Role of Leptin in Diabetes Mellitus
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ABSTRACT
Diabetes mellitus is a global health problem with increasing incidences in the developing countries. Though insulin is still the mainstay for the treatment of diabetes, because of its life threatening complications, it is high time to look for alternative therapies. In this background, the adipokine - leptin could be a potential and beneficial alternative treatment modality that can be thought of with the support of clinical trials for its safety and efficacy. Leptin promotes weight loss, regulation of appetite and can reverse diabetes by improving glucose tolerance. By its central and peripheral actions it can act on hypothalamus and modulate immune system. More importantly, leptin’s role in obesity and preventing insulin resistance can go a long way as far as leptin replacement therapy is concerned. Recently, the physiological role of leptin in energy homeostasis, brain, hypothalamus and bone in relation to diabetes has received much attention. Thus, this review has been designed to explore more on the role of leptin in the etiology and novel therapeutic interventions of diabetes.

Key Words: Leptin, Diabetes, Insulin, Energy homeostasis

INTRODUCTION
In 2010, diabetes mellitus affected approximately 285 million people worldwide and the incidence is increasing in the developing countries and this is estimated to reach 435 million by 2030. The discovery of insulin in 1922 by Banting and Best is one of the miracles of modern medicine, and once a deadly disease – diabetes has turned out to be a manageable one since then. It is now understood that insulin is a key metabolic regulator that is vital to glucose and lipid homeostasis and affects many aspects of growth and development.

Time for Insulin Adjunct Therapy
The incidence of Type1 disease (T1D) has been increasing at an alarming annual rate of 3%, thus indicating that the number of patients with T1D is predicted to raise significantly in the future (Borchers et al., 2010). T1D occurs as a consequence of pancreatic β-cell destruction leading to insulin deficiency, a defect that causes hyperglycemia, hyperglucagonemia, cachexia, ketoacidosis, and other abnormalities. T1D is a deadly condition if not treated. Current life-saving interventions include daily insulin administration, as insulin therapy reduces hyperglycemia, glycosylated hemoglobin, and cachexia and prevents or delays some T1D-associated morbidities. However, even with insulin therapy, T1D secondary complications include debilitating conditions, such as heart disease, neuropathy, and hypertension (Bluestone 2010). Apart from these, because of insulin's lipogenic and cholesterologenic actions, long-term insulin treatment may lead to increased ectopic lipid deposition (in nonadipose tissues) seen in patients with T1D (Liu et al., 2009). Furthermore, insulin therapy significantly increases the risk of hypoglycemia, which can be debilitating and fatal. Therefore, insulin-based therapies, though life-saving, cannot completely restore metabolic homeostasis and instead lead to serious side effects. Thus, better anti-T1D approaches are urgently needed.

Adipocyte-Derived Miracle Molecule: Leptin
In this light, the discovery of leptin, the prototype adipocyte secreted hormone/cytokine (Adipokine), in 1994 has revolutionized our understanding of hormonal regulation of appetite control and energy metabolism, plays a major role in islet cell growth and insulin secretion. Adipose tissue not only functions as an energy storage organ but also an active endocrine organ secreting many adipokines, these are a diverse group of bioactive peptides mediating glucose and lipid metabolisms (Trayhurn and Wood 2004). Number of studies has revealed that the adipocyte-derived hormone, leptin, is a key anorexigenic signal that maintains normal energy homeostasis (Ahima and Osei 2004). It promotes weight loss, which in turn has a beneficial effect on diabetes control. On the other hand leptin may play a key
role in controlling and potentially reversing diabetes, a role that has nothing to do with its link to weight loss.

Impaired insulin action is closely linked to the phenomenon of obesity. The adipose tissue not only releases free fatty acids but also hormones and cytokines such as leptin, adiponectin, resistin, TNF-alpha and others. All those particles modify insulin action. Hence the role of obesity in the generation of resistance to insulin and subsequently leading to impaired glucose tolerance as well as overt type 2 diabetes mellitus has been established (Małecki, 2009). Low circulating levels of insulin is mandatory for the antidiabetic actions of insulin (Kalra, 2009). The two hormones namely leptin and insulin are producing the respective adipose tissue signaling by changing the whole dynamics of energy homeostasis (Scherer and Buettner 2011). Mice deficient in either leptin (ob/ob) or the leptin receptor (db/db) display hyperphagia, decreased metabolic rate, significant changes in insulin action with alterations in carbohydrate and lipid metabolisms (Ahima and Flier 2000).

