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Sexual Dimorphism in Plasma Leptin Concentration*

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ABSTRACT

Leptin, the *obese* (*ob*) gene product, is thought to be a lipostatic hormone that contributes to body weight regulation through modulating feeding behavior and/or energy expenditure. The determinants of plasma leptin concentration were evaluated in 267 subjects (106 with normal glucose tolerance, 102 with impaired glucose tolerance, and 59 with noninsulin-dependent diabetes). Fasting plasma leptin levels ranged from 1.8–79.6 ng/mL (geometric mean, 12.4), were higher in the obese subjects, and were not related to glucose tolerance. Women had approximately 40% higher leptin levels than men at any level of adiposity. After controlling for body fat, postmenopausal women had still higher leptin levels than men of similar age, and their levels were not different from those in younger women. Multiple regression analysis showed that adiposity, gender, and insulinemia were significant determinants of leptin concentration, explaining 42%, 28%, and 2% of its variance, respectively. Neither age nor the waist/hip ratio was significantly related to leptin concentration. Thus, our data indicate that gender is a major determinant of the plasma leptin concentration. This sex difference is not apparently explained by sex hormones or body fat distribution. Leptin's sexual dimorphism suggests that women may be resistant to its putative lipostatic actions and that it may have a reproductive function. (*J Clin Endocrinol Metab* **82:** 579–584, 1997)

LEPTIN, the *obese* (*ob*) gene product, is a 16-kDa peptide hormone secreted by adipocytes (1–4). It is highly conserved in different vertebrates, with approximately 85% structural homology in mouse, rat, and man (1–4). Leptin is thought to be a homeostatic signal that contributes to body weight regulation through modulating feeding behavior and/or energy expenditure (1, 4). Mutations of the *ob* gene that lead to leptin deficiency or production of a truncated inactive protein are associated with hyperphagia, hypometabolism, obesity, and noninsulin-dependent diabetes mellitus (NIDDM) in obese *ob/ob* mice (1). Peripheral or central administration of recombinant leptin to these mice decreased food intake, increased energy expenditure, and caused weight loss (5–9). Similar effects were described in wild-type (5–7) and diet-induced obese (8) mice.

Leptin's role in obesity and NIDDM in man is not known. No mutations in the *ob* gene (10–12) or defects in its expression (12–14) have been found in human obesity. Genetic variations at the *ob* locus do not appear to contribute to NIDDM susceptibility (15, 16), but may be linked to extreme obesity (17, 18). In addition, plasma leptin levels were shown to be elevated in obese subjects (19, 20). Little is known, however, about factors that regulate the plasma leptin concentration or its relation to glucose tolerance. This work was undertaken, therefore, to examine the determinants of leptin concentration in lean and obese subjects across the spectrum of glucose tolerance.

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Subjects and Methods

This study included 267 Asian Indians (127 men and 140 women), aged 45 ± 1 yr (mean ± SEM), residing in Los Angeles, CA. Subjects were participants in a study on diabetes and cardiovascular disease among Asian Indian immigrants to the United States and were recruited by advertisement from the local community. Subjects taking any medications were excluded. The study was approved by the institutional review board of the University of Southern California, and all subjects gave informed consent.

Subjects underwent an examination that included measurement of height, weight, blood pressure, and waist and hip circumferences. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Fat mass was determined by bioelectrical impedance (RJL Systems, Mt. Clemens, MI). Total body water was estimated using sex-specific equations (21). Fat-free mass (FFM) was assumed to have a hydration constant of 0.73 and was calculated with the formula: FFM = total body water/0.73. Fat mass was also determined by dual energy x-ray absorptiometry (22) (DEXA; QDR-2000, Hologic, Waltham, MA) in a subset of 91 subjects (50 men and 41 women). Among these subjects, there was no difference in fat mass, as determined by bioelectrical impedance and DEXA ($P = 0.29$), and both measurements were strongly correlated ($r = 0.89$; $P < 0.001$).

All subjects underwent an oral glucose tolerance test after a 10- to 12-h overnight fast. Blood was collected at −15, 0, 30, 60, 90, and 120 min for determination of plasma glucose and insulin concentrations. According to WHO criteria (23), 106 subjects had normal glucose tolerance, 102 had impaired glucose tolerance, and 59 had NIDDM (Table 1). The plasma leptin concentration was determined at −15 and 0 min for all subjects and after the glucose load for a subset of 10 men and 10 women from each glucose tolerance category.

