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Food intake regulation by leptin: Mechanisms mediating gluconeogenesis and energy expenditure

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ABSTRACT

Regulation of blood glucose levels and body fat is critical for survival. Leptin circulates freely in blood and controls body weight and food intake mainly through hypothalamic receptors and regulates glucose metabolism in the liver both directly through leptin receptors and indirectly via the hypothalamic receptors of central nervous system. Leptin affects food intake regulation and eventually glucose metabolism, lipometabolism, endocrine and immune functions, reproductive function, adipose tissue metabolism and energy expenditure. Leptin also exerts peripheral effects directly on glucose metabolism and gluconeogenesis. Most of obese human subjects have elevated plasma levels of leptin associated to the size of their total adipose tissue mass. Hence gluconeogenic function may be an essential factor in the regulation of nutritional intake and weight gain. The aim of this review is therefore to identify and module the possible effects of leptin with special application in gluconeogenesis. In addition, this review includes the study of fat consumption and energy expenditure in the body. Specific modulation of leptin receptors and adipose tissues functioning could have important inference on therapeutic strategies.

1. Introduction

Leptin, a 16 kD protein containing 146 amino acids (encoded by the *ob* gene), is a hormone synthesized by adipocytes that compose adipose tissue, circulates in blood relatively at lower nanomolar (nM) concentrations after cleaving 21 amino acid signal peptide. It mediates its inhibitory effects on dietary intake after binding to the hypothalamic receptors by decreasing the synthesis and release of different neuropeptides. Ob receptors are present in hypothalamus, cerebral and other tissues, *i.e.*, pituitary gland, kidney, lung, liver and ovary [1]. Plasma leptin is transported into the brain via a saturable transport system present in endothelium and choroids plexus. Leptin is an adipocyte-derived hormone that crosses the blood brain barrier, mediates its actions primarily through the elongated configuration of the leptin receptors (ob-rb), the only isoform capable of activating the Janus kinase-signal transducer and activator of transcription pathway [2]. The exact mechanism of leptin in hepatic glycogen metabolism is still controversial [3]. A number of studies have proved to be an important context to highlight the molecular mechanisms underlying leptin deficiency and direct association with the incidence of Alzheimer's disease hence we can improve novel therapeutic strategies and diagnostic tools [4]. Leptin employs direct actions on liver which is the main site of glucose metabolism. Literature indicates that leptin imitates the anabolic effects of insulin on liver. A study conducted by Morton *et al.* (2011) on perfused mouse liver has shown that leptin increases the inhibitory effects of insulin on gluconeogenesis and glycogenolysis in liver via *in vivo* increase in glycogenesis [5] and results in both inhibition and stimulation of some of the initial events of insulin receptor signaling pathway [6]. In some studies which are conducted on the hepatocytes for *in vivo* evaluation, the results show that the absence of an effect of chronic leptin exposure on hepatic gluconeogenesis directly relates to the lack of adiponectin.

Investigation on the endocrine functions of adipose tissues led towards the discovery of leptin as an adipocyte-derived peptide hormone, the deficiency of which causes significant obesity in human models and mice conclusively recognizing the endocrine functions of adipose tissues [7]. There are two kinds of adipose tissue in mammals, *i.e.*, white adipose tissue that

