ANNUAL REVIEWS

Annual Review of Physiology

Leptin: 30 Years Later

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Annu. Rev. Physiol. 2026. 88:229–50

First published as a Review in Advance on October 3, 2025

The *Annual Review of Physiology* is online at physiol.annualreviews.org

https://doi.org/10.1146/annurev-physiol-042324-100259

Keywords

leptin, adipose tissue, obesity, metabolism, neuroendocrine, immunity

Abstract

The discovery of leptin as an adipocyte-secreted hormone encoded by the *ob* gene whose absence produces severe obesity that is corrected by leptin repletion in both mice and humans was a transformative event in metabolic science. Leptin's discovery in 1994 accelerated the identification of central neuronal circuitry responsive to peripheral signals that regulate energy balance as well as metabolic, neuroendocrine, and other vital functions. Leptin's primary physiological role was initially viewed as preventing obesity by its levels rising, but subsequent research has emphasized the key role of falling levels to signal starvation. Resistance to leptin action, though partial, characterizes common forms of obesity. Despite much being learned about leptin signal transduction over 30 years, the precise molecular mechanisms for leptin resistance and common obesity remain unclear. Leptin therapy is effective in rare patients with congenital leptin deficiency and other low leptin conditions but not common obesity. Interestingly, reducing hyperleptinemia may prove useful in treating common obesity.

HISTORICAL CONTEXT

For many years before leptin's discovery, metabolic scientists wondered about potential mechanisms for regulation of body weight in response to perturbations from both under and over nutrition. Despite the awareness that body fat (adipose tissue) was the major energy storage depot, and that the brain regulated hunger, satiety, and many other responses pertinent to energy storage and expenditure, how these elements communicated and functioned together as a physiologic regulatory system had not been defined.

In 1942, the role of the hypothalamus in energy homeostasis was suggested by a report from Hetherington & Ranson that lesions in the ventromedial hypothalamus (VMH) produced obesity in rats (1). In 1959, Hervey (2) importantly extended this observation by combining VMH lesions with the technique of parabiosis, wherein surgical union between subcutaneous tissue of two animals permits blood exchange between them. These experiments suggested that a VMH lesioned animal overproduced a circulating factor that caused the parabiosed normal animal to reduce its food intake and lose fat mass and weight, while the VMH lesion prevented the lesioned rat from responding to its own factor.

Genetic models of obesity eventually intersected with these lesion studies to further support the idea of a circulating factor involved in weight control. In 1950, the obese (*ob*) gene was identified as a spontaneous recessive mutation causing severe obesity, and in 1966, the diabetes (*db*) gene was identified (3, 4). When bred on the same genetic background, *ob*/*ob* and *db*/*db* mice had the same obesity phenotype, raising the possibility that their gene products might be part of a common regulatory system. Experiments using parabiotic linkages of *ob*/*ob* and *db*/*db* to each other and to wild-type mice advanced this view, suggesting that *ob*/*ob* mice lacked a circulating regulatory factor to which *db*/*db* mice could not respond (5). To advance from this paper to molecular identification of the regulatory components would require cloning of the *ob* and *db* genes 20 years later.

CLONING OF THE *OB* AND *DB* GENES AND IDENTIFICATION OF LEPTIN AND ITS RECEPTOR

Cloning of the *ob* gene was reported in 1994, the outcome of more than a decade-long effort during the early days of positional cloning (6). Cloning revealed that the *ob* gene encoded a secreted 14-kD protein expressed in adipose tissue, present in the circulation of normal mice and absent in *ob*/*ob* mice (6). The protein circulated at high levels in *db*/*db* mice, decreased after weight loss, and increased in diet-induced obese (DIO) mice (7, 8). Critically, when administered by injection, the encoded protein produced weight loss in *ob*/*ob* but not *db*/*db* mice (9–11); hence, the protein was named leptin, from the Greek root leptos for thin, based on the hypothesis that its primary physiologic function was to prevent obesity and maintain leanness (9).

In 1995, the *db* gene was shown to encode a cytokine-family receptor, leptin receptor (LepR), with a number of splice variants of different lengths (12, 13). The original *db*/*db* strain had a mutation affecting only the long LepRb form, revealing this specific form as required for the antiobesity signal (14). LepRb is most highly expressed in the brain, especially the hypothalamus, and early results showed that leptin administration activates signal transducer and activator of transcription 3 (STAT3) via phosphorylation in the hypothalamus of *ob*/*ob* but not *db*/*db* mice (15). Consistent with the key site of action in the central nervous system (CNS), administration of leptin by the intracerebroventricular route was more potent than peripheral injections (10). For further genetic confirmation, selective deletion of LepRb in neurons reproduced the *db*/*db* phenotype, and reexpressing LepRb selectively in neurons rescued the *db*/*db* phenotype (16, 17).

Although LepRb is most highly expressed in selected neuronal populations in the hypothalamus, midbrain, and hindbrain, it is also expressed peripherally, the most physiologically important

being on immune cells (18–21). Short forms of the leptin receptor, such as LepRa, are more widely expressed but do not activate STAT3 signaling like LepRb (18, 20). LepRa is heavily expressed in choroid plexus and brain microvessels, where it appears to play a role in transport of leptin into the CNS (20). Its role in other tissues including lung, liver, kidney and others remains uncertain.

Features of Leptin Receptor Signaling

The LepR is a member of the type I cytokine receptor family (14, 15). Short LepR isoforms, a soluble isoform and a long isoform (LepRb), are derived from alternative splicing of *lepr* transcript. LepRb has an extended intracellular domain that is required for signaling. Earlier studies suggested that LepR formed dimers in the absence of leptin (22). However, recent studies have demonstrated that leptin binding to LepR induces the formation of dimers and trimers in 2:2 or 3:3 stoichiometry (23, 24). Leptin binding to the extracellular domain of LepRb activates receptor-associated Janus kinase 2 (JAK2), which then phosphorylates STAT3, which then enters the nucleus (14, 15) (**Figure 1**). There, pSTAT3 regulates gene expression, such as in pro-opiomelanocortin (POMC)-expressing neurons where POMC messenger RNA (mRNA) encodes appetite-suppressing alpha-melanocyte stimulating hormone (α-MSH) (25, 26). Several lines of genetic evidence support the critical role of the JAK/STAT signaling pathway for energy

