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Leptin – a slimmer’s dream that crashed?

Abstract

The hopes of millions of obese persons were raised in 1994 when the fat-melting hormone leptin was discovered by Friedman and colleagues. Primary experiments on the adipose-tissue-derived hormone leptin seemed very promising and gave new life to obesity research. Drug companies also weathered profit and the human version of leptin was licensed to the biotech firm Amgen Inc. for an initial fee of \$20 million.

But is leptin the drug obese individuals have long waited for or is it just an illusion? This review will try to summarise current data on the role of leptin in body weight regulation.

Keywords: obesity, weight reduction, leptin receptor, reproduction, hypothalamus

Historical background

The idea that the adipose tissue itself participates in the regulation of energy balance is not new. Although obesity is a rapidly increasing problem all over the world (1), most individuals maintain a relatively constant body weight over time (2). This indicates a balance between energy intake and expenditure in order to keep the energy balance at a steady state. In 1953, Kennedy proposed that circulating signals, generated in proportion to the amount of body fat, act on the brain to alter food intake (3). Five years later, Hervey showed that lean rats starved to death when their circulatory systems were surgically joined to rats rendered obese by a lesion of the ventromedial hypothalamus (4). It was suggested that the lean animals starved due to exposure to a factor overproduced in the obese rats. A decade later, Coleman and colleagues provided evidence that such circulating signals exist (5, 6). The circulatory systems of genetically severely obese mice of two different strains (ob/ob or db/db) were surgically joined to those of wild-type animals and to each other. These studies showed that the ob/ob mice lacked a blood-borne anorexic factor, whereas the db/db mice were resistant to the effect of the anorexic factor, suggesting that the db gene encoded the receptor for the anorexic factor. However, it was not until 1994 that Zhang and co-workers (7) cloned the obese (ob) gene and thereby identified the anorexic factor that was absent in the ob/ob mice. The factor was called leptin from the Greek word leptos meaning thin and is a 16 kDa protein mainly produced by adipocytes. Blood levels of leptin and leptin expression reflect the amount of body fat during steady state conditions in man and rodents, where high levels of leptin are associated with high amounts of body fat (8, 9). Studies in mice suggest that leptin

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acts as an afferent signal in a feedback loop (Figure 1) from the adipose tissue to the hypothalamus in the regulation of energy balance (10, 11) .

Besides body fat mass, variations in leptin expression and blood levels are influenced by a variety of factors, including sex (12) , hormonal stimulation, nutritional status, the sympathetic nervous system (13) and adipose tissue distribution (14, 15) . At the same body mass index, women have higher leptin concentrations than men (16) . The reason for this is not clear and both the larger amount of body fat mass, predominantly subcutaneous fat, in women and the influence of sex steroids (17, 18) on leptin levels have been suggested. Leptin levels are also affected by changes in nutritional status and it has been shown that short-term energy restriction leads to a large decrease in blood leptin concentration despite a relatively small weight loss (19) . The opposite effect on leptin occurs during positive energy balance, when a smaller increase in body weight results in a large increase in serum leptin (20) . It has therefore been suggested that circulating leptin levels during non-steady state energy balance reflect the ongoing triacylglycerol synthesis or glucose uptake by adipocytes rather than actual energy stores (19, 20) .

Leptin receptors Leptin exerts its effects via the leptin receptor (Figure 2), which is a member of the cytokine receptor superfamily (21) . Several leptin receptor isoforms exist and the isoforms differ in the length of the intracellular domain (21-23) . The long leptin receptor is predominantly expressed in the hypothalamus and is considered to be the principal signalling isoform, in line with studies on other members of the cytokine receptor superfamily that have shown that both boxes 1 and 2 are required for efficient signal transduction (24) . The short isoforms are widely expressed and they are thought to mediate some signalling, although the significance of this signalling for leptin biology in vivo is unknown (25, 26) . One receptor isoform that lacks the intracellular and transmembrane domains has been identified and this isoform may constitute a soluble receptor (23) . This is consistent with other members of the cytokine receptor superfamily where secreted extracellular domains of the receptors act as specific binding proteins (27) .

