Effect of Dehydroepiandrosterone and the Antiestrogen EM-800 on Growth of Human ZR-75-1 Breast Cancer Xenografts

Steeve Couillard, Claude Labrie, Alain Bélanger, Bernard Candas, Frédéric Pouliot, Fernand Labrie*

Background: In the mammary gland, androgens are formed from the precursor steroid dehydroepiandrosterone (DHEA). Clinical evidence indicates that androgens have inhibitory effects on breast cancer. Estrogens, on the other hand, stimulate the development and growth of breast cancer. We studied the effect of DHEA alone or in combination with the newly described pure antiestrogen EM-800 on the growth of subcutaneous tumor xenografts formed by the human breast cancer cell line ZR-75-1 in ovariectomized nude mice. Methods: Immediately after ovariectomy, mice received daily subcutaneous injections of 0.5 µg estrone (E1) (an estrogenic hormone). EM-800 (15, 50, or 100 µg) was given orally once daily. DHEA was administered percutaneously twice daily (total dose of 0.3, 1.0, or 3.0 mg) to the dorsal skin either alone or in combination with a 15-µg daily oral dose of EM-800. Changes in tumor size in response to the treatments (in relation to measurements made on the first day of treatment) were assessed periodically. At the end of the experiments, tumors were dissected and weighed. Results: A 9.4-fold increase in tumor size in 9.5 months was observed in ovariectomized mice receiving E1 alone. Administration of 15, 50, or 100 µg EM-800 in E1-supplemented mice led to inhibitions of 87.5%, 93.5%, and 94.0% in tumor size, respectively. DHEA, on the other hand, at doses of 0.3, 1.0, or 3.0 mg inhibited terminal tumor size by 50.4%, 76.8%, and 80.0%, respectively. Comparable inhibitions in tumor size were obtained with a daily 15-µg oral dose of EM-800 with or without different doses of percutaneous DHEA. Conclusions: DHEA and EM-800 independently suppressed the growth of E1-stimulated ZR-75-1 xenograft tumors in nude mice. Administration of DHEA at the defined doses did not alter the inhibitory effect of EM-800. [J Natl Cancer Inst 1998;90: 772–8]

Estrogens are recognized to play a predominant role in the development and growth of breast cancer (1–8). On the other hand, clinical studies (9–13) have shown that androgens have an opposite effect and have been used to treat advanced breast cancer in both premenopausal and postmenopausal women. Androgen treatment has a success rate comparable to that achieved with the other endocrine therapies (9–13). These clinical studies are well supported by a series of observations showing that androgens exert a direct inhibitory effect on the proliferation of human breast cancer ZR-75-1 cells under both basal and estrogen-stimulated conditions in vitro (13–21) as well as in vivo in nude mice (22).

More recently, the benefits of combined treatment with fluoroxymesterone and tamoxifen were observed in postmenopausal women with metastatic breast cancer (23), both in terms of the response rate and time to progression of disease. A series of data show that the therapeautic activity of androgens is not restricted to premenopausal patients and is not limited to an inhibitory effect on gonadotropin secretion. There is also genetic evidence in agreement with the protective role of androgens against breast cancer (24, 25). Such a role of androgens as direct regulatory factors of breast cancer growth is well supported by the presence of androgen receptors in a large proportion of human breast cancers (26–29).

In addition to the direct growth-inhibitory effect of physiologic concentrations of androgens demonstrated on human breast cancer cell lines in vitro (14–21) and in vivo (22), we have observed that dihydrotestosterone (DHT) exerts an inhibitory effect on the growth of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors in ovariectomized rats supplemented with estrogens (30). The inhibitory effect of DHT was reversed by simultaneous treatment with the antiandrogen flutamide, thus further supporting an action of DHT via specific binding to the androgen receptor in these mammary tumors (30, 31).

The human adrenals secrete large amounts of the precursor steroids dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), both of which are converted into androgens in target intracellular tissues (32–38). Since these two androgens inhibit breast cancer (9–23, 30, 39), we have studied the possibility that DHEA could inhibit the growth of the human ZR-75-1 breast cancer cell line in vivo in nude mice. To avoid the inhibitory effects of DHEA on gonadotropin secretion and to be able to assess the direct effects of DHEA-derived steroids on breast cancer growth, we have used ovariectomized animals supplemented with estrone (E1). We have also studied the potential interaction of the inhibitory effect of the novel antiestrogen EM-800 with that of DHEA by combined administration of the two drugs.

