Updated survey of the steroid-converting enzymes in human adipose tissues

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ABSTRACT

Over the past decade, adipose tissues have been increasingly known for their endocrine properties, that is, their ability to secrete a number of adipocytokines that may exert local and/or systemic effects. In addition to these hormonal peptides, adipose tissues have long been recognized as significant sites for steroid hormone transformation and action. We hereby provide an updated survey of the many steroid-converting enzymes that may be detected in human adipose tissues, their activities and potential roles. In addition to the now well-established role of aromatase and 11β-hydroxysteroid dehydrogenase (HSD) type 1, many enzymes have been reported in adipocyte cell lines, isolated mature cells and/or preadipocytes. These include 11β-HSD type 2, 17β-HSDs, 3β-HSD, 5α-reductases, sulfatases and glucuronosyltransferases. Some of these enzymes are postulated to bear relevance for adipose tissue physiology and perhaps for the pathophysiology of obesity. This elaborate set of steroid-converting enzymes in the cell types of adipose tissue deserves further scientific attention. Our work on 20α-HSD (AKR1C1), 3α-HSD type 3 (AKR1C2) and 17β-HSD type 5 (AKR1C3) allowed us to clarify the relevance of these enzymes for some aspects of adipose tissue function. For example, AKR1C2 expression down-regulation in preadipocytes seems to potentiate the inhibitory action of dihydrotestosterone on adipogenesis in this model. Many additional studies are warranted to assess the impact of intra-adipose steroid hormone conversions on adipose tissue functions and chronic conditions such as obesity, diabetes and cancer.

Abbreviations: *HSD, hydroxysteroid dehydrogenase; AKR, aldo-ketoreductase; HPA, hypothalamo-pituitary-adrenal; E_2, estradiol; LPL, lipoprotein lipase; FFA, free fatty acids; IL, interleukin; TNF-α, tumor necrosis factor alpha; CYP, cytochromeP450; E_1, estrone; PPARγ, peroxisome proliferator-activated receptor gamma; α-HSD, alpha-hydroxysteroid dehydrogenase; siRNA, small interfering RNA; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulphate; 4-dione, androstenedione; DHT, dihydrotestosterone; UDP, uridine diphosphate; P450SCC, cytochrome P450 cholesterol side-chain cleavage enzyme; BMI, body mass index.*

1. INTRODUCTION

As a result of our modern lifestyles which have been increasingly characterized by physical inactivity and consumption of widely available low-cost, energy-dense foods, we have seen an obesity epidemic emerge in many industrialized societies [1]. Yet, individual responses to this "obesigenic environment" remain highly variable, and body fatness is, consequently, highly heterogeneous [2]. In a similar manner, the susceptibility to develop complications in relation to excess body weight is also highly variable among overweight and obese individuals. Even in the obese range, some appear to benefit from short-term protection from the development of medical problems in relation to their excess body fatness [3-5]. In this regard, one of the most critical predictors of disease in overweight or obese men and women is the presence of visceral obesity, that is, of large, centrally-located fat stores within anatomical structures such as the mesentery and greater omentum [6, 7].

One of the critical determinants of elevated cardiometabolic risk or the metabolic syndrome is adipose tissue function impairments, which include adipocyte hypertrophy, impaired adipogenesis, low free fatty acid uptake, reduced triglyceride synthesis, resistance to the inhibitory effect of insulin on lipolysis, immune cell infiltration and inflammatory cytokine secretion [8]. Body composition is sexually dimorphic in humans as women are often characterized by higher body fat percentages compared to men, who proportionally have higher bone and muscle masses [9-12]. Body fat distribution is also sexually dimorphic in humans [13]. Men usually have an android body fat distribution pattern, with adipose accumulation in the abdominal region, and women often display a body fat distribution pattern described as gynoid with a greater proportion of gluteal and femoral adipose tissue. The amount of fat located inside

the abdominal cavity, termed intra-abdominal or visceral fat, includes omental, mesenteric and retroperitoneal fat [14], and is found in amounts that are significantly higher in men compared to women at every body size [8]. Within a given sex however, large interindividual variations in the amount of visceral fat are found: approximately 10-fold in samples of lean to moderately obese Caucasian men and women [13]. In both males and females, large accumulation of visceral adipose tissue is a critical determinant of obesity-related metabolic alterations which are known to increase the risk of type 2 diabetes and cardiovascular disease [15, 16]. In fact, abdominal-visceral obesity is recognized as the most prevalent manifestation of the metabolic syndrome, and certainly represents an essential feature of the current obesity epidemic [8, 17].

Sex steroid hormones, and more generally steroid hormones, have long been recognized as important modulators of body fat distribution patterns [8]. However, many etiological factors remain to be identified to fully understand preferential deposition of fat within the abdomen in some individuals in conditions of excess energy intake [8]. Of note, the mechanisms by which steroids influence the various aspects of adipose tissue function have generally remained elusive, especially in humans [18]. While physiologists have been aware of the local uptake and conversion of steroid hormones in adipose tissue for many years [2], not all studies have taken into consideration the presence of numerous steroid-converting enzymes that may alter the ultimate fate and action of a given steroid entering adipose cells. A little more than a decade ago, we have published a first survey of the steroid-converting enzymes that had been detected in adipose tissue up to that time [2]. The present article presents an updated survey, and addresses the potential role of steroid-converting enzymes in modulating active steroid availability and

adipose tissue homeostasis in a depot-specific manner. Their involvement in chronic conditions such as abdominal obesity, diabetes or hormone-dependent cancers is reviewed where relevant.

2. MODULATION OF GLUCOCORTICOID DYNAMICS

11β-HSD type 1

Excessive circulating glucocorticoid concentrations, as observed in Cushing's syndrome, create a pathological phenotype with features such as abdominal obesity, dyslipidemia, insulin resistance, and hypertension [19]. For most cases, cortisol hypersecretion originates from the pituitary gland (Cushing's disease) and results from excessive adrenocorticotropic hormone secretion [20]. Although individuals with non-Cushing, idiopathic abdominal obesity share some of the morphological and metabolic alterations of Cushing's syndrome, alterations in the sensitivity and drive of the hypothalamo-pituitary-adrenal (HPA) axis are much more subtle [21, 22]. Hence, there is a distinction to be made between systemic and adipose tissue hormone levels. In non-Cushing abdominal obesity, circulating cortisol is normal and HPA axis alterations are modest at best [22]. Accordingly, detailed analyses of urinary glucocorticoid metabolites in these patients have shown that peripheral conversion of glucocorticoids is altered [23, 24], that adipose tissue cortisol has a slow turnover, and that it is fairly independent from systemic cortisol variation [25]. Increased cortisol synthesis specifically in adipose tissues likely predominates in these cases. The effects of glucocorticoids on adipose tissue are summarized in Figure 1.

