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Tissue-Specific Regulation of Sex Hormone Biosynthesis and Metabolism: Novel Aspects on Hormonal Signalling and Maintenance of Cellular Steroid Levels

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1. Introduction

In this chapter, we intend to review our recent research in the context of contemporary research in the field of sex hormone biosynthesis and metabolism. Our findings have revealed novel aspects on the regulation of sex hormone metabolism and the metabolic control of cellular levels and effects of estrogens, androgens and neurosteroids. We will discuss our results in relation to current knowledge of metabolism and actions of estrogens and androgens. First, an introduction to this research field will be given.

2. Sex hormones: Biosynthesis, metabolism and actions

2.1 Biosynthesis and metabolism of sex hormones: An introduction

The sex hormones, estrogens and androgens, are present in almost all tissues and affect such diverse processes as bone formation, sexual function, brain development, cardiovascular and immune systems and growth of various organs (Arnal et al., 2007; Cheskis et al., 2007; Folkerd et al., 2010; Li & Al-Azzawi, 2009). One of the tissues, where hormonal control of growth is essential, is the prostate, where androgens as well as estrogens play a role (Prins & Korach, 2008; Weihua et al., 2002). Although the physiological levels are different, both androgens and estrogens are needed in both sexes.

The biosynthesis and metabolism of estrogens and androgens involve many different enzymes expressed in multiple organs (Miller et al., 2008; Norlin, 2008; Simard et al., 2005; Vihko et al., 2006). Large amounts of steroids, including sex hormone precursors are enzymatically formed in the adrenals, using cholesterol as starting material, and secreted to the circulation (Fig. 1). The formed sex hormone precursors may then be taken up by gonads and other organs for further metabolism to different androgenic and estrogenic compounds. The most important precursors for sex hormones are androstenedione and dehydroepiandrosterone (DHEA) and its sulphate, DHEA-S (Fig. 1). This large-scale production of precursors, available for transport to other tissues, is essential for reproductive functions and sexual development, including the formation of genitalia

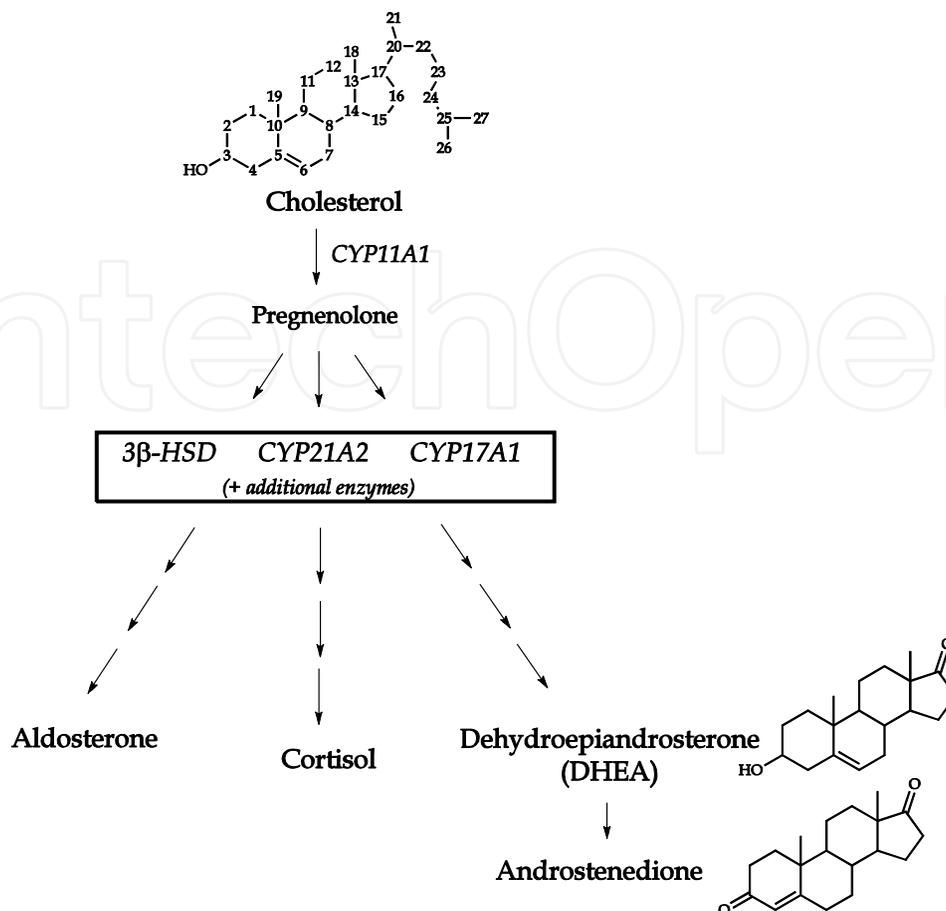


Fig. 1. A simplified overview on the biosynthesis of steroid hormones in the adrenal cortex.

(Rainey et al., 2004; Sultan et al., 2001). A sex hormone precursor may undergo different metabolic transformations in different cells, depending on which enzymes that are expressed in a certain tissue and how these enzymes are regulated. In addition to the uptake of precursors transported from the adrenals, many tissues have the ability to carry out all the steps in estrogen and androgen synthesis. Thus, cell-specific needs for these hormones may be controlled locally in each tissue (Hudak et al., 2006; Penning et al., 2000; Tsuchiya et al., 2005). Local metabolism, dependent on various tissue-specific enzymes, is essential to achieve hormonal effects and to eliminate excess hormone from the cells.

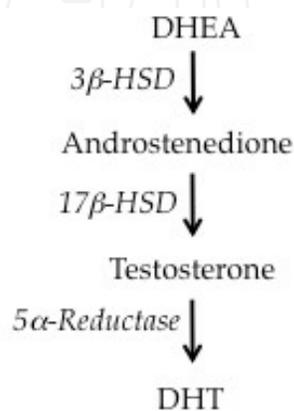


Fig. 2. Formation of androgens. HSD, hydroxysteroid dehydrogenases.

Several androgens are formed in humans (Bauman et al., 2006; Hudak et al., 2006; Weihua et al., 2002). A well-known androgen, testosterone, is formed in large amounts in several tissues, including the Leydig cells of the testes (Fig. 2). Testosterone levels are strongly influenced by the levels of its precursors, androstenedione and DHEA, in the blood circulation. Target tissues can convert testosterone into dihydrotestosterone (DHT), the most potent androgen, 10-fold more potent than testosterone (Fig. 2). Maintenance of adequate cellular levels of DHT is essential for a number of physiological processes, including sexual development and testicular function.

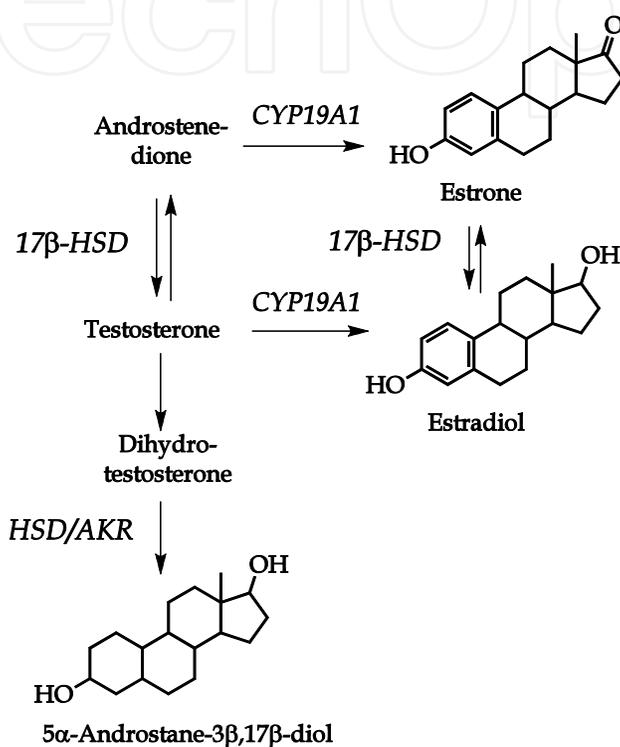


Fig. 3. Formation of some estrogens. HSD, hydroxysteroid dehydrogenases; AKR, aldo-keto reductases

The physiologically most potent estrogen is estradiol (17β-estradiol). The levels of estradiol are dependent on the enzymatic activity of aromatase (CYP19A1) which forms estradiol from testosterone (Bulun et al., 2009; Simpson et al., 2002) (Fig. 3). In addition, there are several other endogenous estrogens that affect various organs and cells (Norlin et al., 2008; Pettersson et al., 2008; Weihua et al., 2002; Zhu et al., 2005). Individual estrogens may be of different importance in different tissues. For instance, 5α-androstane-3β,17β-diol (3β-Adiol) has been described as particularly important for estrogenic function in the prostate (Weihua et al., 2002). An overview of enzymes in the formation of some estrogenic steroids is shown in Fig. 3.

