeled riboprobes (specific activity >5 × 10⁴ cpm/µg) which hybridized to either P-450c and P-450d mRNAs (A) or α₁-antitrypsin (α₁-AT) mRNA (B).]
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TABLE I
Level of induction of cytochrome P-450 mRNAs by MCA

The data were obtained by computerized densitometric scanning of Northern blots as previously described (32). The data represent the average of three replicates which agreed within 5%. Similar data were obtained in at least three independent experiments.

| Relative* level of induction | P-450c mRNA | P-450d mRNA |
|-----------------------------|-------------|-------------|
| Complete HDM                | 32          | 35.1        |
| HDM + 10% FBS               | 29.5        | 35.3        |
| RPMI + 10% FBS              | 26.0        | 8.2         |
| RPMI + 10% FBS + dexamethasone | 35.0      | 37.7        |
| - Insulin                   | 35.8        | 39.3        |
| - Prolactin                 | 30.4        | 38.2        |
| - Thyroid hormone T3        | 28.7        | 33.3        |
| - Growth hormone            | 29.0        | 33.9        |
| - Transferrin               | 30.0        | 35.0        |
| - Linoleic acid             | 34.2        | 36.7        |
| - ZnSO₄                     | 25.2        | 32.7        |
| - CuSO₄                     | 28.4        | 33.3        |
| - Selenous acid             | 31.0        | 31.3        |
| - Collagen                  | 40.5        | 30.3        |
| - Dexamethasone             | 21.3        | 9.7         |

* Relative levels of induction are equal to: (level expressed/α₁-antitrypsin)/(level expressed/α₁-antitrypsin).

Fig. 2. Regulation of P-450d mRNA accumulation by dexamethasone (DEX). Experiments were performed as described in the legend to Fig. 1. The specific growth conditions are indicated over each panel. The presence (+) or absence (−) of the type I collagen substratum is indicated over each panel. The presence (+) or absence (−) of the hormone DEX is indicated over each panel. The presence (+) or absence (−) of the substrate RPMI + serum is indicated over each panel.

Fig. 3. Regulation of P-450d mRNA accumulation by collagen substratum. Experiments were performed as described in the legend to Fig. 1. The specific growth conditions are indicated over each panel. The presence (+) or absence (−) of the collagen substratum is indicated over each panel. α₁-AT, α₁-antitrypsin.
We therefore tested the effects of cell growth on plastic or collagen plates with HDM. As can be seen in Fig. 3 and Table I, MCA induction of P-450d and P-450c mRNA was unaffected by the presence or absence of substratum. High levels of MCA induction were seen in the presence or absence of collagen gels.

**Regulation of P-450d mRNA by Dexamethasone is at the Post-transcriptional Level**—We have previously shown that MCA induction of P-450d mRNA in hepatocytes grown in complete HDM was regulated primarily at a post-transcriptional level (8). In order to determine whether or not the dexamethasone enhancement of MCA induction which we have described is a transcriptionally or post-transcriptionally mediated process, we performed *in vitro* nuclear run-on experiments on cultures grown in the presence or absence of dexamethasone. Nascent [3P]UTP-labeled RNA isolated from cells grown with or without dexamethasone were hybridized under conditions of DNA excess to single-stranded cDNA corresponding to either P-450d or P-450c sense and antisense sequences as well as to actin, α1-antitrypsin, and myosin heavy chain control DNAs. Under the stringent hybridization and washing conditions used, there is no detectable cross-hybridization of P-450c RNA and P-450d probe DNA (8). As can be seen in Fig. 4 and Table II, there is little effect of dexamethasone on the level of transcription of either P-450c or P-450d genes at any time following MCA induction. Comparison of the level of transcription of the genes plus and minus dexamethasone at 0, 12, or 24 h shows that there were no significant transcriptional effects. Although dexamethasone increases the accumulation of P-450d in response to MCA, in the data shown, there may be a slight (~2-fold) decrease in the transcription of P-450d in response to dexamethasone. However, we do not consider this level of change to be significant over the variance from experiment to experiment. As we previously reported, there is a 5-fold MCA induction of P-450c transcription and ~2-fold MCA induction of P-450d in this culture system. It should be noted that levels of transcription of actin decrease over the time period of the experiment and is typical of freshly plated hepatocytes which undergo limited growth upon initial plating.

It is also significant that hybridization of nascent RNA is seen only to the antisense strand of the probe and not to the sense strand. This result eliminates the possibility that the hybridization signal observed at any time point might be obscured by hybridization from a cryptic transcription unit in the opposite orientation.

