Macromolecular Binding of Dexamethasone as Evidence for the Presence of Mineralocorticoid Receptor in Human Breast Cancer

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ABSTRACT

Corticoid (CR)-, estrogen-, and progestin-binding sites were assayed in cytosol from 356 human breast tumors, using dexamethasone (DXM), 11β-methoxy-17-ethynyl-1,3,5(10)estratriene-3,17β-diol (R2858; Moxestrol), or 17,21-dimethyl-19-norpregna-4,9-diene-3,20-dione (R5020; promegestone), respectively. These sites were assayed on the fresh tumors or after storage for 15 days to 6 months in liquid nitrogen. Corticoid binding, measured after incubation for at least 1 hr at 20° and overnight at 0°, was recovered in 70 to 80% of the tumors. The effect of storage on CR, estrogen receptor, or progestin receptor stability was minimal, provided that tumor samples were stored in liquid nitrogen. In studies on the salt stabilization of [3H]DXM-binding sites, 1 mM ethylenediaminetetraacetate had no stabilization effect on CR, while the presence of 10 mM sodium molybdate in buffer inhibited the time-dependent decrease that occurred spontaneously in these sites. In a study with a dextran-coated charcoal adsorption technique on 236 fresh tumors, attempts were made to distinguish between glucocorticoid and mineralocorticoid receptor binding by measuring binding sites with (a) [3H]DXM displaced with cold DXM (defining CR and mineralocorticoid receptor) and (b) [3H]DXM displaced with a 500-fold excess of a highly specific glucocorticoid, 11β,17β-dihydroxy-17α-(1-propionyl)androsta-1,4,6-triene-3-one (RU 26988) (defining glucocorticoid receptor only). Method a showed that 75% of the tumors contained CR (<150 fmol/mg protein; mean, 38 fmol/mg) and that their presence was correlated (p < 0.001) with estrogen and progesterin receptors. Method b indicated that only 32% of tumors contained CR when the specific glucocorticoid was present in excess and that, in 8% of the tumors, RU 26988 was unable to displace [3H]DXM binding while cold aldosterone was effective. In this 8% of tumors, the DXM-binding entity had the properties of a mineralocorticoid receptor: Kd at 0° for aldosterone of 0.81 nM; a number of binding sites of 51 fmol/mg protein; low- and heavy-sedimentation forms in sucrose gradient analysis; and a steroid specificity restricted to mineralocorticoids. These results indicate that the use of [3H]DXM as radioligand and cold DXM as competitor in CR assays does not discriminate between glucocorticoid and mineralocorticoid receptors, the latter being present in a significant proportion of human breast tumors.

INTRODUCTION

The presence of steroid receptors in human breast cancers is thought to reflect hormone dependence. Recently, attention has been focused on the use of steroid receptor assay as independent or associated prognostic factors for predicting response to adjuvant hormone therapy and possibly chemotherapy (2–4, 18, 19). Particular emphasis has been placed on ER2 and PR, since PR results from ER action on target cells (14, 17, 18, 20). However, besides ER and PR, human breast cancers also contain GR and androgen receptor (2–4, 6, 9, 10, 30) the presence and role of which are poorly understood.

Our initial purpose was to investigate the presence and content of GR in relation to the histopathological features of lesions as we have previously done for ER and PR (14–17), but our preliminary studies on GR gave inconsistent results suggestive of instability and/or degradation of GR during assays and lack of specificity for corticosteroids.

We report here that GR assays should be performed in controlled stabilizing conditions that differ from those routinely used for ER and PR. Moreover, the use of [3H]DXM as radioligand and cold DXM as competitor in the classical GR assay does not discriminate between GR and MR which can also be present in some human breast cancers.

MATERIALS AND METHODS

Tumor Samples. Human breast tumor samples were collected and stored in liquid nitrogen as described previously (15). This series consisted of 356 primary tumor samples stored for either less than 2 weeks (236 specimens) or from 2 weeks to 6 months (120 specimens). The pathological features of the tumors were recorded as described previously (15, 17, 29).