The total body levels of sex hormones are regulated by signalling from the pituitary and by mechanisms for excretion by the kidneys or in the bile (Bourdeau & Stratakis, 2002; Hum et al., 1999; Waxman & Holloway, 2009). In addition, cell-specific factors and mechanisms are important for regulation of the local sex hormone synthesis and elimination (Jellinck et al., 2007; Norlin, 2008; Penning et al., 2000; Reddy, 2004). Estrogens and androgens are removed from the body via metabolism into inactive metabolites that are excreted in the urine and/or feces. Local metabolism of importance for tissue hormone levels vary for different steroids

and different tissues. Mechanisms believed to be of importance involve e. g. hydroxylation by cytochrome P450 (CYP) enzymes and conjugation with sulfate or glucuronic acid by the UDP-glucuronosyl transferases (UGT) and sulfotransferases (SULT) (Tang et al., 2006; Turgeon et al., 2001; Zhu et al., 2005) (Figs. 4 and 5).

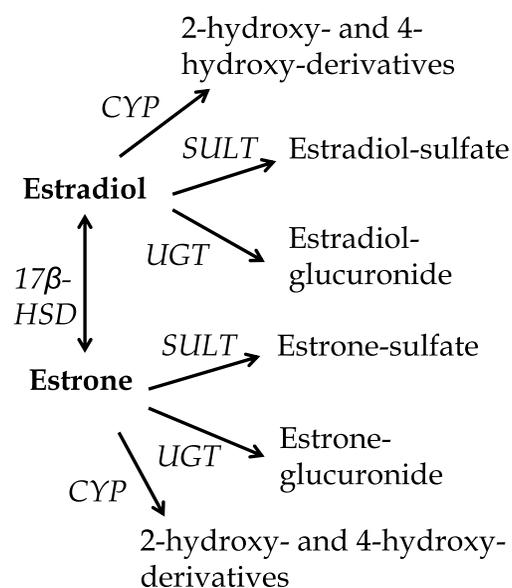


Fig. 4. Metabolic pathways that may affect the levels of estradiol and estrone. Please note that this figure is intended as an overview of potentially important pathways and does not necessarily describe the situation in any particular cell. AKR, aldo-keto reductases; CYP, cytochrome P450; HSD, hydroxysteroid dehydrogenases; SULT, sulfotransferases; UGT, UDP-glucuronosyl transferases.

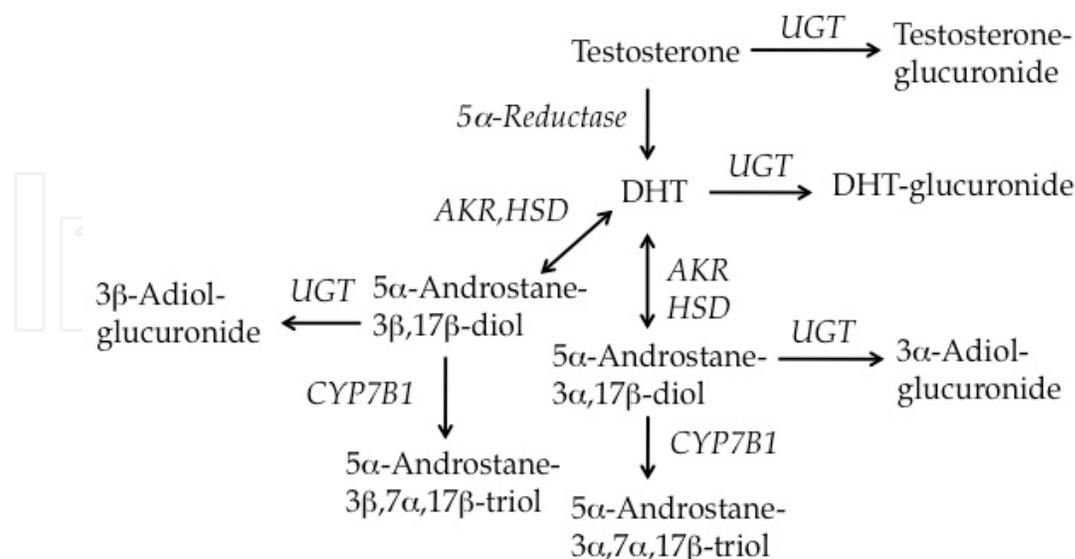


Fig. 5. Metabolic pathways that may affect the cellular levels of testosterone and its metabolites. Please note that this figure is intended as an overview of potentially important pathways and does not necessarily describe the situation in any particular cell. For abbreviations, see legend of Fig. 4.

2.2 Physiological and pharmacological actions of sex hormones and sex hormone-related compounds

Many of the cellular effects of estrogens and androgens are mediated via the classical sex hormone receptors, the androgen receptor, AR, and the two estrogen receptors, ER α and ER β (Brinkmann et al., 1999; Cheskis et al., 2007; Li & Al-Azzawi, 2009; Prins & Korach, 2008). The actions of estrogens and androgens are often mediated via hormone-responsive sequences in target gene promoters, the “androgen response elements” (ARE) and “estrogen response elements” (ERE). Sex hormones are also able to act via mechanisms independent of the AR and ER (Bryant et al., 2006; Cheskis et al., 2007; Lorenzo & Saatcioglu 2008). Such mechanisms may involve signal transduction pathways, for instance MAPK (mitogen-activated protein kinase) or PI3K (phosphoinositide 3-kinase)/Akt signal pathways. Crosstalk between proteins of these signal pathways and estrogen receptors also have been reported for some hormonal targets. Additional pathways for hormonal action are believed to be mediated by different types of hormone receptors located at the cell membrane. Sex hormone-related compounds used in therapy include antagonists of ER and AR and selective hormone receptor modulators (SERMs and SARMs, respectively) (Bhasin & Jasuja, 2009; Cheskis et al., 2007; Jordan, 2007). Selective hormone receptor modulators function as agonists in some tissues and antagonists in others, resulting in different tissue-specific responses.

Despite the essential roles of sex hormones in a large number of physiological processes, excess amounts of these compounds can have a negative impact and even contribute to disease. Adverse effects of estrogens include e. g. intrahepatic cholestasis, which may occur in some women using oral contraceptives or during pregnancy, where this condition can result in premature delivery or fetal death (Yamamoto et al., 2006). Many breast tumours are dependent on estrogen for growth and are reported to exhibit increased estradiol biosynthesis. For this reason, inhibitors of the estradiol-forming aromatase (CYP19A1) are routinely used in treatment of breast cancer (Chen, 1998). Furthermore, although the growth-inducing effect of androgens are required for formation and normal function of the prostate, overproduction of androgens can contribute substantially to unwanted growth of this tissue e. g. in malignancy. Treatment to suppress androgen action and/or formation have therefore proven very useful in prostate cancer therapy as well as in treatment of benign prostate hyperplasia (Bauman et al., 2006; Hudak et al., 2006). In general, transformation into malignancy may elicit changes in both sex hormone concentrations and effects of sex hormones on growth (Bauman et al., 2006; Vihko et al., 2006). Marked changes in androgen and estrogen metabolism have been reported for many malignant cells. However, abnormalities in hormone synthesis and metabolism are not only found in malignancy. Although the functions of sex hormones formed in the CNS have been much less studied than those of the reproductive organs, disturbed synthesis and/or metabolism of several brain steroids have been described in neurodegenerative disease (Cossec et al., 2010; Schaeffer et al., 2006).

2.3 Cell- and tissue-specific steroid metabolism – role(s) for controlling cellular levels and effects of sex hormones

Steroid hormone metabolism is not the same everywhere in the body. Due to the different physiological demands that will arise in various tissues and during different conditions, the level of a certain hormone at a given time need to be carefully controlled. Also, not all cells need the same types of hormones. Often, a steroid hormone may potentially undergo several different metabolic pathways. However, one pathway may be particularly active in a

certain tissue but absent in another tissue where a different pathway dominates. Metabolism of a steroid could also lead to a host of metabolites in the same tissue, via different enzymatic steps, all of which can be differentially affected by endogenous or exogenous regulators. Consequently, since the effect(s) of a hormone are dependent on its concentration, the metabolic pathways in a cell or tissue can have a considerable impact on which cellular actions that takes place.

An example of a steroid metabolized into many different compounds is dehydroepiandrosterone (DHEA) (Norlin, 2008; Rainey, 2004). This steroid is reported to have a number of effects of its own but, as described in the Introductory section, it is also essential as a precursor for a number of other hormones, with their own individual effects. The activity of the enzymes and genes involved in formation of these different products can all be differentially regulated.

Our knowledge on the cellular metabolic events that involve steroid hormones is far from sufficient. A proper understanding of these events would substantially increase the possibilities to intervene in physiological processes involving these hormones, such as cellular growth, dysfunctions of the reproductive and immune systems and a number of processes important for brain function. Even though there is a clear link between the serum levels of a hormone and its physiological effect(s), the levels of hormones present in a tissue often differs substantially from the levels measured in serum. Unfortunately, the steroid levels in tissue material are much more problematical to assay than the serum levels. Other complicating factors are the complex interplay of enzymes and regulatory molecules leading to formation of a certain compound and the existence of different cell-types with specific properties within the same tissue.

