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Structure of Chick Progesterone Receptors[1]

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Abstract

Oviduct progesterone receptors have been purified from both immature chicks and laying hens. The subunits, progestophilins A and B, have different molecular weights, but each is the same from either tissue source. Immunological data show that the subunits are cross-reactive. The hen B protein as isolated to homogeneity contains nonradioactive progesterone in stoichiometric amounts as shown by gas chromatography-mass spectrometry. These studies further confirm our earlier determinations on these proteins.

Introduction

It is thought that steroid hormones exert their effects on target cells by interacting first with specific receptor proteins (7, 11, 16). These intracellular proteins have been the subject of intense study, not only in our laboratory but in numerous others as well. As detailed elsewhere in this volume, steroid receptors have come under study for diagnostic purposes in the evaluation of breast tumor endocrine therapy. Yet, to date there is no clear understanding of how these proteins function at the molecular level, nor indeed is there agreement on their structure, intracellular fate, or pathway to the nucleus.

In our laboratories, we have been studying the chick oviduct progesterone receptor and have determined its subunit structure (2, 18, 19, 20, 22) and the kinetics of its interaction with nuclei (3) and chromatin (10). Recently, *in vitro* studies of the effects of progesterone-receptor complexes on RNA synthesis in oviduct chromatin led us to propose a model for the molecular events associated with the action of these proteins (5, 23, 25). The model has been a useful guide to our experiments and remains an attractive, if unproven, hypothesis.

In attempting to study the action of receptors *in vitro*, we have been led to purify the proteins and to determine their physical characteristics. Because of their lability, low abundancy in the cells, and subunit structure, purification has been a considerable problem and has attracted wide concern (8, 13, 14, 27). Purification now has been completed successfully for both subunits, for the intact receptors, and for receptors from both immature chicks and egg-laying hens. This paper reports our results comparing the materials prepared in different ways.

Materials and Methods

Animals. Immature chicks received diethylstilbestrol implants (20 mg) in Carbowax once per week. They were used 14 days after the second injection when the oviduct weights were 1 to 2 g each. Laying hens were used as the mature oviduct source; these oviducts weighed 25 to 30 g each.

Tissue Preparation. Animals were killed by decapitation, and the oviducts were removed, rinsed in 0.9% NaCl solution in the cold, and dissected free of fat and mesentery.

Cytosol Preparation. High-speed cytoplasmic extracts were prepared in Buffer 1 (0.01 M Tris-0.001 M disodium EDTA-0.012 M 1-thioglycerol, pH 7.4, at 25°) as described in detail elsewhere (18).

Receptor Assays. Where appropriate, receptor concentrations were determined with adsorption to Whatman DE-81 DEAE-cellulose filters by modification of the procedure of Baxter *et al.* (1). Aporeceptor preparations (those containing no progesterone) were titrated with labeled progesterone, and the receptor concentration was determined by Scatchard plot (4). At intermediate steps in the protocols, when receptors were already complexed with labeled progesterone, the receptors were assumed to be saturated with hormone, and the receptor titer was thus determined directly from the amount of labeled steroid in the sample without DEAE filter adsorption.

These filter assays are on the order of 80% accurate; direct measurement of bound ^3H is an underestimate of receptor titer since it measures only functional receptor-hormone complexes and does not evaluate partially denatured proteins that do not bind progesterone or aporeceptors. Experience with relabeling after each step has shown the latter category to be virtually absent.

Radioactive Steroids. [1,2-$^3H_2$]Progesterone was used in all experiments. Specific activity was 48 to 53 Ci/mmol depending upon lot number and was assumed to be 50 Ci/mmol throughout. In some experiments nonradioactive progesterone was added to bring the specific activity to 5 Ci/mmol as noted in the text. Scintillation counting for aqueous samples had a counting efficiency of 30%.

Protein Assays. Several types of protein assay were used. UV absorbance assays at 280 or 235 nm were used with appropriate corrections for absorbance of the buffer, especially at 235 nm. The Lowry assay was used with modification for sulfhydryl-containing solutions (21). Gel electrophoresis under both denaturing and nondenaturing conditions was done as described in detail elsewhere (6, 21).

Gas-Chromatography–Mass Spectrometry. Samples of the hen B receptor were extracted with dichloromethane (twice with 4-volume excess) to elute protein-bound steroid ligands for analysis. The extracts were dried and derivatized for gas-chromatography in comparison to authentic progesterone and metabolite standards. Quantitation of progesterone in the extracts was accomplished by comparison of peak heights to a standard curve.

Progesterone derivatives from the peaks eluting on gas chromatography were diverted on line to an LKB mass

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spectrometer, and molecular ion mass determinations were performed.

