Do circulating leptin concentrations reflect body adiposity or energy flux? \(^{1,2}\)

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Leptin was first identified as the protein missing in the obese mouse (ob/ob), with resulting hyperphagia, diminished energy expenditure, and increased adiposity (1). Leptin administration to ob/ob mice appeared to correct most abnormalities and lower body weight. These observations initially raised hopes that some human obesity occurred for similar reasons and could be treated in the same way. However, nearly all studies of obese humans show a strong and consistent positive relation between plasma leptin concentrations and adipose mass (2, 3). One potential reason for leptin overproduction is a defect in the leptin receptor, such as in diabetic mice (db/db) (4), but leptin receptor defects are unlikely to account for more than a small number of human cases of obesity. Therefore, current research aims to understand the role of leptin in mechanisms regulating appetite and body weight.

The leptin receptor is notably expressed in hypothalamic regions known to be involved in feeding behavior (5). Intracerebroventricular leptin injection decreases food intake in nonobese rats and affects body weight for as long as 6 d (6). Leptin receptors and neuropeptide Y cell bodies are both found in the arcuate nucleus of the hypothalamus (5, 7). Because leptin decreases feeding and increases energy expenditure whereas neuropeptide Y does the opposite, several investigators have suggested that leptin may affect energy balance by altering neuropeptide Y signaling pathways. Recent data confirm that one important way leptin affects energy homeostasis is by decreasing neuropeptide Y biosynthesis in the arcuate nucleus (8).

One hypothesis about leptin function is that leptin provides information about the size of body fat stores to regulatory mechanisms in the brain. That hypothesis has to be tempered by many reports showing that serum leptin concentrations are reduced by food deprivation. Leptin concentrations decrease after a 2–3 d fast or very low energy intakes from 7 d to as long as 3 mo (for review, see reference 9). In these situations, leptin concentrations are disproportionate to changes in adiposity.

In this issue of the Journal, Keim et al (9) report that circulating leptin concentrations decreased during a prolonged, moderate energy deficit in 12 healthy, overweight women. After 1 wk of the restricted diet, body weight and fat mass had not changed significantly, yet leptin and insulin concentrations had decreased by 57% and 49%, respectively. After 12 wk of diet restriction, leptin and insulin concentrations were not significantly below concentrations noted after 1 wk. As one would expect, self-reports of hunger, desire to eat, and a measure of how much one would like to eat increased during the chronic restriction state. These measures also did not seem to be correlated with the length of the diet restriction. Thus, Keim et al found a significant negative correlation between leptin and measures of hunger-related variables.

How then can one interpret the role that leptin plays in regulating energy metabolism? It is a regulator that is missing from obese mice, whereas concentrations are elevated in most obese humans, and it reflects adiposity during a weight-stable period, but does not reflect adiposity during a period of food restriction. It appears likely that the changed state of energy balance is a key variable. When energy balance is in steady state, leptin concentrations correlate well with the amount of adipose tissue. Significant changes in energy balance with non–steady state conditions, particularly total-body energy loss, appear to decrease serum leptin out of proportion to changes in fat mass.

A variety of hormones, regulators, and metabolites change quickly during periods of either acute food deprivation or chronic food restriction. For example, serum cholesterol concentrations drop with food restriction, before major decreases in body weight occur. Similar changes occur in insulin, thyroid hormone, blood pressure, and a variety of constitutive proteins with short half-lives. Sympathetic nervous system activity is also diminished during energy deprivation. Thus, leptin may be responding as other proteins do to the energy status of the individual, which eventually is reflected in body weight. It is also possible that leptin secretion from adipose cells is in part regulated by other factors such as the sympathetic nervous system, insulin, or glucocorticoids (10). A recent report by Wang et al (11) suggests that the hexosamine biosynthetic pathway may serve as a nutrient sensor that regulates leptin gene expression in muscle and fat. The end product of this pathway, UDP-N-acetylglucosamine, results in rapid and marked increases in leptin messenger RNA and protein. Also, leptin synthesis is stimulated with hyperglycemia or hyperlipidemia, which also increases concentrations of UDP-N-acetylglucosamine in rodents. Thus, leptin concentrations may be influenced by a nutrient sensing mechanism, rather than being a simple reflection of total body adiposity.

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The study by Keim et al (9) does support the notion that leptin acts as a regulator of food intake in humans because there was an indirect correlation between self-reported hunger status and leptin concentrations. Of course, such a correlation does not establish a cause-effect relation. Because insulin also decreased within 1 wk of food restriction, and a satiating effect of insulin has been reported (12), it is possible that insulin and perhaps other peripheral signals also participated in the observed effects. However, Keim et al did not find that plasma leptin correlated with changes in plasma insulin.

In a phase I clinical trial reported at the 58th Annual Scientific Sessions of the American Diabetes Association in Chicago (June 1998), daily leptin injection in obese humans who were dieting resulted in an average weight loss of 15.6 lb (~7.1 kg) after 6 mo compared with a weight loss of 3.7 lb (~1.7 kg) in the placebo group. Leptin did not result in weight loss in all obese subjects, which is not surprising because the etiology of obesity is multifactorial. The work of Keim et al indicates that circulating concentrations of leptin may decrease relatively quickly in response to energy restriction, and could contribute to a feeling of hunger. Unfortunately, not all obese persons overeat because of hunger, which might explain why neither leptin nor any one substance can be used as a “cure” for obesity.

REFERENCES