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Steroid-converting enzymes in human adipose tissues and fat deposition with a focus on AKR1C enzymes

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Abstract. – Adipocytes express various enzymes, such as aldo-keto reductases (AKR1C), 11β-hydroxysteroid dehydrogenase (11β-HSD), aromatase, 5α-reductases, 3β-HSD, and 17β-HSDs involved in steroid hormone metabolism in adipose tissues. Increased activity of AKR1C enzymes and their expression in mature adipocytes might indicate the association of these enzymes with subcutaneous adipose tissue deposition. The inactivation of androgens by AKR1C enzymes increases adipogenesis and fat mass, particularly subcutaneous fat. AKR1C also causes reduction of estrone, a weak estrogen, to produce 17β-estradiol, a potent estrogen and, in addition, it plays a role in progesterone metabolism. Functional impairments of adipose tissue and imbalance of steroid biosynthesis could lead to metabolic disturbances. In this review, we will focus on the enzymes involved in steroid metabolism and fat tissue deposition.

Key Words:
Adiposity, AKR1C, Steroid converting enzymes, Adipose tissue, Steroid metabolism.

Introduction

Adipose tissue constitutes an important site for steroid hormone synthesis, metabolism, and storage[1-3].

Plasma dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), androstenedione and testosterone are taken up and transformed to active hormones in adipose tissue by various steroid-converting enzymes[4]. The steroid biosynthetic pathway in adipose tissue depends on the relative expression or activity of steroidogenic enzymes[4].

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Steroid metabolism involves the cytochrome P450 monooxygenases superfamily, aldo-keto reductases (AKRs), short-chain dehydrogenase/reductase oxidoreductases, polyprenol reductases, uridine diphosphate glucuronosyl transferases, catechol-O-methyl transferases, sulfotransferases[5-7], hydroxysteroid dehydrogenases (HSD), like 11β-HSD type 1, 11β-HSD type 2, 3β-HSD, 17β-HSDs, and aromatase (Figure 1). These enzymes are important for steroid biosynthesis and are expressed in preadipocytes and adipocytes[8]. In particular, the most important enzymes for the pathophysiology of adipose tissue are aldo-keto reductases, hydroxysteroid dehydrogenases (HSD), and aromatase, since they regulate the homeostasis of steroid hormones in the adipocytes[9]. In this review, we will focus on the enzymes involved in both steroid metabolism and fat tissue deposition.

11β-Hydroxysteroid Dehydrogenase

Hydroxysteroid dehydrogenase enzymes are known to catalyze hydroxysteroid dehydrogenation. In addition, these enzymes catalyze the reverse reaction as ketosteroid reductases[10].

The 11β-HSD type 1 enzyme *in vivo* functions as a reductase that generates active glucocorticoids. In human visceral adipose tissue, 11β-HSD1 converts inactive cortisone to active cortisol levels[11] to higher levels than in subcutaneous fat[12].

11β-HSD1 knockout mice show lower weight and fat and excellent glucose tolerance, whereas moderate overexpression of the 11β-HSD1 encoding gene in adipose tissue leads to abdominal obesity and metabolic syndrome[13].

11β-HSD2 expression in subcutaneous adipose tissue (SAT) has a negative association with body mass index[14] and is expressed to higher levels in

