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Minireview

Leptin, 20 years of searching for glucose homeostasis

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ABSTRACT

Leptin was discovered in 1994 (20 years ago). In addition to having well-characterized effects on the regulation of energy homeostasis, leptin clearly also plays a major role in metabolic homeostasis. In fact, leptin plays an important role in the regulation of glucose homeostasis independent of food intake and body weight. The mechanism underlying the modulation of glucose metabolism by leptin is not completely understood, although evidence indicates that the effect occurs at both the central and peripheral levels. In this review, we will focus on the role of leptin in glucose homeostasis at the central level and its role in insulin secretion and in counteracting hormones, such as glucagon, growth hormone, cortisol and catecholamines.

Contents

Introduction

Leptin is a peptide hormone containing 167 amino acids that is principally produced in the adipose tissue but is also found in the placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and others [1]. Leptin marks the state of energy storage and body weight, and circulating leptin levels are proportional to body fat content [2].

The role of leptin in glucose metabolism was demonstrated in 1995 using ob/ob (leptin deficient) mice that were extremely obese and diabetic [3]. It was shown that treatment with leptin in low doses, which did not affect the body weight or food intake, normalized severe hyperglycemia [4]. This result demonstrated that leptin exerts direct effects on glucose levels independently of body weight and food intake. This finding raised a question about the mechanism behind this effect. Data gleaned over the last few years have shown that this effect is mediated through a vast array of mechanisms. Thus, in vitro studies

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have shown that leptin inhibits glucose absorption via PKC (protein kinase C), p38MAPK (P38 mitogen-activated protein kinase), PI3K (phosphatidylinositide 3-kinase) and MEK/ERK [5]. In vivo studies performed in mice with a genetic deletion of the leptin receptor in intestinal epithelial cells showed a decrease in the activities of GLUT5-mediated fructose transport and PepT1 (peptide transporter 1)-mediated peptide transport, whereas the Na^+/glucose cotransporter SGLT-1 (sodium-glucose linked transporter-1) and GLUT2 were unaffected [6]. Taken together, these data indicate a regulatory role of leptin in glucose absorption. Nevertheless, it remains to be determined to which point this effect could be under central control from the autonomic nervous system. In addition clear evidences show that leptin influences glucose homeostasis: by regulating insulin-sensitive peripheral tissues, by pancreatic endocrine function or by directly affecting the central nervous system (Fig. 1).

Leptin and glucose homeostasis

Leptin was originally recognized for its role as a satiety factor in the regulation of energy homeostasis; however, leptin has been shown to have important effects in the regulation of glucose homeostasis. This evidence resulted from studies of ob/ob mice (genetic leptin-deficient mice) and *db*/*db* mice (leptin receptor-deficient mice), which both had a phenotype of hyperglycemia, hyperinsulinemia and insulin resistance (similar to human type 2 diabetes) [3,7]. First, it was thought that the effect of glucose alterations is secondary to obesity and hyperphagy, but some evidence suggests that leptin regulates glucose metabolism independently of this effect on energy balance. Experiments using ob/ob mice and a control pair-feeding group supported this independence by showing a marked improvement in hyperglycemia and hyperinsulinemia independent of food intake [7,8]. Consistent with other experiments, the Kieffer group demonstrated that the leptin action in glucose homeostasis precedes changes in body weight and obesity. Following the disruption of endogenous leptin tone with a leptin antagonist in wild-type mice and during fasting, the mice exhibited glucose-stimulated hyperinsulinemia and insulin resistance within 3 days without changes in body weight [9].

Conversely, data from humans with a disease similar to that of ob/ob mice revealed the importance of leptin in glucose homeostasis; these humans had congenital leptin deficiency, due to mutations in the leptin gene, hyperinsulinemia and/or diabetes mellitus, which it is a common feature of this deficiency. Following replacement therapy with leptin, these patients exhibited a marked increase in insulin sensitivity with a decrease in circulating insulin levels and hepatic insulin extraction. On the contrary, patients with mutations of the leptin receptor exhibited normal glucose levels both at fasting or following an oral glucose load in most instances despite the extreme obesity of these patients [10].