Effects of EDTA and Sodium Molybdate on CR. We have previously demonstrated that 1 mM EDTA stabilizes ER and PR in human breast cancer (15). Molybdate stabilizes liver GR, and 10 mM sodium molybdate is thought to specifically inhibit GR activation (12, 22, 25). To establish a routine GR assay, the effects of both 1 mM EDTA and 10 mM sodium molybdate on [3H]DXM-binding site concentrations were investigated in ER-PR-positive breast cancer recurrences from 3 hypophysectomized patients as follows. Cytosol, 0.1 ml (1 mg protein per ml), in GTM buffer, was incubated for various time intervals at 20° and then overnight at 0° with 10 nM [3H]DXM (final concentration) in 0.1 ml of (a) GTM buffer, (b) GTE2M buffer, (c) GTM buffer plus 20 mM sodium molybdate, (d) GTE2M buffer plus 20 mM sodium molybdate, or (e) GTM buffer in which 0.01

2 The abbreviations used are: ER, estrogen receptor; PR, progestin receptor; GR, glucocorticoid receptor; DXM, dexamethasone (9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione); MR, mineralocorticoid receptor; CR, corticoid receptor; GTM buffer, 10 mM Tris-HCl, pH 8.0 at 0°, containing 12 mM monothioglycerol and 10% glycerol (v/v); GTE2M buffer, 10 mM Tris-HCl, pH 8.0 at 0°, containing 12 mM monothioglycerol, 10% glycerol (v/v), and 2 mM EDTA; RU 26988, 11β,17β-dihydroxy-17α-(1-propionyl)androsta-1,4,6-trien-3-one; RBA, relative binding affinity.
ml of GTM buffer containing 10 μM sodium molybdate (final concentration) was added after 4 hr at 20°. Free steroid was removed by the dextran-coated charcoal adsorption technique as described for ER and PR assays except that charcoal slurry was prepared in GTM buffer instead of GTE2M buffer (14, 15).

Steroid Receptor Assay Procedures. ER and PR were assayed by Scatchard analysis as described in detail in Refs. 15 and 26. To homogenize samples in an EDTA-free buffer (see below for GR and MR) while keeping the optimal homogenization buffer for simultaneous assay of ER and PR [GTE2M buffer (15)], the following procedure was adopted. Cytosol, 0.1 ml (1 mg protein per ml), prepared in GTM buffer, was incubated with 0.1 ml of GTE2M buffer containing [3H]-11β-methoxy-17-ethynyl-1,3,5(10)-estratriene-3,17β-diol and [3H]-17,21-dimethyl-19-norpregna-4,9-diene-3,20-dione (0.1 to 2 nm final concentrations) for ER and PR assays, respectively (15, 26). Incubations were overnight at 0° for PR and for 5 hr at 25° and then overnight at 0° for ER (15). In tumor cytosols prepared in GTM buffer, CR content was assayed by using a single-saturating dose assay (11) modified as follows. Cytosol, 0.1 ml in GTM buffer (1 mg protein per ml), was incubated with 0.1 ml of 20 nM [3H]DXM in GTM buffer containing 20 mM sodium molybdate for 3 hr at 20° and then overnight at 0°. In the CR assay, nonspecific binding was evaluated by the addition of either a 100-fold excess of cold DXM or a 500-fold excess of RU 26988 (21, 25, 28). Incubations were overnight at 0° for PR and for 5 hr at 25° and then overnight at 0° for ER (15). In tumor cytosols prepared in GTM buffer, CR content was assayed by using a single-saturating dose assay (11) modified as follows. Cytosol, 0.1 ml in GTM buffer (1 mg protein per ml), was incubated with 0.1 ml of 20 nM [3H]DXM in GTM buffer containing 20 mM sodium molybdate for 3 hr at 20° and then overnight at 0°. In the CR assay, nonspecific binding was evaluated by the addition of either a 100-fold excess of cold DXM or a 500-fold excess of RU 26988 (21, 25, 28). Incubations were overnight at 0° for PR and for 5 hr at 25° and then overnight at 0° for ER (15).

Scatchard analysis of the binding of [3H]aldosterone in cytosol was performed following the same procedure as that for CR assay except that cytosols were incubated with increasing concentrations of [3H]aldosterone (0.1 to 2 nM final concentration). The competition by unlabeled steroids for [3H]aldosterone and DXM-binding sites in 2 different pools of human mammary tumors (see “Results”) was performed as follows. Aliquots of cytosol, 0.1 ml (1 mg protein per ml), were added to 0.1-ml aliquots of GTM buffer containing 20 mM sodium molybdate and 20 nM [3H]DXM or [3H]aldosterone, either alone or with a 200-fold excess of competing steroids. Incubation and determination of protein-bound radioactivity were as in the studies on [3H]DXM binding.

