

The role of leptin receptor signaling in feeding and neuroendocrine function

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The adipose-derived hormone leptin regulates energy balance and neuroendocrine function, and resistance to its appetite-suppressing effects might underlie common forms of obesity. Understanding the intracellular signaling pathways and hypothalamic neural circuitry by which leptin controls satiety and body weight is central to our understanding of leptin resistance and the identification of potential therapeutic targets. Here, we review the mechanisms by which leptin activates intracellular signaling and the roles of two specific leptin-activated signals [phosphatidylinositol 3-kinase and signal transducer and activator of transcription-3 (STAT3)] in the regulation of body weight and neuroendocrine function. The pathway by which leptin activates STAT3 is particularly intriguing because it is crucial for the regulation of feeding but dispensable for the control of reproductive and growth axes.

The production of the hormone leptin by adipose tissue is regulated by energy balance. When energy (i.e. fat) stores are replete, leptin production is high. Conversely, leptin production is inhibited when energy stores are depleted during, for example, prolonged fasting [1,2]. Circulating leptin levels thus reflect the status of body energy reserves, and energy balance throughout the body is regulated via leptin-mediated control of processes that are involved in energy intake and utilization. Leptin signaling permits the expenditure of energy on the processes of reproduction and growth and similarly regulates the autonomic nervous system, other elements of the endocrine system and the immune system [3,4] (Figure 1). Thus, the fall in leptin levels when energy stores are inadequate (e.g. during starvation) enhances appetite and decreases energy utilization. By contrast, when energy stores are adequate, high leptin levels decrease the drive to eat and enable utilization of energy by the systems described above.

Lack of leptin signaling in mice and humans that are genetically null for either leptin (*ob/ob* mice) or the leptin receptor (LR) (*db/db* mice) results in obesity secondary to increased feeding and decreased energy utilization [1,2,5,6]. These animals also have a phenotype that is reminiscent of the neuroendocrine starvation response, including hypothyroidism, decreased growth, infertility and decreased immune function. Exogenous leptin replacement during

food restriction restores each of these functions and also decreases appetite [3]. Additionally, leptin appears to act via the sympathetic nervous system to inhibit the formation of trabecular bone [7].

LRs and sites of leptin action

There are multiple LR isoforms, which result from alternative mRNA splicing of the transcript of the *lepr* gene and/or from proteolytic processing of the subsequent protein products [8,9]. The *lepr* gene contains 17 common exons and several alternatively spliced exons. In mice, the five distinct LR isoforms that have been identified are designated LRA–LRE. In all species, LR isoforms can be divided into three classes: secreted, short and long. The secreted forms are either alternative splice products (e.g. murine LRE, which contains only the first 14 exons of *lepr*) or proteolytic cleavage products of membrane-bound forms of LR. These secreted forms contain only extracellular domains that bind circulating leptin, perhaps regulating the concentration of free leptin [10].

Short forms (LRA, LRC and LRD in mice) and the long form (LRB in mice) contain exons 1–17 of *lepr* and

