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Review Article

Leptin and Its Emerging Role in Children and Adolescents

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Abstract. Leptin is an adipocyte-secreted hormone which plays a key role in energy homeostasis. Recent “proof of concept” studies involving leptin administration to humans support its critical role in regulating energy homeostasis, neuroendocrine and immune function as well as insulin resistance in states of energy/ caloric deprivation. Moreover, interventional studies in leptin deficient children and observational studies in normal girls and boys support a role for leptin as a permissive factor for the initiation of puberty in children. The potential clinical usefulness of leptin in several disease states in children and adolescents, including hypothalamic amenorrhea, eating disorders and syndromes of insulin resistance is still under investigation.

Key words: obesity, insulin resistance, leptin, adipocytokines, physiology, hypothalamic amenorrhea

Introduction

Leptin is a 16 Kd adipocyte-secreted protein. Although originally discovered as an obesity associated hormone (1), subsequent clinical trials revealed that obesity is a leptin resistant state (2). The increasing prevalence of obesity in children and adolescents, (currently 15% in the USA) (3) underlies the importance of leptin research in elucidating the pathophysiology of obesity in children. Since the role of leptin might be more important in energy-deficient states, however, leptin’s role has also been studied in disease states such as exercise-induced amenorrhea and anorexia nervosa. In addition,

recent interventional studies in leptin deficient children and observational studies in normal girls and boys support a role for leptin as a permissive factor for the initiation of puberty in children. In this review we summarize leptin’s effects in humans with particular emphasis for the roles of leptin in childhood and adolescence.

The Physiology of Leptin

Leptin, from the Greek *leptos* meaning thin, is the product of the Ob gene (1). Leptin is expressed primarily in white adipose tissue, but also in the stomach, placenta, and the mammary gland (4), and its tertiary structure suggests that it belongs to the cytokine family.

Although fat mass is an important determinant of leptin levels, other factors are also of relevance, including acute changes in caloric intake, gender, adipose tissue-specific factors such as adipocyte size and visceral vs. subcutaneous fat distribution, other hormones

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(e.g. insulin, glucocorticoids) and cytokines (e.g. TNF- α , IL-1) (5–8).

Leptin mediates its effect by binding to and activating several specific leptin receptor isoforms including the main signaling isoform i.e. the long leptin receptor isoform (ObRb) (9, 10). Leptin receptor isoforms are found in many areas of the brain (4) and in peripheral tissues, including the lung, kidney, liver, pancreas, adrenals, ovaries, haematopoietic stem cells, and skeletal muscle. The soluble leptin receptor isoform functions as a leptin-binding protein in the serum (11, 12–14).

The long leptin receptor isoform is a member of the class I cytokine receptor family. Leptin binding to its long receptor isoform activates several signal transduction pathways including 1) the JAK (Janus Kinase) signal transducer and activator of transcription 3 (STAT3) pathway (implicated in energy homeostasis) (15–17), 2) the phosphatidylinositol-3-kinase (PI3K) signaling pathway (important for food intake and glucose homeostasis) (18), and 3) the mitogen-activated-protein-kinase (MAPK) and the SHC/Grb-2 –Ras pathways (implicated in cell proliferation and/or differentiation) (19). Leptin signaling via the JAK-STAT signaling pathway is inhibited by the induction of molecules such as the suppressor of cytokine signaling protein-3 (SOCS-3) and protein tyrosine phosphatase-1B (PTP-1B) which inhibit and/or decrease tyrosine phosphorylation of JAK2, respectively (20, 21). More studies are needed in order to fully elucidate leptin's signalling pathways.

Leptin has also an important role in the regulation of hypothalamic neuropeptide expression. Leptin upregulates the expression of anorexigenic neuropeptides such as proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and downregulates the expression of orexigenic neuropeptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP) (22). Mutations in almost every step in the pathway downstream of leptin to melanocortin receptors (leptin,

leptin receptors, POMC, proconvertase-1, melanocortin receptors 3 and 4) have been described and are associated with obesity (23–25).

Importantly, leptin alters the synaptic plasticity of hypothalamic neurons in mice (26), and acts as a neurotrophic factor during hypothalamic development (27). This is consistent with its role in the development of hypothalamic circuits regulating energy homeostasis (28), but whether leptin has similar effects in humans is an area of intensive research.

