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Central Leptin Receptor Action and Resistance in Obesity

Christian Bjørbæk, Ph.D.
Department of Medicine, Division of Endocrinology and Metabolism, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215

Abstract - Summary

The discovery of leptin in 1994 has lead to remarkable advances in obesity research. We now know that leptin is a cytokine-like hormone that is produced in adipose tissue and plays a pivotal role in regulation of energy balance and in a variety of additional processes via actions in the central nervous system. This symposium review covers current understandings of neuronal leptin receptor signaling, mechanisms of obesity-related leptin resistance in the central nervous system, and provides recent insights into the regulation of peripheral glucose balance by central leptin action in rodents.

Leptin, an adipocyte-derived hormone, acts principally on the central nervous system to activate its cognate receptor. The absence of leptin or of its receptor in *Lep*$^{ob/ob}$ mice or *Lepr*$^{db/db}$ mice respectively, results in morbid obesity, hyperphagia, neuroendocrine dysfunction, and severe hyperglycemia and insulin resistance (Coleman, 1978; Zhang et al., 1994; Ahima et al., 1996; Chen et al., 1996; Pelleymounter et al., 1995; Friedman and Halaas, 1998).

Leptin receptors are expressed in a number of specific brain regions (Bjorbaek and Kahn, 2004; Scott et al., 2009) and binding of leptin leads to regulation of a range of biological functions and processes, including energy intake and expenditure, body fat, neuroendocrine systems, autonomic function, and insulin and glucose balance (Ahima et al., 2000; Barsh et al., 2000; Friedman, 2000; Schwartz et al., 2000). While the specific function of each brain nucleus in leptin action is yet largely unknown, data suggest that distinct biological actions of leptin are mediated by different brain nuclei, but that overlapping or redundant functional sites also exist. The arcuate nucleus of the hypothalamus (ARC) is a key area for mediating leptin actions on energy homeostasis. Consistent with this, leptin receptor mRNA is densely expressed in the ARC of mice and rats (Elmquist et al., 1998; Mercer et al., 1996), and injection of leptin directly into the ARC is sufficient to acutely reduce food intake (Satoh et al., 1997). Moreover, restoration of leptin receptor expression in the ARC of leptin receptor deficient *Lepr*$^{db/db}$ mice leads to long term reduction of body weight and food intake (Coppari et al., 2005), and arcuate nucleus-specific *Lepr* gene therapy is sufficient to attenuate the obesity phenotype of leptin receptor deficient Koletsky *fa*^{k}/ *fa*^{k} rats (Morton et al., 2003).

The ARC contains at least two subsets of leptin responsive neurons, namely the anorexigenic POMC neurons and the orexigenic Agouti-related peptide (AgRP) neurons. POMC neurons are depolarized by leptin, leading to release of α-melanocyte stimulating hormone (α-MSH), a POMC-derived neuropeptide that mediates its anorexigenic effects through activation of melanocortin receptors (Cone, 2005; Cowley et al., 2001; Schwartz et al., 2000). AgRP is a melanocortin receptor antagonist that potently stimulates feeding (Ollmann et al., 1997). Consistent with this, AgRP neurons are inhibited by leptin, resulting in a reduction in AGRP

Division of Endocrinology and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, E/CLS-734, Boston, MA 02215 Phone : 617 735 3205 Fax : 617 735 3323 cbjorbae@bidmc.harvard.edu.

neuropeptide release (van den Top et al., 2004). Mice lacking leptin receptors only in POMC or AgRP neurons are mildly obese, demonstrating that both groups of cells are required for maintenance of body weight homeostasis by leptin (Balthasar et al., 2004; van de Wall et al., 2007). Further, re-expression of leptin receptors in exclusively in POMC neurons of the receptor-deficient $Lepr^{db/db}$ mice modestly reduces body weight and caloric intake (Huo et al., 2009). The modest body weight changes observed in these studies compared with the morbid obesity in $Lepr^{db/db}$ mice that lack all functional leptin receptors, demonstrates that neurons apart from POMC and AgRP neurons are also important for body weight regulation by leptin.

