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Review

Recent advances in understanding leptin signaling and leptin resistance

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Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. *Am J Physiol Endocrinol Metab* 297: E1247–E1259, 2009. First published September 1, 2009; doi:10.1152/ajpendo.00274.2009.—The brain controls energy homeostasis and body weight by integrating various metabolic signals. Leptin, an adipose-derived hormone, conveys critical information about peripheral energy storage and availability to the brain. Leptin decreases body weight by both suppressing appetite and promoting energy expenditure. Leptin directly targets hypothalamic neurons, including AgRP and POMC neurons. These leptin-responsive neurons widely connect to other neurons in the brain, forming a sophisticated neurocircuitry that controls energy intake and expenditure. The anorexigenic actions of leptin are mediated by LEPRb, the long form of the leptin receptor, in the hypothalamus. LEPRb activates both JAK2-dependent and -independent pathways, including the STAT3, PI 3-kinase, MAPK, AMPK, and mTOR pathways. These pathways act coordinately to form a network that fully mediates leptin response. LEPRb signaling is regulated by both positive (e.g., SH2B1) and negative (e.g., SOCS3 and PTP1B) regulators and by endoplasmic reticulum stress. Leptin resistance, a primary risk factor for obesity, likely results from impairment in leptin transport, LEPRb signaling, and/or the neurocircuitry of energy balance.

THE PREVALENCE OF OBESITY continues to increase rapidly around the globe. Body weight is normally maintained within a narrow range by a balance between energy intake (food intake) and energy expenditure. When energy intake exceeds energy expenditure, excess energy is stored as triglyceride in adipose tissue, resulting in overweight or obesity. A sophisticated neuroendocrine system has evolved in mammals to control energy balance by constantly monitoring energy storage, availability, and consumption. Adipose tissue and the brain are two key components of this neuroendocrine system.

Leptin Controls Energy Balance and Body Weight by Regulating Neuronal Activity in the Hypothalamus

In addition to storing triglyceride, adipose tissue secretes a variety of signaling molecules, including lipids and numerous polypeptides, that regulate systemic glucose and lipid metabolism. Leptin is the primary adipose hormone that conveys an adiposity signal to the brain (Fig. 1). The brain, particularly the hypothalamus, integrates leptin and various other metabolic signals to regulate energy homeostasis and body weight by controlling both behavior and metabolic responses. Leptin decreases body weight both by suppressing appetite and by increasing energy expenditure (25, 76, 158, 185). Leptin deficiency results in morbid obesity in both animals and humans (138, 186, 224). Similarly, genetic deficiency of functional leptin receptors (LEPR) also results in obesity and obesity-associated metabolic diseases (35, 192, 224). In addition to controlling energy balance and body weight, leptin also plays an important role in the regulation of immune responses, bone homeostasis, reproduction, and mood and emotion (22, 96, 112, 123).

Leptin-targeted neurons. LEPR mRNA is highly expressed in the arcuate nucleus (ARC), the ventromedial hypothalamus (VMH), the dorsomedial hypothalamus (DMH), the lateral hypothalamic area (LHA), and the ventral premammillary nucleus (PMV) (31, 46, 74, 116, 117, 133, 177–179). Central administration of recombinant leptin reduces food intake and body weight (25, 75, 185). Neuron-specific deletion of LEPR results in energy imbalance and obesity (36); conversely, neuron-specific restoration of functional LEPR rescues the obese phenotypes in LEPR-null (*db/db*) mice (41). Moreover, restoration of leptin signaling specifically in the ARC corrects hyperphagia and obesity in LEPR-null rats, suggesting that the ARC is a key leptin target (177). In particular, two subpopulations of ARC neurons [proopriomelanocortin (POMC) neurons and agouti-related protein (AgRP) neurons] have emerged as critical mediators for leptin action.

POMC neurons are anorexigenic neurons that coexpress anorexigenic POMC and cocaine- and amphetamine-regulated transcript (CART) (49, 177). Leptin stimulates both POMC neuronal excitability and expression of POMC and CART (39, 49, 108, 137, 178). POMC is proteolytically cleaved to generate α-melanocyte-stimulating hormone (α-MSH), which activates melanocortin-3 and melanocortin-4 receptors (MC3R and MC4R) (28, 55, 63, 89, 170). MC3R and MC4R are G protein-coupled receptors that are highly expressed in the hypothalamus, especially in the paraventricular hypothalamus (PVH) (145). Deletion of either MC3R or MC4R results in leptin resistance and obesity in mice (28, 89). Deletion of both MC3R and MC4R causes more severe obesity than deletion of either MC3R or MC4R alone, suggesting that MC3R and MC4R act together to mediate POMC's anorexigenic effect (28). Genetic defects in either the *POMC* or the *MC4R* genes

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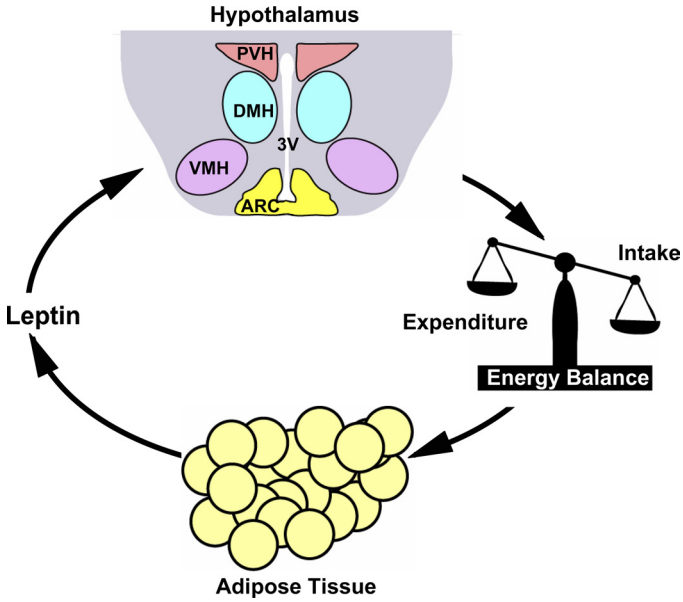

