Estrogen and progestin binding by cytosolic and nuclear fractions of human meningiomas

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Frozen tissue samples were obtained from meningiomas in 42 patients. Both cytosolic and nuclear fractions were tested for estradiol and progestin binding using equilibrium binding assays. The results were correlated with the age of the patient and the histological type and cellular density of the tumor.

Cytosolic estradiol binding was noted in 25 (60%) of 42 tumors, with eight (19%) of the 42 having levels over 10 femtomoles (fM)/mg protein. Nuclear estradiol binding was detected in 16 (57%) of 28 tumors, with six (21%) of the 28 having levels over 10 fM/mg protein. Cytosolic progestin binding was noted in 16 (73%) of 22 samples, with levels in nine (41%) of 22 being greater than 10 fM/mg protein. There was no correlation between the level of cytoplasmic progestin binding and either the level of cytoplasmic estradiol binding or the level of nuclear estradiol binding. In several specimens, levels of cytoplasmic progestin binding in excess of 100 fM/mg protein were found in tissues demonstrating little or no estradiol binding by either the nucleus or the cytosol. This discrepancy differs from the situation found in other hormonally responsive tissues such as breast or uterus, and suggests either a possible derangement of the normal cellular hormonal control mechanism or that the measured hormone binder is a molecule other than a classical hormone receptor.

KEY WORDS - meningioma • estrogen • progesterone • cytoplasm • nucleus • hormone binding

Steroid hormone receptors in meningiomas have been the object of study by numerous investigators over the last several years.2-6,13-15,19,22,24,27,30 These research efforts were prompted by the observation that meningiomas are more common in women than in men,29 that they demonstrate enlargement in relation to pregnancy or phase of the menstrual cycle,1 and that they occur more commonly in women with breast cancer than in a matched population of women without breast cancer.23 For these reasons, and because successful hormonal treatment of breast cancer has been shown to be related to the levels of cytoplasmic estrogen receptor, the early studies of putative hormonal receptors in meningiomas focused on the cytoplasmic estrogen receptor.5,15,19,22 Initially, most investigators found specific estrogen binding in the cytoplasm (EBC) of meningiomas, but only in a small proportion of all tumors and at levels below what are considered positive in breast cancers.5,15,19 Later reports demonstrated relatively high levels of cytoplasmic progesterone binding (PBC) in some meningiomas and suggested that this may be of greater importance in these tumors.2,4,13,22,28,30 Moreover, a recent study14 suggested that in meningiomas the elevated levels of PBC may be unrelated to the levels of EBC. However, since the production of PBC in tissue such as endometrium is regulated by the action of estrogen, including binding to the cytoplasmic estrogen receptor and translocation to the nucleus, it is impossible to firmly conclude that the levels of PBC are unrelated to the levels of estrogen receptor, without measuring the levels of EBC as well as estrogen binding in the nucleus (EBN). Markwalder, et al.14 found no detectable EBN in 12 cases. Therefore, to investigate further the possibility that elevated levels of PBC may be unrelated to the levels of EBC, we have studied 46 surgical specimens of meningiomas from 42 patients and assayed both cytosolic and nuclear fractions for specific estrogen and progestin binding whenever possible.

Materials and Methods

Tumor Specimens

Tissue samples were obtained at the time of operation from an unselected group of 42 consecutive patients with the diagnosis of meningioma at the Massa-
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chusetts General Hospital. All patients were receiving glucocorticoids at the time of surgery. In general, samples were obtained at the beginning of surgery from an area of the tumor immediately beneath the tumor surface. An adjacent sample was taken for frozen-section histological examination, and a portion of this was used for the determination of tumor cell density. The specimens for hormone-binding assay were immediately frozen at -20°C in a cryostat and then stored at -80°C until the time of study.

In three cases we were able to obtain two separate specimens from different parts of large meningiomas in order to evaluate the possible variability of binding levels in relation to tumor heterogeneity. In one other case, an aggressive meningioma recurred during the time of the study and specimens were obtained at both operations. Thus, 42 patients provided 46 specimens for evaluation.

Histological Study and Cell Density Determination

All samples were examined at the time of surgery on frozen sections and again at a later date using specimens permanently fixed with formalin, embedded in paraffin, and stained with hematoxylin and eosin (H & E). The tumors were classified as fibroblastic or syncytial if all areas examined showed one of these histological features; if a mixture of these features was present, the tumor was considered transitional. One tumor showed extensive capillary-body formation with perithelial proliferation and was termed "angioblastic." Three specimens from two male patients exhibited numerous mitotic figures (four or more per 10 high-power fields) and necrosis, and were considered malignant.\(^1\) One of these tumors recurred during the period of study, and the patient required a second operation 8 months after the first.

