The Role of Leptin in Human Obesity and Disease: A Review of Current Evidence

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Purpose: To review recent advances in the pathophysiology and potential clinical applications of leptin, an adipose tissue–derived hormone.

Data Sources: A MEDLINE search of the literature on leptin and the bibliographies of relevant papers.

Study Selection: All 1320 publications on leptin.

Data Extraction: All identified articles were reviewed. Cited publications were selected on the basis of study quality and relevance to human obesity and disease.

Data Synthesis: Leptin is a 16-kilodalton adipocyte-derived hormone that circulates in the serum in the free and bound form. Serum levels of leptin reflect the amount of energy stored in adipose tissue. Short-term energy imbalance as well as serum levels of several cytokines and hormones influence circulating leptin levels. Leptin acts by binding to specific receptors in the hypothalamus to alter the expression of several neuropeptides that regulate neuroendocrine function and energy intake and expenditure. Thus, leptin plays an important role in the pathogenesis of obesity and eating disorders and is thought to mediate the neuroendocrine response to food deprivation. Phase I and II trials recently showed that leptin administration to humans is safe, and ongoing phase III trials are assessing the efficacy of leptin as a treatment for obesity and related disorders. Availability of leptin or smaller and more soluble leptin analogues for clinical studies in humans is expected to significantly advance understanding of the mechanisms underlying energy homeostasis in humans.

Conclusions: Leptin is significantly broadening our understanding of the mechanisms underlying neuroendocrine function, body weight, and energy homeostasis. Elucidation of these mechanisms is expected to result in the development of novel therapeutic approaches for obesity and eating disorders.

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Obesity, the prevalence of which has been progressively increasing worldwide, is closely associated with increased morbidity and mortality caused by several of the most common diseases in the western world, including diabetes, hypertension, cardiovascular diseases, and cancer. The pathogenesis of obesity remains largely unknown, but research on its pathophysiology has recently intensified, largely because of the discovery of leptin 4 years ago (1). However, accumulating evidence suggests that the role of leptin is much broader than that of an antiobesity hormone; leptin also affects several neuroendocrine mechanisms and regulates multiple hypothalamic–pituitary axes.

In this review, I present the current understanding of leptin's role in various physiologic and pathophysiologic states in humans. I also discuss the potential therapeutic implications of our advancing knowledge on energy homeostasis and body weight regulation.

Methods

The role of leptin in the pathophysiology of obesity and related disorders has been reviewed elsewhere (2). However, the number of relevant publications has increased exponentially during the past year. Moreover, unlike early publications that focused on basic science and animal physiology, most of the recent publications provide important information on the role of leptin in human physiology and pathophysiology. Thus, an updated review would be useful for the clinician. I used the keyword *leptin* to search the MEDLINE database for all published articles on leptin in the English, German, French, and Greek literature. To identify additional studies, I reviewed the bibliographies of relevant papers and the abstracts presented at the recent meetings of the Endocrine Society, the American Diabetes Association, and the Eighth International Congress on Obesity. All 1320 publications on leptin were selected for review. Because of space limitations, only some of these studies could be cited here. These studies were selected on the basis of their relevance to human obesity and disease as well as their quality.

The Genetics of Leptin

The *ob* gene, discovered by positional cloning using the leptin-deficient *ob*/*ob* mouse model of obesity (1), is expressed in white adipose tissue (3–5), the stomach, the placenta (6), and, possibly, the mammary gland. The *ob* messenger RNA, now called *leptin* (from the Greek word *leptos,* meaning "thin"), encodes a 167–amino acid protein whose crystal structure suggests that it belongs to the cytokine family (7–9). Leptin circulates in plasma in a free form or bound to leptin-binding proteins.