3. Sex hormones and vitamin D

In recent years, vitamin D has attracted increasing attention for its ability to regulate numerous genes in several physiological processes. In the following sections, a brief overview of the vitamin D hormone and discussion of data regarding the effects on sex hormone biosynthesis and metabolism will be given.

3.1 Vitamin D is activated to a multifunctional hormone with effects on gene expression

The prohormone vitamin D₃ (cholecalciferol) is synthesized in the skin on exposure to ultraviolet light and is also acquired from the diet (Holick, 1987). Vitamin D is needed for regulation of calcium levels in the body and vitamin D deficiency leads to skeletal diseases such as rickets in children and osteomalacia/osteoporosis in adults (Brown et al., 1999; DeLuca, 2004; Dusso et al., 2005; Jones et al., 1998). The role of vitamin D in human health and disease has received increased recognition in recent years. Although it was previously considered to be limited to regulation of calcium levels, recent data from epidemiological studies and basic sciences have expanded our understanding of its pivotal role in many biological processes. Vitamin D is important not only for endocrine functions, such as calcium homeostasis, but also for autocrine and/or paracrine functions, such as regulation of immune system, brain and fetal development, insulin secretion, apoptosis, cell proliferation and differentiation as well as involvement in cancer and the cardiovascular system. Most of these actions are mediated by transcriptional regulation of target genes through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily of

transcription factors (Armas & Heaney, 2011; Atkins et al., 2007; Norman, 2006, 2008; Verstuyf et al., 2010).

The active vitamin D₃ hormone, 1 α ,25-dihydroxy-vitamin D₃ (calcitriol), is formed through metabolic bioactivation by cytochrome P450 (CYP450) enzymes (Jones et al., 1998; Prosser & Jones, 2004; Wikvall, 2001). The activation of vitamin D requires two sequential hydroxylations (Fig. 6). The first step is a 25-hydroxylation of vitamin D₃ producing 25-hydroxyvitamin D₃ or calcidiol. A number of cytochrome P450-enzymes are capable of performing the 25-hydroxylation and in most organisms studied at least two 25-hydroxylases have been found – the mitochondrial CYP27A1 and the microsomal CYP2R1 (Cheng et al., 2003, 2004; Dahlbäck & Wikvall, 1988; Gascon-Barre et al., 2001). The second bioactivation step is a 1 α -hydroxylation of calcidiol producing 1 α ,25-dihydroxyvitamin D₃ or calcitriol. The 1 α -hydroxylation is carried out by CYP27B1 (Fu et al., 1997). Production of the circulating 1 α ,25-dihydroxyvitamin D₃ is initiated by hepatic 25-hydroxylation followed by renal 1 α -hydroxylation. The circulating vitamin D hormone has mainly endocrine function e.g. in regulation of calcium homeostasis and maintenance of bone health. The normal serum levels of 25-hydroxyvitamin D₃ (20-250 nmol/L) are thousand times higher than the levels of 1 α ,25-dihydroxyvitamin D₃ (20-250 pmol/L). 1 α ,25-Dihydroxyvitamin D₃ is the most potent form of vitamin D₃ but 25-hydroxyvitamin D₃ can exert biological effects as well (Lou et al., 2004, 2010; Tuohimaa et al., 2005).

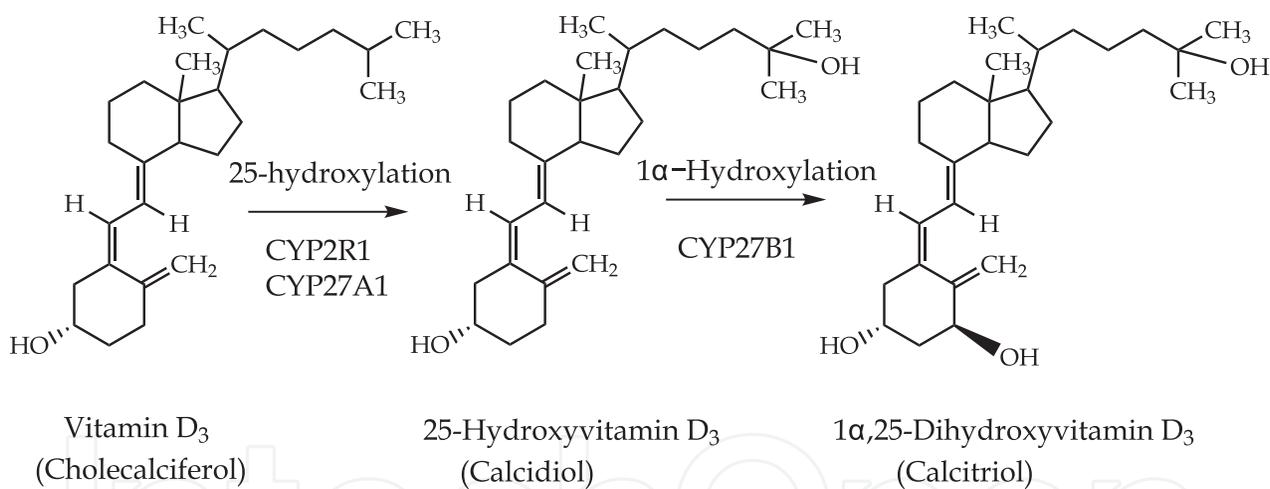


Fig. 6. Bioactivation of vitamin D₃.

Both calcidiol and calcitriol undergo further metabolism by the catabolizing enzyme CYP24A1 (Fig. 7). This enzyme 24-hydroxylates vitamin D metabolites and the 24-hydroxylation is a key point at which degradation of vitamin D begins. 24-Hydroxylated vitamin D metabolites are less biologically active and are then further metabolized by the multicatalytic CYP24A1 via side chain hydroxylation and oxidation to less active substances. Finally, after side chain cleavage, calcitroic acid is formed. Calcitroic acid is then excreted into the bile (Makin et al., 1989; Reddy and Tserng, 1989; Zimmerman et al., 2001).

The expression of both the activating (25- and 1 α -hydroxylases) and the catabolizing (24-hydroxylase) enzymes by cells of certain tissues, indicates that the multifunctional hormone 1 α ,25-dihydroxyvitamin D₃ can be produced locally in some tissues, including cells in the skin, breast, colon, prostate, lung, and various cells of the immune system. The intracellular

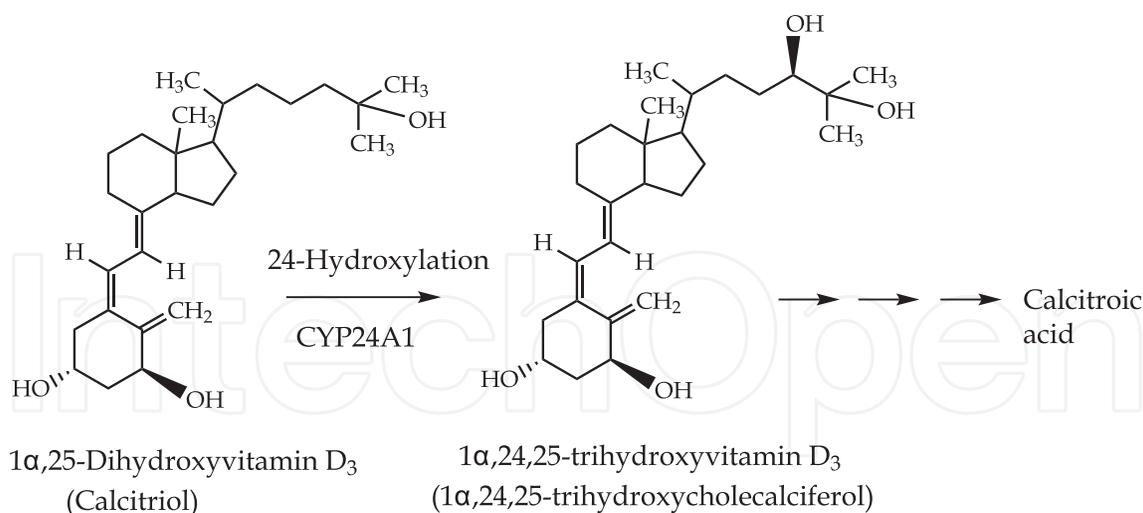


Fig. 7. Metabolism of 1 α ,25-dihydroxyvitamin D₃ (calcitriol) by CYP24A1 into less active metabolites. 25-Hydroxyvitamin D₃ is also catabolized by CYP24A1 in a similar way.

