

Leptin signaling

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Abstract

Leptin is secreted by adipose tissue and regulates energy homeostasis, glucose and lipid metabolism, immune function, and other systems. The binding of leptin to its specific receptor activates various intracellular 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), in the central nervous system and peripheral tissues. Understanding of leptin signaling provides insights into its roles in health and disease.

Introduction

Leptin is primarily synthesized and secreted by white adipose tissue and acts in the brain and several peripheral tissues. Leptin plays important roles in the regulation of food intake, energy expenditure, metabolism, neuroendocrine axis, and immune function. The binding of leptin to its specific receptor in the brain leads to activation of multiple signal transduction pathways. A number of intracellular signaling pathways are involved in modulating leptin's central and peripheral effects. In this review, we will focus mainly on leptin signaling under normal physiological conditions.

Physiology of leptin

Leptin is mainly synthesized and secreted by white adipose tissue and acts in the brain to regulate energy homeostasis. Leptin is also expressed in a variety of tissues, including placenta, ovary, skeletal muscle, pituitary gland, and lymphoid tissue [1]. Circulating leptin levels are directly proportional to the amount of body fat, thereby reflecting the status of long-term energy stores. Leptin levels fluctuate according to changes in calorie intake, with a marked decrease during starvation

and an increase in overfed and obese states [2]. Leptin is secreted in a pulsatile fashion and also displays a circadian rhythm. Leptin levels exhibit a sexual dimorphism. Women have higher leptin levels than men because of an increase in leptin expression in subcutaneous adipose tissue, stimulation of leptin synthesis by estrogen, and inhibition of leptin synthesis by testosterone [3]. Leptin levels are increased by insulin, glucocorticoids, and pro-inflammatory cytokines and decreased by catecholamines [4].

Leptin mediates its effects by binding to leptin receptors (LepRs) expressed in the brain and peripheral tissues. Various alternatively spliced isoforms of LepR have been described, but the long isoform of leptin receptor (LepRb) is primarily responsible for leptin signaling. LepRb is strongly expressed in the hypothalamus and other areas of the brain, where it regulates energy homeostasis, hedonic regulation of feeding, neuroendocrine function, and memory and learning. Leptin-deficient ob/ob mice and LepRb-deficient db/db mice develop hyperphagia, morbid obesity, infertility, and reduced linear growth [5]. Congenital leptin deficiency