Materials and Methods

ZR-75-1 Cells

Human ZR-75-1 breast cancer cells were obtained from the American Type Culture Collection (Rockville, MD). They were routinely cultured as monolayers in RPMI-1640 medium supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 IU penicillin/mL, 100 µg streptomycin/mL, and 10% fetal bovine serum, under a humidified atmosphere of 95% air–5% CO2 at 37 °C as described previously (6, 17). Cells were passed weekly after treatment with 0.05% trypsin–0.02% EDTA (wt/vol). The cell cultures used for our experiments were derived from passage 93 of the ZR-75-1 cell line.

Animals

Female homozygous Harlan Sprague-Dawley (nu/nu) athymic mice (28–42 days old) were obtained from HSD (Indianapolis, IN). The mice were housed in vinyl cages with air-filter tops in laminar air-flow hoods and maintained under pathogen-limited conditions. Cages, bedding, and food were autoclaved.
before use. Water was autoclaved, acidified to pH 2.8, and provided ad libitum. The experiment was conducted in a Canadian Council on Animal Care (CCAC)-approved facility in accordance with the CCAC Guide for the Care and Use of Experimental Animals.

**Cell Inoculation**

One week before tumor cell inoculation, mice were bilaterally ovariectomized under anesthesia. The mice were anesthetized by intraperitoneal injection of 0.25 mL per animal of anesthetic solution (amyl alcohol [0.8 g/100 mL 0.9% NaCl] and tribromo ethanol [2 g/100 mL 0.9% NaCl]). ZR-75-1 cells (1.5 × 10⁶) in logarithmic growth phase were harvested after treatment of the monolayer with 0.05% trypsin-0.02% EDTA (w/vol) and then suspended in 0.1 mL of culture medium containing 25% Matrigel and were inoculated subcutaneously on both flanks of the animals with the use of a 1-inch-long 20-gauge needle as described previously (22). To facilitate growth of the tumors, we gave each animal a daily subcutaneous injection of 10 μg of estradiol (E₂) in vehicle composed of 0.9% NaCl-5% ethanol-1% gelatin for 5 weeks. After palpable ZR-75-1 tumors appeared, their diameters were measured with calipers. Mice having a tumor diameter between 0.2 and 0.7 cm were selected for this study.

**Hormonal Treatment**

All animals, except those in the control ovariectomized group, received a daily subcutaneous injection of 0.5 μg of E₁ in 0.2 mL of 0.9% NaCl-5% ethanol-1% gelatin. In the indicated groups, DHEA was applied percutaneously twice daily at doses of 0.3, 1.0, or 3.0 mg per animal; it was applied in a volume of 0.02 mL on the dorsal skin area outside the area of tumor growth. DHEA was dissolved in 50% ethanol-50% propylene glycol. EM-800, i.e., (S)-(+)-(+)-(7-(2,2-dimethyl-1-oxopropoxy)-4-methyl-2-[4-[2-(1-piperidiny1)-ethoxy]phenyl]-2H-1-benzo[4-3]-phenyl 2,2-dimethylpropanoate (Fig. 1, A), was synthesized as described earlier (40) in the medicinal chemistry division of the Laboratory of Molecular Endocrinology of the CHUL Research Center. EM-800 was dissolved in 4% (vol/vol) ethanol-4% (vol/vol) polyethylene glycol (PEG) 600-1% (wt/vol) gelatin-0.9% (wt/vol) NaCl. Animals of the indicated groups received daily oral doses of 15, 50, or 100 μg of EM-800 alone or in combination with DHEA, while animals of the ovariectomized group received the vehicle (0.2 mL 4% ethanol-4% PEG 600-1% gelatin-0.9% NaCl) alone. Tumors were measured once a week with Vernier calipers. Two perpendicular diameters in centimeters (length [L] and width [W]) were recorded, and tumor area (cm²) was calculated with the use of the following formula: \( L/2 \times W/2 \times \pi \). The area measured on the first day of treatment was taken as 100%, and changes in tumor size were expressed as the percentage of initial tumor area. In the case of subcutaneous tumors in general, it is not possible to accurately access three-dimensional tumor volume; therefore, only tumor areas were measured. After 291 days (or 9.5 months) of treatment, the animals were killed.

