

Mechanisms regulating leptin production: implications for control of energy balance¹⁻³

Peter J Havel

During the past 2 y the leptin field has continued to expand rapidly (from 600 to >2000 citations currently in the MEDLINE database), extending leptin biology into areas well beyond feeding behavior and energy metabolism. For example, there is a growing body of literature linking leptin with the regulation of reproductive function and on the potential involvement of leptin in puberty onset, pregnancy, lactation, and infertility associated with energy restriction and low body adiposity (1). Leptin has also been implicated in roles as diverse as the regulation of the immune system (2) and respiratory function (3). In addition, ongoing studies are clarifying the central nervous system (CNS) mechanisms by which leptin exerts its effects on energy balance (4) as well as suggesting important actions for leptin in regulating peripheral metabolic fluxes (5).

In this issue, Wisse et al (6) report the results of a study of changes in serum leptin and several metabolic variables over 4 wk of energy restriction ranging from 50% of maintenance energy to total fasting in obese women. Leptin decreased in proportion to the degree of energy restriction, decreasing much more than expected (by 50–80%) relative to the more modest decrease (\approx 15%) in body fat mass. Although adiposity-independent reductions in circulating leptin concentrations in response to energy restriction were reported in previous studies, energy intake remains less well recognized than body adiposity as a determinant of circulating leptin concentrations. The ability of adipose tissue to regulate leptin production independently of total adipose mass is likely to have a major adaptive value in the presence of either limited energy availability or increased energy consumption (ie, overfeeding) because adiposity-independent changes in leptin production would promote a compensatory change in food intake, energy expenditure, or both before major alterations in energy stored as fat occur. Thus, leptin appears to function more as a signal of recent energy balance than as an “adipostat.”

Wisse et al also reported that the decrease in leptin during energy restriction was best correlated with changes in glycemia. These results provide important confirmation in obese women of previous findings in normal-weight men and women (7) and support the idea that decreases and increases in adipocyte glucose metabolism are involved in regulating changes in leptin production in response to alterations in energy status (8). One mechanism by which glucose metabolism can increase leptin production is by entry of glucose into the glucosamine pathway via L-glutamine:D-fructose-6-phosphate amidotransferase (9). However, other pathways of glucose metabolism in adipose tissue may also be involved, such as lipogenesis and glucose oxidation.

Insulin-mediated glucose metabolism in adipose tissue may underlie the quantitative and temporal relation between circulating leptin concentrations and insulin responses to meals. For example, delaying meal feeding for 5 h shifts the diurnal leptin pattern by a similar period of time, without affecting the 24-h rhythm of plasma cortisol, a hormone that displays true circadian cyclicality (10). Reduced insulin-mediated glucose metabolism is also likely to contribute to the effect of consumption of high-fat meals to reduce 24-h circulating leptin concentrations, relative to high-carbohydrate meals in human subjects (11). Although some previously published studies did not find an effect of dietary macronutrient composition on fasting leptin concentrations, examination of the 24-h leptin profile showed substantial differences between the effects of high-fat, low-carbohydrate compared with low-fat, high-carbohydrate meals, which were largest 4–6 h postprandially. This time course is consistent with the 4–6 h required to observe significant increases in circulating leptin concentrations during physiologic insulin administration in humans (12). These types of studies illustrate the importance of measuring leptin over 24 h rather than relying on a single fasting value to assess leptin production.

Wisse et al also reported that plasma leptin concentrations increased during a 1-wk period of refeeding and that these increases were positively correlated with an increase in resting energy expenditure. There is growing evidence that, in addition to its better-characterized inhibition of food intake, leptin is involved in the regulation of energy expenditure. However, rather than increasing energy expenditure above basal rates, leptin appears to act primarily to prevent the decline in the metabolic rate observed during periods of decreased energy intake in rodents (13, 14). These effects of leptin on energy expenditure may be secondary to activation of the sympathetic nervous system because leptin administration activates the sympathetic nervous system in rodents (15) and in nonhuman primates (16).


Reports of extreme obesity and hyperphagia caused by autosomal recessive mutations of either the leptin gene (17) or its

¹From the Department of Nutrition, University of California, Davis.

²Supported by NIH grants DK-50129 and DK-35747, the American Diabetes Association, and the US Department of Agriculture.

³Address reprint requests to PJ Havel, Department of Nutrition, University of California, Davis, One Shields Avenue, Davis, CA 95616. E-mail: pjhavel@ucdavis.edu.

receptor (18) clearly show the importance of leptin production and leptin action in maintaining normal energy balance in humans (19). Experiments with leptin replacement in insulin-deficient diabetic rats suggest that low plasma leptin concentrations contribute to diabetic hyperphagia (20). Decreases in circulating leptin concentrations have been related to increased sensations of hunger in dieting women and this relation is independent of body fat loss or the degree of energy restriction (21). Similarly, reduced leptin production during consumption of high-fat diets (11) may contribute to the effects of dietary fat in promoting increased energy intake and obesity in humans and animals (22), whereas increases in leptin could be involved in weight loss during high-carbohydrate, low-fat diets. Therefore, decreases in leptin in response to reduced adiposity and energy intake may contribute to increased appetite (21) and lowered energy expenditure (13, 14) during a weight-loss regimen and therefore to the strong propensity for weight regain after initially successful dieting. If this is the case, then leptin, leptin agonists, leptin secretagogues, or leptin sensitizers may help maintain weight loss by decreasing hunger and subsequent food intake and by preventing or reversing the decrease in energy expenditure induced by restriction of energy intake (6).