Fig. 1. A model of leptin regulation of energy balance and body weight. Leptin is secreted by adipose tissue in proportion to adipose mass and relays information about peripheral energy storage and availability to the brain. Leptin regulates neuronal activity in multiple regions of the hypothalamus, including the arcuate nucleus (ARC), ventromedial hypothalamus (VMH), and paraventricular hypothalamus (PVH). Leptin suppresses appetite (energy intake) and promotes energy expenditure primarily by regulating these neuronal activities. Leptin resistance causes an imbalance between energy intake and expenditure, resulting in obesity. 3V, 3rd ventricle.

are linked to obesity in humans, suggesting that the melanocortin system is an evolutionally conserved leptin target in mammals (35, 109).

AgRP neurons are orexigenic neurons that coexpress orexigenic AgRP and neuropeptide Y (NPY) (73, 177). NPY potently stimulates feeding behaviors (184). AgRP is a potent antagonist of both MC3R and MC4R and opposes the anorexigenic action of POMC (154). AgRP neurons also innervate POMC neurons and inhibit POMC neuronal activity by releasing inhibitory γ-aminobutyric acid (GABA) (39). Genetic ablation of AgRP neurons in adult mice leads to starvation, indicating that these neurons are required for feeding (71, 125). Leptin inhibits not only AgRP/NPY expression but also AgRP neuronal excitability (177, 185, 188). Additionally, leptin inhibits GABA release from AgRP neurons, thus reducing GABAergic inhibition of POMC neurons (39). Blocking presynaptic release of GABA from AgRP neurons increases POMC neuronal excitability, which contributes to increased energy expenditure and decreased adiposity in mice with AgRP neuron-specific deletion of vesicular GABA transporter (195).

Surprisingly, selective deletion of functional LEPR in either AgRP or POMC neurons results in mild obesity (3, 200). Deletion of LEPR in both AgRP and POMC neurons has an additive effect on energy balance and body weight; however, the metabolic phenotypes in these mutant mice are still milder than in systemic LEPR-deficient *db/db* mice (200). These observations suggest that leptin controls energy balance and body weight by regulating both arcuate and extra-arcuate neurons. Consistent with this idea, LEPR mRNA is expressed in multiple areas in the brain, including ARC, VMH, DMH, the lateral hypothalamic area (LHA), ventral tegmental area (VTA), the ventral premammillary nucleus, hippocampus, and the brainstem (46, 50, 62, 83, 117, 132). Deletion of LEPR in the VMH results in mild obesity (13, 44). Activation of LHA LEPRb-neurons suppresses feeding and weight gain (116). Leptin also stimulates LEPR-expressing neurons in the VTA, thereby inhibiting motivated food-seeking behaviors (62, 83). Therefore, these distinct leptin-responsive neurons may act redundantly, in parallel, and/or synergistically to fully mediate the physiological responses to leptin.

Leptin-targeted neural circuitry. The neural circuitry that integrates leptin and other metabolic signals to control energy homeostasis and body weight remains largely undefined. Various components of this circuitry have been described. Both AgRP and POMC neurons (first-order neurons) extensively innervate second-order neurons in the PVH (Fig. 1) (60). The PVH mediates leptin stimulation of the sympathetic nervous system, contributing to the ability of leptin to promote energy expenditure (180). The PVH also contains neuroendocrine cells that secrete numerous anorexigenic factors, including thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH), and leptin stimulates both TRH and CRH secretion (77, 87, 151). α-MSH stimulates TRH biosynthesis and secretion, whereas NPY and AgRP suppress TRH secretion (77, 103, 151). TRH stimulates the pituitary-thyroid axis, thus increasing metabolic rate and energy expenditure. Both AgRP and POMC neurons synapse on VMH neurons that express brain-derived neurotrophic factor (BDNF) (215). Leptin stimulates the expression of anorexigenic BDNF in the VMH, presumably by stimulating MC4R signaling (107, 215). Deletion of BDNF in the VMH/DMH of adult mice results in hyperphagia and obesity (197). Additionally, TrkB (BDNF receptor) deficiency results in hyperphagia and obesity in both mice and humans (215, 217). Moreover, AgRP neurons innervate neurons in the parabrachial nucleus (PBN), a relay center for taste and gastric distension signals from the nucleus tractus solitaries (NTS) to the forebrain (211, 212). AgRP neurons inhibit PBN neurons by releasing GABA, and this inhibition is required for feeding behaviors (211, 212). These findings indicate that the neural circuits that control energy intake and expenditure are extremely complex, and leptin acts on multiple nodes in these circuits.

