COMMEMORATIVE LECTURE

Leptin and the Regulation of Body Weight

Jeffrey M. Friedman

Rockefeller University, New York, USA

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The cloning of the *ob* gene and its gene product, 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. Recessive mutations in the *leptin* gene are associated with massive obesity in mice and humans, establishing a genetic basis for obesity. Leptin circulates in blood and acts on the brain 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. This system maintains homeostatic control of adipose tissue mass. The discovery of leptin has advanced our understanding of metabolic disease in a number of respects. Its identification has revealed a new endocrine system regulating body weight. This system provides a means by which changes in nutritional state regulate other physiologic systems. A number of leptin deficiency syndromes that are treatable with leptin replacement have been identified. The majority of obese subjects are leptin resistant, which establishes that obesity is the result of hormone resistance. Leptin treatment results in weight loss in a subset of obese patients and can also synergize with other anti-obesity agents to reduce weight in the general population. Leptin provides an entry point for studying a complex human behavior. Finally, this research has established that there is a powerful biological basis for obesity, a fact that is (correctly) changing public perception about the pathogenesis of this medical condition. (Keio J Med 60 (1) : 1–9, March 2011)

Introduction

The *ob* gene was cloned in 1994 using the methodology of positional cloning. Leptin, the protein encoded by the *ob* gene, was identified in 1995 and shown to be a hormonal signal that regulates energy balance.[1–4] Since its discovery 15 years ago, 30,943 articles on leptin have been written (S Korres, personal communication, 2009), providing an opportunity to assess, with some hindsight, the impact of this research. What follows is a summary of the conclusions that have emerged from this and subsequent research.

Historical Background

The first law of thermodynamics applies similarly to inanimate and biological systems. Because weight is remarkably stable in animals and humans over long periods of time, especially when taking into account the large number of calories that are consumed, the elaboration of this principle by the Prussian surgeon Hermann von Helmholtz, and others, suggested that organisms would need a means for maintaining constancy of energy stores by regulating energy balance (food intake vs. energy expenditure).[5] A precise balance between energy intake and energy expenditure has been noted in humans over as little as a 2-week time frame, which proved to be long enough to average out day-to-day fluctuations in intake.[6] This stability is also observed in experimental settings in which the body weight of animals that were either overfed or starved returned to that of a control group once food intake returned to normal.[2,7–11] Finally, when animals are fed nutrients in varying dilutions, they adjust their intake to maintain constancy of the number

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Reprint requests to: Jeffrey M. Friedman, MD, PhD, The Rockefeller University, 1230 York avenue, New York, NY 10065, USA, E-mail: friedj@mail.rockefeller.edu

of calories that are consumed, not the volume.[12] In each case, it appeared that the animal had sensed a change in its body weight and in turn adjusted its recent food intake to return weight to control levels.

In aggregate, these data were interpreted to mean that there must be a biologic system that regulated food intake and maintained homeostatic control of body weight.[12] This premise was articulated often during the first half of the 20th century and was further advanced by the demonstration that body weight could be altered, in either direction, by introducing specific lesions in the hypothalamus, with lesions of the ventromedial hypothalamus causing obesity and those of the lateral hypothalamus causing leanness.[13] It was thus suggested that brain centers in the hypothalamus receive peripheral signals that reflect an organism's nutritional state as part of a feedback loop(s) that maintains homeostatic control of body weight.[14,15]

The key question concerned the identity of these putative signals. It was proposed that glucose, fat and protein stores were in some way sensed, as were core temperature, recent food intake and other variables.[14,15] Kennedy first proposed the possibility that one of these signals might be derived from adipose tissue, although neither the nature of this factor nor the mechanism by which it acted was clear. Kennedy[16] and later Hervey[17] invoked a mechanism whereby a fat-derived factor, perhaps a steroid hormone that increased appetite, was partitioned in both the adipose tissue and aqueous compartments and was diluted as adipose mass increased. That this factor might be hormonal was first suggested by data from parabiosis (cross circulation) experiments between obese, ventromedial hypothalamic (VMH)-lesioned and control rats.[18] The observation that the normal rats paired to those with a VMH lesion ate less and lost weight suggested that the lesioned rats overproduced an appetite-suppressing factor secondary to a lesion at its site of action (i.e., the hypothalamus). Although the existence of this factor could be inferred from this and other similar studies, the intrinsic difficulty of implementing a biochemical purification using a behavioral assay of feeding behavior impeded successful efforts to identify it. In retrospect, with the identification of this factor as leptin, it is clear how challenging such a purification would be, even using modern methods, because of the requirement for chronic dosing of leptin to elicit an anorectic effect. A biochemical approach for identifying endogenous appetite suppressants is also complicated by frequent false positives that arise because many compounds exert aversive effects to nonspecifically reduce appetite.