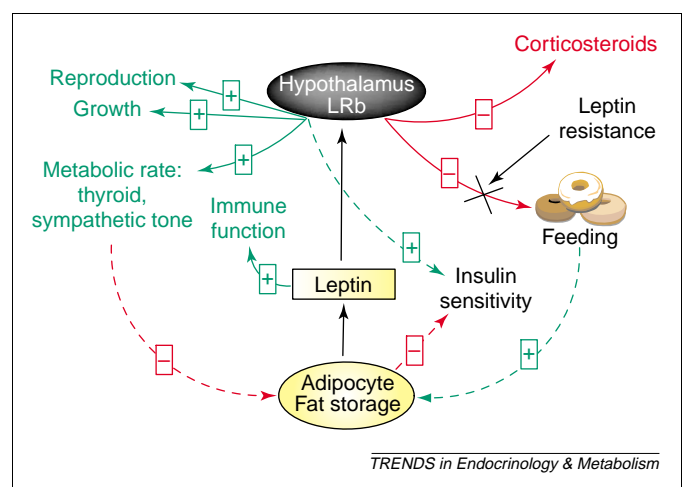


Figure 1. Leptin is secreted by adipocytes as a signal of fat storage. Leptin binds to the long form of the leptin receptor (LRB) in hypothalamic nuclei to increase metabolic rate and sympathetic tone and to enable the production of hormones required for thyroid function, reproductive function and growth. Leptin also acts to suppress feeding (thus reducing body weight) and the production of adrenal corticosteroids. Leptin increases the immune response, presumably by activating LRB on T cells. Leptin also increases insulin sensitivity by a poorly characterized CNS pathway as well as by the regulation of adipose mass. The poorly understood process of leptin resistance in obesity seems to selectively block the inhibition of feeding by leptin. Stimulatory pathways are in green and inhibitory pathways are in red.

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therefore have identical extracellular and transmembrane domains as well as the same first 29 intracellular amino acids, but then diverge in sequence because of alternative splicing of 3' exons. LRc contains only exons 1–17 and truncates three amino acids after the splice junction, whereas exons specific to LRa and LRd add five and 11 amino acids, respectively. LRc-specific and LRd-specific sequences are not well conserved between species. However, LRa (the most abundantly expressed isoform) is conserved, as is LRb, which has an intracellular domain of ~300 residues [8,9].

LRb is crucial for leptin action. Indeed, the *db/db* mice described originally lack only LRb because of a mutation that causes mis-splicing of LRb mRNA, but have a phenotype that is indistinguishable from that of *db^{3J}/db^{3J}* mice (which are deficient in all LR isoforms) and of leptin-deficient *ob/ob* animals [1,8,9]. The function of short-form LRs is less clear, although proposed roles include the transport of leptin across the blood–brain barrier [11,12].

Many of the effects of leptin are attributed to effects in the CNS, particularly in the basomedial hypothalamus, the site of highest LRb mRNA expression [13–15]. Here, leptin acts on neurons that regulate levels of circulating hormones (e.g. thyroid hormone, sex steroids and growth hormone) [13,16]. Leptin action on these hypothalamic neurons also regulates the activity of the autonomic nervous system, although direct effects of leptin on neurons in the brainstem that contain LRb probably also has an important role [17]. The effects of leptin on the immune system appear to result from direct action on T cells that contain LRb [4]. Leptin might also regulate glucose homeostasis independently of effects on adiposity; leptin regulates glycemia at least partly via the CNS, but it might also directly regulate pancreatic β -cells and insulin-sensitive tissues [18–21].

Leptin resistance and obesity

Over 25% of adults in the U.S.A. are obese and the incidence of obesity continues to rise in industrialized nations. Obesity is a major risk factor for type 2 diabetes mellitus, cardiovascular disease and some forms of cancer [22]. Because administration of leptin to rodents decreases food intake and increases energy expenditure, which results in loss of fat mass, leptin was initially hailed as a potential cure for obesity [1,2,8,13,16]. However, with the exception of humans with a rare genetic form of leptin deficiency, circulating leptin levels correlate with body mass index and total body-fat mass. Hence, obese individuals have elevated circulating leptin levels that fail to mediate weight loss, which indicates that in most humans obesity represents a form of leptin resistance. Indeed, although therapy with exogenous leptin does augment weight loss, the effects of leptin are modest at the doses tested. Several potential mechanisms have been postulated to underlie leptin resistance, including defects in leptin access to the brain, LRb signaling and pathways or neurons that mediate downstream leptin action. Indeed, although signal transducer and activator of transcription-3 (STAT3) signaling in response to circulating leptin is impaired in several rodent models of obesity,

administration of high concentrations of leptin directly into the brain activates STAT3 normally in obese rodents [11]. Because leptin might be able to access the basomedial hypothalamus without active transport across the blood–brain barrier [23], we theorize that a defect in signaling that is overcome by the administration of concentrated leptin underlies this leptin resistance.

