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REVIEW

Leptin and leptin resistance in obesity: current evidence, mechanisms and future directions

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Abstract

Leptin, a key adipokine regulating energy homeostasis, has been extensively studied for its potential in the management of obesity. However, its therapeutic efficacy is often limited due to leptin resistance. This review synthesizes animal and clinical evidence on leptin's role in obesity, focusing on models such as genetically deficient mice (e.g., *ob/ob*, *db/db*), diet-induced obesity mice, and clinical conditions such as congenital leptin deficiency (CLD), leptin receptor deficiency (LRD), lipodystrophy, and common obesity. The mechanisms underlying leptin resistance are summarized, including hyperleptinemia, impaired JAK2–STAT3 signaling, reduced blood–brain barrier permeability, defective autophagy, endoplasmic reticulum stress, inflammation, decreased leptin receptor expression, leptin signaling pathway dysfunction, increased mTOR activity, and peripheral leptin resistance. Due to these leptin receptor and/or post-receptor signaling pathway defects, leptin or its analogs usually fail to produce the expected weight-loss effect in individuals with overweight or obesity, although they remain highly effective in individuals with CLD and lipodystrophy, as well as in ob/ob mice. Alternative strategies, such as melanocortin-4 receptor (MC4R) agonists (e.g., setmelanotide) for LRD treatment, are very promising. Future directions include enhancing leptin sensitization, combining leptin with other drugs, and exploring partial leptin reduction to mitigate compensatory responses during weight loss. The review emphasizes the complexity of leptin resistance and the necessity of targeted approaches in obesity therapy.

Keywords: obesity; leptin resistance; partial leptin reduction; weight loss; treatment strategies

Introduction

The prevalence of obesity and associated diseases has been obviously increasing in recent years, and there are growing interests in the pathogenesis of obesity and the development of anti-obesity drugs.

The discovery of leptin by Friedman's team in 1994 marked a watershed moment in obesity research (1). Leptin is a hormone secreted by white adipose tissue (WAT) that plays a pivotal role in regulating food intake, energy expenditure, body weight, and puberty. This adipocyte-derived hormone, a key afferent signal to hypothalamic energy homeostasis centers, demonstrated remarkable anti-obesity efficacy when used to treat *ob*/*ob* mice – the genetically leptin-deficient model, as evidenced by a 50% reduction in body weight within weeks (2). These findings raised hopes for a potential 'hormonal cure' for obesity, culminating in rapid clinical translation. However, early human trials revealed a striking paradox: while leptin replacement produced dramatic anti-obesity benefits in rare congenital leptin deficiency (CLD) cases with obesity (3), it showed marginal efficacy in common obesity (4). This discrepancy between preclinical promise and clinical reality exposed critical gaps in leptin biology.

Emerging evidence suggests that leptin resistance – a state of attenuated biological response despite hyperleptinemia – lies at the heart of this therapeutic

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Table 1 Comparisons of animal obesity models in leptin signaling defects and their therapeutic response to leptin therapy.

Model	Key features	Leptin levels	Response to leptin therapy	Underlying mechanism
ob/ob mice	Mutation in *ob* gene (leptin-deficient); severe obesity, hyperphagia, infertility, low energy expenditure (2)	Very low or absent	Highly responsive: weight loss, improved glucose/lipid metabolism, restored fertility	Lack of leptin; exogenous leptin restores normal signaling via leptin receptors (11, 12)
db/db mice	Mutation in *Lepr* gene (leptin receptor-deficient); severe obesity, diabetes (20)	Very high (hyperleptinemia)	Unresponsive: no improvement in body weight, glucose levels, or metabolism	Leptin receptor dysfunction; impaired binding and JAK–STAT signaling pathway → leptin resistance (10)
Diet-induced obese (DIO) mice	HFD leads to obesity with elevated leptin and impaired leptin sensitivity; mimics common human obesity (24, 25)	High	Poorly responsive: limited or no effect of exogenous leptin	Chronic leptin elevation → impaired BBB transport, decreased receptor expression, and signaling defects → acquired leptin resistance (26, 30)
Lipodystrophic mice	Food-induced or genetically modified mice (32, 33, 34)	Low	Responsive: both metabolic and cardiovascular benefits	Lack of leptin; exogenous leptin supplement improves glucolipid metabolism (32, 33, 34)

JAK-STAT, Janus tyrosine kinase-signal transducer and activator of transcription; BBB, blood–brain barrier; HFD, high-fat diet.

failure (5). Hyperleptinemia is commonly observed in most people with obesity, implying that elevated leptin levels cannot effectively act on pro-opiomelanocortin (POMC) neurons and neuropeptide Y/Agouti-related protein (NPY/AgRP) neurons in the hypothalamus to suppress appetite and increase energy expenditure. This phenomenon is defined as leptin resistance (5). Unlike insulin resistance, which primarily involves peripheral tissues, leptin resistance may manifest as a 'triple defect': impaired blood–brain barrier (BBB) transport (6), disrupted leptin signaling (via suppressor of cytokine signaling 3 (SOCS3) overexpression and leptin receptor (LEPR) mutations) (7, 8), and central as well as peripheral leptin resistance (9).

This review synthesizes current knowledge on leptin biology to address a central question: why does leptin therapy fail in common obesity despite its conceptual elegance? We systematically analyze i) evidence from animal and clinical studies, ii) molecular mechanisms of leptin resistance, and iii) emerging therapeutic strategies.

The effects of treatment for obesity with leptin and its analog based on clinical trials and animal evidence

Animal evidence

Leptin or leptin receptor deficiency (LRD) genetic obesity models

As reported, *ob/ob* and *db/db* mice carry mutations in the *LEP* and *LEPR* genes, respectively. Both *ob/ob* and *db/db* mice exhibit severe obesity, hyperphagia, reduced body temperature and energy expenditure, infertility, and diminished physical activity compared with lean controls (2, 10).

