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Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression

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ABSTRACT

This study investigated the effect of sex steroids and tamoxifen on primate mammary epithelial proliferation and steroid receptor gene expression. Ovariectomized rhesus monkeys were treated with placebo, 17ß estradiol (E2) alone or in combination with progesterone (E2/P) or testosterone (E2/T), or tamoxifen for 3 days. E2 alone increased mammary epithelial proliferation by ~sixfold (P<0.0001) and increased mammary epithelial estrogen receptor (ERα) mRNA expression by ~50% (P<0.0001; ERß mRNA was not detected in the primate mammary gland). Progesterone did not alter E2's proliferative effects, but testosterone reduced E2-induced proliferation by ~40% (P<0.002) and entirely abolished E2-induced augmentation of ERα expression. Tamoxifen had a significant agonist effect in the ovariectomized monkey, producing a ~threefold increase in mammary epithelial proliferation (P<0.01), but tamoxifen also reduced ERα expression below placebo level. Androgen receptor (AR) mRNA was detected in mammary epithelium by *in situ* hybridization. AR mRNA levels were not altered by E2 alone but were significantly reduced by E2/T and tamoxifen treatment. Because combined E2/T and tamoxifen had similar effects on mammary epithelium, we investigated the regulation of known sex steroid-responsive mRNAs in the primate mammary epithelium. E2 alone had no effect on apolipoprotein D (ApoD) or IGF binding protein 5 (IGFBP5) expression, but E2/T and tamoxifen treatment groups both demonstrated identical alterations in these mRNAs (ApoD was decreased and IGFBP5 was increased). These observations showing androgen-induced down-regulation of mammary epithelial proliferation and ER expression suggest that combined estrogen/androgen hormone replacement therapy might reduce the risk of breast cancer

associated with estrogen replacement. In addition, these novel findings on tamoxifen's androgen-like effects on primate mammary epithelial sex steroid receptor expression suggest that tamoxifen's protective action on mammary gland may involve androgenic effects.—Zhou, J., Ng, S., Adesanya-Famuiya, O., Anderson, K., Bondy, C. A. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression.

Key Words: breast cancer • androgen • tamoxifen • monkey

INTRODUCTION

MANY LINES OF evidence suggest that exposure to estrogen is a major risk factor for the development of breast cancer. The risk is presumably due in some part to estrogen's stimulation of mammary epithelial proliferation, although additional carcinogenic effects by estrogen metabolites have also been suggested (1)☐ . Estrogens stimulate uterine epithelial proliferation, and an 'unopposed' estrogen effect is a well-established cause of uterine cancer. The addition of progesterone to estrogen therapy suppresses estrogen's proliferative and cancer-promoting effects on uterine epithelium. Progesterone's effects on estrogen-induced mammary epithelial proliferation are unclear, however. For example, progesterone itself stimulates proliferation of murine mammary epithelium, with effects additive to those of estradiol (2)☐ . Moreover, some studies report that mammary epithelial proliferation is increased in the luteal (i.e., high progesterone) phase of the human menstrual cycle (3☐ 4☐ 5)☐ . Epidemiological data, however, generally have found lower progesterone levels associated with breast cancer cases compared with controls (6)☐ .

In several recent studies, circulating androgen levels have been positively correlated with breast cancer risk in postmenopausal women, leading to the idea androgens may contribute to the risk for breast cancer (7☐ 8☐ 9☐ 10)☐ . This association may, however, reflect the fact that serum estrogen and androgen levels are highly correlated (11)☐ since androgens are precursors for estrogen biosynthesis. Clinical observations suggest that androgens are antimammogenic, e.g., breast atrophy occurs in women with androgen excess. To illuminate the roles of progestins and androgens as modulators of estrogen action on mammary epithelium, we treated ovariectomized rhesus monkeys with placebo, E2 alone, E2 and P4, or E2 and T and compared the effects on mammary epithelium. In addition, since tamoxifen has some androgen-like effects (12☐ 13☐ 14)☐ and tamoxifen responsiveness has been linked to androgen receptor expression in breast cancer patients (15)☐ , a tamoxifen treatment group was included for comparison.