The main reaction of 11β-HSD type 1 is the activation of glucocorticoids with inactive circulating 11-keto steroids as substrates. In humans, 11β-HSD1 reduces inactive cortisone to active cortisol, especially in visceral adipose tissue (reviewed in [2]). In animal models, the

impact of 11β-HSD1 on the development of abdominal obesity has been clearly established. In 11β-HSD1 knockout mice, resistance to hyperglycemia induced by obesity is observed [26]. Conversely, when the 11β-HSD1 gene is overexpressed in adipose tissue, even only moderately, animals develop abdominal obesity and metabolic disorders such as dyslipidemia and insulin resistance [27]. Visceral adipocyte size and non-esterified fatty acid release are also increased in this model [27]. In humans, some studies reported higher expression of the enzyme in omental vs. subcutaneous fat [28, 29]. However, most reported no regional difference [30, 31]. Some found positive correlations between 11β-HSD1 expression in subcutaneous adipose tissue and obesity level [28, 30-32], and a limited number of studies that had access to human visceral fat samples showed positive associations between 11β-HSD1 expression in omental (OM) adipose tissue and overall adiposity [28, 31-33]. In a study of 36 women for whom we had obtained visceral and subcutaneous adipose tissues and performed detailed characterization of body composition and fat distribution [34], we have reported that omental adipose tissue 11-oxoreductase activity on cortisone was positively associated with visceral adipose tissue area measured by computed tomography as well as omental fat cell size. In addition, women with the highest cortisone oxoreductase activity in omental fat were those characterized by increased omental fat cell lipolysis, high lipoprotein lipase activity, low circulating levels of high-density lipoprotein cholesterol, low adiponectin levels, and high insulin resistance index compared to women with low activity [34]. In another study [35], *in vivo* conversion of cortisone to cortisol in subcutaneous adipose tissue was found to be increased in obese diabetic patients compared to non-diabetic obese or lean individuals. Finally, 11β-HSD1 is expressed in immune cells in both mice and humans [36] and it may modulate the inflammatory response [37, 38]. Overall, studies

in humans and rodent models provide strong evidence of a major etiologic role for 11β-HSD1 in abdominal, visceral obesity and related metabolic alterations.

11β-HSD1 has now clearly become a potential therapeutic target for the treatment of type 2 diabetes [39, 40]. For example, 11β-HSD1 inhibitor INCB13739 was added to metformin therapy in type 2 diabetic patients with inadequate glycemic control and was effective in improving hyperglycemia over a 12-week period [41]. Inhibition of 11β-HSD1-generated cortisol in adipose tissue may offer a new approach in the control of abdominal obesity-related alterations and cardiometabolic risk factors in type 2 diabetes.

11β-HSD type 2

11β-HSD2 is highly expressed in the kidney, where it drives the conversion of cortisol into cortisone and by doing so, protects cells from active glucocorticoid exposure [42]. It also has been detected in adipose tissues, the likely source being the stroma-vascular cell fraction [33, 43]. Expression of 11β-HSD2 in subcutaneous adipose tissue was negatively associated with BMI in one study [43]. Moreover, expression of 11β-HSD2 was increased in subcutaneous adipose tissue in an obese rat model compared to lean controls [44]. Overexpression of 11β-HSD2 in mice led to resistance to diet-induced obesity through lower food intake and increased energy expenditure [45]. The enzyme has been suggested to limit excess fat storage by inactivating active glucocorticoids and preventing access to their receptor. However, in a study by our group, expression levels of 11β-HSD2 were 10 times lower than those of 11β-HSD1 and did not track with adiposity levels of the donors assessed by dual-energy absorptiometry and computed tomography [46]. Another study demonstrated that conversion of cortisol to cortisone

in subcutaneous adipose tissue did not correlate with the presence of obesity and type 2 diabetes [35]. The actual physiological impact of this enzyme subtype on human adipose tissue function remains to be established.

3. MODULATION OF ESTROGEN DYNAMICS

Central effects of estradiol (E_2) have been described on energy intake in rodents [47, 48], but other studies also have reported direct estrogen impact on adipose tissue metabolism [49]. Estrogenic action in adipose tissue is supported by the presence of receptor isoforms α and β [50, 51]. Sex- and depot-related differences in estrogen receptor levels have been reported [51-54]. In mice, knockout of the estrogen receptor α is associated with increased adiposity [55]. In women, genetic variants in the genes coding for estrogen receptors α and β are associated with slightly increased body fat mass and visceral fat accumulation [56-58]. In addition, menopause has been related to increased central adiposity and visceral fat accumulation, a phenotype that is attenuated by hormone replacement therapy [59-64]. In a recent study, we found that estrogenic status influences circulating levels of Acylation Stimulating Protein (ASP) as well as gene expression level of its receptor in adipose tissues [65].

Regarding the impact of E_2 on adipose tissue, exogenous administration of the hormone to premenopausal women decreased lipoprotein lipase (LPL) activity in the gluteal fat compartment [66] whereas opposite effects were found in postmenopausal women [67]. Hormone replacement significantly decreased adipose tissue FFA release by 10 to 20% in postmenopausal women [68]. While some studies reported little effects of ovarian hormonal status on basal and catecholamine-stimulated lipolysis in subcutaneous adipose tissue [67, 69], higher LPL and basal lipolysis were

observed in visceral adipose tissue samples of ovarian hormone-deficient women [69]. These results suggest that E_2 may decrease adiposity and abdominal fat accumulation through both central and peripheral effects, some of which take place in adipose tissue (Figure 1). However, more studies are needed to firmly establish the effect of E_2 on adipose tissue homeostasis in pre- and post-menopausal women. For example, *in vitro* E_2 treatment of subcutaneous mature adipocytes leads to a decrease in LPL and to an increase in hormone-sensitive lipase (HSL) expression in subcutaneous mature adipocytes, but only at high concentrations, suggesting a biphasic action on adipose tissue lipogenic and lipolytic capacity [70]. Estrogens may also stimulate preadipocyte proliferation with a more pronounced impact in women than in men [71, 72]. Overall, even if many aspects of estrogenic action remain to be clarified, most investigators agree that E_2 likely plays an important role in the modulation of adipose tissue metabolism and function. Enzymes responsible for E_2 synthesis contribute not only to local availability of the hormone, but also to whole-body estrogen dynamics, as discussed in the sections below.

Aromatase

Estrogens are secreted by the ovaries in premenopausal women, and extragonadal sites represent a significant source, especially in postmenopausal women and men [73]. This occurs mainly in adipose tissue through conversion of androstenedione (4-dione) and testosterone by P450 aromatase. The relationship between aromatase and adipose tissue was first highlighted in the 1970's when Edman and MacDonald [74, 75] observed a correlation between aromatase activity and body weight in pre- and postmenopausal women. Subsequently, conversion of 4-dione to E_1 was reported in the stromal cell fraction of human subcutaneous adipose tissue [76]. A plethora of scientific articles has now firmly established the critical importance of this enzyme for

estrogen dynamics and pathological conditions such as breast cancer and obesity (Reviewed in [77]). As one of many examples, male and female aromatase-knockout mice are obese and show increased visceral fat accumulation [78, 79].