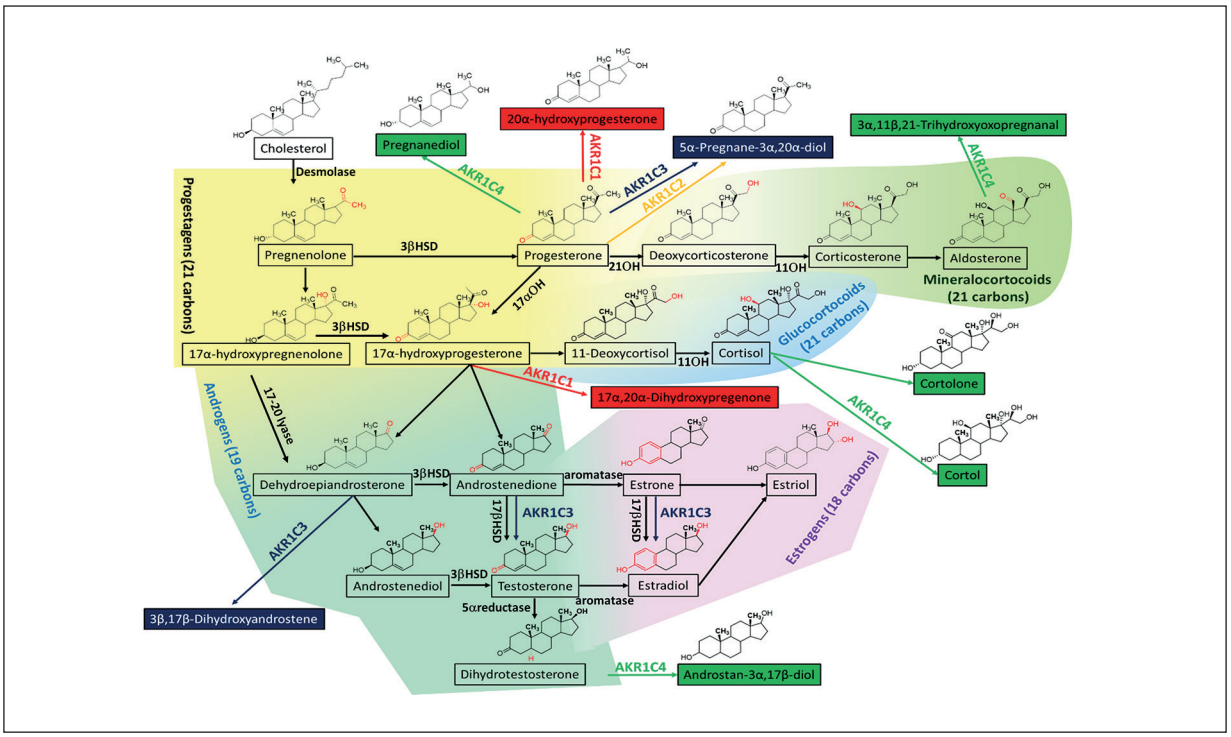

Figure 1. Overview of steroidogenesis pathways. All steroid hormones are derived from a common precursor (cholesterol) through sequential steps involving several steroidogenic enzymes. Cholesterol is introduced into the cells via membrane receptor interactions and further internalized in vesicles and fused with lysosomes. Free cholesterol is released in cells by the action of lysosomal hydrolases which is then converted to pregnenolone in the mitochondria. Pregnolone is metabolized via two pathways: Δ^5-hydroxy steroid pathway leads to the synthesis of 17 α-hydroxypregnenolone, dehydroepiandrosterone and androstenediol, and Δ^4-ketosteroid pathway leads to the synthesis of 17α-hydroxyprogesterone and androstenedione. Androstenedione is further activated to testosterone via catalytic action of AKR1C3 and 5α-reductase. Androstane-3α,17β-diol is a metabolite of dihydroxytestosterone. Alternatively, androstenedione and testosterone can be aromatized by CYP19A1 to form the estrogenic steroid hormones estrone and estradiol, respectively. Cortisol and its precursor 11-deoxycortisol are conversion products of 17OH-progesterone and are dependent on CYP17A1 activity. Progesterone is also reduced to its less active form 20α-hydroxyprogesterone by AKR1C1 activity. 3βHSD = 3β-hydroxysteroid dehydrogenase; 21OH = 21-hydroxylase; 11OH = 11-hydroxylase; 17αOH = 17α-hydroxylase.

SAT of obese rats compared to lean controls[15]. 11β-HSD2 overexpression leads to resistance to diet-induced obesity by decreasing food intake and increasing energy expenditure through inactivation of glucocorticoids and/or by inhibiting access to their receptors[16].

Aromatase

The ovaries and adipose tissue convert androstenedione and testosterone into estrogens through P450 aromatase activity. Aromatase activity is associated with body weight in both pre- and post-menopausal females, and when knocked out[17], both female and male mice show obesity with increased visceral fat[17].

In adipose tissue, cytokines, including IL-6 and TNF-α, increase aromatase activity and transcription of the aromatase gene[18]. In opposition, a pulse of peroxisome proliferator activated receptor gamma agonist (PPARgA) to preadipocyte cultures of human breast cells decreases both transcription and activity of aromatase[19]. In the absence of PPARgA, subcutaneous abdominal preadipocyte expression of the P450 aromatase gene increases several days after induction of differentiation[9,20].

17β-Hydroxysteroid Dehydrogenases

17β-HSD enzymes specifically catalyze estrone to estradiol conversion in human adipose tissue and in preadipocyte cultures[21]. *In vitro*, preadipocyte differentiation to lipid-storage cells increases the activity of 17β-HSD enzyme[21].

In humans, of fourteen isoenzymes, 17β-HSD isoenzyme type 12 plays a significant role in the formation of estrogen by catalyzing conversion of estrone to estradiol, with relatively higher expression levels in organs related to lipid metabolism including liver, heart, skeletal muscle, and kidney. Additionally, the 17β-HSD type 12 isoenzyme has a significant higher expression in endocrine-related organs, like the pituitary gland, pancreas, testis, adrenal gland, placenta, and the gastrointestinal tract, thus suggesting its regulatory role in fatty acid synthesis and steroid metabolism[9,22].

Glucocorticoid-Mediated Steroid Converting Enzymes

Glucocorticoid hormones are a class of corticosteroids secreted by the adrenal cortex. They are required for the regulation of different homeostatic and metabolic functions in the body. The physiological functions of glucocorticoid hormones are regulated by 11β-HSDs that catalyze the interconversion of active cortisol and corticosterone with the inactive counterparts, cortisone and 11-dehydrocorticosterone. The active glucocorticoids bind the glucocorticoid receptor, a ligand-dependent transcription factor[23].

During fasting, glucocorticoids stimulate lipolysis in adipocytes, resulting in the production of glycerol for gluconeogenesis, and free fatty acids for energy production through oxidation[24-26].

Estrogen-Mediated Steroid Converting Enzymes

Estrogens, estradiol, estriol and estrone, have a direct impact on adipose tissue metabolism and function[27]. Enzymes involved in estradiol synthesis also modulate local and whole-body estrogen availability[28]. Knockout mice for estrogen receptor α (ERα) have increased adiposity[8]. In agreement, variants in ER-α and ERβ encoding genes are associated with increased body fat mass and visceral fat accumulation in females. Moreover, low levels of estrogens might also stimulate preadipocyte proliferation, especially in females[29,30]. In white adipose tissue, lipid metabolism is regulated by estrogens through ERα, ERβ and G protein coupled-estrogen receptors.

