Pathophysiological role of leptin for human health: A review

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ABSTRACT
Leptin, a protein secreted from fatty tissue, is believed to control fat accumulation in the body. It is secreted in pulsatile fashion like other hormones and its secretion rate depends on adipose tissues. Leptin is not the obesity but a starvation hormone. It works in body by binding with receptors called ob and stimulates the different signal transduction pathways especially those which contain these receptors. Defects in leptin receptors (db/db) or in leptin genes (ob/ob) may result in numerous metabolic abnormalities in human body and disrupt the normal physiology of body. Appropriate availability of leptin in adipose tissues plays much important role in regulating body functions like energy homeostasis, neuroendocrine function, insulin resistance and metabolic syndrome. Leptin responds differently with high and low energy states in body. Leptin receptors present on hypothalamus stimulate the nervous system to ensure energy homeostasis. Low levels of leptin affect the secretions of reproductive and thyroid hormones further causing complications in pregnancy and metabolic activities. Results from interventional studies in humans demonstrate that leptin administration in subjects with congenital leptin deficiency, lipodystrophy and women with hypothalamic amenorrhea reverses the energy homeostasis and neuroendocrine and metabolic abnormalities associated with these conditions. Furthermore, disturbance in leptin receptors or gene may contribute resistance in insulin functioning and metabolic syndromes. The stated functions can be managed by ensuring optimum levels of leptin in human body.

Key words: Leptin, obesity, energy homeostasis, insulin resistance, metabolic syndromes, neuroendocrine function,

INTRODUCTION
Leptin is derived from the Greek word “Leptos” meaning “Thin”. Its discovery has created great enthusiasm due to possible treatment of obesity. Generally adipose tissues are considered only meant for energy storage; however, recent studies have proven it as active endocrine organ. Initial clinical trials of leptin have proven it an ineffective strategy for obesity treatment (Heymsfield et al., 1999; Sendhofer et al., 2015). However, scientists have undertaken extensive researches on leptin to explain its role in human physiology. These studies are more helpful for understanding leptin role in energy homeostasis, insulin resistance and regulation of neuroendocrine function mainly in obesity state. Leptin is composed of total 167 amino acids and it was primarily identified from the positional cloning of mice gene called ob/ob at Jackson Laboratories (Zhang et al., 1994). Proper examination of these mice has shown mutation in their leptin gene and this alteration was homozygous resulting in deficiency of leptin which cause the conditions like diabetes, abnormalities in neuro-endocrine functions, infertility and hyper-phagia. Adipose tissues are responsible for its synthesis (Considine et al., 1996) and it is secreted in a pulsatile fashion like other hormones. The level of leptin is higher in the early morning hours and in evening (Sinha et al., 1996; Licinio et al., 1997). The presence of leptin in blood circulation reflects alterations in caloric ingestion and consequently higher energy storage in fatty tissues (Boden et al., 1996; Chan et al., 2003; Chan et al., 2008).

Function of leptin starts in body when it binds to specific receptors called Ob receptors which are present in peripheral tissues and brain (Bjorbaek et al., 1998). After binding with receptors, it activates many signal transduction pathways, including pathways of Phosphatidylinositol 3 kinase (PI3K), Janus Kinase Signal Transducer and Activator of Transcription 3 (JAK-STAT3). PI3K is essential for glucose homeostasis and food ingestion (Niswender et al., 2001), JAK-STAT3 pathway, it is important for the proper homeostasis of energy (Bates et al., 2003). Likewise, additional pathways Mammalian Target of Rapamycin (mTOR), Adenosine Monophosphate Protein Kinase (AMPK) and Mitogen Activated Protein Kinase (MAPK) are currently under study (Robertson et al., 2008). Hypothalamic mechanisms involved in the leptin resistance include a) mutation in Ob receptors, b) induce the response of leptin signaling and c) changes in the passage of leptin through the blood-brain barrier (Bjorbaek et al., 1999; Myers et al., 2008; Munzberg, 2008). However, further studies are required to fully understand the role of leptin in different signaling pathways which in turn may provide some useful strategies in the treatment of obesity.

