

The Mouse Obese Gene and Its Human Homologue

The structure of the *ob* gene in mice, which is associated with obesity and type II diabetes mellitus, was determined. The mouse *ob* gene codes for a 167 amino acid peptide. Amino acids 1 to 21 are likely to be a signal sequence, suggesting that the mature protein has 146 amino acids. In accord with the thesis that adipose tissue secretes a substance acting upon the hypothalamus to suppress appetite, messenger RNA of the *ob* gene is expressed only in white adipose tissue in the mouse. In the homozygous *ob/ob* mouse, a mutation in codon 143 prevents translation of this gene product. The *ob* gene homologue is found in the rat, rabbit, vole, eel, sheep, pig, and cow and in humans. The human homologue of *ob* gene product also has 167 amino acids and is 84% homologous with the mouse gene product. The hypothesis examined by Zhang et al¹ is that this peptide is a product of the fat cell and that it is secreted and serves as a negative feedback signal to the ventromedial nucleus of the hypothalamus, thereby establishing a homeostatic mechanism for caloric intake and energy utilization.

Rink,² in an editorial appearing in the same issue of *Nature*, provides an excellent review of the current concepts pertaining to the possibility that such a protein exists. He states that localized damage to the hypothalamus, which is the main control center for satiety and energy expenditure, produces obesity similar to that observed in the genetic *ob/ob* mouse. He also recounts that rats forced to overeat lay down excessive fat, but when offered a normal diet, they eat less until their normal body weight is restored; and removal of a substantial mass of fat is followed by extra eating, which increases the remaining fat stores. Rink also states that the data of Zhang et al support the concept of a fat-derived satiety factor, which is the most promising hypothesis of several that have been proposed. The postulated *ob* protein is likely to be a fat-derived molecule with a long half-life that acts on the hypothalamus to exert long-term overriding control of appetite and, most likely, fuel storage and energy expenditure.

Some cases of morbid obesity in humans may reflect a homozygous condition analogous to that in the *ob/ob* mouse where the protein is not produced. The more common forms of obesity might reflect subnormal production of the protein.

1. Zhang Y, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425-432.
2. Rink TJ. In search of a satiety factor. *Nature* 1994;372:406-407.

Editor's comment: The theories concerning the regulation of obesity include: (1) lipostasis, which is the synthesis and secretion by fat of an agent that inhibits appetite at the level of the hypothalamus; (2) glucostasis, which is a theory that blood glucose values regulate the body energy stores by acting on the hypothalamus; (3) body temperature control of energy utilization and fat storage; and (4) dilution of a hypothetical fat-soluble factor that inhibits feeding. Under this thesis, the greater the body fat mass, the greater the storage of this lipophilic agent, which theoretically lowers its circulating levels and lessens its inhibitory influence on feeding. The reported data do lend support to the lipostasis theory, although the secretion, biologic activity, and mechanism of action of this agent have not been determined.

There are 6 genes that have been associated with obesity in the mouse, which means that much more work is necessary to determine the role of all of these, and possibly other, genes. The biologic activity of the *ob/ob* protein and its pattern of regulation of secretion also need to be determined before therapeutic approaches become evident in the clinic. If this gene product proves to be a satiety factor, an exciting period of experimental observations and therapeutic effort is beginning.

There is much need in this area. Zhang et al have opened the door for this research.

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Estrogen Levels in Childhood Determined by an Ultrasensitive Recombinant Cell Bioassay

An extraordinarily sensitive (0.02 pg/mL estradiol equivalence) bioassay for the measurement of serum/plasma concentrations of estrogen was developed by the investigators. The unknown plasma and standard samples of estradiol are incubated with transformed yeast. An increase in activity of β -galactosidase is determined to measure the response of estrogen in a sample. Overexpression of the estrogen receptor accounts for the extreme sensitivity. Other factors contribute. Specificity for estradiol is surprisingly great, and variants such as ethinyl estradiol, estradiol sulfate, estradiol glucuronide, estrone, estriol, and diethylstilbestrol are recognized only to a slight extent (<3%). At an estradiol concentration of 2 pg/mL, the intra-assay and interassay coefficients of variation were 15% and 13%, respectively.

In 21 prepubertal girls, aged 5.5 to 10.5 years, serum estradiol concentrations measured by the assay were 0.6 ± 0.6 pg/mL estradiol equivalents, with a range of <0.02 to 2.2 pg/mL. In 23 prepubertal boys, aged 4.5 to 13.0 years, the concentrations were measured at 0.08 ± 0.2 pg/mL, with a range of <0.02 to

0.7 pg/mL. Thus, bioactive estradiol levels were substantially greater in prepubertal females than males ($P < 0.05$).

Klein KO, et al. *J Clin Invest* 1994;94:2475-2480.

Editor's comment: This bioassay is 100-fold more sensitive than the most sensitive of established radioimmunoassays for estradiol. Its specificity for estradiol was unexpected but is exceedingly useful since estradiol is the principal endogenous estrogen in children and adolescents. The higher levels of estrogen in prepubertal girls than in boys, as determined by this assay, may explain some of the variations in the growth patterns of the 2 sexes, such as earlier onset of the growth spurt in girls, earlier pubertal maturation of the hypothalamic-pituitary axis, and more rapid advancement of skeletal maturation.

The assay is technically demanding and tedious, but offers promise for the evaluation of the dynamics and regulatory controls of estrogen secretion in infancy, childhood, and early adolescence. An assay with this sensitivity has long been needed.