More interesting data resulted from humans with severe insulin resistance and diabetes due to "lipodystrophy" (characterized by reduced leptin levels due to disorders in adipose tissue development). These patients develop lipodystrophy in the presence of several mutations that impair adipogenesis and limit the capacity to store triglycerides. In humans, the two most common genetic lipodystrophies are CGL (congenital generalized lipodystrophy) and FLP (familial partial lipodystrophy). In CGL, there is an absence of body fat from birth; meanwhile, in FLP, fat loss is progressive and variable during childhood and puberty [11]. One of the consequences of these disorders is that the patients lose the lipid storage capacity of adipocytes, leading to the accumulation of nutrients in different organs, such as the liver, muscle and other tissues. This accumulation translates to a state of insulin resistance and diabetes [10–14]. The relevance of leptin in the development of

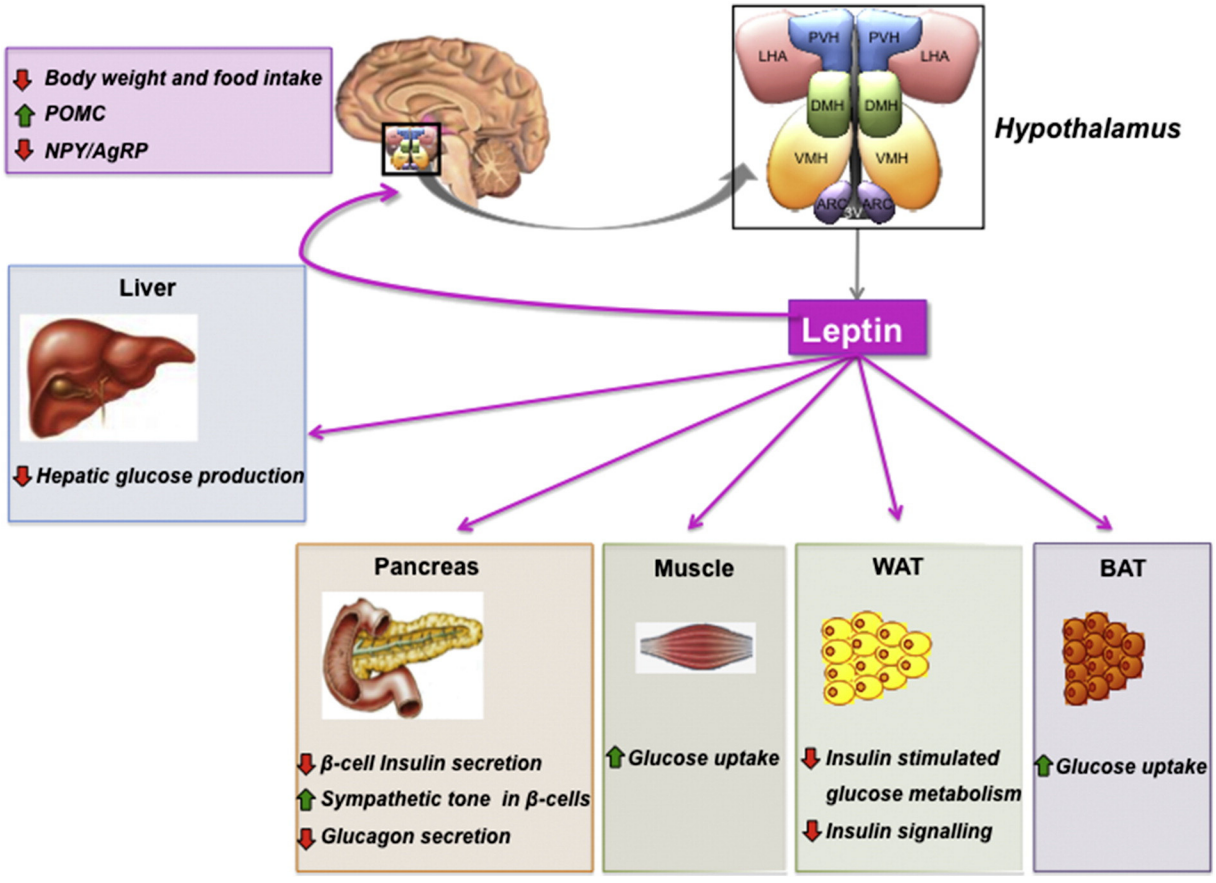

Fig. 1. Effects of leptin on the glucose homeostasis in different organs. Main actions performed by central leptin in different tissues.

