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E26. Selective oestrogen enzyme modulators (SEEMs) and their effect on the breast and endometrium

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1. Introduction

Most breast cancers (approximately 95%), whether in pre- or post-menopausal women, are initially hormone-dependent, where the hormone oestradiol (E_2) plays a crucial role in their development and progression. Consequently, processes that modulate the intracellular concentrations of active oestrogens can affect the aetiology of this disease.

Approximately two thirds of breast cancers occur during the post-menopausal period when the ovaries have ceased to be functional. Despite the low levels of circulating oestrogens, the tissular concentrations of oestrone (E_1), E_2 and their sulphates (E_1S; E_2S) are several times higher than those found in the plasma or in the area of the breast considered as normal tissue, suggesting a specific tumoral biosynthesis and accumulation of these hormones [1,2].

There is substantial data that mammary cancer tissue contains all the enzymes responsible for the local biosynthesis of E_2 from circulating precursors. Two principal pathways are implicated in the last steps of E_2 formation in breast cancer tissues: the 'aromatase pathway' which transforms androgens into oestrogens [3], and the 'sulphatase pathway' which converts E_1S into E_1 by the oestrone–sulphatase [4]. The final step of steroidogenesis is the conversion of the weak E_1 to the potent biologically active E_2 by the action of a reductive 17β-hydroxysteroid dehydrogenase type 1 activity (17β-HSD-1) [5].

Quantitative evaluation indicates that in human breast tumours E_1S 'via sulphatase' is a much more likely precursor for E_2 than is androstenedione 'via aromatase' [6,7].

Steroid sulphotransferases (ST), which convert oestrogens into their sulphates, are also present in breast cancer tissues [8]. Fig. 1 gives a general view of oestrogen formation and transformation in human breast cancer. The presence of sulphatase, 17β-HSD, and sulphotransferases in the uterine endometrium is well documented. We summarise here recent data concerning the enzymes involved in the formation and transformation of oestrogens in these two tissues.

2. Anti-sulphatase agents

The anti-oestrogens: tamoxifen, its 4-hydroxy-derivative, ICI 164,384, various progesterone derivatives (e.g. medrogestone), retro-progesterone derivatives (e.g. dydrogesterone), 19-nor-testosterone derivatives (e.g. norethisterone, norelgestromin), 17-hydroxy-nor-progesterone derivatives (e.g. nomegestrol acetate), 19-nor-progesterone derivatives (e.g. promegestone), tibolone and its metabolites, different synthetic steroidal and non-steroidal compounds, as well as E_2 are very active in blocking the sulphatase activity in breast cancer (for details, see [9,10]). Fig. 2 provides a comparative study of the sulphatase inhibitory effect of different progestins on the conversion of E_1S–E_2 in hormone-dependent breast cancer cells.

3. Anti-17β-hydroxysteroid dehydrogenase agents

The progestins: nomegestrol acetate, medrogestone, promegestone, dydrogesterone, norelgestromin, as well as tibolone and its metabolites, are significant inhibitors of 17β-HSD-type 1 in breast cancer cells (for details, see [9]).

4. Control of sulphotransferase activity

As sulphoconjugates are not biologically active, the control of the formation of these conjugates in breast cells represents an important mechanism in the modulation of the biological activity in this tissue (for details,

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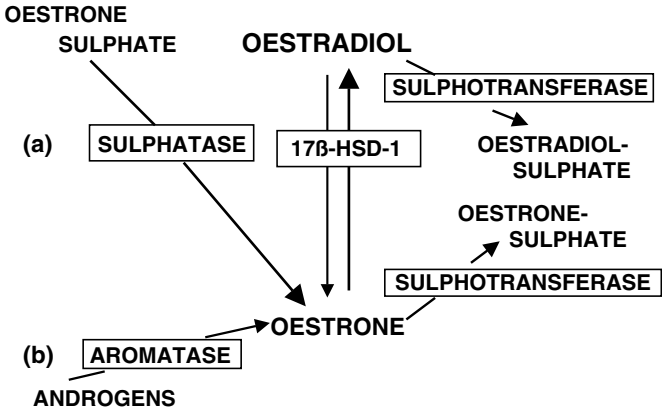

Fig. 1. Enzymatic mechanism involved in the formation and transformation of oestrogens in human breast cancer. The sulphatase pathway (a) is quantitatively 100–500 times higher than that of the aromatase pathway (b) 17β-HSD-1 = 17β-hydroxysteroid dehydrogenase type 1.

