Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism

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Abstract

Leptin is secreted by adipose tissue and regulates energy homeostasis, neuroendocrine function, metabolism, immune function and other systems through its effects on the central nervous system and peripheral tissues. Leptin administration has been shown to restore metabolic and neuroendocrine abnormalities in individuals with leptin-deficient states, including hypothalamic amenorrhea and lipoatrophy. In contrast, obese individuals are resistant to leptin. Recombinant leptin is beneficial in patients with congenital leptin deficiency or generalized lipodystrophy. However, further research on molecular mediators of leptin resistance is needed for the development of targeted leptin sensitizing therapies for obesity and related metabolic diseases.

Keywords

energy homeostasis; hypothalamus; leptin; metabolism; obesity

Introduction

The discovery of leptin changed the knowledge of energy homeostasis and our view of adipose tissue from a simple energy depot to an active endocrine organ [1]. Leptin is mainly produced in adipose tissue and circulating leptin levels correlate well with the amount of body fat, reflecting energy status. Leptin plays an important role in regulating energy homeostasis, neuroendocrine and immune functions, and glucose, lipid and bone metabolism [2, 3]. While leptin administration reverses neuroendocrine and metabolic abnormalities in

individuals with congenital leptin deficiency, common forms of obesity are typically associated with elevated leptin and resistance to leptin's effects on energy homeostasis [4]. Here, we review the biology of leptin, the current understanding of its physiologic and pathologic roles, and potential clinical applications.

Biology of leptin

Leptin is a 167-amino-acid peptide that is mainly expressed in white adipose tissue (WAT), but is also found in a variety of tissues including placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and lymphoid tissue [5]. Circulating leptin levels are directly in proportion to the amount of body fat, thereby reflecting the status of long-term energy stores. In addition, leptin levels fluctuate according to changes in calorie intake with a marked decrease during starvation [6, 7]. Leptin is secreted in a pulsatile manner, displaying a circadian rhythm with lowest levels at mid-afternoon and highest levels at midnight. The pulsatile pattern of leptin secretion is similar in obese and lean subjects, but the pulse amplitude is higher in obese subjects [8]. Leptin levels exhibit sexual dimorphism. Although leptin levels decline significantly after the menopause, women tend to have higher levels than men even after controlling for body fat mass, suggesting a role of sex steroids [9]. Subcutaneous fat produces more leptin than visceral fat, and this may, in part, contribute to higher leptin levels in women compared to men [10]. Besides sex steroids, leptin levels are also regulated by other factors including insulin, glucocorticoids, catecholamine, and cytokines [11] (Table 1).

Leptin exerts its effects through binding to specific leptin receptors (LepRs) located throughout the central nervous system (CNS). Four alternatively spliced isoforms of LepR have been identified in humans. The long isoform of leptin receptor (LepRb) is highly expressed in the hypothalamus and other brain regions, where it regulates energy homeostasis and neuroendocrine function, and considered as the main leptin receptor [12]. While LepRb is primarily responsible for suppression of food intake and stimulation of energy expenditure, the short isoforms of LepR are thought to mediate the transport of leptin across the blood-brain barrier [13]. Evidence suggests that leptin transport into the hypothalamus is mediated by tanycytes through LepR activation [14]. The binding of leptin to LepRb activates several signaling pathways, including Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3), insulin receptor substrate (IRS)-phosphatidylinositol 3-kinase (PI3K), SH2-containing protein tyrosine phosphatase 2 (SHP2)-mitogen-activated protein kinase (MAPK), and 5' adenosine monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC), and other pathways. The leptin signaling cascade is terminated by induction of suppressor of cytokine signaling 3 (SOCS3), which inhibits the JAK2-STAT3 pathway through a negative-feedback loop. Protein tyrosine phosphatase 1B (PTP1B) is also implicated in the inhibition of leptin signaling [2, 3, 15]. Activation JAK2-STAT3 signaling plays a crucial role in leptin's ability to regulate energy homeostasis [16, 17].

Obese individuals exhibit high levels of leptin expression in adipose tissue and have elevated circulating leptin levels, and these high leptin levels fail to reduce excess adiposity, indicating leptin resistance. Moreover, exogenous leptin administration has little effect on

body fat in obese subjects [18]. Mechanisms underlying leptin resistance may include disruption of leptin signaling in hypothalamic and other CNS neurons, impaired leptin transport across blood-brain barrier, hypothalamic inflammation, endoplasmic reticulum stress, and autophagy [19, 20].