A clue to the identity of this circulating factor was provided by parabiosis experiments pairing genetically obese *ob/ob* and *db/db* mice to wild-type mice, or to each other; *ob* and *db* are recessive mouse mutations that cause massive obesity as a result of profound hyperphagia and reduced energy expenditure. In addition, both mutants manifest a pleiotropic set of numerous other physiologic abnormalities (see below).[19] The phenotypes of both mutations are strikingly similar, which suggested that the encoded genes might function in the same physiologic pathway. The results from the parabiosis experiments were consistent with this possibility and further suggested that the *ob* gene encoded a circulating factor that suppressed food intake and body weight and that the *db* gene encoded its receptor. The aforementioned studies using the parabiotic union of mice with lesions of the ventromedial hypothalamus to normal rats further suggested that this receptor was localized in the hypothalamus. In aggregate, these studies were consistent with the parsimonious hypothesis that a circulating factor produced in adipose tissue and encoded by the *ob* gene acted on a receptor in the hypothalamus that was encoded by the *db* locus.

These studies thus suggested that food intake and body weight–or, more precisely, adipose tissue mass–were regulated by an endocrine system and provided a strong impetus for the cloning of the *ob* and *db* genes.

The Cloning of the *ob* Gene and Identification of Leptin Has Uncovered a New Endocrine System Regulating Body Weight

The development of positional cloning, a methodology that enabled the cloning of mutant genes based solely on a detailed knowledge of their position on a genetic map, provided a means for identifying the *ob* and *db* genes. In 1994 the *ob* gene was identified as an approximately 4.5-kb RNA that was expressed exclusively in adipose tissue (**Fig. 1**).[1]

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 two available alleles of *ob* in the original C57/Bl6J *ob/ob* mutation, a nonsense mutation disrupts protein function leading to a secondary increase in the RNA, whereas in the second coisogenic *ob* 2j mutation, a retroviral insertion abrogates expression of the coding sequence altogether.[2,20]

The available data suggested the hypothesis that the polypeptide encoded by the *ob* gene, 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.[1–4] 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 in *db* mice. Finally, the *db* gene should encode the receptor for leptin and be localized in the hypothalamus (and possibly elsewhere).

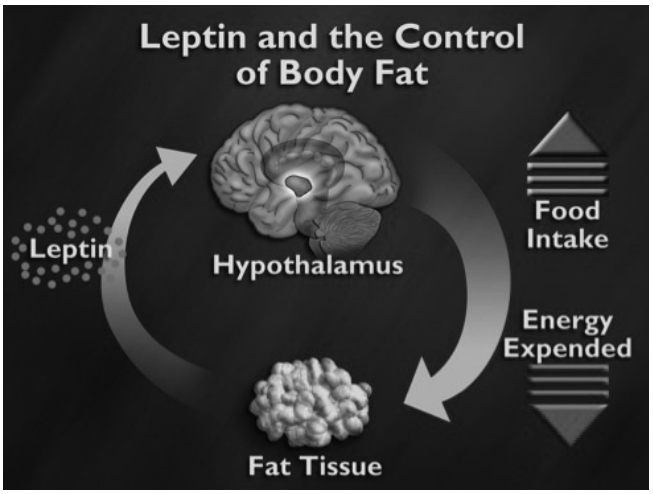

Fig. 1 Leptin is a hormonal signal that maintain homeostatic control and adipose tissue mass.

Leptin circulates in the plasma of all mammals tested, including humans and rodents, as an approximately 16-kDa protein with a single disulfide bond that is required for bioactivity.[2] Leptin levels increase with accretion of adipose tissue mass and decrease when adipose mass is lost.[21] Injections or infusions of leptin reduce food intake and body weight of wild type and *ob* mice but have no effect on *db* mice.[2–4,22] The failure of recombinant leptin to alter food intake or weight in *db* mice established specificity of the effect by excluding the possibility that the protein reduced weight as a result of an aversive or "toxic" effect that made animals feel sick.[2]

The leptin receptor was identified biochemically and shown to be a cytokine family receptor that is expressed broadly.[23] 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-l or LepRb), was mutant in C57Bl/Ks *db/db* mice.[24,25] These mutant mice show an identical phenotype to animals with null mutations of the leptin receptor or leptin itself.[24,25] 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.[24,26] 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.[2] It is now known that the leptin receptor also signals at other CNS sites outside the hypothalamus, including reward centers in the nucleus accumbens, and that its expression at these other brain sites contributes to the broad panoply of leptin's effects (see below). There is compelling evidence that leptin also acts directly on cells of the immune system, but the importance of possible direct effects of leptin on other peripheral cell types is less clear.[27,28] The critical role of leptin's actions directly in the CNS have been established with the findings that a brain-specific knockout of the leptin receptor causes obesity similar to that of *db/db* mice and brain-specific expression of a LepRb transgene can suppress the obesity of *db* mice.[29,30]

In aggregate, these data established 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, energy expenditure and metabolism. 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 very existence of a homeostatic system that many believed did not exist at all.

