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Estrogen, Androgen, Glucocorticoid, and Progesterone Receptors in Progestin-induced Regression of Human Breast Cancer[1]

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ABSTRACT

A study was made of basic mechanisms involved in regression of breast cancer exposed to high levels of synthetic progestins. The possibility that progestins act on breast cancer by way of the progesterone receptor mechanism and subsequent increase of estradiol 17β-dehydrogenase activity could not be confirmed in this investigation. It is demonstrated that the progestins megestrol acetate and medroxyprogesterone acetate are strong competitors for steroids which bind specifically to androgen, glucocorticoid, and progesterone receptors, indicating that the progestins are able to bind to these receptors with high affinity. In contrast, these progestins do not compete with estradiol for estrogen receptor binding. In 34 patients with progressive metastatic breast cancer, results of receptor studies have been correlated with clinical response during treatment with megestrol acetate. Statistically, regressions were significantly associated with tumors containing large amounts of androgen receptors. Clinical correlation with the quantities of glucocorticoid receptor was weak, while such correlations with estrogen and progesterone receptors were absent. However, we did demonstrate relationships between the quantities of the various receptors in breast cancer. Tumors containing a large amount of androgen receptors also generally contain estrogen receptors. It might be that a favorable response to progestins is confined to the group of patients with hormone-responsive breast cancers, as such characterized by the presence of estrogen receptors, and that within this group the actual androgen receptor levels determine response.

INTRODUCTION

Results of clinical trials have demonstrated that synthetic progestins such as MA[3] are useful in the management of metastatic breast cancer (3, 4, 15). At our Institute, 160 patients with metastatic breast cancer have been treated with MA. Objective remission was found in 48 patients (30%), with median time until progression of 9.5 months (1).

It has been suggested that steroid hormone receptors are involved in additive steroid therapy in breast cancer. In patients treated with estrogens, androgens, or glucocorticoids, objective tumor regressions were obtained in 60% of the patients with positive ER values, whereas only 8% of the patients with negative ER values responded favorably (12). There is some clinical evidence, however, that breast cancer patients who respond to progestin therapy do not belong to exactly the same group as do those who respond to the conventional androgenic or estrogenic hormones (15). Furthermore, patients whose tumors were unresponsive to prior therapy with estrogens alone subsequently responded to a combination of estrogen and progesterone (5, 14).

In addition to ER, many breast cancer specimens contain AR, GR, and PR (7, 18, 19). The role of the various receptor sites in progestin therapy has not been established yet, and the mechanisms of action by which additive endocrine therapies cause breast cancer regression are still not understood. In endometrial cancer, however, the observation that the activity of E_2DH increased during progestin therapy provided a basis for understanding the action of progestins (6, 13). E_2DH activation results in a lower intracellular estradiol level and, consequently, reduction of estrogenic activity. Pollow *et al.* (13) suggested that the PR mechanism is involved in E_2DH activation by progestins. Furthermore, a decline of cytosolic ER levels was found during progestin therapy of endometrial cancer (6, 11). Lübbert and Pollow (9) have recently demonstrated the presence of E_2DH in human breast cancers.

In this investigation, the E_2DH activity in breast tumors was studied, and the effect of MA administration on E_2DH activity was examined in 6 patients. To gain some insight into the interactions of progestins with the various receptors of breast cancer, the relative affinity of some progestins for these receptors was determined. In a clinical study, tumor responses during MA therapy were correlated with the amounts of each of the various receptors in the tumors of a series of breast cancer patients.

MATERIALS AND METHODS

Breast Cancer Tissues. Breast cancer specimens were placed on ice immediately after surgery and transported to the pathology department where nontumorous tissue was removed and representative samples were taken for histological examination. Within 30 min after surgery, samples were frozen and stored until analysis in a −70° freezer or under liquid nitrogen.