Several strategies have been developed to deliver leptin and restore metabolic balance in *ob/ob* mice. Multiple studies have demonstrated the efficacy of daily intraperitoneal injections of recombinant leptin (OB protein). Daily intraperitoneal injections of recombinant leptin (OB protein) have been shown to reduce body weight, fat mass, food intake, and serum glucose and insulin, while enhancing energy expenditure, body temperature, and physical activity (2, 11). Different doses of leptin administration also improved glucose metabolism and thermoregulation in *ob/ob* mice (12). Second, the use of leptin analogs has emerged as a promising alternative. Bolze *et al.* (13) developed PAS (600)-leptin, a long-acting leptin analog generated through PASylation, which achieved rapid weight loss, primarily via appetite suppression and enhanced thermogenesis. Third, a novel strategy involving engineered gut-derived cells regulated by the drug mifepristone has been explored for leptin delivery, and it was reported to reduce food intake and improve diabetic phenotypes (14). Finally, transplantation of WAT from wild-type mice has been shown to normalize metabolic and immune dysfunctions, offering an alternative means of leptin restoration (15, 16).

Leptin intervention in *ob/ob* mice not only exerts a weight-reducing effect but also enhances physical activity, lowers blood glucose and insulin levels (11, 17), alleviates hepatic steatosis (18), and improves both myocardial metabolism and mitochondrial function (19). These findings underscore leptin's critical role in energy homeostasis and support its therapeutic potential – at least in cases of leptin deficiency (Table 1).

db/db mice carry mutations in the leptin receptor gene, resulting in nonfunctional leptin signaling. Despite normal or elevated leptin levels, they exhibit severe obesity, chronic hyperglycemia, and pancreatic β-cell dysfunction (20). As reported, exogenous leptin administration in *db/db* mice failed to improve their obesity-related phenotype (21). The *Lepr* gene mutation in *db/db* mice impaired the effective binding of leptin to its receptor and the subsequent activation of downstream signaling pathways, such as the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway (10). Due to LRD, *db/db* mice exhibit severe leptin resistance and fail to regulate appetite, energy expenditure, or lipid metabolism. These findings highlight the importance of intact leptin–receptor signaling and explain the limited efficacy of leptin therapy in leptin-resistant individuals (Table 1).

Diet-induced obesity (DIO) models

DIO models more closely mimic the common forms of human obesity, wherein obesity arises from chronic overconsumption of a high-fat diet (HFD) rather than a single gene mutation. When rodents are fed a hypercaloric HFD over time, they develop obesity characterized by elevated leptin levels and reduced leptin sensitivity (22).

As is known, most individuals with overweight or obesity exhibit markedly elevated baseline leptin levels (23). Following treatment with leptin-based therapies, leptin levels rise even further, yet without meaningful reductions in body weight or fat mass. This lack of response may be attributed to sustained hyperleptinemia, both before and after treatment, aligning with the prevailing notion that chronic hyperleptinemia drives leptin resistance (24). On the other hand, hyperleptinemia has also been proposed as a compensatory response to pre-existing leptin resistance (7). Similarly, studies have shown that under HFD conditions, chronic elevation of serum leptin levels increases susceptibility to obesity in mice (25). In 2010, Knight *et al.* (26) demonstrated that hyperleptinemia drives leptin resistance in HFD-induced obesity. In their study, leptin was exogenously administered to leptin-deficient *ob/ob* mice to maintain serum leptin concentrations within the physiological range. As a result, these mice retained leptin sensitivity even when fed an HFD. In contrast, wild-type mice exhibited elevated serum leptin levels and reduced leptin sensitivity following HFD feeding, accompanied by impaired leptin receptor signaling. These findings suggest that elevated leptin levels contribute to the development of leptin resistance under HFD conditions. Further evidence was provided by Zhao *et al.* (27) and Pretz *et al.* (28), who used leptin transgenic mice or exogenous leptin intervention and confirmed that increased serum leptin levels under HFD-induced obesity accelerated the development of obesity. This was confirmed by metabolic abnormalities such as impaired glucose tolerance, decreased insulin sensitivity, and increased hepatic lipid accumulation. Leptin has been shown to promote lipolysis in a dose-dependent manner within its physiological concentration range (29). However, once the maximal physiological level is exceeded, the lipolytic effect of supraphysiological leptin doses declines significantly (9). In addition, mice with higher leptin sensitivity exhibit markedly greater responsiveness to leptin compared to those with impaired leptin sensitivity (30).

These findings suggest that in the early stages of energy surplus, increased adipose tissue elevates leptin secretion, which acts on the hypothalamus to suppress appetite and promote energy expenditure (Table 1). However, with persistent surplus, chronically high leptin levels paradoxically reduce leptin sensitivity, leading to resistance. As a result, leptin's anorexigenic and lipolytic effects diminish, worsening obesity and creating a vicious cycle of metabolic dysfunction (27, 31). This resistance can arise from impaired leptin transport across the BBB, reduced receptor expression, and signaling defects. Thus, while genetically deficient models highlight leptin's therapeutic potential in rare cases, diet-induced models reveal why it fails in common obesity.

Lipodystrophic mouse models

Several animal studies have demonstrated the beneficial effects of exogenous leptin administration in models of lipodystrophy. In C57BL/6 mice with conjugated linoleic acid (CLA)-induced lipodystrophy, intraperitoneal injection of a PASylated long-acting leptin significantly reduced hepatic triglyceride accumulation, lowered AST levels, and improved hepatic steatosis and insulin resistance (32). Similarly, in Agpat2$^{-/-}$ genetic models of lipodystrophy, leptin enhanced insulin sensitivity and alleviated steatosis largely independent of hepatic leptin receptor signaling, suggesting a peripheral mechanism (33). More recently, in a lipodystrophy mouse model prone to atherosclerosis (Ldlr$^{-/-}$; aP2-nSrebp1c-Tg), daily recombinant leptin treatment (3 mg/kg/day for 8 weeks) reduced GDF15 expression, inflammation, and plaque formation (34). Collectively, these findings indicate that leptin therapy confers both metabolic and cardiovascular benefits in lipodystrophy models.

Clinical trial evidence

Leptin or leptin receptor deficiency conditions

Leptin deficiency is a pathological condition characterized by the inadequate production, secretion, or functionality of leptin (23, 35). Leptin plays a pivotal role in energy homeostasis by signaling satiety and modulating energy expenditure through its interaction with the leptin receptor (LEPR) in the hypothalamus, particularly via the JAK2-STAT3 signaling pathway. Deficiency in leptin or its signaling pathway disrupts

Table 2 Overview of leptin and LRD disorders in clinics: characteristics and therapeutic responses.