Progesterone-Mediated Steroid Converting Enzymes

Progesterone might stimulate fat deposition by enhancing lipid synthesis, lipoprotein lipase activity, and steroid-mediated preadipocytes differentiation. Some researchers[9] have suggested a role for progesterone in the gynoid fat distribution pattern of females due to its anti-glucocorticoid activity in abdominal adipose tissue. In support of this hypothesis, progesterone inhibits glucocorticoid-mediated fat cell differentiation, body fat accumulation or lipogenesis in the omental adipose tissue[32].

In cultured preadipocytes of rodents, progesterone enhances the expression of the sterol regulatory element binding transcription factor 1 (*Srebf1*) gene that subsequently controls fatty acid synthase transcription[33]. After progesterone treatment, the levels of resistin and leptin mRNAs increase, whereas the expression of adiponectin decreases in inguinal white adipose tissue of female rats[34]. Male rats treated with progesterone do not show any effect upon the expression of adiponectin, leptin and resistin in inguinal white adipose tissue because they possess low levels of progesterone receptors[34].

Androgen-Regulated Steroid Converting Enzymes

Androgens regulate the pattern of body fat distribution in males. Low plasma testosterone levels are often observed with increased visceral fat accumulation and abdominal obesity. Furthermore, androgen-based treatment of hypogonadal men results in the decrease of abdominal fat accumulation[35]. Similarly, research studies in males have revealed substantial negative association of DHEA levels with abdominal fat accumulation, indicating that lower levels of DHEA are associated with increased abdominal fat accumulation[36].

AKR1 Enzymes

Hydroxysteroid dehydrogenases regulate the synthesis and inactivation of steroid hormones. These enzymes either belong to the short-chain dehydrogenase/reductase superfamily or aldo-keto reductase (AKR) superfamily[37].

In humans, 13 AKR proteins have been identified to date: the aldehyde reductase AKR1A1; the aldose reductases AKR1B1 and AKR1B10; the hydroxysteroid dehydrogenases AKR1C1, AKR1C2, AKR1C3, and AKR1C4; the Δ4-3-ketosteroid-5-β-reductase AKR1D1; the Kvβ proteins AKR6A3, AKR6A5, and AKR6A9; and the aflatoxin reductases AKR7A2 and AKR7A3[38]. The three-dimensional structures of the above enzymes, except for AKR6A3 and AKR6A9, have been experimentally resolved, showing a conserved motif of eight α-helices and eight parallel β-strands that alternate along the peptide backbone, the typical fold of the TIM barrel[39], with the central cavity hosting the nicotinamide moiety of NADP(H); other than the cofactor, the structures also present the binding modes of several different steroid ligands[40].

Role of AKR1C Enzymes

AKR1Cs enzymes are expressed in different tissues. AKR1C1 is mainly expressed in testis, kidneys and liver; AKR1C2 is mainly expressed in prostate, mammary gland and liver; AKR1C3 shows higher expression in brain, testis, liver, placenta, and kidneys; and AKR1C4 is particularly expressed in the liver[41]. Furthermore, AKR1C1 is highly expressed in the adipose tissue and its activity is induced by adipocyte differentiation[41]. In both males and females, AKR1C1 expression levels are relatively higher in SAT than in omental adipose tissue[41]. The AKR1C enzymes play significant roles in the metabolism of prostaglandins (AKR1C3), steroid hormones (AKR1C1-AKR1C3), and bile acids and xenobiotics/drug detoxification (AKR1C4)[42] (Table I)[8,32,43-47].

The aldo-ketoreductase 1C family member, AKR1C1, exhibits 17-oxoreductase activity that is involved in testosterone synthesis from 4-dione, 20-oxoreductase activity that inactivates progesterone, and 3-oxoreductase activity that

Table I. Publications reporting the activity of AKR1C enzymes in subcutaneous adipose tissue (SAT).

AKR1C enzyme	Activity	Sampling	Tissue expression	Reference
C1	2α-HSD	Women undergoing abdominal hysterectomies	Subcutaneous expression higher than omental	43
C1-C2-C3	11α-HSD-1; 3α-HSD; 17β-HSD	Women with metabolic disorders and obesity	Significantly higher in SAT, mostly for AKR1C3	8
C2	3α-HSD, 5α-HSD	Morbidly obese men undergoing biliopancreatic derivation surgery and lean to obese men undergoing general abdominal surgery	Activity significantly higher in obese men	44
C3	5α-HSD	Women with PCOS	Higher expression in serum of PCOS women than in control	45
C3	17β-HSD	Women with simple obesity	AKR1C3 activity higher in SAT	46
C2-C3	11α-HSD-1; 3α-HSD; 17β-HSD	Men and women with idiopathic obesity	High expression in human SAT	47
C1	20-HSD	*Ex vivo* adipocytes isolated from women	Significantly higher expression in mature adipocytes than in preadipocytes	32

PCOS = polycystic ovary syndrome.

inactivates dihydrotestosterone[48]. It has been reported that women with increased accumulation of visceral fat have higher expression of AKR1C1 mRNA and an increased 20-oxoreductase activity within omental adipose tissue[43,49].

In addition, AKR1C1, AKR1C2 and AKR1C3 catalyze the reduction of progesterone to produce 20α-hydroxyprogesterone, a less potent progestogen[50]. Primarily, AKR1C1 catalyzes the inactivation of progesterone by converting it into 20-progesterone through its 20-α-hydroxysteroid dehydrogenase activity. AKR1C1 is expressed in SAT and in the omental adipose tissue in females, whereas it is not a prominent contributor of adipose androgen in males[46]. Thus, AKR1C1 lowers progesterone and 5α-tetrahydroprogesterone levels in peripheral tissue[46]. Progesterone is important for the inhibition of cell proliferation, stimulation of endometrial cell differentiation and pregnancy maintenance[51-53].

