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Leptin applications in 2015: What have we learned about leptin and obesity?

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Abstract

Purpose of review—To summarize previous and current advancements for leptin therapeutics, we described how leptin may be useful in leptin deficient states such as lipodystrophy, for which leptin was recently approved, and how it may be useful in the future for typical obesity.

Recent findings—The discovery of leptin in 1994 built the foundation for understanding the pathophysiology and treatment of obesity. Leptin therapy reverses morbid obesity related to congenital leptin deficiency and appears to effectively treat lipodystrophy, a finding which has led to the approval of leptin for the treatment of lipodystrophy in the USA and Japan. Typical obesity, on the other hand, is characterized by hyperleptinemia and leptin resistance. Thus, leptin administration has proven ineffective for inducing weight loss on its own but may be useful in combination with other therapies or for weight loss maintenance.

Summary—Leptin is not yet able to treat typical obesity, however, it is effective for reversing leptin deficiency-induced obesity and lipodystrophy. New mechanisms and pathways involved in leptin resistance are continuously discovered, while the development of new techniques and drug combinations which may improve leptin's efficacy and safety regenerate the hope for its use as an effective treatment for typical obesity.

Keywords

leptin; obesity; lipodystrophy; leptin resistance; hypoleptinemia

Introduction

Leptin is an adipocyte-secreted hormone, discovered in 1994 [1] that circulates primarily at levels proportional to the amount of adipose tissue, signaling long-term energy storage, and secondarily at levels modified by acute changes in caloric intake [2]. Altogether, leptin appears to generally regulate energy homeostasis, decreasing energy intake and increasing energy expenditure [2]. Leptin receptors are expressed throughout the body, including the

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Conflicts of interest

None

central nervous system, where leptin acts to regulate neuroendocrine function, feeding behavior and energy expenditure [3]. Leptin is known to cross the blood brain barrier where it acts mainly through the arcuate nucleus of the hypothalamus to regulate energy homeostasis. Specifically, it inhibits neuropeptide Y (NPY) and agouti-related peptide (AgRP), which are orexigenic and increase food intake, and stimulates pro-opiomelanocortin (POMC), which in turn activates anorexigenic factors such as α -melanocyte stimulating hormone (α MSH) that inhibit food intake [4,5,6]. Leptin performs these actions by binding to and dimerizing the leptin receptor, which in turn activates many intracellular signaling pathways that have been summarized elsewhere (**Figure 1**) [7].

More generally, leptin plays a critical role in several hypothalamic pathways, including those for development and reproductive functioning [8,9,10,11]. Leptin replacement in leptin deficient individuals can successfully restore and regulate hypothalamic neuroendocrine axes, including the thyroid, gonadal, adrenocorticotrophic hormone (ACTH)-cortisol and growth hormone axes [9,12,13,14,15]. In terms of broader neural control, leptin also seems to play a role in whole brain cognition, emotions, and memory [16,17,18]. Although leptin should decrease weight when circulating at high levels, many typical cases of obesity demonstrate leptin resistance, which we are only beginning to understand [19]. Thus, we will first discuss how leptin impacts cases of leptin deficiency and then how it may act within cases of leptin resistance, which is often the case for typical obesity.

Leptin deficiency

Many of the early cases of obesity in mice and humans were cases of leptin deficiency, and giving leptin to these humans or mice restored a normal weight [20,21,22,23]. Many human studies of leptin deficiency have been performed without a placebo-control and in a small number of cases, leading to additional questions. We will first discuss congenital leptin deficiency, followed by acquired leptin deficiency and finally, lipodystrophy and lipodystrophy for which leptin has been recently approved.