LR signaling

LRb mediates JAK2 activation

The LR belongs to the interleukin 6 receptor family of class 1 cytokine receptors. These contain an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling domain [8,24]. Cytokine receptors have no intrinsic enzymatic activity, but signal via a noncovalently associated member of the Janus kinase (JAK) family of tyrosine kinases [25,26]. Four members of the JAK family have been identified (JAK1–3 and Tyk2). JAK1, JAK 2 and Tyk2 are widely distributed, whereas JAK3 occurs only in cells of the hematopoietic and immune systems. LRb associates preferentially with and activates JAK2, which is required for LRb signaling [27]. Unliganded LRb exists as a preformed homodimer; leptin binding alters the conformation of this, which enables transphosphorylation and activation of intracellular, LRb-associated JAK2 [8,28,29]. Activated JAK2 phosphorylates other tyrosine residues in the LRb–JAK2 complex to mediate downstream signaling [30,31].

All functional cytokine receptors contain a proline-rich 'Box 1' motif that is required for interaction with and activation of JAKs. Additional, less well-conserved sequences (sometimes referred to as 'Box 2') that are C-terminal to Box 1 are also important for interactions with JAKs and probably function in selectivity for JAK isoforms [24,25]. In the case of LRb, intracellular residues 31–36 (i.e. immediately downstream of the alternative splice junction after intracellular amino acid 29) compose Box 2 [27]. Homology between the Box 2 regions of LRb and other JAK2-associated cytokine receptors indicates that a loosely conserved [E/N]_{x0–2}[E/N]_{x0–2}[L/I] motif mediates association with JAK2 [27]. This motif is not present in the short LR isoforms, which explains the inability of these molecules to mediate leptin action in *db/db* animals [8,27,30].

Phosphotyrosine-dependent signaling by LRb

Tyrosine kinase-dependent signaling generally proceeds via phosphotyrosine-dependent recruitment of signaling proteins that contain specialized phosphotyrosine-binding domains, such as Src homology 2 (SH2) domains [32]. Each specific type of SH2 domain recognizes phosphotyrosine in a specific amino acid context. Thus, although tyrosine phosphorylation acts as a molecular switch that recruits proteins that contain SH2 domains, each tyrosine phosphorylation site recruits only specific proteins because the SH2 domains recognize the surrounding amino acids as well as the phosphotyrosine residue [33]. For example, the SH2 domain of the latent transcription factor, STAT3, is recruited to phosphotyrosine in the context of a Y(P)xxQ motif, and phosphatidylinositol 3-kinase (PI 3-kinase) is recruited to Y(P)MxM motifs [33,34].

Thus, the tyrosine phosphorylation sites on LRb and JAK2, and the SH2-containing proteins that they recruit must be defined to understand signaling by the LRb–JAK2 complex. There are three conserved tyrosine residues on the intracellular domain of LRb, Tyr985, Tyr1077 and Tyr1138 [8,30,31]. Tyr985 and Tyr1138 are phosphorylated during LRb signaling but Tyr1077 is not and does not contribute to signaling [31].

There are, thus, three primary intracellular signaling pathways that emanate from LRb (Figure 2): from tyrosine phosphorylation sites on JAK2; from Tyr985 of LRb; and from Tyr1138 of LRb. The phosphorylation of Tyr985 creates a binding site for the C-terminal SH2 domain of the SH2 domain-containing phosphatase (SHP) tyrosine phosphatase, recruitment of which results in its tyrosine phosphorylation and the recruitment of GRB2, the first step in the canonical p21ras–extracellular-signal-regulated kinase (ERK) signaling pathway. Whereas Tyr985 mediates most ERK stimulation during LRb signaling, a small amount of ERK activity occurs independently of LRb phosphorylation, presumably via tyrosine phosphorylation sites on JAK2 [27,31,35].

Phosphorylation of Tyr1138 recruits STAT3 to the LRb–JAK2 complex, which results in tyrosine phosphorylation and subsequent nuclear translocation of STAT3 to mediate transcriptional regulation [30,31]. STAT3 mediates the transcription of *socs3* [which encodes the SH2 domain-containing feedback inhibitor, suppressor of cytokine signaling 3 (SOCS-3)], as well as other genes [31,36].

