Leptin and the Regulation of Body Weight

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Abstract
The discovery of leptin has led to the elucidation of a robust physiologic system that maintains fat stores at a relatively constant level. Leptin is a peptide hormone secreted by adipose tissue in proportion to its mass. This hormone circulates in blood and acts on the hypothalamus to regulate food intake and energy expenditure. When fat mass falls, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. By such a mechanism total energy stores are stably maintained within a relatively narrow range.

Recessive mutations in the leptin gene are associated with massive obesity in mice and some humans. Treatment with recombinant leptin markedly reduces food intake and body weight. The low leptin levels in patients with leptin mutations are also associated with multiple abnormalities including infertility, diabetes and immune abnormalities all of which are corrected by leptin treatment. These findings have established important links between energy stores and many other physiologic systems and led to the use of leptin as a treatment for an increasing number of other human conditions including a subset of obesity, some forms of diabetes including lipodystrophy and hypothyroidism, amenorrhea, the cessation of menstruation seen in extremely thin women. Identification of a physiologic system that controls energy balance establishes a biologic basis for obesity and further establishes links between leptin and numerous other physiologic responses.

Keywords: Obesity, leptin, diabetes, infertility, homeostasis.

Introduction
A large body of clinical and animal data has indicated that food intake and body weight are under homeostatic control. The elements of this physiologic system were unknown but parabiosis studies had suggested that the ob gene encoded a hormone that regulated body weight and the db gene encoded its receptor. ob and db are fully penetrant recessive mutations that cause massive obesity in mice. The introduction of a methodology that enabled the cloning of mutant genes based solely on a detailed knowledge of their position on a genetic map (positional cloning) provided a means for identifying the ob and db genes and for formally testing the aforementioned hypothesis.

Results
In 1994 the ob gene was identified by positional cloning as an ~ 4.5 kb RNA that was expressed exclusively in adipose tissue. This RNA encoded a predicted 167–amino acid polypeptide with a signal sequence, which indicated that it was secreted and likely to circulate in plasma. The gene is disrupted in the 2 available alleles of ob in the original C57Bl/6J ob/ob mutation, a nonsense mutation disrupts protein function leading to a secondary increase in the RNA, whereas in the second cisogenic ob 2j mutation, a retroviral
insertion abrogates expression of the coding sequence altogether.\textsuperscript{4,5}

The available data suggested the hypothesis that this polypeptide, now known as leptin, derived from the Greek root leptos, meaning ‘thin’, functioned as the afferent signal in a negative feedback loop that maintained stability of adipose tissue mass.\textsuperscript{3,4,6,7} If true, the following criteria had to be satisfied: leptin should circulate in plasma, its concentrations should change proportionately with increases or decreases of fat mass, and the recombinant protein should reduce food intake and body weight in lean and ob but not db mice. Finally, the db gene should encode the receptor for leptin and be localized in the hypothalamus (and possibly elsewhere).

All these criteria have indeed been satisfied. Leptin circulates in the plasma of all mammals tested including humans and rodents as an ~16 kD protein with a single disulfide bond that is required for bioactivity.\textsuperscript{4} Leptin levels increase with accretion of adipose tissue mass and decrease when adipose mass is lost.\textsuperscript{8} Injections or infusions of leptin reduce food intake and body weight of wild type and ob mice but have no effect on db mice.\textsuperscript{4,6,7,9}

The leptin receptor was identified biochemically and shown to be a cytokine family receptor that is expressed broadly.\textsuperscript{10} It was subsequently shown that leptin receptor RNA was alternatively spliced and that only one of the splice variants, referred to as ObRb (also known as LepR-I) was mutant in C57Bl/Ks db/db mice. These mutant mice show an identical phenotype to animals with null mutations of the leptin receptor or leptin itself.\textsuperscript{11,12} This genetic evidence established the critical importance of this receptor isoform in leptin signaling.

ObRb is the only receptor isoform that expresses all the protein motifs required for cytokine receptor signaling. More importantly, while the other receptor isoforms were expressed broadly, ObRb was highly enriched in the hypothalamus in precisely those nuclei that alter body weight when lesioned.\textsuperscript{11,13} These data thus suggested that leptin acted directly on the hypothalamus to regulate food intake and body weight. Consistent with a CNS site of action, infusions of low dose leptin centrally replicate all the effects of peripheral leptin even at intracerebroventricular doses that do not alter plasma leptin levels.\textsuperscript{4} It is now known the leptin receptor also signals at other CNS sites outside the hypothalamus and that its expression at these sites contributes to the broad panoply of leptin’s effects.

