Published in final edited form as:
Front Med. 2013 June ; 7(2): 207–222. doi:10.1007/s11684-013-0263-5.

Leptin signaling and leptin resistance

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Abstract

Leptin is secreted into the bloodstream by adipocytes and is required for the maintenance of energy homeostasis and body weight. Leptin deficiency or genetic defects in the components of the leptin signaling pathways causes obesity. Leptin controls energy balance and body weight primarily by targeting LEPRb-expressing neurons in the brain, particularly in the hypothalamus. These LEPRb-expressing neurons function as the first-order neurons that project to the second-order neurons located within and outside the hypothalamus, forming a neural network that controls the energy homeostasis and body weight. Multiple factors, including inflammation and ER stress, contribute to leptin resistance, and leptin resistance is the key risk factor for obesity. This review is focused on recent advance about leptin action, leptin signaling, and leptin resistance.

Keywords

leptin signaling; leptin receptor; energy balance; leptin resistance; obesity

Introduction

Obesity is closely associated with various metabolic disorders including dyslipidemia, cardiovascular disease, stroke, insulin resistance, and Type 2 diabetes [1]. With the rapid upsurge of global obesity epidemic, obesity is becoming a challenging public health problem. In 2008, more than 1.4 billion adults worldwide were overweight (Body Mass Index, BMI ≥ 25), and approximately 500 million adults worldwide were obese (BMI ≥30) [2]. Medical costs associated with obesity become a heavy social burden.

Body weight is controlled by energy intake and energy expenditure [3]. The energy imbalance results in excessive calorie accumulation in the form of triglycerides in adipose tissues, leading to overweight and obesity. In the normal conditions, adipose tissues closely commute with the brain to maintain energy homeostasis and body weight. Adipose tissues secret a variety of humoral factors, collectively called adipokines, to regulate nutrient metabolism. Some adipokines (e.g. leptin) serve as adiposity signals to convey the

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information about the body energy storage and availability to the brain. The brain, particularly the hypothalamus, senses and integrates these adiposity signals and maintains energy homeostasis and body weight by controlling feeding behavior and energy expenditure.

Leptin is the key adipokine that mediates the adipose tissue-brain communication in the maintenance of energy homeostasis and normal body weight [3]. Leptin is encoded by the *ob* gene that was first cloned by Friedman and colleagues in 1994 [4]. Afterwards, numerous studies established the crucial role of leptin in controlling energy balance and body weight in both rodents and humans. In mice, genetic leptin deficiency (*ob/ob* mice) or lack of functional leptin receptor (*db/db* mice) results in morbid obesity and type 2 diabetes [4, 5]. Albeit rare, congenital leptin deficiency causes severe hyperphagia and early-onset obesity in humans [6–8]. As expected, a leptin replacement therapy reverses obesity and significantly improves obesity-associated metabolic disorders in leptin-deficiency patients [8–11]. However, in most cases, circulating leptin levels are abnormally higher in obesity patients than in normal subjects. These patients are believed to develop leptin resistance, defined by the reduced ability of leptin to suppress appetite and weight gains. How does leptin resistance develop? What are the molecular mechanisms underlying leptin resistance? Can leptin resistance be corrected? In this review, we focus on leptin signaling pathways and highlight the current understanding of leptin resistance.

Leptin and the leptin receptors

Leptin is a 16-kDa polypeptide that is primarily produced in white adipose tissues and secreted into the circulation [12]. Leptin expression is regulated by a variety of hormones, including insulin, glucocorticoids, and leptin itself [13]. FOS-like antigen 2 (FOSL2) is a key transcription factor that controls leptin expression in adipocytes [14]. Circulating leptin levels are in proportion to body fat mass, thus serving as an adiposity signal of the total body energy stores [15, 16]. Circulating leptin levels also fluctuate in accord to changes in nutritional states [17]. Plasma leptin levels are decreased by fasting before fat depletion[17]. Leptin is also expressed at low levels in other tissues, including bone marrow, ovary, placenta, stomach, and lymphoid tissue [13, 18]; however, the physiological function of this locally produced leptin remains largely unknown.

The central nervous system (CNS), particularly the hypothalamus, is believed to be the main leptin target and mediates leptin’s anti-obesity action [19, 20]. Leptin exerts its biological action through binding to and activating the long form of leptin receptors (LEPRb) that is extensively expressed in many brain regions [21–24]. In addition to the brain, LEPRb is also expressed in peripheral tissues, but the physiological function of peripheral LEPRb remains to be determined [5, 25]. A single *Lepr* gene produces six LEPR isoforms (LEPRa, b, c, d, e, and f) via alternative mRNA splicing, and all isoforms have the identical N-terminal extracellular domain that binds to leptin [25, 26]. These isoforms differ in their C-terminal intracellular domains and are divided into three categories: short (LEPRa, c, d, and f), long (LEPRb), and secreted (LEPRe) forms [27]. LEPRb is the only form that has a full-length intracellar domain of approximate 300 amino acid residues and mediates leptin signaling [28–30]. As expected, LEPRb-deficient *db/db* mice display the obesity phenotypes similar to

that in leptin-deficient *ob/ob* mice and in db^{3J}/db^{3J} mice that are deficient of all forms of leptin receptors [20, 27]. The function of short-form LEPRs is less understood and may be involved in leptin transportation and clearance [27, 31, 32].

