The fat controller: obesity and leptin

Sudesh Kumar MD MRCP, Consultant Physician and Senior Lecturer in Medicine Birmingham Heartlands Hospital and University of Birmingham

The fat society

Obesity is stigmatised in modern society and often seen as a result of sloth and overeating. Nevertheless, it is becoming more prevalent today, with about half the adult population in the UK overweight to a clinically significant degree. This has serious consequences for the health of the population, as the risk of a number of diseases increases substantially with obesity (Table 1). In addition, there are major social and psychological effects of obesity for the individual and his/her family. The economic burden of obesity and associated diseases is staggering: in the US, it accounts for an estimated US$69 billion per year in health care costs. In the UK, it has been estimated that about £80 million is spent annually by individuals on meal replacement slimming products alone. The UK Government in its consultative document, The health of the nation, proposed a target for the reduction of obesity: the number of obese men and women is to be reduced to no more than 6% and 8%, respectively, by the year 2005. Sadly, at the present time, we do not appear to have the means to achieve this.

Most major therapeutic advances have followed the synthesis of a new chemical substance or the discovery of a new protein. There was, therefore, a great deal of excitement and anticipation following the report of the cloning of the leptin gene in 1994\(^2\). The discovery of leptin has revitalised interest in research into the pathophysiology of obesity, and has provided a major impetus for efforts to develop better, more effective treatment.

Pathogenesis of obesity

Clearly, it is easier to treat a disorder if its pathophysiology is understood. At first sight, the pathophysiology of obesity appears to be simple: people are eating too much! Indeed, it is true that, ultimately, obesity results from an imbalance between energy intake and expenditure over many years. What is remarkable, however, is the degree of accuracy with which body weight is regulated by matching energy intake and expenditure. This is why, despite today’s calorie-rich environment, most individuals manage to remain non-obese. On a day-to-day basis, the ‘error’ between energy intake and expenditure is minuscule in comparison to the total calorie intake, but over a period of time this ‘error’ can build up to cause significant weight gain. One extra sandwich (about 150 kcal) a day over one year could account for a weight gain of as much as eight kilograms! Furthermore, a number of studies have shown that genetic factors are a significant determinant of the degree of obesity in man, with an estimated 25–40% of body weight attributable to genetic factors alone. The heritability of abdominal

Table 1. Some conditions for which obesity is a recognised risk factor.

- Diabetes mellitus type 2
- Hypertension
- Ischaemic heart disease
- Stroke
- Dyslipidaemia
- Sleep apnoea
- Osteoarthritis
- Cancer (colon, breast, endometrial)
- Skin infections
- Deep vein thrombosis
- Pulmonary embolism
- Gout
- Gallstones, fatty liver, cirrhosis
- Polycystic ovary disease
obesity appears to be even greater. The physiological mechanisms involved in such tight regulation of body weight have until recently been only poorly understood.

Leptin in health and disease

It was hypothesised for many years that there must be a 'satiety' signal of some sort, probably secreted by adipocytes, to regulate appetite. Over 20 years ago, parabiosis experiments involving obese mice (ob/ob) and mice with a normal phenotype suggested that a circulating 'satiety' factor in the latter was able to reverse the abnormalities seen in ob/ob mice. Diabetic mice (db/db) appeared to be resistant to this factor. Using the positional cloning technique, Friedman and his team cloned the leptin (Greek leptos = lean) gene and its human homologue in 1994.

Leptin deficiency

Leptin is a 167 amino acid peptide produced in men exclusively by adipose tissue, but in women also produced by the placenta. In the leptin deficient ob/ob mouse model of obesity, which is due to a mutation of the leptin gene, administration of leptin leads to weight loss. Leptin acts here as a satiety signal to the ventro-medial hypothalamus, where it regulates a number of neurotransmitters that alter appetite. Many of the major effects of leptin may be accounted for by its effects on neuropeptide Y (NPY). NPY normally stimulates feeding and is inhibited by leptin. Circulating leptin binds to its receptor, of which there appear to be at least six isoforms including a short non-signalling form and a 'long' isoform that is abundantly expressed in the hypothalamus. The receptor has a long extracellular domain, a short transmembrane domain and a short intracellular domain that has two JAK-2 binding sites. JAK belongs to the tyrosine kinase family and leads to phosphorylation of STAT (signal transducers and activators of transcription) proteins. Two rodent models of obesity result from mutations in the leptin receptor:

- the db/db mouse, which is hyperleptinaemic and diabetic, and
- its rat homologue, the fatty Zucker fa/fa rat.