Biochemical analyses

The plasma glucose concentration was measured by the glucose oxidase method. Plasma insulin was determined by a specific RIA with

TABLE 1. Characteristics of subjects

	NGT (n = 106)	IGT (n = 102)	NIDDM (n = 59)	P^a
Age (yr)	43 ± 1	46 ± 1	50 ± 1	<0.001
Sex (M/F)	52/54	42/60	33/26	0.18
Body mass index (kg/m^2)	24.0 ± 0.4	24.8 ± 0.3	25.9 ± 0.4	0.003
Body fat (%)	29.8 ± 0.8	32.5 ± 0.7	32.5 ± 0.9	0.016
Waist/hip ratio	0.81 ± 0.01	0.81 ± 0.01	0.84 ± 0.01	0.013

Values are the mean, ± SEM for continuous variables. NGT, Normal glucose tolerance; IGT, impaired glucose tolerance; NIDDM, noninsulin-dependent diabetes mellitus.

[a] *P* values are for comparison among the three groups by ANOVA or the χ^2 method.

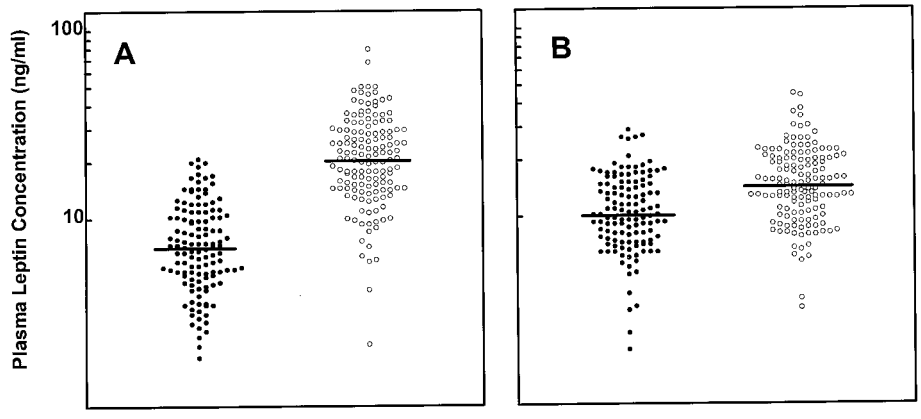

FIG. 1. Fasting plasma leptin concentration in men (*solid circles*) and women (*open circles*) before (A) and after (B) adjusting for percent body fat. *Solid lines* indicate the geometric means. $P <$ 0.001 for differences between men and women in each panel.

reagents from Linco Research (St. Louis, MO), with a detection limit of 6 pmol/L and interassay coefficients of variation from 6–8%. The plasma leptin concentration was measured with a recently developed RIA (Linco Research) that uses a polyclonal antibody raised in rabbits against recombinant human leptin (24). The assay had a sensitivity of 0.5 ng/mL and interassay coefficients of variation from 5–7%. To determine day to day variability, fasting plasma leptin was measured in 10 subjects on 5 different days between 0700–0800 h within a 4-week period. The individual coefficient of variation ranged between 6.9–21.1%, with an average of 11.9 ± 1.4%.

Statistical analyses

Data are expressed as the mean ± SEM or as the mean with 95% confidence interval (CI). Insulin and leptin concentrations were log transformed to normalize the distribution. Statistical analyses were performed with programs from SPSS (Chicago, IL) (25). Comparisons among groups were performed with ANOVA. Linear regression and/or Pearson product-moment correlations were used to evaluate the relation among different variables. Multiple linear regression with a backward-stepwise procedure was used to define the variables most predictive of the fasting leptin concentration.