1 α ,25-dihydroxyvitamin D₃ is mainly used in an autocrine manner as a cofactor in the expression of many genes. This autocrine 1 α ,25-dihydroxyvitamin D₃ binds to VDR and modifies gene transcription. For example, genes involved in cell proliferation, differentiation and apoptosis are believed to be regulated by the internal 1 α ,25-dihydroxyvitamin D₃ of the cell. The activation, effects on gene expression and inactivation of 1 α ,25-dihydroxyvitamin D₃, is contained within the host cell. This active form of vitamin D is the major player in the internal autocrine action, but also 25-hydroxyvitamin D₃ can be formed within the cell and regulate gene expression (Lou et al., 2004; Tuohimaa et al., 2005; Verstuyf et al., 2010).

Recent data have revealed that vitamin D deficiency in the general population and even among young and healthy people is much more common than previously believed. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Interestingly, vitamin D deficiency is associated with increased risks of cardiovascular disease, multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus and deadly cancers, such as prostate, breast and colon cancers (Adorini, 2002; Armas & Heaney, 2011; Giovannucci, 2007; Pérez-López, 2008; Schwartz, 2005; Zittermann, 2003).

The vitamin D receptor is widely expressed and it has been suggested that the active vitamin D₃ hormone may affect the expression of up to 200 genes in humans (Jones et al., 1998; Norman, 2008; Ramagopalan et al., 2010). It is probable that vitamin D₃ may have other roles yet undiscovered.

3.2 Vitamin D₃ exerts tissue-specific effects on estrogen and androgen metabolism

In recent reports from our laboratory, data are presented revealing vitamin D-mediated effects on the production of steroid hormones and expression of crucial steroidogenic enzymes in various cell lines (Lundqvist et al., 2010, 2011). As an example, the active vitamin D hormone 1 α ,25-dihydroxyvitamin D₃ decreases the production of dehydroepiandrosterone (DHEA) and DHEA-sulphate in adrenocortical NCI-H295R cells. DHEA is a precursor for both estrogen and androgen production. mRNA levels and enzyme activities for key enzymes in the steroidogenesis, such as CYP17A1 and CYP21A2 (cf. Fig. 1), were found to be altered by 1 α ,25-dihydroxyvitamin D₃ treatment (Lundqvist et al., 2010).

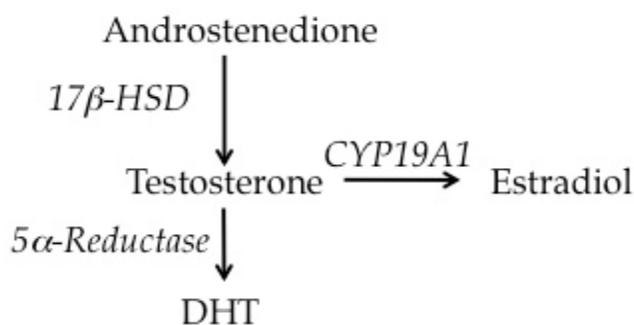


Fig. 8. Some important enzyme reactions in androgen and estrogen metabolism.

Accumulated data have revealed that sex hormone biosynthesis and metabolism may be regulated by vitamin D (Barrera et al., 2007; Krishnan et al., 2010; Lou et al., 2005; Lundqvist et al., 2011; Tanaka et al., 1996). Important reactions in the metabolism of androgens and estrogens are catalyzed by 5 α -reductase and aromatase (CYP19A1) (Fig. 8). These two key enzymes determine the balance between androgen production and estrogen production. In addition to 5 α -reductase and aromatase, the 17 β -hydroxysteroid dehydrogenases are enzymes which regulate intracellular concentrations of active sex steroid hormones. Calcitriol has been found to up-regulate some types of 17 β -hydroxysteroid dehydrogenase in human prostate cancer LNCaP and PC3 cells but not in stromal cells (Wang & Tuohimaa, 2007).

Estrogens are produced from androgenic precursors in a reaction catalyzed by aromatase (CYP19A1) (Figs. 3 and 8). Calcitriol increases aromatase activity in placental cells (Barrera et al., 2007), prostate cells (Lou et al., 2005) and osteoblasts (Tanaka et al., 1996) and vitamin D receptor null mutant mice have a decreased aromatase activity in the ovary, testis and epididymis (Kinuta et al., 2000). Interestingly, it was recently reported that 1 α ,25-dihydroxyvitamin D₃ regulates the expression of aromatase in a tissue-selective manner. Thus, calcitriol significantly decreased aromatase expression in human breast cancer cells and adipocytes but caused increased aromatase expression in human osteosarcoma cells and ovarian cancer cells (Krishnan et al., 2010). Calcitriol exerts cell line-specific effects on both estrogen and androgen metabolism, including the production of estrogens and androgens (Lundqvist et al., 2011). In breast cancer MCF-7 cells, aromatase gene expression and estradiol production were decreased, while production of androgens was markedly increased. In human adrenocortical NCI-H295R cells, 1 α ,25-dihydroxyvitamin D₃ stimulated aromatase expression and decreased dihydrotestosterone production. In prostate cancer LNCaP cells, aromatase expression increased after the same treatment, as did production of testosterone and dihydrotestosterone (Table 1). These findings are of interest for the research fields of breast cancer and prostate cancer. Vitamin D seems to be involved in the control also of prostate cancer cell growth (Flanagan et al., 2010; Tuohimaa et al., 2005). Analysis of effects of 1 α ,25-dihydroxyvitamin D₃ on aromatase promoter activities revealed differences between NCI-H295R cells and MCF-7 cells, where promoter I.3 and promoter I.4 were stimulated and promoter II were down regulated in NCI-H295R cells (Lundqvist et al., 2011) while all three promoters are down regulated in breast cancer MCF-7 cells (Krishnan et al., 2010).

The findings that 1 α ,25-dihydroxyvitamin D₃ specifically down regulates aromatase gene expression and activity and decreases production of estradiol in breast cancer cells are interesting in the context of 1 α ,25-dihydroxyvitamin D₃ as an anti cancer agent (Krishnan et al., 2010, Lundqvist et al., 2011)

	Cell line	Effect of treatment with 1 α ,25-dihydroxyvitamin D ₃
Aromatase mRNA level	MCF-7	↓
	LNCaP	↑
	NCI-H295R	↑
Aromatase enzyme activity	MCF-7	↓
	LNCaP	-
	NCI-H295R	↑
Estradiol production	MCF-7	↓
	LNCaP	-
	NCI-H295R	↑/-
Dihydrotestosterone production	MCF-7	↑
	LNCaP	↑
	NCI-H295R	↓
Expression of promoter specific aromatase transcripts	MCF-7	↓ (p I.3, p I.4 and p II)
	LNCaP	No statistically significant alterations
	NCI-H295R	↑ (p I.3 and p I.4), ↓ (p II)

Table 1. Effects of calcitriol on estrogen and androgen metabolism. Please note that this table only summarizes the data obtained by our group (Lundqvist et al., 2011). Arrows indicate up- and down-regulation; -, unaltered.

Interestingly, 1 α ,25-dihydroxyvitamin D₃ increases androgen production in breast cancer MCF-7 cells (Lundqvist et al., 2011). The production of testosterone was increased by 60% and the production of dihydrotestosterone was increased 4-fold. The markedly increased production of dihydrotestosterone in MCF-7 cells after 1 α ,25-dihydroxyvitamin D₃ treatment appears not to be the result of increased 5 α -reductase expression. An explanation for this effect could be that the decreased aromatase activity increases the concentration of testosterone, which is the precursor for dihydrotestosterone. The increased androgen production in breast cancer cells following vitamin D treatment needs to be studied further to elucidate its potential physiological roles.

The data showing that 1 α ,25-dihydroxyvitamin D₃ exerts tissue-specific effects on sex hormone production and metabolism provide important knowledge for further research in the fields of prostate and breast cancer. Prostate and breast are key tissues for estrogenic and androgenic pathways. Vitamin D deficiency is associated with increased risks of prostate and breast cancers (Holick, 2006; Thorne & Campbell, 2008; Bouillon et al., 2006). It is well-known that the active form of vitamin D, 1 α ,25-dihydroxyvitamin D₃, and analogs via binding to the vitamin D receptor exert anti-proliferative and pro-differentiative effects and have therefore been proposed to be of potential use as anti cancer agents (Deeb et al., 2007;

Masuda & Jones, 2006). Estrogens and androgens play a role in the pathogenesis of prostate cancer and a large group of all breast cancers involves estrogen-dependent mechanisms, i.e. they rely on estrogens to proliferate (Mathiasen et al., 2002; Sasano et al., 2009). The recent findings indicating regulation of intracellular levels of androgens and estrogens by vitamin D open new possibilities in prevention and treatment of prostate and breast cancer.