**Leptin – Energy Homeostasis & Physiological Actions**

Normally, Energy homeostasis is a constellation of afferent signals emanating from the short and long term energy stores with a binding central integration leading to an initiation of compensatory behavioral and physiological responses (Ahima and Osei 2004). In the periphery, leptin modulates immune system, reproduction, angiogenesis and lipolysis (Kalra, 2008). Centrally, leptin is an essential component of the feedback circuitry that integrates energy homeostasis, primarily by modulating the hypothalamic peptidergic network involved in energy intake and expenditure (Kalra 2008). Rodents developed diabetes when they showed leptin deficiency as they developed insulin resistance and hence had impaired glucose metabolism. Leptin improves glucose tolerance and increases the expression of key enzymes, there by influencing the rate of gluconeogenesis and glycogenolysis via melancortin-independent and independent pathways (Gutierrez-Juarez et al., 2004). Leptin is a critical signaling molecule in the hypothalamus influencing appetite and satiety. There is a positive correlation between the circulating levels of leptin and adipocyte number & size (Skurk et al., 2007). This is an indication that leptin levels are elevated in obesity and this can eventually produce many of the deleterious negative effects of weight gain such as local inflammatory response (Fantuzzi 2005), thereby creating a vicious positive feedback loop for feeding behavior through leptin resistance (Scarpace and Zhang 2007).

**Leptin on ARH**

The hypothalamus, in particular the arcuate nucleus (ARH), shows dense leptin receptor (LepRb) expression and the ablation of the LepRb in these areas established the functional importance of leptin signaling at the ARH (Van de Wall et al., 2008). In a study leptin signaling in the ARH mice led to a modest decrease in body weight and food intake. In contrast, unilateral reactivation markedly improved hyperinsulinemia and normalized blood glucose levels. The data demonstrated that leptin signaling in the ARH is sufficient for mediating leptin's effects on glucose homeostasis, hence the ARH has been proposed as an important site of leptin action (Coppari et al., 2005). It has been shown that two neuronal groups located in ARH & Ventromedial hypothalamic (VMH) are the key components that mediate glycemia-lowering actions of leptin T1D (Fujikawa et al., 2010). Specifically POMC neurons of ARH are responsible for glucose homeostasis by virtue of leptin signaling (Hu et al., 2009, Coppari et al., 2005). Whereas VMH neurons on injection of leptin have demonstrated increased uptake of glucose into the skeletal and heart muscles (Minokoshi et al., 1999).

**Leptin on Bone**

It was recently reported that mice lacking Osteocalcin (Osteoblast-derived protein) displayed hyperglycemia in association with markedly reduced blood insulin levels, decreased pancreatic islet cell size and insulin immunoreactivity in pancreatic β-cells. Osteocalcin deficiency undermines the disruptions in glucose-insulin homeostasis was underscored by the finding that osteocalcin administration increased insulin secretion from β-cells and normalized blood glucose levels (Lee and Karsenty 2008). In contrast, a study consistently observed that enhanced expression of leptin in the hypothalams suppressed pancreatic insulin secretion and blood glucose levels concomitantly with fat depletion (Kalra 2008). Hence the study states that elevated osteocalcin levels are associated with suppressed blood insulin levels is not consistent with the proposed stimulatory role of osteocalcin on pancreatic insulin secretion (Iwaniec et al., 2009). Probably the increased leptin signaling from hypothalamus to pancreatic β-cells restrains insulin secretion to an extent that it is not overcome by high circulating levels of osteocalcin or the osteocalcin stimulatory and insulin inhibitory responses are independently propagated by central leptin feedback.