Leptin and energy homeostasis

Leptin acts on LepRb-expressing neurons in the brain. In the arcuate nucleus (ARC), leptin interacts with a complex neural circuit to control food intake, activating anorexigenic neurons that synthesize pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), and inhibiting orexigenic neurons that synthesize agouti-related peptide (AgRP) and neuropeptide Y (NPY). During fasting, circulating leptin levels decline rapidly. The fall in leptin stimulates the expression of AgRP and NPY and suppresses POMC and CART, thereby increasing food intake and decreasing energy expenditure [21, 22]. The lateral hypothalamus contains neurons that express melanin-concentrating hormone (MCH) and orexins, which are decreased by leptin resulting in suppression of feeding [2, 23, 24]. A distinct population of LepRb-expressing neurons in the lateral hypothalamus which do not express MCH or orexins has been identified. These neurons innervate the ventral tegmental area (VTA), linking leptin to the hedonic control of feeding mediated by the mesolimbic dopamine system [25]. Leptin also acts on VMH neurons that express the transcription factor steroidogenic factor 1 (SF-1) [26]. Mice with SF-1 deletion in the VMH are susceptible to diet-induced obesity, associated with impaired thermogenesis [27]. More recently, brain-derived neurotrophic factor in the VMH has been linked to leptin's effects on feeding and energy balance [28].

LepRb-expressing neurons have also been found in the nucleus of the solitary tract (NTS) of the hindbrain, including subpopulations that express glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK). Leptin appears to act synergistically with GLP-1 and CCK in the NTS to promote satiety [29]. Peptide YY (PYY) is released from L cells of the ileum and colon in response to feeding, crosses blood-brain barrier and acts on Y2 receptor on NPY neurons in the ARC to inhibit the release of NPY, thereby reducing food intake in mice and humans [30, 31]. Peripheral administration of PYY in mice also activates neurons in the NTS, which may partly influence food intake. However, compared to wild-type mice, nearly identical reductions in food intake were observed in both leptin-deficient *ob/ob* and LepR-deficient *db/db* mice treated with PYY, indicating that leptin signaling is not essential for the anorectic action of PYY [32]. Clinical studies have shown that PYY levels are reduced in obese people [33–35], and increased after weight loss [36]. Although PYY transgenic mice crossed with *ob/ob* mice exhibit reduced body weight and adiposity, the physiological significance of this finding is unclear [37, 38].

Leptin interacts with the mesolimbic dopamine system and modulates the hedonic drive to feed [17, 39]. Neurons in the ventral tegmental area (VTA) expressing LepRb respond directly to leptin, resulting in suppression of feeding. Moreover, leptin modulates the mesolimbic dopamine system indirectly through the lateral hypothalamus [25, 40].

In addition to regulating food intake, leptin increases energy expenditure through sympathetic nerve activity. In rodents, leptin stimulates brown adipose tissue (BAT) thermogenesis by increasing the expression of uncoupling protein (UCP)-1 [41, 42]. The thermogenic effect of leptin is mediated partly by suppression of MCH and transcription factor Forkhead box O1 (FoxO1) [43, 44]. Mice lacking both leptin and MCH (double null) have less body fat than leptin-deficient *ob/ob* mice. While the mutant mice are similarly hyperphagic, the double null mice have greater energy expenditure and locomotor activity compared to *ob/ob* mice [45]. Mice lacking FoxO1 in SF-1 neurons of the VMH have increased energy expenditure with up-regulation of UCP-1 in BAT due to enhanced sympathetic activity.

Leptin has a neurotrophic effect on hypothalamic neurons implicated in feeding and energy homeostasis, as well as cortical and hippocampal neurons [46, 47]. Leptin-deficient *ob/ob* and LepR-deficient *db/db* mice have reduced brain weight, decreased cortical volume, and structural neuronal abnormalities, suggesting that leptin plays a role in brain growth and neuronal development [48, 49]. Neural projections from the ARC to the paraventricular nucleus are reduced in *ob/ob* mice, and these deficits are restored by leptin treatment during early life [46]. In addition to its role in early neuronal development, leptin modulates synaptic plasticity in adults. Leptin administration in *ob/ob* mice rapidly normalizes synaptic inputs to POMC and AgRP neurons to levels seen in wild-type mice [47]. Leptin's actions in neurodevelopment have been demonstrated in murine cerebral cortex and hippocampus [50]. Brain imaging studies have also revealed structural and functional deficits reversible by leptin treatment in humans with congenital leptin deficiency [51, 52].

