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Oestrogens – their production in the organism and involvement in energy metabolism

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Abstract

Oestrogens are part of a large group of steroid hormones involved in various regulatory processes in the organism. Their activity is not limited to the reproductive system but extends also to bone and adipose tissues, as well as the nervous and muscular systems, among others. In these tissues, oestrogens exert their effects through their receptors (ERα, ERβ and GPER), which are expressed not only in the cell membrane and the nucleus but also in mitochondria. Consequently, oestrogens influence several mitochondrial processes, such as ATP production, mitochondrial fusion and fission, oxidative stress, apoptosis and others. It is also important to emphasise the effects, when the oestrogen production increases or decreases resulting in oestrogen-dependent diseases. All of this makes oestrogens important molecules that deserve considerable attention in research. The aim of this review is to present (1) the pathways of oestrogen synthesis and (2) the broad scope of their activity in the organism, including their relation to the oxidative stress.

Running title: Oestrogens – production in the organism

Keywords: oestrogens, mitochondrial activity, oxidative stress

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Introduction

Oestrogens belong to a large group of steroid hormones that are a very important part of the entire endocrine system. They act through three types of oestrogen receptors: two nuclear receptors – ERα and ERβ (in humans encoded by the *ESR1* and *ESR2* genes) and the G protein-coupled membrane receptor – GPER (gene *GPER1*). The importance of oestrogens lies primarily in the fact that they intensively interfere with the control functions in a number of tissues and sites. Oestrogen receptors are expressed not only in many places of the reproductive system (male and female) but also in extragonadal sites, e.g. adipose tissue, breast tissue, some parts of the brain (e.g. hypothalamus and cerebellum), spinal cord, vascular endothelium, bone cells (osteoblasts, osteocytes and osteoclasts), muscles etc. They also influence the production of other signalling substances and hormones, e.g. oxytocin [1].

The cyclical character of oestrogen production in different reproductive periods and during life is also of note. For example, during the oestrous cycle or during pregnancy, oestrogens affect several specific tissues in the body, which corresponds to a measurable change in their concentrations in the blood. However, for example, in males or in the experimental animals with ovariectomy (removal of the ovaries) or in postmenopausal women, oestrogens act mainly locally [2]. Local oestrogen concentrations can be significantly higher than the concentrations measurable in the blood. This local effect of oestrogens is very significant, and their deficiency or excess can be associated with pathophysiological manifestations.

A very important example of the local influence (control) of oestrogens is their application in the **bone tissue**. Here, oestrogen receptors are present in all three basic types of bone cells (osteoblasts, osteoclasts and osteocytes), thereby controlling their optimal activity. They act specifically by suppressing the production of the RANKL protein (Receptor Activator of Nuclear factor -κβ Ligand) and, thus, inhibiting the formation of osteoclasts and their bone resorption activity. Oestrogens also promote osteoclast apoptosis [3,4]. In addition, oestrogens act in the bone tissue together with other signalling substances or hormones (e.g. glucocorticoids), which brings about further interconnections and expansion of these pathways. Oestrogen deficiency generally disrupts the optimal balance in the bone formation, repair and resorption activity, which can manifest together with other factors (genetics, low body weight, alcohol intake, cigarette smoking, low physical activities etc.) in osteoporosis [3].

Oestrogens are also significantly involved in the physiology of the **muscular system**, in which all three basic types of ER have been identified, while ERα predominates. Induction of oestrogen deficiency in animals (e.g. in rodents) is usually carried out by the ovariectomy or knockout of the relevant ERs. These studies have shown that oestrogen deficiency in the muscular system is generally associated with the onset of sarcopenia, i.e. loss of skeletal muscle and reduction in muscle strength. A decrease in oestrogen production was also associated with up to a 60% reduction in the number and density of satellite cells in the muscles, which are responsible for muscle regeneration [5,6]. Research regarding the involvement of oestrogens in the activity of the muscular system is associated not only with investigations on sarcopenia but also with the study of bioenergetics of mitochondria, due to the significant involvement of skeletal muscle in energy metabolism. ERs were also identified on these organelles and the involvement of oestrogens in mitochondrial apoptosis, oxidative stress, production of antioxidant enzymes etc. was demonstrated (see Chapter 3).