Regulation of Neuroendocrine Axes by Leptin

Leptin plays an important role in reproduction (29). Leptin receptors have been identified at all levels of the hypothalamic-pituitary-gonadal (HPG) axis, including anterior pituitary (30), ovary (31), and endometrium (14). *In vitro*, leptin stimulates gonadotropin-releasing hormone (GnRH) pulsatility and release (32, 33). Ob/ob mice, which are leptin-deficient, have morbid obesity and sterility both of which are corrected by leptin treatment (34–36). Rare cases of functional leptin deficiency in humans due to mutations in the leptin or leptin receptor gene, have also helped to clarify the role of leptin in the regulation of the hypothalamic-gonadal axis (37–44). Specifically, leptin replacement therapy results in significant loss of fat mass, development of a pulsatile pattern of gonadotropin secretion and reproductive maturity in leptin deficient subjects (41, 42). Administration of replacement-dose r-metHuLeptin during fasting in healthy lean men fully prevents the starvation-induced decrease in LH pulsatility and testosterone levels (45), indicating that leptin plays an important role in the HPG axis of normal humans too (about the role of leptin in puberty and in hypothalamic amenorrhea see below).

In mice, acute starvation and stress increases corticosterone and adrenocorticotropin (ACTH) levels, whereas exogenous leptin administration

reverses this activation of the hypothalamic-pituitary-adrenal (HPA) axis by inhibiting hypothalamic CRH (36, 43, 46). Unlike mice, the role of leptin in the regulation of the adrenal axis in humans remains controversial (45). Although observational studies have shown a significant inverse relationship between fluctuations in leptin, ACTH, and cortisol (7), subjects with mutations in the leptin or leptin receptor gene appear to have normal adrenal function (40). In addition, uncontrolled studies have shown that leptin-deficient subjects may have elevated basal cortisol and ACTH levels, but normal urinary free cortisol and response to dexamethasone suppression (39). In placebo controlled interventional studies in normal humans leptin does not seem to have an effect on adrenal steroids (45) but more studies are needed to fully clarify this topic.

Leptin may have a role in the regulation of hypothalamic-pituitary-GH-IGF-1 axis in rodents and humans. Leptin receptors are present in normal pituitary tissue and pituitary adenomas (47), and *in vitro* leptin increases GH secretion from pituitary cells (48, 49). Subjects with functional leptin deficiency due to a leptin receptor mutation had a mild but significant growth delay during early childhood as well as decreased GH secretion and low IGF-1 and IGFBP-3 levels (40). In healthy lean men, leptin replacement during acute fasting partially prevents the fall in IGF-1 but not free IGF-1 levels during fasting, with no apparent effect of leptin on IGFBP-1, 2, or 3 (45). However, the effect of leptin on IGF and IGF-BP during puberty and later in life remains to be fully elucidated (39, 43, 45).

Recent evidence supports an interaction between leptin and the hypothalamic-pituitary-thyroid Axis (HPT) in both animals and humans (36, 42, 50–53). Subjects with mutations of the leptin receptor have evidence of hypothalamic hypothyroidism with low thyroxine, normal basal TSH, and sustained TSH response to TRH (40).

In healthy men, leptin and TSH rhythms exhibit a similar 24-h pattern of variability with significant pattern synchrony of ultradian fluctuations; this is impaired in leptin-deficient subjects (54). Additionally, in healthy lean men, leptin administration in replacement doses increased free T4 levels (within the normal range) and significantly blunted the fasting-induced decrease in TSH pulsatility. This indicates that the suppression of TSH associated with fasting is mediated by leptin and that leptin may have effects on free thyroxine levels (45).

Regulation of Bone Mineral Density by Leptin

Several studies have shown that leptin directly stimulates bone growth *in vitro* and increases bone density in leptin-deficient animals (55–60), raising the possibility that low leptin levels may contribute to bone loss in energy deficient states such as hypothalamic amenorrhea and anorexia nervosa. It has also been reported that leptin may cause bone loss in mice through activation of the sympathetic nervous system (SNS) (55–60), however. In contrast, leptin does not appear to influence the SNS in humans (61, 62) and observational studies (63–71) as well as uncontrolled studies involving leptin treatment of humans with congenital leptin deficiency (42) and lipotrophy (72) have failed to indicate a role for leptin in regulating bone density. Positive (69, 73) negative (74, 75) or absent (68, 76) associations between serum leptin levels and bone mineral density have been reported in observational studies in humans. Thus, larger placebo controlled clinical studies are therefore necessary to determine the role of leptin *in vivo* and to assess the contribution of the central and peripheral role of leptin to the overall maintenance of bone turnover in humans (77).

