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REVIEW

Narrative Review: The Role of Leptin in Human Physiology: Emerging Clinical Applications

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Leptin is a hormone secreted by adipose tissue in direct proportion to amount of body fat. The circulating leptin levels serve as a gauge of energy stores, thereby directing the regulation of energy homeostasis, neuroendocrine function, and metabolism. Persons with congenital deficiency are obese, and treatment with leptin results in dramatic weight loss through decreased food intake and possible increased energy expenditure. However, most obese persons are resistant to the weight-reducing effects of leptin. Recent studies suggest that leptin is physiologically more important as an indicator of energy deficiency, rather than energy excess, and may mediate adaptation by driving increased food intake and directing neuroendocrine function to converse energy, such as inducing hypothalamic hypogonadism to prevent fertilization. Current studies investigate the role of leptin in weight-loss management because persons who have recently lost weight have relative leptin deficiency that may drive them to regain weight. Leptin deficiency is also evident in patients with diet- or exercise-induced hypothalamic amenorrhea and lipoatrophy. Replacement of leptin in physiologic doses restores ovulatory menstruation in women with hypothalamic amenorrhea and improves metabolic dysfunction in patients with lipoatrophy, including lipoatrophy associated with HIV or highly active antiretroviral therapy. The applications of leptin continue to grow and will hopefully soon be used therapeutically.

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Fifteen years ago, the discovery of leptin generated excitement that the treatment of obesity had been found. This prototypical adipocyte-secreted protein cytokine was named "leptin" after the Greek word *leptos,* meaning "thin." This discovery also pioneered the concept that adipose tissue is not an inert energy-storage organ but an active endocrine organ. Subsequent clinical trials led to initial disappointment, however, when leptin was eventually found to be ineffective for the treatment of obesity (1). Research efforts have since expanded to elucidating leptin's role in human physiology and have resulted in a fundamentally renewed understanding of its role in regulation of energy homeostasis, neuroendocrine function, and metabolism, mainly in states of energy deficiency and not energy excess (that is, obesity). In this review, we summarize the biology and physiology of leptin, its role in the pathophysiology of several disorders, and the emerging therapeutic applications of recombinant human leptin.

The Biology of Leptin

Leptin, a 167–amino acid product of the human leptin gene, was originally discovered through positional cloning of *ob/ob* mice, a mouse model of obesity found serendipitously at Jackson Laboratories (Bar Harbor, Maine) (2). These mice were found to have a homozygous mutation of the leptin gene resulting in complete leptin deficiency, which manifested as hyperphagia, extreme obesity, diabetes, neuroendocrine abnormalities, and infertility.

Leptin is secreted mainly by white adipose tissue, and levels are positively correlated with the amount of body fat (3). Like many other hormones, leptin is secreted in a pulsatile fashion and has significant diurnal variation, with higher levels in the evening and early morning hours (4, 5). Circulating leptin levels reflect primarily the amount of energy stored in fat and secondarily acute changes in caloric intake (4–8) (**Table 1**).

Leptin mediates its effects by binding to specific leptin receptors (ObRs) expressed in the brain and in peripheral tissues. Alternative splicing generates several isoforms of ObRs. The ObRa isoform (the short leptin receptor isoform) is thought to play an important role in transporting leptin across the blood–brain barrier (11). The ObRb iso-

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The circulating leptin level mainly reflects the amount of energy stores in adipose tissue and directs the central nervous system in regulating energy homeostasis, neuroendocrine function, and metabolism.

Leptin deficiency results in neuroendocrine deficits, including infertility, as well as metabolic abnormalities.

States of complete or severe leptin deficiency include rare cases of congenital leptin deficiency (due to mutations of leptin-related genes) and congenital lipoatrophy (due to lack of fat available to produce leptin).

States of relative acquired leptin deficiency include more prevalent conditions, such as anorexia nervosa, exercise-induced hypothalamic amenorrhea, and HIV lipoatrophy.

In physiologic replacement doses, recombinant human leptin treatment normalizes neuroendocrine and metabolic abnormalities in states of complete and relative leptin deficiency.

form (the long leptin receptor isoform) mediates signal transduction and is strongly expressed in the hypothalamus, an important site for the regulation of energy homeostasis and neuroendocrine function (12–14).