Results

The fasting plasma leptin concentration ranged from 1.8–79.6 ng/mL, with a geometric mean of 12.4 (95% CI, 11.3–13.6). Women had, on the average, 3-fold higher leptin levels than men [20.3 ng/mL (CI, 18.5–22.3) *vs.* 7.0 (CI, 6.4–7.7); $P <$ 0.001; Fig. 1A]. After adjusting for percent body fat, women continued to have approximately 40% higher leptin levels [14.4 ng/mL (CI, 13.3–15.5) *vs.* 10.3 (CI, 9.5–11.2); $P < 0.001$; Fig. 1B]. Postmenopausal women had higher leptin concentrations than men of similar age [14.9 (CI, 11.7–19.1) *vs.* 10.3 (CI, 8.1–13.0), respectively; $P = 0.03$], but these values were not different from those in younger women ($P = 0.69$) after controlling for body fat. Leptin levels were similar in the three glucose tolerance categories. Women still had significantly higher levels than men in each category independent of body fat (Fig. 2). Plasma leptin did not change significantly during the oral glucose tolerance test in any glucose tolerance group.

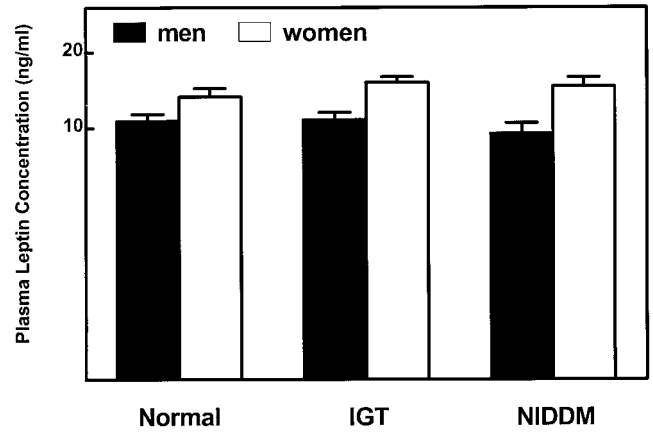

FIG. 2. Fasting plasma leptin concentration, adjusted for percent body fat, in men and women in the three glucose tolerance categories. By two-way ANOVA: $P = 0.178$ for glucose tolerance status, and $P <$ 0.001 for gender.

The leptin concentration correlated significantly with body weight, BMI, percent body fat, and fat mass in men (r = 0.65, 0.75, 0.53, and 0.68, respectively; $P < 0.001$ for each) and women (r = 0.60, 0.67, 0.61, and 0.66; $P < 0.001$ for each). Women had higher leptin levels than men at any body weight, BMI, percent body fat, or fat mass. Figure 3 (*upper panels*) shows the relation between leptin and BMI and fat mass. The sex difference in this relationship was also observed in the subset of subjects whose fat mass was determined by DEXA (Fig. 3, *lower panels*). Leptin correlated weakly with the waist/hip ratios in men (r = 0.22; $P = 0.01$), but not in women (r = −0.06; $P = 0.47$). After adjusting for

