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A Review of the Leptin Hormone and the Association with Obesity and Diabetes Mellitus

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Abstract

Leptin is a protein hormone that regulates food intake. It is secreted by the adipocytes and contains 167 amino acids. The hormone signals the hypothalamus and is released to reduce the desire for food thereby controlling appetite. Research shows that diet-induced obesity results in leptin resistance, so while the level of leptin may be high, it is ineffective. Leptin is also increased in type 2 diabetes mellitus which is strongly associated with obesity and insulin resistance. While leptin may be elevated in both diabetes and obesity, it is not the cause of either disease. It has been suggested that leptin mediates insulin resistance and as such may be a possible treatment for insulin resistance. Diet induced leptin resistance can be reversed through dietary changes and its administration can be effective in combating insulin resistance. Leptin levels may also decrease with increased exercise. The pathophysiology involving leptin resistance is unclear. More leptin studies are needed as it may be an unexplored treatment for diabetes and may be able to provide a more detailed understanding of the disease.

Keywords: Leptin; Obesity; Diabetes; Insulin resistance

Introduction

Leptin which contains 167 amino acids, was discovered in 1994. It is a hormone secreted by adipocytes and has been found to regulate the intake of food [1,2]. Leptin aids in the regulation of eating behavior through central neuroendocrine mechanisms [2]. It is structurally similar to cytokines and contains an intrachain disulphide bond which has functional significance [3]. Leptin is produced primarily by white adipose tissues and released as a 16 kilo Dalton [kDa] protein [3]. This circulating leptin correlates positively with leptin mRNA and protein levels in adipose tissue [3].

The hormone regulates neuroendocrine function and energy expenditure [1], and has since provided significant insights in obesity [4].

The hypothalamus senses the nutritional state of the body through signaling provided by the leptin hormone [5]. Leptin decreases the intake of food through the upregulation of neuropeptides such as α-melanocyte-stimulating hormone, which is known to be anorexigenic [5]. It concurrently downregulates orexigenic factors such as neuropeptide Y [5]. Obesity can be caused by genetic defects in anorexigenic signaling, such as mutations in the melanocortin-4 or leptin receptors [5]. The administration of leptin in humans and mice induces the reduction of excessive eating and obesity [6]. Obesity, however is associated with high leptin levels which can indicate leptin resistance in obese individuals [6].

Leptin works in contrast to ghrelin, a peptide primarily produced by the stomach which stimulates the appetite [7]. An increase in hunger is directly proportional to an increase in the ratio of ghrelin to leptin [7]. Clinical studies show that leptin levels increase with sleep [7,8]. Research also found that ghrelin levels are inversely related to sleep duration [8].

Leptin and obesity

Obesity is a greater proportion of body fat in relation to lean mass which is significant enough to negatively affect health [9]. The disease can be caused by lifestyle or hereditary influences. Obesity is hereditary primarily due to genetic factors [10]. In mouse, the gene which causes obesity was sequenced in 1994 [10]. Mutation of the gene which causes obesity, results in increased food intake, elevated insulin and significant obesity in non-insulin dependent diabetes mellitus [10]. The mutated gene causes the production of inactive leptin or no leptin [10]. Such mutations are however very unlikely in humans [10]. In a more recent study, lack of leptin in mice has been found to cause severe obesity because of increased food intake and reduced energy expenditure [11]. This has similarly been proven in humans [12]. The leptin deficient mice also develop hyperinsulinemia, often times leading to diabetes mellitus [11]. These effects can be reversed through the administration of the Leptin [13]. This adipocyte-specific protein provided the first links to the body's system regulating body weight [14]. Even though leptin generally increases with adiposity, it was found that at each BMI level there is variability in serum leptin concentration. This suggests that there are differences in its secretion rate from fat [15].

Obesity is not only influenced by lack of leptin but also leptin resistance [16]. Leptin has been proven to increase with increasing adiposity in humans and rodents [16]. Given that the presence of leptin reduces food intake and body weight, elevated levels of leptin in obese persons is viewed as leptin resistance [17]. In these cases, humans lack the responsiveness to the appetite reducing effects of leptin [9]. The effects of leptin resistance are however reversible. If the fat content of obese mice is reduced, the mice will recover leptin sensitivity and glycemic control [9]. It is believed that decreased leptin sensing in the melanocortin circuits influences the pathology of leptin resistance [9]. Research done on mice found that the diet induced resistance to leptin occurs in stages [18]. In the first stage, in response

to high fat diet, the mice were sensitive to exogenous leptin. The second stage conveyed a reduced food consumption, increased leptin production and central leptin sensitivity. The final stage conveyed increased food intake and reduced central leptin sensitivity [18]. The leptin resistance caused by high fat diet results from a defect in access to sites of action in the hypothalamus, which significantly decreases the ability of peripheral leptin to activate hypothalamic signaling [19]. The resistance is also caused by an intracellular signaling defect in leptin-responsive hypothalamic neurons [19].