Changes in Nutritional State Regulate Other Physiologic Systems

Leptin-deficient *ob* mice develop a complex phenotype that includes abnormalities in most, perhaps all, physiologic systems.[31] These pervasive abnormalities are distinct from those typically manifest in human obesity. In retrospect, it has been appreciated that all of the abnormalities of massively obese *ob/ob* mice (paradoxically) resemble those that normally develop during starvation of normal animals and humans. This apparent paradox can be most easily understood if one considers the normal response to starvation. With weight loss, fat mass is lost and leptin levels fall.[21] This low leptin level

is sensed and induces a state of positive energy balance by increasing appetitive behavior and also by reducing energy expenditure as part of a biologic response aimed at restoring fat mass. This same starvation signal (i.e., low leptin) also modulates the function of other biologic systems that are elements of the adaptive response to starvation. These responses include, but are not limited to, cessation of female ovulation, reduced immune function, a decrement in insulin signaling, alterations of hemostasis, and the development of a euthyroid sick state.[27,32,33] A role for leptin in ovulation was consistent with the suggestion by Rose Frisch that an adipose tissue-derived factor was required to develop and maintain reproductive capacity in females, see below.[34]

In the absence of leptin production as a result of a genetic mutation, leptin-deficient animals and humans live in a state of perceived starvation. In this state, the absence of leptin not only increases food intake but also triggers additional biologic responses that reduce energy expenditure as a means to conserve adipose tissue mass. Despite the fact that leptin-deficient individuals become obese, the absence of leptin prevents the generation of a leptin-mediated signal that would otherwise suppress a set of physiologic responses act to conserve energy when nutrient is limiting. Thus by down-regulating metabolism, thyroid function, immune function and suppressing menstruation, energy is conserved.

In normal animals and humans, this response is active only in the starved state after plasma levels fall. A key result in support of this conclusion was provided by studying fasted animals coincident with injections of recombinant leptin.[32] In this experiment, leptin was able to suppress the effect of starvation on ovulation, thyroid function and other neuroendocrine responses. Analogous studies have also shown that recombinant leptin can also suppress the immune abnormalities that develop in fasted animals.[27]

In humans, the role of low leptin in inducing this set of alterations has been confirmed by demonstration of the beneficial effect of leptin treatment in a number of states of leptin deficiency. Overall, these human and animal data identify adipose tissue as a bona fide endocrine organ and further confirm that leptin plays a key role in the adaptive response to starvation by modulating the function of other physiologic systems. It is widely accepted that changes in nutritional state alter the function of other physiologic systems and it is now clear that leptin is a key means by which the change in nutritional state is communicated.

Many Leptin Deficiency Syndromes are Treatable with Leptin Replacement

Leptin mutations in humans are associated with massive obesity that is remediable by leptin treatment.[35] While leptin mutations are rare, the demonstration of a profound phenotype in these patients confirms the role of this hormone in human physiology. Note that 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.

Leptin-deficient patients, as mentioned above, also show a set of abnormalities in other physiologic systems and these too are remediated by leptin treatment.[35,36] The realization that leptin deficiency is associated with alterations in the function of other organ systems suggested the possibility that low leptin levels associated with other pathological conditions might also have pathologic consequences that would be ameliorated by leptin replacement therapy. Several such conditions have been identified, the first of which was lipodystrophy.

Lipodystrophy (LD) is a heterogeneous disorder that is associated with the absence or a profound reduction in adipose tissue mass.[37] Lipodystrophy can be complete or partial and is often the result of mutations in genes normally required for adipose tissue development. Lipodystrophy can also be acquired as a result of (presumed) immune alterations or more recently in chronic HIV patients.[38,39] Indeed a substantial number of HIV patients, generally those on HAART triple therapy, develop lipodystrophy with metabolic abnormalities severe enough to require medical treatment.

