 Cellular Retinoic Acid-binding Protein II Gene Expression Is Directly Induced by Estrogen, but Not Retinoic Acid, in Rat Uterus*

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1 The abbreviations used are: RA, retinoic acid; RAR, retinoic acid receptor; RARE, RA-response element; ER, estrogen receptor; ERE, estrogen-response element; CRABP(II), cellular retinoic acid-binding protein(II); E2, 17β-estradiol; CRBP, cellular retinol-binding protein; RPA, RNase protection assay; EMSA, electrophoretic mobility shift assay; wt, wild type.

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3 The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EBI Data Bank with accession number(s) AF226560.

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5 The numerous sites of action of retinoic acid, e.g. from reproductive organs to the respiratory system, suggest that there will be several different factors that regulate its synthesis. One such factor may be estrogen. Administration of E2 to the prepubertal rat leads to a gain of the ability of the uterine lining epithelial cells to synthesize RA (2). Coincident with this gain of ability is the appearance of CRABP(II) within these cells. CRABP(II) is a member of a large family of small proteins that specifically bind lipophilic compounds such as fatty acids and retinoids (3).

Recent work has suggested that CRABP(II) may have a role in the movement of retinoic acid (RA) to its nuclear receptors, thereby enhancing the action of RA in the cells in which it is expressed. RA has also been shown to increase expression of CRABP(II). Previous work from our laboratory has shown that 17β-estradiol (E2) administration to prepubertal female rats leads to acquisition of the ability of the lining epithelium to synthesize RA as well as to express CRABP(II). To determine whether this appearance of CRABP(II) was dependent on the production of RA, both E2 and RA were administered to ovariec
tomized rats. E2 administration induced expression of the CRABP(II) gene in the uterus within 4 h, and this induction was not inhibited by prior administration of puromycin, indicating that the induction was direct. In contrast, RA caused no change in CRABP(II) message level, even at times as late as 48 h after administration. Isolation and analysis of 4.5 kb of the 5′-flanking region of the gene revealed no apparent E2-response element. Using this portion of the gene to drive expression of the luciferase gene in transfected cells allowed identification of a region containing an imperfect estrogen-response element and estrogen-response element half-site, necessary for E2-driven induction. A possible Sp1 binding site in the 5′-flanking region of the CRABP(II) gene was also required for this induction. The ability of E2 to induce expression of CRABP(II) suggests that it can enhance the activity of RA, directly affecting expression of retinoid-responsive genes.

The vitamin A metabolite all-trans-retinoic acid (RA) regulates multiple biological processes, including cell proliferation and differentiation, by virtue of its ability to modulate the rate of transcription of numerous target genes. The transcription activities of this hormone are mediated by a family of proteins, the retinoic acid receptors (RARα, β, and γ and isofoms). These receptors bind to specific response elements in the promoter regions of target genes and work as ligand-inducible transcription enhancers and repressors (1).

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EXPERIMENTAL PROCEDURES

Animals and Tissue Collection—Female ovariectomized Sprague-Dawley rats (180–200 g) were purchased from Harlan Sprague-Dawley Inc. (Indianapolis, IN). Rats were housed in a temperature- and light-controlled room (21 C, lights on 0700–1900 h), fed rat chow (Ralston Purina Co., St. Louis, MO), provided with water ad libitum, and allowed to acclimate for 2 weeks before use. Rats were divided into six groups, each with at least three animals, and injected intraperitoneally with corn oil, puromycin (10 mg/rat), E2 (10 μg/rat), puromycin plus E2, RA (500 μg/rat), or puromycin plus RA, respectively. Puromycin was injected 30 min before injection with E2 or RA, for those experimental groups. After 4 h, uteri were harvested from the animals for RNA extraction. These studies were conducted in accordance with the Na-
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Table I
Sequence of the sense oligonucleotides used for the gel mobility shift assays

| Name  | Length | Sequence (sense) |
|-------|--------|-----------------|
| wtERE | 35     | GTCGCGGAACTCA CTCGA CGA TGACC TGATCA AGG TT |
| EREc  | 41     | GTTCGGCA CTT GTACCT CGTCAC CGAAC TAAAG GTC |
| EREm  | 41     | GTTCGGCA CTT GTACCT CGTCAC CGAAC TAAAG GTC |