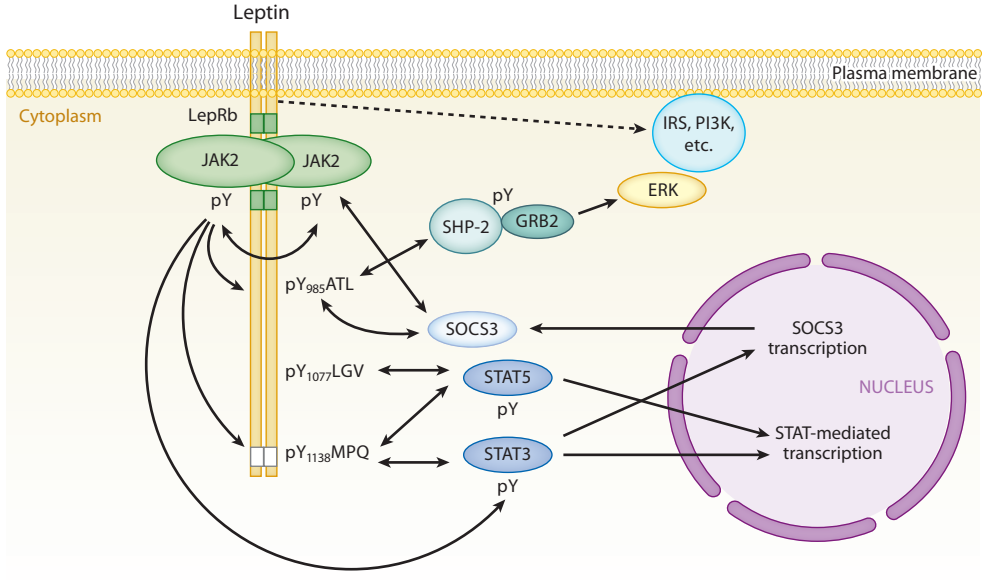

Figure 1

Leptin signaling. The binding of leptin to LepRb leading to the formation of the LepRb/JAK2 complex. Activated JAK2 autophosphorylates and associates with Tyr^{985}, Tyr^{1077}, and Tyr^{1138} in mouse LepRb. In human LEPRb, the respective phosphorylated tyrosines are 986, 1079, and 1141. STAT3 and STAT5 bind to phospho-Tyr^{1138} and phospho-Tyr^{1077} in LepRb and are phosphorylated and activated. Active STAT3 and STAT5 dimers translocate to the nucleus and activate the transcription of neuropeptide target genes in the brain. Leptin stimulates the transcription of SOCS3 via STAT3, and SOCS3 inhibits the JAK2/STAT3 pathway by interacting with phospho-Tyr^{985} of JAK2 and acting as a feedback inhibitor of leptin signaling. Leptin also regulates PI3K signaling through IRS phosphorylation. Abbreviations: ERK, extracellular signal–regulated kinase; GRB2, growth factor receptor–binding protein 2; IRS, insulin receptor substrate; JAK, Janus kinase; LepRb, leptin receptor isoform b (long leptin receptor); PI3K, phosphatidylinositol kinase; pY, phosphorylated tyrosine; SHP-2, Src homology 2–containing protein tyrosine phosphatase; SOCS3, suppressor of cytokine signaling 3; STAT, signal transducer and activator of transcription.

homeostasis. Most features of the *db/db* phenotype are recapitulated by knocking out the site on LepRb to which STAT3 binds, and likewise by selectively knocking out JAK2 and STAT3 in brain (27, 28). Additional signaling pathways activated by LepRb downstream of JAK2 include the PI3K-AKT pathway, the MAPK/ERK (mitogen-activated protein kinase/extracellular signal–regulated kinase) pathway, the AMP-activated protein kinase (AMPK) pathway, and the mechanistic target of rapamycin pathway (28–31).

Inhibitors of Leptin Signaling

Leptin receptor activation in turn inhibits leptin signaling (32) (**Figure 1**). The suppressors of the cytokine signaling class of inhibitory molecules were found to be transcriptionally induced by several cytokine family members, after which they inhibited JAK activity to create a negative feedback loop (33). In 1998 it was shown that peripheral leptin injection specifically induced suppressor of cytokine signaling 3 (SOCS3) mRNA in the hypothalamus of *ob/ob* but not *db/db* mice, and that SOCS3 expression in mammalian cell lines blocked LepRb signaling (32). Genetic manipulation of SOCS3 in mouse models provided additional support for SOCS3 playing a role in energy balance in vivo under a variety of circumstances. Both mice totally lacking SOCS3 in neurons and those haplo-insufficient for SOCS3 in all tissues are more sensitive to leptin action to reduce weight and are partially resistant to diet-induced obesity (34–36). In addition, mice with deletion of SOCS3 in POMC neurons important for anorexigenic action of leptin have increased leptin sensitivity, as assessed by weight loss and food intake, and improved glucose metabolism on a high-fat diet (34, 37).

The protein tyrosine phosphatase PTP1B is another negative regulator of leptin signaling, as mice lacking PTP1B both in all neurons and in neurons expressing LepRb are hypersensitive to leptin and have reduced body weight and adiposity (38–40).

ROLE OF LEPTIN IN ENERGY HOMEOSTASIS AND BODY WEIGHT REGULATION

As stated earlier, the initial concept was that leptin acted as a fat-derived negative feedback signal of energy stores to the brain, with a physiologic role to prevent obesity by reducing hunger and increasing energy expenditure. This explains the choice of its name *leptos*, for thin, and the enormous excitement its discovery generated for treatment for obesity (9). This model's prediction that leptin levels would rise as adipose energy stores increased with obesity was quickly confirmed in humans and animal models (7, 8), but this obesity-associated hyperleptinemia presented a paradox. If leptin levels increased in proportion to adipose mass, why did the rise in leptin not prevent obesity from occurring?