The importance of leptin in energy homeostasis is most evident in leptin deficiency. Thus, *ob/ob* mice with total leptin deficiency develop severe hyperphagia, low metabolic rate and rapid onset obesity, associated with high expression of NPY and MCH, and low expression of POMC in the hypothalamus (Fig. 1). These features are reversed by leptin treatment [11, 53]. As in rodents, humans with congenital leptin deficiency are hyperphagic and obese. Leptin treatment in these individuals results in a marked reduction in energy intake and body weight and fat [54, 55]. In contrast, the vast majority of obese people are insensitive to endogenous hyperleptinemia or leptin treatment, indicating the existence of "leptin resistance" in common forms of obesity arising from overnutrition and sedentary lifestyle [56–58] (Fig. 1).

Leptin and neuroendocrine function

Leptin levels in adipose tissue and plasma fall rapidly during fasting. Circulating leptin levels decrease in overweight men after negative energy balance is achieved with exercise and calorie restriction, indicating that leptin levels reflect energy status [59]. Low leptin levels during fasting trigger metabolic and hormonal responses in mice and humans [11, 60], consisting of hyperphagia, hypogonadotropic hypogonadism, and suppression of thyroid and growth hormone (GH) levels, which are prevented by physiologic doses of leptin [7, 61, 62] (Fig. 1). Leptin administration restores thyroid hormone, testosterone and luteinizing hormone (LH) levels in fasted mice [61], and LH pulsatility and testosterone levels in starved human volunteers [7, 61, 63]. These hormone changes are similar to congenital

leptin deficiency which results in hypogonadism and failure of pubertal development. Leptin replacement facilitates pubertal development in *ob/ob* mice and leptin-deficient humans, establishing a crucial role of leptin in reproduction [54, 64, 65]. Leptin also prevents the pubertal delay associated with starvation, and exerts a permissive effect on the onset of puberty in normal mice [66–68]. Low leptin levels are linked to impaired leptin pulsatility and hypogonadism in hypothalamic amenorrhea and generalized lipoatrophy [69, 70]. Leptin treatment increases mean LH levels, LH pulse frequency, estradiol levels, and corrects abnormal thyroid and cortisol levels in hypothalamic amenorrhea [71, 72]. Similarly, in individuals with generalized lipodystrophy who have low leptin levels and insulin resistance, leptin replacement normalizes LH and sex steroid levels [73]. These findings suggest that leptin is an important signal linking energy stores to the neuroendocrine axis.

Gonadotropin-releasing hormone (GnRH) neurons lack LepR, suggesting an indirect action of leptin in the hypothalamus via NPY, POMC, and kisspeptin [74, 75]. Kisspeptin, a product of *Kiss1* gene, stimulates GnRH secretion and increases LH levels in mice [76, 77]. Mutations in kisspeptin or kisspeptin receptor result in the lack of pubertal maturation and hypogonadotropic hypogonadism [78]. In comparison with wild-type mice, Kiss 1 mRNA levels are reduced in *ob/ob* mice and increase with leptin treatment [68, 77, 79]. However, mice with selective deletion of LepR from hypothalamic Kiss1 neurons show normal pubertal development and fertility, indicating that leptin action in Kiss1 neurons is not essential for puberty and reproduction [80]. A small population of Kiss1 neurons in the ARC express LepR [81, 82], but leptin signaling in these neurons occurs after completion of sexual maturation and is not crucial for leptin action during puberty [83, 84].

