15.6.1.11: Leptin - the Fat Hormone

Leptin

Several strains of laboratory mice are homozygous for single-gene mutations that causes them to become grossly obese.

These fall into two classes:

- **ob/ob** = mutations in the gene for the protein hormone leptin
  
  When *ob/ob* mice are treated with injections of leptin they lose their excess fat and return to normal body weight.

- **db/db** = mutations in the gene that encodes the receptor for leptin

Study of these animals has led to an understanding of the action of leptin in humans.

Human leptin is a protein of 167 amino acids. It is manufactured in the adipocytes (fat cells) of white adipose tissue, and the level of circulating leptin is directly proportional to the total amount of fat in the body.

Leptin acts on receptors in the hypothalamus of the brain where it:

- counteracts the effects of **neuropeptide Y** (a potent feeding stimulant secreted by cells in the gut and in the hypothalamus)

- counteracts the effects of **anandamide** (another potent feeding stimulant that binds to the same receptors as THC, the active ingredient of marijuana)

- promotes the synthesis of **α-MSH**, an appetite suppressant

- the result is the inhibition of food intake
This inhibition is long-term, in contrast to

- the rapid inhibition of eating by cholecystokinin (CCK)
- the slower suppression of hunger between meals mediated by PPY3-36

The absence of a functional hormone (or its receptor) leads to uncontrolled food intake and resulting obesity.

Leptin also acts on hypothalamic neurons responsible for

- the conversion of white adipose tissue (WAT) into "beige" adipose tissue. "Beige" cells metabolize food into heat rather than storing it as fat. In mice, leptin promotes weight loss even with normal food intake.
- the secretion of gonadotropin-releasing hormone (GnRH). Women who are very thin from limited food intake or intense physical training may cease to menstruate because of their lack of leptin-secreting fat cells. Treating them with recombinant human leptin can sometimes restore normal menstruation.
- stimulating the sympathetic nervous system to trigger the breakdown of fat in adipose tissue.

In addition to its effect on the hypothalamus, leptin acts directly on the cells of the liver and skeletal muscle where it stimulates the oxidation of fatty acids in the mitochondria. This reduces the storage of fat in those tissues. T cells where it enhances the production of Th1 cells promoting inflammation. Mice without leptin are protected from autoimmune disease (which may account for the reports that restricting food intake helps humans with rheumatoid arthritis).

Mutations in the gene for leptin, or in its receptor, are rarely found in obese people.

The rare cases:

- Extreme obesity in five members of two families that are homozygous for mutations (frameshift in one family, missense in the other) in their leptin gene; i.e., they are like ob/ob mice.
- Extreme obesity among three members of a family that are homozygous for mutations in their leptin receptor gene; i.e., they are like db/db mice.
- Only moderate obesity in people who are heterozygous (one mutant and one normal) for their leptin genes.

Recombinant human leptin is now available, but trials to see if it can reduce obesity in humans as it does in ob/ob mice have been disappointing.

However, the 16 September 1999 issue of The New England Journal of Medicine reported the results of a year-long trial of recombinant human leptin in a 9-year-old girl who is homozygous for a frameshift mutation in her leptin genes. The findings:

- She began the trial weighing 208 pounds (94.4 kg), of which 123 lbs (55.9 kg) was fat (adipose tissue).
- She was given daily injections of recombinant leptin for one year.
- At the end of that time,
  - she had lost 36 lbs (16.4 kg), most of it fat.
  - Her appetite and thus food intake had decreased.
  - Her immune system made antileptin antibodies but these did not seem to interfere with the action of the hormone.

But trials of recombinant leptin in obese humans who do not have mutations in both their leptin genes have not shown...
any great benefit in weight reduction.

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