**Leptin on Brain**

Recent studies have also shown that leptin action in the brain potently suppresses hepatic glucose production
while increasing tissue glucose uptake despite persistent, severe insulin deficiency and there is compelling evidence that the brain has the capacity to normalize diabetic hyperglycemia in the presence of sufficient amounts of central nervous system leptin (German et al., 2011). Brain is the key site for mediating leptin’s metabolic actions especially in T1D where there is total lack of insulin (Fujikawa et al., 2010). Leptin has the capacity to increase the hypothalamic mammalian Target of Rapamycin (mTOR) signaling which plays a major role in brain that can bring about energy balance, while at the same time inhibition of mTOR signaling can seriously reverse the anorectic effect of leptin (Cota et al., 2006). CNS sites containing leptin receptors have demonstrated the actions of leptin on food intake. It was also indicated that hindbrain leptin receptors have been able to show the same changes (Hayes et al., 2010). In another novel model, medial Nucleus Tractus Solitarius (NTS) containing leptin receptors when knocked out, again the same changes in terms of weight gain and food intake were noticed. In addition to this, when leptin receptor was deleted from NTS, led to an increased metabolic rate secondary to the elevation in food intake (Scott et al 2011).

Leptin & STAT3 Signaling

STAT3 (signal transducer and activator of transcription 3) is absolutely necessary for the acute effect of leptin on glucose metabolism. Although lipoprotein receptors play important roles in lipid uptake, their role in controlling food intake and obesity is not known. It was shown that the lipoprotein receptor (LRP1) regulates leptin signaling and energy homeostasis. LRP1 directly binds to leptin and the leptin receptor complex and is required for leptin receptor phosphorylation and Stat3 activation. The results from the study demonstrated that the LRP1, which is critical in lipid metabolism, also regulates food intake and energy homeostasis in the adult central nervous system (Liu et al., 2011). Central insulin action plays an important role in regulating white adipose tissue (WAT) mass and glucose metabolism via hepatic Stat3 activation (Koch., 2008). Intact STAT3 signaling is important for the hypothalamic regulation of food intake whereas adipose tissue metabolism control by leptin is independent of STAT3 (Buettner et al., 2006). It is understood that activation of STAT3 is required for the activation of Phosphoinositol-3-kinase (PI3K) and leptin modulates glucose metabolism via STAT3 permissive effect (Kitamura et al., 2006). It has been experimentally demonstrated that activation of STAT3 pathway is mandatory for all the metabolic effects of leptin on food intake, appetite and hepatic glucose metabolism (Buettner et al., 2006). Now in summary, it can be said that leptin is capable of activating other metabolically relevant signal transduction cascades, such as mTOR (Cota et al., 2006), AMP-activated kinase (AMPK) (Minokoshi et al., 2004), or PI3K (Hill et al., 2008) in a STAT3-independent manner.

Leptin Replacement & Therapy

Physiologic leptin replacement prevented insulin resistance in T1D via a mechanism independent of food intake or body weight. This effect was associated with reduced total body fat and hepatic triglyceride content, preservation of lean mass, and improved insulin signal transduction via the insulin receptor substrate-phosphatidylinositol-3-hydroxy kinase pathway in the liver, but this is not true in the case of skeletal muscle or adipose tissue. Although physiologic leptin replacement lowered blood glucose levels only slightly, the elevated levels plasma glucagon and corticosterone levels were brought to normal and reversed the hepatic gluconeogenesis enzymes in a rat study model which was on insulin dependent. This is a positive signal in terms of treatment of diabetes in humans and it could give rise to novel therapeutic intervention of both leptin nd insulin deficiencies (German et al., 2010). When leptin is administered centrally all the beneficial effects such as reduced hyperglycemia, increased body weight and survival were observed in both mice and human beings, hence it shows that combination therapy might work well. (Wang et al., 2010, Fujikawa et al., 2010).