Chemicals. 17β-[2,4,6,7-^{3}H]Estradiol (90 to 115 Ci/mmol), 17β-[4-^{14}C]estradiol (50 mCi/mmol), [1,2,4,5,6,7-^{3}H]DHT (110 to 150 Ci/mmol), and [6,7-^{3}H]dexamethasone (35 to 50 Ci/mmol) were obtained from New England Nuclear Chemicals, Dreieich, W. Germany. [17α-*methyl*-^{3}H]R5020 (promegestone; 70 to 87 Ci/mmol) and unlabeled R5020 were kindly donated by Dr. J. P. Raynaud, Roussel-Uclaf, Romainville, France. Unlabeled steroids and other chemicals of analytical grade were obtained from Merck AG, Darmstadt, W. Germany, Serva Feinbiochemica, Heidelberg, W. Germany, and Sigma Chemi-

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[3] The abbreviations used are: MA, megestrol acetate; ER, estrogen receptor; AR, androgen receptor; GR, glucocorticoid receptor; PR, progesterone receptor; E_2DH, 17β-estradiol dehydrogenase; DHT, 5α-dihydrotestosterone; PB, phosphate buffer (0.15 M Na_2HPO_4:KH_2PO_4, pH 7.4); MPA, medroxyprogesterone acetate.

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cal Co., St. Louis, Mo. Dextran T70 was obtained from Pharmacia, Uppsala, Sweden, and Noble's agar was from Difco Laboratories, Inc., Detroit, Mich.

Receptor Assays. Low-temperature agar gel electrophoresis according to the method of Wagner (19) was used, enabling simultaneous assessment of the various receptors. For analysis, frozen tissue was pulverized under liquid nitrogen (Microdismembrator; Braun, Melsungen, W. Germany) and, after thawing, homogenized in 10 mM Tris-HCl:1.5 mM EDTA:0.5 mM dithioerythritol buffer, pH 7.4. Cytosol (supernatant) was obtained by ultracentrifugation (100,000 × *g*, 60 min, 2°). Samples were prepared by incubation of cytosol with ^{3}H-steroids for 2 hr at 4°. Incubation concentrations of ^{3}H-ligands were: 17β-estradiol, 10 nM; DHT, 30 nM; dexamethasone, 10 nM; and R5020, 10 nM. Samples for correction of nonspecific binding were prepared by adding a 100-fold excess of unlabeled 17β-estradiol, DHT, dexamethasone, or R5020, respectively, to duplicate samples. To reduce albumin binding, 17β-estradiol and DHT samples were treated after incubation with charcoal:dextran [0.5% (w/v) Norit A, 0.05% Dextran T70, and 0.1% gelatin in 10 mM Tris-HCl:1.5 mM EDTA:0.5 mM dithioerythritol buffer, pH 7.4] for 90 min, while R5020 samples were treated for 15 min (17). Agar gel electrophoresis was performed on 0.05-ml samples for 90 min (21 V/cm, 130 ma, 4°). After electrophoresis, agar slabs were cut into 9 fractions at the cathodic side and 7 fractions at the anodic side of the origin. ^{3}H content of the fractions was determined by liquid scintillation counting. Results of receptor assays are expressed as fmol/mg protein.

Competition Experiments. In a typical experiment, an excess of tritiated ligand was added to a cytosol:buffer mixture together with varying amounts of unlabeled competitor in a range between 1 and 1000 times molar excess over the radioactively labeled ligand. To enable correction for nonspecific binding, parallel incubations were made containing a 100-fold molar excess of unlabeled ligand. Binding data, corrected for nonspecific binding, were expressed as percentage of the amount specifically bound in the absence of competitors. The results were plotted on a logit scale against the log competitor excess, and linear regressions were fitted to the data. The molar excess of competitor which causes 50% displacement of radioactive ligand was estimated as a measure of affinity of the competitor for the receptor, expressed as relative affinity.

Assay of E_2DH Activity. E_2DH activity was estimated in 800 × *g* supernatants according to the method of Lübbert and Pollow (9) with some modifications. Frozen tissue was pulverized and extracted at 4° for 10 min with 4 parts PB (w/v). An 800 × *g* supernatant was prepared by centrifugation (10 min). The standard reaction mixture contained 2 nmol [^{14}C]estradiol (dissolved in 0.025 ml methanol), 26 nmol unlabeled estradiol (dissolved in 0.01 ml methanol), 0.5 to 2.0 ml 800 × *g* supernatant, and PB to make a total volume of 5.0 ml. This mixture was preincubated at 37° for 10 min. The reaction was started by the addition of NAD$^+$ (0.025 ml of an 80 mM solution in PB) and continued for 30 min at 37°. [^{14}C]Estradiol conversion was stopped by the addition of 0.05 ml of a mixture of 0.02 M estradiol and 0.02 M estrone in methanol. The reaction mixture was then extracted 3 times with 5 ml chloroform:ether (1:3, v/v). Extracts were pooled and evaporated to dryness under nitrogen. The residue was redissolved in 0.2 ml chloroform and transferred quantitatively to a thin-layer plate (precoated Silica Gel 60 F254, 0.25 mm; Merck AG, Darmstadt, W. Germany). Estrone and estradiol were separated with a solvent system of chloroform:ethyl acetate (4:1, v/v). Radioactivity of separated steroids was quantitated on a radiochromatogram scanner (LB 2721; Berthold, Wildbad, W. Germany). E_2DH activity is expressed as nmol estrone formed per 30 min per mg 800 × *g* supernatant protein.