The binding of leptin to the ObRb receptor activates several signal transduction pathways, including Janus kinase signal transducer and activator of transcription 3 (JAK-STAT3), which is important for regulation of energy homeostasis (15), and phosphatidylinositol 3-kinase (PI3K), which is important for regulation of both food intake and glucose homeostasis (16). Other pathways, including mitogen-activated protein kinase (MAPK), 5'-adenosine monophosphate–activated protein kinase (AMPK), and the mammalian target of rapamycin (mTOR), have been proposed to be downstream of leptin and are under investigation (17).

Homozygous mutations of the leptin gene leading to complete leptin deficiency have been described in rare cases of obese humans. Most obese humans, however, have high circulating leptin levels (3) and are either resistant or tolerant to its weight-reducing effects (18). Proposed hypothalamic mechanisms underlying leptin resistance include defects at or downstream of the ObRb receptor, induction of inhibitors of leptin signaling (for example, suppressor of cytokine signaling 3 [19]), and alterations in the transport of leptin across the blood–brain barrier (18, 20). More studies are needed to fully elucidate leptin's signaling pathways and the mechanisms underlying leptin resistance or tolerance in humans, which in turn may lead to the development of novel treatment options for obesity and the metabolic syndrome.

Human Physiology and Pathophysiology

The most significant roles of leptin are regulation of energy homeostasis, neuroendocrine function, and metabolism. Other effects of leptin involving regulation of immune function (21, 22) and bone metabolism are under investigation but are beyond the scope of this review.

Energy Homeostasis

The circulating leptin level is a gauge for energy reserves and directs the central nervous system to adjust food intake and energy expenditure accordingly. Leptin exerts immediate effects by acting on the brain to regulate appetite (**Figure**). Through ObRb-receptor binding in the hypothalamus, leptin activates a complex neural circuit comprising anorexigenic (appetite-diminishing) and orexigenic (appetite-stimulating) neuropeptides to control food intake. Outside of the hypothalamus, leptin interacts with the mesolimbic dopamine system, which is involved in motivation for and reward of feeding, and the nucleus of the solitary tract of the brainstem to contribute to satiety (17).

In addition to immediate effects, long-term leptin administration may result in the rewiring of the connections among hypothalamic neurons (that is, it promotes synaptic plasticity) (25, 26). When administered in leptin-deficient mice, leptin has increased the number of synapses on neurons that secrete the anorexigenic neuropeptide proopiomelanocortin and decreased the number of synapses on neurons that secrete the orexigenic neuropeptide Y (26).

Not only does leptin signal the central nervous system to decrease food intake, it may also increase energy expenditure. In mice, leptin increases sympathetic nerve activity (27) and activates brown adipose tissue thermogenesis (28, 29); these effects have not been confirmed in humans (30).

