Hormonal control of regional fat distribution

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Hormones exert powerful influences on body fat distribution in humans. Studies under fully controlled conditions *in vitro* have indicated that cortisol and insulin facilitate lipid accumulation by expressing lipoprotein lipase (LPL). Growth hormone (GH) abolishes this and turns metabolism towards lipid mobilization. Testosterone and GH inhibit LPL and stimulate lipolysis markedly. Cortisol effects are mediated via a glucocorticoid receptor, and testosterone effects via an androgen receptor, the density of which appears to be higher in visceral than subcutaneous adipose tissue. The receptor-mediated effects are probably expressed via transcription of appropriate genes. The female sex steroids also regulate adipose tissue metabolism, but apparently not directly in the absence of specific cellular receptors. Oestrogens seem to exert net effects similar to those of testosterone. These results of cellular studies agree well with in-vivo studies of triglyceride uptake and turnover in different adipose tissue regions. Furthermore, clinical entities with characteristic disturbances in hormone levels show the expected redistribution patterns.

Key words: cortisol/growth hormone/human adipose tissue/oestrogen/testosterone

Introduction

The regional fat distribution in humans is clearly regulated by hormones, although genetic factors also play important roles. Vague (1947) realized this aspect of fat distribution 50 years ago and described the difference between adipose tissue distribution in men and women. Not only sex steroid hormones are of importance, since adrenal corticosteroids also play a major role. This is seen clinically for example in Cushing's syndrome. In addition, peptide hormones such as insulin and growth hormone (GH) are important regulators of adipose tissue distribution, often on the basis of 'permissive' effects of the steroid hormones. In other words, steroid hormones provide a more long-term adaptation to permit the acute effects of peptide and catecholaminergic hormones.

In the following text, the effects of steroid hormones will be reviewed primarily. Furthermore, since adipose tissue metabolism is highly variable among species, human data will be assessed where possible, and animal research will be included only when human data are missing. First, the general effects of hormones on adipose tissue metabolism will be summarized, and then the regional specificity of endocrine action. This area has been reviewed repeatedly recently, and the reader is referred to these works for detailed references (Björntorp, 1991, 1993). Here a condensed updated version of these reviews is given.

In human adipose tissue the regulation of lipid accumulation at the level of the adipocyte is achieved mainly through the activity of lipoprotein lipase (LPL). The de-novo fatty acid synthesis from carbohydrate substrates is of considerably less quantitative importance. Lipid mobilization is regulated by the activity of the hormone-sensitive lipase, which is under the main, 'acute' control of catecholamines (stimulatory) and insulin (inhibitory) in human adipose tissue. There is also a possibility that under certain conditions an incomplete re-esterification of triglycerides may

contribute to the mobilization of fatty acids, but information on this process is scarce, probably due to methodological difficulties.

Cellular studies

Cortisol

Cortisol exerts major effects on adipose tissue metabolism, both on lipid accumulation and mobilization. In the presence of insulin, lipoprotein lipase (LPL) is markedly expressed. This expression is regulated by an interaction between transcription and a post-translational stabilizing effect (Ottosson *et al.*, 1994). If GH is added, this expression is totally inhibited via a post-transcriptional effect which has so far not been identified (Ottosson *et al.*, 1995b). In relation to lipid mobilization, the addition of cortisol in the presence of insulin exerts slightly inhibitory effects. When GH is also added, activity is shifted dramatically to a lipid mobilizing effect (M.Ottosson, unpublished).

These cortisol effects are mediated via a specific glucocorticoid receptor (GR), with a variable density in different regions of adipose tissue, in a ranking order of visceral > abdominal subcutaneous > femoral subcutaneous fat (Rebuffé-Scrive *et al.*, 1985, 1990; Ottosson *et al.*, 1995a).

In summary, cortisol in the presence of insulin exerts powerful lipid accumulating effects, and these are abolished by GH which inhibits lipid accumulation and also activates lipid mobilization. These effects are probably most pronounced in visceral adipose tissue due to its high density of glucocorticoid receptors (GR).