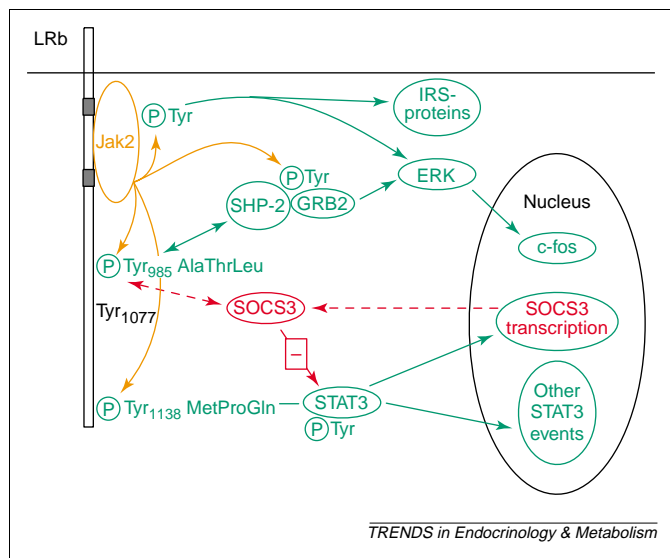


Figure 2. Binding of leptin to the long form of the leptin receptor (LRb) activates the associated Janus kinase 2 (JAK2) tyrosine kinase, which, in turn, phosphorylates Tyr985 and Tyr1138 of the intracellular tail of LRb. Phosphorylated Tyr985, within a Tyr-Ala-Thr-Leu motif, recruits SHP-2, which becomes phosphorylated, recruits GRB2 and activates the extracellular-signal-regulated kinase (ERK) signaling pathway. Phosphorylated Tyr1138, within a Tyr-Met-Pro-Gln motif, recruits signal transducer and activator of transcription-3 (STAT3). This results in tyrosine phosphorylation of STAT3 and its subsequent nuclear translocation and transcriptional activation mediates the translation of several genes including that of the feedback inhibitor, suppressor of cytokine signaling-3 (SOCS3). SOCS3 binds to LRbTyr985 to mediate feedback inhibition of LRb–STAT3 signaling. Multiple signals emanate directly from JAK2, including insulin receptor substrate (IRS)-proteins and weak activation of the ERK pathway (compared to that mediated via Tyr985). Much remains to be learned about the nature of JAK2-dependent signals. Orange arrows indicate JAK2-dependent phosphorylation, green denotes positive downstream signals and red indicates inhibitory pathways. Double arrows indicate interactions. Dashed lines indicate late signaling events.

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SOCS-3 binds to Tyr985 of LRb to mediate inhibition of LRb–STAT3 signaling [37]. Tyrosine phosphorylation of JAK2 during LRb stimulation mediates some signals independently of tyrosine phosphorylation sites on LRb [e.g. a portion of ERK activation and phosphorylation of insulin receptor substrate (IRS)-proteins] [31]. However, most JAK2 tyrosine phosphorylation sites have not yet been defined, which impairs our understanding of the mechanisms by which JAK2-dependent signals are mediated.

Leptin regulation of neural networks and neurophysiology

LRb is present in several tissues, with the highest levels in neurons of the nuclei of the basomedial hypothalamus, including the arcuate (ARC), dorsomedial hypothalamic (DMH) and ventromedial hypothalamic (VMH) nuclei [14,15]. Chemical and physical ablation of these nuclei results in increased feeding and neuroendocrine abnormalities that are similar to the phenotypes of *db/db* and *ob/ob* mice. This indicates that these hypothalamic nuclei, which make up the so-called ‘satiety center’, are crucial sites of leptin action [13,38].

Within these basomedial hypothalamic nuclei, LRb mRNA is expressed most highly in the ARC, where it is found in at least two distinct populations of neurons (Figure 3). One population synthesizes neuropeptide Y (NPY) and agouti-related peptide (AgRP) and the other synthesizes pro-opiomelanocortin (POMC) [13,38]. POMC is processed to produce the powerful anorectic (appetite-suppressing) peptide α melanocyte-stimulating hormone (α MSH) in LRb/POMC neurons. LRb stimulates the