Leptin action on the hypothalamus The hypothalamus is regarded as the main control centre of energy balance (28) and the long leptin receptor

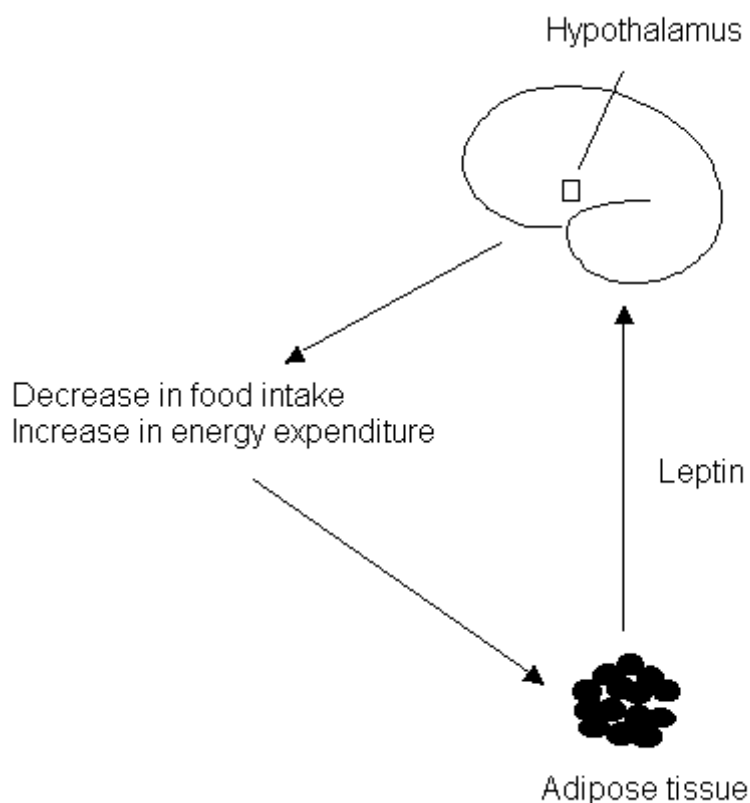


Figure 1. Leptin is secreted by the adipocytes and postulated to act in an endocrine fashion by reporting the size of the adipose tissue mass to hypothalamic leptin receptors. In rodents, high levels of leptin in the blood, indicating high amounts of body fat, reduce the body weight by decreasing food intake and increasing energy consumption. Conversely, low blood leptin levels, indicating small energy stores, increase food intake and decrease energy expenditure.

isoform is expressed there. Leptin has been suggested to pass the blood-brain barrier through a saturable transport system, postulated to be the short form of the leptin receptor, which is highly expressed in the choroid plexus (21) and on capillary endothelia throughout the brain (29, 30). Co-localisation of the long leptin receptor isoform and neuropeptide Y (NPY) has been demonstrated in the arcuate nucleus in the hypothalamus, which suggests that leptin exerts at least part of its effects via NPY neurones (31). NPY participates in the hypothalamic regulation of reproduction and energy homeostasis (32). It exerts a stimulatory effect on food intake and reduces energy expenditure, and leptin has been shown to inhibit NPY effects (33). Elimination of NPY did not completely reverse the ob/ob phenotype, however, indicating that other neuropeptides are involved in the hypothalamic response to leptin (34, 35).

A variety of neuroendocrine signals are suggested to be regulated by leptin (36, 37), indicating that leptin interacts with a multiplicity of neuroendocrine targets.

Leptin and body weight regulation

Both leptin deficiency (ob/ob mice) and leptin resistance (db/db mice) result in severe obesity and infertility in rodents. Administration of recombinant leptin to the ob/ob mice reduced their body weight by reducing their food intake and increasing their energy expenditure (10, 11, 38). Also, their fertility was restored (39), which strongly suggests leptin as a feedback signal in the control of energy balance and reproduction. A role for leptin deficiency in human obesity has been considered, but mutations in the ob gene have only been found in a few obese humans (40, 41). The first report on leptin deficiency concerned two severely obese children from a highly consanguineous pedigree (42). These children had a normal weight at birth but gained weight rapidly postnatally, indicating that leptin also plays a role in the regulation of energy balance in man. At the age of 8 years, the girl weighed 86 kg and had 57% body fat, compared to the reference range 15-25%, and her 2-year-old boy cousin weighed 29 kg with 54% body fat (42). Treatment with recombinant human leptin was tested in the girl at the age of 9 and within two weeks she started to lose weight. After 1 year of treatment the amount of body fat had decreased by 15.6 kg, accounting for 95% of the total weight loss (43). Her eating habits changed dramatically and the marked hyperphagia and constant hunger disappeared. No clear impairment of energy expenditure, as observed in ob/ob mice, was seen in the leptin-deficient children. The phenotype of adult patients with a homozygous mutation in the ob gene suggests that leptin is also necessary for the initiation of human puberty, as leptin-deficient adults exhibit clinical features of hypogonadism (44). Also, a mutation in the human leptin receptor leading to early-onset obesity and delayed pubertal development has been identi-