In addition to the hypothalamic arcuate nucleus, neurons that express leptin receptors are found in a number of other hypothalamic and in extra-hypothalamic brain nuclei (Bjorbaek and Kahn, 2004; Scott et al., 2009), and progress has been made in understanding their roles in leptin action. For example, leptin signaling the ventro-medial hypothalamic nucleus (VMH) can, like the arcuate nucleus, mediate acute caloric intake suppression (Satoh et al., 1997) and long-term weight loss (Dhillon et al., 2006). Further, the VMH may serve a role in regulation of the autonomic nervous system by leptin (Satoh et al., 1999). In addition, leptin signaling in thyrotropin-releasing hormone (TRH) neurons within the paraventricular hypothalamic nucleus of rats may account, at least in part, for leptin's effects on the thyroid axis (Leachan and Fekete, 2006; Hollenberg, 2008). Furthermore, the ventral premammillary nucleus (PMV) is likely critical for leptin's action on the neuroendocrine gonadal axis and reproduction (Donato et al., 2009). Leptin receptors are also expressed in the ventral tegmental area (VTA) of the mid brain. Specifically, leptin directly targets dopamine neurons of the VTA, suggesting that leptin can affect critical brain reward circuitries (Fulton et al., 2006). Indeed, injection of leptin directly into the VTA reduces food intake and stimulates locomotor activity (Hommel et al., 2006). The nucleus tractus solitarius (NTS) located in the caudal hindbrain is a major projection zone for sensory nerve input from the gastro-intestinal system and contains leptin-regulated neurons (Huo et al., 2006). Interestingly, these latter neurons are also responsive to gastric distention in rats (Huo et al, 2008) and intraparenchymal-NTS administration of leptin acutely reduces food intake and body weight (Grill et al., 2002). These latter data combined suggest that the effects of leptin on food intake in the hindbrain may result from modulation of gastro-intestinal signal processing (Grill and Hayes, 2009). The effect of leptin on food intake thus appears to be mediated by leptin receptors in several nuclei within the hypothalamus, in part via reward-neurons located in the mid-brain, and in part by neurons in the NTS of the caudal brainstem. Future studies are needed to determine how different neurons mediate the same behavioral effects by leptin, or whether those neurons in fact serve specific and separate functions under different circumstances.

Leptin is structurally similar to cytokines consistent with its receptor belonging to the cytokine receptor class I superfamily (Tartaglia et al., 1995). Several isoforms of ObR exists, including a long signaling form (ObRb)(Lee et al., 1996). The murine ObRb receptor contains three conserved intracellular tyrosine residues, located at amino acid positions 985, 1077 and 1138 (Bjorbaek and Kahn, 2004). Tyrosine phosphorylation-sites provide binding motifs for src homology 2 (SH2)-domain containing proteins, such as STATs (signal transducer and activator of transcription). Leptin binding to its receptor activates Janus-tyrosine Kinase enzymes (JAK) that are constitutively associated with membrane-proximal regions of the receptor. JAK mediates leptin-dependent tyrosine phosphorylation of the leptin receptor itself (Bjorbaek et al., 1997). Phosphorylated Tyr1138 recruits the latent cytoplasmic transcription factor STAT3 facilitating its phosphorylation by JAK, followed by STAT3 dimerization and nuclear translocation (Leinninger and Myers, 2008). STAT3 plays a role in regulation of *POMC* and *AgRP* gene expression by leptin (Munzberg et al., 2003; Kitamura et al., 2006). In addition, we reported that leptin signaling via the STAT3 pathway rapidly induces hypothalamic expression of suppressor-of-cytokine-signaling-3 (SOCS-3), a potent inhibitor of leptin receptor signaling (Bjorbaek et al., 1998). SOCS-3 by binding to Tyr985 and inhibits JAK2

kinase activity, thereby acting in a negative feedback loop (Bjorbaek et al., 1999; Bjorbaek et al., 2001). Another key negative leptin-receptor regulator is protein-tyrosine-phosphotase-1B (PTP1B) which acts by directly inhibiting JAK2 kinase activity (Zabolotny et al., 2002; Lund et al., 2005; Bence et al., 2006). Tyr1077 has been reported to play a role in binding and activation of STAT5 (Gong et al., 2007; Mutze et al, 2007), but the downstream signaling events of this pathway are yet unknown. Phosphorylated Tyr985 of ObRb also binds SHP-2, a protein that participates in activation of ERK (MAPK) signaling and is important for *c-fos* transcriptional activation (Banks et al., 2000; Bjorbaek et al., 2001), and likely other events. The specific intracellular mechanisms whereby ObRb regulates intracellular signaling via other effector proteins such as insulin-receptor-substrate 2 (IRS2)(Niswender et al., 2001; Niswender et al., 2003; Pardini et al., 2006), phosphoinositol-3-kinase (PI3K) (Niswender et al., 2001; Rahmouni et al., 2003; Xu et al., 2005; Fukuda et al., 2008), mammalian target of rapamycin (mTOR)(Cota et al., 2006; Blouet et al., 2008), Fox01 (Kim et al., 2006; Kitamura et al., 2006), and AMP-activated protein kinase (AMPK)(Minokoshi et al., 2004; Carling 2007; Hayes et al., 2009; Claret et al., 2007), are currently less well understood. Further genetic and immunohistochemical studies are also required to determine whether these proteins are regulated only in first-order leptin-responsive neurons or in down-stream neuro-circuitries, or in both.