RESULTS

Effects of Sodium Molybdate and EDTA on CR Stabilization. In studies upon the salt stabilization of [3H]DXM-binding sites, cytosols were incubated with [3H]DXM first at 20° and then at 0°, since, whatever the buffer components, cytosol CR content was always higher when cytosol was preincubated for at least 1 hr at 20° than when incubated at 0° only (data not shown). Results are presented in Chart 1. In all cytosol prepared either in GTM buffer or in GTE2M buffer, DXM-binding site concentration decreased with time from a maximum value recorded after 1 hr of incubation. In contrast to its action on ER and PR (15), 1 mM EDTA had no stabilizing effect on CR. After 4 hr of incubation at 20°, even the slight presence of EDTA amplified the decrease in DXM-binding sites. On the other hand, 10 mM sodium molybdate in GTM buffer inhibited the time-dependent decrease in these sites. This molybdate stabilizing effect was found to be irreversible and was also abolished by 1 mM EDTA.

DXM-binding site concentrations (CR content) in cytosols prepared in GTM buffer containing 10 mM molybdate and incubated for 3 hr at 20° and then overnight at 0° were 122, 58, and 42 fmol/mg cytosol protein in breast cancer recurrences from hypophysectomized patients. Mean CR content in 24 CR-positive lesions was 18 ± 12 (S.E.), 26 ± 24, and 87 ± 49 fmol/mg protein when assays were performed in GTM buffer, GTE2M buffer plus 10 mM molybdate, and GTE2M buffer plus 100 mM molybdate, respectively. These results confirm the CR-stabilizing effect of molybdate and demonstrate that CR assay should not be performed with EDTA as a buffer component, at least for human breast cancer specimens.

Relationships between ER, PR, and CR in Human Breast Cancers. In this series of 356 human breast cancer specimens (Table 1), ER and PR statuses were in agreement with previous results obtained on a larger population (16, 17). The effect of storage on receptor stability, whether CR, ER, or PR, was minimal, provided that tumor samples were stored in liquid nitrogen (15). In 236 samples stored for less than 2 weeks, and of which 82% contained CR, the mean CR content in CR-positive lesions was 38 ± 36 fmol/mg protein. CR content ranged from 3 to 150 fmol, and 53% of the CR-positive lesions had a CR content greater than 15 fmol. The frequency of CR-positive samples ([3H]DXM binder) was higher than that previously recorded for smaller tumor series (3, 4, 6, 30) for several reasons; the cut-off value of 3 fmol/mg protein was lower than in other CR assay protocols, and the presence of molybdate could have acted as stabilizer.

The percentage of CR-positive lesions was comparable to that of ER and greater than that of PR. A close relationship was noted between the presence of CR and both ER (p < 0.001) and PR (p < 0.001), lending further support to the view that the receptors of different hormone classes are often encountered concomitantly in human breast cancers (3, 4, 9, 18, 19).

Analysis of [3H]DXM Binding. The cross-reactivity of a given steroid hormone with several steroid receptors is a well-known phenomenon that has led to the use of discriminating synthetic
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Table 1

<table>
<thead>
<tr>
<th>Presence of receptors (%)α</th>
<th>No. of specimens (men)</th>
<th>Age of patients (yr)</th>
<th>ER binder</th>
<th>PR binder</th>
<th>DXM binder</th>
<th>RU26988 binder</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor samples stored in liquid nitrogen for &gt;2 wk</td>
<td>120 ± 54 ± 6</td>
<td>65 ± 64</td>
<td>75 ± 45</td>
<td>40 ± 57</td>
<td>73 ± 57</td>
<td>68 ± 59</td>
</tr>
<tr>
<td>Tumor samples stored in liquid nitrogen for &lt;2 wk</td>
<td>236 ± 67 ± 5</td>
<td>78 ± 44</td>
<td>82 ± 53</td>
<td>74 ± 53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α Results are expressed as percentage of steroid receptor-positive lesions in the respective total population. ER versus PR, p < 0.001; ER versus CR, p < 0.001; PR versus CR, p < 0.001 for both DXM and RU 26988 binders.

β CR was evaluated by displacement of specifically bound [3H]DXM either by cold DXM (defining DXM binder) or by the glucocorticoid RU 26988 (defining RU 26988 binder). RU 26988 binders were dichotomized from DXM binder when [3H]DXM displacement by DXM was 40% higher than was [3H]DXM displacement by RU 26988.

c Mean ± S.E.

d DXM-binding site concentration above 3 fmol/mg cytosol protein (limit of detection).

e DXM-binding site concentration above 15 fmol/mg cytosol protein.