RESULTS

Competition Studies. Eight mammary cancers with known receptor concentrations provided cytosols for studying the affinity of MA for the various receptors. For comparative purposes, the competitive effects of MPA and progesterone for AR and GR were also estimated. DHT, dexamethasone, and promegestone (R5020) bind with high affinity to AR, GR, and PR, respectively, although cross-affinity may exist to some degree. To minimize interference of PR binding in experiments with ER, AR, and GR, cytosols were selected containing small amounts of PR (Table 1).

With ER, no significant displacement of radiolabeled estradiol by MA or MPA could be detected. MA competed well for PR, AR, and GR (Chart 1). The relative affinities of MA for PR, AR, and GR were 3, 4, and 8, respectively. MPA was found to compete slightly more strongly for AR and GR (relative affini-

Table 1

Concentrations of various receptors in breast cancer cytosols used in the competition studies

ER, AR, GR, and PR were estimated by low-temperature agar gel electrophoresis.

Tumor	Used in experiments for	fmol/ml cytosol[a]			
		ER	AR	GR	PR
198	ER	6,200	675	700	ND[b]
217	PR	1,470	810	200	2,620
253[c]	PR	630	380	470	21,800
368	AR	2,180	780	770	120
424	GR	1,080	75	525	285
475	GR	290	ND	810	ND
503	AR, GR	635	370	400	920
777	ER	1,150	180	300	760

[a] Protein concentrations of the cytosols ranged from 8.5 to 19.5 mg/ml cytosol.
[b] ND, not detectable.
[c] Tumor 253 was obtained from a patient receiving low-dose estrogen therapy.

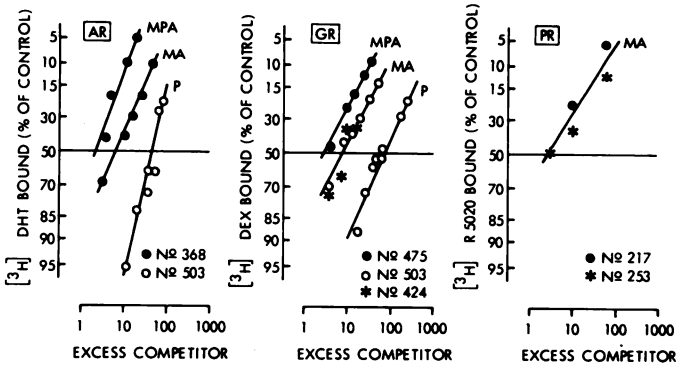

Chart 1. Competition of MA, MPA, and progesterone (*P*) for AR, GR, and PR of human breast cancers. Numbers refer to tumor numbers. For each type of receptor, the binding data, expressed as percentage of specifically bound tritiated ligand, are plotted on a logit scale as function of the log molar excess of competitor. These progestins did not compete significantly for the ER. *DEX*, dexamethasone.

ties, 2 and 3, respectively). The capacity of progesterone to compete for AR and GR (relative affinities, 45 and 71, respectively) was considerably lower.

E_2DH Activities in Breast Cancer Specimens. To demonstrate the presence of E_2DH in breast cancer, the capacity of 800 × *g* supernatants to oxidize estradiol in the presence of NAD^+ was determined in some arbitrarily chosen specimens. E_2DH activity was observed in 10 of 10 primary tumors and in 2 of 4 metastatic deposits.