Leptin alters thyroid hormone regulation via multiple pathways. Leptin increases thyrotropin-releasing hormone (TRH) levels through up-regulation of proTRH gene expression, and by enhancing the processing of proTRH into mature TRH [85, 86]. Leptin-deficient *ob/ob* mice have reduced levels of thyroxine (T4) from birth [17]. Adult wild-type mice develop thyroid axis suppression during fasting [61]. Healthy humans have circadian and pulsatile levels of leptin and TSH, while congenital leptin deficiency results in a highly disorganized secretion of TSH [87]. After leptin replacement, leptin-deficient individuals exhibit an increase in thyroid hormone levels but no change in TSH [54]. Leptin administration prevents the fasting-induced suppression of TSH pulses but does not reverse the fall in tri-iodothyronine (T3) levels [7]. In women with hypothalamic amenorrhea, leptin administration increases free T3 and T4 levels but not TSH levels [71]. Leptin administration to weight-reduced individuals reverses the declines in T3 and T4 levels and in energy expenditure [88, 89].

In contrast to *ob/ob* mice which have reduced linear growth, suppression of the GH axis, and markedly elevated ACTH and corticosterone levels, humans with congenital leptin deficiency have normal linear growth and adrenal function [54, 55]. The mechanisms underlying the species differences in leptin regulation of growth hormone and hypothalamic-pituitary-adrenal axis are unclear.

Leptin and metabolism

Total leptin deficiency in *ob/ob* mice and individuals with congenital leptin deficiency results in insulin resistance, diabetes, steatosis and other features of metabolic syndrome. In *ob/ob* mice, leptin treatment rapidly decreases glucose, insulin and lipids before weight loss is achieved [53, 90] (Fig. 2). In morbidly obese individuals with congenital leptin deficiency, leptin replacement dramatically decreases insulin resistance, steatosis, dyslipidemia and glucose levels [54, 65]. Similarly, central or peripheral leptin administration decreases insulin resistance, steatosis and glucose in generalized lipoatrophy [91–93]. In lipodystrophic humans with severe leptin deficiency, leptin administration results in drastic improvements in glucose and lipid metabolism [73, 94, 95], accompanied by significant reductions in hepatic and muscle triglyceride accumulation [96]. In contrast, leptin does not reverse hyperglycemia in people with moderate leptin deficiency, but decreases plasma and hepatic triglyceride levels [97]. Leptin treatment causes a preferential decrease in visceral fat in rats, promoting fat redistribution [98]. Similarly, leptin replacement in patients with lipoatrophy results in a reduction of truncal fat mass, accompanied by a selective decrease in visceral adiposity [95, 99].

How does leptin regulate glucose and lipid metabolism? In non-obese diabetic mice, peripheral leptin administration normalized glycemia by suppressing glucagon levels and various hepatic intermediary metabolites [100]. Central administration of leptin also decreased glucose and glucagon levels through insulin-independent mechanisms [101]. It has been proposed that leptin replacement may serve as an adjunct therapy to insulin in patients with type 1 diabetes, by improving glucose and lipid metabolism [102, 103]. Studies suggest that leptin affects peripheral insulin sensitivity via CNS mechanisms independent of its effects on food intake and weight [104] (Fig. 2). Leptin potently suppresses hepatic glucose production partly by ameliorating hyperglucagonemia and increases peripheral glucose uptake, via multiple mechanisms including POMC- and AgRP-expressing neurons in the ARC [105–108]. Restoration of LepR expression in the ARC decreases insulin and glucose levels in LepR-null mice. Moreover, selective expression of LepRb in hypothalamic POMC neurons prevents diabetes in LepR-deficient *db/db* mice, independently of changes in food intake and weight [105, 106, 108]. Deletion of leptin targets, SOCS3 or PTP1B, in POMC neurons also improves glucose homeostasis [109, 110]. Furthermore, genetically mediated alteration of PI3K activity in POMC neurons affects hepatic insulin sensitivity [111]. Recent evidence has shown that selective re-expression of LepRb in AgRP neurons mediates leptin's anti-diabetic actions in *db/db* mice by suppressing glucagon [112]. Central leptin administration also suppresses hepatic glucose production and increases tissue glucose uptake through autonomic pathways [107]. Leptin increases AMPK phosphorylation and improves insulin sensitivity in skeletal muscle through activation of PI3K in the hypothalamus [113].

In addition to regulating insulin sensitivity, leptin alters glucose homeostasis through insulin. Leptin inhibits insulin gene expression and glucose-stimulated insulin secretion, and these actions adapt glucose levels to body fat stores [114, 115]. In turn, insulin stimulates both leptin synthesis and secretion, thus establishing an adipose-islet axis [116]. Leptin also protects pancreatic β-cells from lipotoxicity in various animal models [100, 117, 118].