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this phenotype is demonstrated by the success of leptin treatments in these patients. Long-term treatment with leptin in patients with lipodystrophy has been shown to decrease hyperglycemia, dyslipidemia, hepatic steatosis and peripheral insulin resistance. Notably, this decrease was achieved without a concomitant antidiabetic therapy and was devoid of side effects. [10,14–16].

Further evidence of the role of leptin in glucose homeostasis resulted from studies of non-obese rodent models of insulin deficiency that exhibited type I diabetes. The leptin infusion or gene therapy produced a reversion of the hyperglycemia in streptozotocin (STZ)-treated rats (a chemical agent that selectively destroys pancreatic β cells) [17]. The effect of leptin was not restricted to glucose levels and insulin sensitivity; instead, leptin also improved or normalized other parameters, such as water intake, reverse glycosuria and hyperphagia, in insulin-deficient rodents, demonstrating the improved overall health of these animals [18–21].

The normalization of blood glucose levels by leptin therapy in insulin-deficient rodents correlates with increased insulin sensitivity. Additionally, STZ rats treated with leptin have increased insulin sensitivity compared with that of non-diabetic controls. This finding could indicate that the increase of insulin sensitization due to leptin, in this model might compensate for the residual insulin levels in STZ-treated rodents [9]. In addition, when the rats were treated with a combination of low doses of insulin and leptin (at doses devoid of any effect alone), the glucose levels decreased, which was an important finding. Interestingly, in this model, leptin therapy decreased the levels of counterregulatory hormones, which could contribute to the glucose-lowering action of leptin [22].

In humans, another model for leptin deficiency is the uncontrolled insulin-deficient diabetes (uDM) induced by the loss of insulin-secreting β-cells. These patients are characterized by hyperphagia and hyperglycemia but cannot gain weight. The patients have a progressive loss of body fat stores and consequently a high reduction in the circulating levels of leptin and insulin [23,24]. Although insulin deficiency is primarily responsible for the hyperglycemia and weight loss in uDM, some of the beneficial effects of insulin treatment may arise from an associated increase in leptin action because leptin levels are normalized by insulin treatment in uDM rats [24].

Moreover, leptin deficiency has recently been implicated in progressive insulin resistance, as was demonstrated when the administration of leptin at a dose that maintains normal physiological plasma leptin levels prevented the development of severe and progressive insulin resistance in rats with uDM; this prevention was not explained by changes in food intake or body weight [25]. Moreover, the mechanism underlying this effect appeared to preferentially involve the liver because leptin replacement in the subjects with uDM reduced the gluconeogenic gene expression and also restored normal insulin signal transduction in the liver, thus normalizing the circulating levels of glucagon and corticosterone, which are higher in uDM [25].

All these data from ob/ob mice, rodent models of type 1 diabetes and humans with lipodystrophy demonstrated that leptin plays a major role in glucose homeostasis.

Leptin receptors in the CNS

The leptin receptor is encoded by the *db* gene and is expressed by neurons in the central nervous system (CNS). The db gene encodes an alternatively spliced transcript, producing 6 variants of the receptor (Lepr-a to Lepr-f.). Lepr-b (long isoform), which is highly expressed in the hypothalamus, contains the full intracellular domain necessary for the activation of critical second messenger pathways and normal leptin action [26–28], and Lepr-b is thought to mediate all actions of leptin via activation of the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway [29–32].