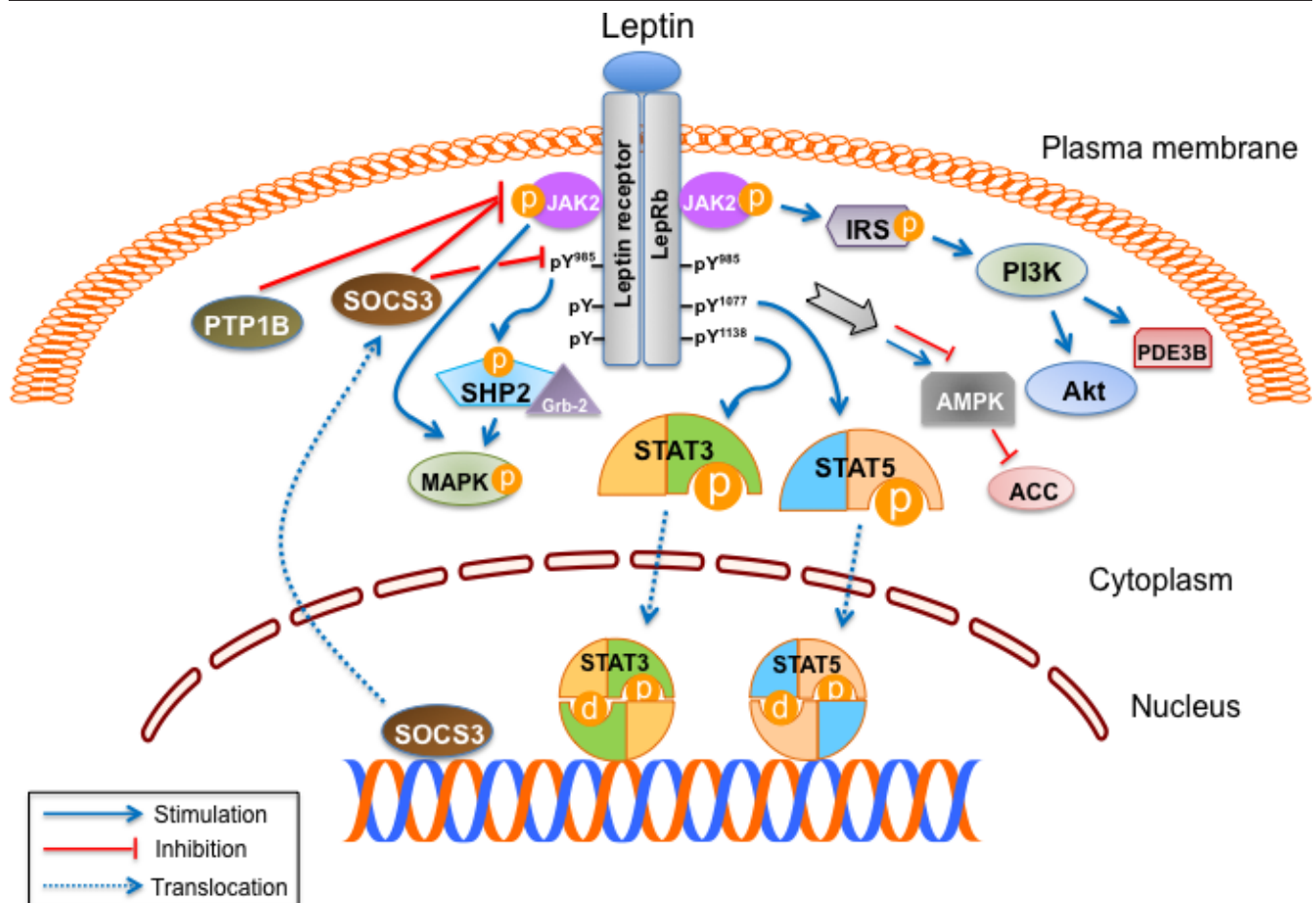
or loss-of-function mutations of the leptin receptor in humans also result in hyperphagia and morbid obesity.

The binding of leptin to LepRb activates a number of signaling pathways, JAK2/STAT 3 and STAT5, IRS/PI3K, SHP2/MAPK, and AMPK/ACC (Figure 1). The leptin signaling cascade is terminated by the induction of a suppressor of cytokine signaling 3 (SOCS3). SOCS3 inhibits JAK2/STAT3 signaling, providing a negative feedback mechanism. In addition, protein tyrosine

phosphatase 1B (PTP1B) is implicated in the negative regulation of leptin signaling (Figure 1) [2,3].

Obese individuals have elevated adipose leptin expression and plasma leptin levels, and these high leptin levels fail to reduce excess adiposity, indicating a state of leptin resistance. On the basis of studies conducted mainly in rodent models, leptin resistance has been attributed to multiple factors, including impaired leptin transport across the blood-brain barrier, disruption of leptin

Figure 1. Multiple leptin signaling pathways



The binding of leptin to the long isoform of leptin receptor (LepRb) results in its dimerization, leading to the formation of the LepRb/Janus kinase 2 (JAK2) complex. The activated JAK2 phosphorylates itself and also Tyr⁹⁸⁵, Tyr¹⁰⁷⁷, and Tyr¹¹³⁸ in LepRb. Signal transducer and activator of transcription (STAT) 3 and STAT5 bind to phospho-Tyr¹¹³⁸ and phospho-Tyr¹⁰⁷⁷ in LepRb and are subsequently phosphorylated. Active STAT3 and STAT5 dimers then translocate to the nucleus and activate the transcription of their target genes, which mediate leptin's anorexigenic effect. Suppressor of cytokine signaling 3 (SOCS3), a target gene of STAT3, inhibits the JAK2/STAT3 pathway by interacting with phospho-Tyr⁹⁸⁵ or JAK2 and acting as a feedback inhibitor of leptin signaling. Protein tyrosine phosphatase 1B (PTP1B) also inhibits leptin signaling through dephosphorylation of JAK2. After JAK2 activation, SH2-containing protein tyrosine phosphatase 2 (SHP2) binds to phospho-Tyr⁹⁸⁵ in the LepRb and recruits the adaptor protein growth factor receptor-bound protein 2 (Grb2), leading to activation of the mitogen-activated protein kinase (MAPK) signaling cascade. Leptin activates MAPK independent of SHP2 and also regulates phosphatidylinositol 3 kinase (PI3K) signaling through insulin receptor substrate (IRS) phosphorylation. Forkhead box O1 (FoxO1), mammalian target of rapamycin (mTOR), and phosphodiesterase 3B (PDE3B) are important downstream targets of PI3K in the leptin signaling pathway. Leptin regulates feeding and metabolism through 5' adenosine monophosphate-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in the brain and peripheral organs.

signaling in the hypothalamus by SOCS3 and PTP1B, inflammation, endoplasmic reticulum stress, and autophagy [3,6,7].

Leptin signaling and energy homeostasis

Leptin is highly expressed in the hypothalamus, particularly in the arcuate nucleus (ARC) and ventromedial hypothalamus (VMH). Leptin directly targets two neuronal populations in the ARC co-expressing pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART), and agouti-related peptide (AgRP) and neuropeptide Y (NPY) [8]. Leptin stimulates POMC/CART expression and inhibits AgRP/NPY expression, thereby reducing food intake, increasing energy expenditure, and decreasing body weight. In addition, leptin inhibits feeding by reducing the expression of melanin-concentrating hormone (MCH) and orexins in the lateral hypothalamic area (LHA). Leptin has also been shown to stimulate the expression of brain-derived neurotrophic factor and steroidogenic factor-1 (SF-1) neurons in the VMH, leading to inhibition of feeding [9,10].

The binding of leptin to LepRb activates JAK2, and the activated JAK2 phosphorylates Tyr⁹⁸⁵, Tyr¹⁰⁷⁷, and Tyr¹¹³⁸ in the cytoplasmic domain of LepRb. Mutation of these three tyrosines in LepRb induces obesity in mice but to a lesser degree than in LepRb-deficient db/db mice, indicating that LepRb affects energy homeostasis through both tyrosine-dependent and -independent mechanisms [11]. Leptin's activation of JAK2/STAT3 signaling appears to play a major role in energy homeostasis and neuroendocrine function. Once phosphorylated, STAT3 is translocated from the cytoplasm into the nucleus, where it binds to *pomc* and *agrp* promoters, stimulating POMC expression and inhibiting AgRP. Indeed, deletion of STAT3 in neurons decreases POMC and increases AgRP and NPY levels, culminating in hyperphagia, obesity, infertility, and thermal dysregulation [12]. Furthermore, a specific deletion of Tyr¹¹³⁸ in LepRb or STAT3 in LepRb-expressing neurons results in hyperphagia and morbid obesity [13,14]. Mice with a STAT5 deletion in the brain develop hyperphagia and obesity but less severely than in mice with a STAT3 deletion, indicating that JAK2/STAT5 plays a minor role in leptin's regulation of feeding and body weight [15].

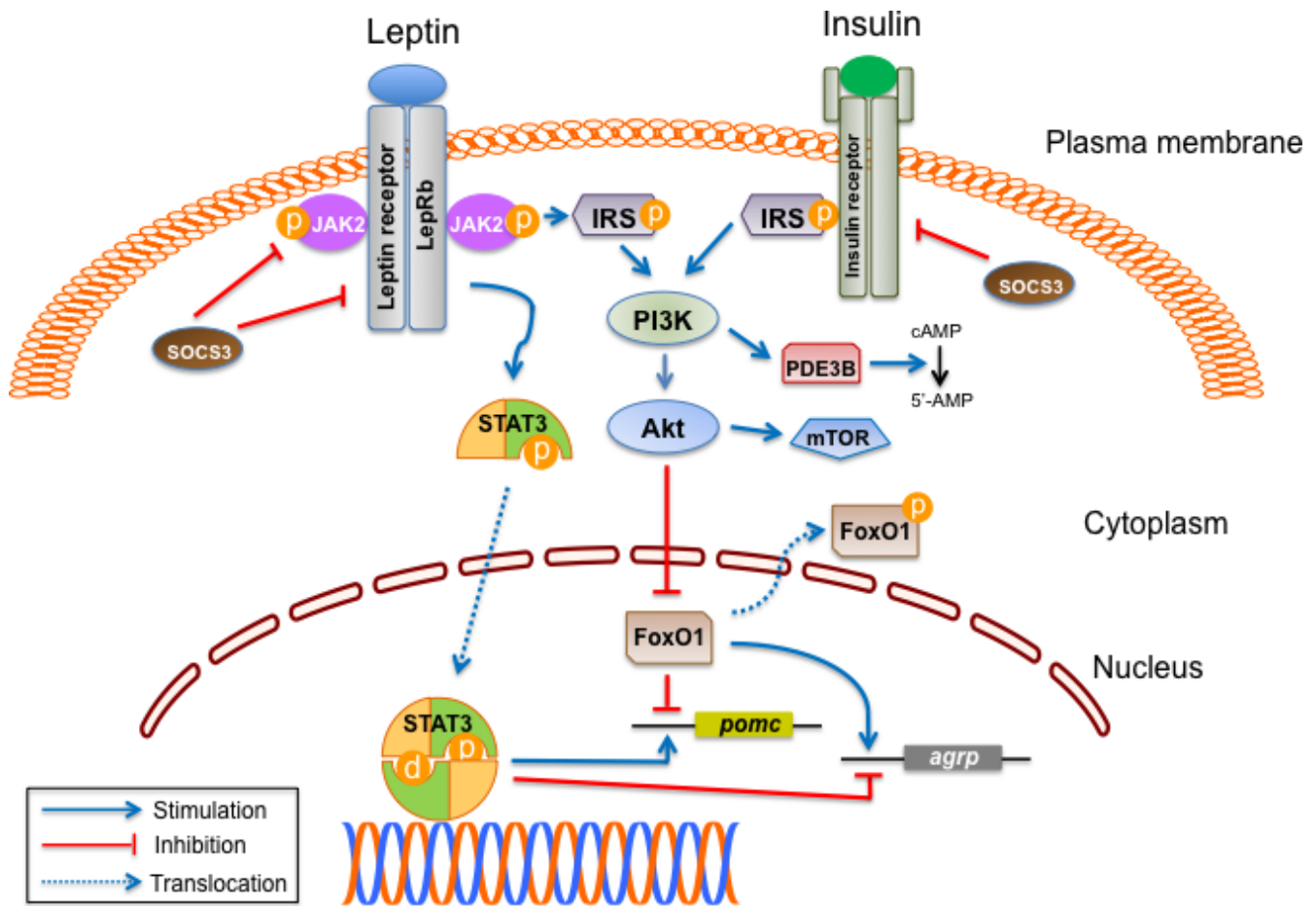
Leptin activates PI3K and Akt through IRS phosphorylation. Interestingly, leptin and insulin signaling have similar intracellular pathways in hypothalamic neurons (Figure 2) [16-18]. The PI3K pathway stimulates POMC-expressing neurons through ATP-sensitive potassium channels and voltage-gated calcium channels [1,19]. Inhibition of PI3K in the brain prevents leptin-induced

anorexia [20]. Mice with targeted PI3K disruption in POMC neurons show blunted responses to leptin-mediated suppression of feeding but exhibit normal long-term body weight regulation [21]. Forkhead box O1 (FoxO1), a transcription factor inactivated by Akt, appears to be an important downstream mediator of PI3K signaling. FoxO1 stimulates expression of NPY and AgRP, inhibits POMC, and blocks STAT3 action in AgRP and POMC neurons. Inactivation of FoxO1 via leptin or insulin signaling allows STAT3 to bind to *pomc* and *agrp* promoters [9,22,23]. A constitutively active FoxO1 in ARC blunts leptin's ability to inhibit food intake in mice [24]. In contrast, deletion of FoxO1 in either POMC or AgRP neurons decreases food intake in mice [25,26]. Another pathway recruited by leptin is the mammalian target of rapamycin (mTOR), a downstream target of PI3K/Akt. Leptin stimulates phosphorylation of p70 S6 kinase (S6K) via mTOR in the hypothalamus. Inhibition of mTOR attenuates the anorexigenic effect of leptin [27]. Systemic deletion of S6K1 or selective inhibition of S6K in the ARC abolishes the anorexigenic action of leptin [28,29]. Leptin also induces phosphodiesterase 3B (PDE3B) activity, which results in a decrease in cyclic adenosine monophosphate (cAMP) levels via the PI3K pathway in the hypothalamus. Inhibition of PDE3B activity reverses leptin's effects on food intake and body weight, suggesting that PDE3B plays an important role in mediating leptin signaling in the hypothalamus [30,31]. Furthermore, it has been shown that leptin administered centrally in mice increases renal sympathetic outflow via activation of PI3K [32].

