Compartmentalized Uterotrophic Effects of Tamoxifen, Toremifene, and Estradiol in the Ovariectomized Wistar (Han) Rat


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The comparative uterotrophic responses of ovariectomized Wistar (Han) rats to tamoxifen, toremifene, and 17β-estradiol have been determined over a period of 72 h. Uterine wet weight; luminal epithelial cell hypertrophy; and BrdU labeling index in the different tissue compartments of the uterus, and the immunohistochemical expression of nuclear estrogen receptor alpha (nERα), and nuclear progesterone receptor (nPR) were examined. Luminal epithelial cell hypertrophy was produced by all three compounds to a similar degree. 17β-Estradiol produced an increase in uterine wet weight due to fluid imbibition over the 3-day period, and an increase in DNA synthesis in the endometrial stromal and myometrial compartments of the uterus, as measured by increased BrdU incorporation. Estradiol increased the expression of nERα and nPR in the myometrium with time and decreased nERα levels from the overexpressed levels in control ovariectomized rat luminal epithelial cells. Tamoxifen and toremifene caused a smaller increase in uterine weight and the BrdU labeling index in the endometrial stroma and myometrium than did estradiol, and they increased the expression of nERα and nPR in the myometrium. Tamoxifen and toremifene differed from estradiol in that they did not decrease the expression of nERα in the luminal epithelial cells of the uterus. The response of PR expression was the same for tamoxifen, toremifene, and estradiol, and was therefore considered to be the most reliable indication of an estrogen-agonist effect in this study. The ability to distinguish differential, compartmentalized effects for agonists of estrogen action in the uterus will allow a better risk assessment for new pharmaceuticals that are used as breast cancer chemotherapeutic agents, especially where their use may also be associated with an increased risk of uterine cancers, in particular.

Key Words: tamoxifen; toremifene; 17β-estradiol; nuclear estrogen receptor α(nERα); nuclear progesterone receptor (nPR); uterotrophic effects.

Tamoxifen, (Z-1-[4-(dimethylaminoethoxy)phenyl] 1,2-diphenyl-1-butene) has been successfully used in adjuvant therapy for the treatment of breast cancer (Riley et al., 1992) and is currently undergoing clinical trials as a chemopreventive agent in women considered to be at high risk of developing breast cancer, but with no evidence of organic disease (Early Breast Cancer Trialist’s Collaborative Group 1998; Powles et al., 1998, Veronesi et al., 1998). Toremifene, (4-chloro-1,2-diphenyl-1-[4-[2(N,N-dimethylamino)ethoxy]phenyl]-1-butene) has been found to be effective in causing regression of 7,12-dimethylbenzanthracene-induced mammary tumors in rats (Di Salle et al., 1990) and is undergoing clinical trials for the treatment of breast cancer. It may be also be used as a chemopreventive drug for breast cancer in the near future.

The finding of an increased risk of endometrial cancer associated with the long term administration of tamoxifen to women, as an adjunct therapy in breast cancer treatment (Dalenbach-Hellweg et al., 1996; Fornander et al., 1993; Kedar et al., 1994; Silva et al., 1994; Van Leeuwen et al., 1994), has focused attention on the mechanism of uterine cancer induction by tamoxifen. Increases in the amounts of tamoxifen-specific DNA adducts, as measured by 32P-postlabeling, have been documented in both human and rat uterine DNA after exposure to tamoxifen (Hemminki et al., 1996; Pathak et al., 1996), although other reports have failed to confirm this (Carmichael et al., 1996, Carthew et al., 1996).

Recently increased amounts of endogenous DNA adducts, detected by 32P-postlabeling, have been found in rat uterine DNA, after tamoxifen treatment (Li et al., 1997). This indicates that it is important to distinguish adducts caused directly by covalent binding of tamoxifen (or its metabolites) to DNA from those endogenous DNA adducts that might be enhanced in number by tamoxifen treatment (Li et al., 1997).

Another possible explanation, or contributing factor, in the association between tamoxifen treatment and the development of uterine cancers could be the estrogen agonist effect of tamoxifen on the uterus. It is well documented that unrelieved estrogen agonist effects in the uterus can increase the incidence of uterine cancers in women (Collins, 1982; Hulka, 1980, Paganini-Hill et al., 1989). If this is the mechanism by which tamoxifen causes an increase in uterine cancers in women, then this could be a class effect with all drugs like tamoxifen that are partial estrogen agonists.