Regulation of Autonomic Function and Blood Pressure by Leptin

Leptin may modulate blood pressure levels in mice through either increasing norepinephrine turnover and sympathetic nerve activity (78, 79) or shifting the renal pressure-natriuresis curve, leading to relative sodium retention (80), which, in turn, result in increased blood pressure in rodents (79, 81, 82). A definite role of leptin in the pathogenesis of hypertension in humans remains to be demonstrated (83, 84) but our own studies have failed to support a role for leptin in regulating autonomic function or blood pressure in humans (unpublished data).

Regulation of Immune Function by Leptin

It has been proposed that leptin plays an important role in the interaction of metabolic and immune systems (85). Leptin deficient *ob/ob* mice have several immune defects (86), and leptin replacement protects the immune system of leptin deficient *ob/ob* or starved mice from lymphoid atrophy (87). Deaths due to infections during childhood have been reported to be more frequent in humans with congenital leptin deficiency but these studies remain anecdotal (39). Decreased serum leptin levels in infants with malnutrition have been correlated with reduced lymphoproliferative responses which are reversed by weight gain (88). Leptin 'polarizes' all levels of immune response towards a pro-inflammatory (Th_1) state (89, 90), and leptin alone or in combination with other immunostimulants induces proliferation and activation of human peripheral blood monocytes/macrophages and naïve lymphocytes ($CD4^+CD45RA^+$) *in vitro* (91–93). In humans, recombinant human leptin (r-metHuLeptin), administered in replacement doses, prevented the starvation induced reduction of $CD4^+CD45RA^+$ peripheral mononuclear blood cells in normal subjects fasting for three days

(94). In children with congenital absence of leptin, leptin also reverses abnormal immunophenotype, T cell hyporesponsiveness and Th_2 cytokine production (42). Finally, in women with hypothalamic amenorrhea and long term leptin deficiency, leptin improved circulating cytokine levels (94, 95). In contrast, no change in pro-inflammatory or other cytokine/chemokine levels was observed in obese hyperleptinemic diabetic subjects by further increasing the already elevated serum leptin levels (irrespective of dose, health status, or duration of treatment). Thus, leptin administration may have a role in immune system modulation in leptin deficient subjects (94), but does not appear to play an etiopathogenic role in inflammation in leptin replete states (95).

Regulation of Hematopoiesis

Expression of the leptin receptor OB-Rb has been detected in yolk sac, fetal liver, bone marrow and $CD34^+$ cells as well as lymphohematopoietic fetal stromal and megakaryocytic cell lines (96, 97). Studies *in vitro*, as well as observational studies in humans and animal studies (97–99) suggest a role for leptin in the induction of proliferation, differentiation and functional activation of hematopoietic cells and particularly the lymphocytic lineage (100), but more studies are needed to fully clarify leptin's role in hematopoiesis.

Regulation of Energy Homeostasis by Leptin

a. Common obesity

Most obese humans have increased leptin levels, indicating that human obesity is a leptin-resistant state (2, 39). Leptin resistance in obese humans is attributed to defects in leptin transport through the blood brain barrier to the hypothalamus and/or to postreceptor defects including induction of inhibitors of leptin signaling in hypothalamic nuclei (101, 102).

Further studies are warranted to clarify the subset of obese individuals for whom r-metHuLeptin treatment would have the greatest effect in weight loss. In this respect, it has been proposed that heterozygotes for leptin gene mutations are overweight or obese but relatively hypoleptinemic and possibly more sensitive to leptin treatment (103).

b. Obesity due to mutations of genes in the leptin pathway

Mutations of the leptin gene or its receptor in humans, although infrequent, underline the importance of the leptin system in the control of energy homeostasis, neuroendocrine and immune function (103) (see above). More than 15 subjects with congenital leptin deficiency have been described to date. These children are normal at birth but develop morbid obesity in early childhood which is responsive to leptin treatment (38, 39, 41). Additionally, heterozygotes for leptin gene mutations have relative hypoleptinemia which may predispose these subjects to develop obesity (103). Finally, several mutations of molecules in the pathway downstream of leptin have been identified as causes of obesity in a significant percentage of obese children (~ 6–8%).