Leptin receptor signaling

LEPRb is a member of interleukin 6 (IL-6)-type cytokine receptor family and has an extracellular domain, a single membrane-spanning domain, and an intracellular domain[28, 29, 33]. LEPRb does not contain intrinsic enzymatic activity but bind to a cytoplasmic tyrosine kinase called Janus kinase 2 (JAK2) [28, 33]. Leptin stimulates JAK2 activation that subsequently autophosphorylates on multiple tyrosines [26, 34]. JAK2 also phosphorylates LEPRb on three tyrosine residues: Tyr^{985}, Tyr^{1077}, and Tyr^{1138} (Fig. 1) [34–36]. Phopho-Tyr^{985}, -Tyr^{1077}, and -Tyr^{1138} serve as binding sites for additional signaling molecules that contain the Src homology 2 (SH2) domain, and recruit these downstream molecules to the LEPRb-JAK2 complex to allow JAK2 to phosphorylate these effector proteins [37]. Aside from JAK2, the Src tyrosine kinase family members appear also to be involved in mediating leptin signaling independently of JAK2 [38].

LEPRb Tyr^{1138}-emanated JAK2/STAT3 signaling

In response to leptin, JAK2 phosphorylates LEPRb on Tyr^{1138}, and phospho-Tyr^{1138} recruits the SH2 domain of signal transducer and activator of transcript 3 (STAT3) [37]. STAT3 is subsequently phosphorylated by LEPRb-associated JAK2, resulting in dimerization and nuclear translocation [39]. In nuclei, STAT3 dimers act as a transcription factor to regulate the expression of STAT3 target genes, including suppressor of cytokine signaling 3 (SOCS3) [34, 40]. A large body of genetic evidence demonstrates that the JAK2/STAT3 pathway is required for the anti-obesity effect of leptin. Disruption of the STAT3 binding site by a replacement of Tyr^{1138} with Ser or Phe results in hyperphagia and obesity to a similar degree as that in *db/db* mice [41, 42]. Either neuron-specific or LEPR-expressing neuron-specific deletion of STAT3 leads to profound obesity in mice [43, 44].

LEPRb Tyr^{1077}-emanated JAK2/STAT5 signaling

Leptin activates STAT5 via phospho-Tyr^{1077}, which binds to the SH2 domain of STAT5 and allows JAK2 to tyrosyl phosphorylate and activate STAT5 [45, 46]. Tyr^{1138} also partially contributes to STAT5 activation [45]. Elimination of STAT5 in the CNS results in hyperphagia and obesity, whereas activation of STAT5 in hypothalamic neurons suppresses food intake in mice [47]. The results suggest the JAK2/STAT5 pathway also contribute to the anti-obesity action of leptin.

LEPRb Tyr^{985}-emanated SHP2/ERK signaling

Phosphorylation of Tyr^{985} provides a binding site for the SH2 domain of protein tyrosine phosphatase 2 (SHP2) [48, 49]. SHP2 mediates leptin-stimulated activation of the extracellular signal-regulated kinase (ERK) pathway [48, 49]. SHP2 may also down-regulate JAK2/STAT3 signaling under some conditions [50]. Deletion of the *SHP2* gene in the brain results in early-onset obesity in mice, suggesting that the SHP2 pathway is also important in mediating leptin's anti-obesity action [51–54]. In agreement with this idea, pharmacological

inhibition of the ERK pathway attenuates the ability of leptin to suppress food intake and stimulate brown adipose tissue (BAT) thermogenesis in mice, indicating the involvement of SHP2/ERK pathway in both anti-obesity and thermogenic effects of leptin [49].

Phospho-Tyr^{985} also binds to the SH2 domain of SOCS3, and SOCS3 in turn suppresses the activation of the LEPRb/JAK2 pathways [55]. It is likely that during the initial phase of leptin stimulation, phospho-Tyr^{985} may predominantly activate the SHP2/ERK pathway that mediates leptin's anti-obesity action. In agreement with this idea, one study reported that elimination of Tyr^{985} phosphorylation by a replacement of Tyr^{985} with Phe promotes diet-induced leptin resistance and obesity [56]. Leptin stimulates the expression of SOCS3 that competes with SHP2 for the phospho-Tyr^{985} and progressively attenuates the SHP2-ERK pathway. Under these conditions, Tyr^{985} phosphorylation provides a SOCS3-meidated negative feedback mechanism to downregulate leptin action. Consistent with this hypothesis, another study reported that elimination of Tyr^{985} phosphorylation protects against diet-induced obesity in female mice [57]. The reasons for this discrepancy between these two studies remain unclear. It is likely that the levels of intracellular SOCS3 may determine the outcome of phospho-Tyr^{985} as either a stimulatory or an inhibitory site for leptin action (Fig. 1).