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functions for accumulation of triacylglycerols and brown adipose tissue for heat generation. Excessive accumulation of adipose tissue causes certain illnesses associated with insulin resistance especially in diabetes and osteoarthritis commonly in cats [8]. In a number of studies, leptin-deficient mice develop obesity, as well as hyperglycemia, hyperphagia and hyperinsulinemia which can be rectified by chronic leptin intake. Leptin impacts the neuroendocrine-axis; hence food intake, metabolism and immunological processes may vary by altering the circulating levels of leptin. Leptin was first recognized as a product of gene expression found scarce in the obese mouse. Thus, leptin may be regarded as a circulating indicator of body's nutritional status 'satiety hormone' or lipostat, originally suggested by Kennedy in 1953 [9–11]. The hypothalamus appears to be the principal site of action, as leptin receptors are located in hypothalamic areas involved in the regulation and control of appetite, growth and reproduction [5]. Regardless of advancements in the understanding of the physiology of body weight control, obesity is increasing in many countries. This implicates that the prevention of excessive body weight gain and the therapeutic strategies of obesity have not been improved over the past few years [9]. Obesity is a serious health problem that is measured by body mass index and is also one of the risk factors for breast cancer [12]. Harmon *et al.* conducted a study in 2017 in which they determined the efficacy of leptin receptor antagonist associated with nanoparticles and concluded that adjuvant therapy with nanoparticles is a useful chemotherapeutic therapy for breast cancer [13]. According to an estimate by WHO, more than 1.3 billion individuals are obese worldwide [12]. In the USA, more than two-thirds of adults are categorized as either obese or overweight, whereas more than 23 million people have been diagnosed with type 2 diabetes mellitus. Though in periods of fasting and feeding, plasma glucose level is maintained within a narrow range between 4 and 7 mM in healthy individuals. This limited control is mediated by balance between glucose production by liver, absorption from the intestinal cells and uptake and metabolism by peripheral tissues [14]. It has been hypothesized that leptin may interfere with glucose metabolism by exerting its direct effects on peripheral tissues. In fact, it is reported that leptin exerts its effect on glucose metabolism directly on skeletal muscles [3] and also on isolated adipocytes [15]. Leptin seems to be analogous in physiological actions with insulin and is one of the main metabolic precursors exerting a direct effect on the liver in the regulation of glucose metabolism. It can reduce hepatic glucose production by enhancing the inhibitory effects of insulin on glycogenolysis *in vivo* [16].

In humans, leptin is considered as a highly effective therapy for diabetes mellitus concomitant with lipodystrophy [17]. A study was performed in 2015 revealing beneficial effects of leptin in deficit conditions such as lipodystrophy [18]. Recent studies have been performed on insulin resistance and acute insulin-independent effects by which leptin supplementation reverses the incidence of ketoacidosis and hyperglycemia [19–21]. In patients with type 2 diabetes, gluconeogenesis from glycerol (hereafter glycerol gluconeogenesis) appears to be the main biochemical phenomenon that accounts for 10% of hepatic glucose production. Increased glycerol gluconeogenesis in type 2 diabetes patients results not only from accelerated lipolysis but also from altered hepatic glycerol uptake and utilization [22]. Leptin replacement therapy with metre leptin has improved lipid profile, insulin resistance and ultimately hepatic steatosis [23]. A study exhibited in 2016 has shown that leptin might prove to be a potential therapy in the field of oncology and hematology like myeloma therapy [24]. Indeed, the physiological significance of leptin has just begun to be unfolded.

2. Factors influencing leptin secretion

Changes in nutritional status or body weight is characterized by variations in circulating levels of many growth factors and hormones regulating the adipocyte development and functions, such as growth hormone, insulin, insulin-like growth factor-I and glucocorticoids; hence altering the circulating and locally produced leptin. In addition, administration of insulin or glucocorticoids increases *leptin* gene expressions, providing that other hormonal factors may also facilitate dietary-induced changes on *leptin* gene expressions [25]. Several studies have shown that acute 48 h fast or chronic diet restriction results in a significant decrease in leptin secretion and functions coexisting with a reduced luteinizing hormone secretion mostly in ruminants like ewe and cow [26–28].

