ABSTRACT

Diabetes is a major worldwide problem. Despite some progress in the development of new antidiabetic agents, the ability to maintain tight glycemic control in order to prevent renal, retinal, and neuropathic complications of diabetes without adverse complications still remains a challenge. Recent evidence suggests, however, that in addition to playing a key role in the regulation of energy homeostasis, the adiposity hormone leptin also plays an important role in the control of glucose metabolism via its actions in the brain. This review examines the role of leptin action in the central nervous system and the mechanisms whereby leptin mediates its effects to regulate glucose metabolism. These findings suggest that defects or dysfunction in leptin signaling may contribute to the etiology of diabetes and raise the possibility that either leptin or downstream targets of leptin may have therapeutic potential for the treatment of diabetes.

Key words: Brain, diabetes, glucose, insulin, leptin

INTRODUCTION

The incidence and prevalence of diabetes is increasing globally.[1] More than 250 million people have diabetes worldwide and this number is expected to exceed 400 million by 2030.[2] This is a major health concern given that diabetes is associated with increased risk of cardiovascular disease and both macro- and micro-vascular diseases including blindness, amputation, and renal disease.[1,2] The burden of diabetes leads to more than a doubling of individual medical expenses, with a total concomitant economic cost of $174 billion in the USA alone.[3] Given its considerable health and financial costs, a better understanding of diabetes pathogenesis is needed in order to develop new strategies for the safe and effective treatment of this disease.

Diabetes is a metabolic disease characterized by the chronic elevation of blood sugar levels (i.e. hyperglycemia) resulting from defects in insulin secretion, insulin resistance, or both. In general, there are two broad categories of diabetes.[4] The first category, type 1 diabetes, accounts for ~5–10% of those with diabetes and is an autoimmune disease that results in the destruction of pancreatic β-cells, causing an absolute insulin deficiency. The other, most common form is type 2 diabetes which accounts for >90% of those with diabetes and is caused by a combination of insulin resistance, with a relative, but not absolute insulin deficiency.[4] Thus, insulin secretion is impaired in these individuals and is insufficient to compensate for the insulin resistance in peripheral tissues.[5]

The control and management of blood glucose levels in both forms of diabetes is important for preventing ketoacidosis and diabetes-related complications. Given that people with type 1 diabetes produce little or no endogenous insulin, administration of exogenous insulin is necessary for survival.[6] However, while insulin therapy improves glycemic control and protects against diabetes-related complications, it also increases the risk of hypoglycemia and weight gain.[7,8] Unfortunately, the tighter the control of blood glucose levels, the greater the risk and severity of these untoward consequences.[7,9] However, because of the essential role of insulin for the treatment of type 1 diabetes, the only real advances in insulin therapy have occurred through modification of the insulin molecule to...
change its plasma half-life, absorption into the circulation, tissue distribution, and potency, and alternative approaches to type 1 diabetes treatment that are insulin independent have yet to emerge.\[^{[10]}\]

For people with type 2 diabetes, exogenous treatment with insulin is generally not required unless lifestyle modifications including better nutrition and increased physical activity or pharmaceutical interventions with oral antidiabetic agents are not sufficient to manage blood glucose levels.\[^{[11,13]}\] Currently, most strategies for treating type 2 diabetes have focused on either increasing insulin secretion from pancreatic β-cells or improving insulin sensitivity in peripheral tissues such as liver, muscle, and adipose tissue.\[^{[14]}\] However, a growing body of evidence suggests that the central nervous system (CNS) plays a key role in the control of glucose metabolism.\[^{[14,15]}\] The goal of this review is to discuss the literature that supports a role for the adiposity hormone, leptin, in the regulation of glucose metabolism and examine whether dysfunction in this system contributes to the pathogenesis of diabetes.

### Leptin Regulation of Glucose Homeostasis

Leptin is a polypeptide hormone produced and secreted by white adipose tissue (WAT)\[^{[16]}\] that circulates in proportion to body fat mass,\[^{[17]}\] enters the CNS in proportion to its plasma level,\[^{[18]}\] and interacts with its receptor expressed in key brain areas that regulate food intake, energy expenditure, and autonomic function.\[^{[19]}\] A large body of evidence suggests that leptin plays a vital role in the regulation of energy homeostasis as conditions characterized by leptin deficiency promote hyperphagia and weight gain,\[^{[16]}\] whereas administration of leptin leads to reduced food intake, increased energy expenditure, and weight loss.\[^{[20-22]}\] However, recent evidence implicates leptin not only in the regulation of energy balance but glucose homeostasis as well.\[^{[14]}\]