Glucocorticoid-binding site heterogeneity has been reported in various tissues (1, 5, 6, 31). Although corticosteroid-binding globulin-like sites are often involved, the binding of [3H]DXM or similar potent synthetic glucocorticoids has generally been taken as evidence for GR receptor binding (1, 4, 6, 13). In our study, CR presence and content were investigated by examining comparatively specific [3H]DXM displacement by DXM (defining DXM binding) and by RU 26988 (defining RU 26988 binding). As shown in Tables 1 and 2, divergent results were obtained for the incidence of specific binding; in 50% of cases, binding site concentrations were higher when DXM rather than RU 26988 was used as displacer. These results strongly suggest that, in human breast cancer, DXM might bind to at least 2 different entities. DXM binding was exclusively due to GR in 32% of lesions and predominantly due to GR in a further 42% of lesions. In the remaining 8% of DXM-positive lesions, DXM binding was presumably due to MR as established below.

Identification of GR and MR in Human Breast Carcinomas.

To determine the identity and specificity of CR [3H]DXM binder), 2 groups of human breast tumor samples were constituted: in Group 1 (12 specimens), the glucocorticoid RU 26988 was able to fully displace [3H]DXM; in Group 2 (7 specimens), RU 26988 was ineffective. The identity of the CR was established by sucrose gradient analysis (Chart 2). Both groups showed the presence of low (4S)- and heavy (8S)-sedimentation forms from which [3H]DXM was displaced by cold DXM. To identify MR, sucrose gradient analysis of [3H]aldosterone binding was performed. The results show: (a) the presence of low and heavy [3H]aldosterone binder forms in cases where aldosterone could, but RU 26988 could not, displace [3H]DXM (Chart 2B, Group 2); and (b) the absence of [3H]aldosterone binding in cases where RU 26988 fully displaced [3H]DXM binding, but aldosterone could not compete (Chart 2A, Group 1). Incubation of Group 2 cytosol with [3H]aldosterone for Scatchard analysis yielded a plot presenting a single class of cytoplasmic binding sites with the affinity characteristics of a MR, an apparent Kd at 0°for [3H]aldosterone of 0.81 nm and a number of binding sites of 51 fmol/mg protein (Chart 3). The specificity of [3H]DXM binding in both groups was further investigated in competition studies using a dextran-coated charcoal method. The results, presented in Table 3, confirm the findings obtained by sucrose gradient analysis. GR is exclusively present in Group 1, and MR is exclusively present in Group 2. Thus a CR assay using [3H]DXM as radioligand and cold DXM as competitor does not discriminate between MR and GR which could be present either alone or together in human breast cancer.

DISCUSSION

Initially devised to investigate the relationships between cortisol ER, PR, and GR in human breast tumors, the present study indicates that the classical DXM binder is in fact constituted of 2 entities. One entity probably represents specific GR since it has the steroid specificity of GR. [3H]DXM binding to this entity was fully displaced by the true glucocorticoid RU 26988 (21, 25, 28). A second DXM-binding entity was found in some tumor specimens and has the properties of a MR: an apparent Kd at 0°for [3H]aldosterone of 0.81 nm; a number of binding sites of 51 fmol/mg protein; low- and heavy-sedimentation forms in sucrose gradient analysis; and a steroid-binding specificity restricted to mineralocorticoids. In particular, this second DXM-binding entity gave cortisol and aldosterone RBA's of 10 and 140%, respectively. These observations support the possibility that not only GR but also MR may be encountered in human breast cancer.

Glucocorticoid-binding site heterogeneity has been reported in various tissues (1, 5, 6, 31). Although corticosteroid-binding globulin-like sites are often involved, the binding of [3H]DXM or similar potent synthetic glucocorticoids has generally been taken as evidence for GR receptor binding (1, 4, 6, 13), although it has also been acknowledged that the situation may

Table 2

<table>
<thead>
<tr>
<th>CR content (fmol/mg protein)</th>
<th>No. of specimens</th>
<th>% of specimens</th>
<th>RU26988 binder (3H)DXM displaced by DXM</th>
<th>RU26988 binder (3H)DXM displaced by RU 26988</th>
<th>No glucocorticoid binder (no displacement of [3H]DXM by either DXM or RU 26988)</th>
<th>3H]DXM displacement from CR by DXM and by RU 26988 in 236 specimens stored for less than 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM binder [3H]DXM displaced by DXM</td>
<td>194</td>
<td>82</td>
<td>38 ± 36a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RU26988 binder (3H)DXM displaced by RU 26988</td>
<td>187</td>
<td>79</td>
<td>47 ± 52</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Subclassification</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>CR content measured with DXM and RU 26988 differ by</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RU26988 ineffective; DXM equivalent to aldosterone</td>
<td>7</td>
<td>3</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α Mean ± S.E.