Leptin-targeted peripheral tissues. In addition to the brain, leptin also acts directly on multiple peripheral tissues, including pancreatic islets, adipose tissue, skeletal muscle, and liver. LEPRb mRNA is expressed in islets, and leptin directly inhibits insulin expression and secretion (52, 111). Deletion of LEPR in the pancreas enhances first-phase insulin secretion and modestly improves glucose tolerance in mice (142). Leptin also directly stimulates fatty acid oxidation in isolated islets, thereby decreasing islet lipid levels (182). In isolated adipocytes, leptin inhibits lipogenesis but stimulates lipolysis and fatty acid oxidation (204). Adipocyte-specific overexpression of LEPRb prevents diet-induced obesity in mice (205). Leptin directly promotes fatty acid oxidation in isolated skeletal muscles, presumably by activating AMPK (136, 148). Leptin decreases lipid levels in isolated livers, and liver-specific overexpression of LEPRb prevents hepatic steatosis in LEPRb-deficient Zucker diabetic fatty (*fa/fa*) rats (88, 115). Surprisingly, genetic deletion of LEPR in these peripheral tissues does not alter energy balance, body weight, or glucose homeostasis in mice (72). Therefore, under normal conditions, leptin con-

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trols energy balance, body weight, and systemic metabolism primarily by activating LEPRb in the brain.

Leptin Stimulates Multiple Signal Transduction Pathways

The *LEPR* gene produces multiple leptin receptor isoforms (a, b, c, d, e, and f) via alternative mRNA splicing (18, 51, 59, 133, 206). All isoforms have an extracellular leptin-binding domain, but only the longest form, LEPRb, contains a full-length intracellular domain required for cell signaling (61). Genetic deficiency of LEPRb results in profound leptin resistance and morbid obesity in animals, indicating that LEPRb is required for leptin action (7, 29, 33, 68, 113). LEPRb belongs to the gp130 family of cytokine receptors (7, 29, 68). It constitutively binds to JAK2, a member of the Janus kinase (JAK) family of tyrosine kinases (Fig. 2). Leptin stimulates LEPRb dimerization, resulting in JAK2 activation and autophosphorylation (4, 42, 54, 209). JAK2 also phosphorylates LEPRb and various downstream signaling molecules on tyrosines (16, 67, 99). JAK2 phosphorylates Tyr^{985}, Tyr^{1077}, and Tyr^{1138} in the cytoplasmic domain of LEPRb, which then act as docking sites for downstream signaling molecules (4, 79, 118). The metabolic phenotypes of mice with deletion of key leptin-signaling molecules are listed in Table 1. Replacement of these three tyrosines in LEPRb with phenylalanines induces marked leptin resistance and obesity in mutant mice, indicating that phospho-Tyr^{985}, -Tyr^{1077}, and/or -Tyr^{1138} mediate the activation of key downstream pathways. However, the mutant mice are less obese and less hyperglycemic than LEPRb-deficient *db/db* mice, indicating that LEPRb can mediate some of the leptin signaling and action independently of phosphorylation on these tyrosines (93).

The JAK2/STAT3/STAT5 pathways. The STAT family members are SH2 domain-containing transcription factors located in the cytoplasm in quiescent cells. Cytokine-stimulated tyrosine phosphorylation of STATs induces homo- or heterodimerization, nuclear translocation, and transcriptional activation (84). Leptin stimulates tyrosine phosphorylation of STAT1, -3, -5, and -6 in cultured cells (7, 68, 171, 190); however, leptin primarily stimulates STAT3 and STAT5 phosphorylation in the hypothalamus in animals (70, 131, 199). Tyr^{1138} in LEPRb is within a YXXQ motif, a consensus-binding motif for STAT3 (183). In response to leptin, STAT3 binds to phospho-Tyr^{1138}, allowing JAK2 to phosphorylate and activate STAT3 (Fig. 2). Mutation of Tyr^{1138} abolishes the ability of leptin to activate the STAT3 but not other leptin pathways in both cultured cells and mice (4, 6, 209). Nonetheless, disruption of the STAT3 binding site in LEPRb, or deletion of neuronal STAT3, results in severe hyperphagia and morbid obesity, indicating that the LEPRb/JAK2/STAT3 pathway in the brain is required for the antiobesity actions of leptin (6, 40, 64, 93).

