Commentary on “Long-Term Calorie Restriction Reduces Energy Expenditure in Aging Monkeys”

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The study by DeLaney and colleagues, “Long-term Calorie Restriction Reduces Energy Expenditure in Aging Monkeys,” in this issue of the Journal (pp. B5–B11) addresses, indirectly, questions that are of major import concerning the pathogenesis and treatment of human obesity. Is there a primary deficit in energy expenditure in the pre-obese; and does the higher body fat of the obese mediate a normalization of this state?

The lowered energy expenditure of these calorie-restricted male rhesus monkeys recapitulates the phenotypes of rodents and humans whose body weights are maintained below “normal.” In weight-reduced humans, maintenance of a lower body weight is accompanied by an approximate 15% decrease in energy expenditure adjusted for metabolic mass (1–3). In these weight-reduced humans, plasma leptin concentrations are normal relative to body fat content, but lower than in the pre-weight-loss state, due to reduced adipose tissue mass (4).

Prospective studies of energy expenditure in infants (5), children (6), and adults (7), have found that lower rates of energy expenditure are predictive of greater subsequent weight gain. There is a close correlation between lean body mass and energy expenditure (resting or total) in both never-obese and obese subjects (8). In fact, both groups plot on the same regression line relating energy expenditure to lean body mass. And the formerly obese—or weight-reduced never-obese—show the same degree of reduced energy expenditure as the pre-obese examined in prospective studies. From these observations, it is possible to infer that adipose tissue is somehow affecting the rate of energy use by the lean body mass. Because adipose tissue itself, comprised mainly of triglyceride, uses little energy, this effect is not a reflection of energy metabolism adipose tissue per se, nor of the slight decrease in energy expenditure required to move the reduced weight.

The recent demonstration of a leptin axis in the control of body weight provides a physiological mechanism for such an effect of fat mass on energy expenditure by lean tissue such as skeletal muscle. Leptin production in adipose tissue is proportional to adipocyte cell mass and cell size, and provides a humoral signal to the hypothalamus indicating the size of somatic energy stores (9). The term leptin is derived from the Greek word leptos, which means “thin” or “small.” Thus the name implies a normal role for leptin in suppressing body weight. However, the physiology of the hormone is more consistent with a primary role in defending the organism against insufficient energy stores in order to ensure normal growth and reproductive function (9–11).

The “normal” concentration of ambient leptin for each individual is probably determined by genetic and developmental processes that affect the sensitivity of the CNS neuropeptide/neurotransmitter response cascade to this hormone. An extreme example of resistance to leptin is produced by the leptin receptor mutations in rodents (11) and humans (12) that lead to severe obesity despite extreme increases in circulating leptin. Other molecular components of this response cascade include NPY, POMC, AGRP, and the melanocortin 4 receptor. The efferent limbs of this control loop include food intake, physical activity, pituitary hormones (e.g., GH), and autonomic nervous system activity (especially the sympathetic nervous system). “Normal” body fat for any individual is the amount required to generate sufficient leptin to overcome the system’s impedance to response.

Thus, the metabolic and other phenotypes of the rhesus monkeys in this study may be regarded as reflecting the consequences of chronic suppression of body fat (“hypoleptinemia”). Their low energy expenditure is probably due, in part, to effects of low leptin on sympathetic nervous activity (13), the thyroid axis (14), growth hormone release (15), and possibly skeletal muscle metabolism (1,16). That is, their chronically reduced weight is perceived metabolically as a chronic deprivation state, and relevant adjustments in energy expenditure have been made. The weight-reduced humans mentioned previously also show evidence of reduced sympathetic autonomic tone (17), and lowered T4 and T3 (3) (with normal TSH) and elevated rT3 (18). This low energy output state is the syndrome that characterizes many formerly obese humans. The high recidivism to obesity is apparently due to a combination of increased metabolic energy efficiency and discomfort related to persistent hunger. The regain of body weight (fat) is, in this paradigm, a normalizing process (19). The persistence of hunger in the weight (fat)—reduced may be explained by the fact that plasma leptin concentration remains below that needed to generate a signal of sufficient intensity within the central nervous system. Humans in this weight-reduced circumstance have circulating leptin that is proportional to body fat, whereas humans ingesting 800 kcal per day have leptin concentrations about 50% of those expected for body fat mass (4). It would be interesting to know the plasma...
leptin concentrations of these animals in relation to their fat mass. Would these plasma concentrations indicate that the 40% caloric restriction was perceived as a chronic deprivation state (leptin < predicted by fat mass), or are these animals fully comparable to a weight-reduced human (leptin appropriate to reduced fat mass)? And, are these animals hungrier than their ad-libitum fed peers?

In weight-reduced humans, most of the reduction in energy expenditure is in the energy cost of physical activity (1,2). Total physical activity, as in these animals, is not reduced. In the animals, unlike humans, there was no correlation between lean body mass and total energy expenditure. This difference is probably due to the fact that physical activity accounts for a greater fraction of total energy expenditure in the monkeys than humans.

A pressing issue in the medical management of human obesity is the development of prophylactic measures that could be imposed in childhood. In rodents, restriction of caloric intake prior to puberty is generally not accompanied by the decrease in energy expenditure seen if the restriction is imposed later in life. The problem with early caloric restriction is that there may be secondary impairment of lean tissue growth (including brain tissue; 20). The decrease in lean body growth may occur, in part, as a result of relative GH deficiency (21). The monkeys reported in DeLany and colleagues’ study were mature when the diet restriction was imposed. It would be interesting to see what the effects of a more modest restriction imposed prior to puberty would be on rates of energy expenditure and adiposity in adulthood, and whether transient restriction before sexual maturity would have permanent effects on rates of obesity (and energy expenditure) in adulthood. In humans, the maintenance of an abnormally reduced body weight (or more precisely, fat content) is associated with a metabolic state that may reflect metabolic status prior to the gain of “excess” body fat (1,7). The monkeys described in the article by DeLany and colleagues shed light on some of the details of the associated phenotype. The deposition of body fat by these animals would almost certainly normalize their energy expenditure phenotype. The level of fatness at which this occurred would be the level of fat that is “normal” for that animal.

An issue of obvious interest in these animals, and presumably the reason for the experiment in the first place, will be the effects of chronic caloric restriction on longevity and cardiovascular and cancer morbidity. This sort of restriction is associated with positive effects on longevity in rodents and other animals (22,23). Obesity is associated with high rates of somatic growth and increased rates of cancer and coronary heart disease (24). Is it possible that the salubrious effects of chronic calorie restriction are due, in part, to suppression of these potential effects of leptin?

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