

OBESITY AND THE ADIPOCYTE

Neuroendocrine factors in obesity

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A number of endocrine morbidities are known in human obesity. Most of these are more pronounced in central, visceral obesity than peripheral, gluteo-femoral obesity. There is evidence that several of these perturbations originate in their central regulation of secretion. This, in turn, suggests a central, neuroendocrine origin.

A central, perhaps primary, lesion of endocrine malfunction in human visceral obesity seems to be a hypersensitivity and/or hyperresponsiveness of the hypothalamo-pituitary-adrenal (HPA) axis. Other endocrine abnormalities in visceral obesity including diminished secretions of sex steroid and growth hormones may be derived from the perturbation of the HPA axis, because both corticotropin releasing hormone (CRH) and cortisol are known to inhibit the gonadal and growth hormone axes (Chrousos & Gold 1992). Furthermore, increased secretions of androgens in visceral-obese women might be a consequence of HPA hyperactivity, stimulating adrenal secretion of these hormones (for review see Björntorp 1993).

Consequently, the HPA axis hyperactivity may be of primary importance for the other endocrine abnormalities of visceral obesity, and its origin therefore becomes of interest. Maximal stimulation of the adrenals (adrenocorticotropin) (Mårin *et al.* 1992) and the pituitary (CRH) (Pasquali *et al.* 1996), results in elevated activity of the distal parts of the HPA axis in women. This has so far not been examined to the same extent in men, and gender differences may well exist. The HPA axis is controlled by central glucocorticoid receptors (GR) via a negative feedback mechanism. This GR function is apparently mildly insufficient in men (Ljung *et al.* 1996) (not yet examined in women), and seen also in peripheral GR function in adipose tissue (M Ottoson, T Ljung, B Gdón, P Mårin, S Edén & P Björntorp, unpublished observations). The explanation might be either a functional down-regulation of GR due to HPA hyperactivity, or a polymorphism at the level of the coding sequence of the GR gene. The regulation of GR expression is also a possible explanation of the abnormalities found and is currently under investigation.

The results of maximal stimulation of the adrenals and the pituitary cannot reveal potential abnormalities in the

sensitivity of the receptors involved. This is, however, the case with central challenges of the HPA axis by laboratory stress tests which provide submaximal stimuli. Such experiments have revealed a hypersensitivity in both women and men (Mårin *et al.* 1992, M Rebuffé-Scrive, personal communication), resulting in elevated cortisol secretion. It is therefore possible that the origin of the HPA axis abnormality resides in the sensitivity of central 'stress' centers, eliciting HPA axis hyperactivity with subsequent down-regulation of GR functions. Genetic susceptibility is most likely involved, GR density regulation being only one of several potential possibilities for genetic influences.

The net peripheral consequences of HPA hyperactivity will then be a multiple endocrine disturbance including, periodically, abnormally increased cortisol secretion following impacts of stressful situations, and low sex steroid and growth hormone secretions. The androgen secretion from the adrenals is probably also elevated in parallel with cortisol. In men this is most likely of minor importance because of the dominance of testicular production of testosterone, but in women the hyperandrogenism characteristic of abdominal obesity might well be of adrenal origin.

This multiple endocrine perturbation is probably followed by peripheral consequences. In adipose tissue, cortisol in the presence of insulin increases the pathways for lipid accumulation, and inhibits those of lipid mobilisation, with a net effect of triglyceride retention. Both sex steroids and growth hormone exert opposite, balancing effects. Elevated cortisol and insulin as well as low sex steroid and growth hormone secretions will then result in an efficient accumulation of triglycerides in adipose tissue. Since visceral adipose tissue contains a higher density of specific steroid hormone receptors, these effects will be more pronounced here than in other adipose tissue regions.