The categories of responses were evaluated as described previously (30,39,41). In short, partial response corresponds to the tumors that regressed to 50% or more of their original size. Stable response refers to tumors that progressed less than 50% of their original size or progressed to less than 50% of their original size. Complete response refers to tumors that were undetectable at the end of treatment. Progression refers to tumors that progressed more than 50% compared with their original size. At the end of the experiment, all animals were decapitated. Tumors, uterus, and vagina were immediately removed, freed from connective and adipose tissues, and weighed.

---

**Fig. 1.** A) Structure of the novel antiestrogen EM-800. B) Effect of increasing doses of dehydroepiandrosterone (DHEA) (a total dose of 0.3, 1.0, or 3.0 mg) administered percutaneously in two doses daily on average ZR-75-1 tumor size in ovariectomized nude mice supplemented with 0.5 μg estradiol (E₂) daily. Ovariectomized mice receiving the vehicle alone were used as additional controls. The initial tumor size was taken as 100%. DHEA (0.3, 1.0, or 3.0 mg per animal per day) was administered percutaneously on the dorsal skin in a 0.02-ml solution of 50% ethanol-50% propylene glycol. C) Effect of treatment with increasing doses of DHEA (0.3, 1.0, or 3.0 mg) or EM-800 (15, 50, and 100 μg) in 0.2 mL 4% ethanol-4% polyethylene glycol 600-1% gelatin-0.9% NaCl alone or in combination (EM-800 at 15 μg and DHEA at 0.3, 1.0, or 3.0 mg) for 9.5 months on ZR-75-1 tumor weight in ovariectomized nude mice supplemented with E₂. **, P<.01, treated versus control ovariectomized mice supplemented with E₂. CTL = control; P.C. = percutaneously; B.I.D. = twice daily; P.O. = by mouth; I.D. = once daily; S.C. = subcutaneously.
Statistical Analysis

The statistical significance of the effects of treatments on tumor size was assessed by use of an analysis of variance (ANOVA) evaluating the effects due to DHEA, EM-800, and time and repeated measures in the same animals performed at the initiation and at the end of the treatment (subjects within group factor). The repeated measures at time 0 and after 9.5 months of treatment constitute randomized blocks of animals. The time is thus analyzed as a within-block effect, while both treatments are assessed as between-block effects. All interactions between main effects were included in the model. The significance of the treatment factors and of their interactions was analyzed with the use of the subjects within group as the error term. Data were log-transformed. The hypotheses underlying the ANOVA assumed the normality of the residuals and the homogeneity of variance.

A posteriori pairwise comparisons were performed by use of Fisher’s test for least significant difference. Main effects and the interaction of treatments on body weight and organ weight were analyzed by use of a standard two-way ANOVA with interactions. All ANOVAs were performed with the use of the SAS program (SAS Institute, Inc., Cary, NC). The significance of differences was declared using the SAS program (SAS Institute, Inc., Cary, NC). The significance of differences was declared by use of a two-tailed test with an overall level of 5%

Categorical data were analyzed with a Kruskall–Wallis test for ordered categorical response variables (complete response, partial response, stable response, and progression of tumor). After an overall assessment of treatment effects, subsets of the results presented in Table 1 were analyzed, with adjustment of the critical P value for multiple comparisons. The exact P values were calculated by use of the StatXact program (Cytel, Cambridge, MA).

Data are expressed as means ± standard error of the mean for 12–15 mice in each group.

Results

As illustrated in Fig. 1, B, the sizes of the ZR-75-1 tumors increased by 9.4-fold over a 291-day period (9.5 months) in ovariectomized nude mice treated with a daily 0.5-μg subcutaneously administered dose of E1; in contrast, in control ovariectomized mice that received the vehicle alone, tumor size decreased to 36.9% of the initial value during the course of the study.