Genetic studies in mice demonstrate that signaling through Tyr1138 of the leptin receptor is required for normal regulation of energy balance. Specifically, mice with Tyr1138 mutated into a serine residue exhibit severe hyperphagia and obesity similar to that of $lepr^{db/db}$ mice (Bates et al, 2003). However in contrast to $lepr^{db/db}$ mice, Ser1138 mice are fertile, longer, and less hyperglycaemic, altogether indicating that STAT3 signaling is critical for leptin's regulation of caloric intake and whole body energy balance, but that signals other than STAT3 are likely important for other leptin actions such as reproduction. In more recent studies also using homologous recombination in mice leading to mutation of Tyr985 into a leucine residue, it was reported that female, but not male, animals had modestly reduced body weight and caloric intake, and were protected from high-fat diet-induced obesity (Bjornholm et al., 2007). The mice also showed increased leptin sensitivity and preservation of reproductive function. Thus, these data suggest that Tyr985 of the leptin receptor may serve to convey inhibition of leptin signaling thereby attenuating the anti-adiposity effects of leptin, especially in females. These data are consistent with *in vitro* signaling studies that strongly point to an inhibitory role of SOCS-3 acting via Tyr985. However, since Tyr985 recruits both SHP2 and SOCS3, either of these proteins could theoretically underlie the lean, leptin-sensitive phenotype. Alternatively, it may be speculated that since the lean phenotype is quiet modest and is only present in one gender that SOCS-3 and SHP2 may have opposite functions with regard to regulation of whole body energy balance by leptin. Further studies are needed to investigate this possibility and to determine the specific cellular functions of individual receptor tyrosine residues, including that of Tyr1077, within each anatomically and chemically separate population of leptin-responsive neurons.

In addition to these global manipulations of leptin receptor signaling, several intracellular proteins down-stream of the leptin receptor have also been investigated with regard to their role in leptin action within specific neurons. For example, the STAT3 transcriptional factor has specifically been deleted from POMC and AgRP neurons in mice. In mice lacking STAT3 in POMC neurons, females exhibited reduced *pomc* gene expression, and a modest increase in fat mass and total body weight (Xu et al., 2007). The animals remained responsive to leptin-induced hypophagia and were not hypersensitive to development of increased weight given a high-fat diet. However, mutant mice failed to mount a normal compensatory refeeding response. These results suggest a role for STAT3 in transcriptional regulation of the *pomc* gene, consistent with previous *in vitro* studies of the *pomc* promoter (Munzberg et al., 2003), and indicate STAT3 expression in POMC neurons plays only a modest role in leptin's anti-obesity