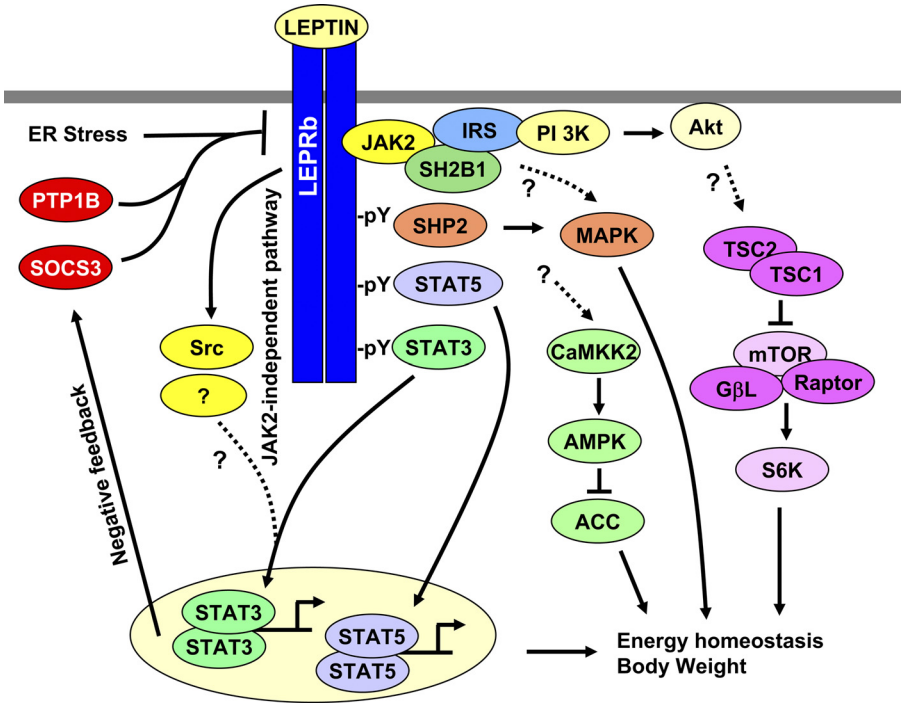

Fig. 2. A model of leptin signaling and leptin resistance. Leptin binds to the long form of the leptin receptor (LEPRb) and activates LEPRb-associated JAK2. JAK2 phosphorylates LEPRb on $Tyr^{985/1077/1138}$. SH2-containing protein tyrosine phosphatase 2 (SHP2) binds to phospho-Tyr^{985} and mediates the activation of the MAPK pathway. Suppressor of cytokine signaling-3 (SOCS3) also binds to phospho-Tyr^{985} and inhibits leptin signaling in a negative feedback manner. STAT5 and STAT3 bind to phospho-Tyr^{1077} and phospho-Tyr^{1138}, respectively, and are subsequently phosphorylated and activated by JAK2. STAT3 and STAT5 activate their target genes, which mediate leptin's anorexigenic effect. JAK2 autophosphorylates on Tyr^{813}, which binds to SH2B1. SH2B1 simultaneously binds to insulin receptor substrate (IRS)-1 and IRS-2 and recruits IRS proteins to the LEPRb/JAK2 complex, which results in JAK2-mediated tyrosine phosphorylation of IRS-1 and IRS-2 and subsequent activation of the phosphoinositide 3-kinase (PI3K) pathway. Leptin also stimulates a JAK2-independent pathway involving the Src tyrosine kinase family members. The JAK2-dependent and -independent pathways act coordinately and synergistically to promote STAT3 activation. Leptin also regulates the CaMKK2/AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) and the mammalian target of rapamycin (mTOR)/ribosomal S6 kinase (S6K) pathways; however, the molecular steps from the LEPRb to these 2 pathways are not clear. These diverse pathways act coordinately as a network to fully mediate leptin responses. LEPRb signaling is negatively regulated by SOCS3, protein tyrosine phosphatase 1B (PTP1B), and endoplasmic reticulum (ER) stress but positively regulated by SH2B1.

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Table 1. *Metabolic phenotypes in mice with tissue-specific deletion of leptin signaling molecules*

Protein	Pathway(s)	Targeted Cells	Cre Used	Leptin Sensitivity	Food Intake	Energy Expenditure	Susceptibility to DIO	Ref No.
LEPR	All	Whole body		↓	↑↑↑	↓↓↓	ND	192
		Brain	Synapsin I	↓	ND	ND	ND	36
		AgRP neurons	AgRP	ND	↔	↓	ND	200
		POMC neurons	POMC	ND	↔	↔	ND	3, 200
		AgRP and POMC neurons	AgRP and POMC	↓	↔	↓	ND	200
		VMH neurons	SF-1	ND	↔	↔	↑	13
SH2B1	JAK2/STAT3 IRS/PI 3-kinase	Whole body		↓	↑	↑	ND	120, 166
STAT3	JAK2/STAT3	Brain	Nestin	↓	↑↑↑	↓↓↓	ND	64
		Hypothalamus	RIP	↓	↑↑	ND	ND	40
		LEPR neurons	LEPRb	ND	↑↑↑	ND	ND	161
		POMC neurons	POMC	↔	↑	ND	↔	214
		AgRP neurons	AgRP	↓	↔	↔	↔	69
STAT5	JAK2/STAT5	Brain	Nestin	ND	↑	↓	ND	114
IRS2	IRS/PI 3-kinase	Whole body		↓	↑↑	ND	ND	24
		Brain	Nestin	↔	↑↑	↓	ND	32, 187
		Hypothalamus	RIP	↔ or ↓	↑↑	ND	ND	32, 110, 122
		POMC neurons	POMC	↔	↔	ND	ND	32
p85α/β	IRS/PI 3-kinase	POMC neurons	POMC	↓	↔	↔	ND	82
PDK1	IRS/PI 3-kinase	POMC neurons	POMC	ND	↑	ND	↑	8
PTEN	IRS/PI 3-kinase	LEPR neurons	LEPRb	ND	↔	↑	ND	163
		POMC neurons	POMC	ND	↑	↔	↑	162
FOXO1	IRS/PI 3-kinase	Whole body		↑	ND	ND	ND	105
TSC1	mTOR/S6K	Hypothalamus	RIP	↓	↑↑	ND	ND	141
		POMC neurons	POMC	↓	↑↑	ND	ND	141
SHP2	SHP2/MAPK	Brain	CaMKIIa	↓	↔	ND	ND	221
AMPKα2	AMPK/ACC	POMC neurons	POMC	↔	↑	↓	↑	34
		AgRP neurons	AgRP	ND	↔	↔	↔	34
CaMKK2	AMPK/ACC	Whole body		ND	↓	ND	↓	1
SOCS3	All	Whole body		↑	↔	ND	↓	86
		Brain	Nestin	↑	↓	ND	↓	140
		Brain	Synapsin I	↑	↓	ND	↓	140
		POMC neurons	POMC	↑	↔	ND	↓	101
		VMH neurons	SF-1	↑	↓	↓	↔	222
PTP1B	All	Brain	Nestin	↑	↓	↑	↓	11

LEPR, leptin receptor; LEPRb, long form of the leptin receptor; AgRP, agouti-related protein; POMC, proopriomelanocortin; VMH, ventromedial hypothalamus; IRS, insulin receptor substrate; PI, phosphoinositide; PDK1, phosphoinositide-dependent protein kinase-1; PTEN, phosphatase and tensin homolog deleted on chromosome 10; FOXO1, forkhead box O1; TSC1, tuberous sclerosis complex 1; mTOR, mammalian target of rapamycin; SHP2, SH2-containing protein tyrosine phosphatase 2; AMPK, AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; SOCS3, suppressor of cytokine signaling-3; PTP1B, protein tyrosine phosphatase 1B; ↑increased; ↓decreased; ↔no change compared with control mice; ND, not determined; DIO, diet-induced obesity; RIP, rat insulin II promoter; SF-1, steroidogenic factor-1.