Condition	Key characteristics	Treatment outcomes
CLD	Rare disorder due to LEP gene mutations causing low leptin levels. Early-onset severe obesity from hyperphagia. Metabolic issues: insulin resistance, diabetes, dyslipidemia. Endocrine abnormalities: hypogonadotropic hypogonadism	• Reduced energy intake, leading to significant weight and fat mass loss (3, 39) • Improved metabolic abnormalities (insulin sensitivity, lipid profiles), restored LH/FSH pulsatility and increased CD4+ T cells. No change in energy expenditure or cortisol (3) • Modulated striatal neural activity, reducing food reward perception (40)
LRD	Autosomal recessive disorder from LEPR gene mutations. Normal/elevated leptin but dysfunctional receptors. Mimics leptin deficiency: hyperphagia, severe obesity, metabolic/endocrine issues	• Ineffective due to receptor defect (41) • Setmelanotide (MC4R agonist) reduced hyperphagia and achieved 10–25% weight loss (46, 47), improved hunger scores and metabolic parameters with good safety profile (46)
Lipodystrophy diseases	Heterogeneous disorders with adipose tissue loss (GL, PL and HALS). GL: near-total fat loss, severe metabolic issues (insulin resistance, diabetes, hypertriglyceridemia, hepatic steatosis). PL: selective fat loss, milder metabolic abnormalities. Leptin levels: GL (1–2 ng/mL), PL (6–7 ng/mL). HALS: acquired lipodystrophy primarily seen in HIV patients on HAART	• Induced modest weight/fat loss in GL and PL (58, 60, 61, 62) • Improved HbA1c, triglycerides and liver volume (greater in GL) (63, 64) • Enhanced insulin sensitivity, reduce gluconeogenesis, and *de novo* lipogenesis (65, 66) • Effective in acquired GL/PL, reducing insulin resistance and hypertriglyceridemia without affecting autoimmune progression (67) • Reversed metabolic issues in childhood cancer survivors with PL (68, 69, 70) • Improved glucolipid metabolism in HALS patients (71, 72, 73, 74, 75)

GL, generalized lipodystrophy; PL, partial lipodystrophy; HALS, HIV-associated lipodystrophy; HAART, highly active antiretroviral therapy; CLD, congenital leptin deficiency; LRD, leptin receptor deficiency.

this regulatory mechanism, leading to hyperphagia, reduced metabolic rate, and subsequent obesity, alongside a spectrum of metabolic and endocrine abnormalities (35). As shown in Table 2, related studies and their findings are summarized.

Congenital leptin deficiency (CLD)

CLD is a rare disorder typically characterized by markedly reduced leptin levels, stemming from mutations in the LEP gene that disrupt the production and/or release of leptin (35). The estimated incidence of this condition is approximately one case per 4.4 million individuals (https://rarediseases.org/rare-diseases/congenital-leptin-deficiency/). Individuals affected by CLD exhibit excessive weight gain from early childhood, driven by pronounced hyperphagia, which progresses to severe obesity (36). Furthermore, these people commonly experience metabolic complications, including insulin resistance, diabetes, and dyslipidemia.

Multiple case reports or clinical trials have documented the use of metreleptin as a treatment (3, 37, 38, 39, 40). Across all reported instances, leptin administration markedly diminished energy consumption, yielding substantial reductions in both body weight and adipose tissue mass (3, 39). In addition to promoting effective weight loss, leptin therapy also significantly improves various metabolic abnormalities in people with CLD. As reported, leptin replacement therapy in CLD has been shown to modulate neural activity within the brain's striatal regions, indicating a diminished perception of food reward alongside an enhanced response to satiety cues following meals (40). Conversely, no alterations in energy expenditure or cortisol concentrations were detected (3). Leptin supplementation additionally altered the lipidome profile, aligning with heightened lipolysis and fatty acid oxidation (38). The gradual decline in fat mass further contributed to progressive enhancements in insulin sensitivity and lipid profiles, evidenced by decreased triglycerides and LDL-cholesterol levels, and elevated HDL-cholesterol levels (3). Furthermore, the therapy restored pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), while also elevating the CD4+ T cell count in blood (3). Collectively, leptin therapy in CLD proves highly efficacious, effectively ameliorating the severe metabolic disturbances characteristic of this condition.

Leptin receptor deficiency (LRD)

LRD is an autosomal recessive condition stemming from mutations in the LEPR gene, leading to dysfunctional or absent leptin receptors, thus mimicking leptin deficiency despite normal or elevated circulating leptin levels (41). The predicted prevalence of LEPR deficiency is 1.34 per 1 million people (42). While exogenous recombinant

leptin (e.g., metreleptin) is ineffective in LRD owing to the absence of functional leptin receptors (43), recent clinical investigations have highlighted the therapeutic potential of melanocortin-4 receptor (MC4R) agonists, particularly setmelanotide, which act downstream of the leptin pathway (44).

A seminal study by Ayers *et al.* (45) reported that setmelanotide administration in three individuals with LRD over 45–61 weeks led to sustained reductions in hyperphagia and significant weight loss (approximately 20~25% of body weight), demonstrating its capacity to bypass the LEPR defect by directly stimulating MC4R-mediated appetite regulation. This finding was corroborated by a phase 3 trial (46), in which 5 of 11 individuals with LRD achieved at least a 10% reduction in body weight after 52 weeks, accompanied by decreased hunger scores and a favorable safety profile. Earlier work performed by Collet *et al.* (47) further suggested that setmelanotide's efficacy in LRD surpasses its effects in heterozygous MC4R deficiency, underscoring its specificity for upstream defects such as LEPR mutations. A recent review (48) synthesized these outcomes, positioning setmelanotide as a precision medicine approach for hypothalamic obesity syndromes, including LRD, with consistent improvements in metabolic parameters. Mechanistically, setmelanotide restores energy homeostasis by activating MC4R, as elucidated in a comprehensive review by Maffei & Giordano (43), which highlights its role in circumventing the leptin signaling blockade. Despite these advances, limitations still persist, including small sample sizes and the need for long-term safety data. Collectively, the evidence establishes MC4R agonists, particularly setmelanotide, as a promising therapeutic avenue for LRD, offering a targeted intervention where leptin-based therapies fail, though broader accessibility and further validation remain critical challenges.