Regulation of Serum Leptin Levels

Leptin levels increase exponentially with increasing fat mass (10, 11), and leptin production is higher in subcutaneous than in visceral fat depots (12–15). Leptin levels reflect not only the amount of fat stored but also energy imbalance; prolonged fasting substantially decreases leptin levels, whereas overfeeding greatly increases them (2, 16–18). The composition of the diet—specifically, intake of macronutrients or micronutrients, such as zinc (19, 20)—and hormonal factors also regulate leptin levels. Prolonged insulin infusions or supraphysiologic insulin levels markedly increase circulating leptin levels (21–30). Isoproterenol (31) and β_3-adrenergic receptor agonists reduce leptin mRNA expression and circulating levels (32); cigarette smoking, which induces a hyperadrenergic state, has been associated with decreased serum leptin levels (30, 33). Glucocorticoids have been shown to increase leptin production in vitro (23, 34), and exogenously administered glucocorticoids produce a sustained increase in circulating leptin levels in humans (35–37). However, data from studies on patients with the Cushing syndrome are inconsistent (38, 39), and experimental data suggesting the existence of a feedback loop between leptin and the adrenals need to be confirmed (40). Several cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6, also alter leptin mRNA expression and circulating levels (41–45). Finally, even after adjustment for fat mass, women seem to have higher leptin levels than men (10, 46–49), either because of their different body fat distribution or the inducing effects of estrogen–progesterone combined with the suppressive effect of androgens on leptin (50, 51).

Although the molecular mechanisms regulating leptin production remain to be fully elucidated, leptin gene promoter is positively regulated by several transcription factors that are important in adipocyte differentiation (52–55). Thiazolidinediones, a class of novel antidiabetic agents that act by binding to peroxisome proliferator–activating receptor-γ (a transcription factor), decrease leptin production by human adipocytes in vitro (56) and in animal models in vivo (57). However, their effect on leptin levels in humans merits further investigation (58, 59). It also remains unknown whether any of the above factors influence leptin pulsatility; plasma leptin levels show significant ultradian and circadian variation with a distinct nocturnal peak (60–63).

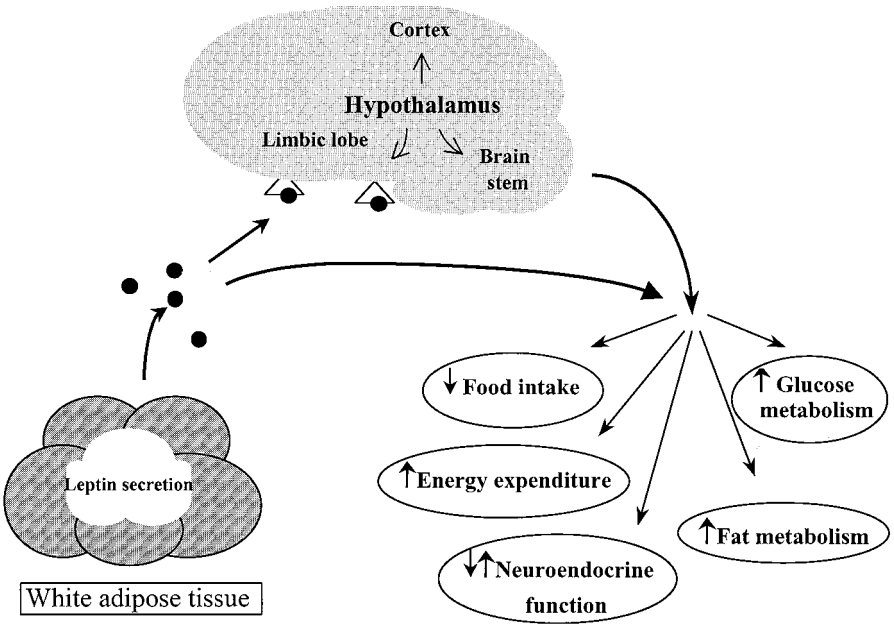

Figure 1. Schematic representation of the actions of leptin. Leptin acts either directly or by activating specific centers in the central nervous system to decrease food intake, increase energy expenditure, influence glucose and fat metabolism, and alter neuroendocrine function.