Leptin has also been associated in the disease atherosclerosis. The thickening of the intima and tunica media is believed to be a marker of the initial stage of atherosclerosis, before symptoms arise [20]. Researchers showed that serum leptin concentrations independently and positively correlated with the intima-media thickness of the common carotid artery [20]. This suggests that increases in leptin concentration is a risk factor for the development of atherosclerosis [20].

Research has found that diet can reduce the levels of leptin [21]. The Palaeolithic diet was found to have a more significant reducing effect on fasting leptin concentration [21]. The reduction in leptin, however, concurs with reduction in weight during the diet [21]. The diet induced reduction in leptin may be due to a concurring loss of fat [21].

Leptin and diabetes

Type 2 diabetes is expected to afflict 300 million persons by 2020 [22]. Not many studies have assessed a direct relationship between leptin concentration and diabetes [23]. Research has however shown that leptin levels are generally higher in persons with diabetes mellitus except when the data is adjusted for body mass index [23]. Leptin has the ability to improve or coonversely induce insulin resistance [24]. This hormone is also known to mediate the release of insulin from pancreatic β cells [24]. Research shows that leptin can be therapeutically useful in the treatment of lipoatrophic diabetes [25]. It is interesting to note that obesity is directly associated with insulin resistance and the development of diabetes mellitus in humans [24]. Given that obesity can be a result of leptin resistance, leptin resistance is likely to be involved in the development of the disease. Like Leptin resistance, leptin deficiency is significant in the pathogenesis of severe insulin resistance in uncontrolled insulin deficient diabetes mellitus [26].

It can however be noted that leptin signaling in neurons can be restored by overexpression of anorexigenic peptides and or repression of orexigenic peptides [27]. Food compounds such as teasaponins, reservatrol, caffeine, taurine and celastrol are able to restore the leptin signaling in neurons using the expression or repression of these peptides [27]. It was also discovered that vitamins A and D improves the transport of leptin across the blood brain barrier [27]. Researchers found that leptin treatment reverses diabetes in lipoatrophic mice [28]. Diet and leptin treatment should be thoroughly explored as a method of diabetes control.

Leptin in athletes

In younger elite kayakers it was observed that short-term detraining resulted in a significant increase in waist circumference, insulin and fasted leptin [29]. The magnitude of the increases in insulin and leptin was dependent on the level of inactivity, where a partially detrained athlete did not express increases as marked as were found in the totally detrained athletes [29]. A study on female athletes concluded that leptin is a possible metabolic signal that provides a link between adipose tissue, energy availability and the reproductive axis [30]. The study however found that sex hormones do not directly regulate leptin (Table 1) [30].

A study on marathon runners found that leptin levels in the runners decrease with body fat [31]. The study also found that after an energy expenditure of 2800 Cal leptin levels decreased suggesting that strong changes in energy expenditure may regulate leptin concentrations [31].

Year	Discovery	Reference
1994	Mice obese [ob] gene and its homolog in humans, cloned.	[32]
1995	The protein product [leptin] of the ob gene was purified.	[13]
1996	Leptin levels in humans vary with the time of the day, peaking nocturnally.	[33]
1997	Increased leptin concentration impairs the action of insulin in rat adipocytes	[34]
1999	Baseline leptin level is associated with the development of diabetes in men	[35]
2001	Leptin shows therapeutic potential to improve diabetes mellitus and reduce insulin resistance.	[25]
2004	Leptin level increases with sleep	[7]
2010	Leptin is significant in the pathogenesis of insulin resistance in uncontrolled insulin-deficient diabetic rats	[26]
2016	The role of leptin in regulating glucose homeostasis appears to be consistent across the vertebrate specie	[36]

Table 1: Chronology of some significant discoveries in Leptin research.

Conclusion

Leptin elevation in diabetes and obesity makes it a significant parameter to assess in clinical research studies. For years it has been known that obesity associated diabetes is linked to insulin resistance as the central basis for the association [37]. Leptin is involved in energy metabolism and changes with physical exercise. Leptin has also been found to have immunological responses [38]. Its signaling can regulate innate inflammatory responses, regulate adaptive immunity and even suppress regulatory T cell differentiation [38]. To date the link between insulin resistance and obesity is not clearly defined as details of the mechanism are not fully understood [37]. Further studies on leptin metabolism and mechanisms of action may be able to define or fill the gap that exists. Research can also explore leptin therapy in combination with dieting which stimulates leptin signaling as a means of controlling diabetes and obesity.

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