While the effect of leptin to reduce food intake and body adiposity can improve insulin sensitivity in peripheral tissues via indirect mechanisms, several observations suggest that leptin can directly affect glucose metabolism independent of its effects on energy balance. Early studies suggested that the insulin resistance and diabetes phenotype of genetic leptin-deficient (\textit{ob/ob} mouse) or leptin receptor-deficient (\textit{db/db} mouse or \textit{fa/}\textit{fa} rat) rodent models could not be fully accounted for by their hyperphagia and obesity. Not only does caloric restriction fail to improve insulin sensitivity or prevent diabetes in models of either genetic leptin or leptin receptor deficiency,\[^{[23,24]}\] but also leptin administration lowers blood glucose and plasma insulin levels in \textit{ob/ob} mice even when differences in energy intake are controlled for.\[^{[25]}\]

Leptin deficiency has also been implicated to play a key role in the severe insulin resistance and diabetes phenotype of genetic disorders that impair adipogenesis, such as lipodystrophy.\[^{[26]}\] Consistent with this, transplantation of body fat from wild-type, but not leptin-deficient, \textit{ob/ob} mice improves glycemia in lipodystrophic mice.\[^{[27,28]}\] While the diabetes phenotype of lipodystrophic mice\[^{[29,30]}\] and humans\[^{[31,32]}\] is ameliorated with leptin treatment. These data suggest that deficient leptin signaling has severe consequences for glucose metabolism, which are remedied by leptin replacement in a manner that is independent of, and additive to, its effects on energy intake and body fat content.

Another model of acquired leptin deficiency is that which occurs in uncontrolled insulin-deficient diabetes (uDM), a model of type 1 diabetes.\[^{[33]}\] Because insulin action on adipocytes is required for both lipogenesis and inhibition of lipolysis, absolute insulin deficiency leads to uncontrolled mobilization of stored triglyceride and depletion of body fat stores. Progressive loss of adipose tissue is accompanied by a pronounced decrease of leptin levels, resulting in a deficiency of all known adiposity signals.\[^{[33]}\] Consequently, uDM is characterized by diabetic hyperglycemia and hyperphagia,\[^{[35]}\] and marked reductions of both plasma leptin and insulin levels have been implicated in these responses.\[^{[33,35]}\] Leptin deficiency has also been implicated in the development of insulin resistance in uDM.\[^{[16]}\] A physiological replacement dose of leptin administered systemically prevented the development of insulin resistance in a rat model of uDM via a mechanism independent of changes in food intake or body weight.\[^{[37]}\] However, while systemic administration of exogenous leptin at doses to maintain physiological plasma leptin levels only lowered blood glucose levels slightly, it normalized the hyperglucagonemia and hypercorticosteronemia characteristic of uDM. However, in contrast to physiological replacement doses of leptin, hyperleptinemia induced by either pharmacological doses of leptin\[^{[38,39]}\] or an adenoviral gene therapy approach\[^{[40]}\] ameliorates hyperglycemia in rodent models of uDM, despite very low insulin levels. Thus, leptin deficiency plays a fundamental role in the pathogenesis of insulin resistance and related endocrine disorders in uDM.

### Central Nervous System Leptin in the Regulation of Glucose Homeostasis

Since most of the effects of leptin on energy homeostasis are mediated by the brain, a similar mechanism has been invoked...
for leptin’s effects on glucose metabolism. Consistent with this hypothesis, intracerebroventricular (ICV) administration of low doses of leptin ameliorates the insulin resistance and diabetes phenotype of both ob/ob and lipodystrophic mice[30,41] to the same extent as much higher doses of leptin given systemically. In a similar manner, leptin administration directly into the brain normalizes blood glucose levels in rodent models of uDM[42-44] at doses that are ineffective when administered systemically. Furthermore, in non-diabetic rats, central leptin gene therapy blocks high fat diet-induced weight gain, hyperleptinemia, and hyperinsulinemia,[47] while acute infusion of leptin directly into the brain reverses diet-induced hepatic insulin resistance in non-diabetic rats exposed to a high fat diet for 3 days.[48] Taken together, these data provide compelling evidence that the CNS mediates key effects of leptin on glucose metabolism.