As demonstrated and reviewed by Simpson [77], P450 aromatase gene expression is controlled by different promoters that are alternatively used, explaining that transcripts of this enzyme in different tissues differ by their 5'-termini. On the other hand, the coding regions and the expressed proteins remain the same among the various tissues. Each promoter is stimulated by a specific pathway. In adipose tissue, promoter I.4 is regulated by inflammatory cytokines such as IL-6 and TNF-α [80, 81]. Glucocorticoids are also required for I.4 stimulation [82].

In human breast preadipocyte cultures, short term exposure to PPAR-γ agonists decreased the mRNA and activity of aromatase [83]. Conversely, we have demonstrated that several days after inducing preadipocyte differentiation, P450 aromatase expression is rather increased, at least in subcutaneous abdominal preadipocytes [52]. Further studies are required to firmly establish the impact of adipogenesis on aromatase activity and expression.

Obesity has emerged as an important risk factor of breast cancer in post-menopausal women [84]. The mechanisms underlying this association are currently being investigated [85-87]. Adipose tissue-derived estrogens may play a role by stimulating breast tumor growth as adipose tissue surrounding breast tumors expresses higher levels of aromatase. Accordingly, aromatase inhibitors now represent a treatment of choice in postmenopausal breast cancer [88].

17β-HSDs

The 17β-hydroxysteroid dehydrogenases (17β-HSDs) play a critical role in the biological activity of estrogens and androgens by catalyzing the reduction of 17-ketosteroids or the oxidation of 17β-hydroxysteroids using NAD(P)H or NAD(P)+ as cofactor [89]. The enzyme activities associated with the various 17β-HSD isoenzymes are widespread in human tissues, not only in classic steroidogenic tissues such as the testis, ovary, and placenta, but also in a large series of peripheral intracrine tissues [90, 91]. In the nineties, several new types of 17β-HSDs were described, indicating a fine, tissue-specific regulation. To date, 14 17β-HSD isoenzymes were identified in mammalians. Even if they participate in the formation of sex steroids, certain types are expressed exclusively in some peripheral tissues [89]. More importantly, many 17β-HSDs have a selective substrate affinity, directional activity in intact cells (reductive or oxidative), and a particular tissue distribution. These characteristics are important determinants of the activity of the 17β-HSD family. Estrogenic 17β-HSDs in particular catalyze the conversion of E_1 to E_2. This activity has been observed in human adipose tissue [91, 92] and in human preadipocyte cultures [93]. *In vitro*, differentiation of preadipocytes to lipid-storing cells has been demonstrated to increase 17β-HSD activity on E_1 [93]. The isoenzyme(s) responsible for estrogenic 17β-HSD activity in adipose tissues remain(s) to be formally identified.

Type 1 17β-HSD is expressed in preadipocytes and differentiated adipocytes, but induction of differentiation does not seem to modulate its expression level [93]. Interestingly, type 1 17β-HSD protein was not detected by immunoblotting in the latter study. Corbould et al. [94] had demonstrated that type 1 17β-HSD mRNA could be detected but that it was incompletely spliced, possibly leading to an inactive protein. Another study reported no significant expression

of this isoenzyme [95]. Type 1 17β-HSD is unlikely to be involved in E_2 synthesis in adipose tissues.

17β-HSD type 12 was initially discovered as mammalian ortholog for yeast (*S. cerevisiae*) microsomal enzyme 3-ketoacyl CoA reductase, which has the ability to elongate long and very long chain fatty acids. Human 17β-HSD type 12 catalyzes the same reaction [96] and also plays a role in estrogen formation as it catalyzes the conversion of E_1 to E_2. The expression rate of 17β-HSD type 12 is high in organs related to lipid metabolism such as liver, kidney, heart and skeletal muscle. 17β-HSD type 12 is also expressed in endocrine-related organs such as the pancreas, pituitary gland, adrenal gland, testis and placenta as well as the gastrointestinal tract, suggesting a role in the regulation of both fatty acid synthesis and steroid metabolism [97].

In our studies [93], the increase in estrogenic 17β-HSD activity taking place with preadipocyte differentiation coincided with an increase in protein level of the type 12 isoenzyme, and mRNA expression of its transcript was substantially higher compared to the very low mRNA expression levels of two other estrogenic 17β-HSD enzymes, namely types 1 and 7. These results indirectly suggest that type 12 17β-HSD may act as one of the steroid-converting enzymes involved in the local conversion of E_1 into E_2 in differentiated adipocytes [93].

The isolation of 17β-HSD type 4 showed its ability to oxidize E_2 to E_1 [98]. The enzyme is expressed in estrogenic tissues and the highest expression level was found in liver [99]. This isoenzyme is also involved in the β oxidation of very long chain fatty acids (like C24:0 and C26:0) [100]. It also plays a role in the β oxidation of branched fatty acids [101] and in the

synthesis in bile acids (di- and tri-cholestanoic acids (DHCA and THCA) [102]. Quinkler et al [95] observed significant expression of this enzyme in omental and subcutaneous adipose tissue. The depot difference in expression levels of this enzyme and its impact on adipose tissue biology are uncertain [95].

17β-HSD type 7 was initially discovered as a prolactin receptor-associated protein [103]. Subsequently, the enzymatic action of 17β-HSD7 was established as the reduction of E_1 using NADPH to produce E_2 [104]. Moreover, the enzyme is involved in postsequalene cholesterogenesis [105, 106] and has an important role in cholesterol metabolism [106-108]. Recently, a shorter form of 17β-HSD7 has been described [109]. This isoenzyme is present in liver, prostate, uterus and placenta. It catalyzes the conversion of E_1 to E_2 and DHT into 5α-androstane-3β, 17β-diol in HEK293 cells [105]. Mackenzie et al measured its expression in adipose tissue and observed that it was more highly expressed in omental than in subcutaneous fat [110]. Its role remains to be established.

17β-HSD type 8 is the protein product of the Ke6 gene which is involved in the development of cystic kidney disease in the mouse [111]. 17β-HSD type 8 is expressed in liver and kidney [112], ovaries and testes [111] and in other tissues [113]. It primarily catalyzes the oxidation of E_2 but also can catalyze the E_1 to E_2 reaction [111]. Recent studies suggested that 17β-HSD type 8 may use fatty acyl thioesters as substrates [114], suggesting a role of 17β-HSD type 8 in fatty acid metabolism rather than in steroid metabolism. Type 8 17β-HSD mRNA was first described in adipose tissue by Blouin et al. in both the omental and subcutaneous depots [115]. Further

studies need to be performed to determine whether this isoform has some relevance for adipocyte physiology.