Leptin receptors are expressed widely in the brain. Different techniques, such as in situ hybridization, immunohistochemistry, and protein and mRNA expression measurements, showed that different hypothalamic areas of the brain are involved in the control of metabolism. Peripheral administration of leptin activates neuronal populations throughout the brain, as demonstrated by measurements of pSTAT3 activation or the induction of c-Fos expression (both can occur in "first-order" neurons activated directly by leptin and "second-order" neurons in a leptin-activated circuit). These areas include arcuate (ARC), ventromedial (VMH), dorsomedial (DMH), paraventricular (PVN) and lateral (LHA) hypothalamic areas, as well as extrahypothalamic areas, such as the nucleus of the solitary tract (NTS), and reward areas, such as the ventral tegmental area (VTA) and substantia nigra (SN) [32–34].

Central control of glucose and leptin effects in the CNS

Central control of glucose homeostasis

The earliest demonstration that the brain is involved in the control of blood glucose levels was provided by Claude Bernard, who showed that hypothalamic lesions induce hyperglycemia in dogs. In 1953, John Mayer proposed that cells located in the hypothalamus could be specialized to monitor variations in blood glucose concentrations and further postulated that these cells translate these variations in glucose concentrations into electrical or chemical signals that control feeding behavior [35,36]. In fact, there are glucose-sensing neurons in many regions of the brain, particularly the hypothalamus, and the presence of such specialized glucose-sensing neurons was demonstrated by electrophysiological analysis of hypothalamic slides. Anand et al. and Oomura et al. independently identified hypothalamic neurons that are able to modulate their firing activity in response to changes in extracellular glucose concentrations [37,38]. The activated signals included signals from hypothalamic K_{ATP} channels (ATP-sensitive potassium channels) that are composed of a subunit of the inward rectifier potassium channel Kir6.2 and a subunit of the sulfonylurea receptor (SUR).

There are two different types of glucose-responsive neurons, which detect changes in blood glucose levels: glucose-excited (GE) neurons, whose firing rate increases in response to increases in extracellular glucose concentrations, and glucose-inhibited (GI) neurons, which are activated when glucose concentrations decrease [39]. Both types of neurons are widely distributed throughout the brain but are highly represented in the hypothalamic nuclei, which are involved in the control of energy homeostasis.

Leptin effects in the CNS

Glucose homeostasis

Several publications sought and provided evidence that CNS mediates the effect of leptin on glucose metabolism. An intracerebroventricular administration of leptin at low doses in mice and rats had a similar effect to that of peripheral administration. Similarly, central administration in STZ-diabetic rats normalized the blood glucose levels at low doses that were ineffective when administered peripherally [21,40,41].

Until recently, there was a general consensus that leptin requires insulin to affect glucose metabolism; however, other evidence from animals with a complete lack of insulin showed that leptin administration improved diabetes, thus revealing a novel mechanism through which the brain normalizes diabetic hyperglycemia without requiring insulin and differing from previous reports where leptin increased the insulin sensitivity in the liver [25].

Leptin receptors, as we explained previously, are expressed widely in the brain. To uncover the main neuronal populations involved in glucose homeostasis, some experiments were performed to assess the effect of leptin following its administration in specific brain areas.

Injection of leptin into the ventromedial hypothalamic nucleus (VMH) enhanced glucose uptake in skeletal muscle, brown adipose tissue and other organs [42]. The selective deletion of the leptin receptor

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from SF-1-positive neurons, which are specific to the VMH, resulted in an obese and insulin-resistant phenotype [43,44], highlighting the importance of this nucleus in glucose control. In addition, VMH neurons send excitatory outputs to POMC (pro-opiomelanocortin) neurons in the ARC [45]; this finding indicated that a subset of VMH neurons are components of the melanocortin (implicated in glucose control, as described below) pathway, suggesting that leptin signaling in the brain participates in the control of glucose metabolism. In 2005, a knock-in of the leptin receptor specifically in the ARC in *db*/*db* mice (Lepr-null mice) led to a modest effect on body weight and food intake but normalization of the hyperglycemia and improvement of the characteristic hyperinsulinemia of these animals. Leptin injection in the ARC increased glucose uptake but only in brown adipose tissue (BAT), whereas injection in the LH [42], DMH or PVN had no effect [46]. Taken together, these data indicate that the ARC is capable of mediating the antidiabetic actions of leptin. Studies in obese Koletsky rats (leptin receptor deficient) provided further evidence of the relevance of the ARC. When leptin receptors were expressed via an adenovirus in the ARC nucleus of these animals, there was a marked improvement in peripheral insulin sensitivity via enhanced suppression of hepatic glucose production, with no change in insulin-stimulated glucose uptake or disposal [47]. These effects were associated with enhanced insulin signaling transduction via PI3K in the liver but not in the skeletal muscle and were associated with reduced hepatic expression of key gluconeogenic genes, such as *G6Pase* and *Pepck*.

