Review Article

Leptin therapy, insulin sensitivity, and glucose homeostasis

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ABSTRACT

Glucose homeostasis is closely regulated not only by insulin, but also by leptin. Both hormones act centrally, regulating food intake and adiposity in humans. Leptin has several effects on the glucose-insulin homeostasis, some of which are independent of body weight and adiposity. Those effects of leptin are determined centrally in the hypothalamus and peripherally in the pancreas, muscles and liver. Leptin has beneficial effects on the glucose-insulin metabolism, by decreasing glycemia, insulinemia and insulin resistance. The understanding of the effects of leptin on the glucose-insulin homeostasis will lead to the development of leptin-based therapies against diabetes and other insulin resistance syndromes. In these review, we summarize the interactions between leptin and insulin, and their effects on the glucose metabolism.

Key words: Diabetes, glucose, insulin, insulin resistance, leptin

Introduction

Leptin is the most abundant hormone produced by adipocytes. It has structural homology with the cytokines of the long-chain helical family that includes interleukin (IL)-6, IL-11, IL-12, and oncostatin M, and therefore is part of the adipokines family. Leptin regulates food intake and energy expenditure, and has also multiple actions in the endocrine and immune systems, including fertility, bone formation, tissue remodeling, and inflammation.[1]

Within the endocrine system, leptin regulates the circadian rhythms of the gonadotropic, thyrotrophic and adrenal axes. It also plays key roles in the regulation of glucose homeostasis and insulin sensitivity, independent of actions on food intake, energy expenditure or body weight.[2]

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In this review, we present evidence for leptin's actions on the glucose-insulin homeostasis, and highlight its current and future applications for treating disorders of the glucose-insulin homeostasis.

Molecular Aspects of Leptin

Leptin is a protein of high molecular mass (16 kDa).[3] Its levels are correlated with fat mass,[4] and the increase in human or rodent fat masses due to genetic manipulation or environmental induction causes an increase in leptin levels.[5] Several metabolic and hormonal factors influence the synthesis and secretion of leptin in the body, such as cytokines, cortisol, catecholamines, fatty acids, glucose, and insulin.[6]

There are at least four different isoforms of the leptin receptor in humans: Ob-Ra, Ob-Rb, and Ob-Rc (membrane-anchored), and Ob-Re (soluble); these are all products of alternatively spliced forms of the Ob-R gene.[7] The membrane-anchored isoforms have identical extracellular, ligand-binding and transmembrane domains, with different lengths of the intracellular domain.[7] The isoform Ob-Rb contains a long cytoplasmic region containing several motifs required for signal transduction and capable of activating

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the JAK-STAT signal transduction pathway.[8,9] Ob-Ra is regarded as the leptin transporter across the blood-brain barrier and leptin degrader.[10] The secreted soluble isoform (Ob-Re) lacks both the intracellular and transmembrane domains, and serves as plasmatic leptin-binding protein.[11] These isoforms are involved in mediating leptin's actions in the brain and in peripheral organs.[12] Two other isoforms have not been identified in humans: Ob-Rd has been identified in mice and Ob-Rf, in rats only.[13]

The transduction of leptin's signals is mediated by known pathways, namely Janus kinase-signal transducer and activator of transcription (JAK-STAT), extracellular signal-regulated kinase (ERK)-1/2, phosphatidylinositol-3-kinase (PI3K), and AMP-activated protein kinase (AMPK). The AMPK pathway is particularly involved in preventing insulin resistance, in part by inhibiting pathways that antagonize insulin signaling.[14,15] Intracellular mechanisms are activated to down-regulate leptin's actions, mediated mainly by the suppressor of cytokine signaling 3 (SOCS3).[16] and protein tyrosine phosphatase 1B (PTP1B),[17] which are implicated in the mechanisms of leptin resistance.[18]

The most important function of leptin is the regulation of energy expenditure and food intake, due to its actions on the arcuate nucleus of the hypothalamus. In this area, leptin binds to its receptors, which are expressed in two different neuronal populations: The ones that express agouti-related peptide (AgRP) and neuropeptide Y (NPY), and those that express the peptide cocaine and amphetamine-related transcript (CART) and the large precursor peptide pro-opiomelanocortin (POMC). Leptin exerts anorexigenic effects by inhibiting the AgRP/NPY neurons and by stimulating the POMC/CART neurons. Several other effects have been attributed to leptin, mostly from studies with leptin-deficient animal and human models.