Table 1. **Factors That Regulate Circulating Leptin Levels**

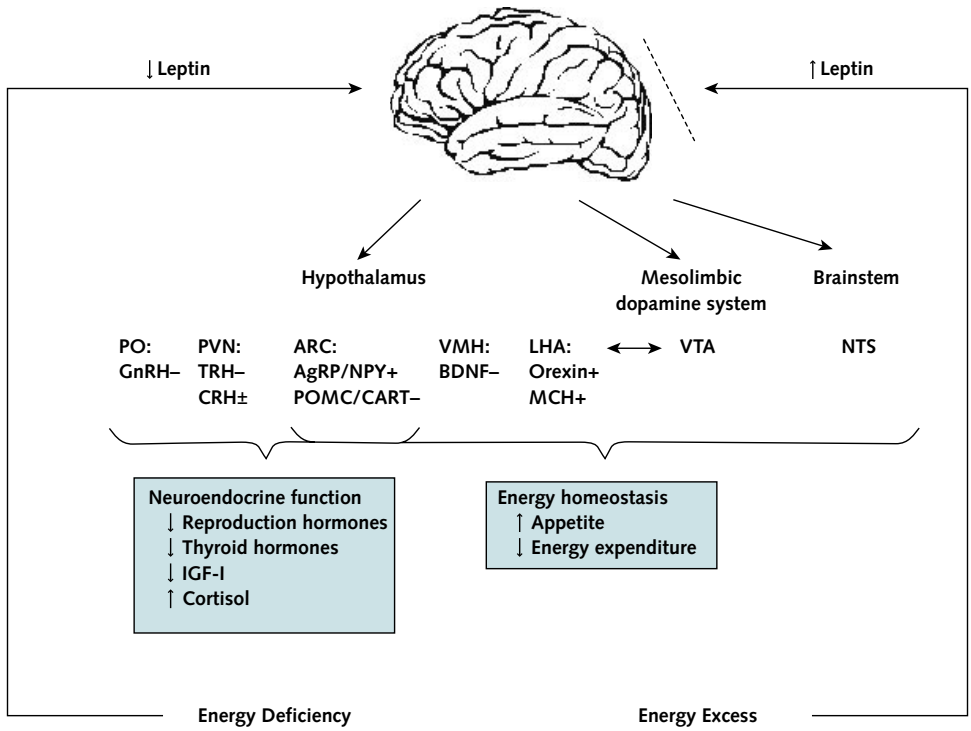
Factors promoting leptin secretion
Excess energy stored as fat (obesity)*
Overfeeding*
Glucose
Insulin
Glucocorticoids
Estrogens†
Inflammatory cytokines, including tumor necrosis factor-α and interleukin-6 (acute effect)
Factors inhibiting leptin secretion
Low energy states with decreased fat stores (leanness)*
Fasting*
Catecholamines and adrenergic agonists
Thyroid hormones
Androgens†
Peroxisome proliferator–activated receptor-γ agonists‡
Inflammatory cytokines, including tumor necrosis factor-α (prolonged effect)

* Denotes major factor influencing leptin levels.

† Women have higher levels than men, even after adjustment for body mass index and the effects of sex steroids, mainly because of different body-fat distribution (9, 10).

‡ Unlike in animals, peroxisome proliferator–activated receptor-γ agonists decrease leptin gene expression but increase subcutaneous fat mass in humans; thus, the net effect is null.

Figure. **The central effects of leptin in states of energy excess and deficiency.**



States of energy excess are associated with hyperleptinemia, but the hypothalamus is resistant or tolerant to the effects of increased leptin (*dashed line*). Energy deficiency results in hypoleptinemia. As a result, a complex neural circuit comprising orexigenic and anorexigenic signals is activated to increase food intake (17). There is increased expression of orexigenic neuropeptides: AgRP and NPY in the ARC (23) and orexin and MCH in the LHA. Furthermore, there is decreased expression of anorexigenic neuropeptides: POMC and CART in the ARC (23) and BDNF in the VMH. In addition to neurons that project from the LHA to the VTA, leptin also acts at the VTA of the mesolimbic dopamine system to regulate motivation for and reward of feeding. Leptin activation of the NTS of the brainstem also contributes to satiety. In addition, leptin has direct and/or downstream effects on the PVN and PO that are important for neuroendocrine responses to energy deprivation, including decreasing reproductive and thyroid hormones. For the sake of comparison, leptin acts only indirectly on the GnRH-secreting neurons in the hypothalamus, and it can act directly and indirectly on TRH-secreting neurons (17). The effect of leptin on cortisol levels during starvation differs in mice and humans. Unlike in normal mice (24), leptin administration does not reverse the elevated adrenocorticotropin levels associated with starvation in humans (7). The mechanism of leptin's effect on the growth hormone axis is unclear. AgRP = agouti-related protein; ARC = arcuate nucleus; BDNF = brain-derived neurotrophic factor; CART = cocaine- and amphetamine-regulated transcript; CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone; IGF-I = insulin-like growth factor I; LHA = lateral hypothalamic area; MCH = melanin-concentrating hormone; NPY = neuropeptide Y; NTS = nucleus of the solitary tract; PO = preoptic area; POMC = proopiomelanocortin; PVN = paraventricular nucleus; TRH = thyrotropin-releasing hormone; VMH = ventromedial hypothalamic nucleus; VTA = ventral tegmental area.

