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Leptin receptor signaling and the regulation of mammalian physiology

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Abstract

The adipocyte-derived hormone, leptin, signals the status of body energy stores to the central nervous system to regulate appetite and energy expenditure. A specific long-form leptin receptor (LepRb), a type I cytokine receptor, mediates leptin action on LepRb-expressing neurons in the brain. Leptin binding to LepRb activates the associated Jak2 tyrosine kinase to promote the phosphorylation of Jak2 and three residues on LepRb; each of these sites mediates a distinct aspect of downstream LepRb signaling, with differing physiologic functions. Tyr₁₁₃₈→STAT3 signaling suppresses feeding, but is not required for a number of other leptin actions. Tyr₉₈₅ binds SHP2 and SOCS3 and primarily mediates the attenuation of LepRb signaling in vivo. The role for Tyr₁₀₇₇, the major regulator of STAT5 during leptin signaling, in the physiologic response to leptin remains unclear, although the obese phenotype of animals deleted for STAT5 in the brain suggests the potential importance of this signaling pathway. Leptin also modulates a number of other signaling pathways in the brain, including PI 3-kinase, mTOR, and AMPK; the pathways by which leptin controls these signals remain unclear, however, and may involve some indirect mechanisms. Important issues regarding leptin action and LepRb signaling in the future include not only the more thorough analysis of intracellular signaling pathways, but the neural substrate by which leptin acts, since most major populations of LepRb neurons remain poorly studied.

Obesity, energy balance, and leptin

Obesity, which increases the risk for a variety of diseases (including diabetes, heart disease, and cancer), affects more than 30% of the population in the United States and its prevalence continues to increase despite all efforts to oppose it (1–3). At its most basic level, obesity develops when energy intake exceeds energy utilization. Ideally, the aggregate actions of a variety of hormones modulate energy intake (feeding) to precisely balance energy expenditure, resulting in relatively little change in body weight or adiposity over time. Of the hormones controlling energy balance, leptin plays a central role (4–7). Leptin, which is secreted by the adipose tissue at levels roughly proportional to fat content, communicates the repletion of peripheral energy stores to the brain, suppressing feeding and permitting/promoting energy expenditure via a variety of neuroendocrine and autonomic mechanisms. In the absence of leptin action, human patients and rodent models eat voraciously and reduce their energy expenditure to promote energy (fat) storage (4,8–10). The lack of leptin does not underlie common forms of obesity, however, as leptin levels are generally elevated in proportion to adipose mass; the failure of high circulating leptin levels in obesity to promote weight loss

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defines a state of so-called “leptin resistance,” the etiology of which remains poorly defined (11–13). It is thus crucial to understand the molecular and neural mechanisms by which leptin acts in order to determine potential pathophysiologic mechanisms underlying obesity.

Leptin receptor (LepRb) signaling

Leptin acts via a cell-surface leptin receptor (LepR) that is a member of the type I cytokine receptor family (14). Alternative splicing of the transcript from a single *Lepr* gene produces multiple LepR isoforms, but a single isoform (LepRb) appears to account for all of leptin action (14–17). While LepRb may be expressed in other tissues, central nervous system (CNS) LepRb accounts for the majority of leptin action (important exceptions include the immune system and the pancreatic beta cell) (18–23).

Within the brain, LepRb is expressed in a variety of regions, including the hypothalamus, the midbrain, and the hindbrain (24–27). While many hypothalamic nuclei contain LepRb-expressing neurons, two populations of LepRb neurons within the hypothalamic arcuate nucleus (ARC) define an important, well-understood and approachable neural circuit (24,28). Leptin promotes the expression and secretion of anorexigenic peptides derived from proopiomelanocortin (POMC) in POMC-expressing ARC neurons, while blocking the synthesis and secretion of orexigenic Agouti-related peptide (AgRP) and neuropeptide-Y (NPY) from ARC neurons that express these peptides. LepRb-expressing neurons in the ventromedial hypothalamic nucleus (VMH) and the ventral tegmental area (VTA) also regulate feeding (29–31), and many other large populations of LepRb-expressing neurons (in regions such as the dorsomedial hypothalamic nucleus (DMH), the lateral hypothalamic area (LHA), the ventral premammillary nucleus (PMv), and others) likely participate, as well (24–27).