Leptin Deficiency

Among mice that are leptin-deficient (ob/ob) or leptin-resistant (db/db, due to mutations in the leptin receptor gene causing lack of leptin signaling), hyperphagia is a constant and obesity, a hallmark. This adipocyte-derived hormone regulates nutritional status by controlling both energy intake and energy expenditure. In the absence of leptin, rodents and humans alike suffer from massive obesity with a voracious appetite and a blunted metabolic rate.[19-22] Subjects with very low plasma leptin concentrations have large body weight gains over relatively short periods of time.[23]

Leptin-deficient mice (ob/ob) carry a spontaneous missense mutation in their leptin gene. They are severely obese due to hyperphagia and blunted metabolic rate. They also have dyslipidemia, hypercortisolism, low levels of growth hormone, central hypothyroidism, hypogonadotropic hypogonadism, and cellular immune deficiency.[19-22,24] In the leptin deficient ob/ob mouse model, obese phenotype is prevented and reversed by the administration of exogenous leptin.[18]

In humans, leptin deficiency can be observed in several conditions, such as lipodystrophy syndromes, anorexia nervosa, hypothalamic amenorrhea, and congenital leptin deficiency. For over 13 years, our group has been evaluating phenotypic findings and the effects of leptin replacement in four unique leptin-deficient adults from a consanguineous extended Turkish family.[25,26] These individuals have a Mendelian recessive mutation in the leptin gene, consisting of a C→T substitution in codon 105 of this gene, resulting in an Arg→Trp replacement in the mature protein.[26]

Physiological doses of recombinant methionyl human leptin (r-metHuLeptin, Metreleptin®, Amylin Pharmaceuticals, USA, 0.02-0.04 mg/kg/day) were initiated on the leptin-deficient individuals being assessed by our group at ages 5 (boy), 27 (male), 30 and 40 (females). Treatment led to significant improvements in weight, endocrine function and behavior.[27] Leptin replacement was lifesaving, as eight members of this family with severe early-onset obesity, whom we presume to have been leptin-deficient, died during childhood due to infections. By evaluating leptin-deficient patients while on leptin replacement, and after brief periods of leptin withdrawal, we have observed that leptin regulates the circadian rhythms of cortisol, thyroid stimulating hormone, luteinizing hormone and follicle-stimulating hormone. In the brain, leptin controls energy balance and body weight, and plays a role in neurogenesis and brain function. Leptin enhances immune response, and regulates inflammation, coagulation, fibrinolysis, and platelet aggregation.[25,26] Within the adipoinsular axis, we have observed that leptin decreases insulin and glucose levels.[28] In its absence, insulin sensitivity is markedly increased due to rapid weight gain (discussed with more detail ahead).[29,30]

Leptin and the Adipoinsular Axis

The adipose tissue plays an important role in total energy homeostasis.[31] Glucose and lipid metabolism are regulated by complex interactions that occur within the adipoinsular axis. Insulin acutely stimulates lipogenesis while decreasing lipolysis,[32] whereas leptin exerts opposite effects.[14,33] Abnormal accumulation of triglycerides in non-adipose tissues, caused by the upregulation of lipogenesis, leads to a deleterious state known as lipotoxicity.[34] Lipotoxicity is characterized as the accumulation of triglycerides

in the surrounding hepatocytes and is thought to be a major contributor to islet cell transplantation failure in diabetics.[35-38] Lipotoxicity also contributes to the increase in insulin resistance. Given that leptin is thought to oppose insulin action by decreasing hepatocyte lipogenesis, leptin administration may result in decreased lipotoxicity, being useful for the treatment of lipodystrophy syndromes.[39] However, when used for treating obesity-associated non-alcoholic fatty liver disease, leptin might instead promote insulin resistance, fibrosis, and hepatocellular carcinoma.[40]

Leptin and insulin play key metabolic roles. A majority of the studies suggest that leptin decreases insulin synthesis and secretion by pancreatic beta cells, and increases insulin hepatic extraction.[41-44] As a result, insulin delivery is reduced by leptin.[28] This so-called adipoinsular axis is part of a leptin-mediated inhibitory feedback on insulin secretion in order to decrease adipogenesis. Leptin also decreases hepatic glucose production, increases insulin sensitivity, and decreases glucagon levels. Insulin, in turn, also plays a role in stimulating leptin production and secretion in the adipose tissue.[44] Table 1 summarizes the effects of leptin.