RNA Extraction and RNA Protection Assays (RPA)—Total RNA was extracted from individual rat uterus using TRIzol reagent (Invitrogen) and quantified by spectrophotometry. The antisense riboprobe for rat CRABP(II) and cyclophilin was transcribed using the MAXiScript kit (Ambion Inc., Austin, TX) and [α-32P]UTP (10 Ci/mmol; PerkinElmer Life Sciences). The RPs were carried out using the RPA III kit (Ambion Inc., Austin, TX) according to the user’s manual. Briefly, samples of total RNA were hybridized for 15–18 h at 50 °C with excess radiolabeled antisense riboprobe (n = 3 individual samples/time point) and digested by RNase at 37 °C for 30 min. The hybridized products were submitted to electrophoresis on 6% acrylamide gels containing 8% urea. Gels were exposed to BioMAX MR film (Eastman Kodak Co.) with intensifying screens for up to 3 days. Loading variation between samples was standardized by including cyclophilin riboprobe in all hybridization reactions.

Cloning, Southern Blotting, and Preparation of DNA Constructs—A portion of the rat CRABP(II) gene was cloned from a Phage library (Incyte Genomics Inc., Palo Alto, CA). The library was screened using PCR primers that amplified a portion of exon 1. The positions of the primers were: 5' primer, +4 to +84, and 3' primer, +162 to +182, numbered according to the transcription start site. One positive clone was identified. It was digested with EcoRI or HindIII, and subsequent Southern blotting analysis identified a 3.5-kb EcoRI fragment and a 14-kb HindIII fragment by hybridizing with the 32P-labeled probe, obtained by PCR labeling using the above primers for exon 1. The 14-kb fragment was purified and cloned. Restriction enzyme mapping and sequencing revealed that it contained 6.6 kb of the 5'-flanking region of the rat CRABP(II) gene. This 14-kb fragment was further digested with KpnI restriction enzyme to obtain a 446-base fragment that contained the basic promoter region. This was ligated to the pGL3 basic luciferase reporter vector (Promega Co., Madison, WI). Further deletions of the −1354, −1211, −1182, −504 fragments were obtained by PCR amplification using the same reverse primer-added KpnI restriction enzyme site, (55/78) 5'GGTCACGGATCCGGCTGTCCTCTCTT-3' and the forward primer: 5'GGTCACGGATCCGGAGTCCTTCT-3'. The forward primer provided KpnI restriction enzyme site, −1354/−1327, 5'GGTACCGGGGATCCGGGCTGTCCTCTCTT-3'. The forward primer was used to generate 1182, 1337, 5'GGTCACGGATCCGGACGGTTGTCCTCTCTT-3'. Each PCR product was digested by KpnI and cloned into the corresponding sites of the pGL3 basic vector. The right orientation was identified by PCR screening. Constructs 6 and 7 were generated by ligating the synthetic fragment of −1211/−1178 to the fragments of −799 or −754, respectively (Fig. 4). All the constructs created by PCR amplification were verified by sequencing.