To clarify the mechanisms underlying the involvement of the ARC in the effects of leptin on glucose homeostasis, several studies assessed the role of Neuropeptide Y (NPY)/Agouti-related peptide (AgRP) and POMC neurons. Neurons are known to be inhibited by leptin [8,48]. Neurons that express POMC are adjacent to the NPY/AgRP neurons, but in this case, leptin stimulates POMC neurons [49,50]. The POMC cleavage product α-MSH is released by these neurons and acts on melanocortin receptors (Mc3r/Mc4r), which mediate the effect on food intake and body weight [51]. Both neuronal populations are known to play an important role in the regulation of energy homeostasis. The administration of SHU9119, an antagonist of NPY and the melanocortin-3/4 receptor, causes insulin resistance and glucose intolerance in a mechanism that is independent of food intake [52,53].

In addition, a study in which leptin-R was selectively restored in POMC-expressing neurons revealed changes in the glucose levels of young mice but it is only a partial effect because it is increased in older mice. The deletion of this receptor, specifically in POMC-expressing neurons, does not produce the expected hyperglycemia, suggesting that other neurons in addition to POMC neurons have a role in the leptin control of glycemia; however, the glycemia-lowering action of leptin via action on POMC neurons is due, in part, to an increase in the insulin sensitivity of the liver [54]. Other neuron populations were studied by targeting specific populations, such as AgRP or the AgRP–POMC combination, leading to the demonstration that AgRP-expressing neurons also have a role in glucose homeostasis. Furthermore, some of the hypothalamic actions of leptin depend on melanocortin receptor activation, particularly its central effect on endogenous glucose production [55,56], whereas the loss of hypothalamic leptin signaling is sufficient to promote obesity or T2DM [30,57].

Pancreatic insulin secretion

Various in vivo studies of the pancreas demonstrated the suppressive action of leptin on basal and glucose-stimulated insulin gene expression and secretion in β-cells. However, studies of islets or a perfused pancreas from non-leptin deficient mice and β-cell lines that evaluated the effect of leptin on insulin secretion showed an inhibitory effect [58–60], no effect [61–63] or even stimulation. Even a study of different transgenic models failed to clarify this issue because LepRb mutations that are specific to the pancreas, such as the mutations in Pdx^{cre} or Rip^{cre} mice, also led to improvements in glucose tolerance [64]. Finally, other mouse models used by Covey showed hyperinsulinemia and fasting hypoglycemia but also found glucose intolerance, impaired glucose-stimulated insulin secretion and insulin resistance [65]. Overall, in view of these discrepancies, it is difficult to reach firm conclusions at present.

Because this review is principally focused on effects at the central level, we searched for information about the central control of the effects of leptin on insulin secretion. Similar to the findings for the central control of glucose homeostasis, evidence supports the inhibition of insulin secretion by leptin through central mechanisms. Studies of neuronal regulation using transgenic mice (Synapsin-Cre) that exhibited disruption of leptin signaling due to a mutated leptin receptor showed hyperinsulinemia without changes in body weight [66]. Although it is not a conclusive finding, the injection of leptin icv as a peptide or as gene therapy lowers insulin levels [67–69]. The action of leptin on insulin levels is consistent with increased sympathetic tone to β-cells because acute icv leptin injection suppresses the insulin secretion that is stimulated in a glucose-dependent manner due to activation of the sympathetic nervous system (SNS) [70].