AKR1C enzymes also function as a 17-ketosteroid reductase in peripheral tissues, reducing estrone, a weak estrogen, to produce 17β-estradiol, a potent estrogen. AKR1C3 enzyme is the most efficient enzyme for this reduction reaction[46].

Role of AKR1C in Subcutaneous Adipose Tissue (SAT) Accumulation

Increased activity and expression of AKR1C enzymes in mature adipocytes might be associated with adipose tissue accumulation[54].

AKR1C2 and AKR1C3 exhibit fine regulatory effects on the availability of androgens within adipose tissue[55] while glucocorticoids reverse the effects of androgens on adipocyte differentiation. In fact, glucocorticoids eliminate androgen inhibitory action on adipogenesis, probably by increasing androgen inactivation mediated by AKR1C. This mechanism might contribute to individual differences in body fat distribution and composition; thus, reduced androgen availability at a local level allows for glucocorticoid-induced adipocytes differentiation[54].

AKR1C2 is the enzyme that plays a significant role in this crosstalk between androgens and glucocorticoids which involves regulation of lipid accumulation and adipogenesis[56,57].

Increased AKR1C2 expression or activity induces adipocyte differentiation by dihydrotestosterone inactivation, whereas AKR1C2-mediated androgen inactivation induced by glucocorticoids promotes adipogenesis in human subcutaneous preadipocytes. Previous studies revealed that expression of the AKR1C2 protein is increased after the maintenance or loss of weight and this increase is linked with changes in BMI, weight, plasma low density lipoprotein and waist circumference[56-59].

Stimulation of AKR1C2 expression and glucocorticoid-mediated dihydrotestosterone inactivation in preadipocytes might eliminate androgen inhibitory effects on adipogenesis favoring progression of adipogenesis[60]. Many scholars[60] have described further interactions between androgens and the glucocorticoid signaling pathways within adipose tissue. Such hormonal signal interactions at local levels might be an important modulators of body fat distribution patterns[9,61]. In **Supplementary Table I**, steroid converting enzymes involved in human adipose tissue homeostasis are listed with functional polymorphisms that modulate their activity.

AKR1C Enzymes in Androgen Metabolism

The expression of AKR1C and dihydrotestosterone inactivation take place in visceral and subcutaneous adipose tissue, and inactivation rates of androgen are much higher in obese individuals[44]. Furthermore, the expression of AKR1C increases with the increase in mass of adipose tissue, particularly, in subcutaneous fat, leading to higher inactivation rates of androgens[44]. Additionally, in adipose tissue, AKR1C enzymes converts dihydrotestosterone, a stronger androgen into an inactive metabolite[44].

The expression of all isoforms of AKR1C increases with an increase of visceral adiposity. It has been proposed that androgens within the adipose tissue mediate central fat accumulation, preferentially causing android fat distribution[62].

Role of AKR1Cs in Androgen Activation/Inactivation

AKR1C2 is primarily involved in the inactivation of androgen by the conversion of the potent androgen dihydrotestosterone into the weaker 3-diol by its 3-reductase activity[63]. Androgens cause negative effects on lipid synthesis and adipogenesis by upregulating androgen receptors for catecholamine, consequently increasing lipolysis[63]. Androgens can also modulate abdominal adipocyte accumulation by decreasing the activity of lipoprotein lipase, required for adipocyte intracellular fatty acid esterification. Hence, androgen and adipose tissue have a bidirectional and reciprocal impact on each other[63].

In a very interesting study[64], the Authors observed an increase in 5-dihydrotestosterone inactivation by AKR1C2 enzyme in omental adipose tissue from females with visceral obesity and proposed that the local inactivation of androgen is the main reaction catalyzed by AKR1C2 in the abdominal tissue of females. Similarly, androgen mediated inactivation of AKR1C2 activity has been observed in isolated adipocytes and in primary stromal cells. The AKR1C2 enzyme appears to have higher activity in SAT than in omental adipose tissue where inactivation of androgen is linked with obesity[46,56]. These findings were further supported by a decrease in dihydrotestosterone levels in SAT as compared to omental adipose tissue. Subcutaneous fat is the main region of AKR1C mediated androgen metabolism both in females and males[65,66].

AKR1C3 inactivates progesterone to 20-hydroxyprogesterone and activates androgen receptor activity by converting androstenedione to testosterone[67]. AKR1C3 expression is induced by the differentiation of adipocytes[67]. In addition, the expression of AKR1C3 is increased in obese individuals, particularly in the SAT as compared to omental adipose tissue[67].

Adipocyte size could also affect the expression of AKR1C3. In fact, AKR1C3 has higher levels of expression in larger adipocytes than in smaller ones from the same subject[45].

AKR1Cs Effects on Neurosteroids

Neuroactive steroids are considered natural endogenous steroid hormone metabolites that exert non-genomic and rapid effects on neurotransmitter receptors present on the membrane. Synthesis of neurosteroids mostly involves steroidal or cholesterol precursors[68].

AKR1C2 induces the synthesis of neurosteroids, whereas AKR1C1 reduces the concentrations of neurosteroids in the human brain through 3α,5α-tetrahydroprogesterone inactivation and elimination of the precursors of synthetic pathways[69]. AKR1C isozymes preferentially work as reductases and regulate the inactive and active androgen, progestin, and estrogen concentrations in target tissues[69].

