

## REVIEW ARTICLE

## LEPTIN : FIGHTS AGAINST OBESITY!

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## INTRODUCTION

Leptin (from the Greek *leptos*, meaning thin), It was originally identified as the gene defect responsible for the obesity syndrome in mice discovered in 1994.<sup>1</sup> It is a 167-amino acid protein hormone with important effects in regulating body weight, metabolism and reproductive function.<sup>2</sup> Leptin, The genetic defect of *ob/ob* mice was first described in the 1950s as the spontaneous mutation that causes a severe obese phenotype due to both overeating and decreased energy expenditure. The gene was named *ob* and the obese mice carrying the mutation were called *ob/ob* mice.<sup>3</sup> Because a defect in leptin led to overeating and obesity, leptin was proposed to be a satiety factor. Circulating leptin levels are directly related to adipose tissue mass.<sup>4</sup> High leptin levels signal the presence of sufficient energy stores to sites in the central nervous system, which respond by reducing appetite and increasing energy expenditure, preventing severe obesity.<sup>5</sup> Therefore, leptin signals the nutritional status from the periphery to the area of the brain involved in the homeostasis of energy balance. However, the primary function of leptin may not be as a satiety factor. Leptin treatment at physiological levels reduces eating (and increases energy expenditure) by *ob/ob* mice to the levels of normal mice, but it does not cause satiety (end of eating). Higher doses of leptin are required to decrease food intake in normal animals.<sup>6</sup> The same relationships are true in humans with the *ob* gene defect and normal humans.<sup>7</sup> Leptin levels are also modulated acutely. For example, leptin levels change rapidly with feeding or fasting disproportionately to the changes in fat depot. Therefore, leptin is not just a readout of the fat stores.<sup>8</sup> Leptin is expressed predominantly by adipocytes, which fits with the idea that body weight is sensed as the total mass of fat in the body, it is a key mediator in the regulation of food intake and energy expenditure. Smaller amounts of leptin are also secreted by cells in the epithelium of the stomach and in the placenta. Leptin receptors, which have sequence homology to members of the gp130 cytokine receptor super family, are widely distributed throughout the body, and its mRNA is known to be expressed in hematopoietic cells and lymphocytes.<sup>9</sup> Leptin receptors are highly expressed in areas of the hypothalamus known to be important in regulating body weight, as well as in T

lymphocytes and vascular endothelial cells. Its level is directly related to the amount of adipose tissue. Leptin inhibits food intake by central action on the hypothalamus. Leptin's functions are quite pleiotropic, and it is implicated in a variety of cellular processes, including the modulation of immune cell function.<sup>10</sup> Leptin is structurally related to the long-chain helical cytokine family, which includes IL-2, IL-12, and growth hormone.<sup>11</sup> Serum leptin levels decrease during starvation, and leptin has been proposed to be a major regulator of the central nervous system-mediated adaptation to starvation. Absence of leptin is responsible for the obese phenotype of *ob/ob* mice, and administration of this hormone to these animals reverses many of the endocrine defects.<sup>12</sup> Short-term fasting results in a rapid and marked decline in leptin levels out of proportion to the loss of fat mass, and it has been proposed that this most likely serves as an adaptive mechanism to promote survival and limit procreation during starvation.<sup>13</sup> Body adiposity has been shown to be a major determinant of circulating leptin, an adipocyte-derived hormone involved in body weight regulation. Whereas women have higher leptin concentrations, even after correction for body fat mass, in both genders the Subcutaneous Fat depot seems to be a stronger predictor of leptin levels than Intra-Abdominal Fat.<sup>14</sup> Furthermore, studies in rodents support a possible role of leptin in regulating adiponectin, showing that fasting, a state that acutely decreases leptin expression and its serum concentration, also decreases adiponectin gene expression in adipose tissue, whereas refeeding normalizes the expression of both hormones.<sup>15</sup>

## PHYSIOLOGIC EFFECTS OF LEPTIN:

**Regulation of Food Intake, Energy Expenditure and Body Weight:**

Leptin is an important component in the long term regulation of body weight. Genetically obese mice with inactivating mutations in the *ob* gene or the gene encoding the leptin receptor (*db* gene) have been known for many years and were instrumental in the initial cloning of the *ob* gene. Recent studies with obese and non-obese humans demonstrated a strong positive correlation of serum leptin concentrations with percentage of body fat, and also that there was a

higher concentration of ob mRNA in fat from obese compared to thin subjects. It appears that as adipocytes increase in size due to accumulation of triglyceride, they synthesize more and more leptin. In essence, leptin provides the body with an index of nutritional status. Leptin's effects on body weight are mediated through effects on hypothalamic centers that control feeding behavior and hunger, body temperature and energy expenditure.<sup>16</sup>

- Decreased hunger and food consumption, mediated at least in part by inhibition of neuropeptide Y synthesis. Neuropeptide Y is a very potent stimulator of feeding behavior.