Clinically, patients with congenital leptin deficiency caused by mutations in the leptin gene or extreme leptin resistance caused by mutations of the leptin-receptor gene are obese because of marked hyperphagia (31, 32). For patients with leptin deficiency, administering leptin in replacement doses reduces food intake through neural circuits that diminish the perception of food reward and enhance the response to satiety signals (33) and normalizes body weight (34). However, leptin administration at pharmacologic doses to most obese humans, who have relatively high levels of leptin and are resistant to it, induces little or no weight loss (1, 35). Thus, accumulating evidence suggests that leptin is physiologically more important as an indicator of energy deficiency and as a possible mediator of adaptation to starvation.

Regulating Neuroendocrine Function

In response to fasting, leptin levels decrease rapidly before and out of proportion to any changes in fat mass (6, 7, 36), which triggers the neuroendocrine response to acute energy deprivation (7, 36, 37). In mice and humans, this response includes decreasing reproductive hormone levels, which prevents pregnancy (an energy-requiring process); decreasing thyroid hormone levels that slow metabolic rate; increasing growth hormone levels that may mobilize energy stores; and decreasing insulin-like growth factor 1 levels, which may slow growth-related processes (7, 37, 38). The interactions between leptin and the growth hormone and adrenal axes are apparently less important in humans than in animal models because patients with congenital leptin

deficiency have normal linear growth and adrenal function, unlike mice (34, 38–40).

We originally observed neuroendocrine abnormalities when starvation-induced decreases in leptin levels reached an average of 0.27 μg/L and leptin administration in physiologic replacement doses restored the changes in luteinizing hormone level pulsatility, decreases in testosterone levels, and decreases in thyroid-stimulating hormone level pulsatility (7). We then ascertained whether there is a minimum leptin threshold to allow reproduction and to maintain other neuroendocrine processes. When we induced leptin deficiency in normal-weight women with higher baseline leptin levels, leptin levels decreased to an average of 2.8 μg/L (36). We observed only modest changes in luteinizing hormone pulsatility. Our findings suggest that a leptin threshold value of about 3 μg/L is necessary to convey the message to the brain that energy stores in adipose tissue are adequate to bring pregnancy to term. Reaching a leptin level above this threshold during growth in children permits the onset of puberty (41) and maintains reproductive and other neuroendocrine processes in older persons.

Given that women with anorexia nervosa and exercise-induced amenorrhea are chronically energy-deprived, we first hypothesized that these conditions are associated with hypoleptinemia. This was confirmed in observational studies (42–45). We then hypothesized that long-standing hypoleptinemia leads to neuroendocrine dysfunction with subsequent anovulation and osteoporosis. We conducted a proof-of-concept trial of leptin treatment in replacement doses in women with hypothalamic amenorrhea and found that it improves or fully normalizes the gonadal; thyroid; and, to a lesser degree, growth hormone axes, as well as bone markers (46).

Insulin Resistance and the Metabolic Syndrome

Both *ob/ob* mice and *db/db* mice, which have a leptin-receptor mutation, as well as humans with congenital leptin deficiency have insulin resistance and other features of the metabolic syndrome. In the *ob/ob* mouse strain, leptin treatment improves hyperglycemia and hyperinsulinemia before weight loss is achieved (47). Leptin treatment in humans with congenital leptin deficiency has also been shown to improve not only hyperinsulinemia but also levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides (39). Both central and peripheral actions mediate these effects, and the mechanisms are still being elucidated.

Similarly, mouse models of lipoatrophy, which lack subcutaneous adipose tissue, are hypoleptinemic because they lack the fat to produce leptin and have metabolic abnormalities, including hyperglycemia, insulin resistance, and hyperlipidemia (48). Given the improvements in metabolic variables in *ob/ob* mice after leptin administration, it was hypothesized that lipoatrophic mice may also be responsive to exogenous leptin (49). Transplantation of adipose tissue (48, 50), which produces leptin, and administration of exogenous leptin (49) in lipoatrophic mice improve hyperglycemia, insulin resistance, hypertriglyceridemia, and hepatic steatosis. This has led to trials in humans with various types of lipoatrophy and associated metabolic abnormalities (51–58) and is further described in the following section.

Leptin plays a pivotal role in the regulation of energy homeostasis, neuroendocrine function, and metabolism in states of energy excess and, more important, in states of energy deficiency. Thus, leptin deficiency results in distinct clinical phenotypes (**Table 2**) with associated neuroendocrine and metabolic abnormalities for which recombinant human leptin is an emerging potential therapy.