AKR1C1 also decreases the neurosteroid cellular concentrations by 5α-dihydroprogesterone and progesterone elimination from neurosteroids synthetic pathways along with the inactivation of 3α,5α-tetrahydroprogesterone[45]. Additionally, AKR1C1 is significantly involved in the production and inactivation of the neuroactive allopregnanolone 3α,5α-tetrahydroprogesterone that allosterically modulates the activity of gamma aminobutyric acid type A (GABAA) receptors, thereby causing analgesic, anesthetic, anticonvulsant and anxiolytic effects[70].

AKR1C Effects on Urinary Metabolites

Several urinary steroid metabolites, like DHEA, androstanediol, 20β-dihydroxycortisone, cortisol, estriol, other estrogens and glucocorticoid metabolites are increased in disorders like polycystic ovary syndrome (PCOS)[70]. The highest increase was found for DHEA, the precursor for both adrenal and ovarian androgens, indicating a pathological mechanism in PCOS that targets both organs and/or overall steroidogenesis[71]. One study[72] reported an increase in the activity of AKR1C1 in women with PCOS, while other studies revealed reduced activities of AKR1C1 and 20β-HSD along with an increase of 3α-HSD activity evaluated by tetrahydrocortisol and α-tetrahydrocortisol conversion to 20α-dihydrocortisol[73]. Table II lists the urinary metabolites associated with AKR1C1 activity.

Conclusions

Adipose tissue is known to have endocrine properties and synthesize steroid metabolizing enzymes, like AKR1 enzymes, 11β-HSD, aromatase, and 17β-HSD. Adipose tissue is recognized as a substantial site for the action and transformation of steroid hormones. AKR1C enzymes are involved in the inactivation of androgen and progesterone which induces adipogenesis, and accumulation, proliferation, and differentiation of adipocytes. Genetic analyses have identified genes crucial for steroid metabolism that are linked with subcutaneous fat accumulation and lipedema[74]. These steroid-converting enzymes mediate the transformation of specific hormones into other hormones that are significantly involved in the metabolic pathways of adipose tissue. Further studies are required to elucidate the complexity of this enzymatic network and its multiple effects on adipose tissue functions.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Table II. AKR1C1 metabolites with potential clinical relevance.

Molecule	Common name
3α-Hydroxy-5α-pregnan-20-one	Allopregnanolone
3α-Hydroxy-5β-pregnan-20-one	Pregnanolone
3β-Hydroxy-5α-pregnan-20-one	Isopregnanolone
3β-Hydroxy-5β-pregnan-20-one	Epipregnanolone
5α-Pregnane-3,20-dione	5α-Dihydroprogesterone
5β-Pregnane-3,20-dione	5β-Dihydroprogesterone
Pregn-4-ene-3,20-dione	Progesterone
20α-Hydroxy-pregn-4-ene-3-one	20α-dihydroprogesterone
5α-Pregnane-3α,20α-diol	Allopregnanediol
5β-Pregnane-3α,20α-diol	Pregnanediol
5α-Androstan-17β-ol-3-one	5α-Dihydrotestosterone
5α-androstane-3α,17β-diol	3α-Androstanediol
21-hydroxy-5α-pregnan-20-one	5α-Dihydrodeoxycorticosterone
3α,21-dihydroxy-5α-pregnan-20-one	3a,5a-Tetrahydrodeoxycorticosterone
Pregnanetriol/17-hydroxypregnanolone	Allotetrahydrodeoxycorticosterone/17-hydroxypregnanolone
15-keto-13,14-dihydro-PGF2α	PGFM
8-iso-Prostaglandin F2α	8-iso-PGF2α