LEPRb appears to be able to regulate nutrient metabolism by an additional mechanism independently of phosphorylation of Tyr^{985}, Tyr^{1077}, and Tyr^{1138}. Mice with a replacement of all the three Tyr with Phe residues display the obesity phenotypes to a same degree as *db/db* mice; however, *db/db* mice have more severe abnormal glucose metabolism [26, 42].

IRS/PI3K signaling

The insulin receptor substrate (IRS)/phosphoinositide 3-kinase (PI3K) pathway is also required for leptin action [42, 58]. Leptin activates the IRS/PI3K pathway both in cultured cells and in the hypothalamus [26, 59–61]. Deletion of IRS2 in the brain causes obesity in mice [62, 63]. Pharmacological inhibition of PI3K in the hypothalamus prevents leptin-induced anorexia in mice [58]. These observations demonstrate the importance of IRS/PI3K cascade in proper leptin receptor signaling and its anti-obesity effects. Mechanistically, we showed that SH2B1, a SH2 domain-containing adaptor protein, binds to both JAK2 and the IRS proteins and mediates the activation of the PI3K pathway (Fig. 1) [64]. Disruption of the *SH2B1* gene results in leptin resistance and obesity [65, 66]. Two downstream events of the PI3K cascades are described below [67].

The FoxO1 signaling branch—One important downstream effector of the PI3K/Akt pathway is forkhead box O1 (FoxO1), a key transcription factor for gluconeogenesis [68]. Akt phosphorylates FoxO1 on multiple sites, resulting in cytoplasmic retention and inactivation of FoxO1 [67]. Overexpression of a constitutively active FoxO1 mutant in the ARC abolishes leptin responses and increases food intake and body weight, whereas overexpression of a transcription-deficient FoxO1 mutant or FoxO1 knockdown in the ARC has an opposite effect [68, 69]. Deletion of FoxO1 in POMC neurons results in decreased food intake and body weight in mice [70]. Deletion of IRS2 in LEPRb neurons leads to energy imbalance and obesity, and deletion FoxO1 reverses the obesity phenotypes in IRS2

null mice [71]. Mechanistically, FoxO1 regulates the expression of important neuropeptides including POMC, NPY, and AgRP, and it also antagonizes the transcriptional activity STAT3 [69, 72].

The mTORC1/S6K signaling branch—The mammalian target of rapamycin (mTOR)/ribosomal S6 kinase (S6K) pathway is another downstream event of the IRS/PI3K pathway [26]. Leptin stimulates the activation of the mTOR complex 1 (mTORC1), which in turn phosphorylates and activates S6K in the hypothalamus [73, 74]. Intracerebroventricular administration of L-leucine activates hypothalamic mTORC1 and decreases food intake and body weight in rats, whereas rapamycin, an mTORC1 inhibitor, exerts an opposite action [73]. Constitutive activation of S6K in the mediobasal hypothalamus (MBH) protects against HFD-induced obesity in rats, whereas inhibition of S6K activity in the MBH results in increased food intake and body weight [75]. These findings establish the critical role of the mTORC1/S6R pathway in mediating leptin regulation of energy homeostasis in mammals [73, 75].

Other signaling pathways

The calcium calmodulin-dependent protein kinase kinase (CaMKK2)/5'-AMP-activated protein kinase (AMPK)/acetyle-CoA carboxylase (ACC) pathway has also been suggested to be involved in the leptin receptor signaling [26, 76, 77]. AMPK is activated by lower ATP/ADP ratios and serves as an intracellular sensor for energy levels [76]. Recently, we showed that glucose enhances leptin signaling through modulation of AMPK activity [78]. However, several key signaling steps of the CaMKK2/AMPK/ACC pathway in the leptin receptor signaling are yet to be defined.

Leptin target neural circuitry in the hypothalamus

LEPRb is widely expressed in many brain regions at different levels [21], among which the hypothalamus express high levels of LEPRb [21–24, 26, 79–81]. Mice with deletion of hypothalamic LEPRb develop early-onset obesity [82]. Additionally, LEPRb is also expressed in some non-neuronal cells in the CNS and may be involved in regulation of energy balance as well as other functions of leptin [83].

Leptin target neurons in the hypothalamus

Leptin target neurons are distributed in all regions of the hypothalamus, including the arcuate nucleus (ARC), ventral premammillary nucleus (PMV), medial preoptic nucleus (MEPO), dorsomedial (DMH), ventromedial (VMH), paraventricular hypothalamic nucleus (PVH), and lateral hypothalamic area (LHA) [21–24, 26, 79–81]. LEPRb-expressing neurons in the ARC have been extensively investigated[21]. Restoration of LEPRb expression in the ARC attenuates the obesity phenotypes of LEPR-deficient rats, establishing a key role of ARC leptin action [84]. At least two subpopulations of ARC LEPRb-expressing neurons, pro-opriomelanocortin (POMC) neurons and agouti-related protein (AgRP) neurons, have been identified in the ARC [26, 85].

