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Review

Leptin in congenital and HIV-associated lipodystrophy

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ABSTRACT

Leptin is a hormone secreted by adipocytes that regulates energy metabolism via peripheral action on glucose synthesis and utilization as well as through central regulation of food intake. Patients with decreased amounts of fat in their adipose tissue (lipoatrophy) will have low leptin levels, and hypoleptinemic states have been associated with a variety of metabolic dysfunctions. Pronounced complications of insulin resistance, dyslipidemia and fatty liver are observed in patients suffering from congenital or acquired generalized lipodystrophy while somewhat less pronounced abnormalities are associated with human immunodeficiency virus (HIV) and the use of highly active antiretroviral therapy, the so-called HIV-associated lipodystrophy. Previous uncontrolled open-label studies have demonstrated that physiological doses of leptin repletion have corrected many of the metabolic derangements observed in subjects with rare fat maldistribution syndromes such as generalized lipodystrophy. In the much more commonly encountered HIV-associated lipodystrophy, leptin replacement has been shown to decrease central fat mass and to improve insulin sensitivity, dyslipidemia, and glucose levels. The United States Food and Drug Administration has recently granted approval for recombinant leptin therapy for congenital and acquired generalized lipodystrophy, however large, well-designed, placebo-controlled studies are needed to assess long-term efficacy, safety and adverse effects of leptin replacement. In this review, we present the role of leptin in the metabolic complications of congenital and acquired lipodystrophy and discuss current and emerging clinical therapeutic uses of leptin in humans with lipodystrophy.

Abbreviations: POMC, pro-opiomelanocortin; NPY, neuropeptide Y; MRI, magnetic resonance imaging; AMPK, adenosine monophosphate-activated protein kinase; HIV, Human Immunodeficiency Virus; HALS, HIV-associated lipodystrophy syndrome; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; CGL, Congenital generalized lipodystrophy; BSCL, Berardinelli–Seip congenital lipodystrophy; HbA1c, glycated hemoglobin; CNS, central nervous system; HAART, highly active antiretroviral therapy; LDL, low density lipoprotein; HDL, high density lipoprotein; FFA, free fatty acids; NRTIs, nucleoside reverse transcriptase inhibitors; TNF-α, tumor necrosis factor alpha; IL, interleukin; NNRTIs, non-nucleoside reverse transcriptase inhibitors; GLUT4, glucose transporter-4; PPAR-γ, peroxisome proliferator-activated receptor-gamma; CoA, acetyl coenzyme A; aP2-SREBP-1c, adipocyte fatty acid binding protein 2 sterol regulatory element-binding protein 1c; IGF-1, insulin-like growth factor 1; GHRH, growth hormone releasing hormone; FDA, Food and Drug Administration; REMS, risk evaluation and mitigation strategy; r-metHuLeptin, recombinant human metreleptin; TZDs, thiazolidinediones.

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1. Introduction

Leptin is an adipocyte-secreted hormone that plays a critical role in energy homeostasis, circulating at levels that primarily reflect available energy stored in adipose tissue and acute changes in energy intake. [1] This 167-amino-acid peptide acts centrally to promote satiety and decrease food intake, while also acting peripherally to increase glucose utilization by skeletal muscle and to decrease gluconeogenesis in the liver through pathways overlapping with insulin, as recently shown in both animal models and humans. [2–4] In the brain, leptin primarily works at the level of the hypothalamus, mediating pro-opiomelanocortin (POMC) and neuropeptide Y (NPY) neurons, which are well-known to regulate food intake and energy expenditure in animals and humans. [5,6] More recently, functional magnetic resonance imaging (MRI) has also shown that leptin acts at the level of the cortex to regulate more complicated food consumption and cognitive functioning. [7–9] Although leptin exerts many actions in the brain, the central effects may mediate leptin's associated peripheral actions via gene regulation. [10,11] For instance, leptin appears to prevent lipid accumulation in skeletal muscle by activating adenosine monophosphate-activated protein kinase (AMPK) which promotes fatty acid oxidation, [12] thus preventing "lipotoxic" effects. Leptin may also exert actions directly at the level of muscle, specifically engaging alpha-adrenergic receptors in muscle and also through the sympathetic nervous system. [12] Its additional actions on skeletal muscle lipoprotein lipase may explain leptin's ability to preserve lean tissues during weight loss but these data need confirmation. [13] The importance of leptin has been repeatedly demonstrated in many human physiology studies pertaining to neuroendocrine function, immunity, obesity, development and reproduction and these are covered elsewhere in this supplement [14–21].