References

1) Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004; 89: 2548-2556.
2) Li J, Daly E, Campioli E, Wabitsch M, Papadopoulos V. De novo synthesis of steroids and oxysterols in adipocytes. J Biol Chem 2014; 289: 747-764.
3) Li J, Papadopoulos V, Vihma V. Steroid biosynthesis in adipose tissue. Steroids 2015; 103: 89-104.
4) Bélanger C, Luu-The V, Dupont P, Tchernof A. Adipose tissue intracrinology: potential importance of local androgen/estrogen metabolism in the regulation of adiposity. Horm Metab Res 2002; 34: 737-745.
5) Rižner TL, Penning TM. Role of aldo–keto reductase family 1 (AKR1) enzymes in human steroid metabolism. SteroidS 2014; 79: 49-63.
6) van der Sluis TM, Vis AN, van Moorselaar RJ, Bui HN, Blankenstein MA, Meuleman EJ, Heijboer AC. Intraprostatic testosterone and dihydrotestosterone. Part I: concentrations and methods of determination in men with benign prostatic hyperplasia and prostate cancer. BJU Int 2012; 109: 176-182.
7) Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev 2011; 32: 81-151.
8) Blouin K, Nadeau M, Mailloux J, Daris M, Lebel S, Luu-The V, Tchernof A. Pathways of adipose tissue androgen metabolism in women: depot differences and modulation by adipogenesis. Am J Physiol Endocrinol Metab 2009; 296: E244-E255.
9) Tchernof A, Mansour MF, Pelletier M, Boulet MM, Nadeau M, Luu-The V. Updated survey of the steroid-converting enzymes in human adipose tissues. J Steroid Biochem Mol Biol 2015; 147: 56-69.
10) Xu Y, López M. Central regulation of energy metabolism by estrogens. Mol Metab 2018; 15: 104-115.
11) Belanger C, Dupont P, Tchernof A. Adipose tissue intracrinology: potential importance of local androgen/estrogen metabolism in the regulation of adiposity. Horm Metab Res 2002; 34: 737-745.
12) Michailidou Z, Jensen MD, Dumesic DA, Chapman KE, Seckl JR, Walker BR, Morton NM. Omental 11beta-hydroxysteroid dehydrogenase 1 correlates with fat cell size independently of obesity. Obesity (Silver Spring) 2007; 15: 1155-1163.
13) Hermanowski-Vosatka A, Balkovec JM, Cheng K, Chen HY, Hernandez M, Koo GC, Le Grand CB, Li Z, Metzger JM, Mundt SS, Noonan H, Nunes CN, Olson SH, Pikounis B, Ren N, Robertson N, Schaeffer JM, Shah K, Springer MS, Strack AM, Strowski M, Wu K, Wu T, Xiao J, Zhang BB, Wright SD, Thieringer R. 11beta-HSD1 inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice. J Exp Med 2005; 202: 517-527.
14) Ferrari P. The role of 11β-hydroxysteroid dehydrogenase type 2 in human hypertension. Biochim Biophys Acta 2010; 1802: 1178-1187.
15) Engeli S, Böhnke J, Feldpausch M, Gorzelniak K, Heintze U, Janke J, Luft FC, Sharma AM. Regulation of 11beta-HSD genes in human adipose tissue: influence of central obesity and weight loss. Obes Res 2004; 12: 9-17.
16) Kershaw EE, Morton NM, Dhillon H, Ramage L, Seckl JR, Flier JS. Adipocyte-specific glucocorticoid inactivation protects against diet-induced obesity. Diabetes 2005; 54: 1023-1031.
17) MacDonald PC, Edman CD, Hemsell DL, Porter JC, Siiteri PK. Effect of obesity on conversion

of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. Am J Obstet Gynecol 1978; 130: 448-455.

18) Iyengar NM, Hudis CA, Dannenberg AJ. Obesity and inflammation: new insights into breast cancer development and progression. Am Soc Clin Oncol Educ Book 2013; 33: 46-51.

19) Komar CM. Peroxisome proliferator-activated receptors (PPARs) and ovarian function-implications for regulating steroidogenesis, differentiation, and tissue remodeling. Reprod Biol Endocrinol 2005; 3: 41.

20) Simpson ER, Michael MD, Agarwal VR, Hinshelwood MM, Bulun SE, Zhao Y. Cytochromes P450 11: expression of the CYP19 (aromatase) gene: an unusual case of alternative promoter usage. FASEB J 1997; 11: 29-36.

21) Bellemare V, Laberge P, Noël S, Tchernof A, Luu-The V. Differential estrogenic 17beta-hydroxysteroid dehydrogenase activity and type 12 17beta-hydroxysteroid dehydrogenase expression levels in preadipocytes and differentiated adipocytes. J Steroid Biochem Mol Biol 2009; 114: 129-134.

22) Sakurai N, Miki Y, Suzuki T, Watanabe K, Narita T, Ando K, Yung TM, Aoki D, Sasano H, Handa H. Systemic distribution and tissue localizations of human 17beta-hydroxysteroid dehydrogenase type 12. J Steroid Biochem Mol Biol 2006; 99: 174-181.

23) Chapman K, Holmes M, Seckl J. 11β-hydroxysteroid dehydrogenases: Intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev 2013; 93: 1139-1206.

24) Akalestou E, Genser L, Rutter GA. Glucocorticoid metabolism in obesity and following weight loss. Front Endocrinol 2020; 11: 59.

25) Gathercole LL, Morgan SA, Bujalska IJ, Hauton D, Stewart PM, Tomlinson JW. Regulation of lipogenesis by glucocorticoids and insulin in human adipose tissue. PLoS One 2011; 6: e26223.

26) Tomlinson JW, Moore JS, Clark PM, Holder G, Shakespeare L, Stewart PM. Weight loss increases 11beta-hydroxysteroid dehydrogenase type 1 expression in human adipose tissue. J Clin Endocrinol Metab 2004; 89: 2711-2716.

27) Paolacci S, Precone V, Acquaviva F, Chiurazzi P, Fulcheri E, Pinelli M, Buffelli F, Michelini S, Herbst KL, Unfer V, Bertelli M; GeneOb Project. Genetics of lipedema: new perspectives on genetic research and molecular diagnoses. Eur Rev Med Pharmacol Sci 2019; 23: 5581-5594.

28) Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013; 93: 359-404.

29) Rezvani R, Gupta A, Smith J, Poursharifi P, Marceau P, Pérusse L, Bouchard C, Tchernof A, Cianflone K. Cross-sectional associations of acylation stimulating protein (ASP) and adipose tissue gene expression with estradiol and progesterone in pre- and postmenopausal women. Clin Endocrinol (Oxf) 2014; 81: 736-745.

30) Anderson LA, McTernan PG, Barnett AH, Kumar S. The effects of androgens and estrogens on preadipocyte proliferation in human adipose tissue: influence of gender and site. J Clin Endocrinol Metab 2001; 86: 5045-5051.

31) Park YM, Erickson C, Bessesen D, Van Pelt RE, Cox-York K. Age- and menopause-related differences in subcutaneous adipose tissue estrogen receptor mRNA expression. Steroids 2017; 121: 17-21.