4. MODULATION OF PROGESTERONE DYNAMICS

Some *in vivo* and *in vitro* studies have shown that progesterone may stimulate fat accretion by increasing LPL activity, lipid synthesis and steroid-mediated differentiation of preadipocytes [116-122]. These results, however, are far from being unanimous. For example, some researchers reported no effect of progesterone on LPL activity in rat adipose tissue [123] while others suggested that progesterone could be involved in the female fat distribution pattern through anti-glucocorticoid action in abdominal adipose tissue [124]. This notion is supported in part by the finding that progesterone inhibits glucocorticoid-induced fat cell differentiation, lipogenesis, or body fat accumulation [125, 126]. In cultured rodent preadipocytes, progesterone increased gene expression of sterol regulatory element binding transcription factor 1 (Srebf1) which in turn controls the transcription of fatty acid synthase [117]. In female rats treated with progesterone, mRNA levels of leptin and resistin increased while there was a decrease in adiponectin expression in inguinal white adipose tissue. In contrast, in male rats treated with progesterone there was no effect on the expression of leptin, resistin and adiponectin in the same tissue compartment [127] (Figure 1). In our experiments, progesterone had no consistent effect on fat cell differentiation and progesterone receptor mRNA expression was barely detectable [128].

20α-HSD (AKR1C1)

A member of the aldo-ketoreductase 1C family, 20α-HSD (AKR1C1), is known to inactivate progesterone (20-oxoreductase activity), synthesize testosterone from 4-dione (17-oxoreductase

activity) and inactivate dihydrotestosterone (3-oxoreductase activity) [129]. Stable transfection assays show, however, that conversion of progesterone to 20α-hydroxyprogesterone is the predominant activity of this enzyme [129]. In adipose tissue, we have shown that 20α-HSD is expressed at relatively high levels and that 20-oxoreductase activity is easily detected [116, 130]. Expression levels are higher in subcutaneous than in omental adipose tissue in both men and women [130, 131]. Moreover, expression of 20α-HSD and 20-oxoreductase activity are both strongly induced by adipocyte differentiation in primary preadipocyte cultures [116]. Consistent with the notion that adipose tissue expansion involves preadipocyte differentiation (hyperplasia) and fat cell hypertrophy, we also have demonstrated that women with higher visceral fat accumulation have higher AKR1C1 mRNA expression and higher 20-oxoreductase activity in omental adipose tissue [130, 132].

We have characterized the metabolites that are generated by preadipocytes and differentiated adipocytes upon incubation with progesterone [128]. Interestingly, we found that preadipocytes efficiently generate a complex mixture of 5α-, 5β-, 20α- and 3α/β-reduced metabolites. Overall metabolite formation increased in differentiated adipocytes, with 20α-hydroxyprogesterone as the main product [116]. Such effective catabolism is consistent with the rather modest effects of progesterone on abdominal fat cell differentiation.

5. MODULATION OF ANDROGEN DYNAMICS

Androgens modulate body fat distribution patterns in men, as described in our review articles on this topic [18, 115, 133]. Correlation studies have confirmed that low plasma testosterone concentrations are often found with abdominal obesity and elevated visceral fat accumulation

[134-137]. Androgen treatment in hypogonadal men leads to a decrease in abdominal fat accumulation, especially when normal plasma androgen level is reached during the treatment and remains within the physiological range [18, 138, 139]. These effects appear to be dose-dependent [140] and lead to concomitant improvements of glucose and insulin homeostasis [138, 141, 142], but they have modest effects on the lipid profile [143].

Our review of the relationship between endogenous DHEA and abdominal obesity [144] showed that in men, most studies assessing the free form of this steroid found a significant negative association between DHEA levels and abdominal fat accumulation [145-147]. Studies which examined the correlation between computed tomography measures of visceral adipose tissue area and plasma DHEA also reported a negative correlation, suggesting that low DHEA levels are associated with greater accumulation of fat within the abdominal cavity [146, 147]. The association between plasma levels of the sulphate ester (DHEA-S) and body fat distribution is less consistent. Some studies reported a negative association between plasma DHEA-S and central fat accumulation [145, 146], and others reported the opposite [147, 148]. The association between computed tomography-measured visceral adipose tissue areas and DHEA-S was negative in one study [146] and positive in another [147]. Studies on DHEA replacement continue to be notoriously discordant with respect to their impact on body fat distribution and variables of the metabolic profile in humans [144, 149, 150]. Some studies convincingly demonstrated that this hormone precursor had relatively small effects which could not be sustained in long-term therapies when given orally [149, 151-153]. Several discrepancies observed in previous studies on DHEA and abdominal obesity could actually result from

interindividual differences in the ability of peripheral sites such as adipose tissues to transform DHEA into more potent hormones.

We have known for a long time that androgens are detectable in adipose tissue [154-158]. DHEA, 4-dione and testosterone are the most abundant [156, 159]. We also detected the most potent androgen, DHT, using more sensitive techniques [159]. Although adipose tissue levels of most androgenic steroids are strongly correlated with levels in the circulation, the amount of steroids is generally higher in adipose tissue than blood [155-157, 159]. Such plasma-to-adipose tissue gradient indirectly supports the notion that adipose tissue is a site for androgen uptake, metabolism and action [155].

We examined differences in the steroid content of subcutaneous and omental adipose tissue in men [159]. Similar testosterone levels were observed in both adipose tissue compartments. However, DHEA, 4-dione and DHT levels were higher in omental compared to subcutaneous adipose tissue. We postulate that regional differences in steroid-converting enzyme activities may partly explain depot differences in the availability of active androgens as discussed below. In obese men, testosterone and DHT levels of omental fat tissue were negatively associated with waist circumference [159]. Moreover, tissue 4-dione, testosterone and DHT levels were all positively associated with adipocyte lipolytic responsiveness to catecholamine stimuli. The correlations were stronger in omental than in subcutaneous adipose tissue and are consistent with the stimulatory effect of androgens on lipolysis [159]. These results support the notion of a depot-specific regulation of androgen action in adipose tissue.

We have previously reviewed the impact of androgens on adipose tissue function [133]. Discrepant results were often reported. Figure 1 summarizes androgenic effects on selected aspects of adipose tissue function. At least 3 studies concluded that androgens had no effect on preadipocyte proliferation in cultures from rodent and human adipose tissues [72, 160, 161]. However, a clear inhibitory effect of testosterone and DHT has been reported on adipogenesis in several models [162-166], including human primary preadipocytes from our patients [167]. We [167] and others [165, 166] found that these effects were partially reversed by anti-androgens flutamide or bicalutamide. One study reported that DHEA inhibits adipogenesis specifically in omental fat [168] which could be mediated by androgenic metabolites of this steroid [169].