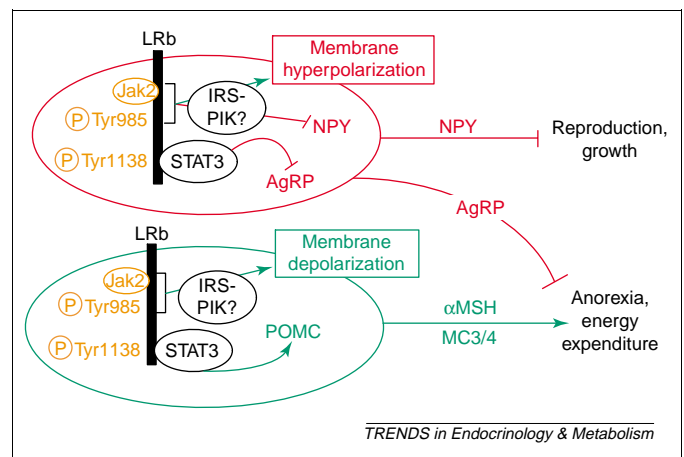


Figure 3. A model of the involvement of signaling by LRb in the control of hypothalamic neuropeptides and physiology. In arcuate neurons that co-express LRb and POMC, leptin increases POMC production via STAT3, which generates an anorectic signal via α MSH, MC3R and MC4R. In neurons that express LRb, NPY and AgRP, leptin inhibits AgRP production, partly via the LRb–STAT3 pathway, which disinhibits melanocortin signaling. Leptin inhibits NPY expression independently of STAT3 signaling, perhaps via the IRS–PI 3-kinase pathway (IRS–PIK). The regulation of membrane potential in both populations of LRb-expressing neurons is probably independent of the LRb–STAT3 signal. Elevated NPY levels (suppressed by leptin) contribute to the regulation of feeding and energy expenditure but strongly inhibit the function of the reproductive and growth axes. Melanocortins stimulate anorexia and energy expenditure. Green arrows denote positive signals and red bars indicate inhibition by leptin. Abbreviations: AgRP, agouti-related peptide; α MSH, α melanocyte-stimulating hormone; LRb, long form of the leptin receptor; MC3R and MC4R melanocortin receptors; NPY, neuropeptide Y; PI 3-kinase, phosphoinositol 3-kinase; POMC, pro-opiomelanocortin; STAT3, signal transducer and activator of transcription-3.

synthesis of POMC and activates LRb/POMC neurons [38,39]. AgRP inhibits α MSH signaling and NPY is an orexigenic (appetite-stimulating) hormone that also suppresses the central LRb-mediated growth and reproductive axes [40–43]. Leptin acts via LRb to inhibit NPY/AgRP neurons and suppress expression of these neuropeptides. Thus, LRb signaling stimulates the production of anorectic neuropeptides and suppresses levels of orexigenic peptides. Conversely, a decrease or deficiency in leptin activity (e.g. during starvation and in *ob/ob* and *db/db* mice) stimulates appetite by suppressing synthesis of anorectic neuropeptides (e.g. POMC) and increasing expression of orexigenic peptides (e.g. NPY and AgRP) [13,38]. In the ARC, neurons that express LRb mRNA, NPY/AgRP and/or POMC also regulate energy expenditure and other elements of neuroendocrine function [3], and other distinct populations of LRb mRNA-expressing neurons might also exist in this nucleus. The neurochemical properties of neurons in the DMH, VHM and elsewhere (including the brainstem) that express LRb mRNA are poorly understood.

LRb signaling in the regulation of physiology

The IRS–PI 3-kinase pathway in the control of energy balance

To date, two LRb signaling pathways have been implicated in leptin action. These are STAT3 (see below) and the IRS–PI 3-kinase pathway. First described as insulin-receptor substrates, IRS proteins (IRS-1–4), are members of a class of intracellular signaling molecules, termed docking proteins, that are phosphorylated by several tyrosine kinases, including insulin receptors and some cytokine receptors [44]. Docking proteins, including the IRS proteins, are devoid of enzymatic activity, but are phosphorylated on multiple tyrosine residues to mediate SH2-protein recruitment and downstream signaling. Although IRS proteins contain tyrosine phosphorylation sites in numerous motifs that recruit several SH2-proteins, most occur in YMXM motifs that bind and activate PI 3-kinase.