In this condition, the reduction of adipose tissue mass (whatever the cause) results in the secondary deposition of lipid in other organs, in particular the liver, and a severe, often intractable insulin resistance develops. Because of the reduced adipose tissue mass, leptin levels are pathologically low in lipodystrophic patients. The contribution of the low leptin level to the consequences of this disease has been clearly established by the profound effect of leptin treatment to correct the hepatic steatosis and insulin resistance in patients with this condition.[37,40,41] The response to leptin therapy was most pronounced in patients with complete lipodystrophy, but beneficial effects were also evident in some patients with partial and HIV lipodystrophy. Finally, leptin also ameliorated the neuroendocrine abnormalities that develop in LD patients despite the fact that a significant loss of adipose tissue mass was observed.[37] This finding and an analogous finding in patients with hypothalamic amenorrhea (see below) uncouple the normal relationship between fat mass and the response to starvation and thus confirm that it is a low leptin level that conveys nutritional information that an individual is pathologically thin, not the fat mass itself.

Hypothalamic amenorrhea (HA) is another condition associated with low leptin levels. Female patients who are extremely thin frequently enter puberty late or some-

times fail to enter puberty at all. In addition, adult females who develop extreme leanness, often associated with protracted vigorous exercise, frequently stop menstruating.[34] Women with this condition show a prepubertal pattern of gonadotrophin secretion and also manifest other neuroendocrine and metabolic abnormalities including premature, severe osteoporosis that in most cases cannot be treated adequately with hormone replacement therapy.[42] This condition is not uncommon and affects 4%–8% of women of reproductive age, accounting for as many as one in three visits by women to an infertility clinic (personal communication, Chris Mantzoros). The contribution of hypoleptinemia to this condition was confirmed by the demonstration that leptin replacement therapy can restore reproductive function in women with HA, some of whom had not menstruated for years.[42] It is this result, as first suggested by Frisch, that confirmed that a fat-derived factor is essential for the development and maintenance of normal reproductive function in women,

HA patients also develop a set of neuroendocrine abnormalities typically associated with starvation, and these too are ameliorated by leptin treatment. Premature osteoporosis is a major problem for HA patients, and there is evidence from serum markers that leptin might also improve the bone pathology that often develops in these patients, though further studies will be necessary to confirm this. Similar to the results for lipodystrophy, these patients show endocrine and metabolic improvement despite losing adipose mass, thus confirming the key role of hypoleptinemia, not of adipose mass itself, in the activation of the set of physiologic responses to starvation.[43]

These data further suggest that leptin might have beneficial effects in other conditions associated with extremely low leptin levels. As noted by Frisch, delayed puberty is often associated with extreme leanness, and failure to enter puberty in the correct temporal window can have significant, life-long consequences.[34] Females with leptin mutations typically do not enter puberty even when at an appropriate bone age; leptin therapy rapidly induces a prepubertal pattern of gonadotrophin secretion which reverts when leptin therapy is stopped.[35] In this setting, leptin is permissive for the onset of puberty, as leptin treatment does not induce puberty in young women or in animals who have not reached the appropriate bone age.[44] Thus, it is possible that in some cases leptin therapy might be of benefit for inducing puberty.

Women with anorexia nervosa and patients with cachexia resulting from cancer or severe chronic infections also show many of the same abnormalities observed in malnourished individuals, including prominent immune abnormalities. These immune alterations often contribute to the high ratio of infectious disease and mortality in these conditions. Consistent with this, patients with leptin mutations also show abnormalities in immune function, and in one extended pedigree segregating leptin mutations, there was a high incidence of premature death from infectious disease.[36,45] While leptin would have the undesirable effect of inducing weight loss in the setting of cachexia, there is evidence from animals that leptin treatment administration can suppress these immune abnormalities at lower doses than are required to suppress food intake or body weight.[46] Thus it is conceivable that very low dose, carefully titrated leptin treatment could have beneficial effects on immune function and other abnormalities in anorectic or cachectic patients, a possibility would require further, controlled clinical testing.

Most Obese Patients are Leptin Resistant

Plasma leptin levels in human are highly correlated with adipose tissue mass and most obese patients have high leptin levels.[21] 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 thus likely to be variable.[22] Leptin's efficacy was first shown to be variable in rodents with different obese strains showing a spectrum of leptin sensitivity with leptin-deficient *ob/ob* mice being the most leptin sensitive and animals with leptin receptor mutations being the most resistant.[22] Animals with obesity induced by a cafeteria or highly palatable diet, often a reliable predictor of drug responses in humans, showed a partial response to leptin administration.