Role in human physiology
Leptin plays critical role in energy homeostasis, metabolism and regulation of neuroendocrine functions (Chan et al., 2005; Park and Ahima, 2015) which are discussed below:
**Energy homeostasis**

Leptin circulation in body helps to measure the amount of stored energy and guides the nervous system to maintain the ingestion of food and expenditure of energy accordingly. It has the immediate effect on brain for appetite regulation and exerts its action by binding with Ob receptors in hypothalamic part of brain (Fig 1).

Leptin responds differently with high and low energy states in body. High energy states are related with high level of leptin. Consequently, in this case appetite inhibiting neuropeptides: Cocaine and Amphetamine regulated Transcript (CART) and Proopiomelanocortin (POMC) reduced in ARC (Cowley *et al.*, 2001) also Brain Derived Neurotrophic Factor (BDNF) in the ventromedial hypothalamic nucleus (VMH). In addition to this leptin also perform its action by acting on ventral tegmental area (VTA) of system called dopamine to adjust stimulus and incentive of food intake. In brainstem, it stimulates the activity of NTS which involve in the control of satiety. In contrary to high energy states, lack of energy is responsible for low level of leptin in human body. Consequently, a complex neural circuit with the help of orexigenic signals triggered the intake of food (Robertson *et al.*, 2008). Due to this process the appetite stimulating neuropeptides (orexigenic): Neuropeptide Y (NPY) and Agouti related Protein (AgRP) increased their expression in arcuate nucleus (ARC) (Cowley *et al.*, 2001) and also Melanin concentrating Hormone (MCH) and orexin in lateral hypothalamic area (LHA). Leptin also showed its direct effects on preoptic area (PO) and paraventricular nucleus (PVN) which are essential for neuroendocrine functions in response to less availability of energy, conditions including reducing thyroid and reproductive hormones. The indirect effect of leptin only on gonadotropin releasing hormone (GnRH), its effect on thyrotropin releasing hormone (TRH) and corticotropin releasing hormone (CRH) may be direct or indirect (Robertson *et al.*, 2008). Its outcome on hormone cortisol during less energy varies in human and mice. Not like normal mice (Heiman *et al.*, 1997), replacement dosage of leptin cannot inverse the raised adreno corticotropin (ACTH) levels related with hunger in humans (Robertson *et al.*, 2008).

Leptin has the ability to cross the blood-brain-barrier in order to reach in hypothalamus where it stimulates the complex neural system. This system is composed of neuropeptides that control the intake of food called orexigenic (stimulate the appetite) and anorexigenic (inhibit the appetite). Leptin also perform its role outside of the hypothalamic part of brain, where it interacts with dopamine, which actually intricate the motivation and reward of feeding and to the nucleus of the solitary tract (NTS) that contribute to satiety (Robertson *et al.*, 2008). In addition to its instant effects, the persistent usage of leptin may result in the connections rewiring between the hypothalamic neurons (Bouret *et al.*, 2004; Pinto *et al.*, 2004). Especially in leptin deficient mice, the long-term administration has been exposed to induce quantities of synapses on neurons (anorexigenic) which are involved in the secretion of pro-opio-melanocortin (POMC) and reduce the synapses number on neuro-peptide-Y (NPY) which are orexigenic (Pinto *et al.*, 2004). Role of leptin not just to give signals to brain for food intake but it also perform its function in energy expenditure. It activates the sympathetic activity and stimulates the thermogenesis in brown adipose tissue in mice (although these effects of leptin have not been established in human beings (Collins *et al.*, 1996; Haynes *et al.*, 1997; Chan *et al.*, 2007). Clinical trials have shown that patients with inherited deficiency of leptin due to alteration in its gene or in leptin receptor are obese specifically with the presence of hyper-phagia (Strobel *et al.*, 1998; Farooqi *et al.*, 2007), and when these patients received the replacement dosage of leptin then they attained the normal body weight (Farooqi *et al.*, 2007).
Regulation of neuroendocrine functions