Preparation of Receptor A and B Proteins from Chicks. Our earlier experiments on progesterone receptor had shown that the material could be resolved chromatographically into 2 hormone-binding protein fractions, A and B (22, 24), with kinetically identical binding sites (9, 22). Their presence in equal amounts in the extracts (22) and later identification of a putative coupled (dimeric) form of the 2 (20) led us to propose that they are subunits of the larger complex. Purification has thus been required for both A and B independently. The protocol for purification of A protein from immature chicks has been published recently (6) and consists of the following steps.

Cytosol without hormone from 150 g of oviducts is passed through a 150-ml bed of phosphocellulose and a 150-ml bed of DNA-cellulose to which the aporeceptor A-B complexed does not bind. The material excluded from DNA-cellulose is labeled with [^{3}H]progesterone (2×10^{-8} M) for 6 to 12 hr and then precipitated at 40% saturation ammonium sulfate. This step precipitates A and B proteins dissociated from each other. The labeled complexes are redissolved and chromatographed on a DEAE-agarose column with a KCl gradient in Buffer 1. Receptor A elutes as a broad peak at 0.1 to 0.15 M KCl, and Receptor B elutes as a sharp peak at 0.2 M KCl.

The Receptor A pool is then diluted and applied to a 20-ml DNA-cellulose column and eluted with a KCl gradient. The Receptor A peak elutes as a sharp peak at 0.2 M KCl.This pool is then applied to a 2-ml phosphocellulose column and also eluted with a KCl gradient. A single radioactive peak elutes at 0.26 M KCl. This material is desalted by gel filtration in 0.05 M ammonium bicarbonate and then lyophilized.

Preparation of Chick Receptor B Protein. The DEAE-agarose column used in isolation of Receptor A protein yields an equal amount of [^{3}H]progesterone-Receptor B, eluting at 0.2 M KCl. This pooled fraction is subjected to the same basic purification scheme as that used for the hen B protein (21). The DEAE pool is diluted with Buffer A and applied to a 20 ml phosphocellulose column, from which the Receptor B elutes at 0.22 M KCl. The phosphocellulose pool is then applied directly to a 2-ml hydroxylapatite column, and the column is eluted with a linear gradient of potassium phosphate, 0.01 to 0.5 M. The Receptor B elutes at 0.18 M. This pool is then chromatographed by gel filtration on Agarose A-1.5 M (BioRad Laboratories, Richmond, Calif.; 5 × 80 cm) in Buffer A containing 0.3 M KCl. The receptor radioactivity peak elutes at $K_{av} = 0.28$, identical with crude Receptor B. This pooled fraction is then concentrated in a dialysis bag placed in solid sucrose.

Results

Specific Radioactivity of the Final Receptor Products. The protocols outlined in "Materials and Methods" and reported in detail elsewhere were designed to yield highly purified, active receptor-hormone complexes for further studies of their molecular functions. Thus, one important criterion of purity is the specific radioactivity and the degree to which this value approaches the theoretical. This determination requires independent measurements of both the proteins' molecular weights and the number of hormone-binding sites. The former values can be determined from studies of the crude proteins, whereas the latter value requires pure protein and is assumed to be unity here for both the B and A proteins (12).

The molecular weights of the A and B proteins can be estimated from studies of the crude proteins, where the Stokes radius and sedimentation coefficients are known. The values have been obtained independently in 2 laboratories and are in good agreement. For A, Stokes radius and sedimentation coefficients are 45Å and 3.6S; for B the values are 63Å and 4.2S (23, 26). These values allow calculation of the molecular weights by the Svedberg equation (21). The calculated values are 71,000 for A and 114,000 for B.

Table 1 is a summary of the properties of chick and hen A and B receptor proteins purified in this laboratory. The molecular weights of the protein bands determined by polyacrylamide gel electrophoresis in 1% sodium dodecyl sulfate are 79,000 and 117,000, respectively, for the 2 proteins. The same molecular weights are obtained for chick and hen; thus the proteins isolated by the protocols described previously are the same in both endocrine states.

From the known molecular weights and ligand specific

Table 1

Purified progesterone receptor subunits from chick and hen

Theoretical maximum is 1.4×10^6 dpm/μg for Subunit A and 0.95×10^6 dpm/μg for Subunit B.

Oviduct source	Receptor subunit	Isolation method	Specific radioactivity (dpm/μg)	% of estimated purity (sodium dodecyl sulfate gels)	M.W.[a]	Ref.
Chick	A	Coty	200,000	100	79,000	6
	B	Schrader	300,000	50	115,000	
	Both	Kuhn	200,000	100	79[b]; 115,000	13
Hen	A	Coty	20,000	33	79,000	
	B	Schrader	20,000	100	115,000	23

[a] Molecular weights determined by electrophoresis on 6% polyacrylamide slab gels in 1% sodium dodecyl sulfate as described in Refs. 6 and 21.