Cell density measurements were performed on the permanently fixed, paraffin-embedded samples stained with H & E. Sections were cut 4 μ thick and examined with a light microscope using × 40 objective and × 10 ocular magnifications and a grid in which each block measured 20 × 20 μ. The number of nuclei was counted in 20 such blocks selected at random, and the cell density was the total number of nuclei counted (that is, the number of nuclei/32,000 cu μ).

Preparation of Cytosolic and Nuclear Fractions

Radiolabeled steroids and the liquid scintillation mixture, Hydrofluor, were acquired commercially.* All other reagents were obtained in the purest grade available.

The frozen tumor sample was weighed, diced with surgical scissors if necessary, and placed into 0.01 M Tris, 1.5 mM EDTA (ethylenediaminetetra-acetic acid), and 0.5 mM dithiothreitol buffer, pH 7.4, containing 10 mM sodium molybdate and 30% w/v glycerol at 4°C. The tissue was then homogenized at 4°C in a Brinkman polytron device† using four short bursts at a medium setting. Between each burst the homogenate was allowed to cool in a 0° to 4°C ice bath. Alternatively, small samples (≤ 50 mg) were homogenized by hand at 4°C using a glass-glass tissue grinder.

The homogenates, depending upon their volumes, were then centrifuged using one of two protocols. For large samples (≥ 100 mg), the homogenates were layered onto 1.2-M sucrose pads and centrifuged at 8500 G for 45 minutes at 4°C, as described by Kelner, et al.\(^11\) The resulting supernatant (above the sucrose layer) was centrifuged again at 105,000 G for 60 minutes at 4°C in order to obtain the usual cytosol preparation. The pellet of the first low-speed spin was the crude nuclear preparation. The homogenates of the smaller samples (≤ 50 mg) were spun directly at 105,000 G for 60 minutes at 4°C, omitting the preliminary spin. It was rarely possible to collect reasonable amounts of nuclear material with such small samples; therefore, to minimize loss of cytosol, direct ultracentrifugation was used. The protein content of all samples was measured according to the technique of Lowry, et al.\(^12\)

In all cases, assays for estradiol and/or progesterin binding were performed on the day of cytosol preparation. On occasion, the nuclear pellets were frozen at -80°C and tested later for steroid binding.

Cytosol Steroid-Binding Assays

Total estradiol binding levels were measured using a single saturation dose assay in which 0.20 ml of cytosol (0.5 to 4.0 mg/ml of protein) was incubated in duplicate with 1.5 to 2 nM of 1,2,6,7-3H-estradiol (106 Ci/mM) in the presence or absence of a 200-fold molar excess of unlabeled diethylstilbestrol (DES) for 60 minutes at 37°C. Total progesterone binding was measured by incubation of cytosol preparations for 4 hours at 4°C using 1.5 to 2 nM of 6,7-3H-R5020 (17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione) (77 Ci/mM) in the presence or absence of a 200-fold molar excess of unlabeled R5020. Following the incubation period, the cytosol preparations were rapidly chilled to 0° to 4°C, and 0.5 ml of dextran-coated charcoal (0.025% w/v and 0.25% w/v, respectively) was added for 10 minutes with shaking. The samples were then cleared of charcoal by centrifugation at 4°C for 15 minutes at 2000 G. Radioactivity was determined in a 0.5-ml aliquot of the resulting supernatant, as described below. Specific binding was considered to be that fraction of the total binding that was competed for by the unlabeled ligand in each case.

Nuclear Steroid-Binding Assays

Crude nuclear fractions of tissue samples were resus-
pended in 1.8 ml of assay buffer, and 0.2-ml aliquots were incubated in duplicate with 1.5 to 2 nM of \(^{3}\)H-
estriadiol or R5020 in the absence or presence of a 200-
fold molar excess of either DES or R5020 for 90
minutes at 30°C to ensure complete exchange with
endogenous hormone. At the end of the incubation
period the samples were rapidly chilled to 0°C to 4°C in
an ice bath and centrifuged at 850 G for 15 minutes at
cold temperatures. The resulting pellet was washed once
with cold buffer and centrifuged again. The bottoms of
the glass test tubes (10 × 75 mm) were cut off and the
samples counted by liquid scintillation in 4.0 ml of
Hydrofluor after vigorous shaking and mixing in a
vortex machine for 10 minutes. This procedure was
sufficient to solubilize the radiolabeled ligands in the
nuclear pellets.

