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Synthesis and regulation of sex hormones in breast tissue during pre- and postmenopause

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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 specific tissues (estrogen E2, 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 = 0.05 vs. E1S in the normal tissue. Quoted from [5].

 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-nor-testosterone 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 $5 \times 10^{-5} - 5 \times 10^{-9}$ 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 ($5 \times 10^{-8}$ M) (57.5 % of inhibition) and this effect is dose-dependent. The IC50 value (the E2 concentration which corresponds to 50 % inhibition) is $1.85 \times 10^{-9}$ 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 breast cancer cells; tibolone and its metabolites Org 30126 and Org 4094 (at $5 \times 10^{-7}$ 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 $5 \times 10^{-8}$ 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...
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 x 10^-7 M) of promegestone (R-5020) can increase the enzyme activity, while higher concentrations (5 x 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 [3H]-E1 (5 x 10^-9 M) in T-47D or MCF-7 breast cancer cells; tibolone and its metabolites Org 30126 and Org 4094 (at 5 x 10^-6 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 x 10^-6 or 5 x 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].

**References:**


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