A similar variability in the response to leptin has been seen in obese humans where leptin-deficient patients are extremely sensitive to the effects of leptin treatment. In obese patients in the general population, there was a statistically significant effect of leptin to reduce weight in a small cohort of obese patients.[47] However, in further studies, only a subset of obese humans (approximately one-third) showed a clinically significant degree of weight loss on leptin therapy (personal communication, Alex DePaoli).[47] These data indicated that the utility of leptin as a monotherapy for the treatment of obesity was likely to be limited to a subset of patients. It is yet unclear whether the individuals that respond to leptin have lower starting leptin levels than nonresponders. At a given body mass index or percent fat, there is substantial variability of leptin levels, and approximately 10%–15% of obese subjects have endogenous levels of leptin that are indistinguishable from lean patients.[21] The demonstration that leptin can have potent weight-reducing effects in some patients with low leptin levels such as those with lipodystrophy and HA, see above, has sug-

gested that leptin may be efficacious in obese patients with low plasma leptin levels.[46] While leptin has been shown to have potent weight-reducing effects in experimental obese animals with low leptin levels, this possibility has not been directly tested in humans.[46]

A key issue for future studies will be to elucidate the molecular mechanisms responsible for leptin resistance. Leptin activates signal transduction in specific neural populations in the hypothalamus and other brain regions.[48] The leptin receptor signals via the JAK-Stat signal transduction pathway, which depends in part on phosphorylation of tyrosine residues of specific protein substrates including Stat3.[48] Signaling by this class of receptors is generally turned off as a consequence of the secondary activation of SOCS proteins, which inhibit JAK kinase, and specific tyrosine phosphatases which shut off cytokine signaling after the signal transduction pathway is initially activated. Consistent with this, the cellular effects of leptin have been amplified in cells lacking either SOCS3 or PT1b, a phosphotyrosine phosphatase. Importantly, mice with haploinsufficiency for either of these genes are resistant to obesity and remain lean on a high-fat diet and retain leptin sensitivity.[49,50] While the contribution of these proteins to the development of leptin resistance is as yet unclear, these data do show that the enhancement of leptin sensitivity can protect against obesity. These results also suggest that chemical inhibitors of SOCS3 or PT1b could have potential as anti-obesity agents, either alone or in combination with leptin. Efforts to develop inhibitors of these proteins are underway.

Recently, the hormone amylin has also been shown to ameliorate leptin resistance, though the molecular mechanism has not been fully established.[51] 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. This agent is approved for the treatment of diabetes as an adjunct to insulin treatment. Amylin reduces glucose absorption, suppresses glucagon secretion and reduces food intake.[51]

Amylin therapy is also associated with a durable weight loss of approximately 5% in humans, establishing it as one of a number of gastrointestinal signals that regulate nutrient intake and disposition. The possibility that amylin could interact with leptin to achieve even greater weight loss was first assessed in diet-induced rats where it was shown that doses of leptin that had no discernible effect as a monotherapy in this setting, could significantly enhance the response to amylin.[51] The data further suggested that there was true synergy between leptin and amylin, and that amylin could restore leptin signal transduction in the hypothalamus of DIO rats. The clinical significance of these findings was also assessed in humans, where the combination of leptin and amylin resulted in a substantial weight loss of 12.9% that was significantly greater than that for either agent alone.[51] Further studies will establish the safety and efficiency of this combination for the treatment of obesity.

Leptin Provides an Entry Point for Studying a Complex Human Behavior

Leptin treatment of leptin-deficient animals or humans has extremely potent effects on food intake. In one instance, the food intake of a leptin deficient child was monitored before and after the first series of leptin injections. Prior to the first injection, this 3-year-old child ate at least 1300 KCal at a single test meal (personal communication, Stephen O'Rahilly). This is approximately one-half the number of calories a full-grown adult might eat in an entire day. After a short period of leptin treatment, this child ate 180 KCal at an identical test meal, which is the age-appropriate intake of a 4 year old. Marked effects of leptin to reduce food intake in lipodystrophic patients and others have also been noted.[37]

The mechanism by which leptin reduces food intake has been partially elucidated. Leptin activates neural pathways that inhibit food intake and inhibits pathways that activate food intake. Some of leptin's actions appear to result from inhibition of NPY/AGRP-expressing neurons in the arcuate nucleus of the hypothalamus, which stimulate appetite, and activation of POMC neurons, which reduce appetite by activating the postsynaptic MC4 receptor in other parts of the brain.[52] However, it is likely that other neural pathways also play a role and it is not clear what aggregate set of pathways accounts for the full effect of leptin treatment. Moreover, it is also not clear whether leptin resistance abrogates leptin signaling by the NPY or POMC neurons or by as yet unknown neural circuits. The identification of the specific circuits that are altered in the leptin-resistant state would provide key entry points for delineating the pathophysiologic molecular mechanisms that lead to obesity.