Aromatase (CYP19A1), the enzyme catalyzing the conversion of testosterone to estradiol, is critical for the progression of estrogen receptor-positive breast cancer in postmenopausal women. The aromatase expression is higher in breast cancer tissue than in normal breast tissue and the local estrogen levels in breast cancer tissue are higher than the circulating levels (Chen, 1998; Miller et al., 1990). Regulation of estradiol production and estrogenic signalling are key strategies in breast cancer treatment. Aromatase inhibitors and antiestrogens have therefore become important drugs in breast cancer treatment. Due to its effects on aromatase gene expression and enzyme activity, $1\alpha,25$ -dihydroxyvitamin D₃ has been proposed as an interesting substance in breast cancer treatment and prevention. The vitamin D-mediated inhibition of aromatase seems to be tissue specific for breast cells, indicating that it is a potential drug target in treatment aiming to prevent estradiol production in breast but not in other tissues. This would reduce the risk of adverse effects due to effects on peripheral estrogen metabolism (e.g. osteoporosis). The vitamin D-induced tissue-selective regulation of aromatase expression and activity is an interesting strategy to affect estrogen levels in breast without effects on the peripheral estrogen metabolism.

High-dose vitamin D treatment will lead to adverse effects e.g. hypercalcemia. Therefore, synthetic vitamin D analogs with less pronounced hypercalcemic effect are potential drugs in treatment aiming to prevent estradiol production in breast but not in other tissues, a strategy that would lead to less adverse effects than the existing treatments. However, the mechanisms for these effects of vitamin D need to be clarified before vitamin D or analogs can be used in breast cancer treatment. It has been reported that the vitamin D analog EB1089 decreases the proliferation of breast cancer cells, especially anti-estrogen resistant breast cancer cells (Christensen et al., 2004; Larsen et al., 2001). EB1089 has undergone clinical trials phase I and II and was found to be a well tolerated substance (Dalhoff et al., 2003). However, it has not yet been tested in clinical trials against breast cancer. The new findings on vitamin D as a tissue-selective modulator of aromatase reinforce the interest for EB1089 as a potential drug in treatment of breast cancer, which may inhibit both estrogen-dependent and anti-estrogen resistant breast cancer.

Human adrenocortical NCI-H295R cells are widely used as a model for human adrenal cortex. It has been proposed that this adrenocortical carcinoma cell line could be suitable in a screening assay to study the effects of different chemicals on estradiol and testosterone production (Gracia et al., 2006; Hecker et al., 2006, 2007; Higley et al, 2010). We have examined whether adrenocortical NCI-H295R cells react in the same way as prostate cells and breast cells when they are treated with $1\alpha,25$ -dihydroxyvitamin D₃. Interestingly, both estrogen and androgen metabolism were affected in a cell line-specific way (Table 1). The largest differences were observed between NCI-H295R cells and MCF-7 cells, where aromatase gene expression, estradiol production, aromatase promoter activity, testosterone production and dihydrotestosterone production were affected in opposite ways in the two cell lines. The discrepancies between NCI-H295R cells and LNCaP cells were smaller, but still noteworthy. Production of both testosterone and dihydrotestosterone was affected differentially in the two cell lines, as was the gene expression of 5α -reductase. Our data

show that NCI-H295R cells respond in a different way than cells derived from important target tissues in estrogen and androgen production and metabolism (Lundqvist et al., 2011). These differences between NCI-H295R cells and cells derived from key endocrine target tissues need to be addressed and clarified if NCI-H295R cells should be used as a model for effects of different chemicals on estrogen and androgen metabolism.

4. Actions of CYP7B1 - potential role(s) for the levels and effects of estrogens, androgens and neurosteroids

In recent years we have carried out several studies on the effects and regulation of catalytic reactions mediated by CYP7B1, a widely expressed enzyme with a number of steroid substrates including DHEA. CYP7B1-mediated catalysis leads to formation of 6- or 7-hydroxymetabolites, mainly 7 α -hydroxyderivatives (Pettersson et al, 2008; Rose et al., 1997; Tang et al., 2006; Stiles et al., 2009; Wu et al., 1999) (Fig. 9). This enzyme has been associated with several physiological processes, including brain function, immune system, cholesterol homeostasis and cellular viability and growth. Scientific publications in various areas have linked altered CYP7B1 levels and/or function to neurodegenerative processes, arthritis, and prostate cancer (Dulos et al., 2004; Olsson et al., 2007; Tsaousidou et al., 2008; Yau et al., 2003). However, the manner in which CYP7B1 affects these processes are in many cases unclear.

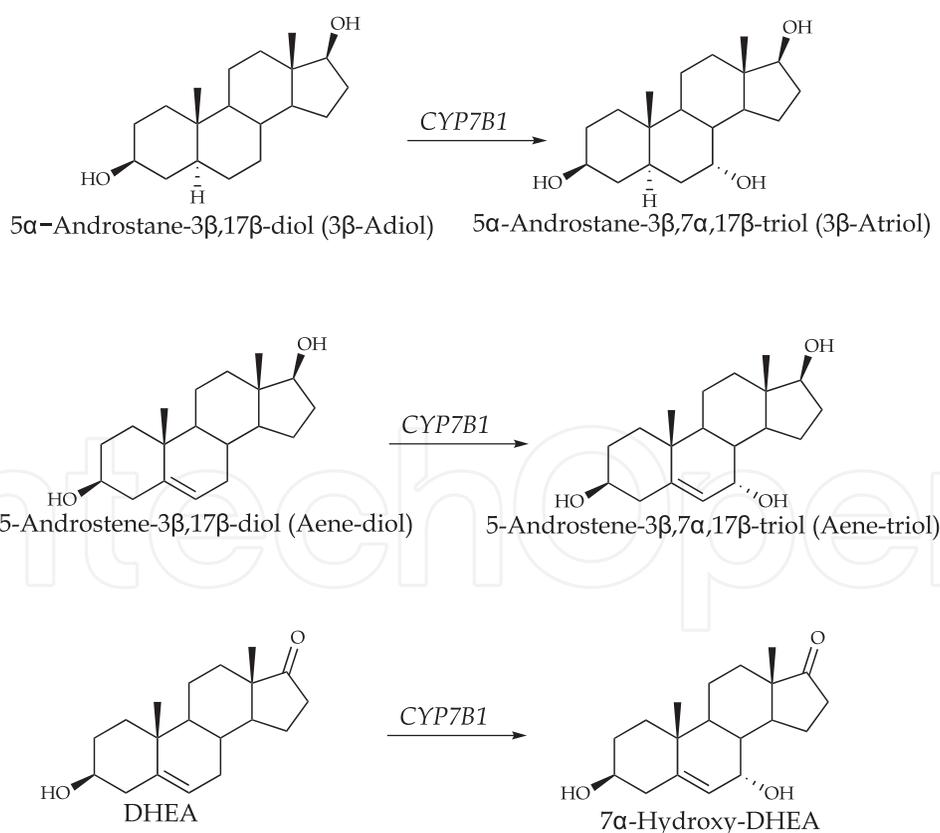


Fig. 9. CYP7B1-mediated catalytic reactions.

Substrates for CYP7B1 are neurosteroids, cholesterol derivatives and sex hormones, including some of the ligands for the estrogens receptors (ER). In recent studies we

examined the role of CYP7B1-mediated catalysis for activation of the ER (Pettersson et al., 2008, 2010). Our studies, using ER-dependent luciferase reporter systems and ER-target genes, indicate significant stimulation of ER-response by the CYP7B1 substrates 5 α -androstene-3 β ,17 β -diol (Aene-diol) and 5 α -androstane-3 β ,17 β -diol (3 β -Adiol), for both ER α and β . In contrast, the CYP7B1-formed metabolites from these steroids have little or no estrogenic effects, indicating that CYP7B1-mediated metabolism abolishes the ER-stimulating effect of these compounds (Pettersson et al., 2010). In the course of our studies we have also found that DHEA induces both ER-dependent and AR-dependent responses in some cell types whereas 7 α -hydroxy-DHEA has no or diminished effect (Norlin M. & Lundqvist J., unpublished results).

Our findings seem to indicate that actions by CYP7B1 might be a way to decrease estrogenic response, at least in some tissues. One of these may be the prostate, where signalling via ER β has been reported to play a role in growth suppression. Gustafsson and collaborators proposed a pathway for hormonal control of proliferation where the role of CYP7B1 would be to counteract anti-proliferative action of ER β by metabolizing its ligand 3 β -Adiol (Weihua et al., 2002). This concept is supported by findings indicating that prostates of CYP7B1-/- mice are hypoproliferative. The roles of estrogens and estrogen receptors in prostate growth are however not well understood (Morani et al., 2008; Prins & Korach, 2008). Interestingly, Olsson et al. (2007) reported high expression of CYP7B1 protein in human high-grade prostatic intraepithelial neoplasia and adenocarcinomas. Enzymatic events of potential importance for intraprostatic hormone levels are of course not limited to actions by CYP7B1. Other enzymes of relevance include e. g. the conjugating enzymes, particularly some of the UDP-glucuronosyltransferases (UGT) expressed in prostate (Barbier & Bélanger, 2008). Also, the enzymes known to form important hormones in this tissue such as CYP17A1, 5 α -reductase and the 3 β - and 17 β -hydroxysteroid dehydrogenases have attracted interest as potential or existing targets for therapy aimed at controlling cellular hormone levels (Hudak et al., 2006; Norlin; 2008; Sharifi, 2010; Vihko et al., 2006).