Clinical Applications: Recombinant Human Leptin as a Treatment of Leptin Deficiency Syndromes in Humans

Obesity Syndromes

Leptin Deficiency in Obesity: Mutations of the Leptin Gene

Patients with congenital complete leptin deficiency due to homozygous leptin gene mutations develop extreme obesity very early in life and respond to recombinant human leptin treatment, which reduces appetite and food intake, leading to dramatic body fat loss (32, 34, 40). Furthermore, these patients have distinct neuroendocrine abnormalities, including hypogonadotropic hypogonadism with failure to reach puberty, which improve with leptin replacement (34). These mutations are rare, but they should be considered in young patients with severe, early-onset obesity and hyperphagia because congenital leptin deficiency is easily treated. Amylin Pharmaceuticals (San Diego, California) provides leptin for congenital leptin deficiency through a compassionate-use program.

Leptin Resistance in Common Obesity

Because mechanisms of leptin resistance remain largely unknown, strategies to address leptin resistance in common obesity have included supraphysiologic doses of leptin and coadministration with presumed leptin sensitizers. An early trial with high pharmacologic doses of leptin resulted in no clinically significant weight loss (1). Recently, amylin, a hormone secreted by the pancreas that also contributes to the regulation of energy homeostasis, was proposed to improve leptin responsiveness in diet-induced obesity (35). A recent study conducted by Amylin Pharmaceuticals found that overweight and obese participants lost significantly more weight when receiving a combination of leptin and pramlintide (an analogue of amylin) compared with either agent alone (64). Of note, the effects seem additive, suggesting that amylin may not improve sensitivity to leptin, and the withdrawal rate was high, at 32%.

A more promising area of clinical interest is the potential role of leptin treatment in weight-loss maintenance. It has been proposed that decreasing leptin levels due to weight loss activate neuroendocrine mechanisms, which

Table 2. **Leptin-Deficient States**

Syndrome	Estimated Prevalence	Associated Features
Congenital leptin-deficient states		
Leptin gene mutations		
Homozygous congenital leptin deficiency	Rare	Early-onset morbid obesity, hyperphagia, hypogonadotropic hypogonadism, advanced bone age, hyperinsulinemia, and immune dysfunction. These manifestations are normalized by leptin treatment in replacement doses.
Heterozygous congenital leptin deficiency	Rare	Less severe obesity that may respond to exogenous recombinant human leptin, although this remains to be studied in interventional studies (59).
Mutations leading to lipoatrophy		
Congenital lipoatrophy	Rare	Lipoatrophy, diabetes, and the metabolic syndrome; metabolic abnormalities improve in response to leptin administration, but no randomized, controlled trials have been done.
Acquired leptin-deficient states		
Generalized decrease in adipose tissue mass		
Anorexia nervosa	Up to 2.2% lifetime prevalence for women (60)	Profoundly decreased body weight and fat mass, amenorrhea or infertility, osteoporosis with stress fractures, decreased thyroid hormone levels, increased growth hormone levels, and decreased IGF-I levels.
Exercise-induced hypothalamic amenorrhea, ovulatory dysfunction, or both	Amenorrhea has been reported in 60%–69% of trained female athletes and ovulatory dysfunction in ≤78% of recreational female athletes (61)	Lower percentage of body fat with or without decreased body weight, amenorrhea or infertility, osteoporosis, and neuroendocrine abnormalities listed above. Abnormalities improved in response to leptin treatment in a proof-of-concept controlled trial (46). Larger randomized, placebo-controlled trials are under way.
Nonathletic forms of hypothalamic amenorrhea	7.6% in women aged 15–24 y, 3.0% in women aged 25–34 y, and 3.7% in women aged 35–44 y (62)	Relatively normal or slightly decreased body weight but lower percentage of body fat, amenorrhea or infertility, and neuroendocrine abnormalities listed above.
Selective decrease in adipose tissue mass		
Acquired severe lipoatrophy and insulin resistance	Rare	Lipoatrophy, insulin resistance, hypercholesterolemia, and hypertriglyceridemia. These metabolic abnormalities improved with leptin replacement in uncontrolled clinical trials (53, 54, 57, 58).
HIV lipoatrophy	15%–36% of all patients with HIV (63)	Lipoatrophy, insulin resistance, hypercholesterolemia, and hypertriglyceridemia. These metabolic abnormalities improved with leptin replacement in both open-label (56) and randomized, placebo-controlled crossover (55) clinical trials.