- Increased energy expenditure, measured as increased oxygen consumption, higher body temperature and loss of adipose tissue mass.

As expected, injections of leptin into db/db mice, which lack the leptin receptor, had no effect. When leptin was given to normal mice, they lost weight, showed profound depletion of adipose tissue and manifest increases in lean mass.

The mechanisms by which leptin exerts its effects on metabolism are largely unknown and are likely quite complex. In contrast to dieting, which results in loss of both fat and lean mass, treatment with leptin promotes lipolysis in adipose tissue, but has no apparent effect on lean tissue.<sup>17</sup>

### **Reproductive Function**

It has long been known that starvation adversely affect reproductive function. For example, very low body fat in human females is often associated with cessation of menstrual cycles, and similar effects are seen in starving or nutritionally-deprived animals. Also, the onset of puberty is known to correlate with body condition as well as age.

Leptin concentrations are low in people and animals with low body fat, and leptin appears to be a significant regulator of reproductive function. These effects are probably due in part to the ability of leptin to enhance secretion of gonadotropin-releasing hormone, and thus luteinizing and follicle-stimulating hormones from the anterior pituitary.

One of the first demonstrations of leptin's effect on reproduction dealt with onset of puberty. Prepubertal mice treated with leptin became thin, as one would expect, but also reached reproductive maturity and began cycling significantly earlier than control mice. Additionally, some humans with inactivating mutations in the leptin receptor gene not only are obese, but fail to achieve puberty.<sup>18</sup>

### **Control of Leptin Synthesis and Secretion**

The amount of leptin expressed by adipocytes is directly correlated with the lipid content of the cells. Once synthesized, leptin is secreted through a

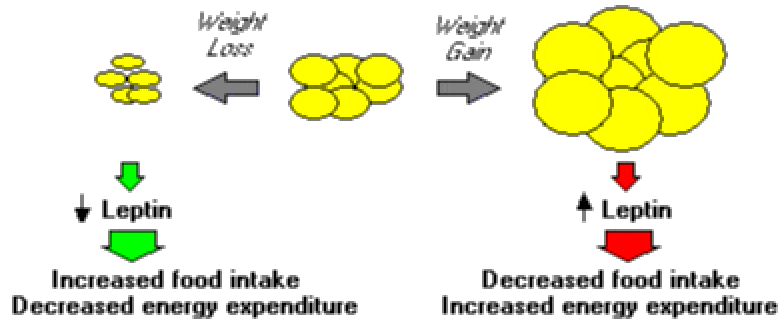
constitutive pathway and not stored in the cell. At this time, the mechanisms responsible for regulating leptin expression in adipocytes are unknown. It is likely that a number of hormones modulate ob gene expression, including glucocorticoids and insulin.<sup>19</sup>

### **Leptin receptors**

The leptin receptor exists in at least six isoforms, one of which (Ob Rb), the so-called 'long form', is thought to be the most important for transmitting the leptin signal in cells. Leptin receptors are found in a variety of tissues, but Ob Rb is located predominantly in the hypothalamus.<sup>20</sup> Under physiological conditions, the amount of leptin produced by fat tissue is directly correlated with both the adipose tissue mass and the mRNA expressed in the tissue. It has also been shown that leptin production is two-fold higher in females than in males, and that it is affected by growth and energy consumption. Leptin is secreted in humans in a circadian and pulsatile pattern (maximal secretion from midnight to 7 AM, and a pulse frequency of 32 pulses/24 hours, each lasting 33 min). The half-life in blood is approximately 25 minutes, and is not modified by body condition (normal or obese).<sup>21</sup> Within the hypothalamus, leptin decreases expression of the orexigenic peptides, neuropeptide Y and agoutirelated peptide, and increases expression of the anorexigenic peptides, POMC and CART, resulting in a decrease in appetite. Many tissues besides adipose tissue have been shown to be able to express leptin and its receptors.<sup>22</sup>

