Can We Pop a Pill to Cure Obesity?

Genetic Studies of a Complex Trait

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Characteristics like obesity and many other behavioural traits are the result of the interaction of various environmental factors and lifestyle with multiple genes. This article describes recent research on the molecular biology of some forms of obesity that suggests possible ways to control the condition.

Is obesity merely the result of eating too much or is it possible that there is a genetic basis for the condition? Scientists have been asking this question for many years and the answer that emerges from recent work is: probably both. Over the years at least five independent single-gene mutations leading to the obese phenotype have been isolated. Obesity[1] is therefore a condition that involves the expression of multiple genes. In addition to being *polygenic*, it is a complex characteristic that requires the interaction of the environment with the products of these genes. Some other traits that fall into this category include intelligence, schizophrenia and congenital heart disease.

Cloning of the *ob* Gene

A *recessive* mouse mutation called *obese (ob)* was first identified in the 1950s. When both copies of the normal *obese* gene are mutated as in the (*ob/ob*) mouse it causes profound obesity and a form of diabetes, often seen in humans. Some scientists recently reported the cloning of the mouse *obese* gene (*ob*) and its human homologue in the journal *Nature*. This gene appears to play an important role in the maintenance of body weight and appetite. The *ob* gene codes for a 4.5 kb[2] mRNA (messenger, ribonucleic acid) capable of making a protein with 167 amino acids (See *Box 1*). Its coding sequence is *highly conserved* or, in other words, largely unchanged among various vertebrate species. When the amino acids of the Ob[3] protein in mice and humans are compared, 84% of them

[1] Obesity implies body weight in excess or equal to 20% above ideal body weight. Generally obesity is determined by comparing standard tables for height and weight or by calculation of body mass index (body weight in kg/height in meters). More precise indications can be obtained by skin-fold measurements.

[2] 1kb = 1000 nucleotide bases

[3] ob refers to the gene while Ob refers to the protein

[4] 1kD = 1000 dalton, 1 dalton = 1.66024×10^{-24} g.

are identical. Such a high degree of sequence similarity conserved across species suggests that the protein plays a very important role in the animal. Ob protein is a single subunit of 16 kD[4] and is synthesised mainly in the adipose tissue. It is now called *leptin*, a term derived from the Greek root *leptos*, meaning thin.

Following the cloning of the *obese* gene, scientists from Amgen Inc., Rockefeller University and Hoffmann-La Roche Inc. independently published some interesting results. They surmised that if a mouse is obese because of a mutant gene product, injections of the normal gene product might correct the condition. Indeed, all three groups showed that when the product of the normal *obese* gene was injected into a mutant mouse it induced weight loss.

Results of the Leptin Experiments

Daily injections of leptin in obese mice had two effects: reduced appetite and increased energy use. These changes led to a reduction in food intake and the percentage of body fat, along with an increase in metabolic rate, body temperature and activity levels. Surprisingly, injections of both the mouse and human leptin (10 μg/g body weight/per day) reduced body weight in obese mice compared to normal animals given a saline injection. When mice that were not obese were given leptin they too lost weight and maintained their new weight as long as they continued to receive the injections.

The results suggest that the Ob protein or leptin plays a role, maybe even a pivotal one, in the regulation of body weight and the deposition of fat. The protein may signal the brain so that if its levels are high, less food is consumed and more calories burnt, while when its levels are low and as appetite increases more food is consumed. Injections of leptin may therefore trick the body into thinking that it is satiated, thereby reducing appetite and burning extra calories (*Figure 1*).

Other Genes Regulating Obesity

For a long time it was suspected that a region of the brain called the hypothalamus may be important in regulating body weight since lesions in this area led to obesity in rats. In

Box 1

The Transfer of Genetic Information

The sequence of nucleotides in the DNA determines the sequence of ribonucleotides in the RNA. The messenger RNA (mRNA) is that class of RNA molecules which is used to synthesise proteins. The sequence of ribonucleotides is read as *triplet codons* where each codon specifies an amino acid in the protein. The synthesis of RNA molecules from the DNA is called *transcription* and the synthesis of proteins from the mRNA is referred to as *translation*. This transfer of genetic information from DNA → RNA → Protein is often called the *central dogma*.