In cultured cells, leptin stimulates STAT3-dependent activation of the *POMC* promoter (105, 147). In mice, deletion of STAT3 in POMC neurons decreases hypothalamic POMC expression (214). STAT3 also binds directly to the *AgRP* promoter and mediates leptin suppression of the *AgRP* promoter in cultured cells (105). However, deletion of STAT3 in AgRP neurons does not alter hypothalamic AgRP mRNA expression, suggesting that STAT3 signaling does not mediate leptin suppression of AgRP in vivo (94). Surprisingly, deletion of STAT3 in either POMC or AgRP neurons only slightly increases food intake and adiposity in mice (69, 214). In contrast, deletion of STAT3 in the entire population of LEPR-expressing neurons results in profound leptin resistance, hyperphagia, and obesity (161). These observations suggest that STAT3 signaling in various subpopulations of LEPR neurons acts coordinately to fully mediate leptin's anorexigenic effect.

Leptin stimulates phosphorylation of LEPRb on Tyr^{1077}, which binds to STAT5 and subsequently mediates STAT5 phosphorylation (70, 79, 149). Deletion of both STAT5A and STAT5B in the brain causes leptin resistance, hyperphagia, and obesity, but to a lesser extent than STAT3 deletion, indicating that the JAK2/STAT5 pathway may also contribute to leptin regulation of energy balance and body weight (114).

The insulin receptor substrate/phosphoinositide 3-kinase pathway. Leptin stimulates phosphoinositide (PI) 3-kinase both in cultured cells and in the hypothalamus (12, 78, 104, 207, 213, 225, 226), and insulin receptor substrate (IRS) proteins, particularly IRS-2, act downstream of LEPRb to activate the PI 3-kinase pathway (24, 110, 122, 128). Leptin-stimulated activation of hypothalamic PI 3-kinase pathway is impaired in diet-induced obesity (134). Inhibition of the PI 3-kinase pathway in the brain blocks the ability of leptin to reduce food intake and weight gain (153, 225). Additionally, inhibition of the hypothalamic PI 3-kinase pathway, but not the STAT3 pathway, blocks the ability of central leptin to suppress lipogenesis in white adipose tissue (23). Forkhead box O1 (FOXO1), a transcriptional factor that is phosphorylated and inactivated by Akt, appears to be an important downstream mediator of the PI 3-kinase pathway (102, 105, 129, 191). Leptin inhibits both the activity and expression of hypothalamic FOXO1 through the PI 3-kinase pathway (102). Adenoviral-mediated overexpression of a constitutively active FOXO1 mu-

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tant in the ARC decreases leptin sensitivity in mice; as expected, food intake and body weight are increased, whereas energy expenditure is decreased by hypothalamic FOXO1 activation (102, 105). Conversely, small interfering RNA-mediated knockdown of FOXO1 in ARC or FOXO1 haploinsufficiency increases leptin sensitivity and decreases food intake and body weight (102, 105). Additionally, POMC neuron-specific deletion of phosphoinositide-dependent kinase 1, a key activator of Akt, induces modest hyperphagia and obesity in a FOXO1-dependent manner (8). FOXO1 binds directly to the *NPY*, *AgRP*, and *POMC* promoters; it stimulates the expression of NPY and AgRP but inhibits POMC expression (102, 105). FOXO1 appears to antagonize STAT3 action in both AgRP and POMC neurons (102, 105, 216). Collectively, these findings indicate that the hypothalamic PI 3-kinase pathway is required for leptin's anorexigenic action.

Leptin appears to differentially activate the PI 3-kinase pathway in discrete hypothalamic neurons. Leptin activates the PI 3-kinase pathway in POMC neurons in hypothalamic slices; in contrast, leptin withdrawn activates PI 3-kinase in AgRP neurons in a synaptic transmission-dependent manner (213). Leptin stimulates POMC neuron depolarization and electrical activity by activating nonselective cation channels (39). Pharmacological or genetic inactivation of PI 3-kinase in POMC neurons abolishes the ability of leptin to excite POMC neurons, indicating that the PI 3-kinase pathway is required for leptin-stimulated POMC neuron activation (39, 82). Surprisingly, POMC neuron-specific inactivation of PI 3-kinase only attenuates acute suppression of food intake by leptin but does not impair long-term regulation of energy balance and body weight (82). Interestingly, deletion of IRS-2 in the brain results in leptin resistance and obesity in mice; in contrast, targeted deletion of IRS-2 in POMC neurons does not alter energy balance and body weight (32, 110, 122, 187). Chronic activation of the hypothalamic PI 3-kinase pathway by LEPR neuron-targeted deletion of phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a PI 3-kinase specific inhibitor, increases leptin sensitivity and decreases adiposity (163); in contrast, deletion of PTEN in POMC neurons results in leptin resistance and hyperphagia (162). Taken together, these studies indicate that the PI 3-kinase pathway in non-POMC hypothalamic neurons appears to mediate the long-term anorexigenic effects of leptin.