c. Leptin in eating disorders

Leptin levels are low in the serum of patients with anorexia nervosa who also have a relatively higher transport of leptin to the cerebrospinal fluid at lower serum leptin concentrations (104). Levels of the soluble leptin receptor, which represent the main binding protein for leptin, are also higher in patients with anorexia (105–108). This results in an even lower free leptin index and suggests a role for leptin binding proteins in the regulation of energy homeostasis. In patients with anorexia nervosa, who preferentially gain fat mass upon refeeding, leptin levels increase in the cerebrospinal fluid and seem to return to normal before body mass index does (104). Amenorrhea

and other neuroendocrine abnormalities, in patients with anorexia nervosa and women athletes who exercise strenuously, are closely associated with low leptin levels reflecting low fat content. Thus, neuroendocrine function and ovulation are inhibited when a certain amount of nutritional reserves is absent. We have recently tested the hypothesis that low leptin levels in women with hypothalamic amenorrhea (HA) may be directly responsible for the reproductive and hormonal abnormalities by administering recombinant methionyl human leptin (r-metHuLeptin) at replacement doses to women with HA related to strenuous exercise or low weight (109). Thus, leptin is a necessary factor for resumption of menses in patients with anorexia nervosa (110), and increasing LH levels in response to refeeding track increasing serum leptin levels very closely (111). Additional studies are warranted to optimize the dose and duration of r-metHuLeptin required to restore reproductive and other neuroendocrine function without inducing an undesirable degree of weight loss in subjects who are already lean.

Leptin and Insulin Resistance

Administration of exogenous leptin to genetically deficient ob/ob mice or mice with congenital generalized lipodystrophy and severe insulin resistance, improves insulin resistance and hyperlipidemia (112, 113). Subjects with lipodystrophy (congenital or acquired) have lower leptin levels. Uncontrolled interventional studies in more than 35 subjects to date demonstrate that exogenous leptin administration to patients with congenital lipodystrophy and insulin resistance decreases insulin resistance, suppresses hepatic gluconeogenesis, improves hyperlipidemia (114–116) and reverses hepatic steatosis (117).

Leptin has also a role in HIV infection and the Highly Active Antiretroviral Therapy (HAART) induced metabolic syndrome. Importantly,

lipoatrophic HIV positive subjects on Highly Active Antiretroviral Therapy (HAART) have low leptin levels and leptin treatment in men with HIV infection resulted in significant loss of central fat mass, and improvement of insulin resistance and hyperlipidemia (118), indicating that leptin may have a role in regulating insulin sensitivity in humans with relative leptin deficiency. Large-scale, placebo controlled interventional trials are needed to fully elucidate the role of leptin in insulin resistant states in humans.

Specific roles of Leptin in Childhood and Adolescence

A significant role of leptin has been established starting as early as neonatal life and continues through adolescence (119). Leptin plays a role in major physiologic processes which take place during these time periods including growth, puberty and bone development and may also underlie the development of diseases, which manifest predominantly during adolescence and early adulthood, such as hypothalamic amenorrhea and eating disorders.

Leptin in the Neonate

The body weight and fat mass of the neonate are positively associated with the level of leptin in cord blood (120–123) derived from both the placenta (124) and fetal tissues (122, 123). Leptin decreases in response to maternal smoking, is lower in preterm infants and those who are small for gestational age, and is higher in those who are large for gestational age (120). Future studies are clearly required to determine whether the intrauterine and early postnatal nutrient environment programs the endocrine feedback loop between adipose tissue and the central and peripheral neuroendocrine systems that regulate energy balance, resulting in an enhanced risk of obesity in adult life (125).

It has been proposed that leptin may also

regulate growth (126) and promote hematopoiesis and lymphopoiesis in newborn infants (99). Leptin is secreted in the breast milk and can pass from the gastrointestinal tract to the blood (127), suggesting that in addition to neonatal leptin, maternal leptin in milk may, as in rodents, play a role in regulating neonatal food intake or growth (127). In agreement with this notion, it has recently been proposed that the production of leptin in breast tissue by human mammary epithelial cells might be regulated physiologically according to necessity and state of the infant (small, large, normal for gestational age) (128). In conclusion, there are many roles of leptin in the neonatal period, which may have importance for physiologic and pathophysiologic processes later in life, but this area needs to be studied further.

