Studies on the Mechanism of Functional Cooperativity between Progesterone and Estrogen Receptors*

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M. Suzanne Bradshaw, Sophia Y. Tsai, Xiaohua Leng, Alan D. W. Dobson, Orla Conneely, Bert W. O'Malley, and Ming-Jer Tsai

From the Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030

Steroid response elements (SREs) cooperate with many different cis-acting elements including NF-1 sites, CACCC boxes, and other SREs to induce target gene expression (Schule, R., Muller, M., Otsuka-Murakami, H., and Renkawitz, R. (1988) Nature 332, 87–90; Strahle, U., Schmid, W., and Schutz, G. (1988) EMBO J. 7, 3389–3395). Induction of gene expression can be additive or synergistic with respect to the level of activation by either transactivators. Two mechanisms have been proposed for how synergism occurs: 1) cooperative binding of transcriptional activators to DNA or 2) simultaneous interaction of individually bound activators with a common target protein. We have shown previously that cooperative binding of receptors is important for synergism between two progesterone response elements (PREs). Here we showed that an estrogen response element (ERE) and a PRE can also functionally cooperate and this synergism between an ERE and a PRE is not contributed by cooperative DNA binding. Furthermore, we have demonstrated that the activation domains of the progesterone receptor (PR) (ClAct) are required for synergism between two PREs and sufficient for confirming cooperative binding. However, these two activation domains of PR are not sufficient for synergism between an ERE and a PRE. Additional regions within the NH2-terminal and COOH-terminal domains are also required for synergistic interaction between two heterologous SREs.

Steroid hormones control gene expression via specific interactions of their cognate receptors with steroid response elements (SREs) in the 5′-flanking DNA of steroid regulated genes (3–5). Once bound, the mechanism by which receptors activate transcription is only partially understood (6, 7). Many eucaryotic genes are under the control of multiple hormones and steroid response elements are usually found in multiple copies or tightly clustered with other cis-acting DNA elements or SREs (1, 3, 8–13). The tryptophan oxygenase gene (8), murine mammary tumor virus long terminal repeat (11), and vitellogenin A2 and B1 genes (9) contain multiple SREs. In addition, the murine mammary tumor virus long terminal repeat (11) and the rat tryptophan oxygenase gene (1) contain other cis-acting elements in close conjunction with SREs. In all of these cases, when one of the SREs or the adjacent cis-acting elements are mutated, steroid responsiveness is greatly diminished. Thus, SREs interact synergistically with each other and with other cis-acting elements to induce gene expression. The mechanism of synergism between SREs and various cis-acting elements is not known.

Ptashne (14) has proposed two models by which synergistic activation occurs. First, synergistic activation can occur when two factors bind cooperatively to adjacent cis-acting elements. Second, synergism can occur when two factors bind independently to DNA but simultaneously interact with a third transcription factor to initiate transcription. Tsai et al. (15) and Klein-Hitpass et al. (7) have demonstrated that progesterone receptor can bind cooperatively to transcriptionally activate two progesterone response elements (PREs). Similarly, Schmid et al. (16) have demonstrated cooperative binding of the glucocorticoid receptor to tandem GRE/PREs. Nevertheless, cooperative binding may not account for the total level of synergism observed between SREs. Carey et al. (17) and Lin et al. (18) have demonstrated recently that synergism occurs between GAL4 binding sites and between GAL4 and ATF sites even when all sites are saturated with activators. This result is consistent with the hypothesis that activators cooperate by simultaneously touching a target protein. The observation that ER can squelch the activation of a progesterone-responsive target gene by the progesterone receptor supports this possibility (19, 20).

In this paper, we demonstrate that the estrogen receptor cooperates functionally with the progesterone receptor, but that the synergism does not result from cooperative binding to their respective SREs. The two activation domains of the progesterone receptor are shown to be essential for synergism both between two PREs and between an ERE (estrogen response element) and a PRE. These two activation domains are sufficient for partial synergism of two PREs but not sufficient for synergism between an ERE and a PRE. Additional domains residing within the NH2-terminal and COOH-terminal regions of the heterologous receptors are required. These data are consistent with the hypothesis that progesterone and estrogen receptors regulate target genes cooperatively via simultaneous protein-protein contacts with a target protein(s) in the transcriptional machinery.