Congenital leptin deficiency is often caused by mutations in leptin which leads to obesity as well as dysregulation of the hypothalamic axes, and which can be corrected by leptin replacement [24,25]. Previously known mutations in leptin or the leptin receptor, as well as those recently discovered [26*,27*,28*], have been well-studied in animal models but represent a very small amount, 5%, of human obesity [29]. Eighteen months of leptin replacement therapy induced significant weight loss, decreased energy intake, increased energy expenditure, and corrected the hypothalamic hormone axes of three patients with congenital leptin deficiency [30]. Leptin administration also changes how these patients respond to visual food cues during functional magnetic resonance imaging (fMRI). In one patient with congenital leptin deficiency, three-day and six-month leptin replacement decreased activity to food cues [14]. In another study of two patients with this same disorder, one week of leptin replacement decreased activation to food images in striatal brain areas [31]. Additionally, in three other patients, leptin replacement reduced activity to food images in attention/satiety-related areas, and increased activation in areas related to cognitive control and satiety [32]. These studies suggest that in leptin deficiency, leptin

replacement may influence neuronal circuitry related to the perception of food reward and thus facilitate weight loss.

On the other hand, acquired leptin deficiency is often observed in cases of low body weight, one example of which is hypothalamic amenorrhea (HA). HA is defined by a lack of menstruation due to hypothalamic-pituitary-gonadal axis dysfunction caused by chronic energy deficiency related to exercise, stress and/or prolonged decreases in food intake [11,33,34,35,36,37]. Similar to patients with congenital leptin deficiency, patients with HA have dysregulated gonadal, thyroid, growth hormone and adrenal axes [34,38,39,40]. These can all be restored to normal levels with leptin replacement therapy [10,12,15,41]. Most recently, we showed that three hypoleptinemic women with HA had no structural brain differences from healthy controls and/or in response to leptin treatment [42*]. However, these hypoleptinemic women showed enhanced activations to food cues in areas related to salience and reward after short-term (1 week) therapy, and decreased activations to food cues in areas involved in attention and reward after long-term (6 months) treatment [42*]. Although similar to congenital leptin deficiency, these women had normal levels of leptin during development, which may account for differences in gray matter volume or brain size changes. Regardless, leptin replacement continues to show actions on the neuroendocrine axis and how the brain views food cues.

At the forefront for leptin due to recent approvals, lipodystrophy is defined by a partial or complete lack of fat, or lipoatrophy, that may co-occur with excesses of fat, or lipohypertrophy, in other body areas [43]. Thus, since lipoatrophy is inadequate fat storage due to a lack of adipose tissue and obesity is a case of inadequate fat storage due to overuse, lipoatrophy can be a useful model for obesity. Since lipodystrophy clearly indicates changes in adipose storage, the resultant altered adipokine levels may lead to the observed metabolic dysfunction in lipodystrophy. Lipodystrophy is characterized by hypoleptinemia and can be congenital or acquired, such as for HIV-associated lipodystrophy syndrome (HALS) or highly active antiretroviral therapy (HAART) [44,45,46*]. Indeed, lipoatrophy is a state of leptin deficiency [45,46*], and leptin replacement therapy improves insulin resistance and metabolic syndrome in animal models of lipoatrophy [47].

In mouse models of lipodystrophy, leptin replacement significantly improved the observed metabolic abnormalities, such as insulin resistance, hepatic steatosis, and hyperlipidemia [48]. These then provided the basis for leptin replacement trials in lipodystrophic humans. In both patients with congenital and acquired lipodystrophy, leptin therapy improves the observed hyperinsulinemia, hyperlipidemia, and neuroendocrine dysfunctions [49,50,51,52,53,54,55,56,57,58,59,60,61,62,63]. For instance, hepatic steatosis, caused by dangerous fat build up in the liver, can be corrected by leptin replacement therapy in these patients [51,55,56,57,60,63]. Hyperlipidemia, or elevated lipids in the blood, is also improved with leptin therapies [51,52,53,54,55,56,58,60,61,62,63]. Fewer studies have examined changes in the hypothalamic hormonal axes. After four months and up to a year of leptin administration in men and women with lipoatrophy, much of the hypothalamic gonadal axes were normalized [58,64]. Insulin-like growth factor 1 (IGF-1) also increased following the leptin therapy [64]. No differences were observed for growth, thyroid, or adrenal hormone levels [64], but since this study in lipoatrophic subjects was uncontrolled,

future studies will need to discover the impacts of metreleptin on neuroendocrine function and/or whether there are effects beyond confounders such as any changes attributable to placebo effects, study participation (and hospitalization in clinical research centers), or time.