The SH2-containing protein tyrosine phosphatase 2/MAPK pathway. Leptin stimulates ERK1/2 activation via SH2-containing protein tyrosine phosphatase 2 (SHP2) in cultured cells and the hypothalamus (14, 16, 104, 165, 189, 221). Leptin stimulates phosphorylation of LEPRb on Tyr^{985}, which is required for maximal activation of the MAPK pathway in response to leptin (4, 27, 118). SHP2 is a ubiquitously expressed cytoplasmic protein-tyrosine phosphatase that contains two NH_2-terminal SH2 domains and one COOH-terminal phosphatase domain. SHP2 binds via its SH2 domain to phosphorylated Tyr^{985} in LEPRb and acts as an upstream activator of the MAPK pathway in leptin-treated cells (Fig. 2) (4, 14, 27, 118). Leptin also stimulates the activation of the MAPK pathway by a Tyr^{985} phosphorylation-independent mechanism, but to a lesser extent (14). Neuron-specific deletion of SHP2 results in leptin resistance and obesity (221). Pharmacological inhibition of ERK1/2 in the hypothalamus also abrogates the ability of leptin to inhibit food intake and weight gain (165). These observations suggest that the SHP2/MAPK pathway is involved in mediating leptin's anorexigenic action.

The AMPK/ACC pathway. 5′-AMP-activated protein kinase (AMPK) is activated by an increase in AMP/ATP ratio and functions as an energy sensor in multiple cell types (95). AMPK phosphorylates and inactivates acetyl-CoA carboxylase (ACC), a key enzyme in fatty acid biosynthesis (95). Leptin inhibits AMPK in multiple regions of the hypothalamus, including the ARC and PVH (2, 135). As expected, leptin stimulates hypothalamic ACC via inhibition of AMPK (65). Inhibition of hypothalamic AMPK is sufficient to reduce food intake and weight gain; in contrast, constitutive activation of hypothalamic AMPK attenuates leptin's anorexigenic response (2, 135). Inhibition of ACC also blocks leptin's anorexigenic action, suggesting that ACC is a downstream mediator of AMPK (65). The Ca^{2+}/calmodulin (CaM)-dependent protein kinase kinase (CaMKK2) is an upstream activator of AMPK in the hypothalamus, and inhibition of CaMKK2 reduces appetite and body weight (1). These findings suggest that the hypothalamic CaMKK2/AMPK/ACC pathway also mediates leptin's anorexigenic action. Consistent with this idea, dietary fat inhibits the ability of leptin to suppress the AMPK pathway in the hypothalamus (127). However, it is unclear whether leptin directly or indirectly regulates this pathway in hypothalamic neurons. Moreover, deletion of AMPK in either POMC neurons or AgRP neurons does not alter leptin sensitivity (34), suggesting that the CaMKK2/AMPK/ACC pathway in extra-arcuate sites mediates leptin's metabolic action.

The mammalian target of rapamycin/S6 kinase pathway. Leptin stimulates phosphorylation of ribosomal S6 kinase (S6K), a major physiological substrate of the mammalian target of rapamycin (mTOR) kinase in the hypothalamus (38). Rapamycin inhibits hypothalamic mTOR and attenuates leptin's anorexigenic effects (38). Systemic deletion of S6K1, or selective inhibition of S6K in the ARC by a dominant negative S6K mutant, also abolishes leptin's acute anorexigenic action in mice (21, 37). Conversely, activation of S6K in the ARC enhances leptin sensitivity (21). The molecular steps of leptin activation of the mTOR/S6K pathway remain unknown. mTOR binds to raptor and GβL to form the mTOR complex 1 (mTORC1), which directly phosphorylates and activates S6K (172). mTORC1 is inhibited by the TSC1/TSC2 complex (66, 90, 193). Akt phosphorylates TSC2 and inactivates the TSC1/TSC2 complex (90). Therefore, the mTOR/S6K pathway is likely to be a downstream target of the PI 3-kinase/Akt pathway in leptin-stimulated neurons. Surprisingly, in mice with POMC neuron-specific deletion of TSC1, the chronic activation of the mTOR/S6K pathway in POMC neurons results in leptin resistance, hyperphagia, and obesity, presumably due to an alteration of the hypothalamic neurocircuitry of energy balance (141). Interestingly, chronic activation of the PI 3-kinase pathway in POMC neurons similarly causes leptin resistance and hyperphagia in mice with POMC neuron-specific deletion of PTEN (162). These observations support the idea that the PI 3-kinase/Akt pathway stimulates the mTOR/S6K pathway at least in POMC neurons; additionally, chronic activation of the PI 3-kinase/Akt/mTOR/S6K pathway in POMC neurons may alter synaptic transmission and/or neural wiring in the hypothalamus, resulting in leptin resistance. It would be interesting to determine whether the mTOR/S6K pathway in POMC neurons is constitutively activated in mice

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with POMC neuron-specific PTEN and whether POMC neuron-specific inactivation of the mTOR/S6K pathway rescues leptin-resistant and hyperphagic phenotypes observed in mice with POMC neuron-specific deletion of PTEN.

The JAK2-independent pathway. We observed that leptin still stimulates the STAT3 and the MAPK pathways in cultured cells that are genetically deficient of JAK2 (92). The Src tyrosine kinase family members appear to be involved in mediating JAK2-independent leptin signaling (Fig. 2) (10, 92, 139). Interestingly, overexpression of kinase-inactive JAK2 enhances leptin signaling in JAK2-deficient cells, suggesting that JAK2 functions both as a tyrosine kinase and as an adaptor to transduce leptin signals (92). The JAK2-dependent and JAK2-independent pathways appear to act synergistically to mediate leptin responses (92). However, the JAK2-independent pathway and its physiological importance have not been verified in animals.

