



Leptin Hormone in Health and Disease: Overview

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ABSTRACT

Leptin, a pleiotropic hormone is a 167-amino acid peptide that is produced predominantly in the white-adipose tissue. It was co-discovered in 1994. It acts on receptors in the hypothalamus where it inhibits appetite, counteracting the effects of neuro-peptide Y and also promotes the synthesis of α -MSH (melanocyte stimulating hormone). Leptin contributes to the regulation of energy homeostasis, neuro-endocrine function, metabolism, immune function, and bone metabolism. Some conditions associated with Leptin dysfunction include weight loss, congenital leptin deficiency, hypothalamic amenorrhoea and lipodystrophy. Leptin may be an elixir to most metabolic disorders.

Keywords: *Leptin, Pleiotropic, White-Adipose Tissue, Neuro-Peptide Y, α -MSH, Energy Homeostasis, Lipodystrophy*

1. INTRODUCTION

Leptin, a pleiotropic hormone is a 167-amino acid peptide with a four-helix bundle moiety (motif) similar to that of a cytokine (Brennan and Mantzoros; 2006, Zhang et al; 1997), it is produced predominantly in the white adipose tissue but is also expressed in a variety of other tissue, including placenta, ovaries, mammary epithelium, bone marrow and lymphoid tissues (Margetic et al; 2002). It was subsequently given the name leptin (Halaas et al; 1995) from the Greek word "leptos" (meaning "thin. Leptin was co-discovered in 1994 by Jeffrey M. Friedman and Rudolph Leibel at the Rockefeller University and Douglas L. Coleman through the study of such mice (Joseph; 2007).

2. MECHANISM OF ACTION

Leptin acts on receptors in the hypothalamus where it inhibits appetite, counteracting the effects of neuro-peptide Y (a potent feeding stimulant secreted by cells in the gut and in the hypothalamus), and also promote the synthesis of α -MSH (melanocyte stimulating hormone); an appetite suppressant. The absence of leptin (or its receptor) leads to uncontrolled food intake and resulting obesity (Joseph; 2007).

Leptin binds to leptin receptors (ObRs) located throughout the central nervous system and peripheral tissues (Fei et al; 1997), with at least six receptor isoforms identified (ObRa, ObRb, ObRc, ObRd, ObRe and ObRf) (Lee et al; 1996). The ObRb receptor is particularly important in the hypothalamus, where it regulates energy homeostasis and neuro-endocrine function (Elmqvist et al; 1998, Fei et al; 1997, Gao et al; 2008

3. PHYSIOLOGICAL ROLE

In humans, the release of leptin into the circulation is pulsatile, and leptin concentrations follow a circadian rhythm (Scheer et al; 2009), are affected by sleep pattern (Gavrila et al; 2003, Mullington et al; 2003), and display highest levels between midnight and early morning and lowest levels in the

early to mid-afternoon (Bluher and Mantzoros; 2009, Licinio et al; 1997, Sinha et al; 1996).

a. metabolic role

Leptin reduces triglycerol (TG) content in various peripheral tissues such as liver, muscle and pancreatic cells (Shimabukuro et al; 1997) and to partition free fatty Acid (FFA) toward oxidation and away from storage in oxidative skeletal muscle (Greg and David; 2000). Leptin enhances insulin sensitivity in normal rats (Chi-Yul et al; 2002), it also decreases plasma glucose and/or insulin concentrations of normal animals in the post-absorptive state (Emilsson et al; 1997).

b. Neuro-endocrine role

i. Hypothalamic-pituitary-gonadal axis

Leptin stimulate LH secretion in rodents both in vitro and in vivo (Yu et. al, 1997), it regulates reproductive function by activating neurons that project afferent input to GnRH neurons in the preoptic area and other hypothalamic areas (Hill et. al, 2008). Leptin is an important mediator of the hypothalamic-pituitary-gonadal axis (Licinio et. al, 1998).

ii. Hypothalamic-pituitary-thyroid axis

Leptin influences the thyroidal axis by regulating the expression of thyrotropin releasing hormone (TRH) (Sanchez et. al, 2004). Leptin directly stimulates TRH-expressing neurons in the paraventricular nucleus (PVN) of the hypothalamus to upregulate proTRH gene expression (Legardi et. al, 1997). Leptin also indirectly influences TRH neurons in the PVN through signals from the arcuate nucleus (Kim et. al 2000, Paz-Filho et. al, 2009). Leptin also blunts the fasting-induced decrease in prohormone convertase-1 and -2 (PC1 and PC2), which cleave TRH from proTRH (Sanchez et. al, 2004).

iii. Hypothalamic-pituitary-growth hormone axis.