Low Leptin As a Starvation Signal

Our early demonstration that leptin expression and levels fell with food restriction led us to entertain another hypothesis regarding leptin biology (41). Might the fall of leptin levels with starvation be a key signal to the brain of energy deficiency, evoking physiologic adaptation responses ranging from increased hunger to changes in the neuroendocrine axis? After showing that 1–2 days of starvation in mice markedly suppressed leptin expression and circulating levels, we designed an experiment to assess the role of leptin in energy deficiency. Mice were fed ad lib or fasted for 2 days, and fasted mice were treated with leptin to prevent its levels from falling. As expected, starvation had strong effects on the neuroendocrine system, with suppression of ovulation in female mice and testosterone in male mice, reduced levels of thyroid hormones, and activation of the hypothalamic-pituitary-adrenal (HPA) axis as evidenced by increased corticosterone levels

(41). Leptin replacement also blunted fasting-induced hyperphagia (41). Strikingly, compared to vehicle-treated control mice, preventing the fall in leptin either prevented or markedly blunted these adaptive responses (41). This led us to propose that regulation of the neuroendocrine system during periods of food restriction could be the dominant physiologic role of leptin (41).

Subsequently, many human studies have demonstrated the ability of leptin repletion to reverse or markedly blunt the suppression of the hypothalamic-pituitary-gonadal (HPG) axis, either in response to experimental starvation, or low leptin associated with hypothalamic amenorrhea (42, 43). Thus, the ability of low leptin to influence energy balance by suppressing energy demanding processes such as reproduction is established in rodents and humans, and this complements the ability of low leptin to resist starvation by stimulating appetite.

Leptin Resistance: Meaning, Mechanisms, and Implications

The short-term administration of leptin to normal-weight mice reduces food intake, body weight, and fat mass, consistent with the initial model of leptin functioning as a feedback signal to prevent obesity (9–11). But soon after its discovery, it became apparent that most obese mice, including those induced by high-fat diets, have increased circulating leptin, with levels rising in proportion to adiposity (7, 8) (**Figure 2**). Thus, while leptin levels reflected the extent of adiposity, endogenous hyperleptinemia did not fully prevent the development of obesity (7, 8). Consistent with this observation, hyperleptinemic obese mice had little or no weight loss when levels were further raised by leptin injections (44, 45). This phenomenon was thus described as leptin resistance, analogous to the term insulin resistance, which is well characterized in patients with obesity and type 2 diabetes (46).

Comparing insulin versus leptin resistance across a number of dimensions provides valuable insights. First, it should be obvious that in neither case of hormone resistance is the resistance

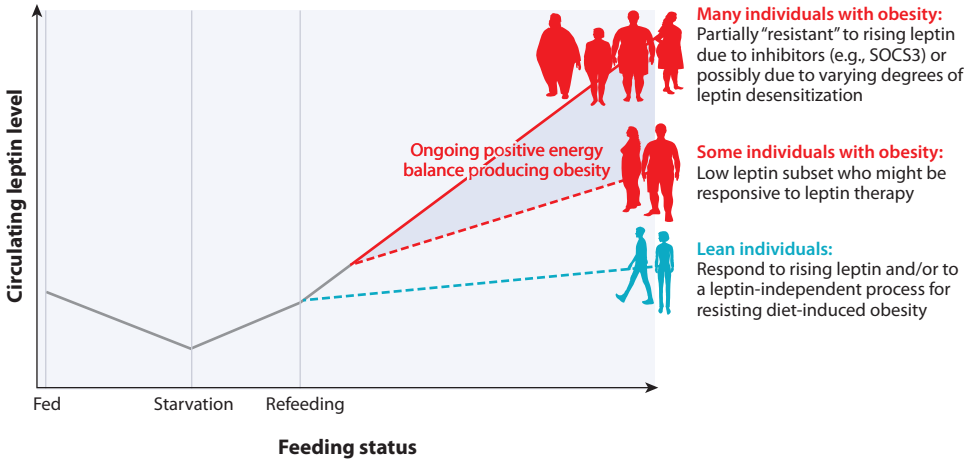

Figure 2

Circulating leptin levels fall with starvation and rise to prior levels with refeeding. It is possible, but not yet demonstrated, that some lean individuals respond briskly to rising leptin to prevent obesity or respond to another as-yet-undiscovered signal to prevent obesity. It is also possible, but not yet demonstrated, that some individuals with obesity with relatively low leptin levels for their degree of obesity might respond to exogenous leptin with weight loss. Most individuals with obesity have high leptin levels to which they are partially resistant, causing them to be unresponsive to exogenous leptin. This so-called leptin resistance may be caused by desensitization induced by hyperleptinemia. Figure adapted from Reference 48 (CC BY 4.0). Abbreviation: SOCS3, suppressor of cytokine signaling 3.

total. If insulin resistance in type 2 diabetes was total, then this disorder would have the same metabolic phenotype of hyperglycemia and ketonemia as untreated type 1 diabetes, where the insulin is absent, which is not the case. Clearly, insulin action is being exerted in type 2 diabetes, though not enough to prevent diabetes. Likewise, if leptin resistance was total in common forms of obesity, the phenotype would be that of *db/db* mice or humans, which is not the case. In most obesity with leptin resistance, the level of adiposity is far less severe than that in *db/db* mice or *LEPR* mutant humans, and features found in *db/db* such as hypothalamic reproductive failure consequent to absent leptin action are not seen in common obesity. So obviously, despite resistance, significant leptin signals are getting through to key target tissues in common obesity. It should therefore be unsurprising that treatment of leptin-resistant DIO mice with a leptin receptor antagonist would stimulate food intake and weight gain, as has been observed (47).

We propose that a limited sensitivity to obesity-induced hyperleptinemia may have evolved to optimize the capacity for energy storage in adipose tissue. If hyperleptinemia prevented energy storage when animals in an environment where food was often limited confronted abundant energy sources, this would limit their survival when food sources again became limited (48) (**Figure 2**).

Returning to the insulin-leptin comparison, despite insulin resistance, most patients with type 2 diabetes have substantial therapeutic glucose-lowering responses when exposed to supplemental insulin. In contrast, most obese mice and patients have little or no weight loss when leptin levels are further raised by exogenous administration of the hormone (**Table 1**). The explanation for this resistance has been widely sought, and the molecular explanations remain uncertain.