This conclusion, based on the results of detailed cellular and molecular studies, is strongly supported by clinical observations and intervention studies. Dysbalance between the lipid accumulating hormones, cortisol and insulin, and the lipid mobilising group of hormones, growth and sex steroid hormones, are seen in several conditions with visceral fat accumulation. These include Cushing's

syndrome (high cortisol and insulin, low sex steroids and growth hormone), menopause or ageing (low sex steroids and growth hormone), excess alcohol intake (periodically elevated cortisol, low sex steroids), smoking (periodically elevated cortisol), total growth hormone deficiency (low growth hormone), as well as depression and anxiety (elevated cortisol). Interventions aiming at correcting these abnormalities are followed by specific diminution, or even normalisation of visceral fat contents. This statement is based on successful treatment of Cushing's syndrome, sex steroid replacement therapy to ageing and/or visceral-obese men or menopausal women, and administration of growth hormone in a physiologically correct manner quantitatively and qualitatively to either totally growth hormone-deficient, or visceral-obese subjects. Taken together, this evidence strongly supports the contention that the endocrine perturbations seen in visceral obesity are actually causing the disproportional accumulation of visceral fat mass (for detailed references see review in Björntorp 1996).

Another consequence of the endocrine perturbations is probably to at least contribute to the pathogenesis of insulin resistance. Cortisol clearly has this effect. The sex steroid hormones are also regulating insulin sensitivity, and the optimal levels seem to be those within a normal, gender-specific window. When above this window, such as in men taking an excess of anabolic steroids, in transsexual women given testosterone, or women with visceral obesity and elevated androgens, insulin resistance follows. Similarly, insulin resistance is seen when men and women are below the window, such as in visceral obesity. Growth hormone is conventionally regarded as a hormone creating insulin resistance. This is true when the concentrations are elevated. However, when present in physiologically correct concentrations and with its gender-specific secretion pattern, this might not be true. Totally or partially growth hormone-deficient subjects (after hypophysectomy or visceral obesity respectively) are insulin resistant. When substituted correctly, this is improved. These observations strongly suggest that the endocrine perturbations following visceral obesity may in fact, at least partly, be responsible for the insulin resistance of this syndrome. It seems likely that insulin resistance is amplified by an abundance of circulating free fatty acids, originating from enlarged, central depots which are sensitive to stimulating hormones and relatively insensitive to the inhibitory, controlling effect of insulin. This interpretation is based on results of studies from the cellular and molecular levels to clinical and intervention observations (for review see Björntorp 1993) and is summarised in Fig. 1.

Factors stimulating the regulatory centers of the HPA axis have been revealed, and include alcohol over-consumption, smoking and traits of depression and anxiety (Björntorp 1993). It may be speculated that socio-economic and psychosocial handicaps found in subjects

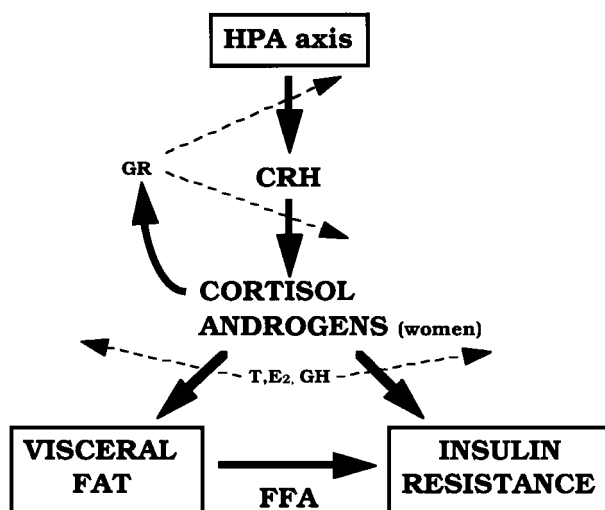


Figure 1 Origin and consequences of an increased activity of the hypothalamo-pituitary-adrenal (HPA) axis in visceral obesity. An increased HPA activity of central origin is amplified by deficient controlling activity by central glucocorticoid receptors (GR). The consequences will be elevated cortisol secretion from the adrenals, redistributing depot fat to visceral adipose tissue and creating insulin resistance, amplified by free fatty acids (FFA). The controlling effects of testosterone (T), estrogen (E₂) and growth hormone (GH) on both visceral fat accumulation and insulin sensitivity are diminished due to inhibited secretions, another consequence of hyperactivity of the HPA axis (for reviews see Björntorp 1993, 1996).

