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J. R. Pasqualini

SYNTHESIS AND REGULATION OF SEX HORMONES IN BREAST TISSUE DURING PRE- AND POSTMENOPAUSE

INTRODUCTION

Most breast cancers (~ 95 %) are in their early stage hormone-sensitive, where the estrogen estradiol (E2) plays an important role in the genesis and development of this tumour [1, 2]. About two thirds of breast cancers occur during the postmenopausal period when the ovaries have ceased to be functional. Despite the low levels of circulating estrogens, the tissular concentrations of estrone (E1), E2 and their sulphates (E1S, E2S) are several times higher than those found in the plasma or in the area of the breast considered as normal tissue (Fig. 1) suggesting a specific tissular biosynthesis and accumulation of these hormones [3–5]. There is substantial information that the mammary gland, normal or pathological, contains all the enzymes responsible for the local biosynthesis of E2 from circulating precursors. Two principal pathways are implicated in the last steps of E2 formation in breast tissues: the "aromatase pathway" which transforms androgens into estrogens [6–7] and the "sulphatase pathway" which converts E1S into E1 by the estrone-sulphatase (EC: 3.1.6.1) [8–10]. The final step of steroidogenesis is the conversion of the weak E1 to the potent biologically active E2 by the action of a reductive 17β-hydroxysteroid dehydrogenase type 1 activity (17β-HSD-1, EC 1.1.1.62) [11–12].

Quantitative evaluation indicates that in human breast tissue E1S "via sulphatase" is a much more likely precursor for E2 than is androstenedione "via aromatase" (Fig. 2) [4, 5, 13]. It is also well established that steroid sulphotransferases, which convert estrogens into their sulphates, are also present in breast cancer tissues [14, 15]. This information extends the concept of "intracrinology" where a hormone can have its biological response in the same organ as it is produced.

Figure 1: Concentrations of estrone (E1), estradiol (E2) and their sulphates (E1S, E2S) in the tumoral tissue and the tissue considered as normal of patients with breast cancer.
The different estrogens were evaluated by RIA. Values (in pg/g tissue) are expressed as the mean ± SEM (n = 14). *p = 0.025 vs. E2 in the normal tissue. **p = 0.05 vs. E1S in the normal tissue. Quoted from [5].

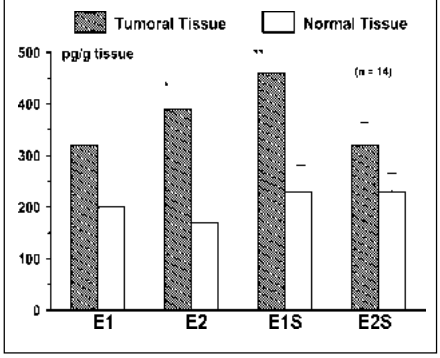
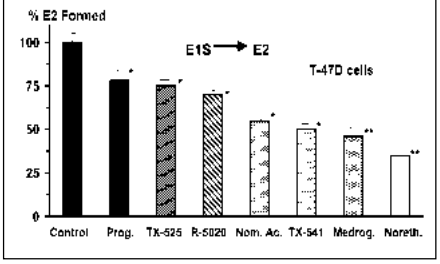


Figure 2: Comparative effects of various progestins on the inhibition of the estrone sulphate (E1S) conversion to estradiol (E2) in the hormone-dependent T-47D human breast cancer cell line.
Preconfluent cells were incubated 24 h at 37 °C with a physiological concentration (5×10^{-9} mol/l) of [^{3}H]-E1S alone or in the presence of progestins at the concentration of 5×10^{-7} mol/l. Results (pmol of E2 formed/mg DNA from E1S) are expressed in percent (%) of control value considered as 100 %. The data are the means ± SEM of duplicate determinations of 3–7 experiments. Prog. = progesterone; TX-525 and TX-541 are 19-norprogestins of Theramex laboratories; R-5020 = promegestone; Nom.Ac. = nomegestrol acetate; Medrog. = medrogestone; Noreth. = norethisterone. *p = 0.05 vs control value, **p = 0.01 vs control value.