We were in the position to make a pilot study of the E_2DH activity in metastatic tissues of 6 advanced breast cancer patients before as well as during MA therapy. The E_2DH determinations in the consecutive samples, which were kept at −70° until analysis, were performed simultaneously. The results are shown in Table 2. Prior to therapy, E_2DH activity was present in 4 tumors and absent in the tumors of 2 patients. No significant increase in E_2DH activity during therapy was observed in any of the patients, although tumor regression was reported in 4 of them.

Correlations between Receptors and Clinical Response. The response to MA administration (daily dose, 160 to 180 mg p.o.) was assessed in 34 postmenopausal breast cancer patients with progressive disease in whom one or more of the receptors had been determined. Therapies lasted for at least 6 weeks, and objective criteria for the assessment of response could be used inasmuch as these patients had other lesions to document the response. Clinicians who evaluated response were unaware of the receptor contents of the tumors. Objective remissions, defined according to the criteria of the EORTC Breast Cancer Cooperative Group, were obtained in 17 patients. The duration of remission varied from 2 months to more than 23 months.

In Chart 2, the distributions of the respective receptors are compared in patients in whom remission occurred (responders) and in those with stable or progressive disease (nonresponders).

Statistical tests revealed a significant difference between these groups in the distributions of the amounts of AR (p = 0.01, Wilcoxon test). A weak correlation was also found with GR (p = 0.07), but there were no statistically significant relationships between clinical responses and quantities of ER and PR (p = 0.34 and 0.24, respectively). While 7 of 17 tumors of responding patients did not contain a measurable amount of PR, this was the case in only 1 of 12 tumors of the nonresponders. This difference is of borderline statistical significance (p = 0.1).

As reported earlier (16), we found relationships between the amounts of ER, AR, and GR in breast cancer. In this paper, these associations, including those with PR, are demonstrated with results of all receptor analyses in breast cancer as performed at present in this laboratory. Associations between the quantities of the several receptors were evaluated using the rank correlation coefficient of Kendall (Table 3). All relationships, except GR-PR, were found to correlate in a statistically significant manner, although the associations are not strong.

Similar associations occur in the receptor values of the present study. All tumors without PR contained no ER or only small amounts of ER (<60 fmol/mg protein). It is of interest to note that all patients with AR levels above a cutoff level of 30 fmol/mg protein were responders. Their tumors also contained ER (range, 12 to 750 fmol/mg protein) and GR (range, 15 to 30 fmol/mg protein), but PR was present in only 5 of 7 cases (range, 0 to 250 fmol/mg protein). In our larger tumor material, 44 of 111 tumors obtained from postmenopausal women contained over 30 fmol AR per mg protein. Of these, 40 specimens also contained ER in varying amounts.

Two remissions were associated with malignant tumors devoid of AR. The best explanation for an unexpected finding of a clinical remission associated with a tumor lacking receptors might be that the specimen was obtained from a patient having receptor-containing as well as receptor-lacking metastases.

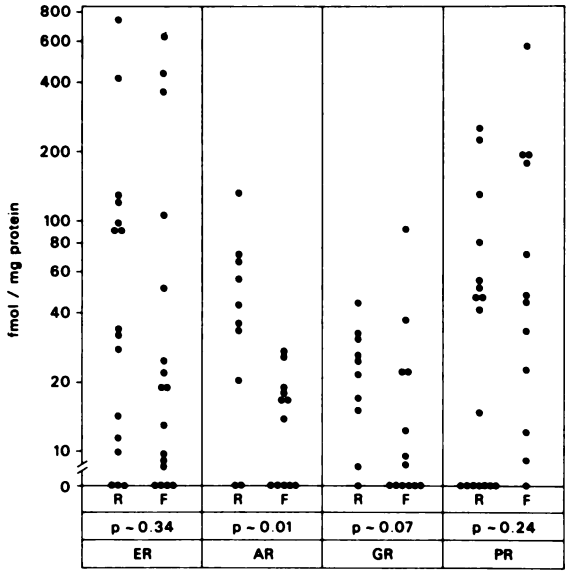

Chart 2. For each type of steroid hormone receptor, the quantities, expressed as fmol/mg protein, are compared between responders (*R*) and nonresponders (*F*) to MA administration. The p values given (2-sided) are from the Wilcoxon test, corrected for ties.