Leptin in Puberty

Inadequate nutrition delays or prevents the onset of puberty (3), and leptin receptors have been found in the ventromedial and arcuate nuclei of the hypothalamus, regions anatomically associated with both control of appetite and reproductive endocrine function (129). Leptin may signal to the brain the existence of a critical amount of fat stores necessary for initiation of puberty and maintenance of menstrual cycles and reproductive ability (130). In normal children, leptin levels increase before puberty as body fat mass increases and reach their peak at the onset of puberty, suggesting that leptin may trigger puberty in humans (131, 132). As stated above, persons with leptin gene mutations or inactivating mutations of the leptin receptor are morbidly obese, remain prepubertal, and have hypogonadotropic hypogonadism (40). In a 9-yr-old leptin-deficient child, leptin replacement therapy for 12 mo resulted not only in marked loss of fat mass, but also the development of a pulsatile nocturnal pattern of gonadotropin secretion consistent with early puberty (41).

This progressed to normal LH and follicle-stimulating hormone (FSH) pulsatility with continued replacement therapy (42). Our group has shown that leptin levels increase prior to the increase of circulating testosterone in peripubertal boys (133) and that administration of replacement-dose r-metHuLeptin during fasting fully prevented the starvation-induced decrease in LH pulsatility and testosterone levels in healthy lean men (45). These findings indicate that falling leptin levels during short-term energy deprivation in healthy men are responsible for the food deprivation-induced decline in reproductive hormones. It may therefore be concluded that leptin plays a role in the regulation of reproduction and may be involved in signaling the onset of puberty and the maintenance of reproductive function thereafter.

Leptin and Hypothalamic Amenorrhea

Hypothalamic amenorrhea is defined by cessation of menstruation secondary to dysfunction of the hypothalamic pituitary gonadal axis in the absence of organic disease or ovarian failure. Women with hypothalamic amenorrhea secondary to intensive exercise or low weight have serum leptin levels lower than those of BMI adjusted controls, reflecting their relative energy deficits. To establish whether lower leptin levels are etiologically linked with hypothalamic amenorrhea, we have recently completed interventional "proof-of-concept" studies involving leptin administration to women with hypothalamic amenorrhea. We found that r-metHuLeptin replacement improved LH pulsatility, neuroendocrine and reproductive function including ovulation, as well as ovarian parameters measured by ultrasonography (109, 134). A subsequent uncontrolled study in women with generalized lipodystrophy and menstrual irregularities or amenorrhea demonstrated that chronic leptin replacement therapy restored regular menses (135). Further longer, placebo

controlled studies are needed to further clarify the role of leptin in the pathogenesis and possibly treatment of hypothalamic amenorrhea and associated osteogenesis and/or infertility.

Other Roles of Leptin in Children and Adolescents

According to recent studies leptin has also been proposed to be involved in the pathogenesis of other diseases such as asthma and cystic fibrosis. Leptin levels are elevated in children with asthma (136), and children and adolescents with cystic fibrosis had elevated leptin levels and reduced gains in fat and fat-free mass (137). It remains unknown, whether the higher leptin levels in those studies are causally related to cystic fibrosis or asthma or whether they are due to stimulatory effects of inflammatory cytokines and whether they may contribute to the anorexia, poor weight gain and growth of those children. Further basic and clinical research is needed in this area.

Conclusions

In conclusion, from the initial simplistic view of leptin as an anti-obesity hormone we now have a far greater understanding of the pleiotropic nature of this hormone. Leptin has an emerging role in children and adolescents. Leptin affects important physiological processes such as neuroendocrine, metabolic, immune, and hematopoietic function, and has a central role in disease states such as hypothalamic amenorrhea and anorexia nervosa. An enormous amount of progress has been made in understanding leptin physiology over the past 11 yr since this molecule was first identified (from *in vitro*, animal, and toxicology studies to human physiology and proof-of-concept treatment studies), but more studies are needed in order to fully elucidate the role of leptin in human physiology and pathophysiology.

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