The first indirect evidence for a potential role of the IRS–PI 3-kinase pathway in leptin action came from the phenotype of IRS-2-null (IRS-2^{-/-}) mice [45]. In addition to other defects, IRS-2^{-/-} animals display increased feeding and decreased metabolic rate in the presence of increased adiposity and circulating leptin. Although this indicates functional leptin resistance, it is not as severe as in *db/db* animals. No such phenotype has been noted in animals that lack any of the other three IRS proteins [46].

Preventing PI 3-kinase activity is thought to abrogate leptin-mediated hyperpolarization (inhibition) of LRb, NPY and AgRP-containing hypothalamic neurons [47,48]. Furthermore, leptin stimulates IRS-2-associated PI 3-kinase activity in the hypothalamus and pharmacological blockade of PI 3-kinase activity in the hypothalamus blocks the anorectic effect of leptin *in vivo* [49]. PI 3-kinase activity is also required for regulation of sympathetic nervous system function by leptin [50].

LRb stimulation mediates the tyrosine phosphorylation of IRS proteins and activation of the PI 3-kinase pathway

[49], presumably via tyrosine phosphorylation sites on JAK2. However, recruitment of IRS proteins and PI 3-kinase by JAK2 is less robust than by the insulin receptor. Indeed, animals in which the expression of neuronal insulin receptors is decreased (NIRKO mice) have a modest obesity phenotype similar to that of IRS-2^{-/-} mice [51]. Insulin activates the IRS-2–PI 3-kinase pathway in the hypothalamus of these animals and PI 3-kinase activity is required for the anorectic activity of insulin in the brain [52]. Thus, both leptin and insulin stimulate hypothalamic IRS-2–PI 3-kinase signaling and both require PI 3-kinase activity for their anorectic effects. Although the relative contributions of insulin and leptin in stimulating PI 3-kinase and functional (anorectic) hypothalamic signaling are difficult to assess, the importance of the IRS-protein–PI 3-kinase pathway is clear. It will be interesting to determine the role of this pathway in leptin resistance. The neuropeptide profile of the neurons in which PI 3-kinase mediates the anorectic actions of leptin and insulin and the role of PI 3-kinase in other leptin functions (e.g. neuroendocrine and immune regulation) also need to be determined.

LRb signaling via STAT3 mediates a subset of leptin actions

The contribution of the LRb–STAT3 pathway to physiological processes has been addressed directly by studying homologously targeted ‘knock-in’ mice in which LRb is replaced by a mutant LRb that contains a Tyr1138Ser substitution in the STAT3 binding site (LRbY1138S) [43]. Although LRbY1138S does not activate STAT3 during leptin signaling, it regulates all other LRb signaling pathways normally. Although it is possible that Tyr1138 of LRb mediates other signals, there is no evidence of this, and the knock-in approach ensures that the expression pattern and levels of LRbY1138S are the same as that of wild-type LRb. This system has several advantages over other approaches, such as the ablation of STAT3 using Cre recombinase [53]. Currently, it is technically difficult to stimulate the synthesis of cre in LRb-containing neurons. Furthermore, even if STAT3 ablation was specific for LRb-containing neurons, it would not only affect LRb function because STAT3 is also required for signaling by numerous receptors that are crucial to brain function.

Similar to *db/db* animals, mice that are homozygous for LRbY1138S (*s/s*) have hyperphagia and decreased energy expenditure, which results in massive early-onset obesity that is associated with increased serum leptin levels. The high circulating leptin levels in *s/s* animals correlate with increased adipose mass and indicate resistance to the energy homeostatic effects of leptin [43]. However, important differences exist between the phenotypes of *s/s* mice (missing only the LRb–STAT3 signal) and *db/db* mice (devoid of all leptin signals) [43]. Whereas *db/db* animals are infertile and demonstrate decreased linear growth, *s/s* mice retain relatively normal gonad function and demonstrate increased linear growth compared with wild-type animals.