IGF-I = insulin-like growth factor I.

may drive patients to regain weight. These mechanisms may include increasing energy intake by increasing hunger and decreasing energy expenditure by decreasing thyroid hormone levels and subsequently slowing metabolism (65). Thus, replacing leptin may restore these neuroendocrine abnormalities and prevent "yo-yo" dieting, which is commonly seen in clinical practice. This replacement is under investigation and, if successful, may have major implications in weight-loss management.

States of Energy Deficiency

Leptin Deficiency With Generalized Decrease in Adipose Tissue Mass: Exercise- and Diet-Induced Hypothalamic Amenorrhea

Hypothalamic amenorrhea is the cessation of menstrual cycles due to dysfunction of the hypothalamic–pituitary–gonadal axis in the absence of organic disease. It is associated with strenuous exercise, stress and reduced food intake and includes patients with anorexia nervosa; female athletes with the well-recognized triad of low energy availability with or without disordered eating, amenorrhea or neuroendocrine dysfunction, and osteoporosis; and normal-weight patients with ovulatory dysfunction.

After our observational studies showed that women with hypothalamic amenorrhea are hypoleptinemic (42–44), our proof-of-concept study demonstrated that leptin replacement in these women normalizes levels of estrogen, thyroid hormones, and insulin-like growth factor I and, more important, restores ovulatory menstruation (46). Leptin also increased markers of bone formation but did not alter bone resorption. More randomized, placebo-controlled studies are elucidating the effects of longer-term recombinant human leptin treatment on neuroendocrine function, immune function, and bone metabolism in these women.

Leptin Deficiency With Selective Decrease in Adipose Tissue Mass: Lipoatrophy

Persons with rare syndromes of congenital lipoatrophy have severe insulin resistance, hypercholesterolemia, and hy-

pertriglyceridemia. Observational studies have shown that these persons have hypoleptinemia (66, 67), and several uncontrolled studies have demonstrated that treatment with recombinant human leptin improves insulin resistance, suppresses hepatic gluconeogenesis, decreases hemoglobin A_{1c} levels by about 3.5%, improves hyperlipidemia (57, 58), and reverses hepatic steatosis (53, 54). Studies have also shown that leptin treatment restores menstrual cycles in women with lipoatrophy and features of the polycystic ovary syndrome (68). Leptin is available for congenital lipoatrophy through a U.S. Food and Drug Administration–approved expanded-access program.

Although congenital lipoatrophy is rare, acquired lipoatrophy has become more prevalent, as 15% to 36% of patients with HIV develop lipoatrophy in association with HIV or highly active antiretroviral therapy (63). We have shown that these patients, who also have increased cardiovascular risk (69), have relative leptin deficiency (51). Subsequently, we demonstrated in our proof-of-concept trial that treatment with recombinant human leptin in individuals with highly active antiretroviral therapy–induced metabolic syndrome and hypoleptinemia improves insulin resistance, improves hyperlipidemia, and decreases central fat mass within 2 months (55). A 6-month independent study confirmed these results (56). Once further clinical trials define the treatment protocols for optimal efficacy and safety, human recombinant leptin alone or in combination with thiazolidinediones, which also improves glucose homeostasis possibly through another adipocyte-secreted hormone adiponectin (70), might serve this growing population.

CONCLUSION

Leptin regulates energy homeostasis, neuroendocrine function, and metabolism. Leptin deficiency is a clinical syndrome associated with distinct phenotypes, which encompass a very small subset of obesity (those from leptin-related gene mutations), hypothalamic amenorrhea, and lipoatrophy. Recombinant human leptin is an emerging potential therapy for these leptin-deficient conditions because in replacement doses, it normalizes neuroendocrine and metabolic functions in recent proof-of-concept clinical trials. Randomized, placebo-controlled clinical trials continue to evaluate leptin as a potential treatment for weight-loss maintenance, and the development of leptin sensitizers for common obesity is greatly anticipated in the near future. We hope that recombinant human leptin will soon find its place in the therapeutic armamentarium.

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