Considering its role in metabolism of ER ligands, CYP7B1 has been linked to estrogenic action by several studies and investigators (Pettersson et al., 2010; Sugiyama et al., 2009; Weihua et al., 2002). However, the actions of CYP7B1 in sex hormone metabolism do not seem to be limited to estrogenic signalling. For instance, some of the steroids that are substrates for this enzyme may affect both estrogen and androgen receptors. This includes DHEA and Aenediol which are reported to be able to trigger both ER and AR signalling. It seems likely that the actual effects of these steroids *in vivo* may strongly depend on their local concentration. In addition, the presence or absence of other hormone ligands with higher affinity for the receptor as well as the effects of tissue-specific comodulators should play important roles. These different possibilities open for enzymatic control of cell-specific actions, depending on e. g. comodulator expression, substrate availability, and substrate competition (Pettersson et al., 2008; Shapiro et al., 2011; Sugiyama et al., 2009).

The most potent androgenic hormone in the human body is dihydrotestosterone (DHT). Maintenance of normal DHT levels is essential for a number of physiological processes. On the other hand, excess levels of androgens, which strongly stimulate growth, may have a negative impact in disease. We recently identified a previously unknown androgenic substrate for CYP7B1 which is a metabolite of DHT (Pettersson et al., 2009) (Fig. 10). This steroid, 5 α -androstane-3 α ,17 β -diol (3 α -Adiol), can itself induce androgenic responses, but since the effects of 3 α -Adiol are weaker than those of DHT, conversion into 3 α -Adiol is

considered a means to reduce DHT-mediated effects on cell growth and other processes. 3α -Adiol can easily be converted back to DHT and is believed to serve as a source for this hormone (Auchus, 2004; Penning et al., 2000). 3α -Adiol is also believed to be of importance in the CNS, where it can modulate the action of gamma-aminobutyric acid A ($GABA_A$) receptors and is reported to have anticonvulsant and analgesic properties (Reddy 2004; Frye, 2007).

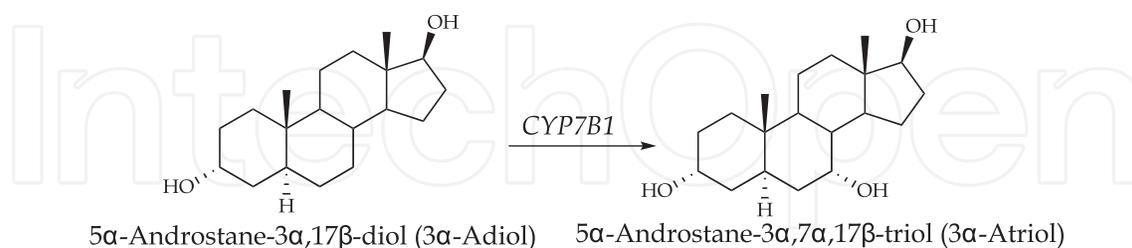


Fig. 10. CYP7B1-mediated metabolism of 5 α -androstane-3 α ,17 β -diol (3 α -Adiol)

Local formation and functions in the CNS are features shared by other, previously characterized, substrates for CYP7B1, including DHEA, pregnenolone, Aenediol and 27-hydroxycholesterol, a cholesterol derivative believed to serve as a regulator of cholesterol homeostasis (Norlin & Wikvall 2007, Pikuleva; 2006). An important role for CYP7B1 in brain physiology is indicated by the recent studies revealing that disturbed function of this enzyme is linked to a human motor-neuron degenerative disease. Tsaousidou et al. (2008) first showed that hereditary spastic paraplegia (HSP) is associated with mutations in the CYP7B1 gene. Mutations in the coding region of this gene, which affects the functionality of the enzyme, is believed to be a frequent cause of this disease. The etiology and molecular mechanisms that underlies hereditary spastic paraplegia are however not known. It has been proposed that the mutated forms of CYP7B1 in patients suffering from HSP might lead to an abnormal brain cholesterol homeostasis due to an increase in 27-hydroxycholesterol levels (Tsaousidou et al., 2008). Despite the role of this steroid for maintenance of cholesterol homeostasis, 27-hydroxycholesterol negatively affects viability of some cells (Dasari et al., 2010). This steroid can also modulate estrogen receptor signalling in some tissues and has been described as an endogenous SERM (Du Sell et al. 2008; Umetani et al., 2008) However, it is also possible that the pathogenic basis for hereditary spastic paraplegia is connected to abnormal levels of other CYP7B1 substrates present in the brain, including DHEA. Although there is still much to be learned in this field, brain steroids are believed to influence several aspects of CNS function (Charalampopoulos et al., 2006; Maninger et al., 2009; Melcangi & Panzica, 2006). Various neurosteroids are considered to be involved in e. g. neuronal development, regulation of inflammatory responses, effects on cellular viability and modulation of the actions of various neurotransmitter receptors.

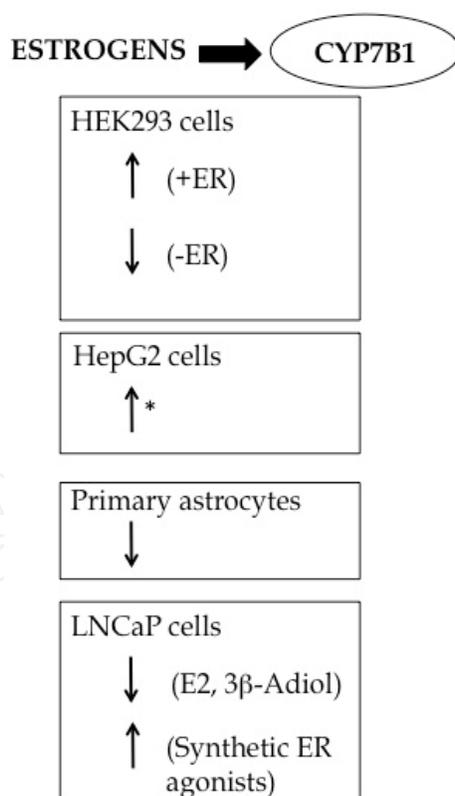
The concept of widely varying cell- and tissue-specific steroid metabolism is illustrated by the differences in metabolism of DHEA in different CNS cell types. Thus, whereas rat microglia, a cell type important for brain immune function, is reported to exclusively convert this steroid to Aenediol, the major route for DHEA metabolism in rat astrocytes seems to be 7 α -hydroxylation, carried out by CYP7B1 (Fex Svenningsen et al., 2011; Jellinck et al., 2001; Jellinck et al., 2007). In contrast, the pathways using DHEA as an obligatory precursor for formation of testosterone and estradiol (see Introductory section), are much more dominant in cells outside the brain and are indeed essential for the development and functions of many endocrine organs. Very recently, we found that treatment with

endogenous and synthetic estrogens strongly decreases CYP7B1-mediated DHEA hydroxylation in primary cultures of rat astrocytes (Fex Svenningsen et al., 2011). Since CYP7B1-mediated metabolism appears to be the main pathway for DHEA metabolism in these cells, we believe that estrogenic effects on this enzyme may lead to increase of the levels of DHEA via suppression of its metabolism. This could be one of the potential mechanisms whereby estrogens affect CNS, and may play a role for estrogen-dependent protection of CNS cells against injury (Brann et al., 2007; Melcangi & Panzica 2006).

5. Role of sex hormones in regulation of steroid-metabolizing enzymes

5.1 CYP7B1 is regulated by sex hormones

Our studies, carried out in several different cell types, indicate regulatory effects of both estrogen and androgens on CYP7B1 expression (Fex Svenningsen et al., 2011; Tang et al., 2006; Tang & Norlin, 2006) (Fig. 11). As described in the previous section, our results in primary rat CNS cultures showed decreased CYP7B1-mediated catalytic activity following estrogen treatment (Fex Svenningsen et al., 2011). In the studies on astrocytes we also found suppressive effects of estrogen on CYP7B1 mRNA levels. These findings, indicating suppression of the CYP7B1 gene, are different compared to some of our previous data concerning estrogen-dependent regulation of CYP7B1 in human kidney- and liver-derived cell lines (Tang et al., 2006, 2008). In kidney-derived HEK293 cells and liver-derived HepG2



* Involvement of the PI3K/Akt pathway (Tang et al., 2008)

Fig. 11. Simplified overview of our findings on the effects of estrogens on the regulation of CYP7B1 in different cell types. For more information see text and references (Tang et al., 2006, 2008; Tang & Norlin, 2006; Fex Svenningsen et al., 2011)

cells, we have found that estradiol up-regulates CYP7B1 gene expression in the presence of estrogen receptors. Without overexpression of ER however, the kidney HEK293 cells, which have very low endogenous ER expression, react similarly as the astrocytes to estradiol treatment, suggesting that there might be both ER-dependent and ER-independent pathways for estrogen-mediated regulation of CYP7B1. Other possibilities are tissue- and/or species-specific differences in regulatory mechanisms. Species differences in enzymes may include enzyme localization. Data obtained by us and others show higher CYP7B1 levels in rat astrocytes than in rat neurons, whereas in humans CYP7B1 expression has been reported to be predominantly located in neurons (Fex Svenningsen et al., 2011; Trap et al., 2005; Zhang et al., 1997). However, in similarity with our results in human renal and hepatic cells, estrogen receptor-mediated upregulation of CYP7B1 has been shown also in mouse kidney and liver, indicating a similar effect in rodents as in humans and supporting an *in vivo* role for this regulatory mechanism (Jelinsky et al., 2003; Yamamoto et al., 2006).