In the commonly studied DIO mouse model, leptin resistance accompanying obesity actually requires hyperleptinemia to develop (49). To demonstrate this, *ob/ob* mice received leptin infusion via minipumps to restore normal levels and achieve normal weight (49). These weight-normalized *ob/ob* mice were then put on a high-fat diet while continuing leptin infusion to maintain normal levels. These mice developed a similar degree of obesity as did wild-type mice on the same diet, despite normal and unchanged leptin levels. Remarkably, *ob/ob*-leptin mice, unlike wild-type mice made obese on a high-fat diet, responded strongly to exogenous leptin with reversal of obesity, demonstrating that hyperleptinemia was required for development of leptin resistance in this setting (49). Notably, *ob/ob*-leptin mice with plasma leptin clamped at normal levels gained as much weight as did mice whose leptin levels rose as they developed obesity on the diet, providing the additional and quite surprising conclusion that rising leptin with adipose expansion in wild-type mice played little or no role to limit obesity in this setting (49). A similar conclusion was also reached in a model of forced overfeeding in *ob/ob* mice with similarly normalized clamped leptin levels (50). When the forced overfeeding that produced obesity was ended, spontaneous food intake was markedly suppressed until adipose mass was normalized. This supported the existence of negative feedback from adipose expansion, not by leptin as might have been expected, but by a nonleptin factor that has not yet been identified (50).

What cellular mechanisms cause leptin resistance, whether induced by systemic hyperleptinemia or other mechanisms? Potential causes include decreased transport of leptin across the blood–brain barrier to neuronal sites of action, increased expression of signaling antagonists such as SOCS3 and PTP1B in LepRb-expressing neurons, and/or processes limiting leptin action downstream of actions in leptin-responsive neurons.

BRAIN LEPTIN TARGETS

With the demonstration that leptin action through LepRb is necessary to prevent obesity and the full *db/db* phenotype, and that the dominant site for this action is within the CNS, it became

Table 1 Leptin therapy in leptin deficient states and common obesity

Clinical study	Outcome	Reference
Congenital leptin deficiency		
Recombinant human leptin (r-met-hu leptin): case report	Leptin reduced weight and fat, hunger and food intake; increased physical activity, FSH, and LH levels	67
r-met-hu leptin: open-label observational study	Leptin reduced appetite, weight and fat, insulin and lipids; increased thyroid hormones and gonadotropins; facilitated pubertal development; and increased $CD4^+$ T cells, T cell proliferation, and cytokines	68
Lipodystrophy		
r-met-hu leptin: open-label observational study in patients with generalized lipodystrophy	Leptin reduced hepatic steatosis, glycated hemoglobin, fasting glucose, and lipids	126
r-met-hu leptin: open-label observational study in patients with partial lipodystrophy	Leptin reduced hepatic steatosis, glycated hemoglobin, fasting glucose, and lipids	78
Hypothalamic amenorrhea		
r-met-hu leptin: open-label observational study	Leptin increased LH, ovarian follicles, estradiol, free T3 and T4, IGF1, IGFBP3, bone alkaline phosphatase, and osteocalcin	43
r-met-hu leptin: RCT	Leptin restored menstruation and corrected dysfunction of gonadal, thyroid, growth hormone, and adrenal axes	80
Common obesity		
r-met-hu leptin: RCT	No significant leptin effect on weight; leptin reduced fat mass	127
Pegylated leptin: RCT	No significant leptin effect on weight, fat, 24-h EE, SMR, RQ, appetite, glucose, insulin, insulin sensitivity, or lipids	128
Pegylated leptin: RCT	No significant leptin effect on weight, glucose, insulin, insulin resistance, lipids, or inflammation	129
Pegylated leptin: RCT	Mild reduction in weight; no significant leptin effect on hunger, fat, FFM, REE, or RQ	130
r-met-hu leptin: RCT	No significant leptin effect on weight, glucose, or lipids	125
r-met-hu leptin: RCT	No significant leptin effect on BMI, total mass, fat, FFM, or insulin resistance	131
r-met-hu leptin: RCT	No significant leptin effect on weight, fat, REE, thyroid hormones, or cortisol	132

Abbreviations: BMI, body mass index; EE, energy expenditure; FFM, fat-free mass; FSH, follicle-stimulating hormone; IGF1, insulin-like growth factor 1; IGFBP3, IGF-binding protein 3; LH, luteinizing hormone; RCT, randomized placebo-controlled trial; REE, resting energy expenditure; RQ, respiratory quotient; SMR, sleeping metabolic rate; T3, triiodothyronine; T4, thyroxine.

critical to identify the specific neuronal populations required for this effect and the downstream circuits they engage (reviewed in 25, 26). Early work demonstrated that leptin signaling involved activation of STAT3 in the arcuate nucleus of the hypothalamus. This was soon followed by demonstration that leptin action suppressed activity of arcuate neuropeptide Y/agouti-related protein (NPY/AgRP) neurons that promote feeding through release of NPY and AgRP, and activated arcuate POMC neurons that inhibit feeding through production of α-MSH (26). It

was also demonstrated that these two pathways converged downstream through signaling on melanocortin-4 receptor (MC4R)-expressing neurons in the paraventricular nucleus, at which α-MSH is an agonist (reducing feeding) and AgRP is an antagonist (stimulating feeding) (26).

Stimulation of arcuate AgRP neurons using optogenetic and chemogenetic approaches revealed their remarkable ability to rapidly drive feeding and the reward value of food (reviewed in 51). Conversely, stimulation of arcuate POMC neurons inhibited feeding, but unlike AgRP neurons, the effect was small and took hours to be seen (51). Interestingly, deletion of LepRb during early development from either of these populations has only modest effects on feeding and body weight, suggesting that developmental compensation occurs in these models (51). This also suggests that LepRb-expressing cells apart from AgRP cells must exist to mediate this compensation. A study using single-nucleus RNA-seq of enriched mouse hypothalamic LepRb-expressing cells identified several previously unrecognized populations of ObRb-expressing hypothalamic neurons (52). Further studies with one of these, GABAergic glucagon-like peptide-1 receptor (GLP1R)-expressing LepRb-expressing neurons, were notable for their functional significance. Removing LepRb from these cells alone produced hyperphagic obesity without reducing energy expenditure (52). In GLP1R-null mice, restoring GLP1 receptors in LepRb-expressing GLP1 neurons restored the ability of a GLP1R agonist to suppress food intake (53). In one model for how this circuit might work, these cells, perhaps in the dorsomedial hypothalamus, project to AgRP neurons in the arcuate to inhibit them in response to leptin (53). Experimental evidence also supports direct leptin action in the brainstem, including the nucleus of the solitary tract, the dorsal motor nucleus of the vagus, and the area postrema to regulate food intake and autonomic function, working together with hypothalamic and other sites of action (25, 26). A more complete discussion of leptin-responsive neurons and their complex and functionally diverging downstream targets is beyond the scope of this review.