POMC neurons express anorexigenic (appetite-suppressing) neuropeptides including POMC and cocaine- and amphetamine-regulated transcript (CART) [86, 87]. Leptin acts via LEPRb

to stimulate the synthesis of POMC that generates α-melanocyte-stimulating hormone (α-MSH) [88–90]. α-MSH reduces body weight by binding to and activating melanocortin-3 receptor (MC3R) and melanocortin-4 receptor (MC4R) [3, 91, 92]. MC4R knockout mice develop leptin resistance and obesity, and MC3R null mice also exhibit the obesity phenotypes, but to a lesser degree [92–94]. Importantly, many genetic variants of the *POMC* and *MC4R* genes have been identified to be associated with human obesity [95–97]. These observations indicate that the central melanocortin system is required for leptin to promote weight loss.

In contrast to POMC neurons, the ARC AgRP neurons express orexigenic (appetite-stimulating) neuropeptide Y (NPY) and AgRP [98]. NPY and AgRP may have complementary rather than identical functions [99]. Adult-onset ablation of AgRP neurons inhibits food intake in mice [100–102], whereas activation of AgRP neurons is sufficient to stimulate food intake in dependently of the melanocortin system [103]. Leptin inhibits both AgRP neuronal activity and expression of NPY and AgRP [26, 27, 88]. AgRP exerts its anorexigenic action by acting both as an α-MSH antagonist and a MC4R inverse agonist [27, 104]. Genetic deletion of the *NPY* and/or *AgRP* genes has a mild effect on body weight in mice, suggesting the existence of other modulators in the AgRP neurons [105]. For example, synaptic release of gamma-aminobutyric acid (GABA) from AgRP neurons is suggested to provide an inhibitory mechanism for ARC POMC neurons [106]. Surprisingly, deletion of LEPRs in either POMC or AgRP neurons results in a very milder obesity phenotype compared with that in *db/db* mice [87, 107]. Restoration of leptin signaling in the ARC of LEPR-null animals modestly alleviates the hyperphagia and obesity phenotypes [108, 109]. These observations suggest that other LEPRb-expressing neurons also mediate leptin's action in addition to ARC POMC and AgRP neurons [110]. Indeed, LEPRs are expressed in many other brain areas beyond the ARC, and these extra-ARC sites account for 80–85% of the total number of LEPR-expressing neurons in the brain [27]. Several recent studies report that LEPRb in the nitric oxide synthase-1 (NOS1)-expressing neurons and GABAergic neurons play an important role in mediating the anti-obesity effects of leptin [110, 111].

Leptin target neural circuits

LEPRb-expressing neurons are clustered in the specific regions and serve as first-order neurons to sense adiposity signals carried by leptin and other hormones and/or nutrients. These first-order neurons project to the second-order neurons located in many hypothalamic areas (VMH, LAH, and PVN) as well as in extrahypothalamic sites (e.g. VTA, and the brain stem), forming a sophisticated neural network that mediates the homeostatic regulation of energy homeostasis and body weight [26, 27]. For instance, the PVH receives intense neuronal projections from the ARC, VMH and DMH and serves as a common output to regulate energy expenditure and satiety [85]. ARC POMC neuron-derived α-MSH binds to and activates the MC4R in PVH neurons, stimulating the expression and secretion of thyrotropin-releasing hormone (TRH) [26, 112, 113]. In contrast, AgRP and NPY inhibit TRH secretion [112, 113]. TRH activates the pituitary-thyroid pathway, thus promoting energy expenditure. PVH-specific restoration of MC4R rescues the hyperphagia and obesity phenotypes of MC4R-null mice [114]. Interestingly, a subset of the PVN neurons also

express LEPRb and leptin activates the LEPRb pathways in these neurons, suggesting that leptin is able to regulate a subset of the PVN neurons both directly and indirectly via the ARC first-order neurons [115]. ARC neurons also innervate VMH/DMH neurons, and leptin stimulates the expression of anorexigenic brain-derived neurotrophic factor (BDNF) presumably via the POMC projections to the VMH [116, 117]. Moreover, the hypothalamic neural connections are bidirectional, and VMH-derived BDNF may modulate ARC neuronal activity [117]. Additionally, the hypothalamic melanocortin system also has cross-talk with the brainstem-derived serotonin (BDS) system, which may also be involved in leptin regulation of bone mass and energy balance [118].

Molecular mechanisms of leptin resistance

Leptin resistance is considered as the primary risk factor for the pathogenesis of overweight and obesity [119]. Many mechanisms have been proposed to explain leptin resistance, including impairment in leptin transportation, leptin signaling, and leptin target neural circuits [119, 120].

Impairment in leptin transportation

The majority of LEPRb-expression neurons in the brain are separated from circulating leptin by the blood-brain barrier (BBB). Leptin is actively transported across the BBB in a saturable manner [121]. Two short forms of LEPRa and LEPRe are believed to mediate leptin transport across the BBB [122–124]. Brain leptin transport is impaired in both humans and mice with obesity, thus contributing to leptin resistance [125–127]. In HFD-fed mice, leptin transport across the BBB is substantially decreased [127]. In obese subjects with severe hyperleptinemia, leptin levels in the cerebrospinal fluid only marginally increase [126]. However, the relative contributions of impaired brain leptin transport to systemic leptin resistance remain to be determined. Firstly, the neuronal projections of the ARC LEPRb-neurons are detected in the median eminence that lacks the BBB, and these neurons may directly expose to circulating leptin [120, 128]. Secondly, HFD feeding attenuates the anorexigenic effect of intracerebroventricular administration of leptin [125]. Thirdly, impairment in the brain leptin transport may be secondary to systemic leptin resistance during the pathogenesis of obesity [120, 129].