Thus, from the results obtained by us and other investigators it seems that CYP7B1 not only affects hormonal actions but is itself regulated by hormones. Our studies have shown effects on CYP7B1 transcription and/or activity by both estrogens and androgens, although we observed differences depending on cell type (Fex Svenningsen et al., 2011; Tang et al., 2006, 2008; Tang & Norlin 2006). This may reflect different functions of CYP7B1 in different tissues or cells. In cell types where formation of estradiol is quantitatively important, the observed ER-mediated induction by estradiol on the CYP7B1-mediated pathway may be a means to divert DHEA from estradiol production, by increasing the amount of DHEA metabolized to 7α -hydroxyDHEA (Tang et al., 2006) (Fig. 12). In this way, estradiol-mediated regulation of CYP7B1 may decrease the levels of DHEA available for synthesis of estradiol in some tissues, functioning as a feed-back mechanism to balance the amount of estradiol formed. This could be of particular importance during fetal development as placental estrogen formation is dependent on C₁₉-steroid precursors such as DHEA which is secreted in large amounts by the fetal adrenal cortex. Although there are few data on the role(s) of CYP7B1 in fetal development, studies on tissues from both humans and rodents show markedly higher CYP7B1 mRNA levels in extrahepatic fetal tissues compared with the corresponding adult ones (Bean et al., 2001; Tang et al., 2006).

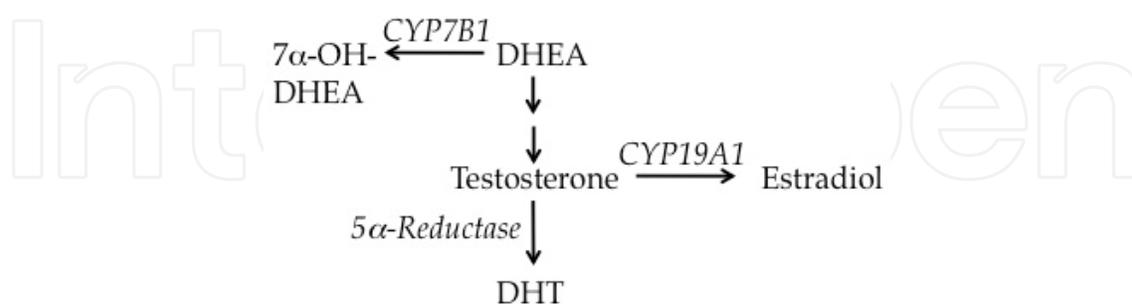


Fig. 12. Some of the alternate pathways for DHEA metabolism

Our data on estrogen-mediated upregulation of the CYP7B1 gene promoter in liver-derived human HepG2 cells showed involvement of the Akt/PI3K (phosphoinositide 3-kinase) cascade in the ER-mediated effects on CYP7B1 (Tang et al., 2008). The link between CYP7B1 and this signalling pathway, which is known to be of importance for cellular survival, suggests a possible connection between CYP7B1 action and viability. Also, as outlined

above, studies on this enzyme in the CNS point towards a potential role connected to neuroprotective events (Bean et al., 2001; Fex Svenningsen et al., 2011; Tsaousidou et al., 2008). Although CYP7B1 expression is abundant in tissues of humans and animals most immortalized cell lines lose their expression of CYP7B1. The reason for this is not known.

The estrogen-mediated regulation of CYP7B1 is of interest also because this enzyme catabolizes 27-hydroxycholesterol, recently identified as the first endogenous selective estrogen receptor modulator, SERM (Fig. 13). 27-Hydroxycholesterol is produced from cholesterol by the sterol 27-hydroxylase CYP27A1. Interestingly, CYP27A1 is also regulated by estrogens and androgens. The regulation of CYP27A1 by sex hormones is discussed below.

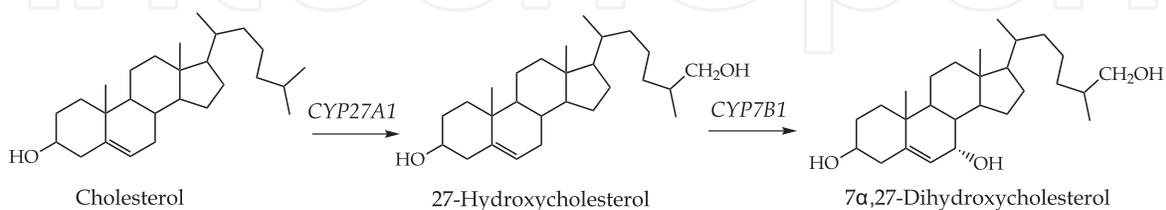


Fig. 13. Formation and metabolism of 27-hydroxycholesterol.

5.2 CYP27A1 is regulated by sex hormones

The sterol 27-hydroxylase CYP27A1 is an enzyme with several important roles (Norlin & Wikvall, 2007). CYP27A1 regulates cholesterol homeostasis including bile acid biosynthesis, cholesterol transport and cholesterol elimination. CYP27A1 is also a vitamin D 25-hydroxylase, catalyzing the first step in the bioactivation of vitamin D into the multifunctional hormone 1,25-dihydroxyvitamin D (Fig. 6). CYP27A1 is essential for the production of 27-hydroxycholesterol (Fig. 13), an oxysterol which has recently been identified as an endogenous selective estrogen receptor modulator, SERM (DuSell et al., 2008, 2010; Umetani et al., 2007, 2011). Considering these important functions, mechanisms for regulation of the human CYP27A1 gene are of great interest.

In studies carried out by our laboratory, we found that the cellular mRNA levels, enzyme activity and promoter activity of CYP27A1 are regulated by estrogens and androgens (Norlin et al., 2011; Tang et al., 2007) (Figs. 14 and 15). The responses to sex hormones are different in various cell lines and cells from different tissues. The hormonal action on the CYP27A1 promoter appears to be complex. In addition to cell-dependent effects, there are also differences between receptor subtypes and different promoter deletion constructs. For instance, whereas ER α suppressed the full-length promoter in HepG2 cells, deletion of a 3.4 kb long part of the promoter resulted in the opposite response. On the contrary, the response of different promoter constructs to ER β was similar. The data available indicate that the CYP27A1 promoter contains sequences able to mediate both stimulation and suppression by ER (Tang et al., 2007). ER-mediated regulation of transcription is often associated with binding of ER homodimers to estrogen response elements (ERE) in target promoters. However, regulation by ER can also involve interaction with sequences containing Sp1 and activator protein (AP-1) sites (Safe, 2001; Schultz et al., 2005). Interestingly, it has been reported that ER-mediated regulation involving AP-1 sites may lead to opposite effects depending on ER subtype (Paech et al., 1997). As mentioned above, the CYP27A1 promoter contains several putative binding sites for ER, AP-1 and Sp1. It seems possible that cell-specific interactions with coactivators may be the reason for the different effects observed with different cell types and receptor subtypes.

