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The adipose tissue metabolism: role of testosterone and dehydroepiandrosterone

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Testosterone (T) and dehydroepiandrosterone (DHEA) are fat-reducing hormones, even though they exert this effect by different mechanisms. In particular, T inhibits lipid uptake and lipoprotein-lipase (LDL) activity in adipocytes, and stimulates lipolysis by increasing the number of lipolytic β-adrenergic receptors. An indirect sign of these effects is the decrease of adipocyte leptin production. Lastly, T inhibits differentiation of adipocyte precursor cells. Concerning DHEA, this hormone does not seen to have any of T effects; however, DHEA stimulates resting metabolic rate (RMR) and lipid oxidation, and enhances glucose disposal, by increasing the expression of GLUT-1 and GLUT-4 on fat cell plasma membrane. The insulin-like effect of DHEA would be associated to a decrease of plasma insulin concentrations and, thus, to an increase of the molar ratio between lipolytic hormones and insulin. Noteworthy, the fat-reducing effect of both T and DHEA seems to be more evident at the level of visceral adipose tissue.
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Testosterone

Experiments performed in a whole cell assay system demonstrated that mature adipocytes derived from male rat fat pad adipose precursor cells have specific receptors for androgens.[1] Unlike most hormones, fat cell exposure to testosterone, but not to dihydrotestosterone, induces an increase in the number of androgen receptors in a dose-dependent way.[1] This effect is mediated by protein synthesis, suggesting the formation of new receptors by testosterone.[1]

Hypogonadism is associated with a significant decrease of lipolytic response to catecholamines, while testosterone treatment normalizes this response and increases triglyceride turnover.[2] The lipolytic effect of testosterone is mediated by an increase in the β-adrenoceptors number, and of adenylate cyclase, protein-kinase A and hormone-sensitive lipase activity.[3–6] An indirect proof of the lipolytic effect of testosterone is represented by the experimental finding that the treatment of male rats with an anti-androgen (cyproterone acetate) decreases the ratio between triglyceride degradation and FFA re-esterification in the adipose tissue,[7] a metabolic short-circuit producing heat and, possibly, regulating body weight. In particular, cyproterone acetate administration induces a decrease of catecholamine-stimulated lipolysis, but it does not modify the activity of the fatty acid-esterifying enzymes.[7] It is interesting to note that the density of abdominal subcutaneous adipocyte α_2-adrenoceptors is higher in men than in women:[8] therefore, although the main effect of androgens is lipolytic, these hormones may also increase the number of antilipolytic adrenergic receptors. This hypothesis is confirmed by experiments performed on adipose tissue obtained from male hamsters.[9]Lipoprotein lipase (LPL) supplies the adipocytes with free fatty acids for intracellular esterification by hydrolyzing triglyceride-rich lipoproteins in the circulation,[10] and it has been suggested that the abnormal activity of the enzyme may be cause of obesity.[11] Incubation of human adipose tissue with testosterone inhibits the expression of LPL.[2] A study from Iverius and Brunzell in obese men demonstrated that abdominal and femoral LPL activity decreased 1 week after parenteral testosterone administration.[12] In contrast, an oral testosterone preparation administered four times daily for 6 weeks caused a significant suppression of abdominal, but not of femoral LPL activity.[13] Seemingly, chronic testosterone treatment of hypogonadic men has been shown to be responsible for a marked decrease of both LPL activity and FFA uptake in abdominal, but not in femoral subcutaneous fat.[14] Moreover, the inhibition of lipid uptake after testosterone administration is more apparent in visceral (retroperitoneal, omental) than in abdominal subcutaneous adipose tissue.[15] These results are in line with recent studies showing that androgen receptors have a higher density in visceral fat cells than in adipocytes isolated from subcutaneous fat.[16] A different regional

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effect of testosterone has also been shown in male rats.[17] At variance with the effects of testosterone, treatment with DHT has no significant effect on LPL activity and lipid uptake in adipose tissue, apart from the anatomical site.[14,15] The relationship between LPL activity and testosterone has been also explored by Ramirez *et al* in sedentary obese men at their usual weight.[18] In this study, both abdominal and femoral adipose tissue LPL activity showed a significant inverse correlation with plasma levels of bioavailable testosterone, which was retained as a predictor variable in a multiple regression model. Therefore, testosterone is a significant negative regulator of adipose tissue LPL activity in men. The testosterone effect on LPL activity may be different in skeletal muscle. In fact, in women, skeletal muscle LPL activity was found to correlate positively with plasma free testosterone and was proposed to reflect a direct regulation of skeletal muscle enzyme by testosterone.[12]