Hypothalamic insulin and leptin signaling play a crucial role in the regulation of glucose homeostasis and in the development of insulin resistance.[45] Centrally, insulin modulates hepatic glucose production, skeletal muscle glycogen synthesis, brown adipose tissue thermogenesis, and white adipose tissue lipolysis. Central leptin, in turn, regulates hepatic gluconeogenesis and insulin sensitivity, skeletal-muscle lipid oxidation and glucose uptake/utilization, brown adipose tissue glucose uptake and white adipose tissue lipolysis, and insulin secretion.[46,47] These effects seem to be mediated by the autonomic regulation of skeletal muscle, liver, pancreas and adipose tissues.[48] In the hypothalamus, the leptin signaling PI3K pathway plays an important role in decreasing peripheral insulin resistance, as central leptin improved tolerance to glucose, increased PGC1 alpha expression, and regulated AKT, AMPK, ACC and JAK2 phosphorylation in the soleus muscle of rats fed with regular chow.[49] In untreated diabetic mice, hypoleptinemia caused by decreased fat mass leads to severe insulin resistance, which is reversed by leptin replacement,[50] giving support to the usefulness of leptin in the treatment of diabetes.

Table 1: Effects of leptin on the glucose-insulin metabolism

Pancreas	Liver	Whole body	Adipose tissue
↓ Insulin synthesis and secretion	↑ Insulin hepatic extraction	↓ Insulin delivery	↓ Lipogenesis
↓ Glucagon synthesis and secretion	↓ Hepatic glucose production	↑ Insulin sensitivity	↑ Lipolysis

It has been shown that direct action of insulin and leptin on the POMC neurons is required to maintain normal glucose homeostasis.[51] In Ob-R deficient mice, restoring leptin receptor expression only at POMC neurons normalizes blood glucose and ameliorates hepatic insulin resistance, hyperglucagonemia, and dyslipidemia, independent of changes in body weight.[2] It has been calculated that 42% of leptin's hypoglycemic action is independent of weight reduction.[52] The effects of leptin can be explained by its actions in increasing hypothalamic insulin sensitivity.[53] However, it has also been demonstrated that leptin ameliorates hyperglycemia by suppressing hepatic glucose production and by increasing tissue glucose uptake, independent of insulin.[54]

Another potential mechanism by which leptin ameliorates glucose levels is the increase in IGF binding protein 2 (IGFBP2) level, which reduces blood glucose in wild-type and diabetic mice, and potently suppresses hepatic glucose production, as well as genes involved in hepatic gluconeogenesis and fatty acid synthesis.[55]

More recently, the bone has been implicated in the control of energy homeostasis. Osteocalcin is a marker of bone formation that is synthesized and secreted by the osteoblasts. Osteocalcin increases insulin expression and insulin sensitivity in animals, and mice that lack osteocalcin are glucose intolerant.[56] It has been shown that the inhibition of insulin secretion exerted by leptin is partly mediated by leptin's effect on inhibiting the metabolic activity of osteocalcin: leptin stimulates the sympathetic tone, which in turn stimulates the expression of *Esp*, a gene that inhibits osteocalcin.[57] In humans, osteocalcin has been associated negatively with insulin resistance, and leptin has been correlated negatively with osteocalcin levels both in cross-sectional and longitudinal analyses.[58] Therefore, obesity may lead to insulin resistance through a leptin-mediated suppression of osteocalcin. However, the stimulatory role of osteocalcin on pancreatic insulin secretion has been questioned by studies showing that elevated osteocalcin is associated with suppressed blood insulin. Wild-type, ob/ob and non-obese, diabetic insulinopenic Akita mice submitted to a single intracerebroventricular (icv) injection of recombinant adeno-associated virus vector encoding leptin gene (rAAV-lep) showed increased blood osteocalcin levels, and decreased insulin levels. This suggests that the inhibitory effect of leptin on insulin secretion is limited by high circulating levels of osteocalcin, or that the osteocalcin stimulatory and insulin inhibitory effects are mediated by independent central leptin feedback mechanisms.[59]

