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Estradiol Metabolites and their Possible Role in Gynaecological Cancer

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Estradiol Metabolites and their Possible Role in Gynaecological Cancer

H. Seeger, A. O. Mueck

Evidence is growing that certain estradiol metabolites are biologically active, especially in the field of cancer. Currently research focuses on the anticarcinogenic effects of 2-hydroxyestrone and particularly 2-methoxyestradiol, as well as the possible carcinogenic properties of 4-hydroxyestrogens and 16 α -hydroxyestrone. The clinical relevance of these activities, demonstrated in in vitro and animal experiments, remains unclear – it is proven, however, that the metabolite production can be altered in certain malignancies such as endometrial-, breast- and cervical carcinoma. Clinical studies, including own investigations, demonstrated a negative correlation between the ratio of 2-hydroxyestrone to 16 α -hydroxyestrone and breast cancer risk. However, the design and interpretation of such studies should consider factors influencing metabolic pattern such as diet, physical activity, smoking as well as internal diseases and certain drugs. **J Reproduktionsmed Endokrinol 2010; 7 (Special Issue 1): 62–6.**

Key words: estradiol metabolites, gynaecological malignancies

■ Introduction

Estradiol metabolites appear to have important physiological functions, such as maintenance of homeostasis in the cardiovascular system, demonstrated in several studies and also in own research work [1]. In addition it is becoming more and more evident that estradiol metabolites also can influence carcinogenesis.

The main metabolites formed by A-ring metabolism are 2-hydroxyestrone and 4-hydroxyestrone, and by D-ring metabolism 16 α -hydroxyestrone and estriol. These metabolites are the ones most highly involved in the metabolic process in the human body. Most estrogen metabolites undergo an additional degradation step by conjugation, either by glucuronidation, sulfation, or methylation [2].

■ Most Important Estradiol Metabolites

Recent investigations indicate that local estradiol metabolism particularly may have a high biological significance [3]. Measurements in tissues, blood or urine may reflect such local changes, and are subject to intensive, and also our own research which can only be conducted in a few specialised groups due to the highly sophisticated laboratory methods needed. The measurement of metabolites may achieve more significance in

the near future, due to the new possibility of measuring even small concentration changes in the systemic circulation.

Kinetic studies have shown that 2-hydroxyestrone is metabolized very rapidly in the blood; more rapidly than other known natural steroids [4]. The conversion takes place in the blood by the enzyme catechol orthomethyltransferase (COMT) which is found in erythrocytes [4]. Evidence that there are differences in the biological behaviour of the methylated and non-methylated forms has been obtained in studies which revealed the antiestrogenic actions of 2-hydroxyestrone after preventing methylation [5]; it suppressed the growth of the breast cancer cell line MCF-7 [6, 7].

2-Methoxyestradiol (2-ME) has no estrogenic activity and has only a low relative binding affinity to the rat uterine cytosol receptor [8].

Both the catechol estrogen metabolites of oxidative C4 metabolism, 4-hydroxyestrone and 4-hydroxyestradiol are detected in only very small amounts in human blood [9]. They still possess estrogenic properties, as murine studies on the uterus have shown, and exert a stimulatory effect on the growth of MCF-7 cells [10].

16 α -hydroxyestrone, the main primary metabolite of D-ring metabolism, is

found in the plasma in pg quantities and in bile, urine and faeces in μ g quantities [11, 12]. 16 α -hydroxyestrone has an estrogenic effect, which, when measured by the increase in uterine weight of ovariectomized rats, is equal to or even stronger than that of estradiol [10].

The metabolites which are currently the subject of intensive research are 2-methoxyestradiol (2-ME), 4-hydroxyestrogens and 16 α -hydroxyestrone.

■ 2-Methoxyestradiol

The growth of cells of different tumours such as lung cancer [13], colon cancer [13], tumours of the nervous system [13, 14], melanoma [13], ovarian cancer [13], renal cancer [13], prostate cancer [13], muscle tumours [14], tumours of the eye [14], cervical cancer [13] and breast cancer [13, 15] has been inhibited by 2-ME. Different levels of sensitivity exist, however; breast cancer cells showed the most sensitive response to 2-ME. A finding of major significance for tumour research was the detection of an antiangiogenic action of 2-ME [6, 13, 15].