The problem then becomes one of how to evaluate the possible increased risk, of endometrial cancer in particular, to women taking drugs in this class. For tamoxifen, there is no animal model at present where the uterine stimulation of the
endometrium, in particular, can be maintained for long periods at a dose which would be clinically relevant to that given to women. The mouse responds to tamoxifen with a hyperplasia of the endometrium, which only lasts for around three months, and the myometrium, interestingly, atrophies during this period (Carthew et al., 1996). Tamoxifen acts as an antagonist of estrogen action in the rat uterus (Tucker et al., 1984).

At present, the carcinogenic effect of tamoxifen in the human uterus is assumed to be due, in part if not totally, to the proliferative effects of its estrogen agonist-like behavior. The uterotrophic assay in ovariectomized rodents is a classic method for estimating the estrogenicity of drugs and chemicals (Jordan et al., 1978, Kallio et al., 1986). However, the increase in weight of the estrogen-deprived uterus in response to an estrogen-like action, may in part be caused by the inhibition of fluid associated with a full estrogen-like activity (Reel et al., 1996). In this respect, it is interesting that in a recent comparison of the methodologies for estimating estrogen-like uterotrophic responses to chemicals and drugs, only estradiol and estriol produced uterine fluid accumulation (inhibition) in ovariectomized rat uteri (O’Connor et al., 1996). Compounds such as tamoxifen and other partial estrogen agonists did not.

Hence, the measurement of the uterotrophic effects of chemicals and drugs relative to estradiol-like effects, using uterine weight as an index, may not be quantitating the same responses as occur with the classic estradiol response. The classical cornification response of the vagina to estradiol has also been found not to occur with raloxifene treatment of ovariectomized rats (Ashby et al., 1997), although there was a uterotrophic response.

To clarify the changes involved in the uterotrophic effects of drugs and estradiol, we have compared the effects of tamoxifen and toremifene with 17β-estradiol on the ovariectomized rat uterus. DNA synthesis in the following uterine compartments has been examined for 3 consecutive days after treatment: luminal epithelium, glandular epithelium, endometrial stroma, and myometrium. The expression of the nuclear estrogen and progesterone receptors (nERα and nPR) in each of the compartments of the uterus was also documented to determine the specificity of their regulation with time and with respect to the onset and maintenance of DNA synthesis.

### MATERIALS AND METHODS

**Animals and treatment regimens.** SPF, Wistar (Han) rats were ovariectomized at 6 weeks-of-age by the supplier, Charles River, U.K. After a recovery period of 3 weeks, groups of 12 ovariectomized rats, approximately 225 g in weight, were administered tamoxifen (1 mg/kg/day), toremifene (1 mg/kg/day), both supplied by Zeneca Pharmaceuticals, or 17β-estradiol benzoate (50 μg/kg/day), obtained from Sigma, in tricaprilin or tricaprilin vehicle as control, subcutaneously, once a day for up to 3 days. Animals were housed 4 to a cage in negative pressure isolators for the duration of the study, and allowed access to food and water ad libitum. BrdU was administered continuously in the drinking water (80 mg/100 ml) to all animals in all groups from 24 h prior to the first treatment dose and for the duration of the study. All animals were fed RM 1 pelleted diet (Special Diet Services, Witham, Essex, U.K.) ad libitum, for the duration of the study. Groups of 4 animals were sacrificed by pentobarbitone overdose at 24, 48, and 72 h after the first administration of drug or control. Body weights and vaginal and pituitary weights were recorded at autopsy. The uteri were re-

#### TABLE 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body wt (g)</th>
<th>Uterine wt (g)</th>
<th>Pituitary wt (g)</th>
<th>Vaginal wt (g)</th>
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<td>Control</td>
<td>225 ± 14</td>
<td>0.14 ± 0.01</td>
<td>0.007 ± 0.0002</td>
<td>0.042 ± 0.004</td>
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<tr>
<td>Tamoxifen</td>
<td>231 ± 7</td>
<td>0.29 ± 0.03*</td>
<td>0.008 ± 0.0004*</td>
<td>0.08 ± 0.008*</td>
</tr>
<tr>
<td>Toremifene</td>
<td>229 ± 14</td>
<td>0.24 ± 0.01*</td>
<td>0.008 ± 0.0003*</td>
<td>0.07 ± 0.005*</td>
</tr>
<tr>
<td>Estradiol</td>
<td>225 ± 6</td>
<td>0.47 ± 0.02*</td>
<td>0.009 ± 0.0004*</td>
<td>0.10 ± 0.004*</td>
</tr>
</tbody>
</table>

* Denotes statistically significant from control at the same time point, using one-way ANOVA. Dunnett’s test for significance at the 5% level.