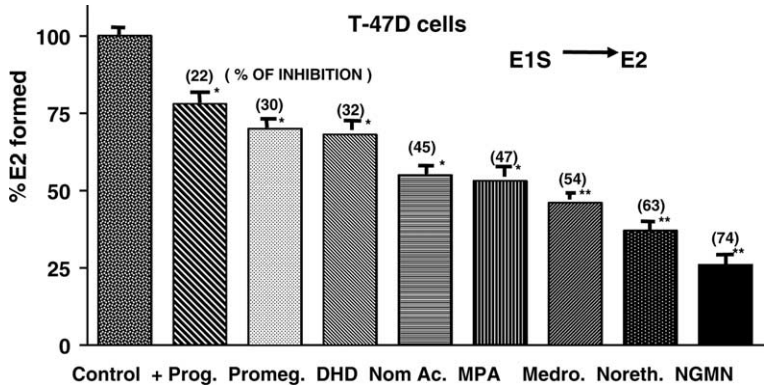

Fig. 2. Comparative effects of various progestins on the inhibition of the oestrone sulphate (E_1S) conversion to oestradiol (E_2) in the hormone-dependent T-47D human breast cancer cell line. Preconfluent cells were incubated 24 h at 37 °C with a physiological concentration (5×10^{-9} mol/l) of [^{3}H]-oestrone sulphate (E_1S) alone or in the presence of progestins at the concentration of 5×10^{-7} mol/l. Results (pmol of E_2 formed/mg DNA from E_1S) are expressed in percent (%) of control value considered as 100%. The data represent the mean ± standard error of the mean (SEM) of duplicate determinations of 3–7 independent experiments. Prog., progesterone; Promeg., promegestone; DHD, 20-dihydro-dydrogesterone; Nom. Ac., nomegestrol acetate; MPA, medroxyprogesterone acetate; Medro., medrogestone; Noreth., norethisterone; NGMN, norelgestromin. *$P \leqslant 0.05$ *vs.* control value; **$P \leqslant 0.01$ *vs.* control value.

see [9]). It was observed that the progestins: medrogestone, nomegestrol acetate, promegestone (R-5020), as well as tibolone and its metabolites, at low concentrations (1×10^{-9}–10^{-8}M), can stimulate the sulphotransferase activity in different breast cancer cells [11,12]. As an example, Fig. 3 indicates the effects of various progestins on the sulphotransferase activity in T-47D hormone-dependent breast cancer cells.

5. Anti-aromatase agents

Aromatase inhibition by anti-aromatase agents has shown very positive results in the treatment of patients with breast cancer. These inhibitors include steroidal and non-steroidal compounds. The most useful are: aminoglutethimide, 4-hydroxy-androstenedione (Formestane; Lentaron®), Vorosole, Letrozole (Femara®), Anastrozole (Arimidex®), Examestane (Aromasin®). A series of Reviews has been published recently on their biological effects and therapeutic applications [13–15].

6. Control of enzyme activity in the endometrium

The presence of various enzymes involved in the transformation of oestrogens is well established: sulphatases [16], sulphotransferases [17], and 17β-HSD [18]. However, data on the control of these enzymes in this tissue are limited. Tseng and Gurpide [19] found 17β-HSD activity was controlled by progestins, while Falany and Falany [20] observed a stimulation of sulphotransferases, also by progestins.