Leptin has many other effects besides regulating body fat mass. It also regulates the thyroid, reproductive and glucocorticoid endocrine systems. A signal of the nutritional status of the individual may have been of great importance during evolution. It would be clearly disadvantageous to reproduce when food is in short supply. Periods of famine are associated with a fall in adipose tissue mass and leptin levels, leading to downregulation of the reproductive and thyroid axis (Fig 1).

Leptin resistance

The finding that leptin concentration in humans correlates with the degree of obesity dashed hopes that human obesity could be cured with leptin. Leptin concentration does not rise acutely with feeding, and it is not a short-term 'satiety' factor in humans. In contrast, the level falls rapidly during starvation, and it is likely that the role of leptin is to protect against starvation rather than to prevent obesity. Evolutionary pressure has always been to try to conserve weight rather than to limit weight gain.

A number of studies have attempted to look at whether leptin gene mutations account for human obesity. A leptin gene mutation with absolute leptin deficiency found in two cousins with massive childhood onset obesity shows that this mechanism for obesity is relevant to man — but for common obesity this is the exception rather than the rule. The correlation of leptin concentrations in man with the degree of obesity led to the concept of 'leptin resistance'. In this respect, human obesity appeared to resemble more the db/db mouse model, and a number of attempts have been made to detect leptin receptor gene mutations in human obesity. So far, only one family with obesity due to a leptin receptor mutation has been found (P Froguel; personal communication). Leptin receptor mutations are therefore unlikely to be a common cause for human obesity.

Leptin and regional obesity

The distribution of body fat has a major impact on the complications of being overweight. Visceral obesity appears to be particularly deleterious to health. Visceral fat has different functional properties, including a greater lipolytic response to catecholamines and

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**Key Points**

- Body weight is tightly regulated by a number of endocrine mechanisms that control both appetite and energy expenditure.
- Obesity is a complex heterogeneous disease which results ultimately from excessive food intake in relation to energy expenditure.
- Genetic and environmental factors both appear to be important in the pathogenesis of common obesity.
- Leptin is secreted by adipocytes, and interacts with receptors in the hypothalamus to reduce appetite and increase energy expenditure.
- Human obesity is associated with high serum leptin concentrations, suggesting leptin resistance rather than leptin deficiency.
- Leptin may also limit weight gain by its effects on peripheral tissues.
- High circulating leptin concentrations in obesity may cause insulin resistance by inhibiting insulin signalling.
The development of obesity. Finally, the finding that leptin receptors are widely expressed in the body has led to the investigation of the peripheral effects of leptin. It has been suggested that leptin may induce insulin resistance by inhibiting glucose uptake in insulin sensitive tissues in man. Epidemiological evidence suggests that hyperleptinaemia clusters with other features of the metabolic syndrome including visceral obesity.

Obesity is therefore a complex heterogeneous disease arising from an interaction between genetic and environmental factors, including social, cultural and psychological factors. Absolute leptin deficiency and leptin receptor mutations are exceptionally rare causes of human obesity. Most common forms probably result from a complex interaction between leptin deficiency and leptin resistance, possibly also with dysregulation of the glucocorticoid and insulin axis. In this respect, there are similarities with diabetes mellitus type 2 in which there is a complex interplay between relative insulin deficiency and insulin resistance.

Treatment of obesity: the way forward

Doctors regularly treat diabetes, dyslipidaemia, chest problems, arthritis and heart disease, but few attempt to address the underlying problem of obesity, at least in part due to a reluctance to regard obesity as a disease. Obesity is a disease that needs lifelong treatment.