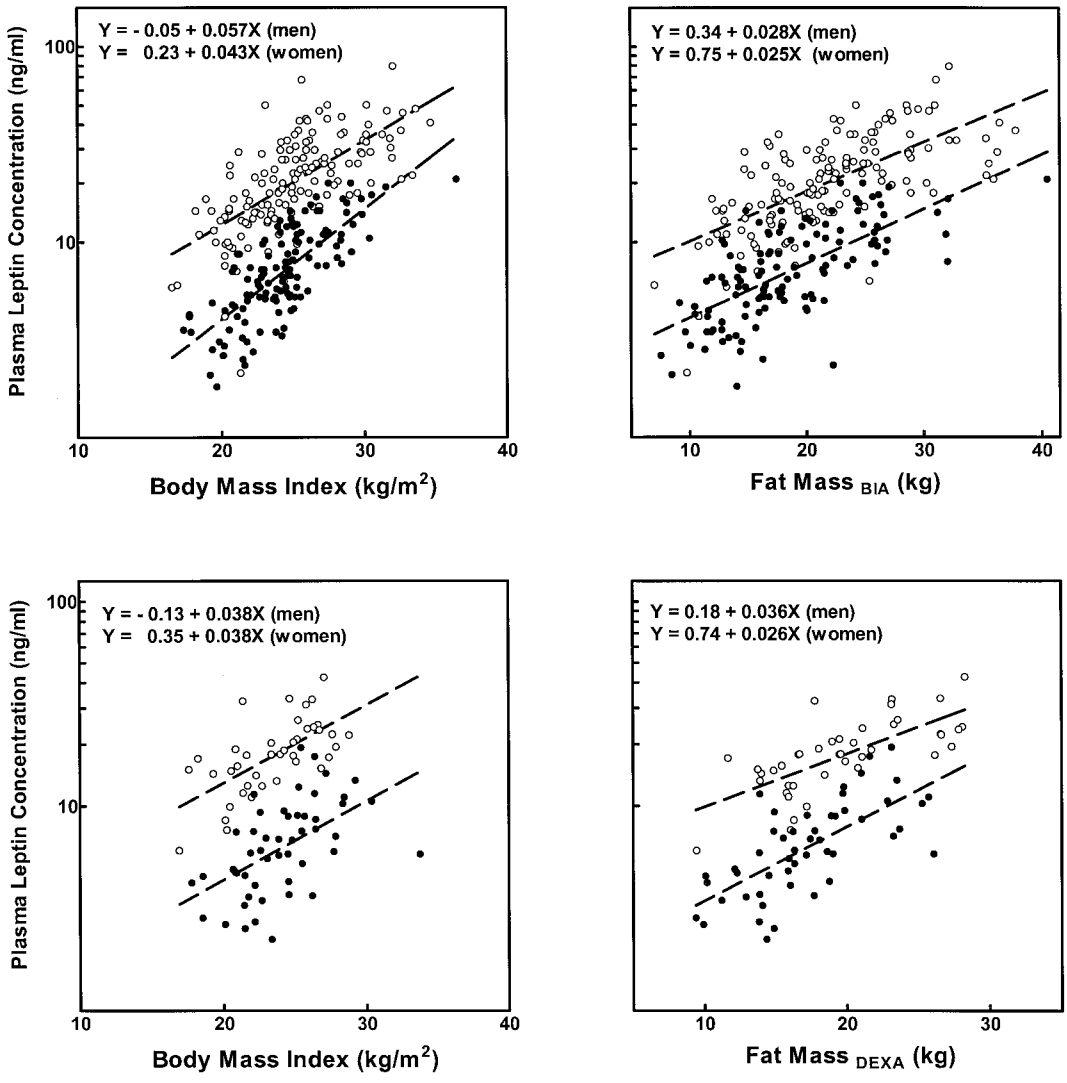

FIG. 3. The relation between leptin and BMI and fat mass in men (*solid circles*) and women (*open circles*). The *upper panels* show data for the whole group; fat mass was determined by bioelectrical impedance (BIA). The *lower panels* show data for a subset in whom fat mass was determined by DEXA. Slopes of the regression lines were significantly different in the *upper left panel* ($P = 0.03$). In all other panels, the slopes of the regression lines were similar, but the intercepts were different ($P < 0.001$).

body fat, the relation was significant in neither men (r = 0.11; $P = 0.19$) nor women (r = −0.04; $P = 0.61$).

The leptin concentration was positively related to fasting insulin in men and women before (r = 0.42 and 0.34, respectively; $P < 0.001$ for both) and after (r = 0.27 and 0.22; $P < 0.01$ for both) adjusting for percent body fat (Fig. 4). Leptin was not significantly correlated with age, blood pressure, or fasting or 2-h plasma glucose levels in men or women. Multiple regression analysis showed that fat mass, gender, and insulinemia were significant determinants of the fasting leptin concentration (Table 2). The model including these variables explained 72% of the variance in leptin concentration. Fat mass could be replaced in the model with percent body fat without a significant change in its strength.

Discussion

In keeping with other studies in man (19, 20), the plasma leptin concentration correlated positively and was primarily determined by fat mass. Human (12–14) and animal (3, 4) data suggest that the increased leptin levels with adiposity are due to augmented *ob* gene expression and increased leptin production. The mechanism of this increase is not known, but possibly involves enlargement of adipocytes. *In vitro* leptin secretion is closely related to fat cell size in genetic and diet-induced obese mice (26). In humans, Hamilton and colleagues (13) showed that small adipocytes expressed less *ob* messenger ribonucleic acid (mRNA) than larger ones from the same individual. As the leptin level varies in proportion to fat mass, it could conceivably serve as an afferent signal that provides sensory input about the degree of adiposity to the central nervous system. In response, adjustments in food intake and/or energy expenditure would be made to ensure long term body weight stability.