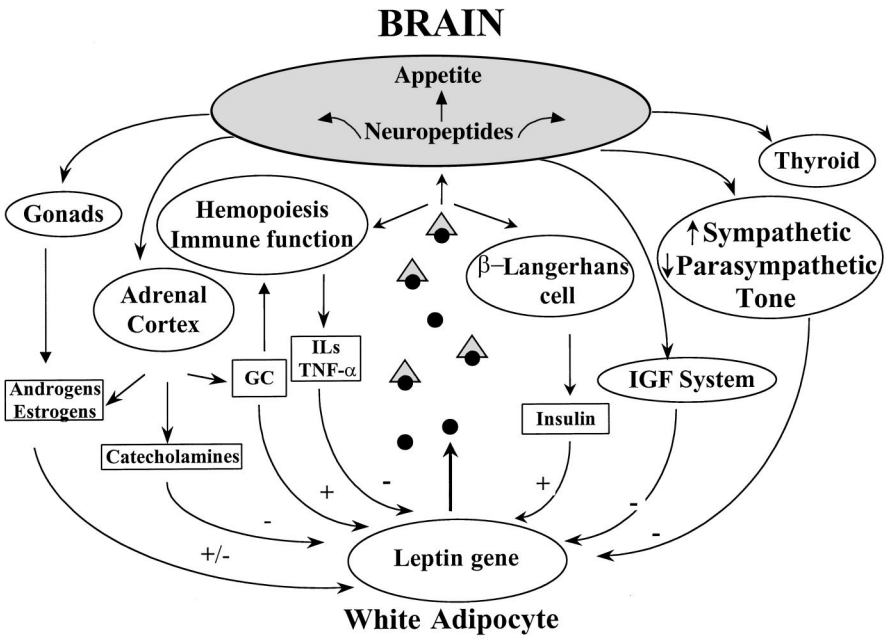

Figure 2. Schematic representation of feedback loops involving leptin. Leptin, an adipocyte-derived hormone, circulates in the serum either in free form or bound to leptin-binding proteins, activates specific receptors in the hypothalamus, and alters expression of several neuropeptides; these in turn decrease appetite, increase energy expenditure by altering sympathetic and parasympathetic tone, and alter neuroendocrine function. Increasing leptin levels activate the thyroid, growth hormone, and gonadal axes and suppress the pituitary–adrenal axis. Leptin, acting directly or indirectly (by altering the levels of other hormones and neuropeptides), also influences hemopoiesis and immune function and improves glucose and fat metabolism. Finally, altered production and circulating levels of hormones and cytokines feeds back to alter leptin production by the adipocytes. GC = glucocorticoids; IGF = insulin-like growth factor; IL = interleukin; TNF-α = tumor necrosis factor-α.

Leptin Action and Clearance

Leptin acts by activating specific leptin receptor isoforms (the long form and numerous short forms) (64, 65). Leptin receptors are found in many areas of the brain, including the hypothalamus, cerebellum, cortex, hippocampus, thalamus, choroid plexus, and brain capillary endothelium (66) (**Figures 1** and **2**). The long leptin receptor isoform, which is a member of the class I cytokine receptor family, activates the JAK (Janus Kinase) signal transducer and activator of transcription (2) and alters expression of many hypothalamic neuropeptides (66–69). The best-studied neuropeptides are neuropeptide Y in the arcuate nucleus, which influences the hypothalamic–pituitary–gonadal axis, and thyrotropin and corticotropin-releasing hormone in the paraventricular nucleus (70–74), which influence the thyroid and adrenal axes (**Figure 2**). In addition, downregulation of neuropeptide Y by leptin results in reduced appetite, increased sympathetic nervous system outflow, and energy expenditure as well as alteration of peripheral metabolic milieu (71). Other targets of leptin in the hypothalamus include the appetite-regulating neuropeptides melanocyte-stimulating hormone and its competitive antagonist, agouti-related protein (74, 75); pro-opiomelanocortin (76); and cocaine and amphetamine-regulated peptide (77). The relation of leptin to other hypothalamic neuropeptides, such as orexin, the tubby transcript (78, 79), melanin-concentrating hormone, neurotensin, and cholecystokinin, has only recently begun to be deciphered (74, 75, 80). In contrast, recent evidence suggests that the leptin pathway for regulation of energy homeostasis is independent of the serotonin pathway, which is known to be activated by such medications as fenfluramine and dexfenfluramine (74, 75, 80). This suggests that the system responsible for energy homeostasis in humans has built-in redundancy.

Leptin receptors are also expressed in peripheral tissues, including the lung, kidney, liver, pancreas, adrenals, ovaries, hematopoietic stem cells, and skeletal muscle, whereas the soluble leptin receptor isoform that circulates in the serum functions as a leptin-binding protein (81–90). Although this wide expression may imply that the role of leptin is much broader than that of a circulating satiety factor (2), the full array of leptin's actions through activation of these receptors has not been fully clarified. However, it seems that short receptor isoforms present in the kidney may mediate leptin clearance (81, 82), whereas those in the brain capillary endothelium (83) and the choroid plexus (84) transport leptin from blood into the brain interstitium and the cerebrospinal fluid by way of a saturable system (85, 86). There is a threshold level of serum leptin (about 25 to 30 ng/mL) above which increases in serum levels are not translated into proportional increases in cerebrospinal or brain leptin levels (86); this, in turn, may result in an apparent leptin resistance and obesity.