Leptin binding to LepRb initiates a cascade of signaling events beginning with the activation of the constitutively receptor-associated Janus Kinase-2 (Jak2), a tyrosine kinase (Figure 1); this represents a crucial step, since LepRb has no intrinsic enzymatic activity of its own (14, 32). In addition to promoting the autophosphorylation of Jak2, the activation of Jak2 stimulates the phosphorylation of multiple residues on the intracellular domain of LepRb- Tyr₉₈₅, Tyr₁₀₇₇, and Tyr₁₁₃₈ (33). Each of these phosphorylation sites lies in a unique amino acid motif, and each of these residues thus recruits a distinct set of downstream signaling proteins when phosphorylated (Figure 1). In cultured cells, phosphorylated Tyr₉₈₅ recruits the SH2-containing tyrosine phosphatase-2 (SHP2; PTPN11) to mediate the first step in the activation of the extracellular signal regulated kinase (ERK) cascade (33–35). Phosphorylated Tyr₉₈₅ also binds the suppressor of cytokine signaling-3 (SOCS3) which serves as a negative regulator of LepRb signaling (36). Tyr₁₁₃₈ recruits the signal transducer and activator of transcription-3 (STAT3), a latent transcription factor that then becomes phosphorylated, translocates to the nucleus, and mediates the regulation of gene expression (34,37). Tyr₁₁₃₈→STAT3 signaling promotes the expression of SOCS3, as the afferent arm of a feedback loop that attenuates LepRb signaling (34,36,38). The phosphorylation of Tyr₁₀₇₇ promotes the recruitment, tyrosine phosphorylation and transcriptional activation of STAT5, although Tyr₁₁₃₈ may also play a minor role in the regulation of STAT5 phosphorylation (33,39). Leptin additionally regulates a number of other intracellular signaling pathways by mechanisms that remain to be clarified, including the activation of phosphatidylinositol kinase-3 (PI3K) and the mammalian target of Rapamycin (mTOR), and the inhibition of the AMP-dependent protein kinase (AMPK) (40–44).

The roles of Tyr₁₁₃₈ and Tyr₉₈₅ in leptin action in vivo

We have probed the function of specific LepRb tyrosine residues/signaling pathways *in vivo* by the generation and study of homologously targeted “knock-in” mice in which sequences encoding substitution mutants of specific LepRb phosphorylation sites replace the endogenous

LepR allele (45,46). This approach expresses *LepRb* mutants from the *LepR* locus, ensuring their correct level and site of expression. This ongoing analysis has revealed a crucial role for Tyr₁₁₃₈ in the regulation of feeding and overall energy expenditure, but has also revealed that this signaling pathway is not required for the fertility, immune function, the regulation of glucose homeostasis, or several other leptin actions (45,47–50). The finding of similarly dysregulated feeding and body adiposity in mice null for STAT3 in the CNS (*NStat3KO*) compared to those mutant for *LepRb* Tyr₁₁₃₈ is consistent with the role for the Tyr₁₁₃₈→STAT3 pathway in energy homeostasis (51). The infertility of *NStat3KO* mice, which contrasts with the reproductive competence of the Tyr₁₁₃₈ mutant animals, likely reflects the importance of neuronal STAT3 in the response to estrogen (and perhaps other factors), as well as leptin (52).

In contrast to the hyperphagic and obese phenotype of animals mutant for Tyr₁₁₃₈, mice carrying a mutation of Tyr₉₈₅ demonstrate a lean phenotype with exaggerated leptin sensitivity (46). Additionally, animals mutant for *LepRb* Tyr₉₈₅ exhibit normal neuroendocrine function. Thus, *in vivo*, the major role of Tyr₉₈₅ appears to be in the attenuation of *LepRb* signaling, presumably via the SOCS3-mediated feedback loop. The physiologic role for SHP2-mediated signaling in *LepRb* action thus remains unclear.