Oestrogens have a similarly significant effect in other systems, such as the **nervous system,** or in the **adipose tissue**, however their description is beyond the scope of this article. It is, therefore, clear that oestrogens play a very important role in controlling functions of many tissues in the organism. They act not only as typical endocrine signalling hormones with wide application but also locally, as a paracrine or even intracrine agents [2]. At the same time, disruption of their production (reduced or increased activity) is associated with a number of diseases, referred to as oestrogen-dependent diseases. Therefore, the topic of oestrogen action is currently receiving great attention in the field of research.

General characteristics of oestrogens and their synthesis

The main and most effective hormone from the oestrogen group is oestradiol (E2); others are estrone (E1), estriol (E3) and estetrol (E4). Oestrogens differ in the number of hydroxyl groups (1-4). The most important and most effective female oestrogen (outside of pregnancy) is oestradiol (17-beta-estradiol). It is produced mainly by ovarian follicles (during pregnancy also by the placenta) and smaller amounts are produced in the adrenal gland and in other tissues (adipose, breast, bone etc.). In males, oestradiol is produced by the testicles and adrenal gland. In testicles, oestradiol is produced by both Sertoli and Leydig cells because both cells contain aromatase.

Oestrogens in the oestrous cycle and during pregnancy

During the oestrous cycle, the concentration of oestradiol changes cyclically and its ovarian (follicular) production can be generally described as follows. Theca cells contain LH receptors. This signal leads to the production of androgens (androstenedione, testosterone), which enters the granulosa

cells. Under the influence of FSH, the production of aromatase is stimulated in the granulosa cells leading to the formation of oestradiol. The production of aromatase (and oestrogens) takes place mainly in the outer granulosa cells, known as mural granulosa cells. The production of oestradiol causes the induction of oestrus and, by feedback, a decrease in the FSH production. The subsequent production of luteinizing hormone from the adenohypophysis results in the maturation of the oocyte and its ovulation.

Overall, the two hormones – LH and FSH interact in two different cells (theca and granulosa) and produce two important components – androgens and oestrogens. Thus, LH stimulates the production of androstenedione and testosterone in theca cells. Since theca cells do not produce aromatase, interaction with granulosa cells is necessary, where aromatase production is controlled by FSH. Subsequently, oestradiol and estrone are produced in the granulosa cells. Ovarian steroidogenesis occurs in mammals under endocrine control of the FSH-LH in two cell types: theca and granulosa. Therefore, this process is sometimes referred to as the "2-cell, 2-gonadotropin hypothesis" [7,8]. During pregnancy, the concentration of all oestrogens increases, but the most significant increase is in estriol (E3) and estetrol (E4), which are produced by the placenta. Specifically, the concentrations of these oestrogens (in humans) during the second and third trimesters are approximately 8 ng/ml (estrone), 16 ng/ml (oestradiol), 14 ng/ml (estriol) and 1.2 ng/ml (estetrol) [9].

Production and effect of oestrogens in the organism

As **figure 1** clearly demonstrates, the basic precursor of all steroid hormones, including oestrogens, is cholesterol, the source of which can be the external environment, or it can be synthesized in the organism. Oestradiol is synthesized mainly from testosterone, estrone from androstenedione and estriol from estrone. Oestradiol can be converted to estrone by oxidation in the C17 position. This process is reversible [10]. During steroidogenesis, several enzymes are used, the most important of which are: 3β-HSD, 17β HSD, steroid sulfatase, ARK1C3 and aromatase. It is also significant that different isoenzymes can be used in different tissues (especially within the enzymes 3β-HSD and 17β HSD). For example, 3β-HSD has two isoenzymes: 3β-HSD1 and 3β-HSD2.