Treatment with increasing doses of percutaneous DHEA caused a progressive inhibition of E1-stimulated ZR-75-1 tumor growth. Inhibitions of 50.4%, 76.8%, and 80.0% were achieved at 9.5 months of treatment with the daily doses of DHEA of 0.3, 1.0, or 3.0 mg per animal, respectively (Fig. 1, B). In agreement with the decrease in total tumor load, treatment with DHEA led to a marked decrease in the average weight of the tumors remaining at the end of the experiment. In fact, the average tumor weight decreased from 1.12 ± 0.26 g in control E1-supplemented, ovariectomized nude mice to 0.37 ± 0.12 g (P <.005), 0.20 ± 0.06 g (P = .001), and 0.17 ± 0.06 g (P = .0009) in the groups of animals receiving the daily 0.3-, 1.0-, and 3.0-mg doses of DHEA, respectively (Fig. 1, C).

At daily doses of 15, 50, or 100 μg, the antiestrogen EM-800 inhibited estrogen-stimulated tumor size by 87.5% (P <.0001), 93.5% (P <.0001), and 94.0% (P = .0003), respectively (Fig. 2, A), when compared with the tumor size in control animals at 9.5 months. The tumor size reductions achieved with the three EM-800 doses were not significantly different between each other. As illustrated in Fig. 1, C, tumor weight at the end of the 9.5-month study was decreased from 1.12 ± 0.26 g in control E1-supplemented, ovariectomized mice to 0.08 ± 0.03 g, 0.03 ± 0.01 g, and 0.04 ± 0.03 g in animals treated with the daily doses of 15, 50, or 100 μg of EM-800, respectively (P <.0001 at all doses of EM-800 versus E1 supplemented, ovariectomized).

As mentioned above, the antiestrogen EM-800 at a daily oral dose of 15 μg caused an 87.5% inhibition of E1-stimulated tumor growth measured at 9.5 months. The addition of DHEA at the three doses used had no statistically significant effect on the already marked inhibition of tumor size achieved with the 15-μg daily dose of EM-800 (Fig. 2, B). Thus, the average tumor weight was dramatically reduced from 1.12 ± 0.26 g in control E1-supplemented mice to 0.08 ± 0.03 g (P <.0001), 0.11 ± 0.04 g (P = .0002), 0.13 ± 0.07 g (P = .0004), and 0.08 ± 0.05 g (P <.0001) in the animals that received the daily dose of 15 μg of EM-800 alone or in combination with 0.3, 1.0, or 3.0 mg of DHEA, respectively (no statistically significant difference was noted between the four groups) (Fig. 1, C).

It was also of interest to examine the categories of responses achieved with the above-indicated treatments. Thus, treatment with the increasing doses of DHEA decreased, although not to a level of statistical significance (P = .088), the number of progressing tumors from 87.5% in the control ovariectomized animals supplemented with E1 to values of 50.0%, 53.3%, and 66.7% in the animals treated with the daily doses of 0.3, 1.0, or 3.0 mg of DHEA (Table 1). Complete responses, on the other hand, increased from 0% in the E1-supplemented mice to 28.6%, 26.7%, and 20.0% in the animals receiving the antiestrogen EM-800 alone or in combination with DHEA.

Table 1. Effect of percutaneous administration of DHEA or oral administration of EM-800 alone or in combination for 9.5 months on the responses (complete, partial, stable, and progression) of human ZR-75-1 breast tumor xenografts in nude mice

<table>
<thead>
<tr>
<th>Group*</th>
<th>Total No. of animals</th>
<th>Category of response, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>OVX</td>
<td>16</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg</td>
<td>16</td>
<td>0 (0)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + DHEA at 0.3 mg</td>
<td>16</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + DHEA at 1.0 mg</td>
<td>15</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + DHEA at 3.0 mg</td>
<td>15</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + EM-800 at 15 μg</td>
<td>17</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + EM-800 at 50 μg</td>
<td>16</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + EM-800 at 100 μg</td>
<td>16</td>
<td>8 (50.0)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + EM-800 at 15 μg orally once daily + DHEA at 0.3 mg</td>
<td>18</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + EM-800 at 15 μg orally once daily + DHEA at 1.0 mg</td>
<td>15</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>OVX + E1, at 0.5 μg + EM-800 at 15 μg orally once daily + DHEA at 3.0 mg</td>
<td>17</td>
<td>6 (35.3)</td>
</tr>
</tbody>
</table>