### **LEPTIN IN OBESITY**

Obesity has become an epidemic in affluent societies and is a pan-endemic health problem in both developed and developing countries. Cohort and cross-sectional studies have shown that obesity is associated with coronary artery disease, diabetes, hypertension, gallbladder disease, and osteoarthritis<sup>23</sup> consequently, obesity increases total mortality. Despite that its deleterious health effects are well recognized, how obesity is biologically linked to the pathogenesis of these disorders, especially atherosclerosis, remains obscure. Obesity is an inevitable consequence of chronic positive energy balance. The regulation of energy balance between intake and expenditure and the subsequent metabolic profile that evolves during positive energy balance are mediated by a complex network of signals originating from a number of endocrine tissues, including pancreas, adipose tissue,<sup>24</sup> and, as recently discovered, stomach.<sup>25</sup> These peripheral signals are integrated in the central nervous system (primarily in the hypothalamus) in the regulation of energy intake and expenditure.<sup>26</sup>



Leptin, the product of the *ob* gene, is also an adipocytokine secreted by white adipose tissue. Originally leptin was proposed to act as a signal indicating abundant adipose stores to the hypothalamus to limit energy intake and increase energy expenditure. Subsequently, it has been suggested that the primary role of leptin is in adaptation to negative energy balance. Accordingly, decreases in circulating leptin are associated with increased hunger, and leptin replacement prevents the compensatory decrease in metabolic rate and thyroid axis function after diet-induced weight loss in humans. Furthermore, there is some evidence linking leptin to a direct regulation of adipose tissue metabolism through inhibition of lipogenesis and stimulation of lipolysis.<sup>27</sup> Circulating leptin concentrations are elevated in obesity and decrease after weight loss. Adipose tissue, long being misconstrued as a mere tissue of fat storage, is now acknowledged to be an active participant in energy homeostasis and other physiological functions. The term “adipocytokines” was recently coined to describe the adipose-derived bioactive factors that modulate the physiological functions of the other tissues in our body. Some well known examples among these factors include leptin, plasminogen activator inhibitor-1, and TNF $\alpha$ . It is highly possible that some of the adipocytokines may, in fact, mediate the systemic effects of obesity on health.<sup>28</sup> Although changes in diet and exercise underlie the current global increase in the prevalence of obesity, there is considerable evidence of a substantial genetic contribution to the regulation of body weight.<sup>29</sup> Causative mutations underlying several recognizable pleiotropic obesity syndromes (e.g., Bardet–Biedl syndrome) have recently been identified, but in no case has a clear mechanistic link between the product of the mutant gene and disordered energy balance been clarified. Study of strains of genetically obese mice has resulted in the discovery of several genes, mutations of which have subsequently been found to lead to severe human obesity.<sup>30</sup>

Deficiency of the adipocyte-derived hormone leptin results in obesity, hyperphagia, infertility, and impaired T-cell-mediated immunity in mice and humans, and the administration of leptin completely reverse all aspects of the phenotype in both species. Proopiomelanocortin is regulated by leptin and is cleaved by prohormone convertases to yield a melanocyte stimulating hormone.<sup>31</sup> In 1997 there were reported two children (child A and child B), first cousins of Pakistani origin, who were homozygous for a frameshift mutation in the *ob* gene that resulted in undetectable circulating leptin and a syndrome of hyperphagia and severe obesity.<sup>32</sup> Obesity in adults and children is accompanied by increased circulating leptin concentrations. Leptin correlates most significantly with BMI and body fat. Several studies have confirmed that serum leptin levels decrease following weight reduction. It has been shown that leptin levels are higher in females as compared with males even after correction for the degree of body fat mass.<sup>33</sup> Different genes influence variations in serum leptin levels between the two sexes. Furthermore, this pattern of sexual dimorphism was eliminated after accounting for the effects of testosterone. Androgens have a suppressive effect on serum leptin levels. Testosterone treatment reduces serum leptin concentrations in adolescents with delayed puberty as well as in hypogonadal and eugonadal men. This difference is probably not estrogen-dependent. The gender difference becomes evident in early puberty in conjunction with developing dimorphism in sex steroid production.<sup>34</sup> Lacking the adipocyte hormone leptin, *ob/ob* mice develop severe obesity as a result of a combination of increased food intake and diminished energy expenditure. In addition to obesity, the congenital deficiency of leptin in mice results in a wide range of other phenotypic abnormalities.<sup>35</sup> Leptin levels in obese humans are proportionate to fat mass and, thus, obese humans have higher leptin levels than do non-obese humans. When leptin was administered to obese human subjects, there were