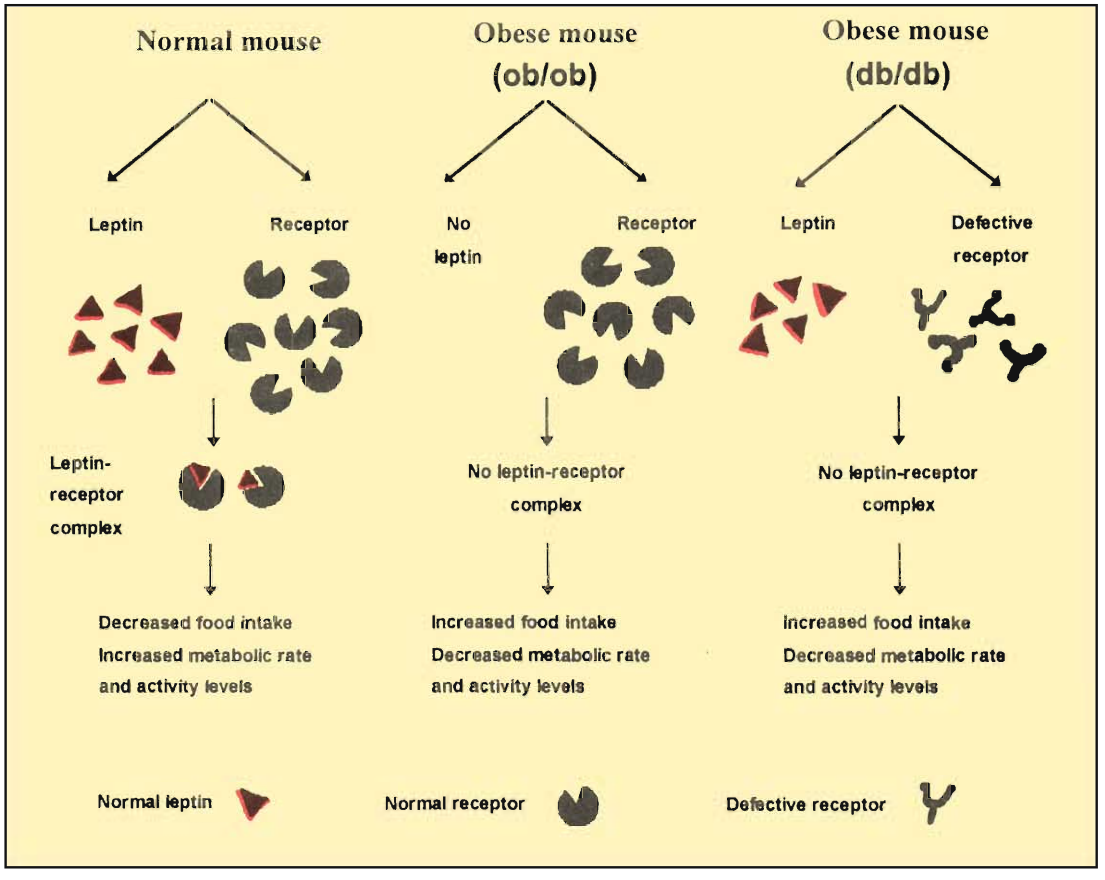

Figure 1 The leptin-receptor complex is formed in the normal mouse but not in the obese mouse with ob/ob or db/db mutations.

December 1995, a research team reported that they had found yet another mutation which resulted in obesity in spite of the presence of normal leptin. They identified the defect in this case to be in the receptor (Ob–R) that is expressed in the hypothalamus and binds to leptin. The gene for the receptor is designated as the db gene. The interaction between leptin and its receptor is essential in the signalling system that involves the hypothalamus and normally results in satiation. When this db gene is mutated, as is the case in the *db/db* mouse, a defective receptor is made and since leptin is unable to bind to it no satiation signal is sent. This consequently leads to obesity (*Figure 1*).

Another team is working on a strain of mice that grows obese when the diet contains excessive fat. This is called *diet-induced-obesity*. Yet another strain of mice stays trim in its youth but puts on weight in adulthood. This is labelled *maturity-onset-obesity*. Since these forms of obesity are similar to those in

humans, their genetic basis is being studied with interest.

The Social Context of Obesity Research

Severe weight gain is a health hazard but we see that weight loss has become a major preoccupation even with the healthy. Since many cultures place increasing emphasis on being thin weight loss products are bound to become very popular. It now appears that some scientists are about to join this profit making diet bandwagon. Amgen Inc., a biotechnology firm in California has paid $20 million to the Rockefeller University for a license to develop products using the *ob* gene. Returning to our original question, does this mean that we are closer to popping a pill to cure obesity? Not really. We know very little about the various genes that regulate body weight, their interactions, the role of the environment, and the possible side effects of popping a pill to cure the condition, even if that were possible. In fact according to Bruce Spiegelman who studies obesity at the Dana-Farber Cancer Institute in Boston, "Nobody has found or developed an organic compound that can mimic insulin, and we have had the insulin receptor in hand for years." Thus, while this finding is interesting for its own sake, at this stage it is still doubtful whether it has direct clinical applications. Perhaps in the long run those with complicated health-threatening obesity could avail of a simple remedy. Unfortunately, what appears more likely in the short-term is the commercial exploitation and consequent potential misuse of this information through the collaboration of two already well established giants: the weight loss and the biotechnology industries.

Suggested Reading

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Grandpa, your blood pressure is getting high and your volume has increased a lot. Is this not a deviation from Boyle's law?

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