Cell Culture, Transient Transfection, and Luciferase Assay—MCF-7 cells obtained from the American Type Culture Collection (Manassas, VA) were routinely maintained in a humidified atmosphere containing 5% CO2. Cells were transfected when they approached 70% confluence in 24-well plate using the SuperFect transfection reagent (Qiagen Inc., Valencia, CA) according to the manufacturer’s instructions. The cells were cotransfected with 1 μg of estrogen receptor (ER) expression plasmid (ATCC) as the endogenous level of ER was low, and 10 ng of pRL-TK vector to normalize the differences in transfection efficiency. Following transfection, cells were changed to phenol free minimum Eagle’s medium (Invitrogen) containing 10% dextrose coated charcoal-stripped fetal bovine serum, and cells were incubated with 100 μl E2 or vehicle for 2 days before harvesting for the luciferase assay. Cells were lysed using 1× passive lysis buffer, and 20 μl of lysate was assayed using Dual-Luciferase reporter assay system (Promega). RESULTS

Expression of CRABP(II) in Rat Uterus Was Induced Directly by E2 but Not by RA—Ovariectomized rats were administered either E2 or RA or vehicle alone and uteri were collected after 4 h. Uteri were also collected from ovariectomized rats that had received puromycin 30 min prior to administration of E2 or RA, or vehicle. Analysis of the DNA obtained from these uterine by RPA revealed a potent induction (16–18-fold) of CRABP(II) message by E2 administration (Fig. 1). Puromycin had no effect on this increase, suggesting that the response to E2 did not require new protein synthesis and was sufficiently rapid to be a direct response. Surprisingly, no increase in CRABP(II) message in the uterus was observed for animals administered RA, in contrast to observations for both the human and mouse CRABP(II) gene, albeit in different systems (11, 16). No increase was noted even at times as late as 48 h after RA administration (data not shown). To confirm that RA had indeed reached the uterus, the
level of expression of cellular retinol-binding protein (CRBP), known to be directly regulated by RA (17), was determined and found to have increased about 5-fold in the animals receiving RA (Fig. 1). Thus, the lack of response of the rat CRABP(II) gene to RA could not be ascribed to delivery failure.

It was considered possible that an RA-induced expression might require exposure of the uterus to E2. To test this possibility, we injected ovariectomized rats with E2 and RA simultaneously and also provided RA 24 h after E2 treatment. When message levels were determined 4 h later, no effect of RA was observed over that of E2 alone (results not shown).

Analysis of the 5'-flanking Region of the Rat CRABP(II) Gene—Previous analyses of the 5'-flanking regions of the mouse and human CRABP(II) gene had not revealed any indication of an ERE. To see whether there might be a species difference in estrogen response, we isolated this region for the rat gene, as described under “Experimental Procedures.” A 3.5-kb EcoRI fragment and a 14-kb HindIII fragment were identified (Fig. 2A). Restriction enzyme mapping analysis revealed that the 14-kb fragment contained about 6.6 kb of the 5'-flanking region (Fig. 2B). Digestion with KpnI produced a fragment that contained the TATA box and transcription start site but excluded the coding region.

The complete sequence of this 4.5-kb fragment was analyzed for known DNA binding protein recognition sites. The palindromic sequences of the canonical ERE (18) were not found. Putative regulatory elements for ubiquitous transcription factors such as AP1 (19), AP2 (20), and Sp1 (21) were evident in the proximal region of this fragment (Fig. 3). The proximal region shown corresponds to the published sequence of the mouse CRABP(II) 5' region, with which it has 85% sequence identity (13). Although we found no response of the CRABP(II)
gene to RA in the uterus of the intact rat, there is a region corresponding to the mouse RA-response element, mRARE2 but no correspondence to the reported mRARE1 (Fig. 3).

**Promoter Activity of the 5'-flanking Region of the Rat CRABP(II) Gene**—To determine whether the cloned 5'-flanking region of the rat CRABP(II) gene contained unidentified response elements allowing transcriptional activation by E2, various 5'-end deletions were ligated into the pGL3-basic luciferase reporter vector (Fig. 4). The cell line chosen for testing these constructs was the MCF-7 human mammary carcinoma cell line as it expresses both CRABP(II) and the ER and, consequently, should contain any cell-specific factors involved in CRABP(II) expression. However, preliminary studies indicated that a better response was obtained if an ER expression vector was cotransfected and all experiments included that vector.