Leptin signaling also has important modulatory effects on dopaminergic neurons that are part of reward pathways that provide input to the nucleus accumbens.[53,54] Consistent with this, fMRI imaging of leptin-deficient subjects has revealed a marked increase in activity in the nucleus accumbens in response to images of food even in the fed state.[55–57] Normal individuals typically show this activity only in the starved state and do not show this response in the fed state. The neural activity that is seen in the accumbens in fed leptin-deficient patients was normalized by leptin therapy.[55–57] In addition, leptin-deficient patients show markedly different food preferences and perception of food than do normal individuals.[55–57] These data establish that leptin plays an important role to regulate feeding, a typical complex motivational behavior. The further delineation of the neural circuit activated by leptin may provide an opportunity to dissect the way in which complex, behavioral decisions are made. Feeding is regulated by many factors includ-

ing leptin, other hormonal and metabolic signals, sensory inputs, emotional factors and volitional factors such as the conscious motivation to diet or in other cases gain weight. It is not known how or even where in the brain these multiple sensory inputs are represented. The full spectrum of the downstream neuroanatomic sites to which leptin-responsive neurons project are largely unknown, and their delineation could help lead to a fuller understanding of how the decision to eat (or not eat) is generated.

Biologic Basis for Obesity

The relevance of specific hypothalamic neural circuits for human obesity has been established in a series of genetic studies in which it has been shown that single gene (i.e., Mendelian) defects account for 10% of cases of morbid human obesity, perhaps more;[58–66] in one cohort, 15% of individuals with severe, early onset obesity were members of consanguineous pedigrees (personal communication, Stephen O'Rahilly). Thus, in addition to mutations in the leptin and leptin receptor genes, significant obesity is also demonstrable in patients with POMC, MC4R and TrkB mutations. This high incidence of Mendelian inheritance exceeds that for most, perhaps all, other complex traits which are commonly accepted to have a genetic basis. Consistent with this, twin studies and other approaches have established a substantial genetic basis for obesity with a hereditability of 0.7–0.9, a level exceeded only by height.[67] While a subset of these individuals show Mendelian inheritance, the majority of these cases appear to be the result of polygenes interacting with environmental factors.

The identification of genetic factors that cause obesity is inconsistent with the widely held notion among the general public that obesity is a personal failing. In the US, the obese are often stigmatized to an extent that would be unacceptable for any other condition (see http://www.newsweek.com/id/215115). In addition, obese individuals on average make less money than their no-better-qualified lean counterparts and are promoted less readily.[68,69]

The identification of human mutations that cause obesity 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 obese people make and more about their biologic makeup. The identification of leptin and other components of 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.[68] Although one can consciously override the basic drive to eat over the short term and transiently lose weight, over the long term this basic drive dominates the conscious drive to eat less. 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

1. Zhang Y, P Proenca, M Maffei, *et al*: Positional cloning of the mouse obese gene and its human homologue. Nature 1994; **372**: 425–432.
2. Halaas JL, KS Gajiwala, M Maffei, *et al*: Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995; **269**: 543–546.
3. Pelleymounter MA, MJ Cullen, MB Baker, *et al*: Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995; **269**: 540–543.
4. Campfield LA, FJ Smith, Y Guisez, *et al*: Recombinant mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. Science 1995; **269**: 546–549.
5. Bray GA, Obesity: Historical development of scientific and cultural ideas. Int J Obes 1990; **14**: 909–926.
6. Edholm OG, JG Fletcher, EM Widdowson, *et al*: The energy expenditure and food intake of individual men. Brit J Nutrit 1955; **9**: 286–300.
7. Wilson BE, GE Meyer, JJC Cleveland, *et al*: Identification of candidate genes for a factor regulating body weight in primates. Am J Physiol 1990; **259**: R1148–1155.
8. Dark J, N Forger, J Stern, *et al*: Recovery of lipid mass after removal of adipose tissue in ground squirrels. Am J Physiol 1985; **249**: R73–R78.
9. Liebelt RA, L Vismara and AG Liebelt: Autoregulation of adipose tissue mass in the mouse. Proc Soc Exp Biol Med 1968; **127**: 458–462.
10. Sims E, E Danforth Jr, G Horton, *et al*: Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res 1973; **29**: 457–496.
11. Weigle DS: Contribution of decreased body mass to diminished thermic effect of exercise in reduced-obese men. Int J Obes 1988; **12**: 567–578.
12. Adolph EF: Urges to eat and drink in rats. Am J Physiol 1947; **151**: 110–125.
13. Hetherington AW and SW Ranson: The spontaneous activity and food intake of rats with hypothalamic lesions. Am J Physiol 1942; **136**: 609–617.
14. Brobeck JR: Mechanism of the development of obesity in animals with hypothalamic lesions. Physiol Rev 1946; **25**: 541–559.
15. Mayer J: Regulation of energy intake and the body weight: the glucostatic theory and the lipostatic hypothesis. Ann NY Acad Sci 1955; **63**: 15–43.
16. Kennedy A, TW Gettys, P Watson, *et al*: The metabolic significance of leptin in humans – gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. J Clin Endocrinol Metabol 1997; **82**: 1293–1300.
17. Mayer J, RG French, CF Zighera, *et al*: Hypothalamic obesity in the mouse: production, description and metabolic characteristics. Am J Physiol 1955; **182**: 75–82.
18. Hervey GR: The effects of lesions in the hypothalamus in parabiotic rats. J Physiol 1959; **145**: 336–352.
19. Coleman DL: Effects of parabiosis of obese with diabetes and normal mice. Diabetologia 1973; **9**: 294–298.
20. Moon BC and JM Friedman: The molecular basis of the obese mutation in ob^{2J} mice. Genomics 1997; **42**: 152–156.
21. Maffei M, J Halaas, E Ravussin, *et al*: Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and

