Leptin in Women With Eating Disorders

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The aim of the present study was to determine the factors controlling leptin secretion and to clarify the role of leptin in eating disorders. The subjects were 152 eating-disordered women with different fat mass, eating behavior, and endocrine abnormalities and 24 age-matched control subjects. The body fat mass, eating behavior score, and plasma leptin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), triiodothyronine (T_3), free thyroxine (T_4), insulin, and cortisol levels were evaluated for each subject. In patients with eating disorder, logarithmic values for leptin were significantly correlated with the body fat mass ($r = .828$, $P < .001$), eating behavior score ($r = .777$, $P < .001$), and LH ($r = .465$, $P < .001$), FSH ($r = .440$, $P < .001$), T_3 ($r = .572$, $P < .001$), insulin ($r = .410$, $P < .001$), and cortisol ($r = -.389$, $P < .001$) levels. After adjusting for fat mass, the partial correlations of log leptin with LH, FSH, insulin, and cortisol were not statistically significant, but log leptin remained correlated with T_3 ($r = .390$, $P < .01$). Stepwise regression analysis showed that the body fat mass and eating behavior score were significant determinants of leptin levels. These results suggest that eating behavior, as well as the body fat mass, is the control factor for leptin secretion in eating disorders.

THE ADIPOCYTE-SPECIFIC gene[1] *ob* encodes leptin, a secreted protein that regulates body weight by influencing energy intake[2] and energy expenditure.[3] Plasma levels of leptin are well correlated with body fat content in human subjects,[4] suggesting that the role of leptin is to inform the brain of the amount of adipose tissue present in the body.[5] In addition, leptin affects several neuroendocrine mechanisms and regulates multiple hypothalamic-pituitary axes.[6] Therefore, the discovery of leptin has opened new opportunities in the investigation of disorders such as obesity and anorexia nervosa.[7]

Anorexia nervosa and bulimia nervosa are psychiatric diseases characterized by abnormal eating behavior and obsessive ideation about body weight.[8] The metabolic abnormalities of patients with anorexia nervosa are those of severe malnutrition. On the other hand, patients with bulimia nervosa more often have a normal weight with alternating episodes of binge eating, vomiting, and purging.[8] It has been reported that anorexia nervosa patients show a severe reduction in plasma leptin correlated with the reduction in the body mass index[9-11] and body fat content.[10] However, there is residual variability in leptin levels even at a given level of adipose mass. Thus, it is not currently known whether leptin merely reflects the amount of adipose tissue or is associated with specific pathology in these patients.

Although a key role has been suggested for leptin in the regulation of eating behavior in animals,[2] its significance in human eating behavior is still obscure.[5,7] