Alfred Nobel Symposium
Energy in Cosmos, Molecules and Life
June 18-22, 2005

Genes, Behavior and Metabolism: Balancing the Energy Equation in vivo

Jeffrey M. Friedman, M.D., Ph.D.
Howard Hughes Medical Institute
The Rockefeller University
New York, NY 10021, USA

The assimilation, storage, and utilization of nutrient energy constitute a homeostatic system essential for life. In vertebrates, particularly land dwelling mammals, the ability to store quantities of energy-dense triglyceride (fat) in adipose tissue permits survival during times when food is unavailable. Adipose tissue can be thought of as a calorie bank into which energy is deposited in times of plenty so that it can serve as a source of energy when food becomes scarce. Excessive leanness is thus associated with an increased risk of starvation and is maladaptive. However, the presence of excess adipose tissue is also maladaptive as obese organisms are more susceptible to predation and less effective at hunting. In addition, the accumulation of excess adipose tissue in humans increases the risk for developing a series of metabolic diseases including hypertension, diabetes and cardiovascular disease, all major causes of morbidity and mortality in western society. These considerations suggest that an important evolutionary advantage to maintaining body fat at a relatively constant, optimal level balancing the relative risks of starvation against those of obesity and metabolic disease. However, the maintenance of relatively constant energy stores poses a formidable problem.

Beginning with the development of the first calorimeter in 1783 by Lavoisier and de la Place, it has been known that living organisms are subject to the same physical laws as inanimate systems. Thus according to the first law of thermodynamics, maintenance of constant weight requires that living organisms precisely balance nutrient intake against energy consumption, lest weight (fat mass) change. The magnitude of this problem is highlighted by the fact that the average adult consumes nearly one million calories of food per year, and tons of nutrients over a lifetime, during which time weight remains extremely stable. Crude estimates based on these numbers have suggested that the biologic system that maintains energy balance operates with greater than ~ 99.6% precision. Thus Nature has apparently developed a means for precisely monitoring the total amount of energy stored as fat and maintaining it at a stable level. How then do humans and other organisms maintain systemic energy balance?

The cloning of the mouse obese (ob/ob) gene and its encoded protein, leptin, has provided an answer to this question. The discovery of leptin has led to the elucidation of a robust physiologic system that maintains fat stores at a relatively constant level. Leptin is a peptide hormone secreted by adipose tissue in proportion to its mass. Leptin functions as a nutritional signal that informs brain centers about the size of adipose tissue stores. This hormone circulates in blood and acts on the hypothalamus, a brain

region that regulates most basic functions, to regulate food intake and energy expenditure. When fat mass falls, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. By such a mechanism total energy stores are stably maintained within a relatively narrow range.

Recessive mutations in the leptin gene are associated with massive obesity in ob/ob mice and some humans and treatment with recombinant leptin markedly reduces food intake and body weight. In one case, a leptin deficient child ate >2000 calories in a single meal (more than the average total daily intake of an adult) and weighed almost 100 pounds. Leptin treatment rapidly normalized the excessive food intake in this child and over time normalized the child's weight. The low leptin levels in patients with leptin mutations are also associated with a number of other abnormalities including infertility, diabetes and immune abnormalities that are corrected by leptin treatment. These findings have established important links between energy stores and many other physiologic systems. These observations have also led to the use of leptin as a treatment for an increasing number of other human conditions also associated with low plasma leptin concentrations including a subset of obesity, some forms of diabetes including lipodystrophy and hypothalamic amennorhea, the cessation of menstruation seen in extremely thin women. The system that controls energy balance thus has pleiotropic biologic effects with a powerful behavioral component. This provides the basis for future research studies to address how a single molecule such as leptin can regulate feeding, a typical complex motivational behavior.