Leptin plays a significant part in the pathophysiology of insulin resistance related to obesity. Leptin replacement reverses insulin resistance and diabetes in mice homozygous for mutations of the ob gene,[60] in aP2-nSREBP-1 c mice with moderate fat deficiency,[61] and in severely lipoatrophic A-ZIP/F-1 mice.[62] In non-obese diabetic (NOD) mice, leptin therapy alone or combined with low-dose insulin reverses the catabolic state through suppression of hyperglucagonemia, mimics the anabolic actions of insulin, and normalizes hemoglobin A1c. In contrast with insulin, leptin lowers lipogenic and cholesterologenic transcription factors and reduces plasma and tissue lipids.[63,64] Therefore, leptin and insulin may become a potential combination therapy for type 1 diabetes, but there are concerns regarding hypoglycemia.[65]

Intracerebroventricular infusion of leptin improved hyperglycemia, hyperglucagonemia, hyperketonemia, and polyuria caused by insulin deficiency in NOD mice,[63] independent of hepatic signaling.[65] Therefore, leptin may improve insulin resistance not only by decreasing body weight and fat mass, but also by activating insulin-sensitive tissues such as the adipose tissue and liver. The activation of the JAK-STAT, PI3K, and AMPK pathways, which overlap with those of insulin, contributes to the leptin-mediated decrease in insulin resistance.[66] However, other *in vitro* and *in vivo* studies are contradictory, suggesting that leptin may in fact increase insulin resistance.[41,67-69]

Gene therapy through icv injection of recombinant adeno-associated virus vector encoding the leptin gene (rAAV-lep) has been shown to normalize glucose levels in animal models of diabetes type 1 and 2, by stimulating glucose disposal, by increasing energy expenditure from peripheral organs such as brown adipose tissue, by improving insulin sensitivity, and by suppressing pancreatic insulin secretion in diabetes type 2 models. Besides being a potentially safe and effective antidiabetic therapy, these results clearly demonstrate that leptin regulates the glucose-insulin homeostasis in the hypothalamus, independent of its peripheral actions.[70,71]

In humans, leptin levels are correlated with adiposity.[72] Moreover, leptin is positively correlated with insulin resistance, independently of body weight or adiposity, both in normoglycaemic and in diabetic patients.[73,74] In obese patients with type 2 diabetes, metreleptin administration did not alter body weight or circulating inflammatory markers but reduced HbA1c marginally, from 8.01±0.93% to 7.96±1.12% ($P = 0.03$).[75] In addition, treatment did not have weight loss-independent, clinically important effects on insulin sensitivity in those patients.[76]

Human studies evaluated the insulin-sensitizing effects of leptin replacement in patients with lipodystrophy.[77-80] Humans with lipoatrophic disorders (exhibiting very low levels of leptin, increased insulin resistance and hyperinsulinemia) experienced a decrease in insulin resistance after treatment with r-metHuLeptin.[77-80] Hemoglobin A1c reduced by 1.5% in a group of 48 patients with lipodystrophy treated with recombinant methionyl human leptin.[81] Those results may be biased because those patients lack adipose tissue, and have a presumably defective adipoinsular axis. Leptin-deficient humans therefore, provide a unique opportunity to evaluate the effects of leptin on insulin resistance.[82-84]

In a cohort of three leptin-deficient adults, we have previously observed that before treatment with metreleptin, all patients had high insulin and lipid levels. The older female was diabetic.[24,27] Leptin replacement normalized serum lipids, insulin and glucose levels, and led to the resolution of type 2 diabetes.[27] Meal tolerance tests performed before and after leptin replacement showed increased insulin sensitivity (by 5.7-fold) and decreased insulin secretion (by 2-fold), while insulin hepatic extraction returned to rates close to normal.[28] Paradoxically, after leptin withdrawal, insulin sensitivity increased further, as measured by euglycemic hyperinsulinemic clamps [Figure 1].[29] This might be attributed to the rapid gain in glucose-absorbing fat mass after leptin withdrawal.[30] The increase in insulin sensitivity when off leptin was clinically evident when the adult male developed severe hypoglycemia during an oral glucose tolerance test.