We recognize that incubation of crude nuclear prep-
Arations at 30°C may decrease to some extent the total
number of available binding sites by denaturation; however, this temperature is necessary to achieve sig-
nificant exchange of nuclear-bound steroid hormone.
Thus, the results listed for nuclear binding may under-
estimate the total binding that may be present.

**Measurement of Radioactivity and Data Analysis**

Tritium-labeled ligands were measured by counting the
Hydrofluor in glass mini-vials by means of an
Isocap 300 refrigerated liquid scintillation counter,; accumulating 5000 or more counts per observation,
and an automatic external standard. Quench correction
curves for the conversion of counts per minute to
disintegrations per minute were constructed using \(^{3}\)H-
labeled toluene and variable amounts of chloroform.

Specific binding data (total binding minus nonspe-
cific binding) were corrected for incubation volume and
protein concentration so that cytoplasmic binding data
presented are expressed as femtomoles per milligram
(fM/mg) cytoplasmic protein, and nuclear binding data
are presented as fM/mg nuclear protein. The levels of
cytoplasmic progesterone binding (PBc) were compared
separately with the levels of cytoplasmic estradiol bind-
ing (EBc) using a linear regression analysis.

**Results**

**Specific Estradiol Binding**

We obtained 46 specimens from 42 unselected pa-
tients with meningiomas for analysis of sex steroid
binding. Of the 42 patients, 32 were women with an
average age of 55 years (range 27 to 79 years, Table 1)
and 10 were men with an average age of 59 years (range
39 to 68 years, Table 2). In each case, the size of the
surgical specimen submitted for assay determined the
number of assays that could be performed. In 12 sam-

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1. **TABLE 1**

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* Expressed as number of nuclei/32,000 cu µ of each sample.
† Estradiol binding in the cytoplasm (EBc) and nucleus (EBr) and
progestin binding in the cytoplasm (PBc) and nucleus (PBn) are
expressed in fM/mg protein. — = not tested.

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2. Examples (seven from women and five from men), we were
able to study specific estrogen binding in the cytoplasm
(EBc) and in the nucleus (EBr), as well as specific
progestin binding in both locations (PBc and PBn). In
other specimens, tissue was not sufficient for all four
assays, and the studies had to be selected according to
the sample size. Thus, EBc was measured in all 46
samples, EBr in 31, PBc in 24, and PBn in 12.

Among the 32 women, the range of values for EBc
was 0 to 36.9 fM/mg protein. Detectable levels of EBc
were found in 21 (66%) of the 32 patients; of these, six
(19%) had EBc levels greater than 10 fM/mg protein
(Table 1). The EBr was measured in all specimens from
10 men. The range of values for EBr was 0 to 95.3 fM/
mg protein. Detectable levels of EBr were found in four
(40%) of the 10 men, but only two (20%) had levels
greater than 10 fM/mg protein (Table 2). Overall, 25
(60%) of the 42 patients had detectable levels of EBc,
with eight (19%) having levels greater than 10 fM/mg protein.

The EBc was assayed in two samples from separate parts of the tumor in three female patients (Table 1). In one of these (Case 25), no binding was found in either specimen. In another (Case 9), low levels of EBc (2.9 and 4.4 fM/mg) were detected in both specimens. In the third (Case 8), levels of EBc were higher in one sample than in the other (7.5 and 26.7 fM/mg). In one male patient with a malignant meningioma (Case 36), no EBc was detected either in the specimen obtained from the initial surgery or in a specimen obtained from a recurrent tumor 8 months later (Table 2).

We could not determine if there was a correlation between EBc, EBn, PBc, or PBn and the histological type because of the preponderance of transitional meningiomas (31 of 42 cases) as compared to only five syncytial, three fibroblastic, one angioblastic, and two malignant meningiomas (Tables 1 and 2). Levels of binding were compared with cell density and with the patient’s age, but were not analyzed statistically. Overall, the mean cell density was 72 nuclei/32,000 cu μ of the median was 70 nuclei/32,000 cu μ. All of the EBc values greater than 10 fM/mg protein occurred in tumors having a cell density in the range of 49 to 71 nuclei/32,000 cu μ, suggesting that higher levels of EBc may be correlated with tumors that are slightly hypocellular as determined by this technique. Low levels of EBc (< 10 fM/mg protein) did not appear to correlate with age; however, higher levels (> 10 fM/mg protein) were most common in patients older than age 50 years. Of 13 patients younger than 50 years of age, only one (8%) had an EBc level over 10 fM/mg, whereas seven (24%) of 29 patients aged over 50 years had such levels.

