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Leptin production and action: relevance to energy balance in humans[1–3]

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The cloning of the gene responsible for obesity in the *ob/ob* mouse in 1994 and the resulting discovery of leptin (1) has spawned a flurry of investigation into the biology of this novel adipocyte hormone, with > 600 papers currently in the MED-LINE database. Studies in human subjects have primarily examined circulating leptin concentrations under a variety of physiologic and pathophysiologic conditions. Numerous studies have reported that circulating leptin concentrations are highly correlated with adiposity (2). In contrast, investigations of the actions of leptin have been conducted almost exclusively in rodents. In the *ob/ob* mouse, a mutation of the leptin gene causes leptin deficiency and results in hyperphagia, decreased energy expenditure, severe obesity, and insulin-resistant diabetes (1). Central or peripheral administration of leptin to rodents leads to acute decreases in food intake; chronic administration of leptin results in marked reductions in body fat (2). The efficacy of small doses of centrally administered leptin and the presence of leptin receptors in areas of the central nervous system involved in regulating energy balance, such as the hypothalamus, suggest that the brain is an important site of leptin action (2).

The study by Luke et al (3) in this issue examined leptin and adiposity in three black populations. These investigators found that both adiposity and circulating leptin concentrations were increased in US blacks relative to Nigerians and Jamaicans; however, the relation between leptin and adiposity was not different among the three populations. Furthermore, this relation was best fit by an exponential function. Accordingly, leptin concentrations are higher per unit adiposity in obese than in normal-weight subjects (4), a finding that has been interpreted to indicate resistance to leptin action in obese subjects (2). In addition, these investigators confirmed the previously reported sex difference in circulating leptin concentrations: women have higher concentrations than men, even after the greater adiposity in women is corrected for. This difference does not appear to be due to an effect of female reproductive hormones (5), but may result from an inhibitory effect of androgens, from differences in body fat distribution, or both.

At the time the paper by Luke et al (3) was submitted, the consequences of leptin deficiency in humans were unknown. The finding that circulating leptin concentrations are elevated in most obese people implies that obesity is associated with leptin resistance and has led to speculation that leptin is simply a marker of body fat stores with no important role in energy homeostasis in humans. However, congenital leptin deficiency was reported recently in two first cousins from a highly cosanguinous family exhibiting hyperphagia, marked obesity (> 50% body fat), and

essentially undetectable serum leptin concentrations (6). The two children, an 8-y-old girl weighing 86 kg and a 2-y-old boy weighing 29 kg, were found to have a frame shift mutation resulting from a single nucleotide deletion in the protein-coding region of the leptin gene. The findings in these patients clearly illustrate, as documented previously in rodents, that the congenital absence of leptin in humans leads to an obese phenotype and confirm a pivotal role for leptin in the regulation of energy balance in humans. Additional evidence that leptin is involved in energy balance in primates is provided by recent studies showing that leptin administration reduces food intake and activates the sympathetic nervous system in rhesus monkeys (M Tang-Christiansen, PJ Havel, RR Jacobs, PJ Larson, JL Cameron, unpublished observations, 1997).

Although circulating leptin concentrations are highly correlated with adiposity in humans (3, 7, 8) and animals (9), fasting or energy restriction decreases leptin concentrations acutely and disproportionately to the relatively modest changes in adiposity (7–10). Thus, factors other than adipose tissue mass are likely to influence leptin secretion. Several studies conducted in vivo and in vitro suggest that insulin and glucose may regulate leptin secretion. For example, infusion of small amounts of glucose sufficient to prevent a decrease in glycemia and insulinemia during fasting in humans also prevents a decrease in plasma leptin (10). In addition, the decrease in circulating leptin concentrations during energy restriction in humans is related closely to the decrease in plasma glucose (8). Thus, adipocyte glucose metabolism may be involved in the regulation of leptin secretion. Consistent with this hypothesis, we reported recently that glucose uptake and utilization are important determinants of leptin expression and secretion from isolated adipocytes (11). Therefore, changes in adipose tissue glucose metabolism may be involved in the effects of fasting and refeeding on circulating leptin concentrations in vivo (7–10). A better understanding of the mechanisms regulating leptin synthesis and secretion may lead to pharmacologic approaches for treating obesity by augmenting endogenous leptin production.

Resistance to the actions of leptin could occur at several points

in the leptin signaling pathway. For example, leptin is hypothesized to enter the brain via transport across the blood-brain barrier. Mice with diet-induced obesity (12, 13) and polygenic obesity (the New Zealand mouse) (13) are resistant to the effects of peripheral but not central leptin administration to reduce food intake, suggesting a potential defect in the transport of leptin into the central nervous system. Reduced central nervous system transport of leptin may also occur in obese humans because the ratio of cerebrospinal fluid to plasma leptin is reduced in obese compared with lean individuals (14). Another potential mechanism for leptin resistance is the failure of leptin to activate the leptin receptor. This defect is observed in obese rodent models with mutations of the leptin receptor gene (*db/db* mice and *fa/fa* Zucker rats) and produces complete leptin resistance (2). However, leptin receptor mutations have yet to be reported in humans. Alternatively, postreceptor defects in the leptin signal transduction pathway or a failure of leptin to act on its hypothalamic targets such as neuropeptide Y− or melanocortin-containing neurons (15) could result in an apparent resistance to leptin action. Accordingly, the agouti (Ay) mouse, which develops obesity as a result of ectopic production of an antagonist of melanocortin receptors, exhibits resistance to both peripheral and central leptin administration (13), suggesting a defect downstream from the leptin receptor.

An additional possibility is that the leptin signal to the hypothalamus can be overcome by the hedonic qualities of highly palatable foods. This idea is supported by a recent study in rats with diet-induced obesity in which central leptin administration reduced the intake of a standard rodent diet but not that of a more palatable high-energy diet (16). This is an important consideration to the extent that consumption of a highly palatable, high-fat diet contributes to obesity in humans. Ultimately, clinical trials with leptin administration in human subjects will be necessary to determine the usefulness of leptin or leptin secretagogues in the treatment of obesity, and the extent to which hedonic factors influence the response to leptin in humans.

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