[b] Erroneously reported as 110,000 in Ref. 13.

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activity, theoretical specific radioactivity can be calculated, assuming one ligand-binding site per protein. Assuming 50 Ci/mmol progesterone, these values are 1.40×10^6 dpm/μg for A and 0.95×10^6 dpm/μg for B. As can be seen in Table 1, these values are approached in the chick preparations prepared by both ion-exchange and affinity chromatography techniques. However, in no case is the theoretical value obtained. This is due most probably to binding site denaturation and dissociation during the purification. The progesterone is not held covalently, and dissociates during dialysis at 0° with a half-life of 80 hr (2). Thus, since the preparations require 48 to 72 hr to complete, the maximum practical specific radioactivity attainable would be perhaps 50 to 75% of the theoretical value. This approximation is attained in some chick preparations. This fact gives further support to the idea that the proteins isolated and seen on the various gel systems are indeed receptor proteins and cannot be accounted for as contaminants.

Progesterone receptors from laying hens were also purified and yielded the results shown in Table 1. Protein B from hen has been obtained in sufficient amounts for some further biochemical studies (12). The table shows that, unlike the chick proteins, specific radioactivity is only a few % of the expected value. This could be due to the presence in the egg-laying hen of high titers of circulating progesterone that bind in the cells to the receptors and prevent their labeling *in vitro*. The anomalously low level of bound [^{3}H]progesterone could also be due to the fact that the hen receptors were only purified partially, resulting in preparations containing mainly contaminants and with receptors comprising only a few percent of the total protein in the sample.

For the test of these 2 possibilities, 3 types of experiment were performed. First, sodium dodecyl sulfate-polyacrylamide gel electrophoresis showed protein bands from hen for both A and B which comigrate with authentic chick receptor proteins at the molecular weights listed in Table 1. Slab gel electrophoresis showed no distinguishable difference in mobility of the bands from hen and chick.

Second, the hen Receptor B was analyzed for bound progesterone. Analysis by UV spectroscopy reported earlier (12) showed the presence of stoichiometric amounts of progesterone, as evidenced by its absorption spectrum and its dissociation from the protein by dialysis in guanidine hydrochloride.

Finally, direct analysis of the extracted ligand was done by gas chromatography–mass spectrometry as shown in Table 2. A Receptor B protein preparation was made, and steroids were extracted with dichloromethane. In this preparation 450 μg of protein were obtained, but only 10 μg of labeled receptor B was present. If all 450 μg of protein were indeed receptor B-containing bound progesterone, 1.49 μg of ligand should have been present. Of this amount, 1.46 μg would be nonradioactive endogenous progesterone, and 0.03 μg would be progesterone added to the preparation to label receptors at the start of purification.

Identity of the ligand as authentic progesterone was made by 2 criteria. First, the extracted steroid coeluted from the gas chromatograph with authentic progesterone standard. Second, the peak of material from the chromatograph was analyzed by mass spectrometry and shown to have a molecular weight of 314, equal to that of authentic progesterone.

A calibration curve for the instrument allowed quantitation of the amount of progesterone in the extract from the sample. As shown in Table 2, 0.5 μg of progesterone was obtained. This amount is 34% of the value expected if all protein were receptor-hormone complexes. When losses during extraction are taken into account, this value is in reasonable agreement with the value obtained by UV spectroscopy.

Significantly, the amount of progesterone is 17 times more than can be accounted for from the radioactive progesterone in the sample. Thus it is certain that a large amount of nonradioactive progesterone was bound to this isolated protein in amounts consistent with the conclusion that the protein with the molecular weight of 117,000 isolated from the hen is indeed receptor-hormone complex B, as claimed from the other analyses.

A summary of the characteristics of purified hen Receptor B is shown in Table 3. Purity of the proteins was established by 4 independent criteria; from these experiments Receptor

Table 2

Analysis of Hen Receptor B ligands by gas chromatography-mass spectrometry

	Receptor B protein subjected to extraction with dichloromethane (μg)[a]	Expected progesterone mass in sample if one filled binding site/protein (μg)	Observed mass of authentic progesterone by gas chromatography (μg)	% recovery calculated if observed progesterone came from only 1 category.
Unlabeled complexes	440[b]	1.46	0.5	34
Labeled complexes	10[c]	0.03	0.5	1700

[a] Receptor B prepared as shown in Ref. 21.
[b] Calculated by direct protein assay.
[c] Calculated from bound [^{3}H]progesterone in final purified sample.