In addition, one study found that in vagotomized rats but not in normal rats, leptin exerts an inhibitory effect on the secretion of insulin stimulated by glucose, and this effect was abolished by sympathectomy [71]. This finding could indicate that although the SNS partly mediates the inhibitory effect of leptin on β-cells, the effects of the SNS might be counterbalanced by the parasympathetic nervous system. All these results would appear to indicate that leptin exerts an inhibitory effect at the central level on β-cell insulin secretion. Further support for the involvement of the CNS in insulin secretion was provided recently by the identification of a new neuronal population that coexpresses the leptin receptor and cholecystokinin in the parabrachial nucleus of the hypothalamus and projects to the ventromedial hypothalamus. These neurons are activated by hypoglycemia and inhibited by leptin, demonstrating that the central SNS modulates all counterregulatory responses in addition to pancreatic insulin secretion [72].

Counteracting hormones

Leptin exerts effects directly and centrally on the pancreas to influence insulin and glucagon levels, but it can indirectly regulate glucose metabolism via modification of other hormones that regulate glucose metabolism. In fact, leptin therapy decreased the levels of counterregulatory hormones [9,18,47,73], which could contribute to the glucose-lowering action of leptin.

One example is glucocorticoids. Leptin inhibits glucocorticoid synthesis and secretion, which could thereby increase insulin sensitivity. At the central level, leptin inhibits the hypothalamic–pituitary–adrenal axis (HPAA) that is stimulated by stress [74,75]. Classical studies from Heiman et al. demonstrated that leptin can inhibit the HPA axis under stress and hypothalamic CRH release [76], thereby increasing insulin sensitivity.

Conversely, the interrelationship between GH (growth hormone) and insulin resistance has been shown in different studies that demonstrated the role of leptin in GH secretion. Different papers indicated that leptin enhances spontaneous GH secretion [77,78] when leptin is administered at the central level (ICV) in fasting states. Other studies in rodents have shown an inverse relationship between adiposity gain and increased leptin levels with circulating GH levels and insulin sensitivity. However, this relationship does not appear in humans because studies of leptin-deficient patients with the impaired GH secretion that usually accompanies obesity showed that this GH secretion blockade is not caused by elevated plasma leptin levels; instead, it is caused by adiposity or some factor linked to adiposity [79].

GLP1 (glucagon-like peptide-1), a potent insulinotropic hormone, reduces glycemia through inhibition of glucagon secretion, gastric emptying and by stimulation of pancreatic β-cells [80–82]. GLP-1-neurons have been identified in the CNS and are expressed in the hypothalamus [83,84]. Leptin may stimulate the activity of GLP-1 neurons to induce

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the GLP-1 regulation of both food intake and energy and glucose balance [34,85,86].

One of the most relevant counterregulatory hormones is glucagon. Interestingly, the suppression of endogenous glucagon or the antagonism of glucagon receptor signaling decreases hyperglycemia in STZ-diabetic rats [87,88]. Moreover, glucagon receptor null mice are resistant to developing the diabetes induced by STZ treatment or *Alloxan* [89], suggesting that glucagon signaling is required for diabetic hyperglycemia. Studies of leptin treatment (at physiological levels) in STZ diabetic rats revealed improved insulin sensitivity and normalization of the elevated plasma levels of glucagon [25]. The hyperleptinemia induced by adenoviral gene therapy ameliorated hyperglycemia, and the effects could be mediated via hyperglucagonemia suppression. Although these studies indicate that the effect of leptin on glucagon levels might contribute to the restoration of euglycemia in diabetic rats, it is unclear at present whether different neuronal populations of the CNS are involved in the secretion of glucagon by pancreatic α-cells.

Conclusion

Data gleaned over the last few years have shown that leptin plays an important role in the regulation of glucose homeostasis. The relevance of this finding is shown by the fact that patients with lipodystrophy are being treated with leptin to maintain normal glucose homeostasis. The mechanisms of action are not yet fully uncovered, but clear evidence indicates that the effects are exerted at different levels, including glucose absorption and the secretion of insulin and counter-regulatory hormones. Furthermore, although they are not fully characterized, many of these effects appear to be mediated at the central level mainly through actions on hypothalamic neurons; however, the most recent evidence also indicates effects at an extrahypothalamic site of action.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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