*OVX = ovariectomized; E1 = estrone; DHEA = dehydroepiandrosterone.
ing the 0.3-, 1.0-, and 3.0-mg daily doses of percutaneous DHEA. Stable responses were measured at 12.5%, 21.4%, 20.0%, and 13.3% in the control E1-supplemented mice and in the three groups of animals that received the above-indicated doses of DHEA, respectively. In control ovariectomized mice, the rates of complete, partial, and stable responses were measured at 68.8%, 6.3%, and 18.8%, respectively, while progression was seen in only 6.3% of tumors (Table 1).

Complete responses or disappearance of the tumors was achieved in 29.4%, 33.3%, 26.7%, and 35.3% of tumors in the animals that received the antiestrogen EM-800 (P<.0006) alone (15 μg) or in combination with 0.3, 1.0, or 3.0 mg of DHEA, respectively (Table 1). Progression, on the other hand, was seen in 35.3%, 44.4%, 53.3%, and 17.6% of the tumors in the same groups of animals, respectively. There was no statistically significant difference between the groups treated with EM-800 either alone or in combination with DHEA.

No statistically significant effect of DHEA or EM-800 treatment was observed on body weight adjusted for tumor weight. As shown in Fig. 3, A, treatment of ovariectomized mice with E1 increased uterine weight from 28 ± 5 mg in ovariectomized control mice to 132 ± 8 mg (P<.01), while increasing doses of DHEA caused a progressive but relatively small inhibition of the stimulatory effect of E1 that reached 26% (P = .0008) at the highest dose of DHEA used. Fig. 3, A, also shows that E1-stimulated uterine weight was decreased from 132 ± 8 mg in control E1-supplemented mice to 49 ± 3 mg, 36 ± 2 mg, and 32 ± 1 mg (P<.0001 at all doses versus control) at a dose of 15 μg of EM-800 in combination with 0.3-, 1.0-, or 3.0-mg daily doses of DHEA, uterine weight measured 46 ± 3 mg, 59 ± 5 mg, and 69 ± 3 mg, respectively.

On the other hand, treatment with E1 increased vaginal weight from 14 ± 2 mg in ovariectomized animals to 31 ± 2 mg (P<.01), while the addition of DHEA had no statistically significant effect (Fig. 3, B). Vaginal weight was then reduced to 23 ± 1 mg, 15 ± 1 mg, and 11 ± 1 mg after treatment with the daily 15-, 50-, or 100-μg doses of EM-800, respectively (overall P and pairwise P<.0001 at all doses versus control). In combination with the 0.3-, 1.0-, or 3.0-mg doses of DHEA and EM-800, vaginal weight was measured at 22 ± 1 mg, 25 ± 2 mg, and 23 ± 1 mg, respectively (not statistically significant for all groups versus 15 μg of EM-800). At the highest dose used, i.e., 100 μg daily, EM-800 decreased uterine weight in E1-supplemented, ovariectomized animals to a value not different from that of ovariectomized controls (Fig. 3, A), while vaginal weight was reduced to a value below that measured in ovariectomized controls (P<.05) (Fig. 3, B). Probably as a result of its androgenic effects, DHEA partially counteracted the effect of EM-800 on the uterine and vaginal weights (Fig. 3).

Discussion

To our knowledge, these data provide the first demonstration of the inhibitory effect of DHEA on the growth of human...
breast cancer xenografts in nude mice. Moreover, this study shows that simultaneous treatment with DHEA (at daily doses ranging from 0.3 to 3.0 mg) has no influence on the highly potent inhibitory effect of the new antiestrogen EM-800 on the growth of ZR-75-1 tumors in E1-stimulated nude mice. A more detailed study is necessary to assess interaction between these treatments at lower doses.