In our own studies we demonstrated that the combination of 2-ME with tamoxifen elicits additive antiproliferative actions in human breast cancer cells [16]. In addition, 2-ME was able to increase the effect of certain cytostatics in breast cancer cells as well as in ovarian cancer

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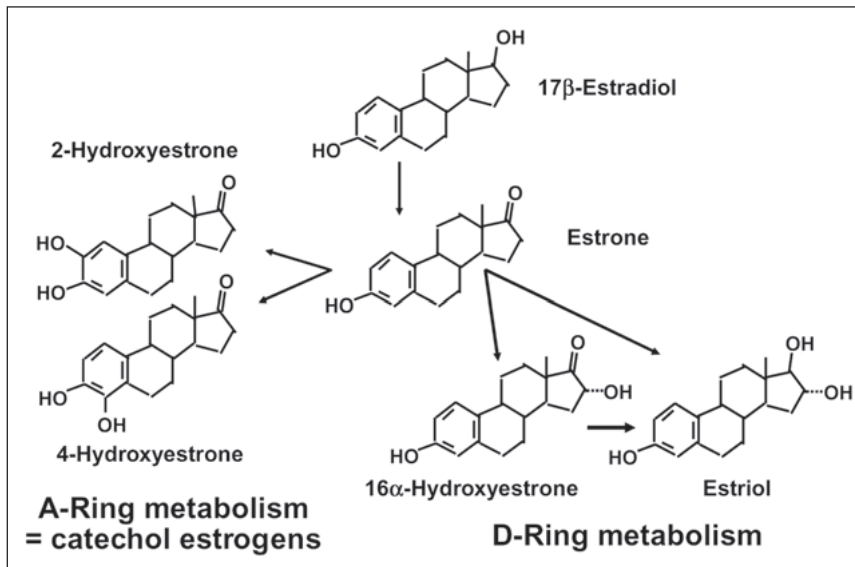


Figure 1: Estradiol metabolism – primary metabolites.

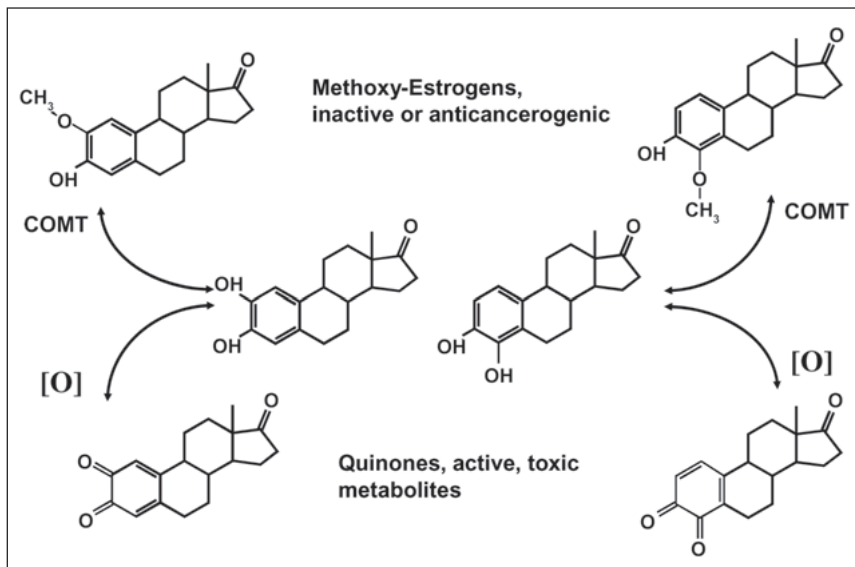


Figure 2: Estradiol metabolism – secondary metabolites.

cells [17, 18]. Own investigations suggest a similar inhibition of the aromatase enzyme by 2-ME as compared to letrozole [17]. NMU-induced mammary tumours of the rat were stimulated by 2-ME at a dosage of 1 mg/kg and inhibited at a dosage of 5 mg/kg [19].

Some clinical studies have already been conducted investigating the possible anti-tumour potency of 2-ME in prostate cancer, recurrent and metastatic breast cancer and solid malignancies [20–23].

In a phase II trial, 31 men with hormone-refractory prostate cancer were enrolled [20]. 2-ME was well tolerated and, despite suboptimal plasma levels and lim-

ited oral bioavailability with the available capsule formulation, still showed some anticancer activity at 1,200 mg/d.

In a phase I trial in men and women with solid tumours, the toxicity profile of an oral formulation of 2-ME was determined [21].