32) Zhang Y, Nadeau M, Faucher F, Lescelleur O, Biron S, Daris M, Rhéaume C, Luu-The V, Tchernof A. Progesterone metabolism in adipose cells. Mol Cell Endocrinol 2009; 298: 76-83.

33) Lacasa D, Le Liepvre X, Ferre P, Dugail I. Progesterone stimulates adipocyte determination and differentiation 1/sterol regulatory element-binding protein 1c gene expression. potential mechanism for the lipogenic effect of progesterone in adipose tissue. J Biol Chem 2001; 276: 11512-11516.

34) Stelmanska E, Kmiec Z, Swierczynski J. The gender-and fat depot-specific regulation of leptin, resistin and adiponectin genes expression by progesterone in rat. J Steroid Biochem Mol Biol 2012; 132: 160-167.

35) Saad F. Androgen therapy in men with testosterone deficiency: can testosterone reduce the risk of cardiovascular disease? Diabetes Metab Res Rev 2012; 28: 52-59.

36) Bélanger C, Hould FS, Lebel S, Biron S, Brochu G, Tchernof A. Omental and subcutaneous adipose tissue steroid levels in obese men. Steroids 2006; 71: 674-682.

37) Penning TM. Molecular endocrinology of hydroxysteroid dehydrogenases. Endocr Rev 1997; 18: 281-305.

38) Barski OA, Tipparaju SM, Bhatnagar A. The aldo-keto reductase superfamily and its role in drug metabolism and detoxification. Drug Metab Rev 2008; 40: 553-624.

39) Wierenga RK. The TIM-barrel fold: a versatile framework for efficient enzymes. FEBS Letters 2001; 492: 193-198.

40) Rižner TL, Penning TM. Role of aldo-keto reductase family 1 (AKR1) enzymes in human steroid metabolism. Steroids 2014; 79: 49-63

41) Penning TM, Wangtrakuldee P, Auchus RJ. Structural and functional biology of aldo-keto reductase steroid-transforming enzymes. Endocr Rev 2019; 40: 447-475.

42) Chen WD, Zhang Y. Regulation of aldo–keto reductases in human diseases. Front Pharmacol 2012; 3: 35.

43) Blanchette S, Blouin K, Richard C, Dupont P, Luu-The V, Tchernof A. Expression and activity of 20alpha-hydroxysteroid dehydrogenase (AKR1C1) in abdominal subcutaneous and omental adipose tissue in women. J Clin Endocrinol Metab 2005; 90: 264-270.

44) Blouin K, Richard C, Brochu G, Hould FS, Lebel S, Marceau S, Biron S, Luu-The V, Tchernof A. Androgen inactivation and steroid-converting enzyme expression in abdominal adipose tissue in men. J Endocrinol 2006; 191: 637-649.

45) O'Reilly MW, Kempegowda P, Walsh M, Taylor AE, Manolopoulos KN, Allwood JW, Semple RK, Hebenstreit D, Dunn WB, Tomlinson JW, Arlt W. AKR1C3-mediated adipose androgen generation drives lipotoxicity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2017; 102: 3327-3339.

46) Quinkler M, Sinha B, Tomlinson JW, Bujalska IJ, Stewart PM, Arlt W. Androgen generation in adipose tissue in women with simple obesity--a site-specific role for 17beta-hydroxysteroid dehydrogenase type 5. J Endocrinol 2004; 183: 331-342.

47) Wake DJ, Strand M, Rask E, Westerbacka J, Livingstone DE, Soderberg S, Andrew R, Yki-Jarvinen H, Olsson T, Walker BR. Intra-adipose sex steroid metabolism and body fat distribution in idiopathic human obesity. Clin Endocrinol (Oxf) 2007; 66: 440-446.

48) Penning TM, Burczynski ME, Jez JM, Hung CF, Lin HK, Ma H, Moore M, Palackal N, Ratnam K. Human 3alpha-hydroxysteroid dehydrogenase isoforms (AKR1C1-AKR1C4) of the aldo-keto reductase superfamily: functional plasticity and tissue distribution reveals roles in the inactivation and formation of male and female sex hormones. Biochem J 2000; 351: 67-77.

49) Blouin K, Blanchette S, Richard C, Dupont P, Luu-The V, Tchernof A. Expression and activity of steroid aldoketoreductases 1C in omental adipose tissue are positive correlates of adiposity in women. Am J Physiol Endocrinol Metab 2005; 288: E398-E404.

50) Beranič N, Brožič P, Brus B, Sosič I, Gobec S, Lanišnik Rižner T. Expression of human aldo-keto reductase 1C2 in cell lines of peritoneal endometriosis: potential implications in metabolism of progesterone and dydrogesterone and inhibition by progestins. J Steroid Biochem Mol Biol 2012; 130: 16-25.

51) Brozic P, Smuc T, Gobec S, Rizner TL. Phytoestrogens as inhibitors of the human progesterone metabolizing enzyme AKR1C1. Mol Cell Endocrinol 2006; 259: 30-42.

52) Sheehan PM, Rice GE, Moses EK, Brennecke SP. 5 Beta-dihydroprogesterone and steroid 5 beta-reductase decrease in association with human parturition at term. Mol Hum Reprod 2005; 11: 495-501.

53) Wiebe JP. Progesterone metabolites in breast cancer. Endocr Relat Cancer 2006; 13: 717-738.