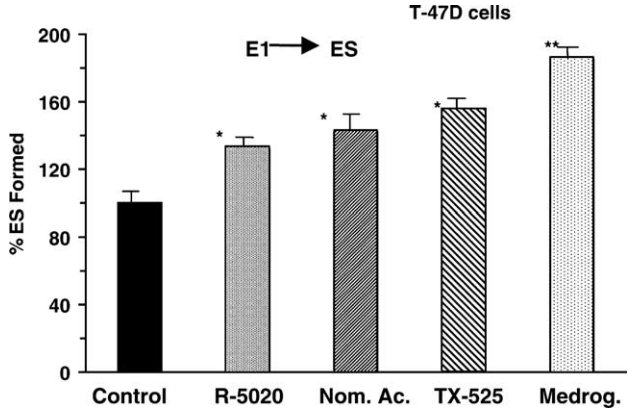

Fig. 3. Comparative effects of various progestins on the conversion of oestrone (E_1) to oestrogen sulphates (ES) in the hormone-dependent T-47D human breast cancer cell line. Preconfluent cells were incubated 24 h at 37 °C with 5×10^{-9} mol/l of [^{3}H]-E_1 alone or in the presence of progestins at the concentration of 5×10^{-9} mol/l. Results (pmol of ES formed in culture medium per mg DNA from E_1) are expressed in percent (%) of control value considered as 100%. The data represent the mean ± SEM of duplicate determinations of 3-6 independent experiments: R-5020, promegestone; Nom. Ac., nomegestrol acetate; TX-525, a 19-nor progestin of Theramex Laboratories; Medrog., medrogestone. $*P \leqslant 0.05$ *vs.* control value. $**P \leqslant 0.01$ *vs.* control value.

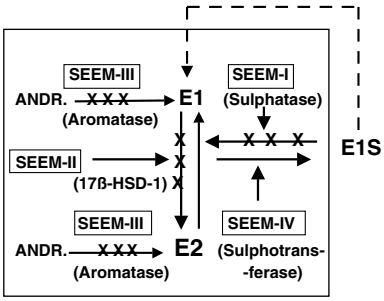

Fig. 4. The selective oestrogen enzyme modulator (SEEM) concept in human hormone-dependent breast cancer cells. The SEEM can control the enzymatic mechanisms involved in the formation and transformation of oestrogens in breast cancer cells, where the sulphatase pathway is quantitatively higher than the aromatase. SEEM-I inhibits the oestrone sulfatase; SEEM-II the 17β-hydroxysteroid dehydrogenase type 1; SEEM-III the aromatase activities, and SEEM-IV stimulates the oestrone sulphotransferase activity. It is suggested that E_1S is present in the tumour outside the cell and reaches the cell membrane where it is in contact with the intracellular oestrone sulphatase. ANDR., androgens; E_1, oestrone; E_2, oestradiol; E_1S, oestrone sulphate.

7. Conclusions

More than 15 years of experience have shown that breast cancer patients treated with the anti-oestrogen, tamoxifen (e.g. Nolvadex), have a significantly reduced risk of recurrence and an increased overall survival. However, another way to block oestradiol is by using anti-enzymes [anti-sulphatase, anti-aromatase, or anti-17β-hydroxysteroid dehydrogenase (17β-HSD)] which are involved in oestradiol biosynthesis in breast cancer tissues. At present, anti-aromatases are extensively used in breast cancer treatment, with positive benefits. However, oestrone sulphatase is quantitatively the most important pathway in oestradiol bioformation in breast cancer tissue. Very interesting data were obtained concerning the inhibitory activity of various progestins (promegestone, nomegestrol acetate, medrogestone, dydrogesterone, norelgestromin), tibolone and its metabolites, as well as other steroidal and non-steroidal compounds on oestrone sulphatase, as well as on 17β-hydroxysteroid dehydrogenase, enzymes involved in the other pathway of oestradiol formation in breast cancer cells. It was also shown that some progestins (promegestone, nomegestrol acetate, medrogestone), as well as tibolone, can stimulate sulphotransferase activity in hormone-dependent breast cancer cells. This is an important point in the physiopathology of this disease, as it is well known that oestrogen sulphates are biologically inactive.

The fact that oestradiol (E_2) can block its own bioformation in the breast cancer cell provides another aspect to this very complex mechanism in breast cancerisation. This paradoxical effect of E_2 could be related to oestrogen replacement therapy (ERT), a treatment that has been observed to have either no effect or to slightly increase breast cancer incidence [21], but significantly decreases mortality [22,23].

For these inhibitory or stimulatory effects on the activity of the enzymes involved in the formation and transformation of oestrogens in breast cancer, we have proposed the concept of selective oestrogen enzyme modulators (SEEM), which is schematically represented in Fig. 4.

The exploration of various progestins and other substances in trials on patients with breast or endometrial cancers, showing an inhibitory effect on sulphatases and 17β-hydroxysteroid dehydrogenase and a stimulatory effect on sulphotransferases, will, in combination with anti-aromatase agents, provide new possibilities for the treatment of this disease.

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