Leptin-dependent STAT5 signaling and the role of neuronal STAT5 in the regulation of energy homeostasis

A variety of cytokines and growth factors, including granulocyte macrophage colony stimulating factor (GM-CSF), growth hormone, prolactin, erythropoietin, and others promote the phosphorylation and transcriptional activation of STAT5 in cells expressing the cognate receptors for these ligands (reviewed in (53)). Recent data revealed that leptin promotes the phosphorylation and nuclear localization of STAT5 in the ARC of rodents (33,54), demonstrating that leptin activates STAT5 *in vivo* as well as in cultured cells and suggesting that *LepRb*→STAT5 signaling may contribute importantly to physiologic leptin action.

Although the two isoforms of STAT5, STAT5a and STAT5b, represent the products of distinct genes, they lie in close proximity, enabling the generation of a conditional *Stat5^{fl}* allele in which the coding regions for both STAT5 isoforms can be excised in a single event (55,56). Deletion of *Stat5^{fl}* in the hypothalamus or throughout the CNS of mice (via *RIP-cre* or *Nestin-cre*, respectively) results in modest obesity, suggesting an important role for STAT5 in the regulation of energy balance (53). It remains unclear whether the obesity of these mice reflects the role for STAT5 in leptin action *in vivo*, however, as many factors other than leptin also regulate STAT5. Indeed, the anorexic response to CNS GM-CSF treatment is attenuated in *Nestin-cre;Stat5^{fl}* animals, demonstrating that at least a portion of the phenotype of these animals likely follows from leptin-independent mechanisms (53). Furthermore, the neuroanatomical site at which STAT5 acts to mediate energy balance is not clear: *RIP-cre* and *Nestin-cre* mediate deletion in some (but not all) *LepRb*-expressing neurons and mediate excision in many non-*LepRb*-expressing neurons. Absence of STAT5 in the CNS does not alter mRNA expression of leptin's known targets within the ARC (i.e. POMC, AgRP, NPY) suggesting that other genes must represent the key transcriptional targets of STAT5 in the regulation of energy balance. STAT5 colocalizes with orexin (OX) neurons in the LHA in normal mice and OX neurons exhibit mild dysregulation in *Nestin-cre;Stat5^{fl}* mice, suggesting that STAT5 may play a role in the regulation of these neurons.

Regulation of the ribosome/translation and the mTORC1 pathway by leptin

An ancient and evolutionarily-conserved kinase that integrates nutritional and hormonal cues of energy sufficiency, mTOR is theoretically well-placed to sense and signal nutrient and

energy levels within the same neural circuits on which leptin acts to regulate energy balance (57,58). Two mTOR complexes exist: mTOR complex 1 (mTORC1, the most-studied and best understood of the complexes), which modulates protein synthesis by a variety of pathways, including via activating S6K1 to mediate the phosphorylation of ribosomal protein S6 and promote cap-dependent translation. Acute Rapamycin treatment specifically inhibits mTORC1.

Administration of leptin or amino acids to the rat CNS activates hypothalamic mTORC1, and intracerebroventricular (ICV) Rapamycin-mediated inhibition of hypothalamic mTORC1 blocks the anorectic effect of leptin or amino acid treatment (40). These findings reveal an important role for mTORC1 in neural circuits that control energy balance, and suggest an important role for mTORC1 in CNS leptin action. We have thus utilized our panel of LepRb variants mutant for specific phosphorylation sites/signaling motifs to explore the mechanisms by which LepRb regulates mTORC1 activity in cultured cells and *in vivo* (33).

While the intracellular signals promoted by LepRb in cultured HEK293 cells fail to meaningfully promote the mTORC1-dependent activation of S6K1, LepRb none-the-less promotes the phosphorylation of ribosomal protein S6 and cap-dependent translation in these cells (33). Furthermore, mutation of Tyr₉₈₅ blocks S6 phosphorylation and receptor-mediated protein translation, suggesting a potential role for the SHP2→ERK cascade, as opposed to mTORC1, in these effects. Indeed, Tyr₉₈₅- and ERK-dependent signals promote the phosphorylation of the alternate upstream regulator of S6 phosphorylation, the ribosomal S6 kinase (Rsk). Thus, at least in cultured cells, leptin poorly promotes the activation of mTORC1, but rather regulates ribosomal function and translation via the ERK→Rsk pathway.