Extracellular signal-related kinase (ERK), a member of the MAPK family, acts downstream of LepRb. Activation of ERK1/2 appears to be mediated by either SHP2 from Tyr⁹⁸⁵ of LepRb or directly from JAK2. Neuron-specific deletion of SHP2 results in obesity and leptin resistance in mice [33]. Pharmacological blockade of hypothalamic ERK1/2 abrogates the anorectic and weight-reducing effects of leptin in rats. Inhibition of ERK also prevents leptin-induced sympathetic activation of brown adipose tissue, indicating that SHP2/MAPK signaling is involved in leptin's regulation of food intake and energy expenditure [34].

Leptin exerts an inhibitory effect on AMPK in the hypothalamus, thereby stimulating ACC and subsequently suppressing food intake. Constitutive activation of hypothalamic AMPK blocks leptin's anorexigenic effect. In addition, inhibition of hypothalamic ACC attenuates leptin-mediated decrease in food intake and body weight [35,36]. Recently, it was shown that mTOR/S6K regulates feeding through leptin-induced inhibition of AMPK in the hypothalamus [37]. Together, these data

Figure 2. Interactions of leptin and insulin signaling in hypothalamus



Leptin activates signal transducer and activator of transcription (STAT) 3 when it binds to the long isoform of leptin receptor (LepRb) in the arcuate nucleus, ventromedial hypothalamus, and other hypothalamic neurons. Activated STAT3 stimulates *pomc* expression and inhibits *agrp* expression in the hypothalamus. Leptin and insulin signaling pathways converge on phosphatidylinositol 3 kinase (PI3K). Activation of PI3K by either leptin or insulin leads to phosphorylation of Forkhead box O1 (FoxO1) through Akt, which can also activate the mammalian target of rapamycin (mTOR). Inactivation of FoxO1 by phosphorylation results in its export from the nucleus and allows for the binding of STAT3 to *pomc* or *agrp* promoter. In addition, the leptin-mediated activation of PI3K recruits phosphodiesterase 3B (PDE3B), thereby reducing cAMP (cyclic adenosine monophosphate) levels. STAT3 increases the expression of suppressor of cytokine signaling 3 (SOCS3), which leads to feedback inhibition of leptin and insulin signaling. Abbreviation: JAK2, Janus kinase 2.

demonstrate diverse interactions of leptin and signaling molecules in energy homeostasis.

Leptin signaling and glucose and lipid metabolism

Leptin has rapid effects on glucose and lipid metabolism independent of body weight regulation [38]. Restoration of LepRb expression in the ARC in obese LepR-deficient mice normalizes blood glucose levels. Moreover, selective expression of LepRb in the POMC neurons dramatically improves glucose levels in db/db mice [39,40]. Deletion of SOCS3 in POMC-expressing neurons improves glucose tolerance and insulin sensitivity

without affecting body weight. Mice with a POMC-specific deletion of PTP1B exhibit improved insulin sensitivity and increased energy expenditure [41,42]. POMC neurons have glucose-sensing capabilities and are likely to mediate leptin's effects on glucose homeostasis [38,43]. Mice lacking FoxO1 in AgRP neurons or FoxO1 in SF-1 neurons show improved glucose tolerance and increased insulin sensitivity, and these pathways may contribute to the central action of leptin [26,44].

Interestingly, mice with a mutation of STAT3-binding sites in LepRb are less hyperglycemic than db/db mice, suggesting that pathways other than tyrosine- or

STAT3-mediated signaling are involved in leptin's effect on glucose homeostasis [8,11,13]. It has been shown that mouse models with the alteration of PI3K activity in POMC neurons have disrupted hepatic insulin sensitivity, suggesting that the PI3K pathway in POMC neurons is involved in glucose homeostasis [45]. Leptin inhibits *de novo* lipogenesis and stimulates lipolysis, but these effects are lost when hypothalamic PI3K signaling is disrupted [46,47]. Central leptin's effect on improving insulin sensitivity in skeletal muscle is dependent on PI3K/Akt modulating AMPK/ACC signaling in skeletal muscle [48,49].