SITE OF LEPTIN ACTION IN THE CENTRAL NERVOUS SYSTEM

While leptin receptors are expressed in several hypothalamic[49,50] and extrahypothalamic areas[51,52] involved in the control of energy balance and autonomic function, several observations implicate the hypothalamic arcuate nucleus (ARC) as an important site for leptin-mediated effects on glucose metabolism. Using a combination of gene targeting and gene therapy techniques, Coppari and colleagues found that unilateral restoration of leptin receptors to the ARC of leptin receptor-deficient mice only had a modest effect on food intake and body weight, but a marked effect to lower plasma insulin and blood glucose levels.[53] In a complementary approach, we used adenoviral gene therapy to express leptin receptors in the ARC of Koletsky (fa/+/fa) rats that develop severe hyperphagia, obesity, and insulin resistance due to genetic absence of leptin receptors. Here, selective rescue of leptin receptor signaling to the ARC of Koletsky rats dramatically improved peripheral insulin sensitivity independent of changes in food intake and body weight,[54] providing further support that the hypothalamic ARC plays a key role in mediating leptin’s effects on glucose metabolism.

Growing evidence, however, suggests that brain areas outside the ARC are also likely involved in leptin’s effects on glucose metabolism. Several lines of evidence implicate a role for the ventromedial nucleus of the hypothalamus (VMH) as neurons in this brain area express the leptin receptor,[50] are activated by leptin (as measured by the induction of pSTAT3, a marker of leptin activation)[55] and administration of leptin to the VMH increases insulin-independent glucose uptake in muscle, brown adipose tissue (BAT), and heart via the sympathetic nervous system (SNS).[56,57] In addition, selective inactivation of suppressor of cytokine signaling (SOCS-3; an inhibitor of leptin signaling) in VMH neurons improves glucose homeostasis without affecting body weight,[58] while deletion of leptin receptors from VMH neurons results in an obese, insulin-resistant phenotype.[59,60] Collectively, these findings support a role for both the ARC and VMH in the regulation of glucose metabolism. However, leptin receptors are also expressed in the paraventricular nucleus (PVN) and the dorsomedial nucleus of the hypothalamus (DMH).[49,50] as well as outside the hypothalamus,[51,52] and future studies examining the role of leptin signaling in these brain areas on glucose metabolism are warranted.

CENTRAL NERVOUS SYSTEM MECHANISMS OF LEPTIN ACTION

One key area of research has been to understand how leptin signaling in the brain improves peripheral insulin sensitivity. In short-term high-fat fed rats, ICV infusion of leptin reverses diet-induced insulin resistance via a suppression of hepatic glucose production, by reducing both glycogenolysis and gluconeogenesis.[58] Moreover, rescue of leptin receptor signaling to the ARC of leptin receptor-deficient Koletsky rats improved insulin sensitivity via enhanced insulin-induced suppression of hepatic glucose production, rather than an increase in glucose uptake.[61] In addition, this effect was associated with improved insulin-induced activation of the insulin signal transduction pathway selectively in liver, relative to muscle and WAT, and was associated with reduced hepatic expression of the gluconeogenic genes, glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate kinase (Pepck).[62] Thus, leptin action in the ARC improves peripheral insulin sensitivity primarily through an action in the liver.

One mechanism to explain how the brain communicates to the liver is via autonomic outflow through the vagus nerve. Recent studies suggest that the effect of intrahypothalamic infusion of insulin[62] or free fatty acids[63] to improve hepatic insulin sensitivity requires intact vagal input to the liver. Consistent with the hypothesis that a similar mechanism mediates the effect of leptin in the brain to suppress hepatic glucose production, the effect of restored hypothalamic leptin signaling to improve hepatic insulin sensitivity in obese Koletsky rats was blocked by selective hepatic vagotomy.[61] These data support a model whereby leptin activates a neural signal between the brain and the liver, which regulates hepatic insulin action.

In addition to regulating hepatic glucose production, leptin also has the capacity to enhance glucose uptake in peripheral tissues through insulin-independent mechanisms.[64] Leptin stimulation of glucose utilization involves the CNS, as either ICV or intrahypothalamic administration of leptin
increases non-insulin–mediated glucose uptake in skeletal muscle, BAT, and heart (but not in WAT) via a mechanism involving the SNS.\textsuperscript{[56,57]} Moreover, leptin-induced increases in glucose uptake in muscle and heart are mediated via the VMH, while leptin signaling in both the ARC and VMH regulates glucose uptake in BAT.\textsuperscript{[63]} Based on these observations, we examined the mechanism whereby leptin action in the brain normalizes diabetic hyperglycemia in uDM. This glucose-lowering effect of leptin occurs via a mechanism that is independent of reduced food intake, increased urinary glucose loss, or recovery of pancreatic $\beta$-cells. Instead, using tracer dilution techniques, leptin was demonstrated to activate a previously unrecognized, insulin-independent mechanism for potently inhibiting hepatic glucose production, while increasing tissue glucose utilization, a combination that fully normalizes blood glucose levels in diabetic animals\textsuperscript{[43]} [Figure 1]. These data establish that the brain has the previously unrecognized ability to normalize diabetic hyperglycemia, and we emphasize that this effect is distinct from the previously reported action of leptin to improve hepatic insulin sensitivity.