Leptin and Brain Reward Circuitry

In modern times, food is available to most people, and excessive food consumption is driven by environmental and psychosocial factors rather than acute energy deprivation. The rising incidence of obesity is mainly driven by eating for pleasure (hedonic) rather than eating for survival (homeostatic). Some individuals with obesity are preoccupied with thoughts of food and experience cravings in the absence of energy deficit. Hedonic eating may be triggered by the sight, smell, taste, or texture of food. Metabolic hormones are involved in the control of the food reward system. Ghrelin stimulates motivation and food reward, while leptin, insulin, GLP1, and amylin dampen food reward (54). Leptin regulates homeostatic feeding through neuronal circuits in the hypothalamus and hindbrain described above and hedonic feeding through lateral hypothalamic and mesolimbic pathways (55–57).

The lateral hypothalamic area contains distinct populations of melanin-concentrating hormone (MCH) and orexin-expressing neurons that project to the nucleus accumbens (NAc) and ventral tegmental area (VTA), respectively (25, 26). MCH and orexin neurons lack Leprb and respond indirectly to leptin through neurons in the arcuate nucleus that inhibit MCH and orexin neurons that project to the lateral hypothalamic area and VTA, leading to a reduction in food intake and decrease in body weight. VTA dopamine neurons regulate reward behaviors including executive function (decision making), attention, impulsivity, and reinforcement. Major VTA projections are the NAc, medial prefrontal cortex, and central nucleus of the amygdala. Leptin directly inhibits VTA-LepRb neurons and prevents sucrose-induced dopamine release into the NAc and food reward behavior. Homeostatic circuits in the hypothalamus are linked to hedonic pathways (58). Thus, the fall in leptin during starvation increases AgRP expression in the arcuate

nucleus, which drives food-seeking behavior and food intake and augments the rewarding effects of palatable food (25).

Neuroimaging has provided insight into brain reward mechanisms. Studies have shown increased activity in reward regions in obese compared to normal weight individuals (59, 60). In congenital leptin deficiency, the lack of inhibitory action of leptin is associated with neuronal activation in striatal regions, which is modulated by leptin treatment to reduce food reward and enhance the response to satiety signals (61). Prader-Willi syndrome is a rare disease characterized by hyperphagia, severe obesity, and hyperleptinemia (62). Hyperleptinemia in Prader-Willi syndrome is associated with increased activation of motivation and reward pathways, indicating leptin resistance (62). Higher circulating leptin level in adolescents is associated with brain motivation-reward response to high-caloric food images, suggesting that the lack of leptin inhibition may increase the risk of overconsumption of these foods and predispose to the development of obesity (63).

REGULATION OF NEUROENDOCRINE AND IMMUNE SYSTEMS

In addition to playing a central role in the regulation of feeding, energy homeostasis, and body weight/adiposity, leptin has pleiotropic roles in modulation of hormone levels, glucose and lipid metabolism, sympathetic activity, vascular function, bone biology, brain development, neuroprotection, hematopoeisis, and immunity. The next section focuses on leptin's actions on the neuroendocrine and immune systems.

Leptin and Reproduction

Mammals require enormous amounts of energy to sustain reproduction. Puberty, ovulation, fertility, pregnancy, and lactation all require optimum nutrition and energy stores. Normal development of gonadotropin-releasing hormone (GnRH) neurons in the forebrain and preoptic hypothalamic area is critical for pubertal maturation and reproduction (64). GnRH is released in the hypothalamic median eminence into the portal circulation and stimulates pituitary gonadotropic cells to produce and secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotropins act on ovaries and testes to regulate the synthesis and secretion of estradiol and testosterone and the production of eggs and sperm. Sex steroids and gonadotropins act via feedback loops in the pituitary and hypothalamus to regulate GnRH.

Prior to the discovery of leptin, it was well known that *ob/ob* and *db/db* mice lacked pubertal development and were infertile (3–5). On a C57Bl/6 genetic background, adult male *ob/ob* mice have lower testicular and prostatic weights, few Leydig cells and sperm, and decreased plasma levels of LH and FSH. Adult female *ob/ob* mice have a hypoplastic uterus, no mature follicles or corpora lutea, and reduced LH and FSH. HPG dysfunction in *ob/ob* mice is reversed by leptin treatment (65, 66). Similarly, null mutations of LEP or LEPR disrupt puberty and fertility in humans, and leptin replacement restores LH level and sex steroids, induces puberty, and corrects menstrual irregularities in patients with *LEP* mutation (67, 68).

The function of leptin in pubertal development is mediated indirectly through the hypothalamic kisspeptin system (69, 70). Leptin is also directly coupled to energy balance through AgRP/NPY and POMC neurons in the arcuate nucleus of the hypothalamus to regulate GnRH, gonadotropins, and sex steroids (64). Leptin acts as a permissive factor together with other factors to regulate the timing of puberty and sexual maturation (71–74). Plasma leptin levels are higher in females than males; the sex diference is due to higher production in subcutaneous adipose in females, stimulation by estradiol, and suppression by testosterone (75).

The fall in leptin during starvation mediates suppression of the HPG axis (41). Fasting decreases sex hormones and fertility in rodents and primates (76). Studies by Ahima et al. (41) and

several laboratories have demonstrated that leptin treatment attenuates the fasting-induced reduction in LH and sex steroids and restores estrus cycles in rodents (69). The effect of leptin on fasting-induced suppression of the HPG axis in monkeys is less certain (76). In contrast, the connection between leptin and the HPG axis has been demonstrated in patients with lipodystrophy in whom leptin replacement therapy increased GnRH sensitivity as well as LH and testosterone levels and improved menstrual function (77–79).