54) Blouin K, Veilleux A, Luu-The V, Tchernof A. Androgen metabolism in adipose tissue: recent advances. Mol Cell Endocrinol 2009; 301: 97-103.

55) Miller WL, Auchus RJ. The "backdoor pathway" of androgen synthesis in human male sexual development. PLoS Biol 2019; 17: e3000198.

56) Bouwman FG, Boer JM, Imholz S, Wang P, Verschuren WM, Dollé ME, Mariman EC. Gender-specific genetic associations of polymorphisms in ACE, AKR1C2, FTO and MMP2 with weight gain over a 10-year period. Genes Nutr 2014; 9: 434.

57) Blouin K, Veilleux A, Luu-The V, Tchernof A. Androgen metabolism in adipose tissue: recent advances. Mol Cell Endocrinol 2009; 301: 97-103.

58) Veilleux A, Côté JA, Blouin K, Nadeau M, Pelletier M, Marceau P, Laberge PY, Luu-The V, Tchernof A. Glucocorticoid-induced androgen inactivation by aldo-keto reductase 1C2 promotes adipogenesis in human preadipocytes. Am J Physiol Endocrinol Metab 2012; 302: E941-E949.

59) Bouwman FG, Claessens M, van Baak MA, Noben JP, Wang P, Saris WH, Mariman EC. The physiologic effects of caloric restriction are reflected in the in vivo adipocyte-enriched proteome of overweight/obese subjects. J Proteome Res 2009; 8: 5532-5540.

60) Wawrzkiewicz-Jałowiecka A, Lalik A, Soveral G. Recent update on the molecular mechanisms of gonadal steroids action in adipose tissue. Int J Mol Sci 2021; 22: 5226.

61) Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, Corrêa JW, Gagnon AM, Gomez-Sanchez CE, Gomez-Sanchez EP, Sorisky A, Ooi TC, Ruzicka M, Burns KD, Touyz RM. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. Hypertension 2012; 59: 1069-1078.

62) Wake DJ, Walker BR. Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 in obesity. Endocrine 2006; 29: 101-108.

63) Lee HK, Lee JK, Cho B. The role of androgen in the adipose tissue of males. World J Mens Health 2013; 31: 136.

64) Blouin K, Richard C, Bélanger C, Dupont P, Daris M, Laberge P, Luu-The V, Tchernof A. Local androgen inactivation in abdominal visceral adipose tissue. J Clin Endocrinol Metab 2003; 88: 5944-5950.

65) Zhang B, Zhu DW, Hu XJ, Zhou M, Shang P, Lin SX. Human 3-alpha hydroxysteroid dehydrogenase type 3 (3α-HSD3): the V54L mutation restricting the steroid alternative binding and enhancing the 20α-HSD activity. J Steroid Biochem Mol Biol 2014; 141: 135-143.

66) Sinreih M, Anko M, Zukunft S, Adamski J, Rižner TL. Important roles of the AKR1C2 and SRD5A1 enzymes in progesterone metabolism in endometrial cancer model cell lines. Chem Biol Interact 2015; 234: 297-308.

67) Fung KM, Samara EN, Wong C, Metwalli A, Krlin R, Bane B, Liu CZ, Yang JT, Pitha JV, Culkin DJ, Kropp BP, Penning TM, Lin HK. Increased expression of type 2 3alpha-hydroxysteroid dehydrogenase/type 5 17beta-hydroxysteroid dehy-

drogenase (AKR1C3) and its relationship with androgen receptor in prostate carcinoma. Endocr Relat Cancer 2006; 13: 169-180.

68) Rupprecht R, Holsboer F. Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. Trends Neurosci 1999; 22: 410-416.

69) Steckelbroeck S, Jin Y, Gopishetty S, Oyesanmi B, Penning TM. Human cytosolic 3alpha-hydroxysteroid dehydrogenases of the aldo-keto reductase superfamily display significant 3beta-hydroxysteroid dehydrogenase activity: implications for steroid hormone metabolism and action. J Biol Chem 2004; 279: 10784-10795.

70) Griffin LD, Mellon SH. Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. Proc Natl Acad Sci USA 1999; 96: 13512-13517.

71) Dhayat NA, Marti N, Kollmann Z, Troendle A, Bally L, Escher G, Grössl M, Ackermann D, Ponte B, Pruijm M, Müller M, Vogt B, Birkhäuser MH, Bochud M, Flück CE; members of the SKIPOGH Study Group. Urinary steroid profiling in women hints at a diagnostic signature of the polycystic ovary syndrome: A pilot study considering neglected steroid metabolites. PLoS One 2018; 13: e0203903.

72) Blumenfeld Z, Kaidar G, Zuckerman-Levin N, Dumin E, Knopf C, Hochberg Z. Cortisol-metabolizing enzymes in polycystic ovary syndrome. Clin Med Insights Reprod Health 2016; 10: 9-13.

73) Tsilchorozidou T, Honour JW, Conway GS. Altered cortisol metabolism in polycystic ovary syndrome: insulin enhances 5alpha-reduction but not the elevated adrenal steroid production rates. J Clin Endocrinol Metab 2003; 88: 5907-5913.

74) Michelini S, Chiurazzi P, Marino V, Dell'Orco D, Manara E, Baglivo M, Fiorentino A, Maltese PE, Pinelli M, Herbst KL, Dautaj A, Bertelli M. Aldo-keto reductase 1C1 (AKR1C1) as the first mutated gene in a family with nonsyndromic primary lipedema. Int J Mol Sci 2020; 21: 6264.