Review

MOLECULAR METABOLISM

The glucoregulatory actions of leptin

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ABSTRACT

Background: The hormone leptin is an important regulator of metabolic homeostasis, able to inhibit food intake and increase energy expenditure. Leptin can also independently lower blood glucose levels, particularly in hyperglycemic models of leptin or insulin deficiency. Despite significant efforts and relevance to diabetes, the mechanisms by which leptin acts to regulate blood glucose levels are not fully understood.
Scope of review: Here we assess literature relevant to the glucose lowering effects of leptin. Leptin receptors are widely expressed in multiple cell types, and we describe both peripheral and central effects of leptin that may be involved in lowering blood glucose. In addition, we summarize the potential clinical application of leptin in regulating glucose homeostasis.
Major conclusions: Leptin exerts a plethora of metabolic effects on various tissues including suppressing production of glucagon and corticosterone, increasing glucose uptake, and inhibiting hepatic glucose output. A more in-depth understanding of the mechanisms of the glucose-lowering actions of leptin may reveal new strategies to treat metabolic disorders.

Keywords Leptin; Diabetes; Glucose metabolism

1. INTRODUCTION

The prevalence of diabetes is rising around the world, with the number of people affected predicted to increase to ~642 million in 2040 [1]. This imposes a substantial economic burden on society with over $100 billion being spent in 2013 in the United States alone [2]. Type 1 diabetes (T1D) results from the autoimmune destruction of insulin-producing β-cells and is treated by delivering insulin by injection or pump. However, insulin therapy is not perfect as periods of hyperglycemia occur, which can result in long-term complications such as retinopathy, nephropathy, and neuropathy, and conversely an excess of insulin can result in hypoglycemic episodes that can be deadly. Type 2 diabetes (T2D), which is more common and highly correlated with obesity, is characterized by insulin resistance and eventual β-cell loss, and can be difficult to manage despite current drug treatments. In recent years, the satiety-regulating hormone leptin has garnered excitement as a potential therapeutic for the treatment of diabetes due to its potent body weight and blood glucose lowering effects.

In humans and rodents, leptin is a 167 amino acid protein secreted primarily from white adipose tissue [3] into the bloodstream and can be transported across the blood-brain barrier [4]. Leptin is also expressed in brown adipose tissue (BAT) [5,6], mammary gland [7], placenta [8,9], skeletal muscle [10], stomach [11], and pituitary gland [12]; however, the relative contribution from these tissues to total circulating leptin levels is negligible [13]. In humans and rodents, leptin levels generally correlate with the total amount of body fat, except during fasting [14]. Circulating leptin levels are similar among lean humans, rats, and mice, typically ranging between ~0.5–15 ng/mL [15–21]. In mice, the leptin receptor gene is alternatively spliced to produce six isoforms, LepRa-LepRf [22]. All isoforms, with the exception of LepRe, have identical extracellular and transmembrane domains but differ in length of the intracellular tail [22]. The long form of the leptin receptor (LepRb) is the only isoform capable of Janus kinase – signal transduction and activators of transcription (JAK-STAT) signaling and is the major mediator of the metabolic effects of leptin [22–25]. JAK2 activation autophosphorylates multiple tyrosine kinase residues in rodents, and activation of these tyrosine residues creates a binding site for STAT molecules [26–28]. Phosphorylation of STAT3 results in dimerization and nuclear translocation such that STAT3 acts as a transcription factor to affect various target genes [29], including suppressor of cytokine signaling 3, which acts in a negative feedback loop to impair leptin signaling after prolonged stimulation [30–32]. The LepRb isoform is distributed in both the central nervous system (CNS) [30,33,34] and the periphery [11,35–38].

Rodents lacking the gene encoding leptin (*ob*/*ob* mice or KiloRat™) [18,39–43] or the leptin receptor (*db*/*db* mice, Zucker diabetic fatty rats, and JCR:LA-cp or SHR/N-cp rats) [41,44–49] are commonly characterized by obesity, hyperphagia, insulin resistance, hyperinsulinemia, impaired glucose tolerance, and, in some cases, chronic hyperglycemia. In humans lacking leptin or its receptor due to rare

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mutations, obesity is also evident [25,50–52], and though impairments to glucose tolerance are not as severe as in rodents, hyperinsulinemia is often present [53]. Leptin therapy in leptin-deficient rodents and humans improves all of their metabolic abnormalities [18,39,53].

The improvement in hyperglycemia following leptin therapy in rodents was initially attributed to the secondary effects of reduced body weight; however, numerous observations suggest that leptin can have metabolic effects independent of reductions in body weight. First, in *ob*/*ob* and *db*/*db* mice, hyperinsulinemia precedes obesity, suggesting that impairments to glucose regulation occur distinctly from weight gain [43,54]. Second, pair feeding *ob*/*ob* mice to consume the same amount of food as leptin treated *ob*/*ob* mice did not improve blood glucose or plasma insulin to the same extent as leptin treatment [55]. Third, a low dose of leptin (1 mg/kg/day) that was unable to lower body weight was still capable of normalizing blood glucose and insulin levels in *ob*/*ob* mice [39]. Fourth, acute disruption of leptin signaling using a leptin antagonist raised blood glucose and plasma insulin levels before altering body weight [56]. Fifth, rodents and humans with lipodystrophy accompanied by loss of fat tissue and extremely low leptin levels also exhibited hyperglycemia, hyperinsulinemia, and insulin resistance which were corrected by leptin therapy [57–59]. Lastly, insulin deficient rodents, which had depleted white adipose tissue (WAT) depots, exhibited hyperglycemia, insulin resistance, and impaired glucose tolerance, all of which were normalized by leptin therapy [19,20,60–66]. Together, these findings demonstrate that leptin signaling can influence glucose regulation independent of its effects on body weight.