First results of a phase I study of the combination of 2-ME with docetaxel revealed a good tolerability [22]. 2-ME did not significantly alter the pharmacokinetics of docetaxel and vice versa. Serum levels of 2-ME achieved after treatment with a dosage of 1 mg were in the range of 100 to 600 nM, but remained below the expected therapeutic range.

To overcome the problems with the limited bioavailability of 2-ME capsules a NanoCrystal Dispersion (NCD) formulation of 2-ME was tested in a recent study in patients with refractory solid tumours [23]. The treatment was generally well tolerated, results on the efficacy are still awaited.

In a very recent study the activity and safety of NCD in 18 patients with advanced platinum-resistant ovarian cancer was investigated [24]. The formulation was well tolerated and few of the patients showed stable disease.

Overall the clinical studies available so far hint at a rather high tolerable estrogenic compound up to very high concentrations. However, no data are known as yet in as far 2-ME at high concentrations may have negative effects in the fibrinolytic/coagulation system and in terms of thrombogenesis, side effects that are familiar for endogenous estrogens.

■ 4-Hydroxyestrogens

The 4-catechol estrogens can stimulate growth of the human breast cancer cell line MCF-7; the effect of 4-hydroxyestradiol is stronger than that of 4-hydroxyestrone [25]. In tumour models in hamsters, rats, and mice, the 4-hydroxyestrogens have carcinogenic effects leading to kidney tumours in hamsters, and to liver tumours in rats and mice [26]. In the same animal studies, however, tumour induction could not be induced with 2-hydroxyestrogens.

They are relatively unstable, i.e. they can be transformed into highly reactive quinones, with the formation of semi-quinones as an intermediate stage [27] (Fig. 2).

Adducts of DNA with 4-hydroxyestrogen quinones, as recent studies have demonstrated, are unstable DNA compounds, which lead via depurination to destruction of the DNA. The DNA adducts with 2-hydroxyestrogen quinones, in contrast, are believed to be more stable, and are reversible without DNA destruction [27, 28]. Elevated 4-hydroxylase enzyme activity has also been found in human breast cancer specimens [29]. 4-Hydroxyestradiol was found in high concentrations in human breast cancer tissues [30, 31] and in addition,

concentrations of quinones were significantly higher in the cancer tissue as compared to control tissue [31]. Animal experiments showed a mutagenic effect of 4-hydroxyestradiolquinones [32, 33].

Of further interest are the results of Salama et al. [34], who demonstrated that catecholestrogens induce oxidative stress in human endometrial cells and trigger malignant transformation that was inhibited by addition of catechol-O-methyltransferase.

The toxic effects of 4-hydroxyestrogens can probably be prevented under normal conditions by various cellular defence mechanisms. The quinones themselves can be inactivated by sulfo compounds, such as the ubiquitous glutathione. Intracellularly formed catechol estrogens are rapidly methylated by the ubiquitous COMT. Patients with a COMT defect, e. g. due to genetic polymorphisms, are especially predisposed and currently it is discussed as it is advantageous to investigate polymorphism e. g. in smokers at the beginning of any treatment with HRT [35, 36].

■ 16- α -Hydroxyestrone

Using primary cultures of cells from the terminal duct lobular unit of the breast (TDLU), measurements were carried out in low-risk patients, i. e. patients undergoing mammary reduction and in high-risk patients, i. e. patients with mammary carcinomas. Comparing metabolite production, 16 α -hydroxyestrone synthesis was only slightly increased in low-risk patients, but was markedly increased in high-risk patients [37]. The authors concluded that there is a connection between the incidence of tumours and the upregulation of C16-estradiol metabolism.

Studies of estrogen metabolism showed that in mice with a high risk of mammary carcinoma, 16-hydroxylation was significantly increased compared to mice with a low tumour risk [38]. 2-hydroxylation showed no risk-dependent differences. Also surprising was the finding that infection with mammary tumour virus was accompanied by an increase in 16 α -hydroxyestrone production. The authors interpreted the results as meaning that a genetically determined increase in 16-hydroxylation signifies an

increased tumour risk and leads to cancer development when other factors, such as the mouse mammary tumour virus are involved.

Studies of estradiol metabolism in both female and male patients with systemic lupus erythematosus (SLE) showed that D-ring metabolism with production of 16 α -hydroxyestrone was increased [39]. Whether this increased production of the D-ring metabolite is associated with the increased risk of cervical cancer observed in patients with SLE remains unknown.