In unpublished data, we have examined the regulation of mTORC1 by nutritional cues and leptin in the ARC of mice by the immunohistochemical detection of S6 phosphorylation (pS6-ir). This analysis confirmed the finding of the Seeley group that leptin modestly increases the number of pS6-ir neurons in the ARC, but also revealed (somewhat counterintuitively) the dramatic activation of S6 phosphorylation during fasting and leptin deficiency. In both instances, ICV Rapamycin treatment inhibited the ARC pS6-ir, revealing its TORC1-dependence. The increased mTORC1/jpS6-ir in states of fasting, leptin deficiency, and LepRb mutation colocalized to a large extent with AgRP neurons and correlated with the activity of these neurons. Indeed, the orexigenic hormone, ghrelin, which depolarizes AgRP neurons promotes pS6-ir and c-fos-ir in these neurons. Thus, the regulation of mTORC1 by leptin and nutrition in the basomedial hypothalamus appears to be more complex than initially thought, and is cell-type and -condition-dependent. Much of the regulation of mTORC1 in the ARC may not be the direct result of LepRb signals, but rather secondary to alterations in neuronal activity, calcium influx, or the like.

Future directions

While we have learned a great deal about LepRb signaling and leptin action over the past few years, many additional questions remain. Clearly, additional animal models are needed to decipher the role of Tyr₁₀₇₇ and the physiological function of STAT5 in the hypothalamus in energy balance and specifically in leptin action. Mice with knock-in mutations of LepRb-Tyr residues have been studied and provided great insight into the individual physiological roles of these specific sites. A similar mouse model would be useful to better understand the mechanisms controlling other aspects of leptin action such as reproduction, glucose control, growth and neuronal plasticity via pathways mediated by Tyr₁₀₇₇ alone or in collaboration with Tyr₁₁₃₈.

As importantly, there yet remains an important and physiologically significant set of leptin signals for which we do not understand the mechanism(s) of LepRb-mediated regulation. While

we have made progress in understanding some of the complexities of mTORC1 regulation, and while others have demonstrated the importance of PI 3-kinase signaling in the regulation of neuronal firing by leptin, the signaling mechanisms by which LepRb engages mTORC1, PI 3-kinase and AMPK remain imprecise. Additionally, while the importance of mTORC1 for anorectic signaling in the hypothalamus is clear, the cellular mechanisms by which mTORC1 mediates these effects remain unknown. While mTORC1 does not appear to play a role in neuronal activity, some investigators have suggested an important role for mTORC1 in the regulation of dendritic physiology and plasticity (59,60).

Perhaps most importantly, however, while it is clear that ARC AgRP and POMC neurons play important roles in the physiologic response to leptin, it is equally clear that these (and other ARC populations) cannot account for all, or even most, of leptin action (61–63). Indeed, ARC LepRb neurons account for only approximately 20% of the total number of LepRb neurons in the brain (27). Thus, defining the molecular phenotypes and physiologic functions of the remaining poorly understood LepRb neurons throughout the brain remains the most pressing need for the future.

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Figure 1.

Mechanisms of LepRb signaling. Leptin binding to LepRb activates the Jak2 tyrosine kinase to initiate tyrosine-phosphorylation-dependent signal transduction pathways. In cultured cells, Tyr₉₈₅ activates the SHP2/ERK cascade which activates RSK and the ribosomal protein S6 to promote translation (and which may modulate neuronal plasticity). Tyr₉₈₅ also serves as a binding site for SOCS3 to inhibit LepRb signaling. Activation of Tyr₁₀₇₇ and Tyr₁₁₃₈ induces phosphorylation of STAT5 and STAT3, respectively (although Tyr₁₁₃₈ may also mediate a minor component of STAT5 phosphorylation), stimulating the translocation of STAT3 and STAT5 to the nucleus. While the pertinent transcriptional targets of STAT5 remain unknown, several STAT3 transcriptional targets have been identified, including SOCS3. We do not yet fully understand the mechanisms by which LepRb activates other signals, such as PI3K and mTORC1, in the hypothalamus.