Besides its actions on liver and peripheral tissues, leptin is also suggested to regulate glucose homeostasis via the islet. One mechanism that has been hypothesized to contribute to the antidiabetic effects of leptin in uDM is the normalization of increased plasma glucagon secretion from pancreatic $\alpha$-cells.\textsuperscript{[40]} Hyperglucagonemia is thought to contribute to diabetic hyperglycemia in uDM, in part, by activating expression of the gluconeogenic genes, G6Pase and Pepck in the liver.\textsuperscript{[66,67]} Consistent with this hypothesis, the glucose-lowering effect of leptin in uDM was accompanied by a normalization of hyperglucagonemia.\textsuperscript{[39,40]} The CNS is implicated in this effect as the glucose-lowering effects of leptin in uDM are mediated via a direct action of leptin in the brain and are accompanied by a normalization of increased plasma glucagon levels.\textsuperscript{[43,68]} Consistent with this, key brain areas including the VMH participate in the control of glucagon secretion\textsuperscript{[69]} via activation of the autonomic nervous system\textsuperscript{[69,70]} during hypoglycemia.\textsuperscript{[71,72]}

Leptin receptors are also expressed on pancreatic $\beta$-cells\textsuperscript{[73]} and systemic administration of leptin has been shown to decrease glucose-stimulated insulin secretion in a dose-dependent manner \textit{in vivo}.\textsuperscript{[74]} Subsequent studies, however, demonstrated that the acute effects of leptin on insulin secretion are mediated through its actions in the CNS via the melanocortin pathway.\textsuperscript{[75]} Consistent with these observations, long-term infusion of ICV leptin decreases glucose-stimulated insulin secretion, an effect that is overcome by an improvement in insulin sensitivity in both normal and diabetic rats (90\% pancreatectomy).\textsuperscript{[76]} Moreover, this leptin-induced reduction in insulin secretion is independent of changes in either pancreatic $\beta$-cell area or mass and is mediated mainly through the SNS.\textsuperscript{[77]} In addition, CNS leptin-transgene expression suppressed plasma insulin levels and improved insulin sensitivity in \textit{ob/ob} mice fed either chow or a high-fat diet.\textsuperscript{[78]} Collectively, these data suggest that intact CNS leptin signaling to the islet may also play an important role in preventing both type 1 and type 2 diabetes.\textsuperscript{[79]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{leptin_normalization}
\caption{Leptin normalization of blood glucose levels in uDM. (a) Type 1 diabetes is characterized by diabetic hyperglycemia and both insulin and leptin deficiency due to the loss of pancreatic $\beta$-cells and the depletion of adipose tissue stores, respectively. This diabetic hyperglycemia is due to both reduced glucose uptake in peripheral tissues and increased rates of hepatic glucose production, in part due to increased glucagon secretion from pancreatic $\alpha$-cells. (b) Leptin administration directly into the brain normalizes diabetic hyperglycemia in uDM by both potently suppressing hepatic glucose production, as well as increasing glucose uptake despite persistent severe insulin deficiency, an effect associated with normalization of elevated plasma glucagon levels.\textsuperscript{[76]}}
\end{figure}
THE HYPOTHALAMIC ARCUATE NUCLEUS

Identifying the hypothalamic neurons that transduce leptin signal into changes of energy homeostasis and glucose metabolism has been the focus of much research. Two well-characterized leptin-sensitive neuronal populations implicated in the control of both energy- and glucose-homeostasis are expressed in the hypothalamic ARC. One of these neuronal subsets expresses pro-opiomelanocortin (POMC) and these cells are stimulated by leptin [80,81] to release alpha-melanocyte stimulating hormone (α-MSH), a peptide that acts on melanocortin receptors (Mc3r/Mc4r) to promote weight loss [82] and improve insulin sensitivity [83]. Adjacent to these cells is a neuronal subset that expresses neuropeptide Y (NPY) and a melanocortin receptor blocker, agouti-related peptide (AgRP) [84]. Both NPY and AgRP promote weight gain [85,86] and insulin resistance [87,88] and, in contrast to POMC neurons, these NPY/AgRP neurons are inhibited by leptin [25]. Therefore, in conditions of reduced leptin signaling such as in ob/ob mice or in uDM, NPY/AgRP neurons are activated whereas POMC neurons are inhibited, a combination of responses that promote weight gain and insulin resistance [19]. Moreover, NPY/AgRP neurons inhibit POMC neurons through release of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) [89]. Thus, in addition to activating POMC neurons directly, leptin also hyperpolarizes NPY/AgRP neurons, thereby reducing the release of GABA onto POMC neurons, therefore disinhibiting POMC neurons [89,90] [Figure 2].