Future studies focusing on signaling and mechanisms are thus required. Little is known about neuroimaging or any neurocognitive effects of metreleptin, the recombinant human analog, in lipoatrophic patients. Only one study has been performed in lipodystrophic patients, who had been treated with metreleptin, as compared to controls, who were not given any medications/placebo while participating in the study [65]. When patients were taken off of therapy for four days, patients showed no changes under fasting, but in the fed state, they showed decreased activations of reward and satiety related areas such as the amygdala, insula, nucleus accumbens, caudate, putamen, and globus pallidus, which were corrected while they were on leptin therapy [65]. These compelling but not always consistent results call for further examination and study of how metreleptin acts in lipoatrophic patients.

Typical obesity and leptin resistance

The obesity epidemic is a serious public health problem affecting both developed and developing countries [66]. Obesity is associated with increased morbidity and mortality as well as a reduced quality of life [67]. Leptin plays a clear role in obesity etiology, pathophysiology and health outcomes, although these have not yet been fully elucidated. Very recently, FDA approved leptin's administration for the treatment of lipodystrophy in the US; in Japan, it has been approved since March 2013 [68], and thus, upcoming publications exploring the use of leptin therapies in human subjects would be expected in a few years from now.

As discussed above, early onset severe obesity could be attributed to specific, rare, mutations of genes involved in the leptin pathway [69] resulting either in congenital leptin deficiency or in ineffective high levels of leptin and in leptin resistance [70]. The modern typical obesity is characterized by elevated leptin levels, or hyperleptinemia, and from resistance to the anorectic and body weight reducing effects of leptin. This was first described in early leptin research where obese people showed an overexpression of the *ob* gene in adipose tissue [71]. Furthermore, a strong positive association among serum leptin concentrations and the percentage of body fat in humans was observed while obese individuals had higher leptin serum levels and adipocyte *ob* mRNA content compared to individuals of normal weight [72,73]. What is more, leptin levels and the *ob* mRNA content fell during weight loss but increased again during weight loss maintenance [73], all evidence indicating leptin resistance. Interestingly, however, a very recent study provided evidence that the cessation of leptin administration didn't result in the expected weight increase obesity-induced hyperleptinemia is related with, indicating that hyperleptinemia, per se, does not mimic the central nervous system consequences of chronic weight gain in diet-induced obese mice, although interpretations of this should be cautious [74**].

Leptin resistance may relate either to a defect in the transport of leptin across the blood brain barrier or to deficits in intracellular signaling mechanisms downstream of leptin [75].

Several mechanisms and pathways related to the development of leptin resistance have been described in the past [76,77] and new ones are continuously discovered. The phosphodiesterase-3B (PDE3B)-cAMP- and Akt-pathways of leptin signaling in the hypothalamus, the fat mass and obesity-related (FTO) gene, transient receptor potential vanilloid type (TRPV)-1 channel, 15-deoxy- (12,14)-prostaglandin J2 (15d-PGJ2), estradiol (E2) and peroxisome proliferator-activated receptor γ (PPAR γ) are some of the recently identified molecules/pathways to be involved in leptin's resistance development in animal studies [78*,79*,80*,81*,82*,83*]. Although this new knowledge creates new pathways for understanding leptin resistance, these still need to be confirmed in humans.