In summary, intensive research efforts in the past 4 years have provided important insights into leptin regulation and action. However, several important questions remain to be answered. First, the mechanism underlying leptin's ultradian and circadian variation (60–63) and its potential physiologic significance remain to be elucidated. The pulsatility of leptin, which depends only in part on nutrition and

sleep, is synchronous with the pulsatility of circulating luteinizing hormone and estradiol (61) and is significantly and inversely related to that of adrenocorticotropic hormone and cortisol (60). What regulates the synchronized secretion of leptin from a disperse tissue such as the adipose tissue? Is there a common regulator or, alternatively, does leptin secretion represent a signal of nutritional origin that modulates neuroendocrine function (60)? These questions are the focus of intensive research efforts. In addition to leptin regulation, the delineation of leptin's molecular targets and complex network of interactions in the hypothalamus, as well as the mechanisms underlying leptin's regulation of hypothalamic neuropeptides, may have important physiologic and therapeutic implications. Mapping these pathways is expected to fully prove the redundancy of the system that controls energy homeostasis and will be invaluable for the design of effective preventive and therapeutic interventions for obesity and eating disorders. Finally, the exact role of leptin receptors in the periphery, such as skeletal muscle, hemopoietic organs, immune function, and growth (87, 88) deserves further study.

The Role of Leptin in Human Physiology and Pathophysiology

Leptin in the Neonate

The level of leptin in cord blood (33, 91–94), derived from both the placenta (6) and fetal tissues (93, 94), is positively associated with the body weight and fat mass of the neonate, decreases in response to maternal smoking, is lower in preterm infants and those who are small for gestational age, and is higher in those who are large for gestational age (33). Apart from signaling energy reserves to the brain, leptin may regulate growth (95) and promote hematopoiesis and lymphopoiesis in newborn infants (96, 97). Leptin is also secreted in the milk and can pass from the gastrointestinal tract to the blood (98), suggesting that in addition to neonatal leptin, maternal leptin in milk may, as in rodents, play a role in regulating neonatal food intake or growth (98).

Leptin in Childhood and Puberty

Leptin may signal to the brain the critical amount of fat stores necessary for initiation of puberty and maintenance of menstrual cycles and reproductive ability (99, 100). Although the exact mechanism by which leptin regulates secretion of luteinizing hormone–releasing hormone and function of the hypothalamic—pituitary–gonadal axis remains unknown (101), administration of leptin to prepubertal mice and nonhuman primates accelerates puberty (102). In normal children, leptin levels increase before puberty as body fat mass increases and reach their peak at the onset of puberty, suggesting that leptin may trigger puberty in humans (92, 103, 104). In contrast, persons with inactivating mutations of the leptin receptor are morbidly obese, remain prepubertal, and have hypogonadotrophic hypogonadism (105).

Leptin and Leptin Resistance in Human Obesity

The dramatic effects of leptin administration to *ob*/*ob* mice, which are leptin deficient because of mutations of the leptin gene, raised expectations that human obesity might also be a leptin-deficient state that could be treated with exogenous leptin administration. Although the first persons with extreme, early-onset obesity due to an inactivating mutation of the leptin gene have been identified and clinically characterized (106), several population studies have failed to demonstrate such mutations (107–109). Thus, leptin-deficient persons probably represent only a minority of obese humans. In contrast, most obese humans have increased leptin levels (11), indicating that obesity is a leptin-resistant state in most obese persons. However, because one sequence polymorphism and linkage of obesity to regions flanking the leptin gene have been reported in association with extreme obesity (110), the leptin gene may prove to be important only in extremely obese persons (111, 112).

Thus, identification of possible receptor and postreceptor defects that could be responsible for leptin resistance in most obese persons has clinical significance. As in rodent models of obesity (7, 64, 113), a mutation that results in a truncated leptin receptor lacking both the transmembrane and the intracellular domain was recently described in members of two unrelated families (111, 114). Patients who are homozygous for this mutation present with early-onset morbid obesity, no pubertal development, and dysfunction of growth hormone and thyroid axes; the hypothalamic–adrenal axis in these patients has not yet been characterized in detail.