Both pharmacological and mouse genetic strategies have been employed to determine the role of leptin signaling in each of these ARC neuronal populations. Using a Cre-loxP approach, deletion of leptin receptors from both NPY/AgRP and POMC neurons results in hyperinsulinemia and an obesity phenotype that is nearly additive with respect to the increase of body weight following deletion of leptin receptors from individual neurons [91]. In contrast, reactivation of leptin signaling in all POMC neurons [92] or selectively in POMC neurons that express the leptin receptor [93] in mice that otherwise lack leptin receptors normalizes blood glucose levels and ameliorates hepatic insulin resistance independent of changes in energy homeostasis [92,93]. Conversely, deletion of leptin receptors from just POMC neurons results in a mild-obesity phenotype and only a small effect on glucose homeostasis [84]. Taken together, these data suggest that leptin action on POMC neurons in the ARC has important effects in the control of glucose metabolism.

Pharmacological studies have also supported a role for the melanocortin pathway in mediating leptin’s effects on glucose metabolism. In non-diabetic animals, the effects of ICV leptin to stimulate hepatic gluconeogenesis are blocked by central administration of the Mc3/4r antagonist, SHU9119, while leptin-induced suppression of glycolysis remains intact, suggesting that leptin stimulation of gluconeogenesis is mediated via a melanocortin-dependent pathway while leptin-inhibition of glycolysis is melanocortin independent [95]. In addition, the effect of leptin administration to the VMH to stimulate glucose uptake is blocked by the Mc3/4r antagonist, SHU9119, suggesting that this leptin effect is also dependent on activation of melanocortin receptors [65]. Moreover, the antidiabetic effects of leptin in uDM require melanocortin signaling as co-infusion of the Mc3/4r antagonist, SHU9119, directly into the brain blocked the glucose-lowering effect of ICV leptin in uDM. [96] However, this effect of the Mc3/4r antagonist could block leptin action in either two ways – by blocking the increased release of α-MSH from POMC neurons or by mimicking the effect of increased release of the endogenous Mc3/4r antagonist, AgRP, from NPY/AgRP neurons, or both. In contrast, activation of the Mc3/4r alone was not sufficient to mimic the glucose-lowering effects of leptin in uDM [96]. These data suggest that stimulation of POMC neurons alone cannot fully explain the actions...
of leptin in uDM, implying an important role for leptin inhibition of NPY/AgRP neurons as well.

**Therapeutic Implications**

The therapeutic potential of leptin for the treatment of obesity has been dampened thus far by its reduced effectiveness to induce weight loss in obese individuals. Except for rare cases, obesity is not caused by leptin deficiency as most obese humans and rodents have elevated levels of circulating plasma leptin levels. Moreover, in rodent models of diet-induced obesity, the ability of leptin to suppress food intake and induce weight loss and to activate its signal transduction pathway (pSTAT3) in the CNS is impaired. This phenomenon is commonly referred to as “leptin resistance” and is thought to be due to impaired leptin receptor signaling in the hypothalamus, the impaired ability of leptin to cross the blood–brain barrier, or both. Identifying the mechanisms contributing to the development of leptin resistance is an active line of research and recently reviewed elsewhere. Experiments investigating whether leptin administration improves glucose metabolism in type 2 diabetic individuals seem warranted given evidence from rodent studies suggesting that leptin has beneficial effects on glucose metabolism at doses that are ineffective at reducing food intake and body weight. A beneficial role for leptin in the treatment of type 2 diabetes is further supported by a recent study demonstrating that systemic administration of leptin improves insulin sensitivity and normalizes fasting plasma glucose levels in University of California, Davis, type 2 diabetes mellitus (UCD-T2DM) rats, independent of energy intake. Given that rodent models of type 1 diabetes treated with leptin are much more sensitive to the effects of insulin, it also raises the therapeutic possibility that supplementing insulin treatment with leptin may be a useful adjunct in the management of type 1 diabetes.

**Conclusions**

In conclusion, in addition to its well-known effects on energy homeostasis, leptin is a hormone that also directly regulates glucose metabolism through its actions via the CNS. Identification of the specific neuronal subsets downstream of leptin action, which link communication between the brain and peripheral tissues to control both hepatic glucose production and glucose uptake, will help facilitate the development of new approaches to diabetes treatment. While there are several hurdles to overcome for targeting the CNS, it nonetheless has untapped potential for the treatment of diabetes.

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