Table 2

E_2DH activity in breast cancer specimens taken subsequently before and during MA administration

Patient	Clinical response	No. of days[a]	E_2DH (nmol estrone/30 min/mg protein) Before	During
540	Regression	7	0.17	0.19
569	Regression	5	0.13	0.15
591	Regression	7	0.13	0.14
564	Regression	6	ND[b]	ND
581	Progression	7	0.24	0.24
532	Stable	84	ND	ND

[a] Number of days between start of therapy and taking of second biopsy.
[b] ND, not detectable.

Table 3

Relationships between the quantities of the various receptors in breast cancer

ER, AR, GR, and PR were estimated by low-temperature agar gel electrophoresis. Total number of patients, 237; mean age, 59 years. Premenopausal, 19%; postmenopausal, 64%; castrated, 16%. Primary tumors, 32%; metastatic tumors, 68%.

Set	No. of patients	Kendall rank correlation coefficient	p
ER-PR	155	0.23	<0.0001
ER-AR	174	0.29	<0.0001
ER-GR	180	0.26	<0.0001
AR-PR	113	0.22	0.0003
AR-GR	164	0.31	<0.0001
GR-PR	118	0.03	0.33

DISCUSSION

The possibility that tumor regression in breast cancer during MA administration proceeds by mechanisms as postulated for endometrial cancer is contradicted by some observations in the present study. As demonstrated, many but not all breast tumors possess *in vitro* capacity to oxidize estradiol. However, no significant increase in E_2DH activity was observed during MA therapy. Furthermore, in the clinical correlation study, 7 of 17 responders lacked PR in their tumors, which contradicts the suggestion that the presence of PR is required for MA action on breast cancer.

From the competition studies, it may be concluded that MA competes strongly with DHT, R5020, and dexamethasone for AR, PR, and GR, respectively. The high-affinity character of binding was also demonstrated recently by MacLaughlin and Richardson (10), who, using tritiated MPA, found dissociation constants of 6×10^{-10} and 5×10^{-10} M, respectively, for the binding to PR and AR. It appears that MA and MPA have a broad receptor specificity, while other steroids interact mainly with only one of the receptors. Therefore, part of the specificity of binding of steroids is determined by their configuration and not solely by the configuration of the receptor binding sites.

In the present study, an estimate of the receptor quantities was made using a single concentration method. With such a method, underestimation of the available number of receptor sites will occur due to equilibrium kinetics. However, no attempt was made to correct for underestimation. In the present study, the receptor amounts are handled by rank-order statistics.

As demonstrated, the quantities of the various receptors found in breast cancers are positively associated with each other, although the relationships are rather weak. With increasing amounts of ER, there is a corresponding increase in the quantities of the other receptors. Recently, Allegra *et al.* (2) reported similar observations with their population of breast cancer patients. In contrast to their study, we found no correlation between the quantities of GR and PR.

There may be a link in the regulation of synthesis of the various steroid hormone receptors, but secondary regulation mechanisms also appear to be present. This is demonstrated by Patient 253 (Table 1), who received low-dose estrogen therapy preceding receptor determinations. The tumor contained a very high level of PR's, but low or moderate levels of the other receptors. It was hypothesized by Horwitz *et al.* (8) that PR synthesis in breast cancer is estrogen dependent.

It may be doubted that ER is actively involved in the mechanism of action of progestins, since the competition studies ruled out the importance of ER binding. However, due to the above-mentioned relationships in the quantities of the various receptors, tumors with high AR levels may largely coincide with ER-containing tumors. Indeed, most (40 of 44) of these tumors contained varying amounts of ER.

In view of these data, it would appear that ER may be a marker for hormone responsiveness of a tumor, irrespective of its role in the regression mechanism. Responsiveness to a particular type of endocrine therapy, however, may actually be determined by one (or more) of the various receptors.

Data from the present study suggest that AR is directly involved in MA-induced regression and that AR acts as a receptor for MA. Furthermore, a high concentration of AR, and not merely its presence, appears to reflect the sensitivity of mammary cancer to MA. A similar observation was made for endometrial cancer, inasmuch as remissions during progestin treatment were reported to be associated with high PR contents of the tumors (20).

This suggests that suppression of tumor growth occurs in cases where a sufficiently high number of receptor:progestin complexes are translocated to the tumor cell nuclei. One may hypothesize that a high nuclear concentration of these complexes is necessary to compete adequately with nuclear receptors for acceptor sites. As a result, some transcription processes operative in hormone responsive tumor cells may be inhibited.

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