Thus, the basic precursor for oestrogen production is cholesterol, which is absorbed by the theca (internal) cells of the follicle. In these cells, it is converted into pregnenolone in the mitochondria, which is generally accepted as the first step in steroidogenesis. The entry of cholesterol into the mitochondria is controlled by the steroidogenic acute regulatory protein (StAR). The resulting pregnenolone being converted to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD, specifically type 2), which is found both in the mitochondria and in the smooth endoplasmic reticulum. Also, DHEA (or DHEA-S) can be formed from pregnenolone (DHEA

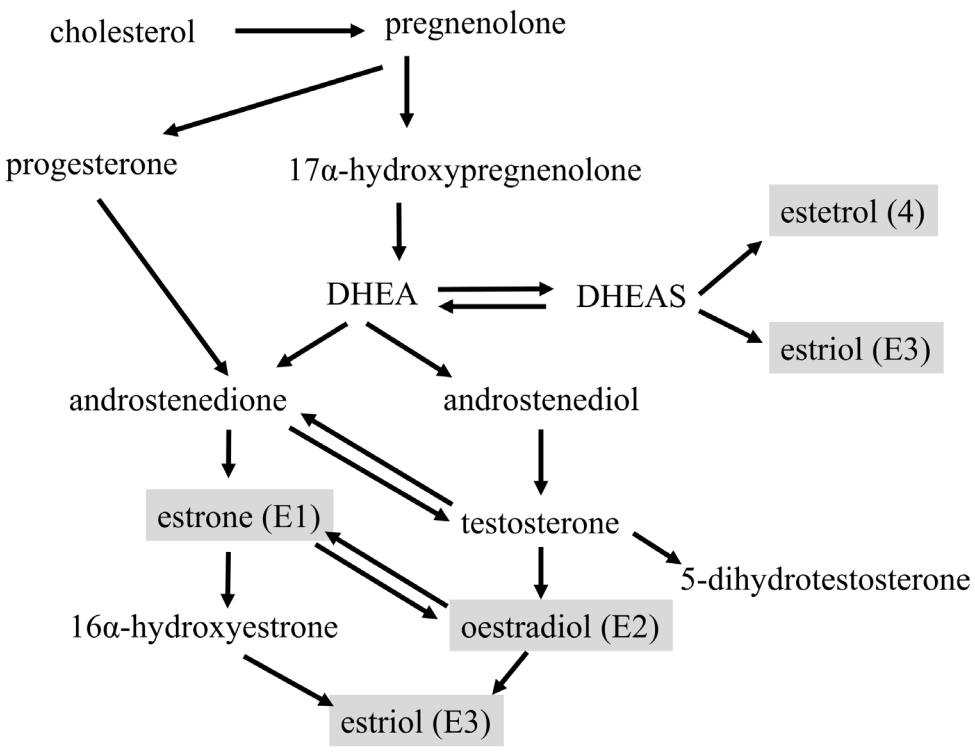

FIGURE 1 Basic scheme of oestrogen production

– dehydroepiandrosterone; DHEA-S – dehydroepiandrosterone sulphate). Androstenedione is subsequently formed from progesterone or DHEA. Androstenedione is converted to estrone or testosterone in granulosa cells; 17-beta-estradiol can be formed from both [11,12]. Estriol and estetrol are formed during pregnancy. Estriol is synthesized mainly via the DHEAS pathway. In the fetal liver, it is hydroxylated to form 16α-hydroxy-DHEAS, which enters the placenta, where estriol is formed from it. Estriol can also be produced via the so-called 'phenolic pathway' by hydroxylation of estrone [13,14]. DHEAS is also the starting compound to produce estetrol, which, together with estriol, is a typical oestrogen of pregnancy.

Oestrogens in the ovarian tissue

Aromatase plays a very crucial role in the oestrogen production, as it is the final enzyme in the production of estrone and oestradiol by converting C19 androgens into C18 oestrogens. Its presence, therefore, determines whether oestrogen production will occur in a tissue. As already mentioned, the main site of oestrogen production (estrone and oestradiol) is the ovary, nevertheless, identical (in terms of molecular structure) oestrogens are also produced in extragonadal sites (adipose tissue, hypothalamus, bone and muscle cells etc.). The difference in oestrogen synthesis in these tissues is that extragonadal tissue uses C19 steroid molecules (testosterone and androstenedione), which they obtain from external sources, while in the ovary, the synthesis of steroids is much broader and begins in theca cells from C27 cholesterol [5].