Table 3

Purification of hen progesterone receptor B subunit

Parameter	Method	Comments
Purity	Sodium dodecyl sulfate gel electrophoresis	1 band; 115 K
	Acid-urea gel electrophoresis	1 band
	NH_2-terminal analysis with dansyl chloride	Lysine only
	Gel filtration in guanidine HCl	1 A_{235} peak; 115 K
Protein is receptor	Nondenaturing gel electrophoresis	1 band; coincident dye and ^{3}H
	UV spectroscopy of native and denatured	1 mol Progesterone/mol protein
	Gas chromatography-mass spectrometry of ligand extracted in dichloromethane	Progesterone only; 0.35 mol/mol protein
Specific activity	[^{3}H]Progesterone bound/mg protein	2% of theoretical
	Total progesterone bound	100% of theoretical

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B purity was estimated to be in excess of 95%. Identity of the protein as receptor-hormone complex was established by 3 independent criteria that showed that labeled progesterone migrated with the protein and that stoichiometric amounts of hormone were present. Finally, the specific activity of the preparation was measured and found to represent 2% radioactive complexes and 98% nonradioactive complexes.

Receptor Identity by Immunological Criteria. A final test of these purified proteins was to attempt to raise antibodies to the purified materials and then to show that the antibodies would adsorb to crude labeled receptor-hormone complexes used as the starting material in the purifications. This approach has now been successful, as shown in Table 4. Antibodies were raised in sheep by repeated injections of 50 μg hen Receptor A protein in complete Freund's adjuvant as described in detail elsewhere (17). An immunoglobulin fraction from this serum was mixed with partially-purified, labeled hen Receptor A and B complexes and analyzed by sucrose-gradient ultracentrifugation by the method of Green *et al.* (8). The table shows quantitative displacement of the labeled complexes by the immune serum immunoglobulins but not by immunoglobulins from the same animal drawn before the injections. This experiment demonstrates 3 things. First, it confirms that the purified preparation did consist of receptor proteins as claimed. Second, it shows that the purified material is immunologically cross-reactive with crude labeled receptor-hormone complexes. Third, since the labeled complexes were an equimolar mixture of A and B receptor subunits, it demonstrates cross-reactivity of the 2 proteins and thus immunological similarity of the 2 to each other. This latter finding is consistent with our other recent studies[3] with proteolytic digestion which also show structural features common to A and B.

Table 4

Immunoprecipitation of labeled crude progesterone-receptor complexes by sheep anti-receptor A antibodies

Methods as described in Ref. 17.

Labeled receptor source	Additions	Sucrose gradient radioactivity in 4S peak (cpm)
[^{3}H]Progesterone complexed to partially-purified hen A and B receptor 4S subunits[a]	None	1800
Same	Sheep IgG before immunization	1200
Same	Sheep IgG after immunization	300
Same	Sheep IgG from injected nonproducer	1700
Free [^{3}H]progesterone only	Sheep IgG after immunization	No binding

[a] Hen receptors purified about 500 times by ion-exchange chromatography.

Discussion

These studies of purified receptor-hormone complexes have shown further evidence to support our contention that the proteins isolated by the published procedures (6, 13, 21) are indeed authentic oviduct progesterone-receptor complexes. The materials isolated in this way are active in DNA-binding experiments with purified DNA fragments of the chicken ovalbumin gene.[4] These efforts are directed toward attempts to understand the nature of these interactions with the genome and the consequences of this interaction upon gene transcription.

The Receptor A and B subunits can be isolated as a large complex containing both proteins together in equimolar amounts, consistent with our interpretation that they are linked as a dimer or higher oligomer *in vivo*. Cross-linking studies with bifunctional cross-linking agents *in vitro* have been successful in stabilizing a covalent dimeric molecule whose properties are identical with the native dimer (2). From our earlier studies on the effects of receptor dimers and subunits on chromatin transcription *in vitro* (5), we have concluded that the dimer is the biologically active material. Further tests of this hypothesis are now ongoing in the laboratory.

The progesterone receptor's subunit structure is apparently very similar to that of other steroid receptors. Rat uterine estrogen receptor[5] and androgen receptor (15) at least can also be resolved into 2 separate hormone-binding molecules. The 2 molecules can also be identified in a higher molecular weight form, also consistent with a dimeric structure. If our observations on the functional significance of such a dimeric form are ultimately shown to be correct, this points to possible avenues for regulation of receptor function by control of subunit assembly *in vivo*. Receptor-containing nonresponsive tumors, for example, may represent tissues containing defects in subunit-subunit assembly. Such a defect might lead to a nonfunctional receptor, which is present in otherwise normal amounts.

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Addendum

We have recently raised a second antibody in sheep against Receptor B; this antibody also cross-reacts with either Receptors A or B from either chick or hen. This is another criterion of proof that the 117,000 g/mol protein isolated in Ref. 12 is indeed progesterone receptor as claimed.

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