MATERIALS AND METHODS

Female rhesus monkeys (*Macacca mulatta*) 6–13 years of age from the NIH Poolesville colony were used in accordance with a protocol approved by the NICHD Animal Care and Use Committee. Ovariectomies were performed under

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ketamine anesthesia via a midventral laparotomy in the late follicular phases of their menstrual cycles. Three weeks after surgery, animals were randomly assigned to 5 groups (n=4–7 each) receiving placebo or hormone-containing pellets inserted subcutaneously between their shoulder blades under ketamine anesthesia. The E2 group received 3 day sustained releases 17ß estradiol pellets (5 mg). The E2/P4 group was treated with both 17ß estradiol (5 mg) and progesterone (10 mg) 3 day release pellets. The E2/T group received 17ß estradiol pellets (1 mg/kg) 3 day release and 42 µg/kg testosterone 3 day release pellets. The tamoxifen group received 50 mg 3 day release tamoxifen pellets. At the end of the dosing periods, the animals were sedated with ketamine and then killed with pentobarbital (65 mg/kg). Mammary tissue was removed, snap frozen on dry ice, and stored at -70°C. Serial sections of 10 µm thickness were cut at -15°C and thaw-mounted onto poly-L-lysine coated slides for histochemical analysis.

Immunohistochemical detection of the proliferation-specific Ki-67 antigen was performed as described previously (16)☐ . To determine the mammary epithelial proliferation index, 200–300 nuclei per section were scored microscopically by a blinded observer. Two to three sections were scored to obtain mean values for each animal. Group means were compared using analysis of variance (ANOVA) and differences were assessed by Fisher's least significant difference test. The observations were replicated by two different observers. Absolute values may vary somewhat between observers but differences between groups were maintained very closely, and the statistical values for comparisons were identical.

Clones used for cRNA probe synthesis included a 3.6 kbp cDNA fragment encoding nucleotides 1–3022 of the human androgen receptor (AR; kindly provided by Dr. Shutsung Liao, University of Chicago). The apolipoprotein D (ApoD) clone (17)☐ was a 369 bp fragment corresponding to bases 440–809 of the human ApoD sequence, obtained from Research Genetics (Image clone 159608; Huntsville, Ala.). The IGFBP-5 clone was a 463 bp fragment encoding the first 150 amino acids of the mature protein kindly provided by Peter Rotwein, Washington University (St. Louis, Mo.). The estrogen receptor (ERα) probe was a 40-mer oligo obtained from Geneka Biotechnology (Montreal, Canada). Probe synthesis and *in situ* hybridization protocols have been described in detail previously (18)☐ . The specificity of the *in situ* hybridization results was confirmed by the hybridization of parallel sections to sense probes. The hybridization signal overlying mammary epithelium was captured at 400x using a monochrome video camera and the results analyzed with NIH image v1.57 software as described previously (18)☐ . A blinded observer obtained 4–6 measurements from 2–3 mammary tissue sections for each animal. Group means were statistically compared using ANOVA. Significant differences among means were determined by Fisher's least significant difference test.

RESULTS

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Effects of sex steroids and tamoxifen on mammary epithelial proliferation

The mammary epithelial proliferation index (MEPI) was determined by immunodetection of the Ki-67 antigen, which is a nonhistone, nuclear matrix protein specific for proliferating cells (16)☐ . Mammary epithelial Ki-67 immunoreactivity is exclusively nuclear and is concentrated in 2–3 focal nuclear

deposits (**Fig. 1**□). The MEPI is quite low in ovariectomized, placebo-treated monkeys and is increased sixfold by E2 treatment (Fig. 1*F*□). Combined P4 and E2 treatment produced the same degree of epithelial proliferation as E2 alone, but the addition of testosterone (T) to E2 treatment attenuated E2's proliferative effects by ~40% ($P<0.002$). Hormone levels in the different treatment groups are shown in Table 1□ . It is noteworthy that the MEPI is significantly reduced in E2/T-treated animals, even though E2 levels were higher in this group compared with the E2 and E2/P4 groups. Tamoxifen treatment of ovariectomized monkeys produced an approximate threefold increase in proliferation compared with placebo (Fig. 1)□ . The effects of tamoxifen and E2/T on MEPI were not statistically different ($P=0.15$).

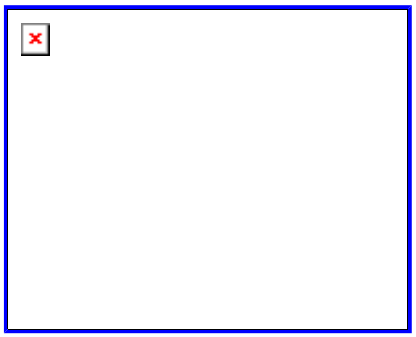

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Figure 1. Mammary epithelial proliferation shown by Ki-67 immunoreactivity in ovariectomized monkeys treated with vehicle (*A*), estradiol (*B*), E2 and progesterone (*C*), tamoxifen (*D*), and E2 plus testosterone (*E*). Representative mammary gland sections are shown in panels *A–E*, and quantitation of the mean percentage of Ki-67 positive nuclei in each treatment group is shown in panel *F*. Data represent means plus SE for 4–6 animals per group. An asterisk connotes $P < 0.01$ with respect to the placebo group. Bar = 100 μ.