ESTRONE SULPHATASE ACTIVITY IN BREAST CANCER AND ITS CONTROL

For many years the endocrine therapy in breast cancer has been mainly by the utilization of antiestrogens (e.g. Nolvadex, tamoxifen citrate) which block the estrogen receptor.

More recently, another endocrine therapy has been explored by inhibiting the tissular E2 production using different anti-enzyme agents involved in the biosynthesis of this hormone. At present, the positive effect of anti-aromatase compounds on the benefit in breast cancer patients is well documented [16–17]. However, as E1S in human breast cancer is quantitatively the most important precursor of E2, new possibilities can be opened to block E2 which is originated through this conjugate via the "sulphatase pathway".

In human hormone-dependent breast cancer cells (MCF-7, T-47D), the estrone sulphatase activity is high. In contrast, hormone-independent breast cancer cells (MDA-MB-231, MDA-MB-468) show very low sulphatase activity in intact cells [18]. The sulphatase mRNAs are present in both the hormone-dependent and hormone-independent breast cancer cells and the expression of this mRNA correlates with the sulphatase activity [19].

Control by progestins

Various progesterone derivatives (e.g. medrogestone), as well as norprogestins (e.g. nomegestrol acetate, promegestone) provoke a significant decrease of E2 formation when physiological concentrations of E1S are incubated with breast cancer cells (MCF-7 and T-47D) [18, 20]. Figure 2 gives a comparative study of the inhibitory effect of different progestins in the conversion of E1S

to E2 in the T-47D hormone-dependent breast cancer cells.

Effect of Tibolone and its metabolites

In another series of studies, the effect of tibolone on the estrone-sulphatase activity was explored. Tibolone (Org OD-14, active substance of Livial®) is a synthetic steroid with a 19-nortestosterone derivative structure. This compound has a tissue-specific action with weak estrogenic, progestagenic and androgenic properties and is extensively used to prevent climacteric symptoms and postmenopausal bone loss. Tibolone and its metabolites Org 4094, Org 30126 (3α and 3β hydroxy derivatives) and its 4-en isomer (Org OM-38) are potent sulphatase inhibitors at low concentrations in hormone-dependent breast cancer cells [21] (Fig. 3).

Estradiol can inhibit estrone sulphatase in human breast cancer cells

Very recent studies of this laboratory have demonstrated that E2 at a concentration of 5×10^{-5}–5×10^{-9} M has a significant inhibitory effect on the conversion of E1S to E2 in T-47D and MCF-7 breast cancer cells. Estradiol inhibits this conversion at very low doses (5×10^{-9} M) (57.5 % of inhibition) and this effect is dose-dependent. The IC50 value (the E2 concentration which corresponds to 50 % inhibition) is 1.85×10^{-9} M [22].

17β-HYDROXYSTEROID DEHYDROGENASE (17β-HSD) IN BREAST CANCER AND ITS CONTROL

Studies on estrogen metabolism have demonstrated that the 17β-HSD (Type I) reductive activity is very high in hormone-dependent breast cancer cells (MCF-7, T-47D) whereas in hormone-independent cells (MDA-MB-231, MDA-MB-468) the oxidative activity is preferential suggesting that there is a change in 17β-HSD phenotype in neoplastic cells [23, 24].

Effect of progestins on 17β-HSD

Using nomegestrol acetate or medrogestone, it was observed that these substances decrease significantly the reductive 17β-HSD activity in hormone-dependent breast cancer cells [23, 25]. This effect is more intense with the PR-rich T-47D cells.

Effect of tibolone and its metabolites on 17β-HSD

After 24 h incubation with a physiological concentration of [^{3}H]-E1 (5×10^{-9} M) in T-47D or MCF-7 breast cancer cells; tibolone and its metabolites Org 30126 and Org 4094 (at 5×10^{-7} M) significantly decrease the conversion of E1 to E2 by the reductive 17β-HSD type 1 activity (see Fig. 4). This inhibitory effect is dose-dependent. The 4-en isomer of tibolone (Org OM-38) shows an inhibitory effect only at the concentration of 5×10^{-6}M [26].