Leptin falls rapidly during short-term fasting in healthy individuals, and leptin replacement prevents HPG axis suppression (42). In some studies, chronic exercise resulted in weight loss and leptin deficiency, causing hypothalamic amenorrhea; leptin replacement therapy for up to 3 months increased LH levels, follicular development, and estradiol levels, and improved ovulatory cycles (43) (**Table 1**). In women with hypothalamic amenorrhea randomized to long-term leptin or placebo treatment, leptin increased estradiol levels and normalized menstrual cycles in 75% of women who continued treatment for 24 months (42, 80). Relative energy deficiency in sport (REDs) is a term used in sports medicine to describe athletes who develop worsening performance and health outcomes due to low-energy diets and excessive exercise (81). REDs predisposes to hypothalamic hypogonadism, irregular menses, infertility, osteopenia, stress fractures, immunosuppression, and anemia (81). These multisystemic disorders likely involve chronic leptin deficiency and disruption of activin-follistatin-inhibin regulation (81, 82). In addition to encouraging sufficient caloric intake and diet quality, it is possible that leptin may emerge as a therapeutic option for treating menstrual disorders and infertility in REDs.

Other Neuroendocrine Roles of Leptin

The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates pituitary release of thyroid-stimulating hormone (TSH). TSH regulates the production of thyroxine (T4) and triiodothyronine (T3), hormones critical for regulation of development and metabolism (83). Falling leptin level during fasting suppresses TRH expression, decreasing circulating thyroid hormones and energy expenditure in order to conserve energy (41, 42, 84). Leptin increases the expression of TRH in the paraventricular nucleus via the arcuate nucleus and restores TSH pulses and T4 secretion (84, 85). *ob/ob* mice exhibit central hypothyroidism corrected by leptin treatment (66); however, thyroid hormone levels appear normal in patients with *LEP* mutation before and after leptin treatment (67, 86). TSH levels did not change significantly after leptin treatment in patients with hypothalamic amenorrhea (43). In contrast, leptin replacement for 5 weeks in 10% weight-reduced individuals reversed the fall in serum T3 and T4 levels and increased energy expenditure (87). Skeletal muscle work efficiency was impaired in the weight-reduced state, and leptin or T3 treatment reversed these metabolic changes to a similar degree, indicating that leptin's stimulation of T3 drives energy expenditure in weight-reduced individuals (88).

Growth hormone–releasing hormone (GHRH) stimulates growth hormone (GH) secretion from the pituitary. GH then acts on the liver to produce insulin-like growth factor 1 (IGF1), which mediates GH effects on tissue growth and repair and other anabolic actions. GH bioavailability is controlled by IGF-binding proteins (IGFBPs), particularly IGFBP3. During fasting, GH secretion increases and promotes gluconeogenesis and lipolysis. Leptin regulates GH via hypothalamic and pituitary mechanisms (42, 81, 89–91). Leptin increases pituitary GH and GHRH receptor expression and hypothalamic GHRH and IGF1 levels in *ob/ob* mice (92). In humans, short-term fasting increases GH, and long-term fasting decreases IGF1 (42). Leptin treatment during 72-h fasting prevented the suppression of IGF1 (42). In female athletes with hypothalamic amenorrhea, leptin treatment significantly increased total IGF1 and slightly increased free IGF1 and IGFBP3 levels (43, 80).

Energy deficiency activates the HPA axis, leading to higher cortisol levels (93). Fasting-induced hypercortisolism stimulates gluconeogenesis, lipolysis, and proteolysis. *ob/ob* mice have high glucocorticoid levels that are reduced by leptin treatment (12); however, human *LEP* mutation is not associated with HPA activation (67, 94). On the other hand, leptin deficiency in congenital lipodystrophy is associated with elevated adrenocorticotropic hormone (ACTH) and cortisol, normalized by leptin replacement (78, 79, 95). REDs is associated with HPA activation; short-term leptin treatment did not affect the HPA axis, but long-term leptin replacement for up to 2 years decreased cortisol levels (43, 80, 81).

Leptin and the Immune System

Immune system dysfunction was described in *ob/ob* and *db/db* mice long before the discovery of leptin (96, 97). *ob/ob* mice exhibit thymic atrophy and decreased T cell numbers, and leptin treatment rescues $CD4^+$ T cell but not $CD8^+$ T cell development (98). The role of leptin in regulating human immune function was demonstrated in patients with homozygous missense *LEP* mutation who were predisposed to childhood infections (68, 86). Fasting-induced hypoleptinemia mediates impaired immunity and increases susceptibility to infection (89, 99, 100).

Leptin plays significant roles in activation and coordination of innate and adaptive immune responses (reviewed in 101–103). Leptin activates neutrophils, prevents apoptosis, and increases chemokines, neutrophil chemotaxis, and oxidative killing of bacteria. Leptin directly stimulates macrophage phagocytosis and proinflammatory cytokine production. In humans, the long leptin receptor isoform LEPR is expressed on various immune cells and signals through the JAK-STAT pathway (102, 104). Leptin stimulates tumor necrosis factor-alpha secretion in human monocytes (105). Leptin's role in adaptive immunity is demonstrated by an increase in Lepr expression on mouse $CD4^+$ and $CD8^+$ T cells and B cells in response to leptin treatment. In contrast, *db/db* mice have reduced $CD4^+$ T cell proliferation and attenuated B cell differentiation into effector B cells (97). Leprb on $CD4^+$ T cells signals through JAK-STAT, increases proliferation and differentiation, and increases production of proinflammatory Th1 cytokines interferon gamma and interleukin 2 (IL-2), while decreasing Th2 cytokine IL-4 (100, 106, 107). Fasting-induced hypoleptinemia suppresses effector T cells and inflammatory cytokine production, and this is prevented by leptin replacement (89, 100, 108).

Leptin mediates the recruitment of immune cells to adipose tissue. In both *ob/ob* and *db/db* mice, the lack of leptin signaling is associated with reduced adipose macrophagic infiltration (109, 110). Leptin is a potent chemoattractant for monocytes and macrophages through the Leprb, JAK/STAT, MAPK, and PI3K pathways (105). Leptin regulates regulatory T cells that ameliorate inflammation in adipose tissue (111). Mice fed a high-fat diet develop obesity and CNS leptin resistance but maintain leptin sensitivity in immune cells (112). Similar results were obtained in obese rats and humans, indicating that peripheral leptin signaling in immune cells promotes inflammation in obesity, leading to metabolic dysfunction (113).