There is apparently a simple solution for obesity: persuade the patient to eat less and exercise more! Yet diet and

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**Figure 1.** Leptin produced by fat cells influences energy intake and output through its action on hypothalamic mechanisms. In the fed state, high leptin reduces energy intake by reducing appetite through its effect on neuropeptide Y, and increases energy expenditure by promoting the release of catecholamines for the pituitary, adrenal and thyroid glands. In the fasting state, low leptin levels are associated with increased appetite, the release of anabolic hormones and suppression of catecholamines (HPA = hypothalamic-pituitary-adrenocortical).

**Table 2. Some of the benefits of a 10% intentional weight loss.**

| Benefit                        | Benefit                  |
|--------------------------------|--------------------------|
| Blood pressure                 | Fall of 10 mmHg systolic, 20 mmHg diastolic |
| Lipids                         | 10% reduction in total cholesterol, 30% in serum triglyceride |
| Diabetes                       | 30–50% reduction in fasting glucose |
| Angina                         | 33% improvement in exercise tolerance |
| Mortality                      | 20–25% fall |
exercise programmes are largely seen as ineffective. This scepticism is reflected in Stunkard's comment that:

most obese people won't enter treatment, most who do won't lose weight, and most who do will regain it.

At the present time, therefore, clinicians may feel that their therapeutic nihilism is justified. It seems unlikely that it will be possible to alter the calorie-rich environment in which we live today, so better treatment strategies will have to be devised based on our new understanding of the biology of obesity. In the meantime, it is worth noting that massive weight loss does not have to be achieved to realise significant health benefits. As little as 10% weight loss may be all that is required to achieve major benefits (Table 2), although this may not be true for those with massive obesity with body mass index in excess of 45 kg/m².

The future of obesity treatment looks promising. Following the discovery of leptin, the pharmaceutical industry has been investing substantially in obesity projects. Clinical trials of leptin in human obesity are in progress, together with efforts to make smaller synthetic analogues of leptin and NPY antagonists. The recent cloning of the genes for uncoupling proteins, UCP2 and UCP3, may shed additional light on the regulation of energy expenditure in man. If these diverse efforts result in the development of an effective treatment for obesity, they are sure to have a major impact on clinical medicine.

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Endocrine hypertension

Stephen J Geland BSc MRCGP, British Heart Foundation Junior Research Fellow
John M C Connell MD FRCP, Professor of Endocrinology
Lancaster University Department of Medicine and Therapeutics, Western Infirmary, Glasgow

Hypertension is a feature of a number of endocrine disorders, including acromegaly, Cushing's syndrome and thyroid disease, in several of which, such as phaeochromocytoma, hypertension is the presenting feature of the condition. Overall, endocrine causes of high blood pressure are relatively rare (estimates vary from 1-3%), although there is evidence (discussed below) that primary aldosteronism may be much more frequent than initially suspected. The importance of endocrine causes of hypertension is twofold:

1 The identification of an endocrine cause of hypertension often leads to cure of high blood pressure, and in some situations a life-threatening disorder (such as phaeochromocytoma) may be corrected.

2 The study of endocrine forms of hypertension has elucidated important aspects of endocrine physiology and pathophysiology. Perhaps the best example of this is the appreciation of the importance of local steroid metabolism (such as cortisol oxidation) in the regulation of access of steroid hormones to glucocorticoid and mineralocorticoid receptors in the kidney and elsewhere.

This brief review will consider the major forms of endocrine hypertension encountered in clinical practice.

Corticosteroids and hypertension

Glucocorticoids

Glucocorticoid excess causes hypertension in humans and experimental animals (see Ref 2 for review). In man, the principal glucocorticoid is cortisol, which acts at specific receptors in a wide range of target tissues. Cortisol excess due to Cushing's syndrome is associated with hypertension in over 50% of cases (Fig 1). This is also a feature of iatrogenic glucocorticoid excess with the use of synthetic hormones such as prednisolone and dexamethasone.

The cause of glucocorticoid-induced hypertension remains uncertain. Cortisol excess causes acute renal sodium retention, but long-term glucocorticoid hypertension (eg in Cushing's syndrome) is not typically associated either with suppression of plasma renin or with hypokalaemia, both of which would be expected in sodium-dependent forms of hypertension. An exception is ectopic adrenocorticotropic hormone (ACTH) syndrome in