In case of any changes in the proportion of body fat mass, leptin stimulates the activity of neuroendocrine toward short-term deficit of energy (Ahima et al., 1996; Chan et al., 2003; Chan et al., 2006). Resultantly leptin lowers the secretion of reproductive and thyroid hormone, causing complications in pregnancy and decrease the metabolic activities respectively. However, it increased the level of growth hormone which mobilize the energy storage in human and mice (Ahima et al., 1996; Chan et al., 2003; Chan et al., 2008). The interactions of leptin with adrenal axes and growth hormone are not so much important in human as compared to the mice. In patients with inherited deficiency of leptin, normal functioning of adrenal glands has been observed (Farooqi et al., 2002; Ozata et al., 1999). Numerous Studies have shown defective neuroendocrine function in prolonged period of starvation (Chan et al., 2003). In another study, leptin deficiency was induced in women with normal weight and higher levels of baseline leptin, there was decrease in leptin levels up to 2.8 nanogram per milliliter (Chan et al., 2006). Later on it was revealed that leptin threshold of approximately 3 nanogram per milliliter is needed to send the messages to brain that stores of energy in fatty tissues are sufficient to bring pregnancy to term. Leptin level greater than 3 nanogram per milliliter in children allows the puberty onset and in old age persons sustains the neuroendocrine functions (Mantzoros et al., 1997). The conditions like anorexia nervosa and amenorrhea (Chan and Mantzoros, 2005) were related with low leptin level or hypoleptinemia in women who were chronically deficient in energy. This hypothesis was confirmed by observational studies (Mantzoros et al., 1997; Audi et al., 1998; Miller et al., 1998). Low leptin levels are associated with neuroendocrine abnormalities following osteoporosis. The study results have shown that when replacement dosage of leptin was given to amenorrhea women, it completely regularized the thyroid, gonadal and less degree of bone markers along with growth hormone.

Insulin resistance and metabolic syndrome

It has been confirmed from previous studies that if there is any disturbance in leptin receptors (db/db) or leptin gene (ob/ob) present in both mice and human may result resistance in insulin functioning (Fig 2) and metabolic syndrome. In ob/ob mice improvement in insulin and glucose levels prior to optimum weight loss is achieved with leptin administration (Harris et al., 1998). In a study leptin treatment given to the patients showed significant improvements in high insulin levels and HDL besides decrease in LDL and triglycerides (Farooqi et al., 2002). Studies regarding lipoatrophy (lack of subcutaneous fat) in mouse models indicate that these models have low level of leptin due to less fatty tissues, which are necessary for leptin production. In such models metabolic anomalies like insulin resistance, high level of lipid and glucose are commonly present (Gavrilova et al., 2000). When the replacement dose of leptin was provided to these lipoatrophic models a positive response towards exogenous leptin was exhibited (Shimomura et al., 1999). Later it was observed that, if adipose tissues are transplanted to these mice (Gavrilova et al., 2000; Kim et al., 2002), which have ability to produce leptin as well as administrated exogenous leptin (Shimomura et al., 1999) it will definitely improve the conditions like hepatic steatosis, insulin resistance, hyperlipidemia and hyperglycemia (Javor et al., 2002; Oral et al., 2002; Ebihara et al., 2004).

![Fig. 2. Leptin and insulin resistance](image)

Leptin therapy in human disease

Leptin therapy has been observed in several leptin deficiency conditions. The main conditions which have been studied are congenital leptin deficiency, lipodystrophy and hypothalamic amenorrhea (Chan and Mantzoros, 2005; Kelesidis and Mantzoros, 2006).

Congenital leptin deficiency

It is a rare autosomal recessive disease triggered by alterations in the lepin gene and associated with insufficient release of Gonadotropin Releasing Hormone (GnRH), revealing the symptoms of hypogonadism, absence of growth spurt, improper secondary sex...
characteristics and disturbances in mensturation (Tsiodras et al., 2010). With the proper dosage of Leptin many symptoms can be reversed which occurred by congenital leptin deficiency, e.g. there is a significant weight loss in five adult patients which were treated with leptin, the average body mass index fall from 51.5 to 29.2 kg/m² (Paz-Filho et al., 2010). It can also improve the symptoms of dyslipidemia and hyperinsulinemia in these individuals (Gibson et al., 2004). Leptin replacement also be helpful in neuro-endocrine function with significant improvements in puberty (Farooqi et al., 2002; Strobel et al., 2003; Licinio et al., 2004). In a study, proper administration of leptin in three subjects with congenital leptin deficiency revealed, a steady rise in gonadotropins level and normalize the release of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) after 24 months of leptin therapy (Strobel et al., 1998). It was also observed in adults that leptin therapy enhanced the testosterone level, axillary hair production and sperm production (Licinio et al., 2004). Leptin also perform its role in immune function, patients with congenital leptin deficiency have a greater prevalence of infection than the normal individuals, reason is to decreased production and functionality of CD4+ T cells, which normalizes with proper leptin therapy. Moreover, Amylin compassionate leptin access program is use for the long term treatment of the subjects with leptin deficiency (Mantzoros, 2010; Fiorenza et al., 2011).