Impairment in LEPRb signaling

Defects in each component of the LEPRb signaling cascades are expected to result in leptin resistance. We describe three potential mechanisms: reduction in the cell surface LEPRb levels, upregulation of negative regulators, and downregulation of positive regulators [26, 120].

The majority of LEPRb are localized in the Golgi apparatus and endosomes, and the function of these intracellular LEPRb is unclear; a small portion of LEPRb is present at the plasma membrane [130, 131]. The LEPRb trafficking to the cell surface is mediated by multiple factors including Bardet-Biedl syndrome (BBS) proteins [132]. BBS deficiency impairs LEPRb trafficking and leptin signaling, resulting in obesity in both humans and mice [132, 133]. Additionally, the plasma membrane LEPRb is constitutively internalized

via endocytosis in a ligand-independent manner [130]. A reduction in the plasma membrane LEPRb expression, caused by a decrease in trafficking and/or increase in endocytosis, is expected to contribute to leptin resistance.

Leptin signaling is negatively regulated by many intracellular proteins, including SOCS3, protein tyrosine phosphatase 1B (PTP1B), and T cell protein tyrosine phosphatase (TCPTP) (Fig. 1) [134–136]. SOCS3 is a leptin target gene and provides a negative feedback regulatory mechanism to prevent over-activation of the LEPRb pathways [134]. In agreement with this idea, mice with LEPRb overexpression in the POMC neurons are more susceptible to HFD-induced obesity [137]. SOCS3 inhibits JAK2 kinase activity by directly binding to JAK2 [138]. As discussed previously, SOCS3 also binds to phospho-Tyr^{985} and inhibits LEPRb signaling, probably by competing with SHP2 for the same binding site [55, 57]. Systemic haploinsufficiency of SOCS3 improves leptin sensitivity and attenuates HFD-induced obesity in mice [139]. Neuron-specific deletion of SOCS3 also protects against diet-induced leptin resistance and obesity [140, 141]. In contrast, transgenic overexpression of SOCS3 in POMC neurons leads to leptin resistance and obesity [142]. The levels of hypothalamic SOCS3 are higher in HFD-fed or aged mice, which may contribute to leptin resistance [134]. PTP1B, a class 1 non-receptor protein tyrosine phosphatase, dephosphorylates and inhibits JAK2 [135, 143]. PTP1B-null mice are protected from diet-induced leptin resistance and obesity [143, 144]. Neuronal deletion of the *PTP1B* gene results in decreased food intake and increased energy expenditure [145, 146]. Ablation of PTP1B in POMC neurons also leads to elevated energy expenditure [147]. TCPTP, another non-receptor PTP, dephosphorylates STAT1 and STAT3 [53]. Inhibition of neuronal PCPTP also improves leptin sensitivity in obese mice, and deletion of both PTP1B and TCPTP in the brain has an additive effect [136]. Furthermore, the expression of hypothalamic PTP1B and TCPTP is higher in mice with diet- induced obesity, providing additional evidence that PTP1B and TCPTP contribute to leptin resistance and the progression to obesity [136, 148, 149]. Additionally, phosphatase and tensin homolog (PTEN) and tyrosine phosphatase epsilon (RPTPe) are also suggested to be involved in the development of leptin resistance [150–153].

We have recently identified SH2B1 as a novel endogenous positive regulator of leptin signaling [64–66, 119, 154]. SH2B1 is an SH2 and pleckstrin homology (PH) domain-containing adaptor protein and was initially identified as a JAK2-binding protein [155]. Deletion of the *SH2B1* gene results in leptin resistance, hyperphagia, and morbid obesity [65], and neuron-specific restoration of SH2B1 reverses the obesity phenotypes of SH2B1-deficient mice [66]. In agreement, ectopic expression of a dominant negative SH2B1 mutant in the brain causes obesity in wild-type mice [119], whereas transgenic over-expression of SH2B1β in the brain protects mice from HFD-induced obesity [66]. SH2B1 appears to enhance LEPRb signaling by several mechanisms. Leptin stimulates JAK2 phosphorylation on Tyr^{813} that in turn binds to the SH2 domain of SH2B1; SH2B1-JAK2 interactions increase JAK2 kinase activity, thus enhancing the activation of the pathways downstream of JAK2 [65, 154]. Leptin also stimulates the binding of SH2B1 to IRS proteins, thus allowing SH2B1-associated JAK2 to phosphorylate IRS proteins [64]. SH2B1-IRS interactions also inhibit tyrosine dephosphorylation of IRS proteins, thus prolonging the activation of the

IRS-PI3K pathway [156]. The metabolic function of SH2B1 is evolutionarily conserved in fruit flies, mice, and humans [96, 157–162]. Genome-wide association studies (GWAS) show that single nucleotide polymorphisms (SNPs) of the *SH2B1* loci are linked to obesity in different ethnic populations [96, 158–162]. Chromosomal deletions of an *SH2B1*-containing fragment are associated with severe early-onset obesity [163].