Common overweight/obesity

Overweight/obesity is primarily caused by energy imbalance, where caloric intake exceeds expenditure over time. Since the discovery of leptin in 1994, a multitude of studies has been conducted on leptin and its role in reducing body weight. Several randomized controlled trials were conducted to explore whether leptin administration could induce weight loss, as shown in Table 3 (4, 49, 50, 51, 52, 53). However, the results of different studies were inconsistent and sometimes controversial. The study by Chris *et al.* suggested that administering 80 mg/week of pegylated human recombinant leptin (PEG-OB) for 46 days, combined with a very-low-energy diet (2.1 MJ/day), resulted in significant weight loss in overweight men with a mean BMI of 28.8 ± 0.5 kg/m^2. The average body weight reduction was 2.80 kg (95% CI: −5.15, −0.45) (50). However, other studies (4, 49, 51, 52, 53) did not show

Table 3 Characteristics of the randomized controlled trials in people with overweight/obesity treated with leptin-based therapies.

Study	Participants	Total (*n*)	Country	Intervention (dose)	Treated (*n*)	Duration
Heymsfield *et al.* 1999 (4)[a]	Obese people (BMI: 27.6–36.0 kg/m^2)	57	USA	r-Met hu leptin (0.01 mg/kg per day)	6	24 weeks
Heymsfield *et al.* 1999 (4)[b]				r-Met hu leptin (0.03 mg/kg per day)	8	
Heymsfield *et al.* 1999 (4)[c]				r-Met hu leptin (0.10 mg/kg per day)	13	
Heymsfield *et al.* 1999 (4)[d]				r-Met hu leptin (0.30 mg/kg per day)	8	
Hukshorn *et al.* 2000 (49)	Obese men (BMI = 33.9 kg/m^2)	30	The Netherlands	PEG-OB (20 mg/week)	15	12 weeks
Hukshorn *et al.* 2003 (50)	Overweight men (BMI = 28.8 kg/m^2)	24	The Netherlands	PEG-OB (80 mg/week)	12	46 days
Zelissen *et al.* 2005 (51)	Overweight and obese people (BMI: 27–37.0 kg/m^2)	284	The Netherlands	Recombinant leptin (10 mg/morning, 10 mg/evening or 20 mg/day (10 mg twice daily))	205	12 weeks
Mittendorfer *et al.* 2011 (52)[e]	Obese subjects (BMI = 35.46 kg/m^2) with newly diagnosed type 2 diabetes who were not being treated with diabetes medications	18	USA	r-Met hu leptin (30 mg/day)	6	2 weeks
Mittendorfer *et al.* 2011 (52)[f]				r-Met hu leptin (80 mg/day)	6	2 weeks
Korner *et al.* 2013 (53)	Women (BMI: 28–50 kg/m^2) who were at least 18 months post-RYGB and lost on average 30.8% of their presurgical body weight	27	USA	Metreleptin (0.05 mg/kg body weight self-administered via subcutaneous injection twice daily)	14	16 weeks

[a]Leptin group participants were treated with r-Met hu leptin 0.01 mg/kg per day; [b]Leptin group participants were treated with r-Met hu leptin 0.03 mg/kg per day; [c]Leptin group participants were treated with r-Met hu leptin 0.10 mg/kg per day; [d]Leptin group participants were treated with r-Met hu leptin 0.30 mg/kg per day; [e]Leptin group participants were treated with r-Met hu leptin 30 mg/day; [f]Leptin group participants were treated with r-Met hu leptin 80 mg/day.

similar trends. The study by Korner *et al.* showed no significant effect of leptin treatment (0.05 mg/kg/d metreleptin via subcutaneous injection) on body weight in women with overweight/obesity (53), and similar results were reported in men with overweight/obesity in a study performed by Hukshorn *et al.* (49), showing that 20 mg/week of PEG-OB also failed to produce a statistically significant weight-loss effect. Further analysis found that the baseline leptin concentrations in individuals with overweight/obesity reported in six studies (4, 49, 50, 51, 52, 53) were significantly higher than normal levels, and the leptin concentrations of these individuals increased notably after receiving leptin-based drug injections, suggesting that the failure of leptin-based therapy to reduce weight and body fat in individuals with overweight/obesity may be due to hyperleptinemia before and after treatment, which was consistent with the current concept that hyperleptinemia drives leptin resistance (23).

Studies performed by Alex *et al.* (54) in 2018 further supported the above suggestions. In one part of this research, individuals with overweight/obesity (BMI 27.0–40.0 kg/m^2) were recruited and divided into three groups according to baseline leptin levels (lower group: <5 ng/mL in females and <2 ng/mL in males, medium group: <8 ng/mL in females and <3 ng/mL in males, higher group: <16 ng/mL in females and <5 ng/mL in males), then they were treated with 10 mg metreleptin twice daily for 24 weeks. The results showed that metreleptin treatment significantly reduced the body weight of people with overweight/obesity when compared with controls, and the weight-loss effects were more pronounced in the lower baseline leptin subgroups. In another part of this research, a total of 267 adults (BMI 27.5–38.0 kg/m^2, 171 women and 96 men) with low baseline leptin (females, ≤16 ng/mL; males, ≤5 ng/mL) were recruited and treated with different doses of metreleptin for 24 weeks. The results showed that subcutaneous metreleptin (20 mg/day) treatment significantly reduced body weight of people with overweight/obesity when compared with controls from the 8th week to the end of the trials (24th week) (54). All these findings further indicated that in people with overweight/obesity with low leptin levels, leptin intervention could reduce weight because leptin sensitivity remained intact at that time.

Lipodystrophy diseases

Lipodystrophy encompasses a heterogeneous group of disorders characterized by abnormal distribution, reduction, or absence of adipose tissue, leading to impaired fat storage capacity and a cascade of metabolic disturbances (55). Broadly classified into different forms, non-HIV lipodystrophy syndromes and HIV-associated lipodystrophy represent two significant clinical entities (23, 55). Despite differing etiologies, both conditions share features of adipose tissue dysfunction, resulting in insulin resistance, diabetes, hypertriglyceridemia, and hepatic steatosis, often linked to reduced leptin levels (56, 57).

Non-HIV-associated lipodystrophy syndromes can be classified into generalized lipodystrophy (GL) and partial lipodystrophy (PL). Compared to PL, GL presents with more severe clinical manifestations and earlier onset of complications. GL is characterized by a near-total loss of both subcutaneous and visceral adipose tissue, whereas PL involves selective loss of adipose tissue in specific anatomical regions. Both forms are associated with pronounced metabolic abnormalities (57). Circulating leptin levels were markedly reduced in GL, with average concentrations ranging from 1 to 2 ng/mL, whereas in PL, leptin levels were only mildly decreased, averaging around 6–7 ng/mL (58). In addition to congenital subtypes, acquired GL and PL were typically associated with autoimmune conditions (e.g., juvenile dermatomyositis) or idiopathic adipose tissue destruction (55, 59).