Leptin regulates lipid metabolism independently of food intake. Central leptin administration inhibits *de novo* lipogenesis and stimulates lipolysis in adipose tissue and liver via activation of the sympathetic nervous system [119, 120]. Leptin stimulates fatty acid oxidation by up-regulating peroxisome proliferator-activated receptor γ-coactivator-1α, and decreasing triglyceride stores within white adipocytes and liver [121]. Leptin also stimulates fatty acid oxidation by activating AMPK in skeletal muscle, and preventing the accumulation of lipid metabolites associated with lipotoxocity [122]. Disruption of LepR in peripheral organs has no significant impact on metabolism, suggesting that leptin acts mainly in the brain to influence glucose and lipid metabolism [123].

Leptin appears to modulate bone metabolism both centrally and peripherally. In rodents, leptin regulates cortical bone formation via β-adrenergic stimulation or GH/ insulin-like growth factor (IGF)-1 effects on trabecular bone remodeling. Leptin may also influence cortical bone metabolism through neuropeptides in the hypothalamus, including NPY, an inhibitor of cortical bone formation [124, 125]. Peripherally, it has been shown that leptin acts on marrow stromal cells to enhance osteoblast differentiation and inhibit adipocyte differentiation. Leptin stimulates osteoblast proliferation and mineralization [126, 127]. Leptin's effect on bone biology is evident in leptin deficient states. For example, leptin treatment increases markers of bone formation, bone mineral density and content in the lumbar spine of patients with hypothalamic amenorrhea [71, 72, 128]. These effects of leptin may involve direct action on bone, increased IGF-1 levels, restoration of estradiol, and reduction of cortisol. Furthermore, leptin exerts anti-osteogenic effects via sympathetic nervous activation in the hypothalamus [129]. Sympathetic activation inhibits bone formation and increases bone resorption mediated by β2 adrenergic receptors in osteoblasts [130, 131].

Leptin and exercise

Successful long-term weight loss requires a reduction in food intake and an increase in physical activity. A negative energy balance achieved in 4 days by combining calorie restriction and exercise in obese subjects resulted in a rapid decline in leptin, indicating that changes in leptin levels reflect energy balance [59]. Human skeletal muscle expresses low levels of LepRb. As with plasma leptin levels, there is a sexual dimorphism in LepRb expression in human skeletal muscle, which could be partly explained by an inverse relationship between free testosterone level and LepRb in skeletal muscle [132]. Leptin is thought to directly increase glucose uptake and fatty acid oxidation in skeletal muscle [133, 134]. Peripheral leptin administration increases IGF binding protein-2 (IGFBP-2) in human skeletal myotubes. Central infusion of leptin in sheep also increased IGFBP-2 in skeletal muscle and improved glucose homeostasis [135, 136].

Leptin receptors and leptin signaling in skeletal muscle particularly in the leg muscles are reduced in obese subjects, suggesting a potential mechanism of leptin resistance in obesity [137]. Sprint exercise or intense intermittent exercise activates AMPK, which is also activated by leptin in human skeletal muscle [122, 138, 139]. Moreover, sprint exercise under fasting conditions enhances leptin signaling in human skeletal muscle [140]. In obese rodents, prolonged exercise suppresses PTP1B activity in the hypothalamus, and improves

leptin signaling [141]. In healthy volunteers, one week of bed rest resulted in an increase in circulating leptin level without a concomitant increase in STAT3 phosphorylation in leg skeletal muscle, indicating an induction of leptin resistance in skeletal muscle. This was explained, at least partly, by an up-regulation of PTP1B expression in leg muscle [142]. Aging is also associated with dysregulation of leptin signaling and increased PTP1B expression in human skeletal muscle [143].

Leptin and immune function

Various studies have shown that leptin has important roles in modulating innate and adaptive immunity [144]. Leptin stimulates neutrophil chemotaxis and promotes macrophage phagocytosis, as well as production of pro-inflammatory cytokines such as interleukin (IL)-6, IL-12, tumor necrosis factor (TNF)-α [145, 146]. Recently, it has also been shown that leptin acts as a negative signal for the proliferation of regulatory T cells, while stimulating T helper 1 cells [144, 147]. Thus, leptin may contribute to the protection from infections and the development of autoimmunity [3, 144].