MATERIALS AND METHODS

Construction of Plasmids—Synthetic oligonucleotides containing the tyrosine aminotransferase PRE and the vitellogenin ERE were...
Functional Cooperativity between Progesterone and Estrogen Receptors

Expression and Partial Purification of ClAct—ClAct protein was expressed as a fusion protein by attachment to the 26-kDa glutathione S-transferase of Schistosoma japonicum and thereby can be purified under non-denaturing conditions (44). pGEX-2T-ClAct was transformed into E. coli strain JM109. Fusion protein GST-ClAct was prepared from E. coli extract by affinity chromatography on prepacked glutathione-Sepharose 4B (Pharmacia). Using procedures furnished by Pharmacia we purified the fusion protein except that the fusion protein was eluted with 10 mM glutathione (Sigma) in 50 mM Tris-HCl and 15% glycerol elution buffer. The glutathione S-transferase carrier was removed from fusion protein by incubation with thrombin (Boehringer Mannheim) (38). More than 95% cleavage occurred after 2-h incubation at room temperature and an enzyme-to-substrate ratio of 1:100. Glutathione was then removed as described by Smith and Johnson (44). Glutathione S-transferase and other glutathione binding proteins were partially removed by affinity chromatography. ClAct preparation was then desalted and concentrated by using Centricon-10 concentrator and stored at -70°C. Band-shift analyses of ClAct on two PREs probes were carried out as described previously (15).

RESULTS

The Estrogen Receptor Can Cooperate Functionally with the Progesterone Receptor—Two PREs have been shown to act synergistically in the absence of a distal promoter element when located near the TATA box (21). To determine if an estrogen response element (ERE) can cooperate functionally with a PRE, we inserted a single ERE 5’ to a single PRE upstream of a minimal promoter fused to the CAT reporter gene to create pOVCAr5-50 (ERE/PRE) (Fig. 1, bottom panel). This reporter plasmid was cotransfected into CV-1 cells with either vectors expressing the progesterone receptor cDNA (PR), the estrogen receptor cDNA (ER), both receptors together.

Expression of the progesterone receptor (PR) was detected by Western analysis using a polyclonal antibody raised against the human progesterone receptor. The ER was detected by Western analysis using a monoclonal antibody raised against the human estrogen receptor. The presence of the fusion protein was detected by Western analysis using a polyclonal anti-human GST antibody.

Experimental conditions and results are shown in the figure legend. The figure shows that coexpression of PR and ER increases the expression of CAT activity in CV-1 cells. The figure also shows that coexpression of PR and ER increases the expression of CAT activity in CV-1 cells.

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**Fig. 1. Cooperativity between progesterone and estrogen response elements.** Top panel, 10 μg of the indicated reporter gene construction and 2 μg of vector expression progesterone receptor (PR), estrogen receptor (ER), both receptors (ER + PR) or control (V) were cotransfected into CV1 cells. Progesterone (10−7 M) and estrogen (10−8 M) were added to every plate. Autoradiograms of TLC plates indicate CAT activity as the conversion of non-acetylated [3H] chloramphenicol (lowest mobility) to its 1-acetylated (middle mobility) and 3-acetylated (highest mobility) forms. 100 μg of protein were assayed overnight; autoradiographic exposure was for 18 h. Bottom panel, schematic representation of pOVCAr5-50 (ERE/PRE). An oligonucleotide corresponding to the ovalbumin sequences (OV) from +43 to −50 was inserted into the CAT vector containing the ovalbumin TATA box. Oligonucleotides containing a GRE/PRE and an ER were inserted at position −50. Orientation is given by the arrows.
gether (PR + ER), or vector control (V). All these experiments were carried out in the presence of their cognate ligands at 10^{-7} M. Fig. 1A shows that PR or ER alone induce very low levels of gene expression, but the two receptors together act synergistically to induce expression. The level of CAT activity with both receptors is 4-8-fold higher than expected for the additive effect of each individual receptor. These data demonstrate that the estrogen receptor can synergize functionally with the progesterone receptor.

Hormone Is Required for Synergism of the Estrogen and Progesterone Receptors—To determine if hormone is required for synergism between estrogen and progesterone receptors, we used anti-estrogens in the cotransfection experiments. Anti-estrogens have recently been shown to interact with the estrogen receptor in such a way that the receptor binds to DNA but is not activated (33). The ERE/PRE containing reporter was cotransfected with both receptors in the presence or absence of various antiestrogens. Fig 2 shows that in the absence of any hormone no induction occurs. The addition of estrogen (E) and progesterone (P) cooperatively induce gene expression. Replacing estrogen with either 10^{-7} M tamoxifen (Tam) or 10^{-7} M nafoxidine (Naf) blocked induction. Thus, DNA binding of a transcriptionally inactive form of estrogen receptor is not enough for synergism between the estrogen and progesterone receptors. Activation by authentic ligand is necessary for the estrogen receptor to synergize with progesterone receptor.