People with GL and PL who received metreleptin treatment experienced modest weight loss or reduced adipose tissue mass (58, 60, 61, 62). Regarding lipid abnormalities, 12 months of metreleptin therapy significantly reduced HbA1c, triglycerides, and liver volume in individuals with GL and PL, with greater benefits observed in GL than in PL (63, 64). For abnormal glucose metabolism, leptin-induced enhancement of peripheral insulin sensitivity promoted greater glucose uptake by peripheral tissues, thereby decreasing the delivery of carbohydrates to the liver, which caused less *de novo* lipogenesis (65). Other trials identified that leptin may reduce gluconeogenesis in people with lipodystrophy by limiting the availability of carbon substrates derived from glycerol, alanine, and lactate (66). In addition, metreleptin could be effective in acquired GL and PL. There were three cases of pediatric individuals with acquired generalized lipodystrophy and distinct active autoimmune diseases who were treated with metreleptin over a period of 4–6 years. It was reported that metreleptin therapy provided significant clinical benefits by reducing insulin resistance and hypertriglyceridemia, without affecting the progression of autoimmune diseases or compromising the effectiveness of immunosuppressive therapies (68). Childhood cancer survivors undergoing hematopoietic stem cell transplantation often developed PL with metabolic abnormalities, which could be reversed by metreleptin administration (68, 69, 70).

As for HIV-associated lipodystrophy (HALS), it is an acquired type of lipodystrophy that primarily occurs in people with HIV treated with highly active antiretroviral therapy. One of the different types is the lipoatrophic HALS, characterized by generalized fat depletion and very low leptin levels (<1–2 ng/mL) (71). Several studies identified that metreleptin administration improved insulin sensitivity and hyperglycemia, with minor effects on body fat and lipid metabolism, while it had

Table 4 Summary of animal models and human conditions of leptin resistance with key features.

Category	Model/condition	Key features
Animal models	*ob/ob* mice	Mutation in *ob* gene (leptin-deficient); severe obesity, hyperphagia, infertility, low energy expenditure
	db/db mice	Mutation in *Lepr* gene (leptin receptor-deficient); severe obesity, diabetes
	Diet-induced obese (DIO) mice	HFD leads to obesity with elevated leptin and impaired leptin sensitivity; mimics common human obesity
	Lipodystrophic mice	Food-induced (e.g., conjugated linoleic acid) or genetically modified (e.g., *Agpat2*$^{-/-}$ or *Ldlr*$^{-/-}$; aP2-*nSrebp1c*-Tg) mice
Human conditions	CLD	Rare disorder due to *LEP* gene mutations causing low leptin levels. Early-onset severe obesity from hyperphagia. Metabolic and endocrine abnormalities: insulin resistance, diabetes, dyslipidemia, hypogonadotropic hypogonadism
	LRD	Autosomal recessive disorder from *LEPR* gene mutations. Normal/elevated leptin but dysfunctional receptors. Mimics leptin deficiency: hyperphagia, severe obesity, metabolic/endocrine issues
	Common overweight/ obesity	Hyperleptinemia. Reduced hypothalamic leptin sensitivity. Overweight/obesity with or without abnormal glucose and lipid metabolism
	Lipodystrophy diseases	Heterogeneous disorders with adipose tissue loss (GL, PL and HALS). GL: near-total fat loss, severe metabolic issues (insulin resistance, diabetes, hypertriglyceridemia, hepatic steatosis). PL: selective fat loss, milder metabolic abnormalities. Leptin levels: GL (1–2 ng/mL), PL (6–7 ng/mL). HALS: acquired lipodystrophy primarily seen in HIV patients on HAART.

GL, generalized lipodystrophy; PL, partial lipodystrophy; HALS, HIV-associated lipodystrophy; HAART, highly active antiretroviral therapy; HFD, high-fat diet; CLD, congenital leptin deficiency; LRD, leptin receptor deficiency.

no effect on hepatic re-esterification or fatty acid oxidation, though longer follow-up periods may be necessary to determine the long-term effects and outcomes (72, 73, 74, 75).

Overall, leptin treatment effectively improves insulin sensitivity, hyperglycemia, hypertriglyceridemia, and hepatic steatosis in both congenital and acquired lipodystrophies, with more pronounced benefits for GL than for PL.

Collectively, evidence from both clinical studies and animal models (Table 4) demonstrates that while leptin supplementation is effective in cases of leptin deficiency, mutations in the leptin receptor, decreased receptor expression, or impairments in downstream signaling components result in leptin resistance, wherein exogenous leptin administration does not elicit meaningful weight-reducing effects.

Possible mechanisms for unsatisfactory weight-loss effects following leptin or leptin analog treatment

The preceding sections have highlighted the differential efficacy of leptin in promoting weight loss, as demonstrated by animal models and clinical trials. However, in the context of common obesity, where leptin levels are typically elevated, exogenous leptin administration fails to achieve meaningful weight reduction due to leptin resistance, both in humans and in animals. This discrepancy underscores the need to elucidate the underlying mechanisms that impair leptin's functionality in common obesity. The following discussion will explore the multifaceted contributors to leptin resistance, including hyperleptinemia, signaling pathway disruptions, and cellular stress responses, to provide a comprehensive understanding of why leptin cannot effectively exert its anti-obesity effects in most individuals with obesity (Fig. 1).