The frequency of leptin receptor mutations in the general population is unknown but is thought to be very low. The search for molecules capable of inducing leptin resistance or mutations in molecules downstream of leptin and its receptor began, and the first information was recently reported. Two persons with pro-opiomelanocortin mutations, a molecule that serves as a downstream effector of the leptin receptor, were found to have severe early-onset obesity and adrenal insufficiency (115). A similar phenotype has also been associated with impaired prohormone processing due to mutations of the *proconvertase 1* gene (116). In addition, recent

evidence suggests that suppressor-of-cytokine signalling-3 is a leptin-inducible inhibitor of leptin signaling and a potential mediator of leptin resistance in obesity (117). Investigators are searching for mutations in other molecules downstream of leptin, such as the melanocyte-stimulating hormone receptor MC-4. These results, as well as data on the frequency of these mutations in the general population, are awaited with great interest because they may provide important insights into the pathogenesis of human obesity, a polygenic disorder.

Peripheral signals, such as glucocorticoids, may also interfere with leptin's interaction with its receptor and produce central leptin resistance (71, 80, 118, 119). Another potential locus of leptin resistance is transport of leptin through the blood–brain barrier (66, 85, 86); saturable transport of leptin into the brain may be a rate-limiting step with respect to leptin action (86). Frequently, leptin doses that have no effect when administered peripherally reduce food intake when administered centrally (7). In contrast, abnormal serum leptin binding or abnormal leptin catabolism does not seem to be the underlying mechanism for the development of human obesity because the estimated half-life as well as the biological activity of circulating leptin is similar in both lean and obese humans (5, 120). Moreover, antileptin antibodies and leptin-binding proteins do not inactivate leptin in obese persons (87, 88). Clarification of the mechanisms underlying leptin resistance is expected to lead to a better understanding of the pathogenesis of obesity and the development of specific and effective treatments for this condition. Similarly, elucidation of leptin's role in mediating the metabolic and neuroendocrine response of obese persons to dieting may have important clinical implications.

Leptin and the Metabolic and Neuroendocrine Response to Food Deprivation

Although most clinicians and researchers view leptin as an antiobesity hormone, it was recently proposed that the leptin system may function as an adaptive mechanism in an environment where food availability is limited. In this context, one of leptin's main roles would be to conserve energy by decreasing thyroid hormone–induced thermogenesis and to mobilize energy stores by increasing the secretion of stress glucocorticoids while suppressing gonadal function and thus preventing the energy demands of pregnancy and lactation (2, 121, 122). Exogenous administration of leptin to starving mice blunts the neuroendocrine abnormalities associated with decreasing leptin levels due to food deprivation; that is, gonadal and thyroid axis activity are suppressed and adrenal axis activity is stimulated (121). This effect is mediated at least in part by neuropeptide Y (70, 95, 121). Experiments of nature have recently confirmed that these findings are also part of human physiology. Functional leptin deficiency due to mutations of the leptin receptor gene results in abnormalities of the hypothalamic–pituitary–gonadal and thyroid axes; the hypothalamic–pituitary–adrenal axis of persons with functional leptin deficiency remains to be studied in detail. In addition, variations in serum leptin levels are related to minute-to-minute changes in adrenocorticotropic hormone and cortisol levels in normal men (60) and luteinizing hormone and estradiol levels in normal women (61). Thus, decreased leptin levels may underlie the metabolic and neuroendocrine changes that characterize anorexia nervosa and that accompany therapeutic dieting for obesity; it may also explain the high recidivism rates among dieters.

Leptin in Hypertension, Diabetes Mellitus, and Polycystic Ovarian Disease

Although in the short term, leptin may function as a potassium-sparing diuretic–natriuretic factor (123), in the long term, it increases norepinephrine turnover and sympathetic nerve activity in rodents (124, 125) and humans (126). This results in increased blood pressure in rodents (125, 127), but a potential role of leptin in the pathogenesis of hypertension in humans remains to be conclusively demonstrated.