actions. Removal of STAT3 or expression of a constitutive active form of STAT3 in AgRP neurons also demonstrates a requirement of STAT3 in those cells for normal energy balance (Gong et al., 2008; Mesaros et al., 2008). For example, deletion of STAT3 from AgRP neurons leads to a slight weight gain of the mice (Gong et al., 2008). These AgRP STAT3-deficient mice were also hyperleptinemic and exhibited high-fat diet-induced hyperinsulinemia. AgRP mRNA levels were unaffected. Behaviorally, mice without STAT3 in AgRP neurons were mildly hyperphagic and hyporesponsive to leptin's intake inhibitory actions. Combined, STAT3 in AgRP and POMC neurons is therefore required for normal energy homeostasis, but suggest that STAT3 signaling in other leptin-responsive neurons also play important roles in promoting leptin's anti-obesity effect. As might be predicted from earlier studies (Bjorbaek et al, 1998; Balthasar et al., 2004), deletion of SOCS-3 selectively from POMC neurons enhances leptin sensitivity, although weight gain with age was normal on a chow diet (Kievit et al., 2006). However on a high-fat diet, the rate of weight gain was reduced. Interestingly, on the chow diet where the body weights were normal, baseline glucose levels were reduced. This altogether supports a role of POMC neurons in leptin's control of glucose balance (Pelleymounter et al., 1995, Huo et al., 2009) and suggests a role of SOCS-3 in those cells in the increased weight response to a high-caloric diet (Munzberg et al., 2004; Enriori et al., 2007. In addition to those studies, the PI3K pathway has been examined in significant detail in POMC neurons. Mice with genetically disrupted PI3K signaling lack the normal response of leptin-induced POMC neuronal depolarization and increased firing frequency (Hill et al., 2008). In addition, the suppression of feeding elicited by leptin was blunted. Interestingly however, despite these alterations in POMC neuronal function, the mice had normal body weight. However in apparent contrast to these studies, inactivation of PTEN, a phosphatidylinositol3,4,5-trisphosphate (PIP3) phosphatase, specifically in POMC cells resulted in hyperphagia and a sexually dimorphic diet-sensitive obesity. Interestingly, and in contrast to the study by Hill et al., leptin failed to stimulate POMC electrical activity (Plum et al., 2006). Similar however to the study by Hill et al., leptin was not able to acutely inhibit caloric intake. Finally, younger mice with selective inactivation of 3-phosphoinositide-dependent protein kinase 1 (PDK1), an upstream activator of PI3K, in POMC-expressing cells display hyperphagia and increased body weight (Belgardt et al., 2008). The reasons for the electrical discrepancies between these studies of PI3K signaling in POMC neurons are yet unclear. The observed metabolic differences between the studies may relate to variable impacts on the activity of the hypothalamic-pituitary-adrenal axis, since the employed genetic-strategies also leads to gene-alteration in pituitary corticotrophs due to the activity of the POMC promoter driving CRE expression in those cells. Importantly, and in contrast to the studies of mice with leptin-receptor mutations or the cell-specific leptin receptor deletions or over-expression, the interpretation of metabolic data from mice with alterations of intracellular proteins (such as PI3K, PTEN, PDK1, and AMPK) suffers significantly from the fact that these proteins are regulated by many stimuli in addition to leptin. Furthermore, these enzymes affect a number of different signaling pathways that vary depending on the stimuli. It is therefore unclear whether the observed metabolic phenotypes are specifically due to alteration in leptin action or to changes in other signaling systems, or both.

Most mouse and rat strains develop obesity when given free access to a high-fat/high-carbohydrate containing diet. Such Diet-Induced-Obese (DIO) rodents are principal models of common type human obesity. Rodent and human obesity is characterized by hyperleptinemia and by leptin resistance that has yet to be understood (Frederich et al., 1995; Maffei et al., 1995). Leptin likely enters the brain via the blood-brain barrier (Bjorbaek, et al., 1998; Hileman et al., 2000; Banks, 2008) and decreased transport of leptin into the brain of DIO animals has been reported (Banks et al., 1999). However impaired blood-brain-barrier leptin transport may be acquired during development of obesity (Banks et al., 2003; Levin et al., 2004), suggesting that down-stream intracellular signaling defects may be primary causes of leptin resistance. Interestingly, phospho-STAT3 immunohistochemistry on brain sections from leptin-treated

DIO mice and rats have demonstrated regional differences in leptin sensitivity. Specifically, leptin signaling within the arcuate nucleus of the hypothalamus is dramatically decreased while other hypothalamic and extra-hypothalamic nuclei appear to remain relatively leptin sensitive (Munzberg et al., 2004). The decreased leptin signaling the arcuate nucleus includes POMC and AgRP neurons and is associated with altered release of these neuropeptides and with increased expression of SOCS-3 (Munzberg et al., 2004; Enriori et al., 2007). This suggests that the ARC is selectively leptin-resistant in DIO mice and may therefore play a direct role in the development of diet-induced obesity in rodents. SOCS-3 deficiency in the brain (Mori et al., 2004) and specifically in POMC neurons (Kievit et al., 2006) enhances leptin-induced weight loss and protects mice from development of diet-induced-obesity. Similarly, neuronal deletion of PTP1B increases leptin-sensitivity and attenuates weight gain of high-fat fed mice (Bence et al., 2006). Altogether, these data suggest that defects in leptin action specifically within the arcuate play a critical role in the pathogenesis of leptin-resistant obesity and that drugs aimed at ameliorating arcuate leptin-resistance might prevent the development of diet-induced obesity. The mechanism by which the arcuate become resistant to leptin and the process leading to increased SOCS-3 expression of DIO mice, and the causal-relationship between these events and the appearance of obesity, are critical issues that have yet to be resolved.