Cooperative Binding Does Not Contribute to Functional Synergism of Heterologous Receptors—We have demonstrated previously that progesterone receptor and estrogen receptor bind specifically to their target PRE and ERE (28, 34). In addition, we have shown that the progesterone receptor has higher affinity for a PRE when an adjacent PRE is already occupied (15). Using an in vitro transcription assay we have demonstrated that this cooperative binding contributes to functional synergism between two PREs (7). To determine if cooperative binding contributes also to functional synergism between heterologous receptors, we used a band-shifting competition assay. A fragment of DNA containing both steroid response elements was labeled and incubated with either PR alone or PR and ER. Fig. 3, A and B, show that in the presence of unlabeled PRE oligonucleotide the rate of competition was the same for the complex containing either PR alone or both receptors. This result suggests that the specific binding of ER does not stabilize the binding of PR to a nearby PRE. Thus, functional synergism between an ER and PR must occur by a mechanism other than cooperative binding to DNA.

Two Regions of the Progesterone Receptor Are Required for Cooperativity—To determine what regions of PR are required for cooperativity, we utilized PR deletion mutants (24, 25). PRC1H contains only the amino terminus and the DNA binding domain of PR. PRC1C2 contains only the DNA binding domain and the carboxyl terminus. Each of these constructions was cotransfected with a reporter containing an ERE/PRE. Neither mutant alone, or with ER, was able to induce gene expression (Fig. 4). Thus, synergistic induction

**Fig. 2.** Effect of hormone on cooperativity. Cotransfections were as described in Fig. 1A. Hormone added to the plates was: no hormone (none), 10^{-7} M estrogen and 10^{-7} M progesterone (E + P), 10^{-7} M tamoxifen and 10^{-7} M progesterone (Tam + P), or 10^{-7} M nafoxidine and 10^{-7} M progesterone (Naf + P). Expression vectors added were: vector control (V, solid bar), progesterone receptor (PR, unshaded bar), estrogen receptor (ER, leftward striped bar), or both receptors (rightward striped bars). CAT activity is given as percent conversion.

**Fig. 3.** Binding affinity of progesterone receptor to ERE/ PRE. A, competition analysis of PR-ER and PR-DNA complexes by PRE oligonucleotides. Amounts of competitor are as indicated. B, Quantitation of complexes formed in band-shifting reaction at different competitor/PRE molar ratios. Gel slices containing complexes with estrogen and progesterone receptors (filled circles) or progesterone receptor alone (open circles) were excised and counted in a Beckman scintillation counter. Results are plotted as percent complex remaining after competition and are average of three different experiments.
is lost upon deletion of the NH₂-terminal (aa 1-280) or COOH-terminal (aa 369-659) regions of the receptor.

To further define the important regions of PR, we used oligonucleotide site directed mutants of PR (Fig. 4). Each of these mutants has been shown to bind DNA and hormone with wild-type affinity (24). Fig. 4 shows that mutants PR14, PR16, and PR17 have at least wild-type ability to cooperate with ER. However PR18 and PR5 have much reduced ability to cooperate with ER to induce target gene expression. Similarly, Dobson et al. (24) have shown that these same two mutants have greatly reduced ability to induce transcription from a target gene containing two PRES. Thus, the two subregions of the receptor characterized in the previous experiment are indeed the activation domains of PK, we would expect that these two regions, one of which is fused either to the COOH-terminal activation domain, or next to the DNA binding domain, would activate individually or together to the DNA binding domain of PR.