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Table 1. Sex steroid levels[a]

Androgen and estrogen receptors

To determine whether testosterone's inhibitory effects on the MEPI could be androgen receptor mediated, androgen receptor expression was examined using *in situ* hybridization (**Fig. 2**□). AR mRNA is concentrated in mammary epithelium but is also detected in scattered stromal cells (Fig. 2*A*□). AR mRNA levels are equal in ovariectomized and E2-treated animals, but are significantly reduced by E2/T and by tamoxifen (**Fig. 3A**□). Estrogen receptor (ERα) mRNA is uniformly distributed in the mammary epithelium and is abundant in the wall of mammary arteries (Fig. 2*B, C*□). ERα mRNA is increased by ~50% in the E2-treatment group; combined E2/P4 treatment has a lesser but still significant positive effect on ERα expression (Fig. 3*B*□). Addition of testosterone to E2 treatment, however, completely inhibited E2's positive effect on ERα expression. Tamoxifen treatment resulted in reduction of ER mRNA levels below control (placebo-treated ovariectomized monkeys) values (Fig. 3*B*□). ERß mRNA was not detected in the primate mammary epithelium. Noting that combined E/T and tamoxifen treatments had parallel effects on

estrogen and androgen receptor expression pattern, we investigated ApoD gene expression in the mammary gland, since this factor is known to be androgen regulated in mammary cells (17) . ApoD mRNA is significantly reduced by both E2/T and by tamoxifen treatments (**Fig. 4A**). In another study examining insulin-like growth factor binding protein (IGFBPs 1–6) gene expression in these mammary glands, we found that there were no significant sex steroid effects on IGFBP mRNA levels (18) except for IGFBP5. IGFBP5 mRNA is not affected by E2 alone but is increased by E2/T and tamoxifen (Fig. 4*B*).

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Figure 2. AR (*A*) and ERα (*B, C*) mRNA localization in primate mammary gland. The hybridization signal appears as red grains. The signal for both receptors is concentrated over alveolar epithelial cells. ERα mRNA is also abundant in the intima media of mammary arteries (*C*). Nonspecific signal generated by sense probe hybridization is seen in panel *D*. Bar = 250 μ.

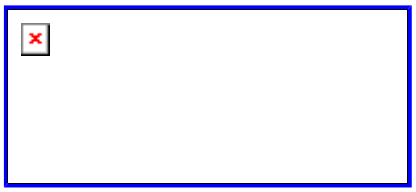

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Figure 3. Effect of sex steroids and tamoxifen on androgen (*A*) and estrogen (*B*) receptor mRNA levels in primate mammary epithelium. mRNA values are in grains per 400 μm^2. Data are the means + SE for 4–8 animals per group. a, $P < 0.03$; b, $P < 0.006$; c, $P < 0.0001$; d, $P < 0.0004$ compared to the relevant control group.

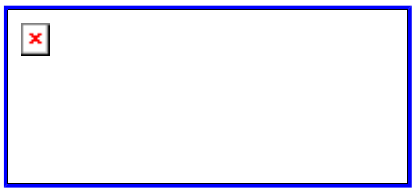

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Figure 4. Effect of sex steroids and tamoxifen on apolipoprotein D (*A*) and IGFBP5 (*B*) mRNA levels in primate mammary epithelium. mRNA values are in grains per 400 μm^2. Data are the means + SE for 4–8 animals per group. a, $P < 0.005$; b, $P < 0.002$; c, $P < 0.001$; d, $P < 0.05$ compared to the relevant control group.

DISCUSSION

Estrogen-induced proliferation of breast epithelium is thought to underlie the association between estrogen exposure and breast cancer, but it has been difficult to demonstrate a relation between mammary epithelial proliferation and hormone levels in normal cycling women (3 4 5) . The present data clearly demonstrate that over the short term, E2 is a robust stimulant of mammary epithelial proliferation and that luteal phase progesterone levels do not modulate E2's proliferative effects. We have shown, however, that E2's proliferative effects are significantly reduced by coadministration of testosterone. The demonstration of androgen receptor gene expression in the mammary epithelium and its down-regulation by testosterone treatment suggests that testosterone's antiproliferative effects on mammary epithelium are directly mediated by the androgen receptor. This study has also shown that combined testosterone and estrogen treatment prevents E2-induced up-regulation of mammary epithelial ER expression, suggesting a possible mechanism for testosterone's antiproliferative effects.

