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Review

The dialectic role of progesterone

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ABSTRACT

Progesterone is known to be metabolized into various metabolites exerting various effects, predominantly into 5α-pregnanes and 4-pregnenes. Studies on uterine tissues showed numerous progesterone-converting enzymes such as 5α-reductase (5αR), 5β-reductase, 3α-, 3β-, 20α-, and 20β-hydroxysteroid oxidoreductases and others. The main progesterone-metabolizing enzymes in human breast tissues are 5αR, 3α-HSO 3β-HSO, and 20α-HSO. Tumor genesis in the breast has been shown to be enhanced by high 5αR activity and suppression of 3α-HSO and 20α-HSO. A major determinant of 5αR, the breast's gate-keeping enzyme activity is the genetic variation in the enzyme's gene. Two polymorphisms within the steroid 5αR type 2 gene, Ala > Thr at codon 49 and Val > Leu at codon 89 have been reported to strongly affect the enzyme's activity, even in regard to breast cancer risk. As steroid hormones are known to be converted into many other steroids occupying different receptors and thereby exerting various different effects, progesterone receptors are important factors when mediating the hormone's effects. The progesterone receptor (PR) gene is transcribed from one gene by two alternative promoters and translated into PR-B, a potent transcriptional activator, and PR-A, the shorter isoform, necessary to oppose the effects of PR-B. In addition, endocrine reactions are modulated by epigenetics. The expression of progesterone receptors has been shown to be up- and downregulated by various epigenetic mechanisms. Many factors must be also taken into account in hormonal (replacement) therapy. Thus natural steroids should not be disparaged as treatment options for gender-specific diseases. An update on endocrinological knowledge and experience is rather mandatory for gynaecologists.

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1. Introduction

Steroid biogenesis is connected to the evolution of the atmosphere. The evolution of oxygen led to the association of this single atom to the former aliphatic compound squalene in position 3. According to biophysical principles, steroids were born.

Until now, adding and removing of oxygen or a hydroxyl group remain important principles in metabolism and generation of new steroids. Hydroxylation of the estradiol-molecule in different positions leads to generation of hormones with various biological effects: for example, 2-hydroxy-estrogen exerts angiostasis and has a low affinity to estrogen-receptor alpha (ER-α), whereas 4-hydroxyestradiol has a high ER-α affinity and strong angiogenetic and mitotic power, also generating the dangerous depurinated DNA adducts. As this metabolic switch is needed for nidation and implantation and thus contributes to reproductive processes, endocrine related tissues in the female organism developed into

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highly vascularized organs in order to guarantee these early events of reproduction [1].

Testosterone, produced in the ovarian theca cells, can also be converted into different androgenic metabolites with different functions in the female breast as well as in the brain [1].

2. Progesterone metabolites

As estradiol and testosterone are transformed into various metabolites exerting various effects, progesterone can also be converted into other progesteronic steroids.

Progesterone is predominantly converted along two biochemical highways—(i) 5α-pregnanes and (ii) 4-pregnenes.

5α-pregnanes are known to enhance the mitotic rate in breast cells and are locally overrepresented in breast cancer. But why is progesterone metabolized via 5α-reductase (5αR) into such a steroid exerting a strong mitotic and antiapoptotic effect? Again, it's all about reproduction: 5α-pregnanes have a strong tocolytic effect. Thus 5αR activity increases during pregnancy, whereas it declines during the postpartum period.

Studies on uterine tissues from rats [2,3], guinea pigs [4,5], goats [6], and humans [7–11], as well as human placentae [12] showed numerous progesterone-converting enzymes as summarized by Wiebe in 2006 [13]. Similarly, incubations with ovarian tissues (especially granulosa cells) from rats [14–19], chickens [20,21], and humans [22] as well as incubations with testicular cells or homogenates from trouts [23], frogs [24], mouses [25], rats [26–30], rabbits [31], and humans [32,33] revealed various progesterone-converting enzymes. The group of progesterone-metabolizing enzymes includes 5αR, 5β-reductase (5βR), 3α-, 3β-, 20α-, and 20β-hydroxysteroid oxidoreductases (3α-HSO, 3β-HSO, 20α-HSO, 20β-HSO, respectively), 6α(β)-, 11β-, 16-, 17-, and 21-hydroxylase, and C17–20-lyase.

These enzymes are encoded by their responsible genes, which exhibit a high genetic variability, associated with a high differentiation in enzyme activity and velocity, expressing an individual enzyme pattern in a given patient.

A physiologically important enzyme with oncolcogical aspects in the breast is 5αR converting progesterone into 5α-pregnane-3,20-dione. The reaction of 5αR is irreversible. However, the further steps of metabolization are reversible: 5α-pregnane-3,20-dione is converted into 3- and 20-hydroxy pregnanes by the action of 3α-HSO, 3β-HSO, and 20α-HSO, respectively.