Analysis of neuropeptide expression reveals that, similar to *db/db* mice, *s/s* mice have decreased levels of POMC mRNA and increased AgRP mRNA in the

hypothalamus [43]. By contrast, NPY mRNA is induced dramatically in the hypothalamus of *db/db* animals but is near normal in *s/s* animals. These data indicate that LRb–STAT3 signaling is a crucial regulator of hypothalamic melanocortin action, and that dysregulated melanocortin signaling (as opposed to alterations in NPY) accounts for the obesity of *s/s* animals. Hence, LRb–STAT3 signaling does not appear to regulate the expression of NPY mRNA in the hypothalamus and non-STAT3-mediated LRb signals are crucial regulators of NPY expression in LRb/NPY-containing neurons. Additionally, STAT3 is probably not involved in the leptin-mediated regulation of membrane potential in ARC neurons because this effect occurs too rapidly to be mediated by the transcriptional action of STAT3 [47,39].

These results are consistent with the proposed role for NPY in suppressing the hypothalamic growth and gonadal axes. Thus, the increased NPY signaling in *ob/ob* and *db/db* mice might increase feeding only modestly, but might be primarily responsible for infertility and growth retardation in these mouse models. Indeed, the phenotype of *ob/ob* mice that are null for NPY (*ob/ob Npy*^{-/-}) has important similarities with the *s/s* phenotype [54]: the hypothalamic/gonadal axis is restored in both and there is increased linear growth with only modestly attenuated obesity compared with *ob/ob* and *db/db* mice. Similarly, other animals with disruptions in melanocortin signaling caused by either expression of melanocortin antagonists or disruption of melanocortin receptors display obesity and increased linear growth. The increased linear growth observed in these models probably results from decreased release of NPY, either alone or in combination with the disrupted melanocortin action inherent in these models, caused by the hyperleptinemia that results from obesity [43,54,55].

The phenotype of *s/s* animals does not indicate that non-STAT3 pathways are physiologically irrelevant, but that STAT3 signaling is important for the regulation of energy homeostasis. We suggest that the JAK2–IRS–PI 3-kinase pathway represents a major STAT3-independent mediator of LRb action. Data from numerous laboratories indicate that PI 3-kinase activity regulates the membrane potential in LRb/NPY neurons [48,56]. Similarly, PI 3-kinase activity might control membrane potential in LRb/POMC neurons. Although untested, one hypothesis is that PI 3-kinase activity might control the repression of NPY by LRb. However, we cannot rule out the possibility that signals mediated by phosphorylation of Tyr985 of LRb and the subsequent binding of SHP-2 could control NPY expression and/or membrane potential. Furthermore, other uncharacterized signals mediated by tyrosine phosphorylation sites on JAK2 might also be involved.

Returning to the concept of leptin resistance in common forms of obesity, we expect that dysregulation of the NPY pathway should result in neuroendocrine abnormalities (e.g. infertility or growth retardation) that are not generally observed in obesity. By contrast, alterations in STAT3-mediated pathways (e.g. melanocortin action) could generate a phenotype in which impaired energy balance is coupled with relatively normal neuroendocrine function.

Leptin signaling and physiology: the state of the field

Leptin binding to LRb activates intracellular signaling pathways via phosphorylation of several tyrosine residues on JAK2 and of Tyr985 and Tyr1138 on the intracellular tail of LRb. The JAK2–IRS–PI 3-kinase signal is important for the regulation of membrane potential in LRb-containing neurons in the hypothalamus and is crucial for the control of appetite and sympathetic nervous system function by leptin. However, the function of this pathway in most other aspects of neuroendocrine function is untested. The Tyr1138–STAT3 signal is also important in the regulation of feeding but is not required for the regulation of other hypothalamic functions of leptin, such as the control of reproduction and growth.

A great deal more work is required to fully understand the contributions of PI 3-kinase and Tyr1138–STAT3 signaling to the regulation of neuroendocrine function by leptin, as well as potential interactions between these two pathways. The analysis of the role of other JAK2- and Tyr985-mediated signals in LRb action *in vitro* and *in vivo* is an important next step in understanding the mechanisms by which LRb regulates mammalian physiology. Furthermore, insulin and nutrients appear to regulate neurons that contain LRb [51,52,57,58] and it is vital to understand the interplay of these pathways with specific LRb-mediated signals.

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