**Discussion**

In aggregate, these data establish that leptin is a novel hormonal signal in a negative feedback loop that maintains homeostatic control of adipose tissue mass by modulating the activity of neural circuits that regulate food intake and energy expenditure (Fig. 1). These conclusions are important not only because key elements of the homeostatic system regulating weight were identified but also because the identification of leptin and its receptor confirmed the existence of a homeostatic system, the existence of which was often debated. Although centuries of earlier work dating to Antoine Lavoisier suggested that energy balance in living organisms was likely to be under homeostatic control, at the time that leptin was identified this hypothesis had become controversial in part because of the intrinsic difficulty of identifying its molecular elements. In the decades leading up to the identification of leptin, the absence of definitive evidence confirming the existence of a physiologic system regulating energy balance in the form of the molecules that compose it left a void that was filled by innumerable, largely incorrect theories about how or even if weight was regulated biologically.

Leptin mutations in human are associated with massive obesity that is remediable by leptin treatment.\textsuperscript{14} While leptin mutations are rare, the demonstration of a profound phenotype in these patients confirms the role of this hormone in human physiology. Note, the low incidence of leptin mutations is similar to that observed for other key hormones such as insulin; a complete loss of hormone function is
often catastrophic in an evolutionary context (for example, leptin deficient humans and animals are infertile and leptin deficient animals are likely to be more susceptible to predation) and thus strongly selected against.

Most obese patients however do not have leptin mutations. Plasma leptin levels in human are highly correlated with adipose tissue mass and most obese patients have high leptin levels. The presence of a high endogenous hormone level in the absence of an evident hormone effect (in this instance, leanness) suggests that there is resistance to that hormone. Thus, the initial data indicating that endogenous leptin levels are elevated in animal and human obesity suggested that obesity is most often the result of leptin resistance and that the response of obese subjects to exogenous leptin was likely to be variable.

Leptin’s efficacy was first shown to be variable in rodents with different obese strains showing a spectrum of leptin sensitivity; leptin deficient ob/ob mice are the most leptin sensitive and animals with leptin receptor mutations being the most resistant. Animals with diet induced obesity induced by a cafeteria or highly palatable diet, often a reliable predictor of responses in human, showed a partial response to leptin administration.

A similar variability in the response to leptin has been seen in obese humans. Thus while a statistically significant effect of leptin to reduce weight was observed in a small cohort of obese patients, only a subset of obese humans (~ 1/3) showed a clinically significant degree of weight loss on leptin therapy (personal communication, Alex DePaoli). These data indicated that the utility of leptin as
a monotherapy for the treatment of obesity was likely to limited to a subset of patients. At a given body mass index or percent fat, there is substantial variability of leptin and ~ 10-15% of obese subjects have endogenous levels of leptin that are indistinguishable from lean patients. The demonstration that leptin can have potent weight reducing effects in some patients with low leptin levels in other settings such as lipodystrophy and HA, see above, has suggested leptin may be efficacious in obese patients with low plasma leptin levels. While leptin has been shown to have potent weight reducing effects in obese animals with low leptin levels, this possibility has not been directly tested in humans.

Recently, the hormone amylin has also been shown to ameliorate leptin resistance though the molecular mechanism has not been fully established. Amylin is a peptide hormone secreted from pancreatic β-cells that has a number of effects to reduce plasma glucose that are synergistic with insulin. The combination of leptin and amylin resulted in stable ~13% weight loss in a cohort of obese patients.

The identification of human mutations that cause obesity, including leptin, its receptor and other factors including the MC4 Receptor and TrkB, and that a combination of leptin and amylin, two natural products can reduce body weight requires that we modify the explanation that is often invoked to explain the pathogenesis of obesity, ‘The obese eat too much and exercise too little’. Although this is undoubtedly true, the deeper question is, ‘Why do the obese eat more and exercise less?’ The answer appears to be less about the conscious choices that the obese make and more about their biologic makeup. The identification of leptin and other components in a physiologic system that maintains energy balance has established that feeding is at its core a basic biologic drive analogous to thirst, breathing and reproduction. Although one can consciously override the basic drive to eat over the short term and lose weight, over time this basic drive to eat dominates. There are innumerable instances in each of our common experience when basic drives overwhelm a conscious desire. The world would be a fairer place if the people who are inclined to deride the obese kept this in mind.

References


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