The role of androgens in mammary growth has not been well studied. Clinical data suggest that androgens normally inhibit mammary growth, e.g., suppressed androgens or androgen blockade in men is associated with breast growth (19 20 21) . Furthermore, inactivating mutations of the androgen receptor have been linked with breast cancer in men (22 , 23) . Labrie et al. have shown that dihydrotestosterone suppresses ER expression and estrogen-induced proliferation in ZR-75–1 breast cancer cells and blocks the development of estrogen-dependent mammary tumors in rats (22 , 24) . This group has also shown that androgen significantly retards breast cancer cell cycling even in the absence of estrogen, suggesting that androgens have antiproliferative effects independent of estrogen antagonism (25) . These *in vitro* findings, coupled with the present *in vivo* data showing that testosterone decreases E2-induced mammary epithelial proliferation and prevents E2-induced up-regulation of ER expression, indicate that androgens inhibit mammary epithelial proliferation by antagonizing estrogen action (receptor down-regulation) and by estrogen-independent antiproliferative effects.

The present study shows a significant estrogen agonist effect by tamoxifen on primate mammary epithelial proliferation *in vivo*. Studies in human breast cancer cell lines have also shown that tamoxifen has ER-mediated proliferative effects (reviewed in ref 26). Whereas tamoxifen-induced mammary epithelial proliferation appears to be an estrogenic or ER agonist effect, tamoxifen has other effects on mammary epithelium that are opposite to those of estrogen and parallel to those of combined E2/T treatment (Table 2). For example, in this *in vivo* model system, estradiol increases whereas tamoxifen decreases ER mRNA levels. Tamoxifen treatment is also associated with suppression of ER expression in human breast cancer tissue (27 , 28) . Testosterone likewise appears to reduce mammary epithelial ER expression, since the addition of testosterone to E2 treatment suppresses estradiol's augmentation of ER expression (Fig. 3) .

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Table 2. Tamoxifen has estrogen- and androgen-like effects on the primate mammary epithelium

Although E2 alone has no apparent effect on mammary androgen receptor expression, both tamoxifen and combined E2/T treatments reduced androgen receptor mRNA levels (Table 2). Given the parallel effects of tamoxifen and combined E2/T on mammary estrogen and androgen receptor expression, we considered the possibility that tamoxifen may interact with the androgen receptor. Thus, we investigated tamoxifen's effects on mammary ApoD expression, since expression of this protein is distinctively regulated by androgens in breast cancer cell lines (17). Whereas androgens increase ApoD gene expression in the breast cancer cell lines, we found that androgen treatment significantly decreased ApoD mRNA in the primate mammary gland *in vivo* (Fig. 4). This may be explained by the fact that in the normal mammary gland, ApoD mRNA is localized in mammary stromal cells and not detected in epithelium (our unpublished data). The cancer cell lines are epithelial in origin and are mutant, so the androgenic mechanisms regulating ApoD in these cells may be quite different from those pertaining to normal stromal cells *in vivo*. In any case, with respect to tamoxifen's mechanism of action, the fact that both E2/T and tamoxifen reduce ApoD expression suggests that tamoxifen does indeed have androgen-like effects. This view is supported by the additional observation that E2/T and tamoxifen both increase IGFBP5 expression (Fig. 4).

Some clinical observations also support an androgen receptor-mediated effect by tamoxifen. For example, responsiveness to tamoxifen therapy in breast cancer has been linked to tumor androgen receptor expression (15) and some women taking tamoxifen have experienced androgenic effects (14), although these appear to be rare. Some *in vitro* studies have also suggested androgenic effects by tamoxifen; for example, tamoxifen and androgens but not estrogen induce prostate specific antigen expression by breast cancer cell lines (12). Taken together with the present data, these observations suggest that some of tamoxifen's protective effects on breast could derive from interaction with the androgen receptor.

In summary, the present data show that addition of androgen to estrogen treatment reduces mammary epithelial proliferation and ER expression, suggesting that androgens may protect against breast cancer, by analogy with progesterone's protective effects on the uterus. Androgens have actually been used to treat breast cancer with some success in the past (reviewed in ref 24). If androgen is in fact protective, then conventional menopausal hormone replacement regimens may promote breast cancer risk both by increasing estrogens and decreasing endogenous androgens. Oral estrogen therapy reduces free androgen levels by stimulating increased hepatic production of sex hormone binding globulin (29) and by suppressing LH, which drives ovarian androgen production after menopause (30). These considerations suggest that balanced estrogen/androgen 'replacement' therapy may be beneficial to menopausal women.

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