The EBn was measured in tumors from 22 women and seven men (Tables 1 and 2). Among females, EBn levels ranged from 0 to 39.5 fM/mg. Detectable levels of EBn were found in 11 (50%) of 22 women; five (23%) of these 22 had levels above 10 fM/mg protein. Among the men, EBn was found in five (71%) of seven specimens tested, but only one (14%) had a level greater than 10 fM/mg protein. Therefore, 16 (55%) of a total of 29 patients tested had detectable EBn, with six (21%) having levels over 10 fM/mg protein.

In two tumors from female patients, separate specimens from two different areas of the tumor could be compared. In the specimens from Case 8, EBn values of 16.8 and 27.2 fM/mg were recorded. In specimens from Case 9, EBn levels of 0 and 6.2 fM/mg were noted (Table 1). Of the samples measured for EBn, the median cell density was 60 nuclei/32,000 cu μ. Of the six samples that had EBn levels over 10 fM/mg, five were at or below the median cell density, again suggesting higher EBn levels in the slightly hypocellular tumors. An equivalent percentage of tumors from patients 50 years of age or younger (two of 10, or 20%) and older than 50 years (four of 19, or 21%) had EBn levels over 10 fM/mg protein. However, among these patients, the mean level of EBn of those aged 50 years or younger was 14.3 fM/mg, whereas the mean level of those aged 51 years or older was 25.6 fM/mg.

### Specific Progesterone Binding

The PBc was measured in tumors from 14 women and eight men. Detectable PBc levels were found in nine (64%) of the 14 women, with five (36%) having PBc levels over 10 fM/mg. Seven (88%) of the eight men had detectable PBc, with levels in four (50%) being more than 10 fM/mg. Therefore, of all 22 patients tested for PBc, 16 (73%) had detectable PBc and, of these, nine (41%) had levels in excess of 10 fM/mg protein. Levels of PBc were equally spread about the median for cell density, and no relationship between these two factors could be established. In the one case in which PBc could be measured in two separate samples (Case 25), the values (4.1 and 6.6 fM/mg) were similar (Table 1). In correlating PBc with age, there were too few of these samples from the lower age group to draw firm conclusions; however, eight (47%) of 17 patients aged 51 years or older had PBc levels over 10 fM/mg in contrast to only one (20%) of five in the group age 50 years and younger.

The most interesting finding is the lack of any apparent relationship between the levels of PBc and either EBc or EBn (Tables 1 and 2) (correlation coefficient of 0.48 and 0.59, respectively; p < 0.05). Indeed, in several specimens, levels of PBc in excess of 100 fM/mg protein were found in tissues in which negligible or no level of EBc or EBn could be detected.

### Discussion

Most meningiomas are benign tumors that can be cured by complete removal. Total extirpation remains the preferred treatment whenever possible. However, some meningiomas are located in areas where complete
of all breast cancers, only 30% to 40% are ER-positive, cancers that have receptors respond, whereas those lack-data and those of others and found that 87 (77%) of in culture. endometrium and in human MCF-7 breast cancer cells ship of progesterone receptor (PR) to ER and to clinical and only two-thirds of these show a response to any over 10 fM/mg is termed "ER-rich" or "ER-positive." Currently, a breast cancer with a cytoplasmic ER level correlated with clinical response to hormone therapy. showed that cytoplasmic estrogen receptor (ER) levels of these tumors. The critical studies c~me later and showed that PR is induced by estrogen in normal observation that PR is induced by estrogen in normal meningiomas had detectable levels of EBc, with a range of 24 to 2430 fM/gm tumor, respectively. In 1980 and 1982, Poisson, et al., 13,19 reported finding putative ER in 13 (59%) of 22 and 30 (79%) of 38 meningiomas, respectively. In 1982, Yu, et al., 30 found estrogen “receptors” in 15 (94%) of 16 meningiomas. In contrast, Schnegg and coworkers 22 in 1981 reported that, of 10 meningiomas studied, “no meningiomas were found to have estrogen receptor.” However, it is not clear whether those termed “negative” had no detectable receptor or a binding level below some arbitrary level, such as 10 fM/mg protein. A study by Blankenstein, et al., 2 also failed to show high-affinity binding for estradiol in the cytoplasm of meningiomas. A recent investigation by Markwalder and colleagues 4 showed that 20 of 34 meningiomas tested contained low levels of a cytoplasmic estradiol binder, in the range of 0 to 181 fM/gm tumor or 0 to 7 fM/mg protein. However, in contrast to the findings of Yu, et al., 30 who reported a correlation of PBc with EBc, Markwalder, et al., 14 found no such correlation and noted no EBn in any of the 12 samples they tested.