Although adjuvant treatment with tamoxifen delays breast cancer recurrence, improves survival in patients with early stage breast cancer, and induces remission in patients with advanced disease, its benefits are frequently limited by the development of tamoxifen resistance (42–47). In the in vivo model in which nude mice were used, tamoxifen was found to inhibit MCF-7 tumor growth for 4–6 months, but tumor growth was observed to continue after this period despite tamoxifen treatment (48,49). Similar to tamoxifen, Gottardis et al. (50) have observed the acquired ability of tamoxifen to stimulate rather than to inhibit tumor growth. Since pure antiestrogens can inhibit the stimulatory effect of tamoxifen (42,51,52), it is reasonable to conclude that the stimulatory effect of tamoxifen observed during long-term treatment is due to the intrinsic estrogenic activity of the compound or its metabolites and that more potent and long-lasting inhibitory effects are expected from pure antiestrogens (53,54).

Treatment of nude mice bearing MCF-7 xenografts with 10 mg of ICI 182,780 once a week led to a transient decrease in tumor size, which was followed by a stabilization of tumor size for about 200 days after which tumor progression occurred (52). In mice treated with ICI 182,780, regrowth or resistance to ICI 182,780 occurred in most tumors (52).

Of all the compounds tested, the novel nonsteroidal prodrug EM-800 and its active metabolite EM-652 have been reported to exert the most potent antagonistic effects on E2-induced proliferation in T-47D cells (55). Furthermore, the absence of a stimulatory effect on basal cell proliferation in the three estrogen-sensitive human breast cancer cell lines used shows that EM-652 and EM-800 are pure antiestrogens devoid of partial agonist activity in human breast cancer tissue. Moreover, the antiestrogenic activity of EM-652 and EM-800 on E2-induced proliferation in T-47D cells was found to be at least two orders of magnitude more potent than tamoxifen, 2.5-fold to 3.6-fold more potent than OH-tamoxifen, and 3.8-fold, 2.7-fold, and 16.3-fold more potent than OH-toremifene, ICI 182,780, and ICI 164,384, respectively. On the other hand, EM-800 was 46-fold more potent than droloxifene in inhibiting E2-induced T-47D cell proliferation. As mentioned above, EM-800 and EM-652 have no estrogenic activity in the three breast cancer cell lines studied, while OH-tamoxifen, droloxifene, and toremifene cause a statistically significant stimulation of ZR-75-1 and/or MCF-7 human breast cancer cell proliferation (55).

The DMBA-induced mammary carcinoma in the rat has been widely used as a model of hormone-sensitive breast cancer in women (2,30,56). As mentioned...
above, androgens have been successfully used to treat breast cancer in women and have achieved an objective response comparable to that seen with other hormonal therapies (9–13,57,58). In addition, androgens such as dromostanolone propionate and testosterone as well as DHEA, a precursor of androgens (32,34,36–38,59,60), have been shown to exert a potent inhibitory effect on the development of DMBA-induced mammary carcinoma in the rat (30,61–65).

In the ovarioctomized mouse, exogenous DHEA represents the only source of sex steroids in peripheral tissues, including the mammary gland. Moreover, by itself, DHEA does not possess any significant androgenic or estrogenic activity, its activity being dependent on its transformation into androgens and/or estrogens in peripheral target intracrine tissues (32). Thus, the inhibition of tumor growth seen after DHEA treatment in ovarioctomized animals results from its intracrine conversion into androgens in the mammary gland (32,34,36–38). We have recently shown that DHEA exerts an almost exclusively androgenic effect in the rat mammary gland (66). In fact, DHEA is known to be converted into androgens, and treatment with DHEA thus induces androgen-sensitive gene expression in the rat ventral prostate (33,34). Taken together, these data strongly suggest that DHEA exerts its inhibition of breast cancer through its conversion to androgens and activation of the androgen receptor.

References


Notes

Editor’s note: S. Couillard, C. Labrie, A. Belanger, B. Candas, and F. Pouliot received salary support from Endorecherche (Quebec, Canada), which provided support for research on EM-800 and in part for research on DHEA. F. Labrie is the President of Endorecherche. Endorecherche is a privately owned company supported by funding from pharmaceutical companies, among other sources.

Supported in part by Medical Research Council of Canada, Fonds de la Recherche en Santé du Quebec, and Endorecherche.

Manuscript received June 12, 1997; revised December 4, 1997; accepted March 18, 1998.