The longest fragment tested contained, with respect to the transcription start site, the region from +4411 to +77, ending 72 nucleotides prior to the initiation codon for translation (construct 1). After treatment with E2 for 48 h, the transcription activity of this fragment was about 13-fold higher than the basal promoter level (Fig. 4). Treatment with 1 μM RA gave no increase in transcription (data not shown). Various deletions from the 5'-end of this fragment were examined, and induction remained at this level until +1210 (constructs 2 and 3). Deletion constructs shorter than +1210 were substantially lower, falling to a 2–3-fold increase over basal levels (constructs 4 and 5), indicating that the +1210 to +1178 region was critical for E2 response. The sequence of this region contained an imperfect consensus ERE, GCTCANNNCGACC, and an ERE half-site, TGTCA (Table I).

To examine whether the GC-rich regions, putative Sp1 binding sites, might also contribute to the ability of E2 to induce transcription, as has been observed for other genes, the +1210 to +1178 sequence was ligated to the proximal promoter region at position +799, just proximal to the second GC-rich sequence at +781 to +755 (construct 6). Induction was similar to that seen with the full-length construct (+8-fold versus +12-fold). However, ligation of the +1210 to +1178 fragment to the proximal region at position +754 reduced induction to the 2–3-fold increase seen when the +1210 to +1178 fragment was not present (construct 7; compare with construct 4). This suggested that the fragment +1210 to +1178 and the region +799

![Fig. 3. Nucleotide sequence of the selected 4.5-kb fragment of the 5'-flanking region of the CRABP(II) gene. The nucleotides are numbered according to the transcription start site, which is indicated as +1. The TATA signal and ATG start codon are boxed; possible AP1, AP2, Sp1, and RARE binding sites and the sequence of the oligonucleotides used for P1 screening and the probe used for Southern blotting are underlined. Underlined EREc indicates the non-canonical ER binding site for CRABP(II) identified in this study. The imperfect consensus sequences are written in bold and italic. The position and sequence of the primers used for P1 screening and probe for Southern blot are shown in italic.](image-url)
to −754 are both required for the E2-induced transcription of the rat CRABP(II) gene. The possible additional requirement of the more proximal GC-rich region was not examined.

We further examined the response of this promoter region to E2 in the rat hepatoma cell line H-4-II-E, which does not express CRABP(II) or the ER. The results were essentially the same for each construct as found in the MCF-7 cell line (data not shown), which suggested that no factor specific to a cell type was required in this in vitro deletion assay.

**Test of the Putative ERE by ER Binding Studies**—Known EREs are able to bind activated ER in vitro, as shown by electrophoretic mobility shift assays (EMSA). The −1210 to −1178 fragment, designated EREc (Table I), was tested for the ability to bind purified, activated ER. As a control, a sequence containing a canonical ERE was also used (wtERE).

When ER was incubated with 32P-labeled oligonucleotide EREc, a protein-DNA complex was formed, as revealed by EMSA (Fig. 5A, lane 1). This protein-DNA complex was confirmed to be an ER-DNA complex by the ability of ER antibody to supershift the complex in a dose-dependent manner (Fig. 5A, lanes 2–5).

As a further test of EREc as a potential ERE, gel mobility competition assays were performed with 100−400-fold molar excess of unlabeled wtERE over 32P-labeled EREc (Fig. 5B) and 200−800-fold molar excess of unlabeled EREc over 32P-labeled wtERE (Fig. 5C). A 400-fold excess of wtERE competed for all detectable binding of labeled EREc, whereas an 800-fold excess of EREc was required to compete for all detectable binding of wtERE. This suggested that the affinities of the ER for these sequences were similar but that the wtERE appears to bind more tightly to the ER. As a final test of specificity of binding of the ER to the EREc sequence, competition was tested for a 3-base mutant, EREM, with two base changes in the imperfect ERE region and one in the half-site (Table I). No apparent competition was observed for either a 400- or 800-fold excess. These results established that the −1120 to −1178 contained an imperfect ERE that can bind specifically to ER in vitro.