In one genetically leptin-deficient individual, administration of exogenous leptin reversed the marked weight gain and induced a 14.7-kg ($\approx 17\%$) weight loss over 9 mo (23). In a double-blind, placebo-controlled trial, leptin administration produced significant but variable weight loss in normal weight and obese humans (23). It is possible that one or more factors influence the effectiveness of exogenous leptin in inducing a state of negative energy balance. One could speculate that baseline leptin concentrations may influence subsequent sensitivity to exogenous leptin. If this is the case, leptin may be relatively more effective in subjects in whom endogenous leptin production has first been reduced by dieting. Another factor influencing responsiveness to leptin may be differences in the ability of exogenously administered leptin to gain access to the CNS. Although leptin concentrations in cerebrospinal fluid increase in humans after leptin administration, the increases are not proportional to those of circulating leptin concentrations (23). There may be a relative impairment in the transport of exogenous leptin into the CNS when leptin concentrations are elevated, as suggested by previous studies of ratios of plasma to cerebrospinal fluid leptin concentrations in human subjects (24, 25). Thus, although the leptin system is an attractive target for obesity treatment, more comprehensive trials with leptin and new approaches for enhancing leptin action or leptin transport into the brain will likely be necessary to fully assess the clinical potential of this approach for treating obesity. 

REFERENCES

- Cunningham MJ, Clifton DK, Steiner RA. Leptin's actions on the reproductive axis: perspectives and mechanisms. *Biol Reprod* 1999; 60:216–22.
- Loffreda S, Yang SQ, Lin HZ, et al. Leptin regulates proinflammatory immune responses. *FASEB J* 1998;12:57–65.
- O'Donnell CP, Schaub CD, Haines AS, et al. Leptin prevents respiratory depression in obesity. *Am J Respir Crit Care Med* 1999;159: 1477–84.
- Schwartz MW, Baskin DG, Kaiyala KJ, Woods SC. Model for the regulation of energy balance and adiposity by the central nervous system. *Am J Clin Nutr* 1999;69:584–96.
- Barzilai N, Wang J, Massillon D, Vuguin P, Hawkins M, Rossetti L. Leptin selectively decreases visceral adiposity and enhances insulin action. *J Clin Invest* 1997;100:3105–10.
- Wisse BE, Campfield LA, Marliss EB, Morais JA, Tenenbaum R, Gougeon R. Effect of prolonged moderate and severe energy restriction and refeeding on plasma leptin concentrations in obese women. *Am J Clin Nutr* 1999;70:321–30.
- Dubuc GR, Phinney SD, Stern JS, Havel PJ. Changes of serum leptin and endocrine and metabolic parameters after 7 days of energy restriction in men and women. *Metabolism* 1998;47:429–34.
- Mueller WM, Gregoire FM, Stanhope KL, et al. Evidence that glucose metabolism regulates leptin secretion from cultured rat adipocytes. *Endocrinology* 1998;139:551–8.
- Wang J, Liu R, Hawkins M, Barzilai N, Rossetti L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. *Nature* 1998;393:684–8.
- Schoeller DA, Cella LK, Sinha MK, Caro JF. Entrainment of the diurnal rhythm of plasma leptin to meal timing. *J Clin Invest* 1997; 100:1882–7.
- Havel PJ, Townsend R, Chaump L, Teff K. High fat meals reduce 24 h circulating leptin concentrations in women. *Diabetes* 1999;48:334–41.
- Saad MF, Khan A, Sharma A, et al. Physiological insulinemia acutely modulates plasma leptin. *Diabetes* 1998;47:544–9.
- Scarpace PJ, Matheny M, Pollock BH, Tumer N. Leptin increases uncoupling protein expression and energy expenditure. *Am J Physiol* 1997;273:E226–30.
- Doring H, Schwarzer K, Nuesslein-Hildesheim B, Schmidt I. Leptin selectively increases energy expenditure of food-restricted lean mice. *Int J Obes Relat Metab Disord* 1998;22:83–8.
- Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI. Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest* 1997;100:270–8.
- Tang-Christensen M, Havel PJ, Jacobs RR, Larsen PJ, Cameron JL. Central administration of leptin inhibits food intake and activates the sympathetic nervous system in rhesus macaques. *J Clin Endocrinol Metab* 1999;84:711–7.
- Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997;387:903–8.
- Clement K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998;392:398–401.
- Havel PJ. Leptin production and action: relevance to energy balance in humans. *Am J Clin Nutr* 1998;67:355–6.
- Sindelar D, Havel P, Seeley R, Wilkinson C, Woods S, Schwartz M. Low plasma leptin levels contribute to diabetic hyperphagia in rats. *Diabetes* 1999;48:1275–80.
- Keim NL, Stern JS, Havel PJ. Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women. *Am J Clin Nutr* 1998;68:794–801.
- Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr* 1998;68:1157–73.
- Greenberg AS, Fujioka K, Heymsfield S, et al. Clinical effects of leptin in obesity. In: *Proceedings of the 81st Annual Meeting of the Endocrine Society, San Diego, CA*. Bethesda, MD: Endocrine Society, 1999.
- Schwartz MW, Peskind E, Raskind M, Boyko EJ, Porte D Jr. Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. *Nat Med* 1996;2:589–93.
- Caro JF, Kolaczynski JW, Nyce MR, et al. Decreased cerebrospinal fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet* 1996;348:159–61.