We used Western analysis, to demonstrate that the receptor mutants described in Fig. 4 are expressed to similar levels in transient transfections. Fig. 5 shows that wild-type receptor (79K) and mutant receptors PR18 and PR5 are expressed to similar levels in transfected cells. These recombinant receptors migrated on gels to a position approximately to that of partially purified progesterone receptor (form A) from chicken oviduct (lane 2). The molecular sizes of the mutants are not expected to be significantly smaller than the wild-type receptor, because the deletions are too small to be detected by this

*FIG. 4. Regions of the progesterone receptor important for cooperativity between ERE and PRE. Cotransfections were as described in Fig. 1A. The reporter contained an ERE and a PRE (Fig. 1B). Progesterone mutants are shown in the bottom of the panel with brackets indicating the position of the deletion. Amino acids deleted are indicated at the right. Top panel shows percent conversion of each mutant alone (striped bar) or each mutant in the presence of estrogen receptor (solid bar).*

*FIG. 5. Western analysis of PR mutants. 10 µg of vector expressing wild-type progesterone receptor (79K) and various PR mutants (PR18 and PR5) were transfected into COS cells. 300 µg of protein from each transfection, from cells not transfected (mock), and 50 ng of partially purified progesterone receptor A (PR) were run on sodium dodecyl sulfate-polyacrylamide gel electrophoresis and blotted on nitrocellulose. Filters were probed with PR22 antibody and visualized with 125I-protein A. Size markers are indicated at the left.*

*FIG. 6. Effect of activation domains on cooperativity. Schematic representation of wild-type progesterone receptor and activation domain constructions. The DNA binding domain was fused to aa 368-421 (C1-5) or aa 199-287 (C1-18). A fragment from PR spanning aa 250-417 including the DNA binding domain (C1Act) was also used. Percent conversions are indicated for a reporter containing two PRES (PRE2) or a reporter containing an ERE and a PRE (ERE/PRE). The numbers indicate the amino acid number at the border of each region. ERE/PRE containing constructions were cotransfected in the absence (-ER) or presence (+ER) of estrogen receptor and the presence of estradiol (10⁻⁷ M). 2% of background activity in the absence of both ER and PR was subtracted from these data.*

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We conclude that the reduced CAT expression driven by PR5 and PR18 is not due to instability of these mutants in transfected cells.

*Different Regions of PR Are Required for Regulation of Two PREs and ERE/PRE—If the two subregions of the receptor characterized in the previous experiment are indeed the activation domains of PR, we would expect that these two regions, in conjunction with the DNA binding domain, would activate transcription. To test this hypothesis, we fused these regions individually or together to the DNA binding domain of PR. Fig. 6 shows the constructions in which the DNA binding domain is fused either to the COOH-terminal activation domain, pC1-5 (aa 368-421), or the NH₂-terminal activation domain, pC1-18 (aa 199-287). Neither of these constructions was capable of inducing expression of reporters containing either two PRES or an ERE/PRE (Fig. 6). pC1Act (aa 250-417) contains both activation domains flanking the DNA*
Functional Cooperativity between Progesterone and Estrogen Receptors

binding domain. In the absence of ER, wild-type PR and all three of these above activation constructions produce less than 5% of these above activation percent conversion when cotransfected with the reporter containing an ERE/PRE (data not shown). When pC1Act was cotransfected with the reporter containing two PREs, it induced expression at 38% of the level of wild-type PR. However, when the reporter contains an ERE/PRE, no significant induction occurred in the presence of ER (9.8 versus 7.3).

To investigate the regions of PR, in addition to the two activation domains, that are required for synergism between an ERE and a PRE, we subcloned a fragment containing aa 250-659 (pC1ActC2) and a fragment containing aa 1-411 (pNC1Act). The construction pC1ActC2 contains both activation domains and the carboxyl terminus. It differs from deletion mutant PRClC2 in that the latter does not contain the 5′ activation domain. When pC1ActC2 or pNC1Act was cotransfected with the reporter containing two PREs, CAT activity was induced to 50% of wild-type PR in both cases (data not shown). In contrast, when the reporter contains an ERE and a PRE, the recombinant receptor forms did not induce expression in the presence of ER (Fig. 7). C1ActC2 is identical to C1Act except that C1ActC2 also contains the entire COOH terminus. Yet, C1ActC2 appears to have lower levels of expression in the presence of ER. This is due to a difference in transfection efficiencies in the experiments in Fig. 7. The lower transfection efficiency of these experiments indicated by the lower level of wild-type PR + ER expression. Therefore, the carboxyl- or amino-terminal region alone is not sufficient to induce expression of an ERE and a PRE, suggesting that multiple regions in both NH2- and COOH-terminal domains are required for functional synergistic interaction with an estrogen receptor.