Classic mechanisms

Hyperleptinemia

Hyperleptinemia, characterized by elevated circulating leptin levels, is a hallmark of obesity and a key contributor to leptin resistance, a state where leptin fails to effectively suppress appetite and promote energy expenditure. Long-term studies have consistently demonstrated that hyperleptinemia drives leptin resistance in obesity, perpetuating a vicious cycle of weight gain and metabolic dysfunction (26, 27, 28). Hyperleptinemia arises from increased leptin production by expanded adipose tissue in obesity, but paradoxically, this elevation fails to suppress appetite, indicating a state of leptin insensitivity. At the cellular level, the mechanisms underlying leptin resistance induced by high leptin levels involve decreased sensitivity of the leptin signaling pathway and a saturation effect on leptin receptors (LEPR). Frühbeck *et al.* (30) demonstrated that chronic exposure to high leptin concentrations desensitizes LEPR, reducing downstream signaling efficiency, particularly through the JAK2-STAT3 pathway, which is critical for appetite suppression. This saturation effect leads to a diminished

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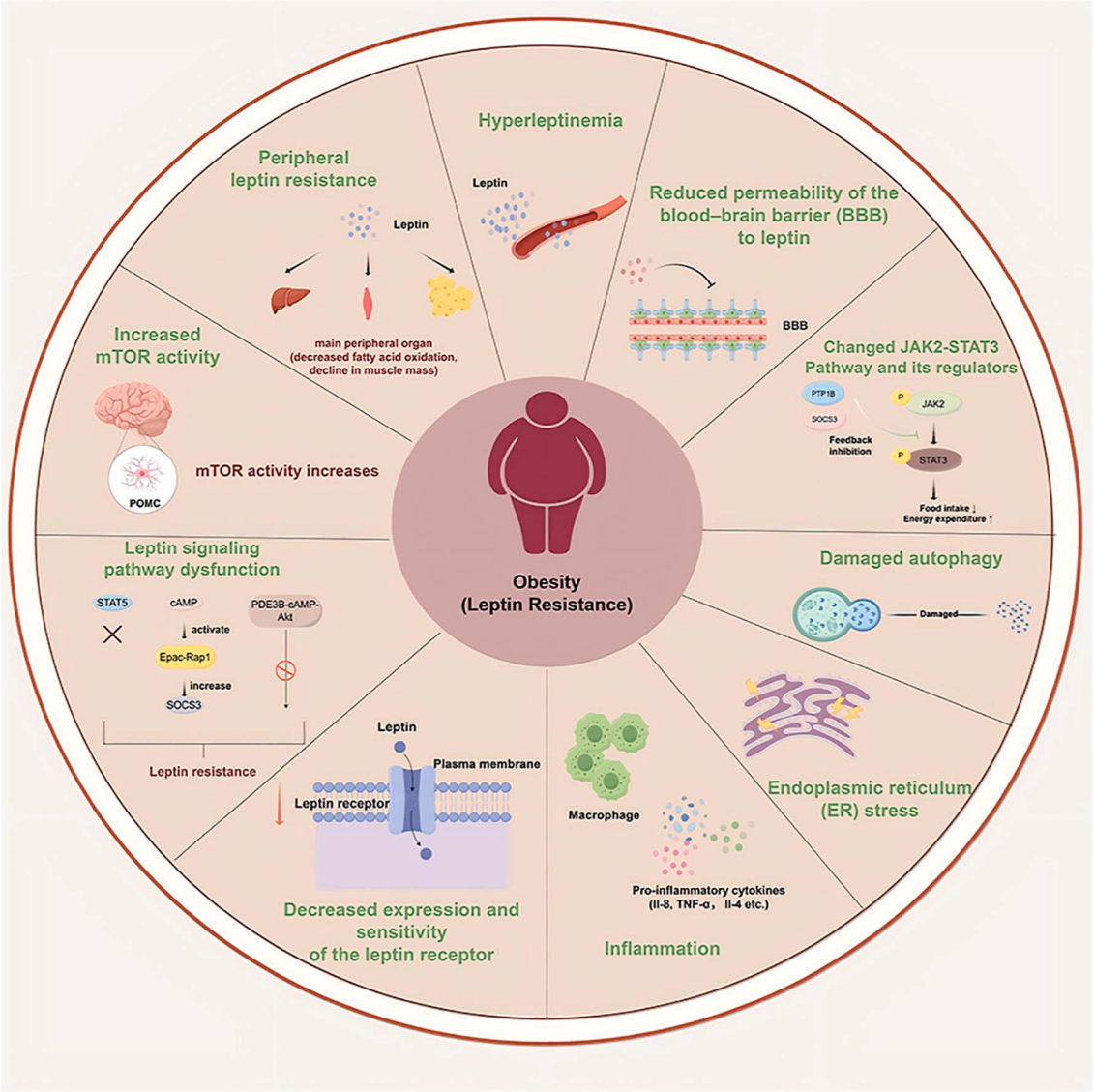

Figure 1

The complexity of leptin resistance. This figure summarizes multiple factors contributing to leptin resistance in obesity, including hyperleptinemia, reduced BBB permeability, impaired JAK2–STAT3 signaling, damaged autophagy, ER stress, inflammation, decreased leptin receptor expression/sensitivity, signaling pathway dysfunction, increased mTOR activity, and peripheral leptin resistance.

response to additional leptin, perpetuating hyperphagia and weight gain (30).

Further supporting this concept, research studies performed by Dr Scherer's group revealed that a partial reduction in serum leptin levels can mitigate the development of obesity and its associated metabolic dysfunctions. In the DIO mouse model, Zhao *et al.* (27) found that lowering leptin levels prevented HFD-induced obesity, improved glucose metabolism abnormalities, and ameliorated leptin resistance by restoring hypothalamic sensitivity to leptin signaling. This suggests that hyperleptinemia not only contributes to resistance but also exacerbates metabolic dysregulation, creating a vicious cycle in obesity (27). Similarly, it has been reported that sustained hyperleptinemia in individuals with obesity correlates with increased SOCS3 expression, a negative regulator of leptin signaling, further impairing JAK2-STAT3 activation and reinforcing resistance (7).

Reduced permeability of the blood–brain barrier to leptin

The BBB plays a critical role in regulating the transport of leptin into the central nervous system (CNS) to modulate

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appetite and energy expenditure via hypothalamic signaling. However, obesity and prolonged exposure to a HFD impair this process by decreasing specific leptin transporters and compromising the integrity of the BBB, ultimately obstructing leptin's ability to cross into the brain and exert its anorexigenic effects (6). Obesity and chronic HFD consumption lead to a marked reduction in specific leptin transporters, such as the short isoform of the leptin receptor (LEPRa), which facilitates leptin transport across the BBB. Early studies established this phenomenon, demonstrating that HFD-fed rodents exhibit decreased LEPRa expression in brain endothelial cells, correlating with reduced leptin uptake into the CNS (76, 77). Obesity can impair leptin transport across the BBB, preventing the brain from receiving leptin's satiety signal. This disruption promotes overeating, exacerbates obesity, and may contribute to the development of various metabolic disorders (78).