Aromatase biosynthesis is significantly influenced also by various inhibitors or activators. This area is the significant focus of current research, as imbalances in the oestrogen production are associated with serious oestrogen-dependent diseases.

Aromatase is encoded by the *CYP19* gene (P450arom), which is a highly polymorphic group (family) of enzymes and the aromatase gene expression is regulated by tissue-specific promoters of this gene. For example, in humans, 10 tissue-specific promoters of the aromatase gene have been identified [15]. This tissue specificity of promoters is determined by different signalling pathways. Specifically, aromatase expression in the placenta is controlled by the retinoid promoter in the distal part (I.1); expression in the skin is controlled by the I.4 promoter; expression in adipose tissue is controlled by the proximal ovarian promoter II etc. [2,16]. Stimulation of aromatase production, therefore, occurs primarily by the FSH and by tumour necrosis factor α (TNFα), prostaglandin E2 (PGE2) and some cytokines (IL-6).

The concentration of aromatase, as well as oestradiol, changes notably during the oestrous cycle with aromatase reaching its highest concentration in the pre-oestrus cycle period. Within an antral follicle, the highest expression of aromatase is in the outer layer of the follicle, in mural granulosa cells [17]. The production of aromatase can be significantly influenced by several compounds, both by increasing its production and by inhibiting it. An example of stimulation of aromatase production can be IGF-I (insulin-like growth factor-I), which is significantly expressed in ovarian granulosa cells and markedly increases activity of aromatase. On the contrary, some growth factors, such as EGF (epidermal growth factor) or FGF (fibroblast growth factor), can inhibit its synthesis [7,17]. This increase or inhibition of aromatase activity can be mediated by various signalling pathways, e.g. by influencing the activity of FSH, cAMP, miRNA etc. It is important to mention, however, that the action of these growth factors is in several different tissues of the organism with diverse effects. For example, a total of 22 variants were detected within FGF, of which 11 variants were found in the ovarian tissue of mammals (FGF1, FGF2, FGF7, FGF8, FGF9, FGF10, FGF16, FGF17, FGF18, FGF21, FGF22). The production of these FGFs does not have to take place exclusively by one specific type of cells (theca cells, oocytes or granulosa cells). For example, FGF8 is produced by all three of these cell types, while FGF1, FGF2 and others are produced primarily by theca cells [12].

Steroidogenesis in granulosa cells is also influenced by a large group of adipokines produced by adipose tissue. Examples include leptin, aprosin, adiponectin and others, whose receptors have been identified in granulosa or theca cells. However, there may be certain interspecies differences with the folliculogenesis phase also playing a major role.

Steroidogenesis in the ovarian tissue is, therefore, a process that involves a number of cells, enzymes and signalling molecules that can stimulate or inhibit the signal. Research has been focused in recent years on the area of aromatase inhibition, as aromatase is the last step of biosynthesis. It is significant that inhibition of aromatase production (last step of biosynthesis) will reduce oestrogen production, but the production of other signalling substances, that are part of the entire steroid metabolism pathway, is not affected [15]. Therefore, aromatase inhibitors are currently a very important topic.

Involvement of oestrogens in mitochondrial energy metabolism

As mentioned above, oestrogens interact not only with nuclear DNA through their receptors, but also with mtDNA through their receptors on mitochondria. These receptors have been identified in various tissues, e.g. skeletal muscle, bone tissue, adipose tissue, neuronal system etc. From the point of view of energy metabolism, oestrogens and their relationship to mitochondria are studied mainly in the most energy-intensive tissues, such as brain activity, skeletal muscle, cardiac muscle and others.