An *in vivo* study with *ob/ob* mice and short-term fasted normal mice showed that leptin treatment protected these mice from immune dysfunction associated with hypoleptinemia [148]. Compared to healthy subjects, individuals with congenital leptin deficiency have a higher incidence of infection, probably due to a reduction of circulating CD4+ T-cells and impaired T cell proliferation and cytokine release, all of which are normalized with leptin administration [54]. In women with hypothalamic amenorrhea who have chronic leptin deficiency, leptin replacement has been shown to increase soluble TNF-α receptor and restore both CD4+ T-cell counts and their *in vitro* proliferative responses, proving that leptin can facilitate immune reconstitution in subjects with chronic hypoleptinemia. In contrast, leptin administration has no major effects on immune cells or serum cytokines in individuals with acute leptin deficiency from short-term starvation [63, 149, 150].

Leptin can influence the development of autoimmune diseases. Leptin treatment potentiates experimental autoimmune encephalomyelitis, an animal model for multiple sclerosis in humans, in susceptible strains of mice, while leptin-deficient *ob/ob* mice are resistant to the induction and progression of the disease. Moreover, leptin treatment accelerated disease onset in susceptible mice [151, 152]. Patients with multiple sclerosis have increased leptin levels in blood and cerebrospinal fluid and reduced number of peripheral regulatory T cells compared to controls [153]. Taken together, these findings suggest potential roles of leptin in inflammatory and autoimmune diseases.

Clinical applications of leptin

As mentioned earlier, leptin treatment has robust effects in states of leptin deficiency [154] (Fig. 1). Leptin replacement dramatically reduces body weight and fat, and reverses neuroendocrine and metabolic abnormalities in individuals with congenital leptin deficiency [54, 65]. Leptin administration in women with hypothalamic amenorrhea restores normal menstrual cycles, corrects abnormalities in the gonadal, thyroid and adrenal axes, and improves bone mineral density and markers of bone formation [72, 128]. In subjects with

congenital or acquired lipoatrophy, leptin treatment improves several metabolic parameters, including insulin sensitivity, dyslipidemia, and hepatic steatosis [94, 95, 155].

In contrast, common forms of obesity and type 2 diabetes are accompanied by leptin resistance (Fig. 1) [57, 58]. A combination therapy of leptin and leptin sensitizers has been suggested to overcome leptin resistance. Amylin acts synergistically with leptin to reduce body weight and adiposity in diet-induced obese rodents, while preventing the compensatory reduction in energy expenditure associated with weight loss [156, 157]. Clinical studies have shown that a combined treatment of leptin and amylin analog pramlintide results in more weight loss in obese subjects than either treatment alone. The effect of weight loss appeared to be additive rather than synergistic, implying that amylin does not improve the sensitivity to leptin [157, 158]. The additive actions of leptin and amylin involve overlapping intracellular signaling pathways in peripheral tissues in humans [159]. Unfortunately, a clinical trial of pramlintide/leptin therapy for obesity was discontinued due to induction of leptin antibodies [154]. In rodents, metformin, exendin-4, and fibroblast growth factor (FGF)-21 have been shown to enhance leptin sensitivity when co-administered with leptin [160, 161]. Co-administration of leptin with either exendin-4 or FGF21 resulted in restoration of leptin responsiveness in diet-induced obese mice after an initial body weight loss of 30% [161]. Exercise also acts as a leptin sensitizer and could be used to enhance leptin signaling in human skeletal muscle [140].

Recent work suggests that leptin plays a more important role in the maintenance of weight loss than weight loss *per se*. Reduced leptin levels during weight loss activate neuroendocrine mechanisms that may drive weight-reduced subjects to regain weight. In clinical studies of subjects with relative leptin deficiency due to weight loss, leptin treatment restored thyroid hormone levels, sympathetic nerve activity, and energy expenditure, and reversed declines in satiation in weight-reduced subjects, suggesting a role of leptin in weight loss maintenance [88, 89]. In addition, functional brain imaging has shown that leptin treatment prevents the changes in neural activity involved in the regulatory, emotional, and cognitive control of food intake following weight loss [162]. Studies are under way to determine whether leptin replacement can be an effective therapy for maintenance of weight loss [163].