On the basis of all the above results one can conclude that men with lower free testosterone levels have lower lipolytic reponse to catecholamines and higher LPL activity in adipose tissue, and that these metabolic changes may contribute to the lower triglyceride turnover and body fat accumulation characterizing these patients. Interestingly, a strong negative association between leptin and free testosterone plasma levels has recently been shown in men, independently of the plasma levels of insulin and of other metabolic parameters.[19] Since leptin is a marker of adipose tissue accumulation,[20] these data seem to confirm that a progressive decrease of testosterone plasma levels is associated with a corresponding increase of body fat. These results are in line with recent findings of Wabitsch *et al*, who showed that testosterone can inhibit in a dose-dependent way the production and secretion of leptin in newly developed human adipocytes in primary culture obtained from obese children and adolescents.[21] Testosterone was also found to suppress leptin mRNA using the semiquantitative reverse transcriptase-PCR method.[21] All these findings may possibly explain higher serum leptin concentrations in females as compared with males.[20] How testosterone is able to exert the negative effect on leptin production is currently not clear. Apart from a direct effect of testosterone at the gene level, it is possible that this suppression is mediated by indirect mechanisms of action such as an increase of β-adrenoceptors and a stimulation of lipolysis and FFA release. In addition, fatty acids have been reported to decrease leptin expression.[22]

Together with the metabolic effects on adipose tissue, testosterone has been shown to influence fat cell growth potential. In fact, castration is associated with an enlargement of the epididymal and the perirenal fat depots. Lacasa *et al* recently investigated the effect of castration on the mitogen-activated protein kinase (MAP kinase) cascade, which plays a crucial role in the cell proliferation and differentiation.[23] Experiments performed in adipose precursor cells showed that castration is associated with a higher activity of MAP kinase in proliferating epididymal and perirenal preadipocytes, thus possibly explaining the increased proliferation of preadipocytes of these anatomical sites. Testosterone treatment did not modify this specific alteration, but it corrected the effects of castration on Raf-1, that is a kinase activating two MAP kinase kinases (MEKs), which in turn activate MAP kinase. James *et al* also demonstrated that testosterone administration inhibited the percentage of differentiating (significantly) and undifferentiating (not significantly) adipose precursor cells in the inguinal depot of rats ovariectomized in the peripubertal phase, with a concomitant increase in fibroblasts and decrease in adipocyte cell number.[24] By contrast, even though testosterone decreased the weight and the adipocyte number in the retroperitoneal fat depot, it had no effect on the preadipocyte pools in this anatomical site.[24] Thus testosterone may act in a tissue-specific manner to regulate fat cell growth potential in the femoral region in the female. Nilsson *et al* also demonstrated that neonatal testosterone imprinting of female rats (high dose of testosterone subcutaneously within 3 h after birth) is followed after 10 weeks by changes in adipose tissue distribution, with parametrial, retroperitoneal and inguinal adipose tissues showing a decrease of their weight, while mesenteric adipose tissue tends to increase.[25] A condition of peripheral insulin resistance was also found in these rats; however, all the changes occured without elevation of circulating testosterone.[25] Figure 1 summarizes the metabolic effects of testosterone on adipose tissue.

So far, the testosterone effect on lipolysis in men and in male rats has been described. However, the regulation of lipolysis in hyperandrogenic women affected by polycystic ovary syndrome (PCO) seems to be opposite to that shown in males. Ek *et al* examined the lipolytic responsiveness of abdominal subcutaneous adipocytes to adrenergic agonists and postreceptor acting agents in nonobese healthy

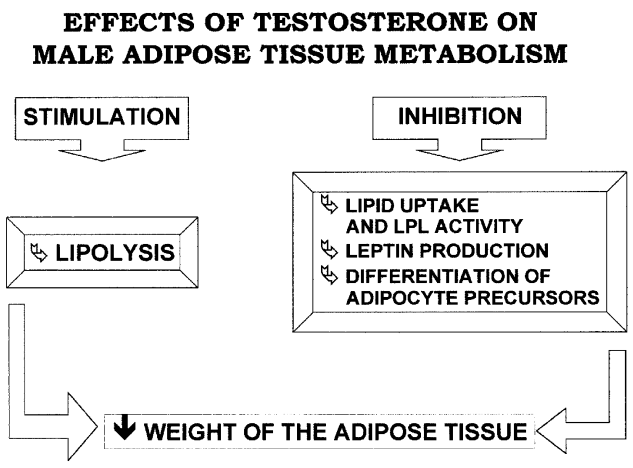

Figure 1 Effects of testosterone on male adipose tissue metabolism.

women and in women with PCO matched for BMI.[26] They found that women affected by PCO have lower lipolytic responsiveness to the agonists of β_1- and β_2-adrecoceptors, to the agonist of the adenylate cyclase catalytic unit and to the agonist of the protein-kinase–hormone-sensitive lipase complex, suggesting a defect at different levels in the lipolytic cascade. As for the number of β-adrecoceptors, they found a decrease of β_2- but not of β_1-adrecoceptor number. These lipolysis defects are identical to those observed in the insulin resistance syndrome and could be a primary pathogenic mechanism for the development of these disorders.

As for the influence of testosterone on insulin effects, adipocytes obtained from women affected by PCO have a condition of insulin resistance on both glucose transport and lipolysis. In fact, the EC5O, that is the insulin concentration needed to obtain the half-maximal effect on the glucose transport and on the inhibition of lipolysis is significantly higher in women affected by PCO than in the controls.[27] Rosenbaum *et al* also demonstrated that the insulin resistance on the glucose transport is strictly associated with a decreased expression of GLUT-4 glucose transporters in adipocytes.[28]

Dehydroepiandrosterone (DHEA)

A sex hormone whose metabolic effects arouses general interest is dehydroepiandrosterone (DHEA), a hormone intermediary in the testosterone- and estrogen-synthetizing pathway.