Impairment in leptin target neural circuits

The melanocortin system governs the hypothalamic neural circuitry that controls energy homeostasis. Deficiency of MC4R results in morbid obesity in both mice and humans [164–167]. Leptin stimulates the expression of BDNF in the VMH via a MC4R-dependent mechanism [116]. Inhibition of the BDNF/TrkB pathways results in leptin resistance, hyperphagia, and obesity in both mice and humans, whereas activation of the BDNF/TrkB signaling induces weight loss in rats[116, 168–170].

Potential contributors to leptin resistance in obesity

Many factors have been reported to cause leptin resistance in obesity. Here we discuss four factors: hyperleptinemia, inflammation, and endoplasmic reticulum (ER) stress, and defective autophagy.

Hyperleptinemia

Hyperleptinemia *per se* is a contributing factor to development of leptin resistance. Chronic exposure to high levels of circulating leptin (hyperleptinemia) causes leptin resistance, presumably by over-activating negative feedback regulators [171]. In agreement with this idea, expression of a constitutively active form of STAT3 in POMC neurons results in leptin resistance, hyperphagia, and obesity [172]. Lowering plasma leptin levels through clamping does not prevent diet-induced fed obesity but significantly improves leptin sensitivity [172]. Both inhibiting adipocyte leptin production and increasing kidney leptin clearance are able to restore leptin sensitivity in mice [173].

Inflammation

Low-grade, chronic inflammation is closely associated with various metabolic disorders including obesity [174]. HFD-feeding promotes inflammation not only in the peripheral tissues but also in the hypothalamus [175, 176]. Saturated fatty acids, which are elevated in obesity, are able to bind to and activate toll-like receptor 4 (TLR4) [177]. Intracerebroventricular administration of TLR4 neutralizing antibody diminishes the ability of saturated fatty acids to induce hypothalamic inflammation and suppress food intake and weight gain in rats [178]. Deletion of neuronal TLR adaptor molecule MyD88 protects from HFD-induced leptin resistance and obesity [179]. Both systemic and neuron-specific deletion of c-Jun amino-terminal kinase 1 (JNK1), a key regulator of inflammation, protects mice from HFD-induced obesity [180, 181]. Activation of the hypothalamic IKKβ/NF-κB pathway induces leptin resistance, whereas inhibition of hypothalamic IKKβ protects against obesity in mice [176].

ER stress

The ER is a cellular organelle where most secreted and transmembrane proteins are synthesized, folded, and sorted [182]. The ER processing capacity is affected by both the state of the cell and environmental conditions [182]. Protein overloading results in accumulation of unfolded or misfolded proteins in the ER lumens, causing ER stress. ER stress activates the unfolded protein response (UPR) pathways, including the inositol-requiring protein-1 (IRE1), activating transcription factor-6 (ATF6), and protein kinase RNA (PKR)-like ER kinase (PERK) pathways [182]. The UPR relieves ER stress by decreasing protein synthesis and influx into the ER, increasing protein-folding capacity of the ER via up-regulating the expression of ER chaperons, and clearing unfolded or misfolded proteins from the ER through proteasome-mediated degradation [182]. Cell death is triggered if the UPR fails to relieve ER stress [182]. ER stress is associated with a variety of metabolic diseases including obesity, insulin resistance, and diabetes[183]. Recently, several groups have reported the role of ER stress in the development of leptin resistance and obesity [176, 184, 185]. Hypothalamic ER stress is observed in HFD-fed mice [184]. Deletion of neuronal X-box binding protein 1 (XBP-1), an important regulator of ER homeostasis, results in hypothalamic ER stress and leptin resistance [184]. Central administration of pharmacological ER stress inducers impairs leptin signaling, whereas treatments with chemical ER chaperons relieve hypothalamic ER stress and decrease body weights in *ob/ob* mice [184–186]. Physical exercises improve hypothalamic leptin sensitivity at least in part through suppressing hypothalamic IKKβ and ER stress in rodents[187].

Defective autophagy

Autophagy has been reported to be involved in the regulation of energy homeostasis [188–191]. Leptin treatments induce autophagy both in cultured cells and in animals [188]. Inhibition of autophagy in the mediobasal hypothalamus by knocking down autophagy-related protein 7 (Atg7) leads to energy imbalance and obesity in mice [189]. POMC-neuron specific Atg7-knockout mice display leptin resistance [191]; in contrast, AgRP neuron-specific Atg7-knockout mice exhibit reduced body weight and adiposity without altering food intake [190]. Clearly, more studies are warranted to clarify the cell type-specific actions of autophagy under normal and obesity conditions.