Obesity, hypertension, and insulin resistance are closely related in humans (128). However, although administration of leptin improves insulin resistance in mice (129) and insulin resistance has been associated with increased leptin levels in one study in humans (130), several independent studies have shown that serum leptin levels are similar in patients with type 2 diabetes mellitus and controls (41, 58, 120, 131). The role of circulating leptin has also been investigated in a heterogeneous group of patients with the polycystic ovary syndrome, which is associated with insulin resistance (131). In most studies, serum leptin levels in women with the polycystic ovary syndrome did not differ from those of normal women (59, 132–134), but in one study (135), a group of women with the polycystic ovary syndrome had increased leptin levels. However, because recent data indicate that leptin may directly affect glucose and fat metabolism and because leptin receptors have been identified in the ovaries (136), it has been proposed that locally acting leptin (137, 138) may be more important than circulating leptin in the pathogenesis of the polycystic ovary syndrome and type 2 diabetes.

Leptin in Eating Disorders

Serum leptin levels in patients with anorexia nervosa, bulimia, nonspecific eating disorders (139,

140), and depression (141) are similar to those of healthy persons with comparable body mass index (142). However, a longitudinal study of patients with anorexia nervosa suggested a relatively higher transport of leptin to the cerebrospinal fluid at lower serum leptin concentrations (143). In patients with anorexia nervosa, who preferentially gain fat mass, leptin levels in cerebrospinal fluid and seem to return to normal before body mass index does (143, 144). These findings may explain both the symptoms of anorexia nervosa and the clinically observed difficulty that these patients have in regaining weight. In addition, the low leptin levels in patients with anorexia nervosa (145) and women athletes who strenuously exercise are closely associated with neuroendocrine abnormalities. Amenorrhea, for example, is closely associated with low leptin levels, indicating that the human body senses its own fat content through leptin and inhibits ovulation when a certain amount of nutritional reserve is not present (100). Thus, leptin is a necessary factor for resumption of menses in patients with anorexia nervosa (145), and increasing luteinizing hormone levels in response to refeeding track increasing serum leptin levels very closely (146).

Leptin in Other Clinical States

Leptin levels are increased in patients with end-stage renal disease (147), but more studies are needed to clarify the potential role of increased leptin levels in cachexia associated with end-stage renal disease. Although thyroid hormones regulate the expression of leptin messenger RNA and secretion of leptin by adipocytes in vitro (148, 149), leptin concentrations do not change in response to hyperthyroidism (148, 150); instead, they decrease and are positively correlated with the decreases in energy expenditure seen in hypothyroidism (150). The functional significance of lower serum leptin levels in hypothyroidism remains unknown and merits further study. Finally, because cytokines regulate circulating leptin levels in humans, it has been hypothesized that leptin could mediate cancer- or AIDS-associated cachexia (41–43). Serum leptin concentrations were thus measured in men infected with HIV (151, 152), but conflicting data were obtained. Thus, further studies are needed to elucidate the role of leptin in AIDS- and cancer-associated cachexia.

Clinical Trials of Leptin

Treatment with leptin reduces weight in all mammalian species tested, including the rat, the dog, and the monkey (7). In addition, the metabolic effects of leptin seem to differ qualitatively from those produced by food restriction. Leptin-induced weight loss is completely specific for loss of adipose tissue, whereas food restriction results in loss of both adipose tissue and lean body mass in mammals (7). However, although therapy with leptin is expected to be efficacious in the few persons with leptin deficiency, it remains to be shown whether leptin is a safe and effective treatment for most obese persons. Although most obese people have high endogenous leptin levels, indicating leptin resistance, it is not known whether increased endogenous leptin levels indicate complete or relative resistance to exogenous leptin. Moreover, whether relative leptin resistance could be bypassed and normal weight loss achieved by using high doses of leptin (similar to insulin treatment in type 2 diabetes) also remains to be shown. It is possible that only a small percentage (about 5% to 10%) of obese persons—those with relatively low serum leptin levels—will be fully sensitive to leptin treatment (7) and that most obese persons are leptin resistant. However, because decreased leptin levels may be responsible for the high recidivism rates in dieting (144, 153) the efficacy of leptin replacement in dieting-induced hypoleptinemia is also of clinical interest (144).