Plasma concentrations of DHEA are inversely related to age and decrease in association with the increased incidence of diabetes mellitus, obesity and atherosclerosis, and it has been hypothesized that the decline in DHEA levels with advancing age in humans may play a role in the development of visceral obesity and insulin resistance.

Plasma levels of this pro-androgen are significantly lower in morbid obesity,[29] and are inversely correlated with total body fat, the area of subcutaneous adipose tissue and, in particular, the area of visceral adipose tissue, all measured by computed tomography (CT).[30] These relationships might be the expression of a lower adrenal gland DHEA production and/or of a higher DHEA uptake in adipose tissue, as well as of a lipomobilizing effect of DHEA. The latter possibility seems to be demonstrated by a study by Nestler and coworkers, who showed that treatment with DHEA for 1 month induces a 30% decrease of body fat mass in normal men.[31] It is also known that DHEA administration inhibits body fat accumulation in young rodents,[32] whereas it decreases body fat and body weight in adult rats.[33] Hansen *et al* also demonstrated that feeding rats a diet providing 50% of the energy as fat for 4 weeks resulted in a two-fold greater visceral fat mass, but that rats fed high-fat diet plus 0.3% DHEA were largely protected against the increase in visceral fat.[34] Interestingly, these authors showed that the reduction in visceral fat accumulation mediates the protective effect of DHEA against development of muscle insulin resistance in rats on a high-fat diet.[34] The exact mechanism of DHEA is still unclear, but we know that its effects are not mediated by a reduction in caloric intake[32] or by an increase in basal and catecholamine-stimulated lipolysis.[35] However, it appears that DHEA prevents accumulation and/or storage of energy as body fat by increasing resting metabolic rate, at least in rodents, possibly via an increase in futile cycling[36] and/or an increased flux of fatty acids through the peroxisomal β-oxidation pathway.[37] In support of these possibilities, DHEA-treated rats have been reported to have a higher resting metabolic rate and heat production than untreated controls.[32] Hypothetically, the lipomobilizing effect of DHEA might also be due to the antagonistic action upon the effects of cortisol.[38]

Administration of DHEA to diabetic anomals ameliorates hyperglycemia, and this observation suggests that DHEA may exert a favorable effect on glucose homeostasis by directly regulating glucose disposal. Experiments performed in our laboratory demonstrated that the exposure of 3T3-L1 adipocytes to DHEA induces a significant increase of glucose uptake acutely and chronically.[39,40] The acute insulin-like effect of DHEA on glucose transport is not associated with a change in the total content of GLUT-1 and GLUT-4 in fat cells, with increased expression of GLUT-1 and GLUT-4 at the plasma membrane, as a consequence of GLUT-1 and GLUT-4 translocation from an intracellular compartment.[39] The effects of DHEA are not inhibited by a number of agents that block several steps involved in the insulin signaling pathway, including Wortmannin and LY294002, inhibitors of P13-kinase, Rapamycin, an inhibitor of PP70S6 kinase, and PD98059, an inhibitor of MAP kinase kinase, suggesting that the insulin-like effects of DHEA on glucose uptake are not mediated by the insulin signaling pathway. In

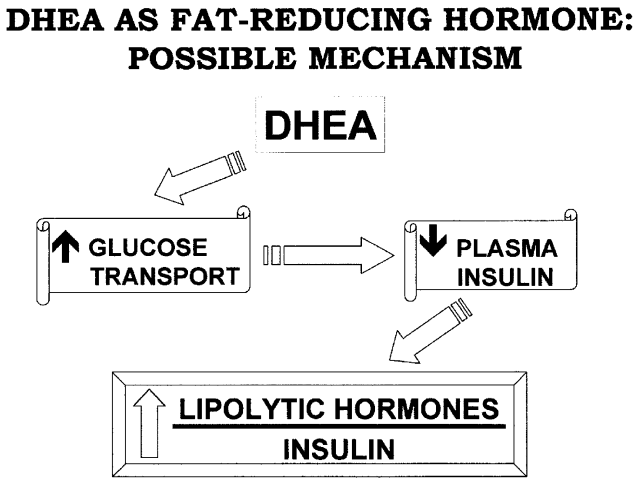

Figure 2 Dehydroepiandrosterone (DHEA) as fat-reducing hormone: possible mechanism.

contrast, the effects of DHEA on both the glucose transport and the translocation of GLUT-1 and GLUT-4 to the plasma membrane are abolished by GF1092203X, an inhibitor of protein kinase C (PKC), suggesting that the effects of DHEA are mediated by PKC (Giorgino F *et al*, unpublished data). Regarding the action of DHEA as a fat-reducing hormone, it is possible that this hormone reduces the peripheral requirement for insulin by increasing glucose disposal, and that the lower insulin levels are associated with a higher plasma ratio between lipolytic hormones and insulin, and a higher efficiency of lipolysis and loss of body fat (Figure 2).

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