weight-reduced subjects. Nat Med 1995; **1**: 1155–1161.
22. Halaas JL, C Boozer, J Blair-West, *et al*: Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc Natl Acad Sci USA 1997; **94**: 8878–8883.
23. Tartaglia LA, M Dembski, X Weng, *et al*: Identification and expression cloning of a leptin receptor, OB-R. Cell 1995; **83**: 1263–1271.
24. Lee GH, R Proenca, JM Montez, *et al*: Abnormal splicing of the leptin receptor in diabetic mice. Nature 1996; **379**: 632–635.
25. Chen H, O Charlat, LA Tartaglia, *et al*: Evidence that the diabetes gene encodes the leptin receptor: Identification of a mutation in the leptin receptor gene in db/db mice. Cell 1996; **84**: 491–495.
26. Fei H, HJ Okano, C Li, *et al*: Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues. Prod Natl Acad Sci USA 1997; **94**: 7001–7005.
27. Lord G: Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 1998; **394**: 897–891.
28. Ceccarini G, R Flavell, E Butelman, *et al*: PET imaging of leptin biodistribution and metabolism in rodents and primates. Cell Metab 2009; **10**: 148–159.
29. Cohen J, X Wang, S Grundy, *et al*: Variation at the hepatic lipase and apolipoprotein AI/CIII/AIV loci is a major cause of genetically determined variation in plasma HDL cholesterol levels. J Clin Invest 1994; **94**: 2377–2384.
30. Chua SC, Jr, DW White, XS Wu-Peng, *et al*: Phenotype of fatty due to Gln269pro mutation in the leptin receptor (Lepr). Diabetes 1996; **45**: 1141–1143.
31. Bray G and D York: Genetically transmitted obesity in rodents. Phys Rev 1971; **51**: 598–646.
32. Ahima RS, D Prabakaran, C Mantzoros, *et al*: Role of leptin in the neuroendocrine response to fasting. Nature 1996; **382**: 250–252.
33. Bornstein SR, DJ Torpy, GP Chrousos, *et al*: Leptin levels are elevated despite low thyroid hormone levels in the "euthyroid sick" syndrome [letter; comment]. J Clin Endocrinol Metab 1997; **82**: 4278–4279.
34. Frisch RE and JW McArthur, Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974; **185**: 949–951.
35. Farooqi I, S Jebb, G Langmack, *et al*: Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999; **341**: 879–884.
36. Farooqi I, G Matarese, G Lord, *et al*: Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest 2002; **110**: 1093–1103.
37. Oral EA, V Simha, E Ruiz, *et al*: Leptin-replacement therapy for lipodystrophy. N Engl J Med 2002; **346**: 570–578.
38. Bacchetti P, B Gripshover, C Grunfeld, *et al*: Fat distribution in men with HIV infection. J Acquir Immune Defic Syndr 2005; **40**: 121–131.
39. Kosmiski L, P Bacchetti, D Kotler, *et al*: Relationship of fat distribution with adipokines in human immunodeficiency virus infection. J Clin Endocrinol Metab 2008; **93**: 216–224.
40. Lee J, J Chan, E Sourlas, *et al*: Recombinant methionyl human leptin therapy in replacement doses improves insulin resistance and metabolic profile in patients with lipoatrophy and metabolic syndrome induced by the highly active antiretroviral therapy. J Clin Endocrinol Metab 2006; **91**: 2605–2611.
41. Shimomura I, RE Hammer, S Ikemoto, *et al*: Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature 1999; **401**: 73–76.
42. Welt C, J Chan, J Bullen, *et al*: Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med 2004; **351**: 987–997.
43. Oral EA, E Ruiz, A Andewelt, *et al*: Effect of leptin replacement on pituitary hormone regulation in patients with severe lipodystrophy. J Clin Endocrinol Metab 2002; **87**: 3110–3117.
44. Chehab FF, K Mounzih, R Lu, *et al*: Early onset of reproductive function in normal female mice treated with leptin. Science 1997; **275**: 88–90.