Ongoing clinical trials in humans are expected to answer these and similar clinical questions soon. A recent report showed that daily subcutaneous administration of leptin over 9 months to a leptin-deficient patient decreased body weight by 14.7 kg and greatly improved the patient's metabolic profile (154). In addition, recent phase I and II studies of the safety of leptin therapy found that subcutaneous doses ranging form 0.01 to 0.30 mg/kg per day are safe; the only side effect was local erythema. Moreover, leptin treatment in addition to a diet reduced by 500 kcal/d resulted in highly variable but statistically significant weight reduction at 1 month (mean reduction, 1 kg [range, 0.4 to 1.9 kg]) and 6 months (mean reduction, 5.4 kg [range, 0.7 to 7.1 kg]) in the few patients who completed the study or who discontinued therapy because of local side effects (these patients were analyzed by using the last-observation-carried-forward method) (Greenberg AS, Heymsfield SB, Fujoka K. Preliminary safety and efficacy of recombinant methionyl human leptin administered by subcutaneous injection in lean and obese subjects [orally presented abstract]. 58th Annual Meeting, American Diabetes Association, Chicago, 1998). Whether these results will be confirmed by larger, ongoing phase III and IV clinical trials of the therapeutic efficacy of exogenous leptin administration in obese and diabetic persons remains to be seen.

These trials raise several interesting questions. First, was the leptin dose used appropriate? Experiments in rodents that have demonstrated efficacy

used leptin doses at least one order of magnitude higher than those used in humans. Because leptin is not a very soluble protein, subcutaneous administration of relatively higher doses once or twice daily may create significant problems with respect to local side effects and compliance with treatment. Second, is subcutaneous injection the best method of administering leptin? Recent studies in rodents indicate that continuous subcutaneous infusion of lower doses of leptin (in the range used in the aforementioned trials) is more efficacious and possibly better tolerated than higher subcutaneous doses; thus, one could argue that leptin should be administered continuously by using a subcutaneous pump (155). It is unknown, however, whether effects similar to those seen in rodents will also be observed in humans, nor is it known how appealing this method of treatment would be to most obese persons. Further work on optimizing leptin doses and administration is clearly needed. Third, is it possible to deliver leptin so that it bypasses the blood–brain barrier, a locus of leptin resistance? This could in theory be accomplished either by intrathecal administration of leptin, a method with significant practical problems, or by administration of peripherally smaller, more soluble, and, possibly, more potent leptin analogues. Clinical trials of leptin analogues developed on the basis of its crystal structure and the possible localization of leptin bioactivity to specific amino acid sequences may help establish leptin's therapeutic potential and further clarify the physiology of leptin in vivo.

In any case, results from the recent phase I and II trials confirm the notion that leptin, in the doses used in these trials, does not seem to be the "magic bullet" for the treatment of obesity. If these findings are not the result of the specific dose and formulation used, they may also indicate that any drug used to treat obesity could activate compensatory mechanisms that would prevent further decrease in body weight after a certain point has been reached. Of note, the degree of weight loss induced by leptin in the above preliminary trials is of the same order of magnitude as that seen in response to other drugs, including sibutramine or orlistat. Moreover, the pattern of weight loss with almost all antiobesity medications studied to date shows a similar initial sharp decrease followed by a slower decrease of body weight until the sixth month of treatment, after which it reaches a plateau. This may indicate that in cases of mild obesity, diet or use of only one medication might be sufficient, but effective treatment of severe obesity may require the simultaneous attack of more than one pathway in the complex and redundant system that controls energy homeostasis. We have entered an exciting area of clinical research that is expected to answer all of these questions soon and that may benefit persons who are striving to control excessive body weight.

Future Directions

Despite the recent advances in our knowledge of the physiology and pathophysiology of leptin, many important questions remain. Regardless of whether leptin has a place in the therapeutic armamentarium of the 21st century, studies on leptin are contributing greatly to our knowledge of the physiology of energy homeostasis and, on this basis, may lead to the development of novel therapeutic approaches to obesity. Thus, the recent cloning of potential peripheral targets of leptin, such as the uncoupling protein genes (*UCP-2* and *UCP-3*) that regulate thermogenesis (156), the identification of several neuropeptides that transduce the leptin signal (75), and investigations on potent anorexigenic agents that act by way of mechanisms that are similar to but independent of leptin (155–157), have substantially broadened our horizons. Future research is expected to discover new important molecules in the leptin pathways (or in parallel to them) that regulate appetite and energy expenditure (74, 158–160). It is believed that information on actions of or interactions among these factors and downstream effectors of leptin action will prove extremely valuable with respect to the pathophysiology and treatment of obesity and eating disorders.

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