The connection of oestrogen (oestradiol) with nuclear receptors (ERα; ERβ) creates a chaperone complex that binds to a specific promoter site in DNA. This complex interacts with oestrogen response element (ERE) or other transcription factors, such as activator, specific proteins – AP1 or SP1, and regulates subsequent gene expression. Oestradiol also activates the transmembrane G-protein coupled receptor – GPER1, which is markedly expressed, for example, in the central nervous system and granulosa cells [18-20].

From the perspective of energy metabolism, several studies have shown that oestrogens, through their receptors, are prominently involved in the regulation of some mitochondrial functions such as mitochondrial bioenergetics (oxidative phosphorylation), mitochondrial fusion and fission, apoptosis and other processes. An example of the influence of these processes by oestrogens (ERα) is an increase in the expression of PGC1α (peroxisome proliferator-activated receptor gamma, coactivator 1-alpha) or NRF-1 (nuclear respiratory factor-1), which are subsequently involved in several metabolic pathways. Specifically, PGC1α increases the mitochondrial transcription factor TFAM (transcription factor A, mitochondrial), which binds to mtDNA and stimulates transcription [18]. At the same time, NRF-1 promotes expression of three important factors engaged in the transcription of mtDNA: TFAM (mitochondrial transcription factor A), TFB1M (mitochondrial transcription factor B1) and TFB2M (mitochondrial transcription factor B2) [21]. This regulates mitochondrial respiratory genes, which are very important both in terms of ATP and free radical production.

In general, the antioxidant effect of oestrogens is accepted by stimulating the production of some antioxidant enzymes, influencing uncoupling proteins (UCP) or by the involvement of mtERβ in anti-apoptotic activities [22-24]. Expressly, Unfer et al. [25] demonstrated that the hormone (oestrogens, progestins) therapy increases activity of MnSOD and CuZnSOD in the blood of post-menopausal women, which was associated with increased total antioxidant capacity in the blood plasma. Similarly, Strehlow et al. [26] reported that oestrogen can have an antioxidant effect by stimulating the activity of MnSOD in vascular smooth muscle cells. Increased expression of MnSOD was also observed after application of 17-β-oestradiol to neutrophil granulocytes incubated *in vitro* [27]. Singh and Bhat [28] also reported that sex hormones are involved in the control of antioxidant gene expression, similarly as Razmara et al. [29,30] demonstrated that oestrogen suppressed mitochondrial oxidative stress in the brain of rats (female and male). The authors also reported that oestrogens inhibited mitochondrial superoxide production, increased activity of MnSOD and, in general, increased mitochondrial energy production.

Thus, several studies have revealed not only the involvement of oestrogens in the prevention of antioxidant protection but also that the reduced cellular redox state and the manifestation of oxidative stress could be eliminated by some antioxidant supplementation [29-33]. However, the success of this therapy may be tissue-specific.

In summary, oestrogens have a positive effect on maintaining optimal mitochondrial functions and reducing oxidative stress, which is also contributed by the very close communication between nuclear and mitochondrial DNA. When evaluating the relationship between oestrogens and mitochondria, many of contexts must be taken into account, such as gender differences, different effects of oestrogens in different tissues and the difference in their effect, when their production is fundamentally increased or decreased. On the other hand, the manifestation of oestrogens under pathophysiological conditions is highly discussed and controversial, when several authors have demonstrated their pro-oxidative state in cancerous cells and the connection between increased oestrogen concentrations and oestrogen-dependent diseases. These topics requires further investigation.

Conclusions

Oestrogens are used in many signalling pathways at various tissues and sites. They are also characterized (in females) by cyclical ovarian production during different reproductive periods. At the same time, it is significant that their activity can be inhibited or enhanced by several other signalling molecules. The relationship of oestrogens with the balance between oxidants and antioxidants and, therefore, with the manifestation of oxidative stress is also notable. This is very challenging in ensuring optimal oestrogen homeostasis in different physiological periods, since disruption of this balance is associated with oestrogen-dependent diseases, where anti-oestrogen therapy becomes an important topic. Simultaneously, knowledge of these mechanisms allows for new procedures in treatment and health care in the human and animal spheres.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest

The authors declare they have no conflict of interest.

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