Conclusions and future directions

Leptin has been firmly established as the essential hormone for the maintenance of energy homeostasis and body weight, and leptin resistance has been widely recognized as the key risk factor for obesity. Leptin promotes weight loss primarily by activating the LEPRb pathways in the brain, particularly in the hypothalamus. These pathways act coordinately to mediate leptin's anti-obesity action. LEPRb-expressing neurons are located in many brain areas, and these neurons form a sophisticated network to control energy balance and body weight. Multiple factors, including inflammation and ER stress, have been identified as causal factors for leptin resistance. Genetic studies, including mouse genetic analysis and GWAS, have provided important information about potential obesity genes. However, the anatomic connection and synaptic transmission of the brain neural circuitry that control

energy homeostasis and body weight remain largely unknown. The interactions between the neural circuits that mediate homeostatic and hedonic regulation of food intake are unclear. It is also unclear how the different branches of the LEPRb pathways act specifically and/or coordinately to regulate different aspects of feeding behavior and energy expenditure. A large portion of molecular events that lead to leptin resistance remains to be identified. Additionally, we just begin to appreciate the contribution of hypothalamus plasticity and neurogenesis to the maintenance of energy homeostasis and body weight. We expect to have exciting new findings in these areas in the future.

Acknowledgments

This work was supported by grants RO1 DK065122 and DK091591 from the NIDDK (to L.R.).

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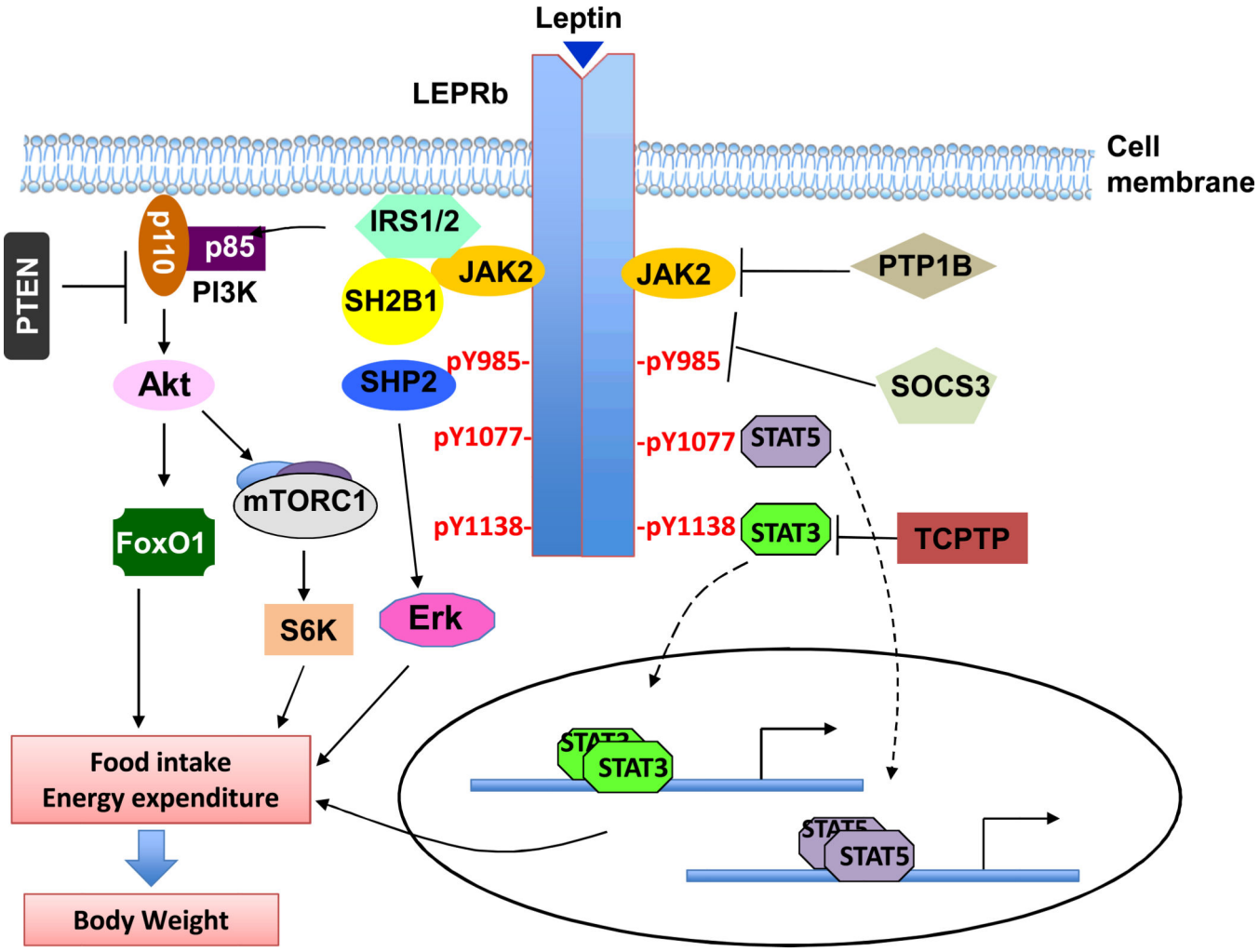

Fig. 1. Leptin signaling pathways

Leptin binds to LEPRb and activates JAK2. JAK2 phosphorylates LEPRb on Tyr^{985}, Tyr^{1077} and Tyr^{1138}. Phospho-Tyr^{985}, -Tyr^{1077} and -Tyr^{1138} bind to downstream molecules and activate the JAK2/STAT3, JAK2/STAT5, PI3K/IRS/AKT, and SHP2/ERK pathways. These pathways act coordinately to regulate energy balance and body weight. LEPRb signaling is regulated both negatively by SOCS3, PTP1B, TCPTP, PTEN and RPTPe and positively by SH2B1. Many factors, including hyperleptinemia, inflammation, ER stress, and defective autophagy, contribute to leptin resistance.