In addition to its role in energy homeostasis, leptin can regulate peripheral glucose and insulin balance via the central nervous system. For example, leptin-deficient $Lep^{ob/ob}$ mice exhibit profound diabetes that can be fully prevented after three-weeks of low doses of leptin that do not affect body weight and food intake (Pelleymounter et al., 1995). In addition, intracerebroventricular leptin can acutely stimulate glucose uptake in skeletal muscle (Cusin et al., 1998; Haque et al., 1999; Kamohara et al., 1997; Minokoshi et al., 1999) and inhibit hepatic glucose production (Pocai et al., 2005; van den Hoek et al., 2008). Moreover, leptin dramatically improves insulin sensitivity in human lipodystrophy and in lipodystrophic mouse models which are characterized by low serum leptin levels and by severe insulin resistance (Oral et al., 2002; Petersen et al., 2002; Shimomura et al., 1999). This combined suggests that leptin has an independent specific capacity to regulate glucose balance, but the neurons mediating this action have remained elusive.

Lack of central melanocortin receptor action in mice results in marked obesity, hyperinsulinemia, and late-onset hyperglycemia (Huszar et al., 1997), and insulin resistance is detectable before the onset of obesity in these melanocortin-4-receptor deficient mice (Fan et al., 2000). In addition, ventricular infusion of α-MSH enhances acute insulin-stimulated muscle glucose uptake and reduces hepatic glucose production, while a melanocortin receptor antagonist exerts opposite effects (Obici et al., 2001). Furthermore, loss of glucose-sensing by POMC neurons and subsequent glucose-dependent α-MSH release, leads to impaired whole body glucose tolerance (Parton et al., 2007). Moreover, genetic studies in diabetic mice suggest that the arcuate nucleus plays a major role in mediating effects of leptin on glucose balance (Coppari et al., 2005), however the specific arcuate neurons responsible remain unspecified.

Given that arcuate POMC neurons express leptin receptors and that both leptin and the melanocortin system can influence glucose homeostasis, we hypothesized that specifically POMC neurons mediate this leptin action, and recently reported that CRE-mediated expression of ObRb only in POMC neurons in the morbidly obese and severely diabetic leptin-receptor-deficient $Lepr^{db/db}$ mice, remarkably leads to a complete normalization of blood glucose levels (Huo et al., 2009). This occurred entirely independently of changes in caloric intake and body weight. In addition, insulin sensitivity was enhanced and hypothalamic α-MSH neuropeptide levels were greatly elevated in the transgenic mice. Based on these data we conclude that leptin signaling in POMC neurons is sufficient to prevent diabetes in $Lepr^{db/db}$ mice, and that this action might be mediated by the central melanocortin pathway. Future studies are needed to

explain how deletion of leptin receptors in POMC of normal mice does not lead to significant impairments in glucose balance (Balthasar et al., 2004), but that re-expression of receptors in POMC neurons of diabetic *Lepr*$^{db/db}$ mice leads to this dramatic correction of blood sugar levels (Huo et al., 2009). Regardless, POMC neurons and their down-stream neuro-circuitries hold promise for identifying novel pathways which may eventually help develop anti-diabetes drugs for humans suffering from severe insulin-resistant diabetes and morbid obesity.

Future Perspectives

Important questions and future area's of research include: a) Determination of the role of individual brain nuclei and specific neuronal groups in each of leptin's actions; b) Identification of the mechanism underlying the redundancy of different brain regions each capable of mediating leptin's effects on intake inhibition; c) Studies aimed at explaining how different groups of neurons have additive effects on body weight regulation; d) Experiments directed towards increasing our understanding of how leptin receptor re-expression in POMC neurons of diabetic *Lepr*$^{db/db}$ mice appears to play a major role in glucose control, while deletion of the receptor from POMC neurons in normoglycemic lean mice does not lead to impairment of glucose homeostasis; e) Elucidation of the specific neuro-circuitries downstream of POMC neurons and the peripheral processes responsible for the control of blood glucose by leptin in *Lepr*$^{db/db}$ mice; f) Identification of specific roles and relative importance of individual intracellular leptin receptor signaling pathways in neuronal functions, including regulation of electrical activity, neuro-modulation, and gene expression; and g) Determination of the primary causes of diet-induced obesity and the role of leptin resistance in its development.

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