Leptin deficient mice and humans have many neuroendocrine and metabolic dysfunctions that can be corrected by leptin replacement. [22–26] Indeed, leptin administration in congenitally leptin deficient *ob/ob* mice normalizes hyperglycemia and hyperinsulinemia, even before weight loss, suggesting that leptin affects glucose and insulin independently. [27,28] In congenitally leptin-deficient humans, leptin therapy successfully reduces obesity, restores reproductive functioning, and alleviates the other hypothalamic dysfunctions associated with leptin deficiency. [29] Two such sub-groups of leptin-deficient individuals are observed in patients with congenital lipodystrophy or acquired lipodystrophy, both having lower levels of leptin than their healthy counterparts. [30] Recently, leptin replacement has been found to help with insulin and neuroendocrine dysfunctions in patients with either congenital lipodystrophy [31,32] or Human Immunodeficiency Virus (HIV)-associated lipodystrophy syndrome (HALS), [30,33] and has gathered much interest in its application as an effective therapy for lipodystrophy and its complications.

2. Lipodystrophy: diagnosis, development and characterization

Lipodystrophy is an assorted group of clinical disorders, characterized by complete or partial lack of adipose tissue (lipoatrophy) that may occur in combination with an excess of subcutaneous fat (lipohypertrophy) elsewhere. [9,34] The diagnosis of lipodystrophy is a clinical one, as clear consensus on its definition is lacking, and is often made based on clinical measurement such as limb circumferences, skin fold measurements, or other physical measurements. Such anthropometric data offer a reliable and cost-effective way to estimate fat redistribution and loss. In conjunction with recent radiological modalities of computed tomography (CT) scan, dual-energy x-ray absorptiometry, MRI, and ultrasound imaging, clinical quantification of fat within tissues and body mass may be appropriately measured for a concrete diagnosis of lipodystrophy to be made for research purposes [35].

The sequencing of the human genome along with translational mouse studies has provided knowledge on underlying mechanisms for the biology/pathogenesis of lipodystrophies. Fat tissue is derived from multipotent mesenchymal stem cells and is destined to become either white or brown fat based on the presence of the surface myogenic factor Myf5 (Fig. 1). Indeed, normal white adipocyte differentiation from mesenchymal cells involves a complex, well-regulated signaling network controlled by a variety of gene activations. Any abnormality in this process may lead to the development of a particular lipodystrophy (Fig. 2). Patients with lipodystrophy primarily have a loss of mature, functional adipocytes, as opposed to an absence of lipids in otherwise normal adipocytes. [36–38] The underlying defects are understood to be signaling errors associated with failure of adipogenesis, adipocyte apoptosis, or a failure to store triglycerides in existing adipocytes because of ineffective lipogenesis or excessive lipolysis (Fig. 3).

Lipodystrophy may further be categorized as either congenital or acquired, the former being exceedingly rare and the latter becoming increasingly more common, especially following HIV infection and its treatment.

2.1. *Congenital lipodystrophy*

2.1.1. *Characteristics of congenital lipodystrophy*

Congenital lipodystrophic syndromes are quite rare, with only several hundred cases described in the literature, with likely fewer than 1000 patients in total in North America. [39,40] They may further be grouped as generalized or partial lipodystrophy, based on their distinct clinical presentation and unique patterns of adipose tissue distribution. Congenital generalized lipodystrophy (CGL), or Berardinelli–Seip congenital lipodystrophy (BSCL), is a rare syndrome characterized by near-complete absence of body fat. Inherited in an autosomal recessive fashion, it is seen most in cases of parental consanguinity. Currently, approximately 300 patients of various ethnic backgrounds [41–43] have been reported, with the highest frequency in Brazil. The four different subtypes of CGL with their gene mutations, affected chromosome and protein, and demographics are summarized in Table 1. The rare acquired generalized syndrome of total lipoatrophy, also known as Lawrence Syndrome, is similar to that of CGL except that it develops in a previously healthy individual over days to weeks, often during childhood and adolescence, usually after a nonspecific febrile illness.

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