with central distribution of body fat might provide a basis for a cortisol-generating, 'depressive', stress reaction which acts in concert with the abuse and the psychiatric traits in sensitising the HPA axis. This contention is strongly supported by results in other primates (monkeys) where mild psychosocial stress results in HPA axis activation, down-regulation of central GR function, and sex steroid secretions, as well as visceral accumulation of body fat with associated metabolic perturbations and early signs of coronary atherosclerosis, insulin resistance and glucose intolerance (Jayo *et al.* 1993). These results provide considerable support to our interpretation that psychosocial and socio-economic stress factors are involved in the human syndrome, since the controlled studies in another primate show that stress followed by a depressive reaction produce an identical syndrome to that which we have observed in humans.

Since the endocrine abnormalities, particularly those of the HPA axis, are of central pathogenetic importance, one might rightfully wonder whether they are of primary origin or a consequence of visceral obesity. If the interpretations of the consequences of the endocrine perturbations described above are correct, both alternatives would lead to visceral obesity with its consequences. With the second alternative, the endocrine abnormalities caused by the positive energy balance, the excess fat would be

directed to visceral depots, and insulin resistance would be created because of the abnormal hormonal secretions. An interesting pathogenetic mechanism along this line would be excess energy intake, perhaps with a dominance of fat, combined with alcohol intake. The latter is known to activate the HPA axis (Cicero 1980), and would therefore direct excess fat to visceral depots and create insulin resistance. Consequences of fat feeding might also be of importance. This is an eating and drinking pattern which is not infrequent, particularly in middle-aged men, and may well, in addition, be combined with smoking and stress.

In summary, the current status of our working hypothesis is that sensitivity to central 'stress' stimuli, alcohol, smoking and psychiatric traits are pathogenetic factors in the central visceral distribution of body fat. The impact and sensitivity of such factors are probably different depending on personality factors and genes, and may be expressed as a sensitisation of the HPA axis. Interestingly, this sensitisation may explain, not only other endocrine abnormalities in visceral obesity, but also the typical central redistribution of body fat and associated risk factors for prevalent disease. The endocrine perturbations might be primary, but equally they could be secondary to eating and drinking habits. Genetic factors are probably involved at several levels, but have so far not been extensively examined. Our approach to this problem is first to try to reveal the phylogenetic expression of the condition of

visceral obesity, and secondly to examine indicated candidate genes.

References

- Björntorp P 1993 Visceral obesity: a 'civilization syndrome'. *Obesity Research* **1** 206–222.
- Björntorp P 1996 The regulation of adipose tissue distribution in humans. *International Journal of Obesity* **20** 291–302.
- Chrousos G & Gold P 1992 The concept of stress and stress system disorders. *Journal of the American Medical Association* **267** 1244–1252.
- Cicero TJ 1980 Sex differences in the effects of alcohol and other psychoactive drugs on endocrine function. In *Research Advances in Alcohol and Drug Problems*, pp 544–593. Eds Y Israel, O Kalant & H Kalant. New York: Plenum.
- Jayo J, Shively C, Kaplan J & Manuck S 1993 Effects of exercise and stress on body fat distribution in male *Cynomolgus* monkeys. *International Journal of Obesity* **17** 597–604.
- Ljung T, Andersson B, Björntorp P & Mörin P 1996 Inhibition of cortisol secretion by dexamethasone in relation to body fat distribution: a dose–response study. *Obesity Research* **4** 277–282.
- Mårin P, Darin N, Amemiya T, Andersson B, Jern S & Björntorp P 1992 Cortisol secretion in relation to body fat distribution in obese premenopausal women. *Metabolism* **41** 882–886.
- Pasquali R, Anconetani B, Chattat R, Biscotti M, Spinucci G, Casimirri F, Vicennati V, Carcello A & Labate AMM 1996 Hypothalamic–pituitary–adrenal axis activity and its relationship to the autonomic nervous system in women with visceral and subcutaneous obesity: effects of the corticotropin-releasing factor/arginine–vasopressin test and of stress. *Metabolism* **45** 351–356.