SH2B1 Is an Important Positive Regulator of Leptin Sensitivity

SH2B1 is a SH2 and PH domain-containing adaptor involved in cell signaling in response to a variety of hormones, growth factors, and cytokines (174). We observed that genetic deletion of SH2B1 results in severe leptin resistance, hyperphagia, morbid obesity, hepatic steatosis, and type 2 diabetes in mice (120, 166). Neuron-specific restoration of SH2B1 restores leptin sensitivity and reverses the obesity phenotype in SH2B1-null mice (167). Additionally, neuron-specific overexpression of SH2B1 protects against diet-induced leptin resistance and obesity (167). These data indicate that SH2B1 in the brain is a key regulator of leptin sensitivity, energy balance, and body weight. Interestingly, single nucleotide polymorphisms within the *SH2B1* loci have been linked to leptin resistance and obesity in humans (91, 168, 194, 210), suggesting that the metabolic functions of SH2B1 are conserved in mammals.

SH2B1 enhances leptin signaling by at least two mechanisms. We reported that leptin stimulates JAK2 autophosphorylation on Tyr^{813} (121). SH2B1 binds via its SH2 domain to phospho-Tyr^{813} and markedly enhances JAK2 activity, thereby promoting the activation of the leptin-signaling pathways downstream of JAK2 (121, 152, 173). Additionally, SH2B1 also binds directly to IRS-1 and IRS-2 (47). Leptin stimulates the formation of JAK2/SH2B1/IRS protein complexes, thereby specifically promoting JAK2-mediated phosphorylation of IRS proteins and subsequent activation of the PI 3-kinase pathway (47, 121, 166) (Fig. 2). SH2B1 forms homodimers via its NH_2-terminal regions (43, 152), and this likely provides a platform to initiate the formation of JAK2/SH2B1/IRS protein complexes and/or to stabilize these complexes in response to leptin. Our recent data show that the SH2B1-IRS-1/2 interaction inhibits tyrosine dephosphorylation of IRS-1/2, thus increasing and/or prolonging the activation of the PI 3-kinase pathway (143).

The SH2B family consists of three members (SH2B1, SH2B2, and SH2B3) (130). In contrast to SH2B1, SH2B2 and SH2B3 do not appear to be required for the maintenance of normal leptin sensitivity, energy balance, and body weight (120, 201). Interestingly, SH2B2β, an alternative splicing variant of SH2B2 that lacks the COOH-terminal SH2 domain, binds directly to SH2B1 and antagonizes SH2B1 action (119). These findings suggest that the ability of SH2B1 to enhance leptin sensitivity can be modulated by other members of the SH2B family.

Leptin Resistance Is Induced by Multiple Mechanisms

Leptin resistance, referring to the reduced ability of circulating leptin to suppress appetite and weight gain and to promote energy expenditure, is a primary risk factor for the development of obesity. Leptin resistance likely results from defects in leptin transport into the brain, leptin signaling, and/or the hypothalamic neural circuitry that regulates energy homeostasis. The onset of leptin resistance may vary among discrete LEPRb-expressing neurons. For instance, diet-induced leptin resistance is developed initially in the ARC and later in the VMH, DMH, and PMV (134, 146). Additionally, the impairment in the PI 3-kinase pathway precedes that of the STAT3 pathway (134).

Impaired leptin transport. Obesity is associated with a reduction in leptin transport into the brain, suggesting that impaired leptin transport contributes to leptin resistance (26, 48, 176). Leptin is actively transported across the blood-brain barrier by a saturable transport mechanism (5). LEPRa, a short form of the leptin receptor that lacks the entire cytoplasmic domain, mediates leptin transport across the blood-brain barrier (80, 81, 97). LEPRe, a soluble form of the leptin receptor, inhibits leptin transport by antagonizing LEPRa's action (196). However, a subpopulation of LEPR-expressing neurons in the ARC sends projections into the median eminence (ME), a circumventricular organ that lacks tight junctions and is permeable to blood-borne hormones (56, 175). These neurons are directly activated by circulating leptin via their projections into the ME (56). Thus, additional studies are needed to clarify the contribution of impaired leptin transport to the pathogenesis of leptin resistance in obese subjects.

Impaired LEPRb trafficking. Most LEPRb is located in the *trans*-Golgi network and small vesicles, and only a small portion of LEPRb is present on the plasma membrane to mediate leptin signaling (9, 45). Bardet-Biedl syndrome proteins mediate/promote LEPRb trafficking to the plasma membrane (181). Deletion of Bardet-Biedl syndrome proteins impairs cell surface LEPRb expression, resulting in leptin resistance and obesity (164, 181). However, the contribution of defects in LEPRb trafficking as well as in LEPRb expression to leptin resistance remains to be determined in obese animals and humans.

Impaired LEPRb signaling. LEPRb signaling is regulated by both negative [e.g., suppressor of cytokine signaling-3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B)] and positive (e.g., SH2B1) regulators. Leptin stimulates the expression SOCS3, which provides a critical negative feedback mechanism to prevent overactivation of leptin-signaling pathways (Fig. 2) (17, 18). SOCS3 binds to JAK2 and inhibits JAK2 activity (17, 18). SOCS3 also binds to phospho-Tyr^{985} in LEPRb and inhibits leptin signaling in cultured cells (19, 54). Replacement of Tyr^{985} with Leu increases leptin sensitivity in mice (20). Additionally, SOCS3 haploinsufficiency, or neuron-specific deletion of SOCS3, enhances leptin sensitivity and attenuates diet-induced leptin resistance and obesity (86, 140). POMC neuron-specific deletion of SOCS3 slightly increases leptin

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sensitivity and protects against diet-induced obesity (101). Deletion of SOCS3 in the VMH increases leptin sensitivity; however, long-term body weight is not altered due to a reduction in both food intake and energy expenditure (222). Therefore, SOCS3 appears to negatively regulate leptin sensitivity in multiple hypothalamic sites. SOCS3 expression is significantly increased in the hypothalamus in leptin-resistant animals, suggesting that increased SOCS3 expression contributes to leptin resistance (15, 53, 146, 160).

