

UCLA
Nutrition Bytes

Title

The Adipose Neural Connection: Leptin

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Journal

Nutrition Bytes, 2(1)

ISSN

1548-4327

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Publication Date

1996

Peer reviewed

Obesity is a very common disorder which affects a large percentage of the population. Complications of obesity include non-insulin-dependent diabetes mellitus, and atherosclerosis, which in turn can lead to hypertension, heart disease, stroke, cancer, and other vasculature and metabolic abnormalities (Grundy & Barnett, 1990). Although obesity has been associated with many types of premature death, the pathophysiology of obesity has remained, for the most part, elusive. Obesity has a large number of possible etiologies since the disorder can be due to a complex combinatorial array of genetic and non-genetic factors.

Recently, mechanisms have been elucidated involved with the adipose cell secretion of a hormone which is detected by receptors in the hypothalamus. This hormone, leptin, is produced in proportion to the body fat composition and has the function of signaling feelings of satiety. The name Leptin comes from the Greek leptos, meaning thin.

Mutations in mice can produce an obese phenotype and in 1950 the first of these mutations (Ingalls et al.) was termed the obese mutation (ob). Homozygous ob mice have significant obesity and type II diabetes mellitus. These mice were known to be deficient in a blood born agent which can signal satiety. A homozygous ob/ob mutant can be surgically joined to a normal animal so that there is exchange of blood between the two animals. These experiments showed that the normal mouse had the ability to partially correct the obesity disorder in the ob/ob mutant (Sahagian et al., 1989). Additionally, adipose tissue of overfed rats implanted into normal rats can suppress food intake for over 12 hours (Rink, 1994). The conclusion drawn from these experiments was that there must be a fat-derived "messenger" circulating in the blood, which exerts a dominant control over appetite.

The exact nature of the mutation in the ob gene has remained unclear until the recent cloning of the ob gene (Zhang et al., 1994). The mRNA produced by this gene is 4.5 kb which codes for a 167 amino acid protein, leptin. The protein sequence is 84% homologous between human and mouse. The 5' flanking region of the mouse ob gene contains a promoter with several consensus C/EBP binding sites. The C/EBP- α transcription factor is believed to induce endogenous expression of leptin (Hwang et al., 1996). Cotransfection experiments with C/EBP- α caused a 23-fold activation of leptin expression in adipose tissue (He et al., 1995).

Studies have addressed questions about the role of leptin in the pathophysiology involved in human obesity. Serum concentrations of leptin and body fat index was measured in a lean group of humans (n = 136) and an obese group. The obese group were defined as having a body mass index greater than 28 (n = 139) (Considine et al., 1996). Serum leptin concentrations in the obese subjects were significantly greater than the lean group by a factor of 4. For all subjects there was a strong positive correlation between their serum leptin concentration, and their percentage of body fat. Leptin mRNA was assayed from biopsied human adipose tissue and found to be twice as high in the obese subjects than in the normal subjects (Considine et al., 1996). Additionally, mRNA levels correlated well with levels of body fat in these subjects. The effects of weight loss in obese subjects were studied by putting them on a liquid-protein diet (Optifast 800) until their body weight was reduced by 10% (Considine et al., 1996). Mean serum leptin concentration, as well as mRNA levels in adipocytes significantly decreased at this lower body fat composition.

Overfeeding of normal animals has been found to change the expression of leptin (Masuzaki, 1995). In a model of acquired obesity, normal rats were overfed on a high fat diet. These rats developed a moderate degree of obesity, hyperglycemia, and hyperlipidemia as compared to rats fed a normal diet. Both groups of rats showed expression of leptin mRNA selectively in all types of adipose tissue. Expression of leptin was augmented in the fat rich diet group over the animals in the normal diet group in all the adipose tissue examined. Expression of leptin also strongly correlated with blood lipid levels (Frederich et al., 1995).

Leptin is not only regulated by nutritional status but also by the surrounding temperature. Acute exposure (2-4 hours) to close to freezing temperatures led to the reduction in leptin mRNA in the white adipose tissue of mice (Trayhurn et al., 1995). This thermoregulatory property of leptin has been postulated to be under sympathetic nervous system control (Trayhurn et al., 1995). The proposed mechanism is that

decreased levels of leptin would increase an animal's appetite for food, which is a source of energy for heat production. Thus, leptin might serve as a master regulatory hormone in controlling satiety.

Accumulating knowledge of leptin endocrinology has led to attempts to modulate body fat composition. With no apparent toxicity, administration of exogenous leptin has been found to cause weight loss in normal mice and to a greater extent in the ob/ob mutant mice (Pellemounter et al., 1995; Halaas et al., 1995). The weight loss effect was attributed to a decrease in appetite and an increase in energy expenditure. Leptin administered as a single morning injection (5-100 mg) to the ob/ob mutant mice reduced feeding in a dose dependent manner (Weigle et al., 1995). Injections in normal mice, twice daily, resulted in a reduction in their body fat from 12.2% to 0.7% (Halaas et al., 1995). Insulin injection in fasting animals increased leptin mRNA to a level similar to control animals (Saladin et al., 1995). Regardless of the glucose levels, insulin regulates leptin expression. Questions remain as to how leptin expression and secretion are causally related to fat intake and percentage body fat.

Knowledge of the complete pathway by which leptin exerts its satiating effects is not completely understood. The db/db mutant is another form of genetically obese mice (Coleman, 1989). The phenotype of these mice is similar to the ob/ob mice. Blood from the db/db mice can reverse the obesity in the ob/ob mice, but the reverse is not true (Coleman, 1989). So perhaps there is a down-stream effector of leptin missing in the db/db mice. This could be a receptor and or post-receptor signal transduction cascade element. Injections of leptin in the db/db mice produce no reduction food intake or change in body weight (Pellemounter et al., 1995; Halaas et al., 1995; Campfield et al., 1995).

It has been well established that the hypothalamus possesses a satiety center that is responsive to signals indicative of global energy status (Bray, 1989; Friedman & Leibel, 1992). Binding sites for leptin have been found in the choroid plexus and hypothalamus (Tartaglia et al., 1995; Stephens et al., 1995). The choroid plexus is a tissue area involved with filtering blood to produce cerebrospinal fluid (CSF) in the ventricular system. This region contains transporters necessary for maintaining the fluid composition of the CSF. Genetic mapping of the gene encoding this hypothalamic binding site shows that it is within the 5.1 cM interval of the mouse chromosome 4 which contains the db locus (Tartaglia et al., 1995). The ventromedial nucleus of the hypothalamus (VMH) is considered to be the most important satiety center. Lesions of the VMH is a result of both increased food intake and increased energy expenditure (Brobeck, 1946).

Natural selection can help explain in part, the large prevalence of the genetic obesity. Mice who are heterozygous for the ob mutation have enhanced ability to survive a prolonged fast (Coleman, 1979). Similar mutations in humans may exist as a selective advantage in human populations which have been adapted to caloric deprivation.

Phase I human clinical trials of leptin may start soon, and several researchers are focusing on leptin, and its receptor in order to develop treatments for type II diabetes mellitus, and obesity. On March 22, 1996, Progenitor Inc. a majority-owned subsidiary of Interneuron Pharmaceuticals Inc. announced it is seeking an international patent covering the leptin receptor protein, the gene for the receptor, expression vectors, and genetically engineered cells carrying the gene. The marketing and business wars have begun.

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