Leptin's role in human obesity is unclear. No mutations in the *ob* gene (10–12) or defects in its expression (12–14) have been found in obese subjects. Our data and others (19, 20)

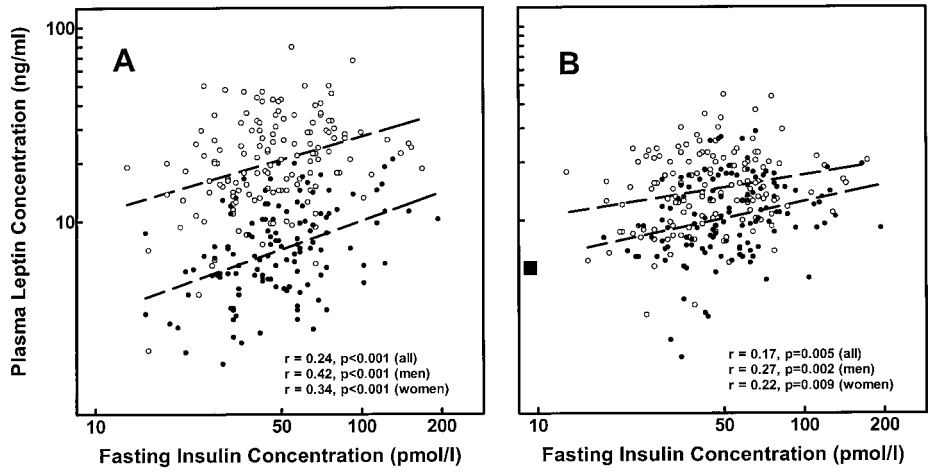

FIG. 4. The relation between fasting plasma insulin and leptin concentrations in men (*solid circles*) and women (*open circles*) before (A) and after (B) adjusting for percent body fat. The slopes of the regression lines were similar, but the intercepts were different ($P < 0.001$) in both panels.

TABLE 2. Determinants of fasting leptin concentration (multivariate regression analysis), [dependent variable: fasting leptin (ng/mL)]

Variable	B (95% confidence interval)	% of variance explained	*P*
Fat mass (kg)	0.025 (0.022–0.029)	42	<0.001
Gender (M = 1, F = 2)	0.376 (0.331–0.421)	28	<0.001
Fasting insulin (pmol/L)	0.115 (0.015–0.215)	2	<0.025

Fasting insulin and leptin concentrations were log-transformed (base 10).

suggest that human obesity is not caused by leptin deficiency, because its levels increase progressively with fat mass. Nonetheless, interindividual variability in leptin production and/or sensitivity to its actions could contribute to the development of obesity. Leptin levels differed considerably in subjects with similar fat mass. For example, leptin levels ranged between 1.8–14.4 ng/mL (median, 5.9; n = 19) in men and from 7.2–28.9 ng/mL (median, 11.6; n = 11) in women with a fat mass of 14–16 kg. Likewise, Maffie *et al.* (19) described significant heterogeneity in leptin concentrations among subjects with similar BMI. It is possible, therefore, that subjects whose leptin levels are appropriate for their fat mass are more able to keep their weight stable, whereas those with inadequate levels are more prone to weight gain. Individuals may also differ in their sensitivity to leptin. Some animal models of obesity, such as the *db/db* mouse and the *fa/fa* rat, are leptin resistant due to mutations in its receptors (27, 28). Moreover, leptin resistance could be induced in mice by a high fat diet (29). Further studies are needed to explore whether genetic or acquired leptin resistance exists in man.

Women had higher leptin levels than men at any percent body fat or fat mass. Two studies (19, 20) described similar findings in relation to BMI, but found no difference when men and women with similar percent body fat were compared. This discrepancy could be explained by differences in sample size, subject characteristics, or methodology. The current study included a larger and more homogeneous group of subjects belonging to a single ethnic group with a balanced sex distribution. Conversely, the other studies (19, 20) included subjects of mixed ethnicity, with a preponderance of women. Although ethnicity does not appear to affect the leptin level or its relation to adiposity (19, 20, 30, 31), the precision of different methods of body composition determination varies in various ethnic groups (32, 33). Therefore, we used two different methods of body composition determination, bioelectrical impedance and DEXA, to confirm our findings. Moreover, we found a similar sex difference in the relation between leptin and body fat in African-Americans and Hispanics using yet a third method (underwater weighing) for body composition determination (unpublished observations). Leptin may circulate, however, in several biochemical or molecular forms that vary in men and women and are not equally detected by our immunoassay and those used in the other two studies (19, 20).