Leptin has conspicuous central action on hypothalamus by regulating appetite, body weight, energy homeostasis, neuroendocrine function and significant direct peripheral actions on many tissues. Leptin causes insulin secretion, where as glucose and insulin in turn causes leptin secretion. Leptin increases insulin sensitivity thereby decreasing insulin secretion from beta cells of pancreas. This makes sense because the problem in diabetes is hyperinsulinemia, a condition relieved by leptin. Glucose uptake by muscle is increased and hepatic glucose output is suppressed as these are add-on actions of leptin. Hence congenital hypoleptinemic patients would require leptin therapy along with antidiabetic agents but before going in for this kind of combination therapy more research has to be done to see the feasibility as the sole aim is to maintain glucose homeostasis in diabetics (Yildiz and Haznedaroğlu 2006).

Leptin is the first of a group of adipocyte-secreted hormones to be used clinically to treat hypoleptinemic states. In children with congenital leptin deficiency
associated with extreme obesity, leptin induces satiety and a dramatic loss of weight. This is a perfect therapy in such children. In hypoleptinemic patients with extreme insulin resistance and lipodystrophy, leptin potentially reduces insulin resistance, hyperglycemia, hyperinsulinemia, dyslipidemia and hepatic steatosis. Hence this is a perfect scenario where leptin treatment can provide efficient solution beyond doubt (Gorden and GavriloVA 2003). A novel study on mice revealed administration of neurokinin-1 receptor (NK-1R) and Substance P (SP) have substantially improved insulin signaling and glucose metabolism by altering adipose tissue responses to an increased fat intake. This is important because obesity related pathologies show an altered glucose metabolism due to insulin resistance and glucose intolerance. Hence this study can throw a light in the dark tunnel potential, can be a therapeutic approach for the treatment of type 2 diabetes mellitus (Karagiannides et al., 2011).

Previous findings suggested that leptin, may be substituted or used in combination with insulin to treat T1DM more effectively (Wang M et al., 2010). Very recently, an alternative mechanism was proposed in which leptin was found to regulate insulin-like growth factor-binding protein 2 (IGFBP2) expression in liver, and pharmacologic IGFBP2 levels reversed both T1d and T2D in mice (Hedbacker et al., 2010). Whether IGFBP2 induction is necessary for leptin’s action on glucose homeostasis or to normalize glycemia in insulin-deficient states is unknown.

Adverse Effects of Leptin Therapy

It is essential to consider potential adverse effects of leptin apart from its efficacy. One of them is, Leptin can raise blood pressure. Leptin therapy can cause thrombosis by promoting platelet aggregation leading to impaired endothelial function, immune function and foster inflammation and angiogenesis, all of them could produce or worsen diabetic complications (Koh et al., 2008). This can make diabetics life worse. This is where wisdom and caution are exercised. But fortunately, till date, such adverse effects have not been reported in leptin-deficient lipodystrophic patients treated with replacement doses of leptin. However, if higher than normal leptin levels are needed to effectively lower glycemic levels in T1D humans (because they are not leptin deficient), leptin’s potentially adverse effects may become significant. Such cases must alert doctors and adequate care must be taken to prevent any eventualities. Furthermore, leptin’s effect to suppress glucagon may place T1DM patients at increased risk for severe hypoglycemic episodes by impairing the counterregulatory response necessary to restore glycemia (Kraus et al., 2010).

CONCLUSION

Leptin, a hormone known mainly for regulating appetite control and energy metabolism, plays a major role in islet cell growth and insulin secretion. This finding opens up new avenues for studying leptin and its role in islet cell biology, which may lead to new treatments for diabetes. Leptin can curtail insulin release directly. But there's also a back-door route that researchers are still trying to piece together. Scientists knew that leptin nudges osteoblasts, which manufacture osteocalcin, a protein that stimulates insulin release. Aside from keeping blood sugar and insulin levels down, the rodents that received gene therapy also lived longer than obese rodents that did not. Currently we do not know if that is due to the correction of the diabetes or many of the diseases associated with diabetes. More specifically, interventional studies have demonstrated that several neuroendocrine, metabolic, or immune disturbances in these states could be restored by leptin administration. Extensive studies compounded with clinical trials will be needed to determine long-term safety and efficacy.

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