■ Estrogen Metabolism in Gynaecological Malignancies

Changes in estradiol metabolism have already been described for several neoplastic diseases, especially in gynaecological malignancies. Some studies have investigated the ratio between the 2 main metabolic pathways of the A and D-ring.

Breast Cancer

Observational trials have demonstrated that the ratio of 2- to 16 α -hydroxyestrone is decreased in women with breast cancer. However, existing studies had different designs, have been conducted in different populations, and some have extremely small sample sizes. Thus their results are inconsistent, with some showing a strong inverse association of increasing levels of the 2-OHE1/16-OHE1 ratio with breast cancer [40, 41], some showing a modest association [42–45], and still others showing no association [46, 47]. A study conducted in China [43] found an inverse association of the 2/16 ratio with breast cancer using urine samples collected before surgery but a positive association using post-surgery samples. In an own case/control study including 144 and 292 cases respectively, we found lower excretion of 2-hydroxyestrone and higher excretion of 16 α -hydroxyestrone in the cases as compared to controls, but only in postmenopausal women [48]. In a recent large population-based case-control study an inverse association of breast cancer risk with 2/16 ratio was found to be mostly consistent for premenopausal women with invasive breast cancer [49].

The reasons for these discrepancies in the clinical studies concerning the 2/16

ratio are currently unknown. Perhaps further elucidation might be available if epidemiologic studies using sophisticated laboratory methods to measure estrone, estradiol, 2-OHE, 4-OHE, 16-OHE, and estriol were conducted.

Endometrial Cancer

As in the case of breast cancer, an increase in estradiol metabolism via the D-ring was also found in cancerous endometrial tissue [50]. The fact that these results were found in postmenopausal women in whom no monthly endometrial shedding occurred leads to the question of whether these changes are due to cancer cells, i. e. are the cause of the disease, or if an enhanced D-ring metabolism has induced carcinogenesis of endometrial cells.

Cervical Cancer

In vitro studies showed that cells in the transformation zone of the cervix can form C16-hydroxy metabolites, and the growth of HPV-transformed cervical cells is stimulated by 16 α -hydroxyestrone [51]. In women with cervical intraepithelial neoplasias, urinary excretion of 2-hydroxyestrone and 16 α -hydroxyestrone was examined and compared with that of a group of healthy women [52]. The A-ring to D-ring quotient was significantly lowered with the severity of disease, i. e. the histopathological changes. Accordingly, growth of HPV-affected cervical carcinoma is presumably accompanied by a change in estradiol metabolism in favour of D-ring metabolism.

■ Factors Influencing Estradiol Metabolism

The assessment of estradiol metabolism has to consider factors which can influence this metabolism. For example endocrine diseases such as hypothyroidism or drugs like L-thyroxine and H2-antagonists can change estradiol metabolism [2]. In addition, diet, physical activity and possibly the type and stage of obesity may be of importance [53, 54].

Our own interest currently focuses on estradiol metabolism in smokers, as delineated elsewhere [55]. It is already known that oral estrogen therapy in postmenopausal women leads to an increase of 4-catechol estrogens and concomitantly a decrease of 2-methoxyestrogens

as compared to non-smokers which the authors correlated with an increased breast cancer risk [56]. According to own investigations metabolic changes can be partly avoided by the use of transdermal applications. In different clinical studies we demonstrated that estradiol metabolism in postmenopausal women treated with estrogen therapy can depend on application mode as well as on the type of progestogen addition [57–59].

■ Conclusion and Possible Practical Consequences

Important estrogenic actions obviously have to be assessed as a net effect of the existing metabolic pattern. This pattern depends on endogenous and exogenous factors which should be considered and explored more extensively in the near future, in case measurements of metabolites have practical consequences as a preventive strategy, or for any hormonal or anti-hormonal therapy. It is doubtless that estradiol metabolites are involved in the carcinogenesis of gynaecological malignancies. Research on estradiol metabolites can help to elucidate possible mechanisms of the carcinogenic or anti-carcinogenic activity of certain metabolites. This may have practical consequences, for example in choosing a hormonal treatment. The new development of the DNA chip technology may allow, in the near future, the evaluation of defects on the defence system of enzymes involved in estradiol metabolism due to genetic polymorphisms. Some risk groups such as women with a high breast cancer risk, smokers etc. may especially benefit from this rapid and certainly soon to be inexpensive method.

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