Decreased expression and sensitivity of the leptin receptor

Leptin receptor expression tends to decrease as a protective response under conditions of elevated leptin levels in obesity, likely due to receptor saturation (79). This is supported by studies reporting reduced hypothalamic leptin receptor mRNA expression in DIO mice, despite their increased circulating leptin levels (79, 80). In addition, there is a mismatch between high leptin and the amount of leptin receptor expression in DIO, indicating that despite high circulating leptin levels, leptin receptors in the brain or other target tissues may be reduced or exhibit diminished responsiveness. In this case, the reduced leptin receptor sensitivity and leptin signaling might play a causal role in obesity (7).

The JAK2-STAT3 pathway and its negative regulatory factors

Leptin resistance in obesity hinders its therapeutic potential by disrupting JAK2-STAT3 signaling in the hypothalamus. Key negative regulators, including protein tyrosine phosphatase 1B (PTP1B), T-cell protein tyrosine phosphatase (TCPTP), and SOCS3, play significant roles. PTP1B and TCPTP inhibit JAK2 activation and STAT3 phosphorylation, respectively, impairing leptin signaling (81, 82, 83). Studies showed PTP1B inhibition in mice with obesity restored leptin sensitivity (7). SOCS3, induced by hyperleptinemia, further suppresses JAK2-STAT3 signaling, exacerbating resistance (84). Recent research confirms that inhibiting the expression of SOCS3 could improve leptin resistance and counteract the impaired metabolism (85). Hypothalamic deletion of PTP1B and TCPTP in mice with obesity enhanced central leptin and insulin sensitivity, suppressed food intake, promoted browning of adipose tissue, reduced adiposity, and improved glucose metabolism (86). Targeting these regulators may enhance leptin sensitivity.

Emerging mechanisms

Leptin signaling pathway impairment

Beyond STAT3, other leptin signaling pathways, such as STAT5, cAMP, and Epac-Rap1, are damaged in obesity (7, 87). These pathways, which regulate energy expenditure and glucose homeostasis, become less responsive, diminishing leptin's metabolic effects (83). Deletion of STAT5 in the CNS may result in increased food intake and significantly more weight gain, which is consistent with the increase in circulating leptin and insulin levels (7). Recent investigation revealed that the Epac-Rap1 signaling pathway, activated by cyclic AMP (cAMP), plays a significant role in this dysfunction. Specifically, activation of Epac-Rap1 increases SOCS3 levels in the hypothalamus, blunting POMC neuronal activation and inducing leptin resistance. In addition, elevated circulating glucose-dependent insulinotropic polypeptide (GIP) or cAMP levels stimulate brain Rap1 activity, further contributing to leptin resistance (88, 89). In addition, targeted deletion of activating transcription factor 4 (ATF4) in either AgRP or POMC neurons suppresses FoxO1 expression, thereby enhancing leptin sensitivity and promoting body weight reduction (83). On the other hand, leptin signaling involves the PI3K-phosphodiesterase-3B (PDE3B)-cAMP-Akt signaling pathway, which is impaired during the development of DIO. This defect constitutes one of the principal mechanisms of central leptin resistance (90).

Damaged autophagy

Autophagy is a fundamental cellular process that degrades and recycles damaged organelles and proteins, maintaining cellular homeostasis and energy balance (91). This process is particularly critical in metabolically active tissues such as the hypothalamus, liver, and adipose tissue, where it regulates neuronal function and energy homeostasis. However, overnutrition, a hallmark of obesity, disrupts autophagic flux, leading to the accumulation of dysfunctional cellular components, which exacerbates metabolic disorders such as obesity and type 2 diabetes (92). It was reported that the deletion of the autophagy-related gene Atg7 in the hypothalamus impairs autophagy, leading to increased food intake, weight gain, leptin resistance, hypothalamic inflammation, and hyperleptinemia (93). Studies have demonstrated that activation of the AMPK-mTOR signaling pathway in the liver could enhance autophagy progression to recover leptin sensitivity (94). In addition, it was suggested that rats fed fructose showed leptin resistance as well as reduced expression of autophagy markers (Atg7, Lc3β, Lamp2) and LEPR in adipose tissue (95).

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Endoplasmic reticulum (ER) stress

Dietary fat may directly inhibit leptin signaling or trigger cellular processes, such as ER stress and inflammation, which reduce the leptin sensitivity of neuronal cells (7). ER stress, a cellular condition marked by the accumulation of misfolded or unfolded proteins, plays a pivotal role in the development of leptin resistance. In mice with obesity, increased ER stress and protein misfolding in the hypothalamus disrupt leptin receptor signaling pathways (7). Studies demonstrate that ER stress disrupts leptin signaling through multiple mechanisms, including impaired POMC processing, induction of inflammation, and interference with leptin signaling pathways by upregulating negative regulators such as PTP1B and SOCS3 (96). Long-chain saturated fatty acids primarily activate toll-like receptor 4 (TLR4) signaling to induce ER stress in the hypothalamus (97). Ultimately, the forced activation of hypothalamic IKKβ/NF-κB disrupts central leptin signaling and its effects (7, 97).

Inflammation

Obesity triggers inflammation in both adipose tissue and the brain. The infiltration of activated macrophages and elevated levels of pro-inflammatory cytokines contribute to leptin resistance within the brain (98). Elevated levels of cytokines such as TNF-α, IL-8, and IL-4 could lead to disruptions in leptin secretion patterns and the development of leptin resistance through modulation of downstream signal transduction pathways (99). In addition, hypothalamic inflammation, initiated by the intake of high quantities of dietary fat, plays a crucial role in the onset of central leptin resistance (100).

Increased mTOR activity

A study showed that in DIO mice, elevated mTOR activity in POMC neurons played a central role in causing leptin resistance (101). The researchers found that inhibiting mTOR with rapamycin restored leptin sensitivity and reduced fat mass in DIO mice, but only when leptin and melanocortin signaling pathways were intact. Conversely, activating mTOR in POMC neurons induced leptin resistance, while disrupting mTOR activators in these neurons protected against weight gain (101).