2.1. Cyclic adenosine monophosphate (cAMP) integrates leptin and insulin signaling

Leptin suppresses hepatic glycogenolysis and gluconeogenesis. Leptin binding to its hypothalamic receptors stimulates appetite suppression while in adipose tissues and muscle, hepatocytes and pancreatic islets, it stimulates glucose metabolism [1]. In the liver, binding of leptin to its receptor causes activation of JAK2, dimerization of receptor and hence JAK2-mediated phosphorylation of the intracellular receptor portion. JAK2 activation cascades signaling via both IRS-1 and IRS-2 that are responsible for cascading the downstream targets including phosphoinositide 3-kinase. Activated phosphoinositide 3-kinase and phosphorylates phosphatidylinositol-4,5-diphosphate to phosphatidylinositol-3,4,5-triphosphate which subsequently activates other downstream molecules, such as Akt and phosphodiesterase 3B, the chief cAMP degrading enzyme present in the liver [17]. Although leptin and insulin receptors are structurally different, they share various resemblances in their signal transduction pathways. Keeping in view of the molecular mechanism of actions, several studies have shown an interaction between insulin and leptin actions. The key role of cAMP levels in integrating signal transduction pathways from insulin and leptin receptors on the glycogen catabolism can be inclined to gluconeogenesis. Therefore, cAMP levels play an important role in the communication between both hormones and for the insulin-like effects of leptin [1,26].

3. Leptin and glucose metabolism in fixation of hyperinsulinemia

Leptin helps glucose regulation by two distinct ways: 1) energy balance (food intake and expenditure); 2) direct action on tissues/genes. Leptin administration fixes hyperinsulinemia and hyperglycemia even when food intake is controlled. Leptin competes with insulin's effects on fatty acid catabolism in muscles and exerts metabolic effects independent on nutritional intake and body weight [29]. A recent study has shown an additive effect of leptin and insulin in stimulating glycogen storage in hepatocytes

and inhibiting the phosphorylase enzyme demonstrating that the major action of leptin in hepatocytes is to increase glycogen storage and to suppress gluconeogenesis. The influence of gluconeogenesis on hepatic glucose production is significant [30]. By suppressing glucagon action on liver, leptin opposes the catabolic effects of total absence of insulin by enhancing the insulin-like actions of insulin-like growth factor-I on skeletal muscles hence suggesting therapeutic approaches rendering type 1 diabetes as insulin-independent [31].

Balance in gluconeogenesis or glycogenolysis is required to maintain blood glucose levels controlled by hepatic glucose production [32]. The major effect of leptin in hepatocytes is to improve glycogen synthesis and storage. It may be a significant compensatory mechanism for the inhibition of insulin secretion. Inactivation of phosphorylase by leptin causes the conversion and storage of glucose in form of glycogen [33]. Leptin therapy seems to favorably help insulin signaling in liver (not in other tissues) so it alone cannot normalize glucose. Leptin levels can also prevent glucose oxidation by reducing complete metabolism of glucose by peripheral tissues especially adipose tissue. Numerous studies on rodents have established that leptin can inhibit gluconeogenesis or enhance insulin inhibitory effect of glycogenolysis. Elevation in hepatic gluconeogenesis is the consequence of increased glycogen accumulation. Glucagon (enzyme for gluconeogenesis) signaling is required for hyperglycemia and leptin is involved in decreasing blood glucagon [34]. Melanocortin pathway is also involved in insulin signaling and inhibits glycogenolysis through a separate, melanocortin-independent pathway. Leptin also enhances the temporary stimulation of glycogenesis by insulin. Such effects of leptin have been associated with inhibition of phosphorylase enzyme [33,35].

4. Contribution of leptin in maintenance of body's energy balance

Control of energy balance is one of the inspiring areas of neuroscientific research [36]. Leptin can increase or decrease plasma glucose levels depending on body's needs. Increased circulating leptin will increase energy expenditure proportional to body fat (adipose tissue) and decrease food intake. The potential role of leptin on heat production and energy expenditure is an area of recent study in human physiology, as energy expenditure relates to serum leptin but serum leptin does not correlate with any alterations in energy expenditure in many human studies. Leptin effects on energy expenditure was first proposed after injection of leptin into *ob/ob* mice leading to consequent elevation in body temperature and an additional study establishing an increased oxygen consumption following leptin injection into *ob/ob* mice and rabbits [37,38]. Leptin may function to increase energy expenditure by triggering the uncoupling protein action. Therapeutic supplementations of protein and amino acids can increase muscle mass and muscle-derived leptin hence proved to be a beneficial therapy for the elderly to prevent in the incidence of falls and fracture [39].