Studies on androgens and lipolysis are not unanimous. Testosterone treatment enhanced norepinephrine-stimulated lipolysis in abdominal subcutaneous fat of normal men [170]. Studies in human and rodent adipocytes confirmed these observations using testosterone [171] and DHEA [172]. However, others [173] observed an inhibitory effect of testosterone on catecholamine-induced lipolysis in differentiated subcutaneous preadipocytes. Modulation of β-adrenoreceptors and hormone-sensitive lipase as well as adenylate cyclase activity have been proposed as mediators of androgenic action on lipolysis [173-177]. Androgen effects on lipolysis likely occur through the androgen receptor as they are blunted by flutamide [160]. Most studies also reported that androgens reduce lipid uptake and synthesis in adipose tissue. Testosterone supplementation in men decreased lipoprotein lipase activity and triglyceride uptake in abdominal adipose tissue compartments [170, 178]. Discordant effects were reported in isolated mature adipocytes [160] or in fat from monkeys that were castrated and replaced with testosterone [179]. Finally, adipokine/cytokine concentrations may also be influenced by

androgens. Testosterone administration in men lowered plasma adiponectin and leptin levels [180-182]. Leptin and adiponectin secretion were also decreased by DHT in subcutaneous explant cultures and in differentiated 3T3-L1 cells [183, 184]. Others [185] corroborated the inhibitory effect of androgens on leptin, but found no modulation of adiponectin by androgens. DHEA-S also inhibited adiponectin expression in omental adipocytes [186]. Finally, testosterone replacement in hypogonadal men also lowered TNF-α, IL-1β and increased IL-10 plasma levels [187].

Overall, active androgens testosterone and possibly DHT seem to favor fat mass reductions that manifest through inhibition of adipogenesis and lipogenesis and possible stimulation of lipolysis. Adipokine and inflammation are likely modulated, but the impact on adiponectin is uncertain. Effects have been reported to vary according to the fat depot examined and as a function of the nature and dose of the androgen tested. Considering the clear impact of androgens on adipose tissue distribution patterns, local synthesis or inactivation of active androgens could logically have depot-specific effects on androgen availability and possibly adipose tissue accumulation. This is addressed in the next few sections.

17β-HSDs

17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) catalyzes the conversion of active 17β-hydroxysteroids into less active 17-ketosteroids, which for example decreases tissue levels of active estrogens and androgens with NAD+ as a cofactor [188]. It is highly expressed in placenta which means that this isoenzyme may affect steroid dynamics in this tissue [189]. In adipose

tissue, 17β-HSD2 is expressed at higher levels in omental adipose tissue than in subcutaneous adipose tissue [52]. Its relevance for adipose tissue physiology and obesity is unknown.

17β-HSD type 3 converts 4-dione to testosterone [89]. It is expressed in human subcutaneous and visceral adipose tissues [52, 94, 110]. However, no expression level difference is observed between these depots [52]. In preadipocyte cultures, differentiation tends to increase expression of this enzyme [52, 95]. Its specific contribution to the availability of androgens in adipose tissue remains unclear at this time. The ratio of 17β-HSD3-to-aromatase mRNA in intra-abdominal adipose tissue was positively correlated with BMI in a study [190], which led the authors to suggest increased androgenicity in visceral fat. This hypothesis remains to be functionally tested in light of the presence of 17β-HSD type 5, which is expressed at much higher levels than type 3 (see below).

17β-HSD type 5 (AKR1C3) is involved in the conversion of 4-dione to testosterone. Expression level of the enzyme was found to be associated with visceral as well as overall adiposity indices and with the waist-hip ratio [191]. Its expression is strongly induced by adipocyte differentiation. For example, testosterone formation is increased by 5 fold in differentiated adipocytes from the subcutaneous and omental fat depots, and expression levels of AKR1C3 follow a similar pattern [52, 93, 192]. Expression levels of the enzyme are higher in the subcutaneous depot [52, 192]. In addition, adipocyte size could have an impact on AKR1C3 expression since some observed that it is expressed at higher levels in larger than in smaller adipocytes from the same subject [193]. It remains to be confirmed whether increasing expression levels and activity of this enzyme with obesity contribute to make adipose tissue more androgenic. The role of 17β-HSD type 5 in the

synthesis of prostaglandins, which are known modulators of PPARγ [194], or its impact on estrogens could also mediate its relationship with obesity.

5α-reductases

DHT can be produced either by 5α-reduction of testosterone, or from 5α-reduction of 4-dione and subsequent 17-oxoreduction by 17β-HSDs. Literature in general assumes that the main reaction is that of testosterone to DHT [195]. However, work by our group in the sebaceous gland has shown that DHT formation also likely results from 4-dione transformation [196]. Enzymology data indirectly support that this possibly also applies to adipocytes [197]. In primary preadipocytes, we reported that DHT formation from testosterone decreased very significantly upon induction of differentiation [52].

Literature currently assumes that one out of two isoenzymes of 5α-reductase mediates local DHT formation, but a third isoform of 5α-reductase (designated type 3) has been identified [198]. The enzyme seems to be expressed in many tissues, although fat was not tested [198]. The 5α-reductase isoenzyme playing a role in adipose tissue androgen homeostasis remains to be determined. In addition to androgens, 5α-reductases may contribute to the metabolism of other steroids including progesterone metabolites [116] and glucocorticoids [199].

3α-HSD type 3 (AKR1C2) and UDP-glucuronosultransferases

We have published original studies suggesting increased circulating levels of the DHT metabolite 3α-diol-glucuronide in abdominal obese men [200-202]. These initial results were later confirmed in a large cohort study by a Swedish group [203]. We have previously shown

significant expression of UDP-glucuronosyltransferase in adipose tissue [204]. Our work has also shown that the conversion of DHT to the inactive androgen metabolite 3α-diol was detected in fat tissue of both men and women [131, 132, 192]. Activity was higher in subcutaneous compared to omental fat, and, most importantly, androgen inactivation rates in omental fat were positively correlated with measurements of obesity level including BMI, fat cell size and visceral adipose tissue area assessed by computed tomography [131, 132, 192]. The enzyme responsible for most of the DHT-to-3α-diol conversion in humans is 3α-HSD-3 (AKR1C2).

Our initial finding of higher expression and activity of AKR1C2/3α-HSD3 in subcutaneous vs. omental fat of both men and women [131, 132, 192] suggested that cell composition of the tissue might affect the enzyme. Accordingly, we found that mature adipocytes had higher rates of androgen inactivation compared to preadipocytes [131]. Further experiments showed that induction of fat cell differentiation increased androgen inactivation rates and AKR1C2 mRNA expression [52].

Androgen-glucocorticoid interaction

We have examined various factors that could modulate DHT inactivation rates in preadipocytes. We were intrigued by the finding of a robust, dose-dependent stimulation of androgen inactivation by dexamethasone alone [52]. Such stimulation was apparent after only 24 hours, was completely reversed by the glucocorticoid receptor antagonist RU486, and did not require additional lipogenic factors (insulin or PPAR-γ agonist). These results suggest that this stimulation is an early event in the process of fat cell differentiation.

Active glucocorticoids stimulate adipogenesis and are synthesized locally by 11β-HSD-1 in proportion to mature adipocyte size and number [27, 205]. On the other hand, as mentioned, androgens inhibit adipogenesis and are inactivated locally by enzymes that are responsive to glucocorticoids. We have suggested that the stimulation of AKR1C2 expression and DHT inactivation by glucocorticoids in preadipocytes may remove some of the inhibitory effect of androgens and allow adipogenesis. Other interactions have been noted in adipose tissue between the androgen and glucocorticoid signalling pathways [206, 207]. Interaction of these hormonal signals at the local level may represent a significant modulator of body fat distribution patterns.