Future potential areas of leptin therapy include neurodegenerative disorders such as Alzheimer's disease. A growing body of evidence suggests that leptin has a positive influence on neurogenesis, axon growth, synaptogenesis, and neuroprotection [50, 164]. Prospective studies have shown that high leptin levels, especially among non-obese individuals, are associated with a lower risk of dementia and Alzheimer's disease, implying a possible therapeutic role of leptin [165–167]. Furthermore, leptin may be targeted for diagnostic or therapeutic uses in the regulation of immunity and bone health.

Concluding remarks

Leptin is an adipocyte-secreted hormone that regulates food intake, energy homeostasis, neuroendocrine function, metabolism, and immune function. Studies have shown that leptin acts mainly on neuronal targets in the brain. Leptin replacement is an effective therapy in

severe leptin deficiency, such as congenital leptin deficiency or generalized lipodystrophy. Further studies are needed to better understand the mechanisms underlying leptin resistance in common forms of obesity, and how these could be targeted specifically to treat obesity, diabetes and related metabolic diseases.

Acknowledgement

Abbreviations

ACC	acetyl-CoA carboxylase
AgRP	agouti-related peptide
AMPK	AMP-activated protein kinase
ARC	arcuate nucleus
BAT	brown adipose tissue
CART	cocaine-and amphetamine-regulated transcript
CCK	cholecystokinin
CNS	central nervous system
FGF	fibroblast growth factor
FoxO1	Forkhead box O1
GH	growth hormone
GLP-1	glucagon-like peptide 1
GnRH	gonadotropin-releasing hormone
IGF	insulin-like growth factor
IGFBP	IGF binding factor
IL	interleukin
IRS	insulin receptor substrate
JAK2	Janus kinase 2
LH	luteinizing hormone
LHA	lateral hypothalamic area
MAPK	mitogen-activated protein kinase
MCH	melanin-concentrating hormone
NPY	neuropeptide Y
NTS	nucleus of the solitary tract
LepR	leptin receptor

LepRb	long isoform of leptin receptor
PI3K	phosphatidylinositol 3-kinase
POMC	pro-opiomelanocortin
PTP1B	Protein tyrosine phosphatase 1B
PYY	peptide YY
SF-1	steroidogenic factor 1
SHP2	SH2-containing protein tyrosine phosphatase 2
SOCS3	suppressor of cytokine signaling 3
STAT3	signal transducer and activator of transcription 3
T3	tri-iodothyronine
T4	thyroxine
TNF	tumor necrosis factor
TRH	thyrotropin-releasing hormone
TSH	thyroid stimulating hormone
UCP	uncoupling protein
VMH	ventromedial hypothalamus
VTA	ventral tegmental area
WAT	white adipose tissue