4.1. Fat consumption underlying leptin associated obesity

Recent literature associates cellular inflammation in the pathogenesis of obesity-induced metabolic damage in adipose tissues [40]. Excessive body adiposity is accompanied by activation of monocytes into macrophages and increased circulating proinflammatory mediators in various peripheral tissues including skeletal muscles, liver, white adipose tissue and the vasculature [11,41]. Recent evidence suggests that inflammation in the hypothalamus can also be induced by ingestion of a high fat diet, an effect that could result in weight gain by decreasing the neuronal response to ascend from circulating leptin and insulin [42]. Therefore, hypothalamic inflammation seems to be both sufficient and necessary for high fat-associated obesity. Liver is exposed to excessive free fatty acid concentrations through the portal circulation owing to enhanced lipolysis in visceral adipose tissues of abdominally obese patients [27]. Chronic elevation of free fatty acid levels in the body affects protein levels and gene expression of enzymes intricate in hepatic glucose and lipid metabolism. However, it is still unclear how these molecular mechanisms affect the physiology of glucose and lipid metabolism in the liver [34,43].

4.2. Impact of insulin resistance on gluconeogenesis

Insulin resistance in the liver, reflecting the increased hepatic glucose output, is known to stimulate gluconeogenesis depending upon the fatty acids oxidation in the liver as a source of energy. In adipose tissues, rising levels of triglyceride storage and enhanced leptin production could function as an indicator to the brain to increase energy expenditure, decrease food consumption and ultimately resist obesity [38]. Chronic administration of leptin improves glucose tolerance by decreasing fat mass and caloric intake. It is suggested by recent studies that leptin plays a major metabolic role in the choice of fuels and homeostasis of energy storage to be utilized under various nutritional status [44–46].

In conclusion, discovery of leptin has improved the understanding of correlation between adipose tissues, energy expenditure, heat regulation and homeostasis. Leptin and insulin have overlapping effects and may share similar mechanisms but they act on different subsets of neurons and have varying effects based on physiological context. Leptin influences glucose production mostly by direct effects on *hepatic* gene expression and insulin secretion more than glucose uptake. Leptin exerts its effect on glucose metabolism in the liver that encompasses insulin-like actions on glycogenolysis and glucagon-like actions on gluconeogenesis. An increased circulating concentration of leptin may help overcome hepatic glycogen turnover and thus maintain euglycemia in conditions like obesity. Major role of leptin is glucose homeostasis by central nervous system that regulates signals from both long-term and short-term energy storage and then generates response. Both of adiponectin and leptin can decrease hepatic gluconeogenesis. These are essential for coordinating peripheral glucose uptake and insulin secretion in order to retain glucose homeostasis. In this way, leptin decreases need of food intake as well as increases energy expenditure. Leptin controls body energy expenditure by adenosine monophosphate-activated protein kinase. It triggers adenosine monophosphate-activated protein kinase in skeletal muscles both directly and indirectly through the hypothalamic-sympathetic nervous system via the suppression of adenosine monophosphate-activated protein kinase activity in the hypothalamus. Inflammation in adipose tissue is a major factor in the hepatic insulin sensitivity and regulation. Elevating the central availability of leptin may be a novel therapy for diet-induced resistance to insulin. Leptin affects energy maintenance and

glucose metabolism through separate mechanisms, most of which require further studies. It is expected that recent advancements in molecular and cellular physiology will result in new therapeutic strategies that not only improve the efficacy of body weight but may also reorganize body weight regulation to a minimum set point, perhaps even allowing a more focused and individualized approach in prevention and therapy of obesity.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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