Leptin enhances growth hormone-releasing hormone (GHRH)-induced GH secretion in rat anterior pituitary cells in vitro (Pombo et al. 2001). In humans leptin may regulate not GH secretion per se but mainly the effect of GH (Chan et al, 2008) to regulate secretion of IGF-I and its binding proteins in the periphery.

iv. Hypothalamic-pituitary-adrenal axis.

Corticotropin-releasing hormone (CRH) is synthesized in the PVN, and leptin causes a dose-dependent stimulation of CRH release in vitro (Costa et al, 1997).

v. Regulation of Immune Function

Leptin enhances phagocytic activity in macrophages (Mancuso et al, 2002); promote production of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6, and interleukin-12 (Loffreda et al, 1998); and stimulate chemotaxis in polymorphonuclear cells (Brennan and Mantzoros 2006, Caldefie-Chezet et al, 2003). Leptin also promotes lymphocyte survival in vitro by suppressing Fas-mediated apoptosis (Papathanassoglou et al, 2006). Overall, leptin promotes Th1 cell differentiation and cytokine production (Matarese et al, 2005).

vi. Regulation of Bone Metabolism

Leptin decreases bone mass through mechanisms linking the central regulation of bone remodeling and energy metabolism (Karsenty and Oury 2010). Leptin affects bone metabolism through both central and peripheral pathways. In mice, leptin appears to regulate the formation of cortical bone via sympathetic activation (Hamrick., 2007).

4. DISEASE

The main conditions that have been studied are weight loss, congenital leptin deficiency, hypothalamic amenorrhoea and lipodystrophy (Chan and Mantzoros; 2005, Kelesidis and Mantzoros; 2006).

a. Weight Loss

Leptin levels are higher in most obese subjects (Mantzoros et al; 1997) and reduced in the setting of acute starvation. The reduction of fat mass occurring during weight loss results in decreased leptin concentrations (Monzillo et al; 2003, Mantzoros et al; 1998). Leptin may play a more important role in weight loss maintenance rather than weight loss per se. As leptin levels fall, energy expenditure, sympathetic nervous system tone, and thyroid hormones decrease to collectively drive patients to regain weight (Rosenbaum et al; 2005).

b. Congenital Leptin Deficiency

Congenital leptin deficiency is a rare autosomal recessive disease caused by mutations in the leptin gene. In addition to marked obesity mainly due to hyperphagia, congenital leptin deficiency is associated with inadequate secretion of GnRH,

manifesting in hypogonado-tropic-hypogonadism and, in most cases, failure to reach puberty, including absence of growth spurt, secondary sex characteristics, and menarche (Strobel et al; 1998).

c. Hypothalamic Amenorrhoea

Hypothalamic amenorrhea is a common cause of absent menstrual periods and infertility. It is typically seen in women who are in a state of relative energy deficiency, such as those who exercise vigorously or have a low body fat mass such as in anorexia nervosa, these women are hypo-leptinaemic (Bluher et al; 2009, Kelesidis et al; 2010).

d. Lipodystrophy

Lipodystrophy and lipoatrophy are disorders of adipose tissue characterized by loss of subcutaneous adipose tissue, usually associated with an increase in visceral adipose tissue. Congenital lipoatrophy is a rare autosomal recessive condition often associated with consanguineous marriage (Nishiyama et al; 2009, Pardini et al; 1998).

5. CONCLUSION

Leptin contributes to the regulation of energy homeostasis, neuro-endocrine function, metabolism, immune function, and bone metabolism. Leptin may be that metabolic elixir that can revolutionize our understanding of metabolism and diseases associated with its dysfunction.

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