**DISCUSSION**

The work presented in this paper clearly demonstrates that a hormonal component of the medium, dexamethasone, is the major factor required for maximal MCA-induced accumulation of P-450d mRNA in cultured primary rat hepatocytes. The effects of other media components and extracellular matrix components were shown to be minimal. Addition of dexamethasone to cells cultured in only minimal salts and FBS, conditions which are relatively nonpermissive for the induction of P-450d mRNA, resulted in essentially complete restoration of the maximally inducible phenotype. This demonstrates that dexamethasone is most likely a positive acting factor in the induction process and that there are probably no negative acting factors present in serum. Interestingly, the differential effects of hormones and extracellular matrix on the expression of cytochrome P-450c mRNA are negligible. P-450c is MCA responsive under essentially all conditions tested. This implies that P-450c regulation is affected by a fundamentally different mechanism than P-450d in cultured hepatocytes.

*In vitro* nuclear run-on experiments were also performed on cells grown in the presence and absence of dexamethasone. These clearly demonstrated that removal of dexamethasone from HDM had no significant effect on the transcription rates of either P-450 gene in the presence or absence of MCA. We have previously performed nuclear run-on experiments on cells grown in HDM on collagen substratum or on nuclei

![Fig. 4. Effect of dexamethasone (DEX) on transcription rates of the P-450 genes in primary cultures treated with MCA. *In vitro* run-on experiments were performed on cells grown in the presence or absence of dexamethasone and treated with MCA for the times indicated. Labeled RNA (2 x 10⁶ cpm, 0 h; 8 x 10⁶ cpm, 12 and 24 h) was hybridized under conditions of DNA excess to either double-stranded cDNA inserts corresponding to γ-actin (A), α1-antitrypsin (L), and skeletal muscle myosin heavy chain (MHC) or to single-stranded cDNA in M13 vector corresponding to sense (−) or antisense (+) strands of P-450d or P-450c gene-specific clones. Single-stranded M13 DNA was also included as an additional control. Filters were washed stringently, treated with ribonuclease A, and subjected to autoradiography as described previously (8). Densitometric scans were performed on exposures in the linear range of the film sensitivity.

**TABLE II**

|        | MCA        |
|--------|------------|
|        | 0 h        |
| P-450c | + Dex 0.54  |
|        | - Dex 0.90  |
| P-450d | + Dex 0.24  |
|        | - Dex 0.63  |
| α1-Antitrypsin | + Dex 1.00 |
|        | - Dex 1.00  |
| Actin  | + Dex 1.20  |
|        | - Dex 1.00  |

**Quantitation of signals in Fig. 4 was performed by densitometric scanning of appropriate exposures. Relative transcription rates were normalized to the signal from the liver-specific α1-antitrypsin gene and were corrected for insert size. Numbers in parentheses refer to induction relative to 0 h MCA treatment. ([density of signal − background]/insert size)/(α1-antitrypsin signal). Data represent the average of two separate experiments. Similar data were obtained in at least three independent experiments.**

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...derived from rat liver tissue, and found that MCA treatment of cells had little effect on the rate of transcription of the P-450d gene. This demonstrated that MCA induction of P-450d is mediated primarily at the post-transcriptional level both in rat liver and in rat liver cell culture (8). Taken with the results presented above, it appears that dexamethasone must act as a potentiator of a post-transcriptional regulatory step, since removal of dexamethasone from the defined medium results in a reduction of MCA-induced P-450d mRNA accumulation.

Work by others has demonstrated that dexamethasone acts on a variety of genes at the transcriptional level by a receptor-mediated event that represents perhaps the best studied mammalian transcriptional regulatory process (27). It has also been shown that several genes appear to undergo post-transcriptional regulation in response to dexamethasone (28, 29). Recent experiments indicate that in at least the case of one of these genes, α1-acid glycoprotein, both a transcriptional and post-transcriptional step may be modulated by dexamethasone (28, 30). The P-450d mRNA accumulation is induced by MCA in the presence of dexamethasone, but is not induced by dexamethasone. Thus dexamethasone is acting as a cofactor in this response and is not a primary mediator of the accumulation. Perhaps, dexamethasone induces a factor which interacts with P-450d mRNA and can result in higher levels of mRNA accumulation. Dexamethasone has been shown to post-transcriptionally induce at least one other form of cytochrome P-450, P-450b (31). Treatment of rats with the glucocorticoid results in an overall 10-12-fold accumulation of P-450b in the absence of any other treatment. In the case of P-450d, however, dexamethasone treatment alone fails to induce this mRNA. Rather, dexamethasone appears to enhance the effect of MCA on induction of P-450d. Whether the dexamethasone effects seen on these two different genes are related to each other awaits further characterization of the underlying mechanisms of their induction.

It is not apparent why other investigators have previously failed to obtain MCA-induced expression of P-450d in primary hepatocyte cultures (1, 3-6). We were unable to define cellular conditions in which P-450d mRNA was not induced by MCA. We observed less than a 5-fold difference between the conditions which produced the lowest levels of induction and those which produced the highest. Furthermore, the maximum levels of induction were similar to the levels of induction of P-450d, however, dexamethasone treatment alone fails to induce this mRNA. Rather, dexamethasone appears to enhance the effect of MCA on induction of P-450d. Whether the dexamethasone effects seen on these two different genes are related to each other awaits further characterization of the underlying mechanisms of their induction.

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