**Cooperative Binding of C1Act to Two PREs**—As shown in Fig. 6, C1Act construct has 38% of the wild-type PR activity on the PRE reporter and has very little activity above the basal level on the ERE/PRE reporter (compare +ER or +PR with ER or PR alone, 9.8 versus 3.0 or 7.3, respectively. These results indicate that C1Act of PR can synergize with one another but not able to do so with ER. Since synergistic induction of PRE reporter is through cooperative binding (7, 15) and the fact that C1Act can not synergize with ER, it suggests that C1Act synergizes with one another through the same mechanism. In order to confirm this, we synthesized C1Act protein in an E. coli expression system. C1Act was synthesized as a fusion protein by attaching it to glutathione S-transferase so that it can be easily purified through glutathione-Sepharose 4B affinity column. The fusion protein was then cleaved by thrombin to generate C1Act. The protein purified in such a manner has a major band at 18 kDa and a small amount of partially cleaved products. Band shift experiments were then carried out to examine whether the C1Act cooperatively binds to probe containing two PREs. As shown in Fig. 8A, two protein-DNA complexes (II and IV) were observed. The identity of two complexes were confirmed by binding of C1Act to a probe containing a mutation in one of the PRE sites (15). As shown in Fig. 8A, the formation of complex IV was drastically decreased when one of the PRE site is mutated. In contrast complex II is not effected by this mutation. These data together with those obtained in our earlier paper (15) indicate that complex II represent the binding of C1Act dimer to one of the PRE site and complex IV represent binding of two dimers to both PREs.

To examine cooperative binding of C1Act, we next carried out binding experiments with increasing concentrations of C1Act. Fig. 8, B and C, shows that formation of complex II is transient and never reach more than 20% of the total probe before complex IV taking over. This suggested that C1Act binds to PREs probe in a cooperative manner. Using the equation derived in our earlier publication (15), one can calculate the relative $K_d$ for the binding of C1Act to first PRE and the subsequent binding to the adjacent PRE. We estimated that C1Act binds to the PRE with an affinity of 20 times higher when the adjacent PRE site is already occupied as compared to that when the adjacent site is unoccupied. Thus, cooperative binding of C1Act to PREs contributes to the synergistic induction of PRE template.

**DISCUSSION**

We have shown that the estrogen receptor can cooperate functionally with the progesterone receptor. Induction is 4-8-fold higher than expected for the additive effect of each individual receptor. Ankenbauer et al. (35) have previously demonstrated synergism between an ERE and GRE in the chicken vitellogenin II gene. Using a weak GRE, they demonstrated a 2.5-5-fold synergism with an ERE which is analogous to the 4-8-folds of synergism observed by us. In the present study, we have extended these studies to demonstrate a likely mechanism of synergism between an ERE and a PRE.

Ptashne (14) proposed that transcriptional synergism can occur by two mechanisms (Fig. 8): A, cooperative binding of factors to adjacent cis-acting elements and B, cooperative transactivation of a target protein by two independently bound activators. We have reported previously that progesterone receptors bind cooperatively to two PREs from the TAT gene (15). In contrast, no cooperative binding of cognate receptors occurs between an ERE and a PRE. This deduction is further supported by the anti-estrogen data since these drugs allow the receptor to bind but not activate, yet anti-estrogens block synergism of the estrogen receptor with the progesterone receptor (23). Therefore, binding of estrogen receptor to DNA is not sufficient for synergism with progesterone receptor, suggesting that cooperative transactivation may occur.

Recently, Carey et al. (17) and Lin et al. (18) have shown that multiple GAL4 sites or GAL4 and ATF sites can act synergistically in the absence of cooperative binding. This was demonstrated by adding an excess of activators in vitro and in transfections to saturate available binding sites so that cooperative binding could not affect the interpretation of their results, yet synergism was still observed. Their results suggest that synergism can occur when activators simultaneously
Functional Cooperativity between Progesterone and Estrogen Receptors

Fig. 8. Binding of C1Act to PRE/PRE or PRE/PREm. Probes: DNA fragment containing PRE/PRE or PRE/PREm was prepared and labeled to 1–7 × 10^6 cpm/µg as described (15). The concentration of C1Act used in band-shift assays was about 700 µg/ml. A, each binding reaction contained 0.4 ng of ^32P-labeled probe, 4.8 µg of poly(dI-dC). + and – indicate the presence and the absence of touch a target protein. In contrast, Klein-Hitpass et al. (7) showed that addition of progesterone receptor to an in vitro transcription system stimulates transcription of test genes harboring one and two copies of PREs 5- and 27-fold, respectively. When similar experiments were carried out in a vast excess of progesterone receptor, the levels of transcription of a test gene containing two PREs were only 2–4-fold higher than a test gene containing one copy of a PRE. Taken together with our earlier published data (15) these results reveal that cooperative binding of progesterone receptors occurs to two PREs and that binding affinity is the primary reason for synergism in this system. This is different, however, from interactions between receptors at an ERE and a PRE. In this case, cooperative transactivation may occur even when the binding sites are saturated.