SULPHOTRANSFERASE ACTIVITY IN BREAST CANCER AND ITS CONTROL

It is well established that estrogen sulphates do not bind to the estrogen receptor and have no estrogenic effect, consequently increase of sulphotransferase activities in breast

Figure 3: Comparative effects of tibolone (Org OD14, active substance of Livial®) and of its main metabolites on the inhibition of the estrone sulphate (E1S) conversion to estradiol (E2) in the hormone-dependent T-47D human breast cancer cell line.
Preconfluent cells were incubated 24 h at 37 °C with 5×10^{-9} mol/l of [^{3}H]-E1S alone or in the presence of tibolone or its metabolites at the concentration of 5×10^{-7} mol/l. Results (pmol of E2 formed/mg DNA from E1S) are expressed in percent (%) of control values considered as 100 %. The data are the means ± SEM of duplicate determinations of 3–5 experiments. Org OM38 = 4-en isomer of tibolone; Org 4094 = 3α-hydroxy derivative of tibolone; Org 30126 = 3β-hydroxy derivative of tibolone. *p = 0.001 vs control value, **p = 0.0005 vs control value.

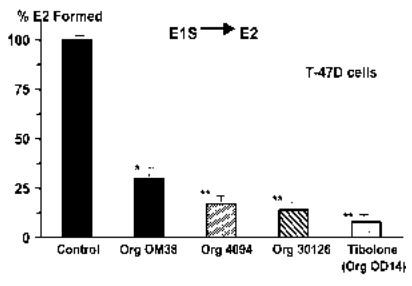
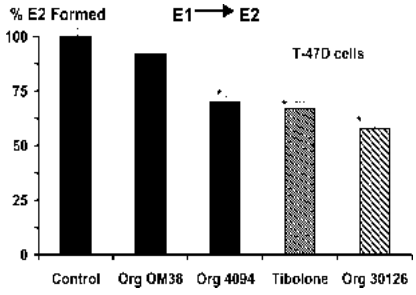


Figure 4: Comparative effects of tibolone (Org OD14, active substance of Livial®) and of its main metabolites on the inhibition of the estrone (E1) conversion to estradiol (E2) in the hormone-dependent T-47D human breast cancer cell line.
Preconfluent cells were incubated 24 h at 37 °C with 5×10^{-9} mol/l of [^{3}H]-E1 alone or in the presence of tibolone or its metabolites at the concentration of 5×10^{-7} mol/l. Results (pmol of E2 formed in cell compartment/mg DNA from E1) are expressed in percent (%) of control value considered as 100 %. The data are the means ± SEM of duplicate determinations of 3–4 experiments. Org OM38 = 4-en isomer of tibolone; Org 4094 = 3α-hydroxy derivative of tibolone; Org 30126 = 3β-hydroxy derivative of tibolone. *p = 0.05 vs control value.



cancer can diminish the estrogenic activity.

Effect of progestins on estrogen sulphotransferase

Recent data have shown that in hormone-dependent breast cancer cells (MCF-7, T-47D) low concentrations (5×10^{-7} M) of promegestone (R-5020) can increase the enzyme activity, while higher concentrations (5×10^{-5} M) decrease this activity. This dual effect is correlated with the mRNA expression of EST, which is modulated by promegestone in a similar manner [27].

Effect of tibolone and its metabolites on sulphotransferase activity

After 24 h of incubation with a physiological concentration of [^{3}H]-E1 (5×10^{-9} M) in T-47D or MCF-7 breast cancer cells; tibolone and its metabolites Org 30126 and Org 4094 (at 5×10^{-8} M) significantly increase the conversion of E1 to estrogen sulphates (see Fig. 5). It is remarkable that this stimulatory effect occurs at low doses. At high concentrations (5×10^{-6} or 5×10^{-5} M), we observed either no effect or an inhibitory effect of the sulphotransferase activity. The 4-en isomer of tibolone (Org OM38) shows no stimulatory effect [28].