Testosterone

On the lipid accumulating side, testosterone exerts inhibitory effects on LPL and glycerophosphate dehydrogenase, which are accentuated in the presence of GH (Figure 1; Xu *et al.*, 1990b; Rebuffé-Scrive *et al.*, 1991). This effect also occurs in the presence of cortisol. In other words, testosterone inhibits the LPL-activating effects of cortisol (M.Ottosson, unpublished). Testosterone also regulates lipid mobilization in a powerful and multifacetted manner. Here testosterone and GH clearly have synergistic effects, since responses are much less pronounced with each of the hormones alone

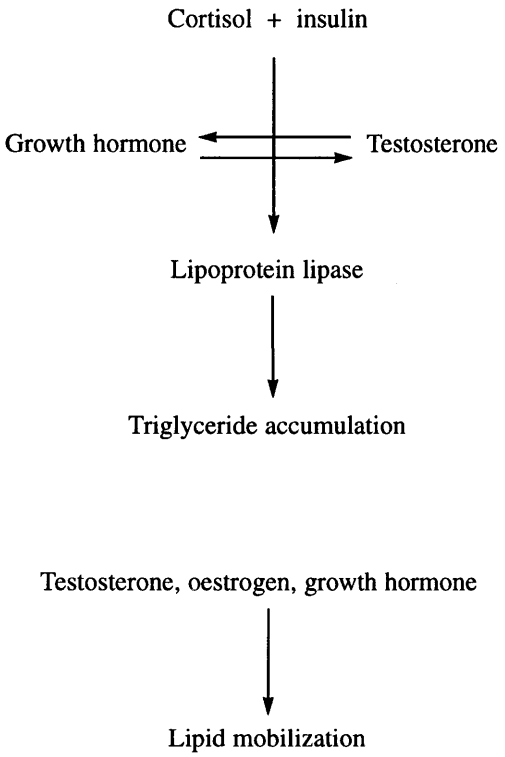

Figure 1. Overview of hormonal regulation of adipose tissue metabolism. Cortisol and insulin are the major lipid accumulating hormones. These effects are counteracted by sex steroid and growth hormones, which in addition facilitate lipid mobilization. These effects are more pronounced in visceral tissue than in other fat depots due to a higher density of steroid hormone receptor.

(Rebuffé-Scrive *et al.*, 1991). The regulatory steps affected seem to involve the lipolytic β-adrenergic receptors and the cyclase, together with the protein kinase and/or hormone sensitive lipase. G-proteins do not seem to be affected (Xu *et al.*, 1990b, 1991, 1993).

The transcriptional effects of appropriate genes are also expressed via a specific androgen receptor (AR) (De Pergola *et al.*, 1990b). This receptor is interesting because it is apparently autoregulated by its ligand testosterone, which seems to up-regulate the density of the AR (De Pergola *et al.*, 1990). In this way testosterone will amplify its own effects. The density of the androgen receptor is also apparently higher in visceral than subcutaneous adipose in the rat (Sjögren *et al.*, 1995), and there is indirect evidence that this is also the case in humans (Björntorp, 1991). By analogy with

cortisol, this would mean that androgen effects would be more pronounced in visceral than subcutaneous adipose tissues.

The summary above concerns the influence of testosterone on male adipose tissue. Female adipose tissue also contains an androgen receptor, apparently identical to that in males as judged from its specificity and affinity determinations (M.Li and P.Björntorp, unpublished). It seems, however, that the effects of testosterone on female adipose tissue may differ from those in males. Full substitution of the lipolytic machinery after oophorectomy can be achieved with oestrogen but not with testosterone (De Pergola *et al.*, 1990a). Furthermore, the androgren receptor seems to be down-regulated by oestrogen, suggesting that protection from androgen effects is provided by oestrogen (M.Li and P.Björntorp, unpublished). At the clinical experimental level, hyperandrogenic women tend to accumulate visceral fat (Rebuffé-Scrive *et al.*, 1989), a phenomenon also witnessed after testosterone treatment of transsexual women (Elbers *et al.*, 1995).

In summary, in male adipose tissue testosterone plus GH prevents lipid accumulation and stimulates lipid mobilization through an androgen receptor. The density of this receptor seems to be up-regulated by testosterone. This action is probably most pronounced in visceral fat where the androgen receptor density seems to be higher than in other regions. The net effect then would be to diminish the visceral fat depot mass, which has been detected clinically in men treated with testosterone (Mårin *et al.*, 1993), or with testosterone plus GH (Bengtsson *et al.*, 1993). The situation seems different in female adipose tissue where the net effects of testosterone seem to be the contrary, accumulation of visceral fat mass.