45. Ozata M, I Ozdemir and J Licinio: Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab 1999; **84**: 3685–3695.
46. Ioffe E, B Moon, E Connolly, *et al*: Abnormal regulation of the leptin gene in the pathogenesis of obesity. Proc Natl Acad Sci USA 1998; **95**: 11852–11857.
47. Heymsfield S, A Greenberg, K Fujioka, *et al*: Recombinant leptin for weight loss in obese and lean adults. JAMA 1999; **282**: 1568–1575.
48. Vaisse C, JL Halaas, CM Horvath, *et al*: Leptin activation of Stat3 in the hypothalamus of wild-type and ob/ob mice but not db/db mice. Nat Genet 1996; **14**: 95–97.
49. Bjorbaek C, JK Elmquist, JD Frantz, *et al*: Identification of SOC-3 as a potential mediator of central leptin resistance. Mol Cell 1998; **1**: 619–625.
50. Zabolotny J, Y Kim, L Welsh, *et al*: Protein-tyrosine phosphatase 1B expression is induced by inflammation *in vivo*. J Biol Chem 2008; **283**: 14230–14241.
51. Roth J, B Roland, R Cole, *et al*: Leptin responsiveness restored by amylin agonism in diet-induced obesity: evidence from nonclinical and clinical studies. Proc Natl Acad Sci 2008; **105**: 7257–7262.
52. Friedman JM: The alphabet of weight control. Nature 1997; **385**: 119–120.
53. Pissios P and E Maratos-Flier: More than satiety: central serotonin signaling and glucose homeostasis. Cell Metab 2007; **6**: 345–347.
54. Hommel J, R Trinko, R Sears, *et al*: Leptin receptor signaling in midbrain dopamine neurons regulates feeding. Neuron 2006; **51**: 801–810.
55. Farooqi I, E Bullmore, J Keogh, *et al*: Leptin regulates striatal regions and human eating behavior. Science 2007; **317**: 1355.
56. Baicy K, E London, J Monterosso, *et al*: Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. Proc Natl Acad Sci 2007; **104**: 18276–18279.
57. Licinio J, M Milane, S Thakur, *et al*: Effects of leptin on intake of specific micro- and macronutrients in a woman with leptin gene deficiency studied off and on leptin at stable body weight. Appetite 2007; **49**: 594–599.
58. Farooqi I, T Wangensteen, S Collins, *et al*: Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med 2007; **356**: 237–247.
59. Montague CT, IS Farooqi, JP Whitehead, *et al*: Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; **387**: 903–908.
60. Clement K, C Vaisse, N Lahlou, *et al*: A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; **392**: 398–401.
61. Farooqi I, J Keogh, G Yeo, *et al*: Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003; **348**: 1085–1095.
62. O'Rahilly S, IS Farooqi, G Yeo, *et al*: Minireview: Human obesity-lessons from monogenic disorders. Endocrinology 2003; **144**: 3757–3764.
63. Farooqi I, G Yeo, J Keogh, *et al*: Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest 2000; **106**: 271–279.
64. Yeo G, I Farooqi, S Aminian, *et al*: A frameshift mutation in

MC4R associated with dominantly inherited human obesity. Nat Genet 1998; **20**: 111–112.
65. Loos R, C Lindgren, S Li, *et al*: Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 2008; **40**: 768–775.
66. Vaisse C, K Clement, B Guy-Grand, *et al*: A frameshift mutation in human MC4R is associated with a dominant form of obesity. Nat Genet 1998; **20**: 113–114.
67. Stunkard AJ, JR Harris, NL Pedersen, *et al*: The body-mass index of twins who have been reared apart. N Engl J Med 1990; **322**: 1483–1487.
68. Friedman J: Modern science vs the stigma of obesity. Nat Med 2004; **10**: 563–569.
69. Friedman JM: A war on obesity, not the obese. Science 2003; **299**: 856–858.