Conclusions

Very attractive data were obtained concerning the action of various progestins (promegestone, nomegestrol acetate, medrogestone) as well as tibolone and its metabolites, on the inhibition of estrone-sulphatase and 17β-HSD enzymes involved in the formation of estradiol in breast cancer cells.

Recent data show also that some progestins (promegestone, nomegestrol acetate, medrogestone) as well as tibolone in hormone-dependent breast cancer cells can stimulate sulphotransferase activity. This is an important point in the physiopathology of this disease because it is well known that the estrogen sulphates are biologically inactive. For these inhibitory or stimulatory effects on the control of the enzymes involved in the formation and transformation of estrogens in breast cancer, we propose the concept of: Selective Estrogen Enzyme Modulator (SEEM) (Fig. 6).

The exploration of various progestins, tibolone and its metabolites, in trials with breast cancer patients, showing an inhibitory effect on sulphatases and 17β-HSD and a stimulatory effect on sulphotransferases, will provide a new possibility in the treatment of this disease.

The paradoxical effect of E2 in blocking sulphatase activity in breast cancer cells could be related to estrogen replacement therapy in which it is observed that this treatment in post-menopausal women has no effect or can reduce breast cancer mortality [29, 30].

Figure 5. Comparative effects of tibolone (Org OD14, active substance of Livial®) and of its main metabolites on the conversion of estrone (E1) to estrogen sulfates (ES) in the hormone-dependent T-47D human breast cancer cell line.

Preconfluent cells were incubated 24 h at 37 °C with 5×10^{-9} mol/l of [^{3}H]-E1 alone (control; non-treated cells) or in the presence of tibolone or its metabolites at the concentration of 5×10^{-9} mol/l. Results (pmol of ES formed in culture medium / mg DNA from E1) are expressed in percent (%) of control value considered as 100%. The data are the means ± SEM of duplicate determinations of 3–4 experiments. Org OM38 = 4-ene isomer of tibolone; Org 4094 = 3α-hydroxy derivative of tibolone; Org 30126 = 3β-hydroxy derivative of tibolone. *p = 0.05 vs control value [^{3}H]- E1 alone, **p = 0.01 vs control value.

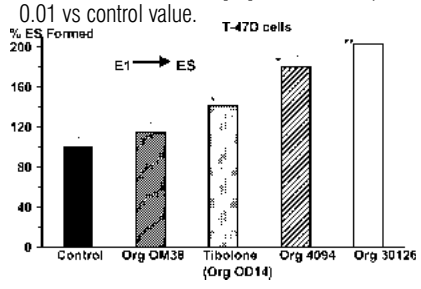
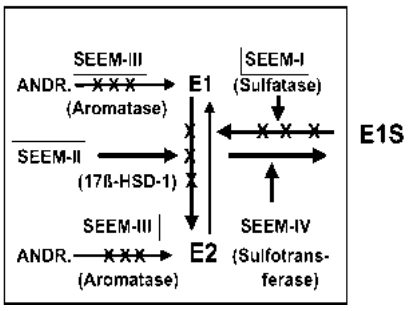


Figure 6: The Selective Estrogen Enzyme Modulator (SEEM) concept in human hormone-dependent breast cancer cells.

The SEEM can control the enzymatic mechanisms involved in the formation and transformation of estrogens in breast cancer cells, where the sulphatase pathway is quantitatively higher than the aromatase. SEEM-I inhibits the estrone sulphatase; SEEM-II the 17β-hydroxysteroid dehydrogenase type 1; SEEM-III the aromatase activities and SEEM-IV stimulates the estrone sulphotransferase activity. It is suggested that E1S is present in the tumour outside the cell, and reaches the cell membrane where it is in contact with the intracellular estrone sulphatase (see [29]). ANDR. androgens; E1 estrone; E2 estradiol; E1S estrone sulphate.



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