Our results in this study show that EBc was detectable in 25 (60%) of 42 meningiomas, with eight (19%) having levels higher than 10 fM/mg protein. These levels are similar to those in our previous series 5 in which EBc was found in seven (70%) of 10 tumors, with higher levels (comparable to an EBc of > 10 fM/ mg protein) in two (20%) of the 10. They are also similar to two recent reports, 3,6 in which an EBc level over 10 fM/mg protein was found in 17% and 19% of tumors, respectively. The reason for the discrepancies between various laboratories is not clear, but may relate to the handling of the specimens, the assay technique, or even to pretreatment of patients with glucocorticoids or other medicines. However, it is clear that several laboratories using different techniques (that is, dextran-coated charcoal or sucrose density gradient centrifugation) have detected estrogen binding in a subset of meningiomas. 2,13,19 Recent studies in the United States report comparable results, 3,6 but the clinical significance of this finding awaits further biological and clinical evaluation.

The results of the progesterin-binding assays in menin-
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giomas are even more intriguing than those of the estrogen assays. In our initial series of 10 meningiomas, we noted PBC in two of three samples tested. In one specimen, PBC was high (345 fM/gm tumor) while EBC was low (24 fM/gm tumor); in the other, PBC was present (67 fM/gm tumor), but no EBC was detectable. Other studies have noted a similar pattern in which there was a higher overall rate of PBC compared to EBC, with some tumors having high PBC levels with low or absent EBC. For example, Markwalder, et al., noted detectable levels of PBC in 26 (76%) of 34 tumors. Two of these had levels of 9 fM/mg protein; 24 had levels of 10 fM/mg protein or greater. In this report, we have detected PBC in 16 (73%) of 22 patients, with nine (41%) having levels in excess of 10 fM/mg protein. This finding is similar to that in a recent report by Cahill, et al., who noted PBC levels over 10 fM/mg protein in 31% of the meningiomas in their study. However, of more interest is the relationship of progesterin-binding levels to estrogen-binding levels. Studies in hormonally responsive tissues, such as normal endometrium and MCF-7 breast cancer cells in culture, show that cytoplasmic PR is elevated when cytoplasmic ER is present and is stimulated by estrogen. This causes cytoplasmic-to-nuclear translocation of ER, with the stimulation of protein metabolism, including the production of PR. Therefore, the presence of high levels of cytoplasmic progesterin binding with low levels of cytoplasmic estrogen binding is usually not found in such cells. In contrast, the results of our present investigation suggest that PBC levels can be elevated in meningiomas containing little or no evidence of EBC or EBN. We would therefore agree with the suggestion proposed by Markwalder, et al., that the PBC component of meningiomas “is not regulated via an estrogen-ER system as in other classic estrogen target tissues.” We disagree with the suggestion that the elevation of PBC should lead to clinical trials of progestational agents such as medroxyprogesterone acetate or megestrol acetate, because no study has yet shown biological activity of any of these compounds in meningiomas, either as causing cytoplasmic-to-nuclear translocation of the binder by the hormonel or as producing an effect on cell metabolism or on cell growth. Therefore, we would urge a more cautious approach to the problem and recommend that the specificity and the biological activity of these hormones and their blocking agents first be assessed in studies in vitro. Such an approach would allow the testing of multiple agents and their interactions with a number of meningiomas having different hormone-binding levels. It could establish whether or not biological activity of these binding molecules is present, and might help to establish subsets of meningiomas, some of which are better treated with one agent than with another. Moreover, it would allow the direct testing of the hypothesis that in some meningiomas PBC is elevated independent of the estrogen-ER system. Also, since one study suggests that, in addition to acting via the ER, anti-estrogens may act via binders other than the ER, this avenue of potential tumor modulation could also be explored. Such in vitro studies could be performed more expeditiously than corresponding clinical studies due to the low incidence of meningiomas, the small number of these tumors that are refractory to surgical care, and the slower growth of meningiomas relative to breast cancer. Once such data are acquired, then clinical studies can be performed. In vitro studies have their own limitations and artifacts and do not always correspond with clinical treatment. In the end, the clinical result must be the final arbiter of whether or not hormonal therapy has any role in the treatment of meningiomas.

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References


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