6. OTHER ENZYMES

3β-HSD

The conversion of DHEA to 4-dione and of androst-5-ene-3β,17β-diol (5-diol) to testosterone is catalyzed by 3β-HSD. This enzyme was found to be more highly expressed in subcutaneous adipose tissue than in omental adipose tissue [52]. Expression of 3β-HSD is also higher in subcutaneous adipose tissue of women with polycystic ovary syndrome compared to control women [208]. Expression levels of 3β-HSD (HSD3B1) were found to be decreased in visceral adipose tissue in mice that gained weight under a high-fat diet, suggesting decreased androgen synthesis [209]. Fujioka et al. [210] tested the effect of testosterone and DHEA on preadipocyte differentiation in the 3T3-L1 murine preadipocyte cell line and showed that both steroids decreased adipogenic proliferation and differentiation. Interestingly, the effects of DHEA were abolished in the presence of 3β-HSD inhibitor Trilostane, suggesting that conversion to androgens or other steroids through this enzyme is required to observe an effect of DHEA in adipocytes [210]. In addition to their androgenic action, 3β-HSDs can also convert 17-OH-

pregnenolone into 17-OH-progesterone and pregnenolone into progesterone [2, 211]. Overall, the specific role of 3β-HSD activity in adipose tissue steroid homeostasis remains to be formally established.

Steroid Sulfatase

Steroid sulfatase (STS) converts DHEA-sulfate (DHEA-S) and estrone-sulfate (E_1-S) into their free forms, DHEA and E_1 [212]. While it is uncertain that adipose tissue generates *de novo* DHEA and E_1 directly from cholesterol, the sulfated forms of these steroids are highly abundant in the circulation and may represent a significant source for these steroids in adipose tissue, provided that STS is indeed, active [213]. Martel and colleagues [214] were the first to describe that mesenteric fat from rhesus monkeys displays significant DHEA and E_1 sulfatase activities. More recently, STS mRNA, protein and activity have been observed in human subcutaneous adipose tissue from men and women [215]. We reported that mRNA expression of STS is strongly induced by differentiation in primary preadipocyte cultures [52]. Since DHEA-S and E_1-S are positively charged, they need a transporter from the organic anion transport polypeptide family (OATP) to enter adipocytes. These transporters, more specifically OATP-B, OATP-D and OATP-E, have been detected in subcutaneous adipose tissue [215]. The physiological importance of the conversion of sulfated precursors to free steroids with estrogenic activities by STS is recognized in breast cancer, where these steroids are proven to stimulate tumor cell proliferation through the estrogen receptor [216]. This pathway may also provide a significant source of estrogens that would originate from breast adipose tissue. On the other hand, consistent with their high circulating E_1 and E_1-sulfate levels, obese individuals may produce increased amounts of estrogenic steroids that may have some physiological relevance [215].

7α-hydroxylase (CYP7B1)

The 7α-hydroxylase enzyme is a hydroxylase which transforms steroids into their corresponding 7α-hydoxysteroid form. Seven-α hydroxylation of DHEA to 7α-hydroxyl-dehydroepiandrosterone (7α-OH-DHEA) is one of its known activities [217]. This gene is mainly expressed in the liver, brain, kidney and pancreas and to a lower extent in other tissues [217]. To our knowledge, CYP7B1 expression has not yet been investigated in human adipose tissues. On the other hand, 7α-hydroxylation predominates in differentiated breast adipose tissue stromal cells metabolizing DHEA [218, 219]. In differentiated 3T3-L1 adipocytes incubated with DHEA, 7α-hydroxylase activity is also detected [220]. Recent observations in a population of obese boys showed that circulating levels of 7α-hydroxy-dehydroepiandrosterone were more elevated than in lean boys and correlated positively with anthropometric data [221]. These results indirectly suggest that adipose tissue may be a site for 7α-hydroxylation of DHEA. This possibly plays a role in modulating the availability of hormones regulating fat storage and distribution. Some studies reported that 7α-hydroxy-dehydroepiandrosterone has antiobesigenic effects in humans [222]. 7α-hydroxylated metabolites of DHEA also have a role in triggering the immune response in mice [223].

P450SCC, StAR and 17α-hydroxylase

De novo steroid hormone synthesis from cholesterol requires Steroidogenic acute regulatory protein (StAR) and P450 side chain cleavage enzyme (P450SCC or CYP11A1), which are implicated in the delivery of cholesterol to the inner mitochondrial membrane and cholesterol side-chain cleavage, respectively [224]. StAR has low mRNA expression level in subcutaneous

and visceral adipose tissue samples of obese subjects [225]. However, this transcript was much more highly-expressed in the adrenal gland than in adipose tissues of women [110]. In the C57BL/6J mouse model, P450SCC expression in visceral adipose tissue was reduced in animals fed a high-fat vs. a low-fat diet [209]. In obese rats, vitamin C supplementation was shown to reduce StAR expression in subcutaneous fat and also to decrease body fat mass [226]. It may be tempting to extrapolate that *de novo* steroid synthesis from cholesterol takes place in adipose tissue. However, Mackenzie et al. [110], when showing that 17α-hydroxylase (P450C17 or CYP17) was not detected, stated that cholesterol use for steroid hormone synthesis was not possible. Moreover, since 11β-hydroxylase (CYP11B1) and 11/18β-hydroxylase (CYP11B2) were also undetectable, these authors concluded that 11-deoxycorticosterone may be the final product of *de novo* steroid synthesis in adipose tissue. Conversely, Puche et al. [227] showed significant 17α-hydroxylase activity in subcutaneous adipose tissue of women. Yet, another study failed to detect 17α-hydroxylase activity in subcutaneous adipose tissue [208]. Thus, although unlikely, the ability of adipose tissue to synthesize active steroid hormones from cholesterol remains to be formally excluded.

Aldosterone Synthase (CYP11B2)

Aldosterone induces the differentiation of 3T3-L1 cells into lipid-storing adipocytes [228]. The impact of the renin-angiotensin-aldosterone system on adipose tissue is considerable. Its hyperactivity inhibits preadipocyte differentiation and contributes to the formation of large and dysfunctional adipocytes that are more insulin resistant and will generate inflammatory adipokines [229, 230]. During preadipocyte differentiation, the expression of angiotensinogen, angiotensin-converting enzyme (ACE) and renin mRNA is increased. Aldosterone alone has a

stimulatory effect on adipocyte differentiation which is mediated through activation of the mineralocorticoid receptors found in adipose tissue. The renin-angiotensin-aldosterone system is now a target of interest for the treatment for type 2 diabetes since development of the disease is found to be altered by ACE inhibitors and angiotensin receptor blockers by improving insulin sensitivity in high-risk patients (reviewed in [230]). Some studies observed a positive correlation between the degree of obesity and plasma aldosterone concentrations, a finding that is reversed when hypertensive obese patients lose weight [231]. While this may be mediated by changes in steroid production by adrenocortical cells in response to other factors, the hypothesis that it may involve mineralocorticoids produced by adipocytes has been considered.