The cooperative transactivation model predicts that in many instances the activation domains of receptor should be important for such interactions with a target protein. We have used progesterone receptor mutants to delineate regions of the receptor important for induction of transcription. Two regions, aa 262–287 (PR18) and aa 383–411 (PR5), located on either side of the DNA binding domain, are important for activation of templates containing either two PREs or an ERE and a PRE. These regions contain the activation domains of the progesterone receptor. In conjunction with the DNA binding domain, these two activation domains are sufficient for induction of transcription from two PREs. Neither region alone is active, suggesting that both activation domains are required for cooperativity.

Since the transactivation model does not play much role in the synergistic induction of two PREs, we predicted that this synergistic activity is derived from cooperative binding. DNA binding data suggested that this indeed occurs with C1Act. Therefore the sequence important for cooperative binding must reside within the expressed sequence. The lack of synergistic induction on PRE template when individual activation domain was used suggests that both activation domains may be required for the cooperative binding. We are currently attempting to identify the sequence(s) important for the cooperativity. It is interesting to point out that in our DNA binding assay, we did not observe monomer binding of C1Act to the PRE half-site, suggesting that either C1Act already dimerizes in solution or the monomeric C1Act has very low affinity for the half-site as compared with C1Act dimer. This observation differs significantly from our previously published results when DNA binding domain of mouse glucocorticoid receptor was used in similar studies (28). In that case the DNA binding domain readily binds to PRE half site as a monomer (28). It is likely that C1Act may contain the dimerization domain.

There are two forms of chicken progesterone receptor derived by translation from two AUGs in the same reading frame (19). Cato and Ponta (36) identified the amino terminus of the chicken progesterone receptor (B-specific region) to be essential for synergism with the estrogen receptor. However, our wild-type PR constructions contain only form A of the receptor and do not contain the amino acids identified by

2 S. Y. Tsai, B. W. O'Malley, and M.-J. Tsai, unpublished data.

C1Act. Lanes 2 and 3 contained 1 µl of C1Act. B, formation of C1Act-DNA complex at different protein concentration. The amount of C1Act used in each reaction is as specified. Arrows denote the bands of complexes II and IV. C, quantitation of the two different complexes at different concentrations of C1Act. Gel slices containing complexes II and IV and free DNA were excised and counted in a Beckman scintillation counter. Results are plotted as the percent DNA bound in complexes II and IV.
these authors to be essential for synergism. Yet, we observe excellent cooperation with the progesterone and estrogen receptors. We and others (19, 20) have shown that the NH2-terminal 128 amino acids of the chicken progesterone receptor constitute a promoter specific activation domain. Since the reporter gene used in these studies (PRE/ERE OVCAT-50) differs from that used by Cat0 and Ponta (PRE/ERE TKCAT), this difference may account for the discrepancy between the two sets of data. Furthermore, these data would lead us to speculate that different activation domains of the progesterone receptor contribute to cooperative transactivation in a promoter-specific manner.

The PR expression vector, CIAct, contains the two activating domains flanking the DNA binding domain. This construction partially induces transcription from a promoter containing two PREs but is insufficient for induction from an ERE/PRE construct. Maximal activation requires additional sequences in both the carboxyl and amino termini of PR. We conclude that multiple regions throughout the promoter are essential for synergism. Yet, we observe these authors to be essential for synergism. Yet, we observe excellent cooperation with the progesterone and estrogen receptors. We and others (19, 20) have shown that the NH2-terminal 128 amino acids of the chicken progesterone receptor constitute a promoter specific activation domain. Since the reporter gene used in these studies (PRE/ERE OVCAT-50) differs from that used by Cat0 and Ponta (PRE/ERE TKCAT), this difference may account for the discrepancy between the two sets of data. Furthermore, these data would lead us to speculate that different activation domains of the progesterone receptor contribute to cooperative transactivation in a promoter-specific manner.

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Functional Cooperativity between Progesterone and Estrogen Receptors