Here we assess studies aimed at addressing the mechanisms by which leptin regulates blood glucose. We describe the ability of leptin to lower blood glucose through critical pathways within the CNS, CNS-mediated effects on the periphery, as well as direct effects on peripheral tissues. Studies performed *in vitro* and *ex vivo* have been used to examine the direct effect of leptin on various tissues; however, due to the lack of physiological environment (e.g. innervation and interaction with hormones from other tissues), the outcomes may not reflect the actions of leptin in the whole organism. The use of techniques including central or systemic delivery of leptin, and genetic deletion or overexpression, have helped to elucidate the role of leptin action *in vivo*. In addition, the use of dietary and pharmacological manipulation to mimic metabolic diseases including obesity and insulin-deficient diabetes has provided insight into the role of leptin in disease states. However, many caveats may hamper the analysis of *in vivo* studies, such as promiscuous or ineffective cre recombinases when using cre-lox technology, the inability to distinguish between direct and indirect effects of leptin, lack of reproducibility between studies due to differences in experimental design or facilities, and difficulty in translating results from animal models to human physiology. These caveats should be considered when interpreting studies aimed at elucidating the mechanisms of leptin in regulating glucose homeostasis.

2. ROLE OF LEPTIN IN REGULATING GLUCOSE HOMEOSTASIS

2.1. Effects of leptin on the central nervous system

The expression of the long form of the leptin receptor (LepRb) is higher in the CNS relative to peripheral tissues [30,33,34]. Intracerebroventricular (ICV) injection of leptin that results in negligible peripheral leptin levels restores euglycemia and insulin sensitivity in *ob*/*ob* [67], high fat fed [68], and insulin deficient rodents [60,66,69,70], providing compelling evidence that central leptin signaling alone is sufficient for potent glucose-lowering actions of leptin. To better understand the specific CNS regions involved in leptin mediated glucose regulation, studies have been performed involving leptin injection into specific brain regions or genetic deletion or restoration of the leptin receptor in specific neuron populations.

Leptin receptors are expressed primarily in GABAergic and, to a lesser extent, in glutamatergic neurons, in several regions of the hypothalamus including the ventromedial nucleus of the hypothalamus (VMH), arcuate nucleus of the hypothalamus (ARC), lateral hypothalamic area (LHA), and dorsomedial hypothalamic nucleus (DMH) [35,71–73], as well as extra-hypothalamic regions [34]. Leptin-responsive neurons in these regions consist of heterogeneous populations that have not been entirely characterized. However, the main populations that have thus far been implicated in leptin-mediated effects on glucose homeostasis are well-studied neurons in the VMH and ARC, as discussed below (Figure 1).

Injection of leptin into the VMH of lean rats did not affect blood glucose or plasma insulin levels but stimulated glucose uptake into BAT, muscle and heart [74,75]. However, in rats rendered diabetic using streptozotocin (STZ), injection of leptin into the VMH completely normalized blood glucose levels and hepatic glucose production but had no effect on glucose uptake into BAT or muscle [76]. The differences in the results of these studies may be due to the effect of insulin depletion and hyperglycemia in the diabetic vs lean state. Within the VMH, glutamatergic steroidogenic factor-1 (SF1) expressing neurons have been implicated in body weight and glucose regulation [77]. To investigate the role of leptin receptors in these neurons, leptin receptors were knocked out of SF1 neurons of mice, which resulted in modestly increased body weight and adiposity, as well as hyperinsulinemia and glucose intolerance [78,79]. However, *db*/*db* mice

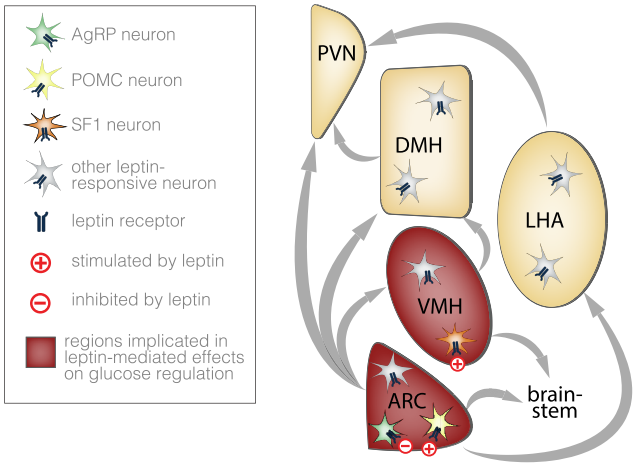

Figure 1: Leptin responsive regions of the hypothalamus. Within the hypothalamus, heterogeneous populations of leptin-responsive neurons are found in the ARC, VMH, DMH, and LHA. The ARC and VMH regions have been implicated in the leptin-mediated control of glucose regulation, including the AgRP and POMC neurons of the ARC that are inhibited and stimulated by leptin, respectively, and the leptin-stimulated SF1 neurons of the VMH. Further research is necessary to determine whether other leptin-responsive neurons in these regions and in the DMH and LHA may also play a role in glucose regulation. There are extensive interconnections among these four hypothalamic regions (arrows) as well as the PVN, a region that mediates downstream effects of AgRP and POMC neurons on food intake and energy expenditure via MC4Rs. There are additional projections to extra-hypothalamic regions including brainstem regions that mediate autonomic outputs. Thus, the full pathways that translate leptin action within specific hypothalamic neuronal populations to a final peripheral effect on glucose homeostasis may be multi-synaptic, and remain to be fully delineated.