PTP1B binds to and dephosphorylates JAK2, thereby inhibiting leptin signaling (98, 150, 220). PTP1B is expressed in the ARC, VMH, and DMH, and both systemic and neuron-specific deletion of PTP1B improves leptin sensitivity and reduces adiposity in mice (11, 30, 220). The expression of hypothalamic PTP1B is increased in leptin-resistant animals, suggesting that PTP1B also contributes to leptin resistance (144, 208).

We showed that SH2B1 functions as an endogenous leptin sensitizer to enhance leptin sensitivity (120, 121, 166, 167). Interestingly, overexpression of SH2B1 counteracts PTP1B-mediated inhibition of leptin signaling in cultured cells (120, 166). Therefore, cellular leptin sensitivity may be determined, at least in part, by a balance between positive (e.g., SH2B1) and negative (e.g., SOCS3 and PTP1B) regulators.

Endoplasmic reticulum stress. Secreted and transmembrane proteins are synthesized by the endoplasmic reticulum (ER) and folded into biologically active forms within the ER lumen. Unfolded and misfolded proteins are removed by proteasome-mediated degradation (202). ER homeostasis is maintained by balancing ER loading of nascent proteins with ER capacity to fold these proteins (202). An imbalance results in an accumulation of unfolded/misfolded proteins in the ER lumen, generating ER stress (169, 202). ER stress induces the unfolded protein response (UPR), which involves the activation of multiple intracellular signaling pathways (169). The inositol-requiring protein-1 pathway, the activating transcription factor-6 pathway, and the protein kinase RNA-like ER kinase pathway are well-characterized UPR-signaling pathways that play key roles in maintaining ER homeostasis (169). In response to short-term ER stress, the UPR restores ER homeostasis by reducing protein synthesis and increasing both ER folding capacity and degradation of unfolded/misfolded proteins (169). However, excessive or long-term ER stress induces apoptosis (169).

ER stress is increased in multiple tissues in leptin-resistant and obese animals, including the liver, adipose tissue, and the brain (155, 156, 223). Overnutrition stimulates the mTOR pathway, which promotes ER stress (157). Interestingly, ER stress is sufficient to inhibit leptin signaling in cultured cells, whereas pharmacological inhibition of ER stress improves leptin signaling (85, 157). Moreover, inhibition of ER stress in the hypothalamus by either genetic or pharmacological means markedly improves leptin sensitivity and decreases food intake and body weight in mice (157, 223). These findings suggest that chronic ER stress, presumably by activating various UPR-signaling pathways, contributes to leptin resistance and obesity. However, the cross-talk between UPR and leptin-signaling pathways remains unclear.

Defects in leptin-targeted neural circuitry. MC4R- and TrkB-expressing hypothalamic neurons are key components of the neural circuitry that mediate leptin's anorexigenic action, as discussed above. Impairment in MC4R signaling in the PVH or TrkB signaling in the VMH has been well documented to induce leptin resistance, hyperphagia, and obesity (57, 58, 100, 124, 126, 159, 197, 198, 203, 215, 217–219). Genetic as well as environmental factors may modulate ongoing synaptic remodeling and neural circuitry rewiring of the leptin neural circuitry, thus altering leptin sensitivity and energy metabolism. In further support of this idea, ciliary neurotrophic factor, which also induces weight loss, stimulates hypothalamic neurogenesis in obese adult mice, and pharmacological inhibition of hypothalamic proliferation blocks the long-term anorexigenic effects of ciliary neurotrophic factor (106).

Concluding Remarks and Future Perspectives

A large body of evidence suggests that leptin relays a critical adiposity signal to the brain, and leptin resistance is a primary risk factor for obesity. Leptin directly targets multiple chemically defined neurons (e.g., AgRP and POMC neurons) located in different hypothalamic regions (e.g., ARC, VMH, DMH, LHA, and PMV). These leptin-responsive neurons broadly connect to other neurons in the brain, thus forming a sophisticated neurocircuitry that also integrates other forms of metabolic signals to control the balance between energy intake and expenditure. Genetic and environmental factors may modulate the synaptic remodeling and rewiring of this circuitry, thus regulating leptin sensitivity and body weight. It is extremely important to anatomically, chemically, and electrically characterize this neurocircuity in the future. Leptin controls energy homeostasis and body weight primarily by activating LEPRb in the hypothalamus. LEPRb activates numerous JAK2-dependent and -independent signaling pathways that act coordinately as a network to fully mediate leptin's action. The activation of individual pathways in the leptin signaling network appears to be differentially regulated in discrete subpopulations of LEPRb-expressing neurons. These pathways are also likely to be regulated by various hormonal, neuronal, and metabolic signals that cross-talk with leptin. It is important to determine whether and how positive (e.g., SH2B1) and negative (e.g., SOCS3 and PTP1B) regulators of LEPRb signaling, ER stress, metabolic state, and/or neuronal activity regulate the activation of the leptin signaling networks in a cell type-specific manner. Additionally, leptin resistance appears to be caused by multiple mechanisms (e.g., impairment in leptin transport, LEPRb signaling, and the hypothalamic neurocircuitry) that may vary considerably among different obese patients. It will be challenging to develop diagnostic approaches for the different forms of leptin resistance and design personalized healthcare programs to treat obesity.

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