The discovery of leptin generated a new hope for the treatment of obesity. Leptin therapy was studied in the past for inducing weight loss and maintaining lost weight. However, leptin replacement with metreleptin reversed morbid obesity only in leptin deficient animals and humans [84,85], while leptin administration in typically obese individuals with elevated leptin levels had limited efficacy [86,87*,88]. Weight loss resembles a condition of relative leptin insufficiency and results in several metabolic adaptations that are correlated, at least partly, with the change in leptin levels [89*,90*,91]. Furthermore, leptin administration in a state of reduced weight may prevent weight regain. Specifically, leptin administration in obese people who lost at least 10% of their initial body weight prevented reductions in energy expenditure, sympathetic nervous system tone, and bioactive thyroid hormones and also increased skeletal muscle work efficacy, promoted delayed satiation and reduced neural sensitivity to food cues reversing the decline in hypothalamic activation following weight loss [92,93,94,95]. Furthermore, leptin replacement has been found to diminish sweet cravings in women that have undergone Roux-en-Y gastric bypass despite no further weight loss [96**,97]. The short half-life of leptin [98,99], the reduced transportation through the blood brain barrier or the central non-responsiveness to leptin [75], the development of antibodies against leptin [88] along with several adverse events related to its administration are just some of the obstacles that need to be addressed. Although leptin's use in humans has been very recently re-approved for lipodystrophic states, the development of safer and longer-lasting leptin analogs and/or molecule combinations may bring back the hope for treating certain leptin-sensitive obese individuals.

New techniques, like PASylation of leptin for prolonging its half-life [100**] or chemical modification of the native leptin with P85 for increasing leptin's transport through the blood brain barrier [101*] could increase leptin's efficacy. Furthermore, the efficacy seems to increase when leptin is co-administered with other molecules and several combinations have been tested so far. The combination of pramlintide/metreleptin, was one of the most promising ones, although the clinical trial was halted in 2011 due to undesirable laboratory findings [102]. Recent examples from animal studies indicate that drugs that activate the 5-hydroxytryptamine (5-HT)_{2C} receptors, such as meta-chlorophenylpiperazine, could act as leptin sensitizers and can have additive body-weight lowering effects when co-administered with leptin in diet-induced obese mice [103*]. Furthermore, the administration of leptin along with insulin presents a synergistic effect on hypothalamic neurons to promote browning of the white adipose tissue and facilitate weight loss in mice [104*]. What is more, the combination of leptin and liraglutide generates an additive effect in reducing cumulative food intake and body weight through reduced meal frequency in lean rats [105*]. Research

on this field is very promising and exciting but these results need to be confirmed in humans. However, these new discoveries hold strong promise for the development of an effective therapy against obesity.

Conclusions

Over the past 20 years since the discovery of leptin, research has delved into how leptin can be successfully implemented as a therapeutic tool. Although leptin has been effective for only a small number of individuals with obesity and leptin deficiency, the recent approval of leptin for lipodystrophy provides a useful model for studying how leptin may interact with metabolic dysfunctions of obesity. Findings from these populations have really illuminated how leptin acts peripherally and perhaps more importantly, centrally to influence how the brain views and reacts to food cues. Furthermore, despite leptin resistance in typical obesity, leptin may still be a valuable therapeutic for obesity in the context of weight loss and/or in conjunction with other therapies. Future research will continue to improve upon these findings and to illuminate the usefulness of leptin for obesity.

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Key Points

- Leptin therapy is useful in treating obesity related to congenital leptin deficiency.
- Leptin has been recently approved for lipodystrophy, which is a model for typical obesity.
- Typical obesity presents with leptin resistance but leptin may still be valuable after weight loss or in conjunction with other therapies.

Figure 1. Leptin dimerizes the leptin receptor (LepR) and activates a number of intracellular signaling molecules

JAK2 phosphorylates three tyrosine sites on the LepR and activates STAT3, which inhibits melanocortin, PI3K, which in turn acts on the insulin receptor, AKT, and mTOR pathways, and STAT5, whose function is not yet well defined. At Tyr985, SOCS3 and SHP2 both feedback to inhibit JAK2, and SHP2 activates ERK pathways. At Tyr1077, STAT5 activation leads to gene expression changes. At Tyr1138, STAT3 alters gene expression and activates SOCS3, which feeds back to inhibit JAK2.