Although leptin acts mainly in the brain, evidence suggests a direct action in peripheral tissues. Leptin directly stimulates fatty acid oxidation and glucose uptake through activation of AMPK in skeletal muscle. In contrast to its inhibitory effect in the hypothalamus, leptin activates AMPK, thereby inhibiting ACC in skeletal muscle, preventing steatosis and lipotoxicity [50]. In addition to AMPK, p38 MAPK may contribute to leptin's effect on fatty acid oxidation [1]. Peripheral leptin administration also stimulates fatty acid oxidation by a p38 MAPK-dependent mechanism in isolated rat cardiomyocytes [51].

Leptin suppresses hepatic glucose production by ameliorating hyperglucagonemia and stimulating peripheral glucose uptake through central mechanisms, possibly involving POMC and AgRP neurons in the ARC, and the modulation of the autonomic nervous system [38,52,53]. Leptin directly regulates glucose metabolism in isolated hepatocytes via PI3K-dependent activation of PDE3B [54]. Leptin also inhibits glucose-stimulated insulin secretion by acting directly on pancreatic β cells. Although the precise mechanisms are unknown, it is possible that leptin-mediated PI3K-dependent activation of PDE3B is involved in β -cell regulation [55]. Leptin inhibits insulin synthesis via JAK2/STAT/SOCS3 signaling, while an induction of SOCS3 by leptin inhibits STAT3/5b-dependent regulation of preproinsulin 1 gene promoter [56,57].

Leptin signaling and immune function

Leptin has important roles in modulating both innate and adaptive immunity. Leptin binds to its receptor in monocytes and macrophages, stimulating neutrophil chemotaxis and promoting macrophage phagocytosis. Leptin increases the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-12, and tumor necrosis factor-alpha (TNF- α) [58,59]. Leptin also protects neutrophils from apoptosis through PI3K- and MAPK-dependent signaling. Leptin regulates the maturation of dendritic cells through Akt activation, and induces CD40 expression in murine dendritic cells

[60,61]. In addition, leptin promotes natural killer cell activation and cytotoxicity through STAT3 activation [62,63].

Leptin regulates the adaptive immune response in normal and pathological conditions, and it promotes the proliferation of native T cells and the switch toward T helper 1 cell immune responses by increasing interferon- γ and TNF- α in memory T cells [64]. Recently, it was reported that leptin acts as a negative signal for the proliferation of human regulatory T (Treg) cells that are involved in the prevention of autoimmune diseases [65]. Leptin has been shown to activate the mTOR pathway in Treg cells [66]. Moreover, leptin activates human B cells to secrete cytokines, such as pro-inflammatory IL-6 and TNF- α and anti-inflammatory IL-10, via the activation of JAK2/STAT3 and p38 MAPK signaling pathways, indicating a role of leptin in inflammation and immunoregulation [64,67].

Conclusions

The discovery of leptin 20 years ago enhanced our understanding of nutritional physiology and provided molecular tools for studying mechanisms underlying feeding behavior, energy homeostasis, neuroendocrine regulation, and other systems. Here, we have discussed how central and peripheral leptin signaling interacts with various intracellular molecules to affect energy homeostasis, glucose and lipid metabolism, and the immune system. Further studies are needed to determine whether leptin signaling can lead to novel diagnostic and therapeutic strategies for obesity, diabetes, and related diseases.

Abbreviations

ACC, acetyl-CoA carboxylase; AgRP, agouti-related peptide; AMPK, 5' adenosine monophosphate-activated protein kinase; ARC, arcuate nucleus; cAMP, cyclic adenosine monophosphate; CART, cocaine- and amphetamine-regulated transcript; ERK, extracellular signal-related kinase; FoxO1, Forkhead box O1; IL, interleukin; IRS, insulin receptor substrate; JAK2, Janus kinase 2; LepR, leptin receptor; LepRb, long isoform of leptin receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NPY, neuropeptide Y; PDE3B, phosphodiesterase 3B; PI3K, phosphatidylinositol 3 kinase; POMC, pro-opiomelanocortin; PTP1B, protein tyrosine phosphatase 1B; S6K, p70 S6 kinase; SF-1, steroidogenic factor-1; SHP2, SH2-containing protein tyrosine phosphatase 2; SOCS3, suppressor of cytokine signaling 3; STAT, signal transducer and activator of transcription; TNF- α , tumor necrosis factor-alpha; Treg, regulatory T; VMH, ventromedial hypothalamus.

Disclosures

The authors declare that they have no disclosures.




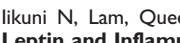



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