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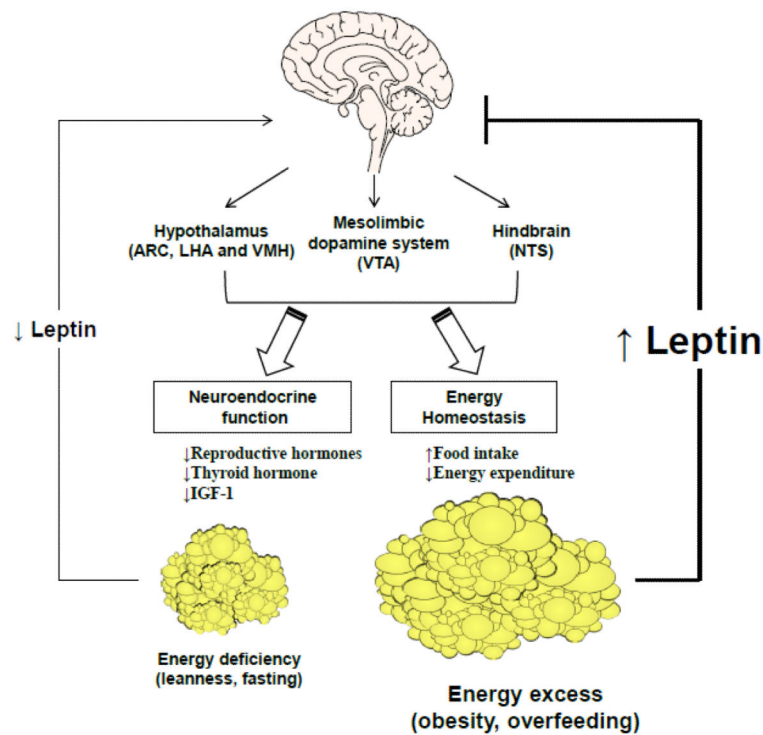
Figure 1. The effects of leptin in states of energy excess and energy deficiency
In states of energy deficiency such as fasting, circulating leptin levels decrease. As a result, food intake increases due to increased expression of orexigenic neuropeptides and decreased expression of anorexigenic neuropeptides. In addition, the decline of leptin modulates mesolimbic dopamine system and hindbrain circuits to increase food intake, and also has effects on neuroendocrine function and sympathetic nervous system, to decrease energy expenditure. In states of energy excess such as obesity and overfeeding, leptin levels increase; however, leptin's effects in the CNS are blunted due to leptin resistance. Recombinant leptin administration results in improvement in neuroendocrine and metabolic abnormalities in leptin-deficient states such as congenital leptin deficiency, hypothalamic amenorrhea, and congenital or acquired lipoatrophy. On the other hand, in states of leptin excess such as common forms of obesity and type 2 diabetes, recombinant leptin confers minimal benefits, indicating leptin resistance. The latter may be overcome with co-administration of amylin, leptin sensitizers or exercise. Leptin enhances weight loss maintenance in obesity by suppressing food intake and increasing energy expenditure. Abbreviations: ARC, arcuate nucleus; CNS, central nervous system; IGF, insulin-like growth factor; LHA, lateral hypothalamic area; NTS, nucleus of the solitary tract; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.
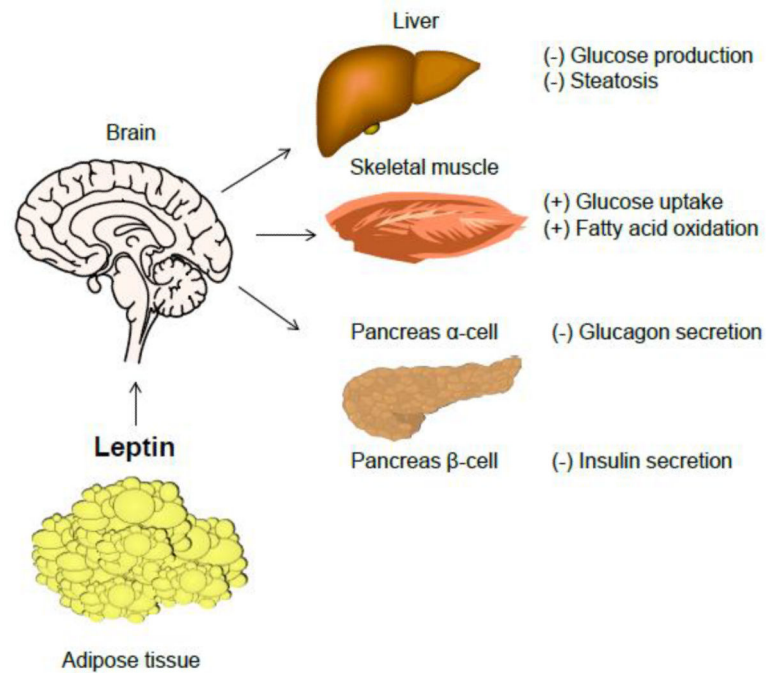
Figure 2. The effects of leptin in glucose and lipid metabolism
Leptin can affect glucose homeostasis through a variety of mechanisms, including modulation of ANS, hepatic glucose production, muscle glucose uptake, and glucagon secretion from pancreatic α-cells. Leptin inhibits insulin secretion, and stimulates fatty acid oxidation. Abbreviations: ANS, autonomic nervous system.

Table 1

Factors regulating circulating leptin levels

Factors increasing leptin	Factors reducing leptin
Excess energy stored as fat (obesity)	Low energy states with decreased fat stores (leanness; lipoatrophy)
Overfeeding	Fasting
Glucose	Cold exposure, and adrenergic agonists
Insulin	Thyroid hormone
Estrogen	Testosterone
Proinflammatory cytokines (TNF-α, IL-6)	

Adapted from reference [3]. IL, interleukin; TNF, tumor necrosis factor.