**DISCUSSION**

Previous work from our laboratory has shown that the expression of CRABP(II) in certain cells of the rat uterus and ovary correlates with the production of RA by those cells (2, 22). Recent studies by others have demonstrated an ability of the RA-CRABP(II) complex to translocate to the nucleus and mediate a direct transfer of RA to RARs, an ability not shared by the closely related protein CRABP (6, 7). The association of CRABP(II) with the nuclear receptor complex has been demonstrated to enhance the expression of RA-responsive genes (23).

In the work presented here, the demonstration that E2 directly induced the expression of CRABP(II) indicates that the effects of E2 on a particular tissue/cell may well result in the induction or modulation of expression of RA-responsive genes, in addition to E2-responsive genes. This would appear to greatly increase the number of genes accessible by the E2 signal and provides a direct link between the action of a steroid hormone and the action of RA.

Interestingly, we saw no change in expression of the endogenous CRABP(II) gene or of the reporter constructs when RA was provided. Previously, we had observed that E2 administration to the prepubertal female rat led to acquisition of the ability of the lining epithelium to synthesize RA as well as to express CRABP(II). That expression of CRABP(II) would then appear to be independent of RA synthesis by those cells. This
result is different from other studies in which CRABP(II) gene expression was strongly increased by RA either in human skin in vivo or in cultured human skin fibroblasts in vitro (24). RA also was shown to increase expression of CRABP(II) in the F9 murine cell line (16). These differences might be explained by species or cell-type differences. However, it was observed that this increase of expression in both intact human skin and in the F9 cell line was blocked by inhibition of protein synthesis, suggesting that the effect was indirect. Nuclear run-on experiments suggested that the increase was controlled by a post-transcriptional mechanism (25). Still, we observed no increase in CRABP(II) expression at times up to 48 h, suggesting that even an indirect regulation by RA was not occurring in the rat uterus under the conditions examined here.

Analysis of the 5′-flanking region of the rat CRABP(II) gene showed 85% sequence identity to the proximal 1 kb of the corresponding sequence reported for the mouse gene, including an identical DR1 mRARE2 repeated motif (13) and some ubiquitous transcription factor binding sites, such as Sp1, AP1, and AP2 (fig. 3), but there was no sequence corresponding to an unidentified functional DR2 mRARE1. It should be noted that this region of the mouse promoter did lead to RA-stimulated transcription of a reporter gene in transfected cells, whereas we did not observe such an increase. This may explain why RA has no effect on rat CRABP(II) gene expression in vivo or when transfected in MCF-7 cells in vitro and may suggest a species difference in regulation by RA. However, it should be stressed that the actual direct regulation of the native gene in both human and murine cells by RA remains in question.

No obvious ERE was noted in the analysis of the 4.5-kb fragment, but it is well established that E2-directed gene regulation can be quite complex. Many naturally occurring copies of the 13-base pair consensus ERE are imperfect (26–31). Also, several genes activated by E2 involve both ERE and GC-rich Sp1 binding sites, such as creatine kinase B (32), bcl-2 (33), uteroglobin (34), insulin-like growth factor-binding protein-4 (35), transforming growth factor α (36), RARα (37), and LDL receptor (38), or ERE interaction with USF-1 and USF-2 as in the cathepsin D promoter (39). That proved to be the case here as well. The identified region that bound the ER contained three imperfect palindromic EREs, not obvious from sequence analysis alone. In addition, a possible Sp1 binding site was required to obtain the E2 response in vitro. Thus, this appears to be another version of a complex E2-responsive promoter.

Our preliminary studies indicate that E2 also directly regulates expression of the enzymology of RA synthesis. It will be of interest to examine whether this regulation shares features observed for the CRABP(II) gene.

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