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**FIG. 1.** Changes in the uterine weight of ovariectomized rats after treatment with tamoxifen, toremifene, and estradiol for up to 72 h. *Statistically significant at the 5% level.
moved and weighed (with and without fluid, if present). Representative sections of both horns of the uteri were fixed in 10% neutral-buffered formalin (NBF) for light microscopy and morphometry, and in Carnoy’s fluid for the determination of the BrdU incorporation labeling index. At least 4 transverse uterine sections were incorporated in each paraffin block for representative quantitative evaluation.

Immunostaining for BrdU incorporation into DNA and nuclear ERα and nuclear PR in the uterus. Paraffin sections (5 μm) from Carnoy’s-fixed uterus were rehydrated. For staining for BrdU incorporation, sections were treated first with a monoclonal rat anti-BrdU antibody (1:100 dilution, a gift from Dr M. Omerod, Institute for Cancer Research, Sutton, Surrey, U.K.) and then with an anti-rat peroxidase conjugated second antibody (1:100 dilution, Dako Ltd., High Wycombe, Bucks, U.K.) (Green et al., 1992). All procedures were carried out at room temperature. Immunoreactive nuclei or cells in S-phase were visualised using 3,3′-diaminobenzidine/H₂O₂. Sections were lightly counterstained with haematoxylin. Rat duodenum, processed at the same time, served as positive internal controls in all tissue sections.

NBF-fixed uterine sections (5 μm) were routinely stained with hematoxylin and eosin for hypertrophy measurements and for immunohistochemistry staining for nERα and nPR, were dewaxed with xylene, taken to water, and microwaved in citrate buffer pH 6.0 for 20 min at full power (700 W). Following microwaving, the sections were placed in distilled water at room temperature and endogenous peroxidase activity was blocked with 3% hydrogen peroxide in water. The mouse monoclonal anti-human estrogen receptor antibody (NCR-ER-6F11) was obtained from Vector Laboratories, Ltd., and used at a dilution of 1:25 (Carthew et al., 1997). NCR-ER-6F11 recognizes the full length ERα; it does not recognize full length ERβ by Western blot comparison (Vector Laboratories, personal communication). The mouse monoclonal anti-progesterone receptor antibody was purchased from Immunotech (Marseille, France) and used at a dilution of 1:50 in PBS with 2 mg/ml bovine serum albumen (BSA). This antibody was prepared using a recombinant hormone-binding domain located on the C-terminal domain of the human progesterone receptor, conjugated to BSA. A control positive of human endometrium was included in all batches of immunostains. Immunoreactive nuclei were visualised using 3,3′-diaminobenzidine/H₂O₂. Sections were lightly counterstained with hematoxylin.

Quantitation of hypertrophy and BrdU labeling index (LI). Hypertrophy of the luminal epithelial cells was measured using the NIH Image program (Dr. Wayne Rasband, National Institutes of Health). Four measurements of luminal epithelial height were made per transverse uterine cross-section for 3 different sampling sites in the uterus representing the proximal, medial, and distal parts, and the mean value was calculated for 4 animals per group. BrdU labeling indices were calculated for the luminal epithelium and glandular epithelium by examining 100 nuclei per transverse uterine cross-section for 3 different sampling sites in the uterus, representing the proximal, medial, and distal parts per animal (4 per group). The labeling indices for the endometrial stroma were determined by examining 1000 nuclei per animal (excluding the glandular epithelium) and 1500 nuclei per animal for the

FIG. 2. Hypertrophy, estimated by luminal epithelial height in ovariectomized rats after treatment with tamoxifen, toremifene or estradiol for up to 72 h. *Statistically significant at the 5% level.

FIG. 3. Treatment and time related BrdU labeling indices in the luminal epithelium of ovariectomized rats after tamoxifen, toremifene or estradiol for up to 72 h.
derivation of the LI for the myometrium. The labeling index was expressed as a percentage of the number of DAB-stained nuclei over the total number of nuclei examined.