Peripheral leptin resistance

In addition to its central effects, leptin also acts on peripheral tissues and organs, such as skeletal muscle, liver, and adipose tissue (102). When leptin's physiological actions in peripheral tissues are impaired, the condition is referred to as peripheral leptin resistance, which primarily occurs in skeletal muscle (83). Studies have shown that increased expression of SOCS3 and PTP1B can inhibit leptin-mediated AMPK and SENP2 signaling pathways, thereby inducing leptin resistance by reducing fatty acid oxidation. Moreover, a decline in muscle mass can also contribute to the development of leptin resistance (103). In addition, evidence suggests that peripheral leptin resistance in omental adipose tissue and the liver is associated with metabolic dysfunction-associated steatotic liver disease (MASLD) in humans (104).

Future treatment strategies based on leptin

Leptin sensitization

In the context of DIO, a hallmark feature is leptin resistance accompanied by hyperleptinemia, characterized by a diminished responsiveness to exogenous leptin administration. Therefore, an effective strategy to restore leptin sensitivity is to reduce adiposity and circulating leptin levels through appropriate therapeutic interventions (7, 83).

Studies have shown that a low-calorie, low-glycemic index diet could effectively reduce BMI, body fat percentage, and leptin concentrations, as demonstrated in a randomized block design trial involving 26 women with overweight/obesity (105). Furthermore, there is some evidence indicating that the histone deacetylase 6 (HDAC6) inhibitor, tubastatin, promotes weight loss by enhancing leptin action (83, 106, 107). HDAC6-regulated adipokines have been identified as leptin sensitizers, suggesting HDAC6 as a potential therapeutic target for obesity. Inhibition of HDAC6 in adipose tissue has been shown to enhance central leptin sensitivity and induce subsequent weight loss (106). In addition, metformin, a drug commonly used to improve insulin resistance, also functions as a leptin sensitizer. It mediates weight-reducing effects in the brain and increases plasma levels of soluble leptin receptor (sOb-R) in newly diagnosed individuals with type 2 diabetes mellitus (T2DM) (108).

Combination treatment of leptin with other drugs

The limited efficacy of leptin monotherapy in treating obesity, largely due to leptin resistance, has prompted investigations into combination therapies that enhance leptin's effectiveness by targeting complementary pathways or mitigating resistance mechanisms. Combining leptin with other drugs, such as amylin analogs, GLP-1 receptor agonists, or insulin sensitizers, has shown promise in preclinical and clinical studies by synergistically addressing appetite regulation, energy expenditure, and metabolic dysfunction. For instance, a pivotal study demonstrated that co-administration of leptin with pramlintide (an amylin analog) in individuals with obesity resulted in a significant weight loss of approximately 12–13% over 24 weeks, far

surpassing the effects of either drug alone, likely due to pramlintide's ability to enhance leptin sensitivity in the hypothalamus (109). Similarly, combining leptin with exendin-4, a GLP-1 receptor agonist, in rodent models of DIO restored leptin responsiveness, reduced food intake, and promoted weight loss by amplifying satiety signals and improving hypothalamic signaling (110). Recent studies have further explored leptin's synergy with metformin, an insulin sensitizer, showing improved glucose homeostasis and modest weight reduction in people with obesity as well as type 2 diabetes, possibly by reducing ER stress and inflammation that contribute to leptin resistance (111). In addition, investigation of the combination of leptin with FGF21 analogs in obese mice suggested a potential role for this combination in overcoming leptin resistance through complementary metabolic pathways (110). Despite these advances, challenges still remain, including variable responses across patient populations and the need for long-term safety data. Combination therapies hold significant potential to improve leptin's therapeutic utility, but further clinical validation is required to establish standardized protocols.

Partial leptin reduction

As previously mentioned, due to the presence of hyperleptinemia and leptin resistance in the majority of individuals with obesity, exogenous administration of leptin – which further elevates circulating leptin levels – fails to produce the expected weight-reducing effects. In light of findings suggesting that hyperleptinemia itself may drive leptin resistance and obesity, Professor Philipp E. Scherer from the University of Texas Southwestern Medical Center recently proposed a novel concept: 'partial reduction of leptin to combat obesity' (27). By using *ob* gene homozygous or heterozygous knockout mouse models, as well as adipocyte-specific leptin-deficient mice, the team of Professor Philipp E. Scherer demonstrated that a partial reduction in serum leptin levels could prevent HFD-induced obesity and related glucose metabolism disorders (27). Further experiments showed that both congenital adipocyte-specific heterozygous leptin knockout mice and systemic heterozygous leptin knockout mice exhibited resistance to HFD-induced obesity, with consistent effects observed in both male and female mice (112). Moreover, the literature reports have indicated that the resensitization of leptin signaling through neutralizing antibodies represents a promising strategy for weight reduction. Consequently, human anti-leptin antibodies appear to be a potential therapeutic approach for combating leptin-resistant obesity (7, 113). In addition, similar outcomes were achieved by attenuating leptin signaling through intravenous administration of leptin-neutralizing antibodies or long-acting leptin antagonists. In these cases, HFD-fed mice exhibited significantly less weight gain, improved glucose tolerance, restored hypothalamic leptin sensitivity, and enhanced downstream leptin receptor signaling (27, 28).

However, the anti-obesity and metabolic benefits of partially lowering serum leptin levels – either through leptin-neutralizing antibodies or long-acting leptin antagonists – remain at the preclinical stage. Current research involving the development of leptin monoclonal antibodies and related trials in non-human primates is still ongoing. Clinical trials in humans have not yet been initiated, but further investigations and future experimental results are highly anticipated.

In the future, the development of leptin-based weight-loss drugs continues, with current research aimed at enhancing leptin sensitivity through combination therapies, novel leptin analogs, and targeting downstream signaling pathways. Strategies to overcome leptin resistance, such as using adjuvants that modulate immune response or enhance leptin receptor activity, hold promise for improving clinical outcomes.

Conclusion

Leptin resistance significantly limits the therapeutic efficacy of leptin in obesity, arising from multiple mechanisms, including hyperleptinemia, impaired JAK2–STAT3 signaling, defective autophagy, ER stress, inflammation, reduced leptin receptor expression, signaling pathway dysfunction, increased mTOR activity, and peripheral resistance. While effective in CLD and lipodystrophy, leptin fails in LRD and common obesity, necessitating other alternatives. Future strategies should focus on leptin sensitization, combination therapies, and partial leptin reduction to overcome these challenges and improve obesity treatment outcomes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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