β For each lesion, the ratio of the number of binding sites determined with cold DXM over the number determined with cold RU 26988 was calculated. Specimens were divided into 3 groups according to whether measurements with cold DXM were greater by <10%, by 10 to 40%, and by >40%. Lesions with receptor contents of less than 10 fmol/mg protein (whatever the ligand) were systematically classified in the no-difference (i.e., <10%) group.
be more complex (5, 7, 31). In human breast tumors, 2 different types of glucocorticoid binding have been detected (6). One binder was presumably corticosteroid-binding globulin, present in unusually high quantities; the other was characterized as a DXM binder and was, until now, considered to be GR (6). The data we report here strongly support the view that, in human breast cancer cytosol, DXM binding may represent binding to 2 different entities, namely, GR and MR. This DXM binding will partly (<40% of total binding) result from MR binding in 50% of DXM-positive lesions and predominantly (>50% of total binding) from MR binding in 10% of these.

The cross-reactivity of DXM with respect to GR and MR has been well documented in human and rat kidneys (7, 8). We show here that in human breast cancer as in kidney (7, 8); (a) [3H]aldosterone binds specifically to a single class of cytoplasmic sites which show the steroid specificity appropriate for physiological MR’s; and (b) in the presence of cold aldosterone, [3H]DXM binds to a class of sites with the characteristics of GR.

Table 3

<table>
<thead>
<tr>
<th>Competitor</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>100 (112)</td>
<td>100 (42)</td>
</tr>
<tr>
<td>RU 26988</td>
<td>120</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>&lt;0.1</td>
<td>140</td>
</tr>
<tr>
<td>Cortisol</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>Progesterone</td>
<td>&lt;0.1</td>
<td>20</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Estradiol</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
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</table>

*Displacement of 10 nM [3H]DXM by a 200-fold excess of cold DXM is expressed as 100%, and displacement by competing steroids is expressed as a percentage thereof.

Numbers in parentheses, CR contents (homologous DXM displacement) in fmol/mg cytosol protein.

The specificity of [3H]DXM binding was investigated in competition studies using the dextran-coated charcoal method (14). Two groups of tumor samples were constituted from the results presented in Table 2. In Group 1 (12 pooled samples), the true glucocorticoid RU 26988 was able to fully displace [3H]DXM binding; while in Group 2 (7 pooled specimens), RU 26988 was ineffective. The data we report here strongly support the view that, in human breast cancer cytosol, DXM binding may represent binding to

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The demonstration of a MR in neoplastic breast lesions raises the question of its biological significance. It is not clear whether MR has a functional role in mammary cells, since data concerning the influence of mineralocorticoids on the breast are scarce (24). However, aldosterone could, for instance, affect ionic movements throughout the mammary epithelial structure. On the other hand, the biological significance of the presence of MR could perhaps be sought in the observation that all steroid receptor types, i.e., estrogen, progesterin, and glucocorticoid, can occur simultaneously in human breast cancer. Our results are in agreement with previous reports from other groups who have observed on smaller numbers of tumors that steroid receptors are frequently present concomitantly (3, 4, 18, 19). Inasmuch as receptors of different hormone classes are being identified in the same tissue (we demonstrate here the presence of MR in human breast cancer), the understanding of the hormone dependence of tumors is becoming increasingly complex. In particular, a major question remains to be answered. Is hormone dependence a complex endocrine regulation involving estrogen as well as influences from other hormones acting through their own receptors? If this were the case as suggested by McGuire et al. (9, 19), growth and differentiation of target cells would be expressed under the control of an endocrine unit. In other words, some hormones would be prerequisites and others would be subsequently necessary for a given hormone effect. Alternatively, is hormone dependence a simpler phenomenon in which only estrogen and progesterone are involved? In this case, a tentative explanation for the presence of receptors for other hormone classes could be furnished by the hypothesis of an all-receptor common precursor moiety (25, 27). These apparently unnecessary receptors would result from aberrant synthesis due to malignant transformation. This would then explain the apparent lack of correlation between the concomitant presence of various steroid hormone receptors and the responses to either endocrine therapy or disease-free interval in breast cancer patients (2–4). Additional data from both clinical and laboratory investigations are needed for this alternative to be solved.

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