Statistical analyses. Results are given as the means ± the standard deviation of the means, and were tested using analysis of variance (ANOVA) with Dunnett’s test for significance at the 5% level. The BrdU-labeling indices were transformed to log10 before analysis by ANOVA.

RESULTS

Treatment-Related Effects on Body and Organ Weights

The changes in body, uterine, pituitary, and vaginal weights with estradiol, tamoxifen, and toremifene treatment at 72 h after the first treatment are shown in Table 1. Body weights in all treatment groups did not differ significantly over the treatment period, so comparison of absolute organ weights was subsequently used for determination of significant changes. The increases in uterine weights for estradiol were consistently greater than ovariectomized controls at all time points (Fig. 1). The increases in uterine weights of tamoxifen- and toremifene-treated animals were significantly greater than the ovariectomized control value, and significantly less than the mean for estradiol-treated animals at 72 h after treatment (Table 1), but were not significantly different from each other. Similarly, the increases in pituitary and vaginal weights were also significant for tamoxifen, toremifene, and estradiol treatment by 72 h after treatment (Table 1).

Hypertrophy of the Luminal Epithelial Cells of the Uterus in Response to Treatment

Estradiol, tamoxifen, and toremifene all caused luminal epithelial hypertrophy from 24 h after the first treatment (Fig. 2). The degree of hypertrophy increased for the next 48 hrs, with no difference between the treatment groups at 72 h (Fig. 2). From a comparative point of view, it was interesting to note that the myometrial cells of the uterus also underwent hypertrophy with estradiol treatment. The nuclear area of myocytes exposed to estradiol was increased significantly (data not shown) compared with the ovariectomized myocyte nuclei, for tissues fixed in 10% NBF and Carnoy’s fluid. Tamoxifen- and toremifene-exposed myocytes did not show any significant increase in myocyte nuclear area (data not shown).

Treatment-Related Changes in the BrdU Labeling Indices in Compartments of the Ovariectomized Uterus

The BrdU labeling indices in the luminal epithelial cells did not show any treatment-related effects when compared with their corresponding controls at the same time points (Fig. 3).
However, the labeling indices in the glandular epithelial cells in the toremifene group were significantly greater than the control at 48 and 72 h, while the tamoxifen and estradiol groups were significantly increased at 72 h (Fig. 4). Labeling indices in the endometrial stroma were significantly increased for toremifene at 48 and 72 h, while tamoxifen and estradiol increased the endometrial stromal labeling indices at 24, 48, and 72 h (Fig. 5). The myometrial labeling index was elevated at 48 and 72 hrs for tamoxifen toremifene and for estradiol at all time points (Fig. 6). A peak of mitotic activity was seen in the luminal epithelium of the estradiol group at 48 h (Fig 7), which was not apparent in the tamoxifen- and toremifene-treated animals at any time point examined.

**Treatment-Related Changes in Nuclear ERα and PR Expression in Compartments of the Ovariectomized Uterus**

The expression of nERα and nPR in the different compartments of the uterus, after treatment, was scored by comparison with the expression seen in the control ovariectomized rat uterus. In control ovariectomized rat uterus, nERα (Fig. 8A) and nPR (Fig. 8B), expression in the luminal epithelium was increased from that seen in estrogen-exposed ovariectomized rats (Fig. 8C), which was the same as epithelial staining during estrus in normal rats. As the levels of expression of luminal epithelial nuclear nERα and nPR were the greatest in ovariectomized rats, all of the other uterine compartment staining was scored by comparison with this, in intensity and the number of nuclei stained. Scoring the overexpressed luminal epithelial staining (which was present in almost 100% of cells) as +4, the ovariectomized glandular epithelial nuclear stain was also +4, while the endometrial stroma was scored +2 (approximately 50% of cell nuclei stained), and the myometrium was +1, (approximately 30% of cell nuclei stained).