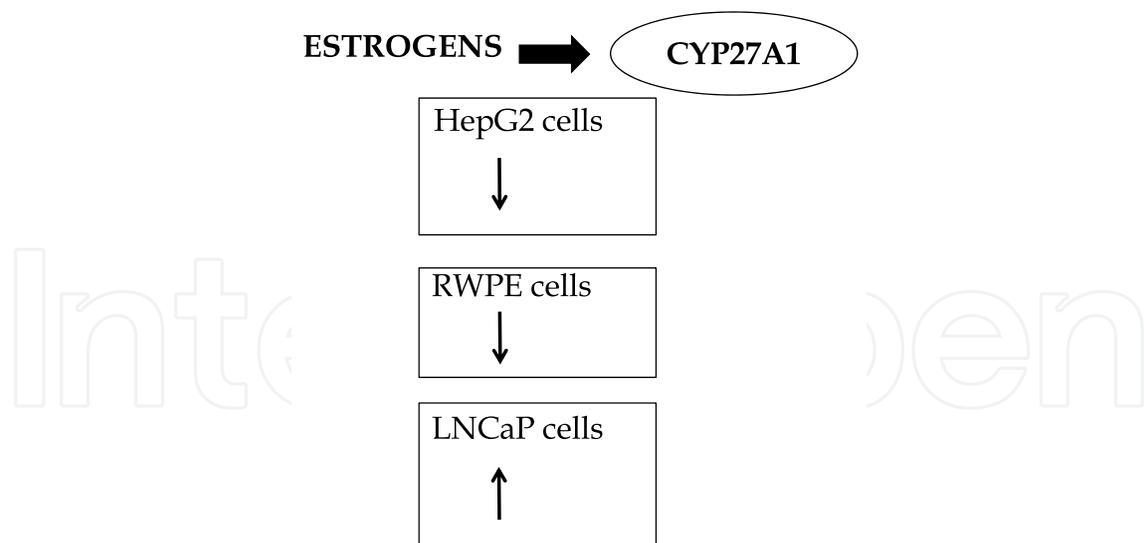
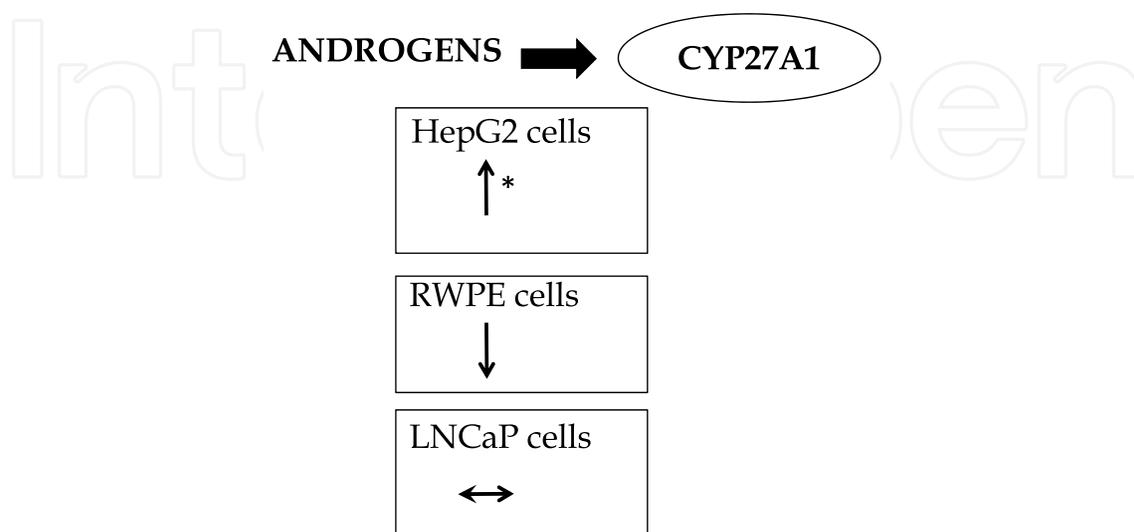


Fig. 14. Simplified overview of our findings on the effects of estrogens on the gene regulation of CYP27A1 in different cell types. For more information see text and references (Norlin et al., 2011; Tang et al., 2007).

Our studies on the mechanisms for the hormonal regulation of CYP27A1 have indicated the involvement of the JNK (c-jun N-terminal kinase)/c-jun pathway in androgen-mediated regulation of this enzyme (Norlin et al., 2011). It has been reported that the androgen receptor (AR) is phosphorylated by JNK and that stress kinase signaling regulates AR phosphorylation, transcription, and localization. Crosstalk between the JNK protein kinase and AR has been reported in several studies (Gioeli et al., 2006; Lazarevic et al., 2008; Lorenzo & Saatcioglu, 2008;). The link to JNK signaling is interesting since inflammatory processes, which can induce the JNK/c-jun pathway, may upregulate CYP27A1 to clear cholesterol from peripheral tissues.

The findings that estrogens downregulate and androgens upregulate CYP27A1 expression in liver-derived HepG2 cells are of interest for several reasons (Tang et al., 2007). The results are consistent with reports on an increased risk for cardiovascular disease in postmenopausal women treated with estrogen plus progestin. Also, increased testosterone levels in men have been associated with a favorable lipid profile (Alexandersen & Christiansen, 2004; Steinberg, 2006; Stoll & Bendszus, 2006; Tchernof et al., 1997; Zmuda et al., 1997). The difference in prevalence of atherosclerotic coronary disease between men and women can not be explained by effects of estrogens and androgens solely on CYP27A1 expression. However, the effects by sex hormones on the expression of CYP27A1 may have impact on several processes in cholesterol homeostasis. The findings that CYP27A1 is regulated by sex hormones imply that endogenous sex hormones as well as pharmacological compounds with estrogenic and androgenic effects may have an impact on several processes related to CYP27A1-mediated metabolism, such as cellular survival and growth, CNS function and cholesterol homeostasis. Because estrogens are used in oral contraceptives, in hormone therapy of postmenopausal women and in cancer treatment, the question arises how CYP27A1 is influenced by estrogens in different tissues. This question is of particular interest considering that anti-atherogenic properties have been ascribed to CYP27A1. The possibility of a tissue-specific regulation by sex hormones is supported by results with prostate cancer cells where estrogen increases the CYP27A1 transcriptional

activity. The results also show that effects of sex hormones on CYP27A1 regulation are different in non-cancerous prostate RWPE-1 compared with prostate cancer LNCaP cells. Whether this difference in regulatory effects is due to different properties of different prostate cell lines or to altered properties of the CYP27A1 regulation in prostate cancer remain to be established.



* Involvement of the JNK/c-jun kinase signalling pathway (Norlin et al., 2011).

Fig. 15. Simplified overview of our findings on the effects of androgens on the gene regulation of CYP27A1 in different cell types. For more information see text and references (Norlin et al., 2011; Tang et al., 2007).

5.3 Effects of sex hormones on vitamin D metabolism

Activated vitamin D metabolites, that can be formed by CYP27A1, are known to have beneficial effects on cell growth in extrahepatic tissues, such as in prostate cells and prostate cancer cells. As discussed above, novel data indicate that estrogens and androgens might regulate the intracellular levels of active hydroxyvitamin D₃ metabolites in prostate cells via regulation of CYP27A1 gene expression (Norlin et al., 2011; Tang et al., 2007). Another observation indicating that androgens can influence intracellular levels of active vitamin D metabolites was reported some years ago (Lou and Tuohimaa, 2006). These authors demonstrated that dihydrotestosterone (DHT) significantly suppressed the expression of the catabolizing enzyme CYP24A1 in androgen-sensitive prostate cancer LNCaP cells. Their data demonstrated that DHT enhances the antiproliferative activity of vitamin D₃ hormones by inhibiting their inactivating enzyme at physiological concentration of androgen. They suggested that the combined use of androgen and vitamin D₃ metabolites could be a promising treatment for prostate cancer.

6. Concluding remarks

Recent research using cell models has revealed novel and tissue-specific actions of sex hormones and vitamin D₃ in the regulation of enzymes in steroid metabolism. The active vitamin D hormone, calcitriol, has been found to affect genes in androgen and estrogen metabolism. Sex hormones regulate genes in neurosteroid metabolism and cholesterol

homeostasis, including the CYP7B1 and CYP27A1 genes. The data available on the actions of the multifunctional and widely expressed CYP7B1 indicate potentially important roles of this enzyme for regulation of neurosteroid levels in the CNS as well as for control of the levels of sex hormones important in estrogenic and androgenic signalling in various cell types and tissues. Observed differences in effects and actions related to this enzyme reflect cell- and tissue-specificity of steroid-metabolizing enzymes of importance throughout the body. The new knowledge discussed in this review should be of importance for future research on brain function, endocrine signalling as well as treatment of estrogen- and androgen-dependent cancers, such as breast and prostate cancer.

7. Acknowledgments

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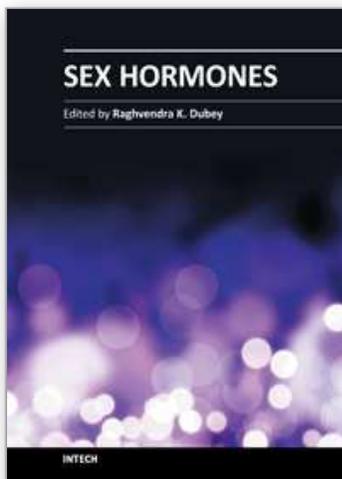
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Sex Hormones not only regulate reproductive function, but they also play a prominent role in the biology and physiology of several organs/tissues and in the pathophysiology of several diseases. During the last two decades, the information on the mechanisms of action of sex hormones, such as estrogens and androgens, has rapidly evolved from the conventional nuclear receptor dependent mechanisms to include additional non-nuclear, non-genomic and receptor-independent mechanisms. This highlights the need to update the current knowledge on sex hormones and their mode of action. Increasing evidence that exogenous/epigenetic factors can influence sex hormone production and action highlights the need to update our knowledge on the mechanisms involved. This book provides a systematic and updated overview of the male/female sex-hormones and their impact in the biology and physiology of various organs. Additionally, the book discusses their positive and negative association with the pathophysiology of various diseases (e.g. osteoporosis, cardiovascular-disease, hypogonadism, reproduction, cancer) and their therapeutic potential.

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