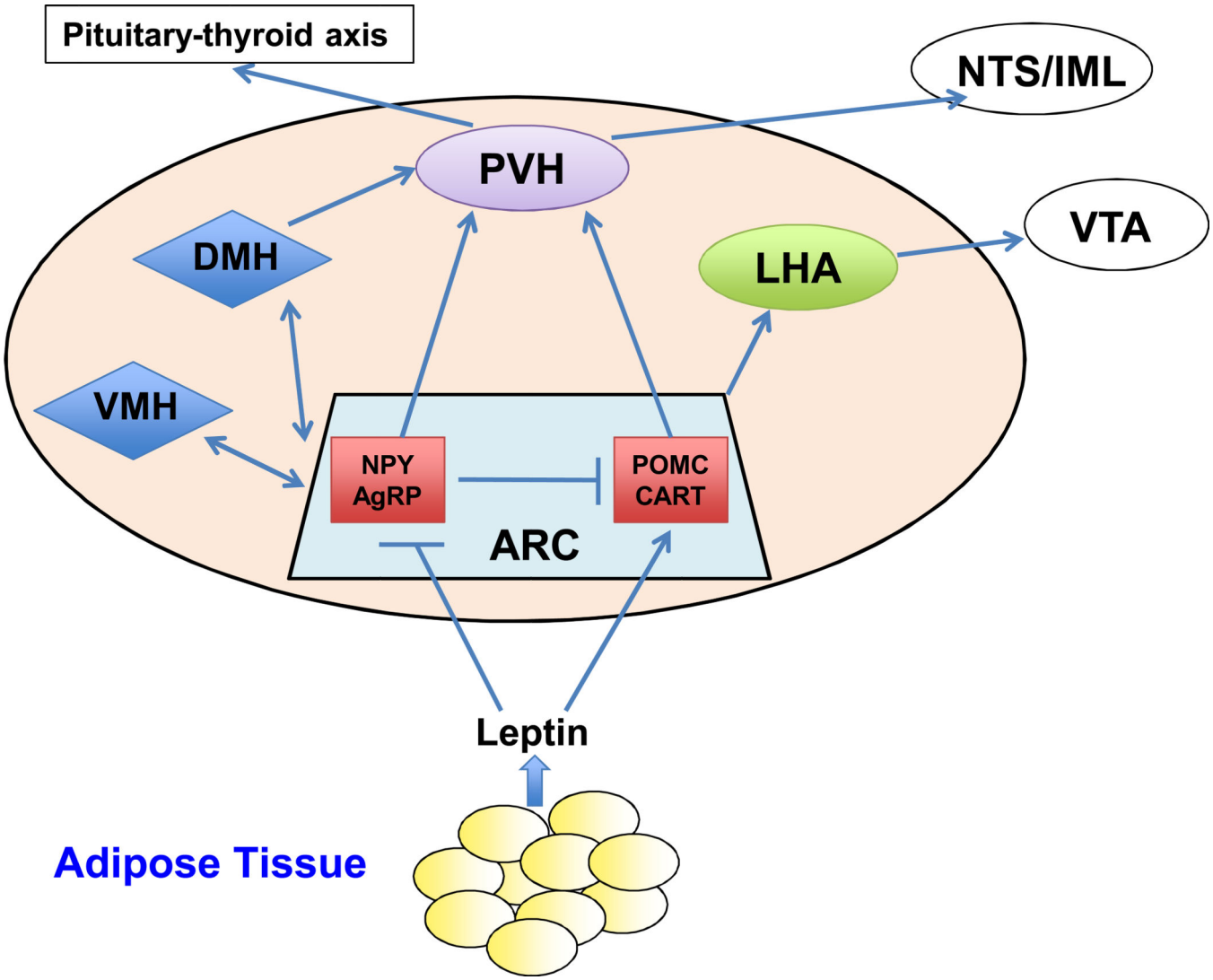

Fig. 2. Leptin-targetedt neurons and neural circuits

Leptin directly suppresses NPY/AgRP neurons and stimulates POMC/CART neurons in the ARC. ARC neurons project to multiple hypothalamic areas including the DMH, VMH, PVH, and LHA. Leptin also directly activates LEPRb in DMH, VMH, PVH, and LHA neurons. The PVH and LHA are important hypothalamic output pathways that mediate leptin's anti-obesity action. VTA: ventral tegmental area; NTS: solitary nucleus; IML: intermediolateral cell column.