only small changes in body weight, indicating that whatever leptin receptor function abnormality might occur in humans, administration of leptin subcutaneously will not lead to complete amelioration of obesity. Nevertheless, testing of leptin receptor function might be helpful in understanding the pathogenesis of obesity.<sup>36</sup>

#### **LEPTIN IN THE PITUITARY**

Intact Ob-R is present in fetal human pituitaries, indicating that leptin may be involved in the regulation of normal pituitary development. Furthermore, leptin receptors have been found in the choroid plexus and hypothalamus, as well as in the pituitary of different species, such as rat and mouse,<sup>37</sup> pig,<sup>38</sup> sheep,<sup>39</sup> and human. Finally, high concentrations of leptin inhibit pituitary proliferation in human and rat pituitary cell lines, implicating leptin in the regulation of growth and differentiation of pituitary cells.<sup>40</sup>

#### **LEPTIN IN REPRODUCTIVE ORGANS**

Endocrine and/or direct paracrine effects of leptin on the gonads are suggested by the expression of functional leptin receptors on the surface of ovarian follicular cells, including granulosa, theca, and interstitial cells,<sup>41</sup> as well as Leydig cells. In particular, several lines of evidence indicate that leptin acts directly on the ovary. High-affinity receptors for leptin have been identified in ovarian granulosa and thecal cells of adult human ovary and in rat ovary, and leptin receptor mRNA has been detected in human granulosa and thecal cells,<sup>42</sup> mouse oocytes,<sup>43</sup> and porcine ovary/corpora lutea.<sup>44</sup> Furthermore, leptin has direct effects on cultured granulosa cells *in vitro*.<sup>45</sup>

#### **Direct leptin activity on testis cells**

As described above, the direct role of leptin on testis function is still under discussion. However, leptin receptors and/or their mRNA exist in rat Leydig cells,<sup>46</sup> and in porcine<sup>47</sup> and mouse testes.<sup>48</sup> Furthermore, testicular leptin receptor gene expression is developmentally regulated and sensitive to regulation by LH and FSH. Similar to thecal cells, leptin inhibits hCG-induced testosterone secretion from adult rat testicular slices.<sup>49</sup> The role of leptin is primarily inhibitory towards gonadal function in the male, at least in the rat. By contrast, studies in primates and mice suggest that leptin may not affect testicular steroidogenesis.<sup>50</sup> In particular, it has been reported that a very small amount of plasma may pass across the blood-testis barrier, and that leptin receptor mRNA is not present in Leydig cells or Sertoli cells of mice.<sup>51</sup>

#### **Role of leptin in uterine and placenta function**

Although leptin mRNA is not detectable in the uterine tissue of rats and mice, leptin receptor mRNA in the uterus increases 2.7-fold during pregnancy in rats. Its function, however, is currently unknown. A recent study in women showed that subfertile patients with recurrent endometrial maturation defect are deficient for functional leptin receptor expression.<sup>52</sup>

#### **LEPTIN IN THE MAMMARY GLAND**

The leptin gene is expressed in the mammary tissue of cows, sheep and goat.<sup>53</sup> In ovine species, the expression of both leptin<sup>54</sup> and its receptor<sup>55</sup> changes significantly during pregnancy and lactation, with high levels during the first half of pregnancy and a decrease at delivery. Leptin has been found in mammary adipocytes during early phases of pregnancy and in epithelial cells during lactation, while receptor mRNA has been found only in epithelial cells. Leptin could play a paracrine role in cell proliferation, differentiation, growth and apoptosis of epithelial cells. This data suggests a role for leptin in the development and function of the mammary gland. Leptin may derive either from maternal circulation or from local production by breast fat or mammary epithelium. In fact, leptin production has been demonstrated in human and mouse mammary epithelium.<sup>56</sup>