Our findings are supported by Lönnqvist *et al.* (14), who found a 75% higher *ob* gene expression in obese women than in obese men. Moreover, Schwartz *et al.* (34) have found higher cerebrospinal fluid leptin concentrations in women than in men after controlling for age, BMI, and plasma leptin level. A sex difference has also been described in mice; Frederich *et al.* (29) showed that female mice had higher plasma leptin levels and adipose tissue *ob* mRNA than males at any given body fat content. It appears, therefore, that female fat cells produce more leptin than those of males with similar body composition.

The mechanism of the sexual dimorphism in leptin production is unclear. Sex hormones do not appear to be the culprit. Postmenopausal women had leptin levels higher than men of similar age and not different from those of younger women after adjusting for body fat. Differences in fat distribution might play a role. Masuzaki *et al.* (2) found subcutaneous fat to express more leptin mRNA than intraabdominal fat. Thus, central (or visceral) android adipose tissue may produce less leptin than peripheral gynecoid fat, accounting for the differences between men and women. Leptin levels were not, however, related to the waist/hip ratio independent of the total fat mass. A further possibility is a sex difference in the hypothalamic regulation of leptin production. Sainsbury *et al.* (35) reported that intracerebroventricular administration of neuropeptide Y increased *ob* gene expression in white adipose tissue in normal rats. Sexual dimorphism characterizes several hypothalamic nuclei (36) as well as neuropeptide Y gene expression (37) and

secretion (38). Finally, female adipose tissue may be more sensitive to hormones (*e.g.* insulin) or other substances that stimulate leptin production.

The sexual dimorphism in leptin levels suggests that women may be less sensitive than men to its lipostatic actions, leading to compensatory increase in its production and possibly its transport to the cerebrospinal fluid (34). Leptin may also have a reproductive function. Ahima *et al.* (39) recently reported that leptin administration prevented the starvation-induced delay in ovulation in female mice and the fall in testosterone concentration in males. These effects were associated with an increase in LH levels, suggesting that leptin acts at the level of the hypothalamic-pituitary axis. In addition, an isoform of leptin receptor has been described in murine and human reproductive organs (40). Leptin deficiency in the *ob/ob* mouse is associated with sterility. Leptin administration to homozygous female *ob/ob* mice corrected their sterility, resulting in ovulation, pregnancy, and parturition (41). This effect was independent of weight loss, as diet restriction failed to correct sterility. Moreover, mutations of the leptin receptor in the *db/db* mouse result not only in leptin resistance and adiposity but also in aberrant regulation of sex steroid sulfotransferase genes, virilization of hepatic metabolism, and sterility (42). Obesity in humans can also be associated with reproductive dysfunction. Further work is needed to explore the implications of leptin's sexual dimorphism and its role in reproduction.

Insulinemia explained only 2% of the variance in leptin concentration. No increase was observed in leptin levels during the oral glucose tolerance test despite the increase in insulinemia. In addition, leptin concentrations do not change significantly after meals (19, 20) or after short term insulin infusion (43, 44). However, a long term effect of insulin on leptin production could be shown *in vivo* and *in vitro* (44), suggesting that insulin is involved in regulating leptin production, but not its release. Insulin may, therefore, contribute to the increased leptin levels in obesity that is commonly associated with hyperinsulinemia.

Obesity is a major risk factor for impaired glucose tolerance and NIDDM. Leptin levels were not correlated, however, with fasting or 2-h postload plasma glucose concentrations and were not different among the three glucose tolerance categories controlling for adiposity. These findings agree with those of others (45, 46), who reported no difference in leptin levels between subjects with and without NIDDM. Leptin may not, therefore, be directly related to glucose intolerance.

In conclusion, adiposity and gender are the major determinants of leptin concentration. Women had 40% higher leptin levels than men with similar fat mass. This sex difference is not related to sex hormones or fat distribution, but possibly to differences in hypothalamic regulation of leptin production or in adipose tissue biological characteristics. Leptin's sexual dimorphism suggests that women may be resistant to its lipostatic actions and that it may have a reproductive function. Further work is needed to explore the mechanism and implications of leptin's sexual dimorphism.

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