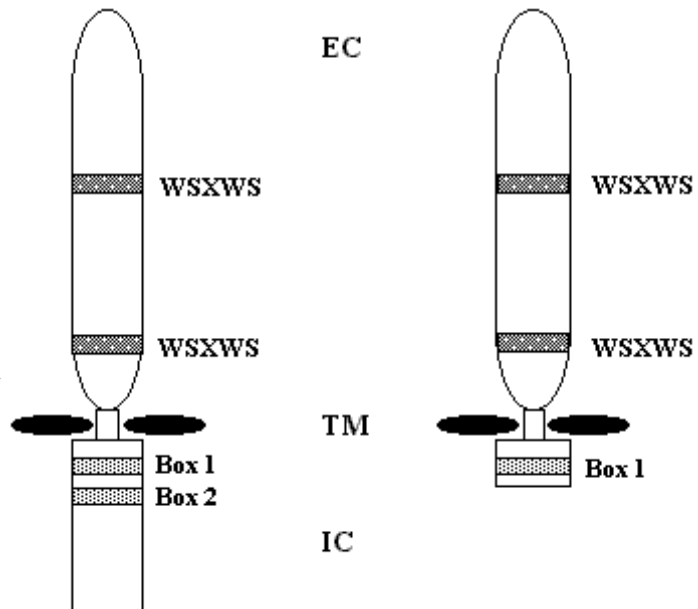


Figure 2. Schematic illustration of the long (left) and short (right) leptin receptor isoforms. The long leptin receptor isoform contains both boxes 1 and 2 and is considered to be the principle signalling isoform. WSXWS (Trp-Ser-X-Trp-Ser) is a sequence motif highly conserved in the cytokine receptor superfamily. EC, extracellular; TM, transmembrane; IC, intracellular.

fied (45) but, as for the leptin gene, these mutations are rare (46, 47) .

The first clinical trial of leptin administration in lean and obese humans with no known defects in the *ob* or leptin receptor genes has been performed. The study showed that subcutaneous injections of recombinant leptin resulted in weight loss in some individuals. In the responders, fat loss accounted for more than 95% of the weight loss (48) . However, statistically significant differences between placebo and leptin groups were only noted in obese subjects given the two highest leptin doses (49) . Recombinant leptin seems to have an acceptable short-term safety, although local reactions at the injection sites occurred in a majority of the included subjects, causing some of the participants to drop out (48) . A considerable variability in the individual response to leptin administration was noted, but on average weight loss increased with increased leptin dose. Mean weight changes after 24 weeks of leptin administration to obese subjects ranged from -0.7 kg for the lowest leptin dose to -7.1 kg for the highest dose. At the same time, controls, given no drugs, had lost 1.3 kg (48) . For a subset of patients, leptin treatment therefore seems suitable and an interesting task is to identify what factors made some individuals more responsive than others to leptin (49) . About 5% of the obese population can be regarded as relatively leptin deficient as they have decreased leptin production relative to the amount of body fat and this small subpopulation might benefit from leptin treatment (20) . Leptin treatment is also useful as substitution therapy during rare conditions with leptin deficiency. Additionally, leptin treatment to increase the compliance with a hypocaloric diet and as an aid to maintain an achieved lower amount of body fat mass is theoretically plausible. However, the role of leptin as an anti-obesity drug is today questionable and the possibility of using a leptin receptor agonist in obesity treatment is considered.

Although the word leptin implies that its primary function is to provide a signal to suppress body fat mass, its main function may be the opposite. Serum leptin levels change more during weight loss than during weight gain (50) . Therefore, the leptin system might have guaranteed survival during evolution, since low leptin levels, indicating a low energy reservoir or starvation, would stimulate hyperphagia, increase food intake, decrease energy expenditure (in rodents) and impair fertility to protect women from the increased metabolic demands during pregnancy (50) .

Additional effects of leptin

It is known today that leptin interacts with a wide range of organs, suggesting additional effects of the hormone besides the regulation of energy balance. For example, leptin has been shown to be involved in reproduction, foetal growth, immune or proinflammatory responses, nutrient intestinal absorption, angiogenesis and lipolysis (51) . In addition, leptin seems to be involved in the pathogenesis of some obesity-associated conditions, such as anovulatory infertility (52) and non-insulin-dependent diabetes mellitus (53) .

The rapidly increasing prevalence of overweight and obesity underscores the importance of understanding the molecular mechanisms behind the

regulation of energy balance and obesity-associated conditions in order to facilitate prevention and development of efficient treatment strategies. Although the discovery of leptin was not the slimmer's dream millions of obese persons hoped, it has nevertheless brought new life to the field of obesity research and it has provided new insights into the role of adipose tissue in the regulation of a wide range of biological processes.

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