**Lipodystrophy**

It is an adipose tissue disorder with decreased the rate of subcutaneous adipose tissues and increase in visceral adipose tissue. Lipodystrophy is a autosomal recessive disorder, related with consanguineous marriage (Nishiyama et al., 2009). Exogenous Leptin administration has been observed in nearly 100 subjects with this disorder. The results of these studies revealed that leptin therapy significantly improves insulin sensitivity and dyslipidemia in these subjects and decreases hepatic gluconeogenesis, glycosylated hemoglobin and intrahepatic fat content (Petersen et al., 2002; Javor et al., 2005). Additionally, many studies in humans and rats have exhibited that leptin therapy has its direct effect glucose metabolism enhancement and activating the signaling pathways (Brennan and Mantzoros, 2006) in metabolically important tissues (muscles), but these pathways are not much similar with the normal pathways for insulin activation (Moon et al., 2011). Most prevalent condition of this disorder is HIV-associated lipodystrophy, affecting approximately 14.9 to 35.6% of HIV infected subjects and is also linked with abnormality in metabolism of adipose tissues and insulin resistance (Tsiodras and Mantzoros, 2006; Sekhar et al., 2011). In a study, randomized double blind, interventional study, we observed that leptin in significant dosage improves hyperlipidemia, truncal fat mass and insulin resistance in subjects (Lee et al., 2006). It was also observed from the study that demonstration of leptin in HIV lipoatrophic subjects which were taken pioglitazone also improves glucose metabolism (Magkos et al., 2011). The promising effects of leptin on glucose metabolism in these subjects could be due to strong effect of pioglitazone (a thiazolidinedione) on adiponectin secretion and plasma concentration because leptin therapy alone could not cause alterations in adiponectin levels (Gavrila et al., 2005).

**Hypothalamic amenorrhea**

It is a condition of infertility and major cause of absent menstrual periods and usually seen in hypoleptinemic women who are in very low energy state, e.g. who suffer from anorexia nervosa and who exercise vigorously (Bluher et al., 2009; Kelesidis et al., 2010). The promising treatment for infertility in such women is Leptin replacement therapy (Bluher and Mantzoros, 2004). In a study, proper administration of leptin showed, an improvement in the release of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) after 24 months of leptin therapy (Welt et al., 2004). Results of another nine-month randomized, double blind and placebo controlled study of leptin therapy revealed (Chou et al., 2011). That there was continuation of menstrual periods in approximately 70% of the women, while nearly 60% of them who menstruated were enter in the phase of ovulation. Most Importantly, increase in the dose of leptin in women which were not menstruate due to less leptin level turned to menstruate and resolve the amenorrhea. Moreover, ten weeks administration of leptin also useful in increasing the bone forming markers in women with hypothalamic amenorrhea, but study results shown no alterations in in total and regional bone mass density, which was not shocking because the short period of study (Welt et al., 2004).

**Conclusion**

Leptin is not the obesity but a starvation hormone it plays a fundamental role in some important body functions including energy homeostasis, regulation of neuroendocrine function, insulin resistance and metabolism, not just in surplus energy conditions but, most importantly, in the situations of insufficient energy and starvation. The stated functions can be managed by ensuring optimum levels of leptin in human body. Randomized, controlled clinical trials were proved that proper leptin administration has potential to correct the abnormalities such as congenital leptin deficiency, lipodystrophy and hypothalamic amenorrhea, and also
play important role in the development of leptin sensitizers for common obesity.

REFERENCES