The rise in obesity in Western countries is associated with increasing incidence of autoimmune diseases, e.g., multiple sclerosis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, type 1 diabetes, and autoimmune thyroid disease (101, 103, 104, 114). Elevated leptin levels have been associated with progression of multiple sclerosis and rheumatoid arthritis (103, 115, 116). Leptin has been suggested to participate in tissue damage in rheumatoid arthritis and the inflammatory process in psoriasis (117, 118). Obesity is a known risk factor for development, progression, and exacerbation of allergic asthma (119, 120). In children, factors affecting asthma severity include metabolic dysfunction, airway and systemic inflammation, altered microbiome, and reaction to air pollutants. Asthma is linked to hyperleptinemia, leptin-dependent Th2 cell proliferation and

activation, activation of MAPK signaling, inhibition of caspase-mediated cell death, and induction of the release of proinflammatory cytokines and chemokines (119, 120).

The link between leptin and susceptibility to infection has been studied in animal models and humans (102). *ob/ob* mice are prone to infection and have high mortality when exposed to lipopolysaccharide, and leptin treatment is partially protective (121, 122). *db/db* mice are prone to staphylococcal infection (97). Rare patients with *LEP* or *LEPR* mutations have immune deficits, are prone to infections, and suffer greater mortality due to infections (68, 86, 89, 94). Leptin replacement increases $CD4^+$ T cell numbers and restores $CD4^+$ T cell proliferation and cytokine production (68). Leptin decreases bacterial infection and improves survival in mice infected with *Mycobacterium tuberculosis*, *Klebsiella* pneumonia, or pneumococcal pneumonia (103, 104). Starvation reduces leptin levels, which is associated with impaired innate and adaptive immunity and susceptibility to viral, bacterial, and parasitic infections such as influenza, bacterial pneumonia, and cellulitis (89, 99, 108, 123). On the other hand, common obesity also increases susceptibility to COVID-19, influenza, and bacterial infections (102, 104). We propose that enhanced peripheral leptin signaling persists in the immune system during hyperleptinemia in obesity, driving excessive inflammation, proinflammatory cytokine production, and adverse systemic outcomes.

LEPTIN AS A THERAPEUTIC AGENT IN HUMANS

The discovery of leptin provided new insight into the pathophysiology of obesity and led to initial high expectations for leptin-based therapies. The contextual framework for leptin therapeutics was compared to the pathogenesis and treatment of diabetes. Type 1 diabetes is caused by insulin deficiency from autoimmune destruction of beta cells in pancreatic islets. The logical therapeutic approach is insulin replacement. Type 2 diabetes occurs mostly in individuals with obesity, associated with insulin resistance and relative insulin insufficiency, and can be treated with exogenous insulin. In a similar context, it was expected that leptin replacement would effectively correct biological abnormalities in individuals with leptin deficiency, and individuals with common obesity may be managed using higher doses of leptin. Surprisingly, the history of leptin therapeutics has been dormant.

Leptin Therapy in Leptin Deficiency

Metreleptin is a recombinant methionyl leptin analog that is effective and safe in leptin-deficient states, i.e., congenital leptin deficiency, lipodystrophy, and hypothalamic amenorrhea (43, 67, 68, 78–80, 124) (**Table 1**). After 30 years since the discovery of leptin, metreleptin remains the only pharmaceutical form of leptin approved for clinical use. Metreleptin was approved by the US Food and Drug Administration in 2014 as adjunct replacement therapy with diet to treat the complications of leptin deficiency in congenital generalized lipodystropy and acquired generalized lipodystrophy. In the European Union, metreleptin was approved in 2018 as adjunct replacement therapy with diet to treat the complications of leptin deficiency in adults and children $\geq$2 years, congenital generalized lipodystropy or acquired generalized lipodystrophy in adults and children $\geq$12 years, or familial partial lipodystrophy or acquired partial lipodystrophy in adults and children $\geq$12 years in whom diet and standard treatment have failed to achieve adequate metabolic control.

Leptin Therapy in Common Obesity

In contrast to lipodystrophy, leptin administered as metreleptin or pegylated leptin had little or no effect in many clinical trials in individuals with common forms of obesity (67, 68, 78, 125–132) (**Table 1**). Most individuals with common obesity display hyperleptinemia, weight gain despite rising endogenous leptin levels, and a failure to respond to exogenous leptin treatment (48). These

features indicate leptin resistance, akin to obesity in mice fed a high-fat diet (48). In DIO mice, leptin resistance is at least in part mediated through negative feedback inhibition of leptin signaling via induction of SOCS3 and PTP1B and other factors (32, 38, 44, 46, 49, 133).

How might leptin therapy work in common obesity? Leptin transport across the blood–brain barrier may provide a logical approach to leptin therapy in certain clinical contexts (20, 134–136). Obesity-related obstructive sleep apnea and obesity hypoventilation syndrome cause intermittent hypoxia during sleep and predispose to severe metabolic dysfunction and cardiovascular morbidity and mortality. Obstructive sleep apnea and obesity hypoventilation syndrome are associated with hyperleptinemia and leptin resistance. Lepr-expressing neurons of the dorsomedial hypothalamus regulate metabolism and breathing in DIO mice through reciprocal leptin and serotonergic pathways (137, 138). Remarkably, acute intranasal, but not intraperitoneal (systemic), leptin administration decreased oxygen desaturation events in REM sleep and increased ventilation in non-REM and REM sleep in DIO mice (137, 138). Chronic intranasal leptin administration decreased food intake and body weight, but systemic leptin had no effect (138). Intranasal leptin activated STAT3 in hypothalamic and medullary neurons involved in energy homeostasis and sleep regulation (138). Future research should investigate intranasal leptin as a viable therapy for obesity-related sleep disorders and other diseases.