Conclusions

Leptin and insulin share common effects in the control of food intake and energy metabolism. In the blood glucose homeostasis, both play important roles. Leptin and insulin directly regulate each other: leptin inhibits insulin; insulin stimulates leptin synthesis and secretion. Leptin also increases insulin sensitivity, not only by decreasing adiposity and lipotoxicity, but also insulin-independent action, both centrally and peripherally. Leptin also decreases hepatic production of glucose, contributing to its glucose-lowering effects. The bone, through osteocalcin, also plays a role in regulating the glucose-insulin homeostasis [Figure 2].

In leptin-deficient humans, leptin therapy has been shown to determine remarkable effects, by increasing insulin sensitivity on the long term, by decreasing insulinemia, and ultimately by reversing type 2 diabetes in one previously diabetic patient. In lipodystrophic patients, leptin therapy also has positive metabolic effects. However, no clinically evident benefits have been observed in patients with type

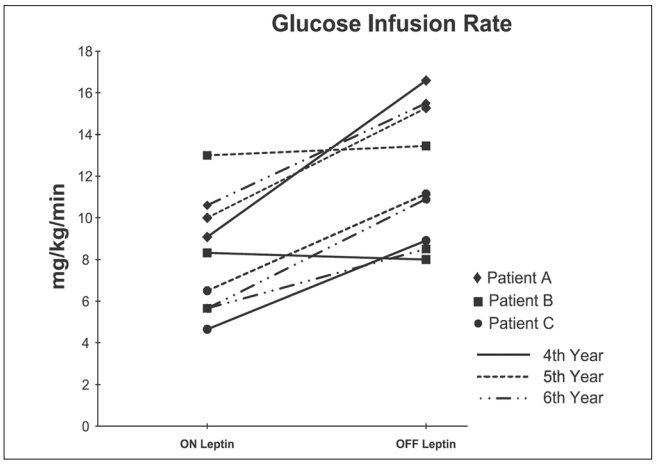

Figure 1: Euglycemic hyperinsulinemic clamps of leptin-deficient patients while on leptin and after brief periods of leptin withdrawal (from Paz-Filho *et al.*[29]). Glucose infusion rates increased in eight out of nine times when leptin therapy was briefly interrupted. The substantial weight gain after leptin withdrawal was responsible for acutely increasing insulin sensitivity

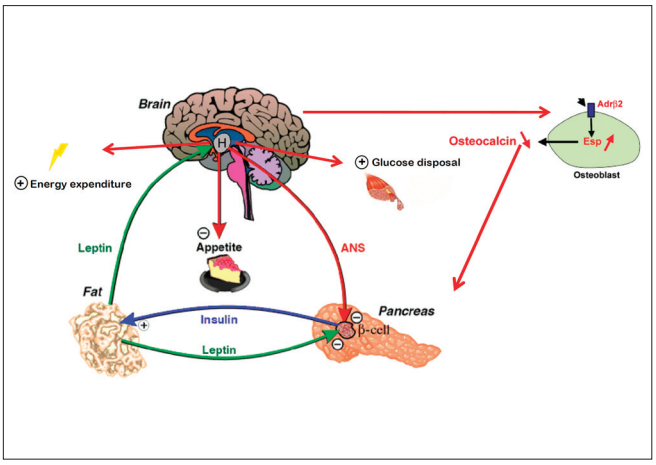

Figure 2: Interactions between fat, brain, pancreas and bone. Leptin activates the sympathetic tonus, which inhibits insulin secretion and stimulates *Esp* expression in the osteoblast (via stimulation of the adrenergic beta 2 receptor). *Esp* inhibits osteocalcin, decreasing insulin expression. Leptin inhibits pancreatic insulin. Insulin, in turn, stimulates leptin expression in the white adipose tissue. Adapted from Kieffer and Habener.[43] H: Hypothalamus

2 diabetes. The effects of metreleptin in patients with type 1 diabetes are currently being evaluated in a clinical trial (ClinicalTrials.gov Identifier NCT01268644).

For the development of leptin-based therapies for treating diabetes and disorders that present insulin resistance, further human studies need to elucidate the effects of leptin on the glucose-insulin homeostasis, both in the leptin-sensitive and in the leptin-resistant milieus.

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