#### **LEPTIN IN THE MILK**

A potential role for leptin in neonate physiology is suggested by the presence of leptin in human, mouse, bovine,<sup>57</sup> porcine,<sup>58</sup> and ovine milk.<sup>59</sup> Leptin, as a cholostral protein, could enhance the newborn immune response and/or intestinal cell function. Leptin in milk during the early stages of lactation may provide a mechanism for thermoregulation, satiation and homeostatic endocrine and metabolic control in the neonate. It has been shown that breast-fed infants are leaner than formula-fed infants because of a decrease in energy intake, and it has been hypothesized that leptin in milk could mediate the satiety of infants fed human milk.<sup>60</sup>

#### **LEPTIN IN THE GUT**

Leptin mRNA and leptin protein have been detected in the chief cells of human gastric mucosa and rat gastric fundic mucosa. It has been reported that leptin concentrations in the stomach are influenced by the nutritional state and the administration of coelchistokinin (CCK). Furthermore, the synthesis and the secretion of gastric leptin involve a 19 kD leptin precursor, which is not involved in leptin production in adipose tissue and the level of leptin is lower after a meal than during fasting conditions. In

the rat, gastric leptin is decreased slightly by starvation, but does not differ significantly from the fasted state. Refeeding of fasted rats decreases gastric leptin to 66% in 15 min and induces a small increase in plasma concentration. In gastric juice, leptin is free and stable and increases under the stimulation of secretin and pentagastrin. Leptin has also been detected in the endocrine cells of the stomach. Secretory granules of P cells in the basal portions of glands stain positively for leptin.<sup>61</sup> Leptin receptor has been detected in the human fundic mucosa and jejunum, suggesting that the gut is a direct target of gastric leptin.<sup>62</sup>

### **LEPTIN IN KIDNEY**

Very recently, it has been reported that the kidney is not only a site of leptin metabolism, but also a target organ for leptin action in pathophysiological states. This organ expresses only a small amount of the full-length receptor Ob-Rb, but high concentrations of the truncated isoform of the leptin receptor Ob-Ra. Both cultured glomerular endothelial cells and mesangial cells obtained from the diabetic db/db mouse possess the Ob-Ra receptor, but it remains unknown whether the biological effects of leptin are transduced through this receptor.<sup>63</sup>

Serum leptin levels are directly proportional to adipocyte mass. Normally, a low leptin level signals starvation and directs the body to adapt to this condition. One way to gain insight into the physiological importance of leptin in humans is to study the conditions associated with its absence or deficiency. Patients with a complete deficiency of leptin as a result of mutations in the leptin gene are morbidly obese from infancy and have a number of hormonal abnormalities, including insulin resistance and hypogonadotropic hypogonadism. Physiologic replacement with recombinant leptin for one year in one such patient led to a substantial weight reduction and an improvement in the hormonal abnormalities. Severe lipodystrophy, caused by a deficiency or destruction of adipose cells, is another state characterized by low leptin levels.<sup>64</sup> Other abnormalities in this condition include hypertriglyceridemia and severe insulin resistance, which is usually accompanied by diabetes mellitus. There are several genetic and acquired forms of lipodystrophy in humans, and studies of a variety of genetically engineered animal models demonstrated that the metabolic abnormalities develop as a consequence of fat loss.<sup>65</sup> Why is adipose tissue so vital to the prevention of the metabolic abnormalities? One hypothesis is that the adipocyte hormone leptin has a critical role in preventing the insulin resistance and hypertriglyceridemia of lipodystrophy. Interestingly, leptin-replacement

therapy at a level meant to achieve physiologic levels led to a dramatic improvement in insulin resistance, hyperglycemia, hypertriglyceridemia, and hepatic steatosis in a mouse model of lipodystrophy. Therefore, we sought to determine whether such treatment would improve the insulin resistance, diabetes, and hypertriglyceridemia of patients with lipodystrophy.<sup>66</sup>

### **CONCLUSION**

Obesity has been the problem in affluent societies of developing and developed world. Hence the diseases, which are common manifestation of obesity, are prevalent in obese persons. To get rid of those diseases it is necessary to avert obesity. In light of above discussion it is proposed that the Leptin may be a vital tool to fight against obesity and prevent such diseases like hypertension, MI, diabetes mellitus before their occurrence.

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