Whether adipose tissue generates its own pool of aldosterone is controversial. The CYP11B2 gene encodes aldosterone synthase (11/18β-hydroxylase) which is responsible for catalyzing three reactions for converting of 11-deoxycorticosterone into aldosterone inside the mitochondria of the zona glomerulosa in rat adrenal cortex [232-234]. Briones et al. observed significant expression of CYP11B2 mRNA and protein in 3T3-L1 preadipocytes and adipocytes, with a higher expression in adipocytes and with angiotensin II treatment [231]. As proposed by these authors, the mechanism for aldosterone production by adipocytes would involve angiotensin II modulation of the calcineurin/nuclear factor of the activated T cells (NFAT) system, which would enhance expression of CYP11B2. Conversely, a review of possible non-adrenal aldosterone production sites proposed that adipose tissue production of aldosterone was unlikely [110, 235].

7. CONCLUSION

Since body fat distribution is sexually dimorphic, sex hormones have been suspected as key regulators. For a very long time, adipose tissue physiologists have been aware of the capacity of adipose tissue to act as a steroid reservoir and site of steroid conversion [2]. In this review we have provided an updated survey of the steroid-converting enzymes that are detected or may be present in adipose tissues (Figure 2). The large body of evidence supporting the existence of such an elaborate set of steroid-converting enzymes in adipose tissue can no longer be ignored when considering the biological impact of steroid hormones on fat cells. We have discussed the role of some enzymes which may be involved in the modulation of the effects of steroid hormones in adipose tissue. The transformation of a given hormone to another by steroid-converting enzymes may modulate metabolic pathways and other adipose tissue functions. Additional studies should be performed to further decipher the complexity of this enzyme network and its effects on adipose tissue functions.

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FIGURE HEADINGS

Figure 1: Summary of documented androgen, estrogen, progesterone and glucocorticoid effects on adipose tissue function and metabolism.

Figure 2: Pathways of steroid hormone metabolism in adipose tissue. Grey arrows and steroids indicate putative pathways requiring confirmation. Black arrows and steroids indicate confirmed pathways. StAR: Steroidogenic acute regulatory protein, P450SCC: side-chain cleavage enzyme, 3β-HSD: 3β-hydroxysteroid dehydrogenase, 3β-HSD1: 3β-hydroxysteroid dehydrogenase type 1, 3α-HSD3 (AKR1C2): 3α-hydroxysteroid dehydrogenase or aldo-ketoreductase 1 C type 2, 11/18β-hydroxylase: aldosterone synthase, 11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1, 11β-HSD2: 11β-hydroxysteroid dehydrogenase type 2, OATP: transporter from the organic anion transport polypeptide family, 17β-HSD2: 17β-hydroxysteroid dehydrogenase type 2, 17β-HSD3: 17β-hydroxysteroid dehydrogenase type 3, SRD5A1-2: steroid 5α-reductase type 1-2, 17β-HSD5 (AKR1C3): 17β-hydroxysteroid dehydrogenase type 5 or aldo-ketoreductase 1 C type 3, 17β-HSD12: 17β-hydroxysteroid dehydrogenase type 12. *: Progesterone can also be transformed by 20α-hydroxysteroid dehydrogenase (20α-HSD or AKR1C1) into 20α-hydroxyprogesterone and a mixture of 5α-, 5β-, 20α- and 3α/β-reduced metabolites through activity of other enzymes (see text).

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Figure 1:

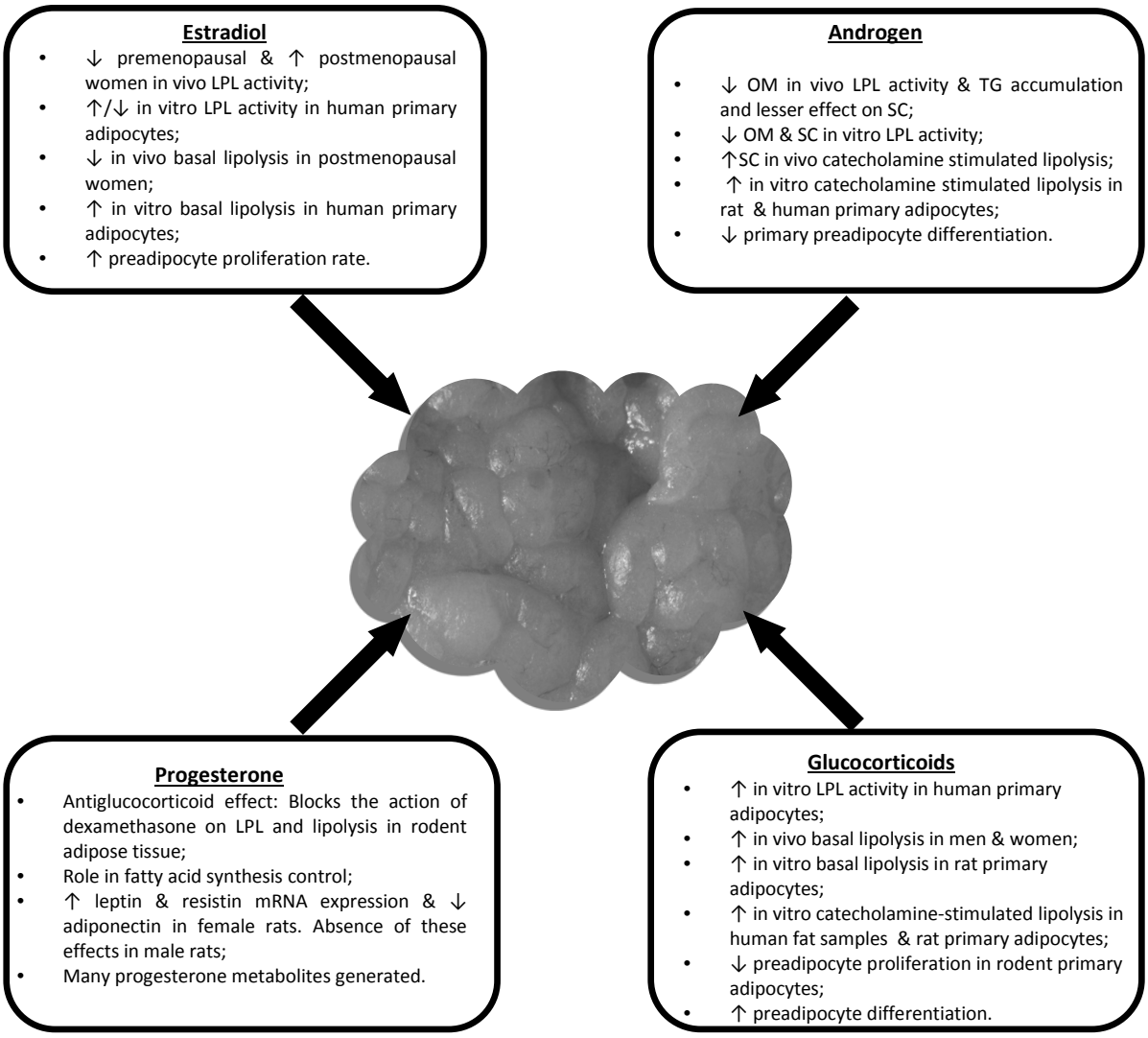
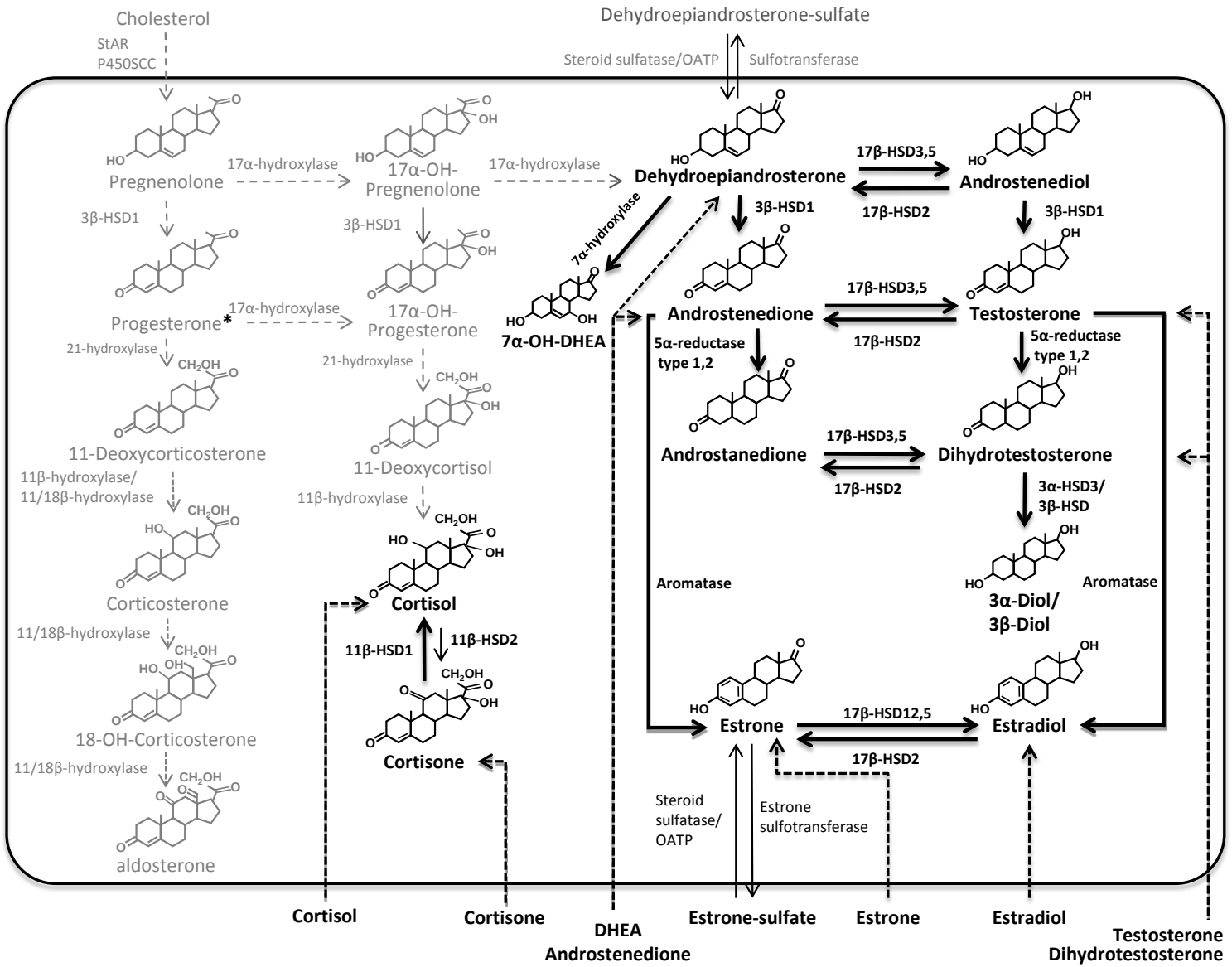

Estradiol
• ↓ premenopausal & ↑ postmenopausal women in vivo LPL activity;
• ↑/↓ in vitro LPL activity in human primary adipocytes;
• ↓ in vivo basal lipolysis in postmenopausal women;
• ↑ in vitro basal lipolysis in human primary adipocytes;
• ↑ preadipocyte proliferation rate.
Androgen
• ↓ OM in vivo LPL activity & TG accumulation and lesser effect on SC;
• ↓ OM & SC in vitro LPL activity;
• ↑SC in vivo catecholamine stimulated lipolysis;
• ↑ in vitro catecholamine stimulated lipolysis in rat & human primary adipocytes;
• ↓ primary preadipocyte differentiation.
Progesterone
• Antiglucocorticoid effect: Blocks the action of dexamethasone on LPL and lipolysis in rodent adipose tissue;
• Role in fatty acid synthesis control;
• ↑ leptin & resistin mRNA expression & ↓ adiponectin in female rats. Absence of these effects in male rats;
• Many progesterone metabolites generated.
Glucocorticoids
• ↑ in vitro LPL activity in human primary adipocytes;
• ↑ in vivo basal lipolysis in men & women;
• ↑ in vitro basal lipolysis in rat primary adipocytes;
• ↑ in vitro catecholamine-stimulated lipolysis in human fat samples & rat primary adipocytes;
• ↓ preadipocyte proliferation in rodent primary adipocytes;
• ↑ preadipocyte differentiation.

Figure 2:


Cholesterol
StAR
P450SCC
Pregnenolone
17α-hydroxylase
17α-OH-
Pregnenolone
3β-HSD1
Progesterone*
17α-hydroxylase
17α-OH-
Progesterone
21-hydroxylase
11-Deoxycorticosterone
21-hydroxylase
11-Deoxycortisol
11β-hydroxylase/
11/18β-hydroxylase
Corticosterone
11β-hydroxylase
Cortisol
11/18β-hydroxylase
18-OH-Corticosterone
11/18β-hydroxylase
aldosterone
11β-HSD1
11β-HSD2
Cortisone
Dehydroepiandrosterone-sulfate
Steroid sulfatase/OATP
Sulfotransferase
Dehydroepiandrosterone
7α-hydroxylase
7α-OH-DHEA
3β-HSD1
17β-HSD3,5
17β-HSD2
Androstenediol
Androstenedione
Testosterone
5α-reductase
type 1,2
Androstanedione
Dihydrotestosterone
3α-HSD3/
3β-HSD
3α-Diol/
3β-Diol
Aromatase
Estrone
17β-HSD12,5
Estradiol
Steroid
sulfatase/
OATP
Estrone
sulfotransferase
Cortisol
Cortisone
DHEA
Androstenedione
Estrone-sulfate
Estrone
Estradiol
Testosterone
Dihydrotestosterone