Treatment with estradiol reduced the luminal epithelial expression of nERα and nPR, in terms of intensity and the number of cell nuclei stained, at 24, 48, and 72 h (Figs.8C and 8D show 48-h expression). The relative overexpression of the ovariectomized rat uterine luminal epithelial nERα was not decreased by tamoxifen or toremifene at any time point (Fig. 8E), although the expression of nPR in luminal epithelial cells was decreased to the same degree as treat-
FIG. 8. (A) Immunostaining for expression of nERα in the ovariectomized rat uterus, showing strong staining in the luminal epithelial cells, the glandular epithelial cells, and in about 50% of the endometrial stromal cells. Immunoperoxidase. (B) Immunostaining for expression of nPR in the ovariectomized rat uterus, showing strong staining in the luminal epithelial cells, the glandular epithelial cells and in about 50% of the endometrial stromal cells. Immunoperoxidase. (C) Immunostaining for expression of nERα in the ovariectomized rat uterus at 48 h after estradiol treatment. Note the decreased intensity of nERα staining in
ment with estradiol (Fig. 8F). Estradiol (Fig. 8G), tamoxifen, and toremifen increased the myometrial ERα expression throughout the treatment period compared to the levels seen in ovariectomized myometrium (Fig. 8H). Estradiol slightly increased the endometrial stromal ERα expression from +2 to +3 (approximately 75% of cell nuclei stained) at 48 and 72 h. Estradiol also decreased the glandular epithelial nERα expression at 48 and 72 h, whereas tamoxifen and toremifiene did not.

The extent and intensity of expression of nPR was very similar to that of nERα in the ovariectomized rat uterus (Fig. 8B). With estradiol, tamoxifen, and toremifen treatments, nPR expression was reduced (compared to the ovariectomized levels, which were the most intense) in the luminal (Fig. 8D) and glandular epithelia, and increased from the ovariectomized levels in the endometrial stroma and myometrium. The only difference was in the time of induction of change. Estradiol induced these changes from 24 h (except for the glandular epithelium, which started at 48 h), whereas tamoxifen and toremifene induced them from 48 h. The changes in nERα and nPR in the various ovariectomized uterine tissue compartments are summarized in Table 2.

**DISCUSSION**

Uterine wet and dry weight and vaginal cytological changes have been used extensively as indicators of uterine response to estrogen and estrogen-like effects (Reel et al., 1996). Uterine and vaginal weights were found to be consistently increased by treatment of ovariectomized rats with estradiol, tamoxifen, and toremifene. The increases in uterine weights with tamoxifen and toremifene were not significantly different from one another at the dose of 1 mg/kg body weight, used in the present study. Although one previous study using the immature 21-day-old rat described a 10-fold difference in terms of uterotrophic response between tamoxifen and toremifene (Di Salle et al., 1990), this was not found in 2 subsequent studies, where relatively little difference was found between tamoxifen and toremifene (Branham et al., 1993, Medlock et al., 1997). Fluid increase was only found with estradiol treatment, not with tamoxifen or toremifene, as has been shown previously (O’Connor et al., 1996). The luminal hypertrophy induced by estradiol, tamoxifen, and toremifene was similar to that found with exposure of the immature rat to these compounds (Branham et al., 1993, Medlock et al., 1997, Branham et al., 1996). There was an interesting difference between estradiol and tamoxifen/toremifene with respect to the induction of hypertrophy in the myometrium. Whereas estradiol induced myometrial nuclear hypertrophy, tamoxifen, and toremifene did not, again indicating a measurable difference between the action of a full agonist and a partial agonist of estrogen action in the myometrial compartment of the uterus.

No detailed study of the response of the different compartments of the uterus to estrogen agonist stimulation has previously been carried out, but it has been shown that the response of the uterus to the partial agonist tamoxifen can cause differing responses in the mouse endometrium (hyperplasia) and myometrium (atrophy) simultaneously (Carthew et al., 1996). In the present study, DNA synthesis was found to be significantly increased in the glandular epithelium, myometrium and endometrial stroma for estradiol and the partial agonists tamoxifen and toremifene. This is consistent with the previous finding, that endometrial stromal cell proliferation was the most sensitive marker of ER agonism (O’Connor et al., 1997). The luminal epithelial DNA synthesis was not significantly increased by any treatment and therefore indicates that the ovariectomized rat is less likely to undergo sustained hyperplasia in response to agonists (partial agonists) of estrogen action. This would be an important consideration in attempting to model sustained hyperplasia of all compartments of the endometrium, to produce endometrial tumors by the estrogen agonist effect of drugs.