The second metabolic highway of progesterone in the breast is covered by the actions of 3α-HSO and 20α-HSO catalyzing the generation of 4-pregnen-3α-ol-20-one (3αHP) and 4-pregnen-20α-ol-3-one (20αHP). In contrast to 5α-pregnanes, expression of 4-pregnenes leads to increases in apoptosis and decreases in mitosis [13].

Thus, the main progesterone-metabolizing enzymes in human breast tissues are 5αR, 3α-HSO 3β-HSO, and 20α-HSO. Investigations and documentation of the individual enzyme activity might become important, maybe allowing an individual risk assessment for endocrine related cancers in the future.

As in vitro studies suggest, tumor genesis in the breast may also be enhanced by high 5αR activity and suppression of 3α-HSO and 20α-HSO.

However, the gate-keeping enzyme in the breast is 5αR; its activity depends on several endocrine and paracrine circumstances: for example, prolactin acts as a paracrine/autocrine mutagenic agent in breast cells and inhibits 20α-HSO expression in corpora lutea [34]. Different cytokines such as interleukin-4, -6, or -13 regulate activity and expression of 3β-HSO [35,36]. In addition, estrogen stimulates 5αR activity as demonstrated in the uterus [37]. Cellular milieu such as temperature, pH, cofactors such as ions, phospholipids, and other molecules also modulate the enzyme's activity and expression.

3. Genetic variation in progesterone metabolism

A major determinant of 5αR activity is the genetic variation in the enzyme's gene. Two polymorphisms within the steroid 5αR type 2 (SRD5A2) gene, Ala > Thr at codon 49 (A49T) and Val > Leu at codon 89 (V89L) affect the activity of the SRD5A2 enzyme and have been investigated by several study groups.

The Ala > Thr Codon 49 polymorphism increases the activity of SRD5A2, whereas the Val > Leu Codon 89 polymorphism decreases the activity of SRD5A2. The A49T polymorphism appears to result in a strongly increased enzymatic activity also in females, but this polymorphism is relatively rare, with the frequency of the Thr allele being <4% [38].

In regard to the V89L polymorphism, the Leu allele appears to be related to lower levels of 5α-androstane-3β,17β-diol-17β-glucuronide, a metabolite of dihydrotestosterone, which is commonly used as an in vivo measure of 5αR activity [39,40]. The V89L polymorphism is fairly common with the Leu allele frequency in Caucasian control populations being 30% [39–41].

This polymorphism has been examined in relation to breast cancer risk in one study [42], reporting a decreased risk for Japanese women with two Leu alleles. Another study examined this polymorphism in relation to breast cancer prognosis [43] and showed that the Leu allele was associated with lower breast tumor extract concentrations of prostate specific antigen, an earlier onset of breast cancer and a shorter disease-free and overall survival [43].

However, another trial found no evidence for a consistent relationship between the V89L SRD5A2 polymorphism and breast cancer risk. However, the Leu/Leu genotype was associated with larger tumor size, higher frequency of positive lymph nodes, higher TNM stage, and as a result, shorter survival than the Val/Val or Val/Leu genotypes [44].

These conflicting data can be explained by the dialectic role of 5αR effect in the breast. On the one hand side, progesterone is metabolized in 5α-pregnane-3,20-dione with tocolytic and anxiolytic effects, but also with stimulated proliferation rates, changed cell-to-cell and cell-to-substrate adhesion and cytoskeletal and adhesion molecules, enhancing growth regulating signals and mitogenic growth signaling pathways. On the other hand side, 5αR converts testosterone into dihydrotestosterone that is further metabolized by hydroxysteroid-dehydrogenase into androstenedione, which cannot be aromatized to estrogen and thus a decrease in the substrate for aromatase takes place.

In regard to the breast, 5αR exerts a ying-yang mechanism. Metabolization of progesterone into 5α-pregnane-3,20-dione burdens breast tissue, whereas conversion of testosteron to dihydrotestosterone protects the breast gland.

Treatment with dihydrotestosterone not only completely reverses the stimulatory effect of estradiol on breast tumor growth but also decreases total tumor area to $48 \pm 10\%$ of its original size. The androgen dihydrotestosterone is thus a potent inhibitor of the stimulatory effect of estradiol on ZR-75-1 human breast carcinoma growth in in vivo athymic mice. Ovariectomized animals supplemented by exogenous estrogen were used in these studies. These data support the hypothesis of a direct inhibitory action of androgens on tumor growth under in vivo conditions [45,46].

Former studies with several human breast cancer cell lines such as ZR-75-1 [47–49], T47-D [48,50], MDA-MB-231 [50,51], MFM-223 [52], and CAMA-1 cells [53] and with DMBA-induced rat mammary tumors [54] have shown that both testosterone and dihydrotestosterone inhibit cell growth more or less to the same extent. However, testosterone is further metabolized into estradiol.

5α-pregnane-3,20-dione has anaesthetic and analgesic effects via mechanisms involving calcium channels, gamma-aminobutyric