Since the discovery of insulin more than a century ago, there have been major advances in the development of natural insulin preparations and insulin analogs for the treatment of diabetes (139). In contrast, there has been little progress in the development of leptin analogs beyond metreleptin. The history of GLP1 therapeutics also has a lot to teach us about peptide drug development (140–142). GLP1 was discovered originally as an incretin hormone primarily involved in glucose regulation. The development of GLP1 mimetics resulted in potent antidiabetic drugs, e.g., exenatide. Subsequently, the development of long-acting GLP1 analogs, liraglutide and semaglutide, led to very potent antidiabetic drugs in addition to the identification of antiobesity actions of GLP1R agonism in satiety and weight loss as well as anti-inflammatory and cardiovascular and renal benefits (141, 142). It is time for the pharmaceutical industry to partner with academic investigators to discover new and effective leptin mimetics and analogs, with better brain penetration and specific actions on brain targets mediating feeding and metabolism.

An area of interest is whether a subset of individuals with common obesity might have lesser degrees of hyperleptinemia or relative hypoleptinemia and may therefore respond to metreleptin or long-acting leptin analogs (143). A long noncoding RNA has been identified that is associated with leptin-responsive obesity (144). It is possible a subset of obese individuals with relative hypoleptinemia may show a robust response to exogenous leptin. It will be important to determine whether such individuals might be distinguished from most people with common obesity. It is noteworthy that current leptin assays are not standardized across clinical trials, and the most frequent clinical measures of leptin action, i.e., weight loss or change in body mass index (BMI), may not fully capture leptin's effect on adiposity.

Another potential therapeutic strategy quite distinct from identifying leptin-responsive patients would be to reduce hyperleptinemia to overcome leptin resistance in common obesity (145–148). Scherer's group (146–148) demonstrated in mouse models that a partial reduction of endogenous plasma leptin levels using neutralizing antibodies restored hypothalamic leptin sensitivity, reduced weight gain, and improved insulin sensitivity. In subsequent experiments, they showed that fibroblast growth factor 21 (FGF21) and GLP1R agonist liraglutide induced weight loss and rapidly reduced plasma leptin levels (146, 147). Lowering of leptin levels enhanced GLP1R agonism in inducing weight loss, while maintenance of plasma leptin levels using a transgenic approach blunted the weight loss action of GLP1R agonist. A leptin-neutralizing antibody administered in combination with FGF21 or liraglutide synergistically induced greater weight

loss and improvement in glucose homeostasis. Antibody blockade of circulating leptin induced greater leptin signaling in hypothalamic neurons. These results highlight that a partial reduction in endogenous hyperleptinemia in obesity could improve leptin sensitivity, providing a potential therapy for obesity and associated diseases (146–148).

Another potential approach to overcome central leptin resistance involves combining leptin with a weight loss drug that acts on similar pathways in the brain. For example, amylin augments the effect of leptin to reduce food intake and body weight (149, 150). In a 24-week randomized, double-blind human clinical trial, pramlintide (amylin analog) administered in combination with metreleptin resulted in greater weight loss compared with either leptin or pramlintide alone (151). However, metreleptin treatment induces antibodies that may limit efficacy (152).

SUMMARY AND CONCLUSIONS

The cloning of the leptin gene 30 years ago and demonstration that the encoded protein leptin reversed obesity in *ob/ob* mice and patients with congenital leptin deficiency were hailed as seminal events in biomedical research. Since then, there has been much progress in our understanding of leptin receptor and signaling pathways, mainly based on rodent models. However, the biology of leptin in common forms of human obesity remains an enigma. This knowledge gap is highlighted by a lack of understanding of mechanisms of leptin resistance in common forms of human obesity and whether these pathways could be potentially targeted for treatment of obesity.

In stark contrast to the experience with insulin and incretin hormones, few studies have been performed with leptin in humans to fully understand the physiology of energy homeostasis and pathophysiology of obesity and related diseases. Logical studies include investigation of metabolic dose responses of leptin on feeding, metabolism, and other systems in lean versus obese individuals during weight loss and weight gain. We need reagents beyond metreleptin to unravel the biology of human leptin, and specific tissue biomarkers and clinical tools to assess in vivo leptin action.

Why have academic institutions, funding agencies, and the pharmaceutical industry not prioritized mechanistic studies to address leptin's roles in normal physiology and pathophysiological pathways? The limited availability or unavailability of recombinant leptin and other reagents for human clinical investigations is an obvious hurdle. Obesity is a major health crisis with enormous socioeconomic consequences. The discoveries of potent insulin analogs and GLP1R and GLP1R/GIPR agonists have radically transformed the treatment of diabetes and obesity as well as provided new insight into multiple systems. Regrettably, after 30 years, the research and therapeutic potential of leptin remains largely dormant. It is hoped the coming decade will witness a resurgence of research into leptin that will lead to better understanding of fundamental and translational biology and therapies for human obesity and related diseases.

SUMMARY POINTS

1. The discovery of leptin as an adipocyte-secreted hormone encoded by the *ob* gene, whose absence causes severe obesity corrected by leptin repletion in mice and humans, was a transformative event in metabolic science.
2. Using leptin as a physiologic tool in rodent models accelerated identification of neuronal circuitry responsive to leptin that integrates peripheral signals and regulates energy balance and metabolic, neuroendocrine, and other functions.

3. The fall of leptin levels in response to caloric restriction revealed that low leptin is a clear signal of energy deficiency that evokes survival responses to conserve energy and increase food seeking. Evolutionary considerations suggest this switch between starvation and the fed state is a critical, if not the dominant, physiologic role of the hormone.
4. Most animals and humans with obesity have elevated leptin levels (hyperleptinemia) proportional to their fat mass and have little or no response to exogenous leptin supplementation, a state described as leptin resistance.
5. In common cases of obesity, leptin resistance is only partial, because obesity is far less severe than seen with mutant leptin or leptin receptors, and features such as hypothalamic hypogonadism are not seen.
6. Much has been learned about leptin signal transduction and intracellular antagonists of leptin signaling, but the explanation for leptin resistance in common obesity is not yet established.
7. Leptin therapy has been useful in congenital leptin deficiency and lipodystrophy, and it is possible that a subset of obese individuals with relatively low leptin might benefit from leptin therapy.
8. Hyperleptinemia appears to be a causal factor in inducing leptin resistance, and antagonizing leptin may, paradoxically, be found to have efficacy in obesity treatment, either alone or in conjunction with other therapies.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

R.S.A. is supported by a Bloomberg Distinguished Professorship.

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