The anti-human nuclear ER antibody used in the present study was prepared against the full-length estrogen receptor alpha molecule, and did not cross react with the beta form of the receptor (Kuiper et al., 1996). The ERα expression of the luminal epithelial cells was decreased by estradiol, but not by tamoxifen, or toremifene. This is consistent with a previous report which showed that ER levels in ovariectomized rats treated with estradiol decreased, while there was an increase in ER levels with both tamoxifen and toremifene (Kallio et al., 1986). The induction of an increase in the myometrial expression of ERα is consistent with the increase in DNA synthesis seen for all treatments that gave a positive response, although this was more persistent with estradiol. The changes in PR expression were similar for all compounds, with the increase in ERα in the the luminal epithelial cells, relative to (A). Immunoperoxidase. (D) Immunostaining for expression of nPR in the ovariectomized rat uterus, at 48 h after estradiol treatment. Note the decreased intensity of nPR staining in the luminal epithelial cells, relative to (B). Immunoperoxidase. (E) Immunostaining for expression of ERα in the ovariectomized rat uterus, at 48 h after tamoxifen treatment. Note the lack of effect on the levels of expression of ERα in luminal epithelial cells, compared to the ovariectomized levels (A) and estradiol (C). Immunoperoxidase. (F) Immunostaining for expression of nPR in the ovariectomized rat uterus, at 48 h after tamoxifen treatment. Note the effect on the levels of expression of nPR in luminal epithelial cells, compared to the ovariectomized (B) and similarity to estradiol (C). Immunoperoxidase. (G) Immunostaining for expression of ERα in the myometrium of the ovariectomized rat uterus, at 48 h after estradiol treatment. Note the increase in staining intensity of ERα compared to the levels seen in ovariectomized rat myometrium (H), and the enlargement of the myometrial cell nuclei, indicating hypertrophy. Immunoperoxidase. (H) Immunostaining for expression of ERα in the myometrium of the ovariectomized rat uterus. Note the relatively less intense staining compared to (G). Immunoperoxidase × 475.
myometrium being matched by an increase in the nPR expression in the myometrium, as should occur if the activation of these two receptors is linked in the stimulation of uterine growth. Increased nPR expression for all compounds seemed to be a more sensitive marker of estrogen-like action than nERα expression, at least for tamoxifen and toremifene. The decreased expression of nPR in the luminal and glandular epithelium of the uterus was similar to the effect of estradiol on nERα expression. For tamoxifen and toremifene in particular, nPR, rather than nERα expression, was more consistently like the effect seen with estradiol in the ovarioctomized uterus.

The spectrum of responses in terms of imbibition of fluid, hypertrophy, cell division, DNA synthesis, and expression of the nERα were found to be different for estradiol when compared with tamoxifen and toremifene. Neither of these decreased the expression of the nERα in the luminal epithelial cells of the ovarioctomized rat uterus, as did estradiol. They also did not cause as great a response in terms of DNA synthesis, although the same tissue compartments were affected. The nPR expression was consistently affected in a similar manner, and to a similar extent, in all compartments of the uterus over the time period of exposure to estradiol, tamoxifen, and toremifene. The only qualification to this was that nPR regulation was affected earlier with estradiol, after only 24 h. The changes in myometrial hypertrophy, regulation of DNA synthesis in the endometrium and myometrium, and nPR expression, in particular, will form useful additions to the variables used to interpret the estrogen agonist, partial agonist, or antagonist actions of new pharmaceuticals on the uterus. These findings will also be relevant to the evaluation of any environmental chemicals that are thought to have the potential for estrogenic effects, and in the experimental modeling for the potential risk of drugs and chemicals to cause endometrial cancer.

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tr>
<td>Summary of the Major Changes in Nuclear ERα and Pr Expression with Treatment and Time in Ovariectomized Wistar (Han) Rat Uteri</td>
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<table>
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<th></th>
<th>Day 1</th>
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<td>nERα</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>MM↑</td>
<td>MM↑</td>
<td>MM↑</td>
</tr>
<tr>
<td>Toremifene</td>
<td>MM↑</td>
<td>MM↑</td>
<td>MM↑</td>
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<td>nPR</td>
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<td></td>
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<td>LE, GE↓; ES, MM↑</td>
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*Note.* Uterine tissue compartments: luminal epithelium (LE), glandular epithelium (GE), endometrial stroma (ES), and myometrium (MM). ↑ indicates increase, ↓ indicates decrease.

ACKNOWLEDGMENTS

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REFERENCES