Oestrogen and progesterone

Studies of the cellular effects of these hormones have given inconclusive results (Figure 1). Direct effects in cell culture systems have not been demonstrated, and we have found no evidence for the presence of physiologically significant numbers of specific receptors in human adipose tissue (Rebuffé-Scrive and Björntorp, 1985; Brönnegård *et al.*, 1994). Nevertheless, systemic administration, particularly of oestrogen, no doubt exerts effects on metabolism (Rebuffé-Scrive *et al.*, 1986), and distribution (Haarbo *et al.*, 1991) of adipose tissue. These observations suggest that indirect effects of these hormones occur in women, perhaps via an interference with the growth hormone secretion (Rebuffé-Scrive *et al.*, 1985; Xu *et al.*, 1990c), regulation of AR density (M.Li and P.Björntorp, unpublished), or any other mechanisms.

In-vivo studies

The studies referred to above have mainly been performed in fully controlled cell culture systems. Such studies do not take into account the fully integrated conditions in adipose tissue *in situ* with its blood flow and nerve supply, which are important determinants for the net effects of hormones on adipose tissue.

An integrated approach can be studied by the administration of labelled lipid, given orally, followed by uptake and turn-over analyses and serial adipose tissue biopsies in different regions. These analyses may then also be verified by mass changes as a results of hormonal interventions, determined precisely with computerized tomography (CT) scans.

Cortisol

The label administration and turn-over method has not been applied to test the effects of cortisol. However, Cushing's syndrome, with an excess of cortisol, clearly involves enlarged visceral fat masses, normalized by successful treatment (Lönn *et al.*, 1994).

Testosterone

In normal men, the uptake of lipid occurs in the order visceral > abdominal subcutaneous > femoral subcutaneous adipose tissues, and turn-over is proportional to this rank order in the steady state (Mårin *et al.*, 1996). Upon administration of testosterone to slightly hypogonadal men, this difference is exaggerated (Mårin *et al.*, 1995, 1996). Furthermore, the substitution of testosterone (Mårin *et al.*, 1993) and of GH to totally GH-deficient men (Bengtsson *et al.*, 1993) induces a specific diminution of visceral fat mass.

Oestrogen and progesterone

No data are as yet available for these steroids using the labelling method. However, when postmenopausal women are substituted with oestrogen their metabolic profile of adipose tissue regions become similar to that of pre-menopausal women, a picture facilitating lipid accumulation in the sex-specific gluteo–femoral depot (Rebuffé-Scrive *et al.*, 1986). Furthermore, with replacement therapy, the tendency to accumulate visceral fat at the menopause is prevented (Haarbo *et al.*, 1991). In summary, it seems therefore, that as far as visceral fat is concerned, oestrogen appears to exert similar effects to testosterone in men, i.e. it decreases visceral fat mass. This is apparently also a regional specific effect on femoral subcutaneous adipose tissue which accumulates lipid. The effects of progesterone alone have not been tested in these systems.

Clinical studies

The cellular and experimental studies referred to above are in agreement with the following integrated picture. Cortisol, in the presence of insulin, favours lipid accumulation in visceral depots. Testosterone and oestrogen have opposite effects. This opposition seems to be amplified by GH.

How does this fit with observations at the clinical level? We see that cortisol and insulin are coupled to lead to visceral fat accumulation while sex-specific steroid hormones in the presence of GH exert opposite effects. In fact, it seems likely that the balance between these two groups of opposing hormones actually determines the net outcome of body fat distribution to subcutaneous and visceral fat masses. This is illustrated by the following review of certain clinical conditions.

Cushing's disease (high cortisol and insulin, low testosterone, oestrogen and GH) accumulates visceral fat, reversible by successful treatment. Ageing is often followed by low testosterone, oestrogen and GH but normal cortisol and insulin secretion, and visceral fat accumulation is a logical consequence. In the polycystic ovary syndrome, cortisol and insulin are elevated, and visceral fat accumulation seems to occur in spite of elevated androgens. Smoking and alcohol are also characterized by larger than normal visceral depots, probably a consequence of a combination of elevated cortisol and low sex-specific steroid hormone secretions. Finally, visceral obesity is characterized by elevated cortisol and insulin levels, and low sex steroid and GH secretions, which then probably provides a background to the elevation of visceral fat masses (for references, see Björntorp, 1993).

In summary, these clinical observations are in excellent agreement with the findings from studies at the cellular, experimental and interventional levels, indicating that the cortisol plus insulin couple directs storage fat to visceral depots, while the sex-specific steroid hormones and GH have opposite effects. The androgen effects on female adipose tissue are, however, unclear.

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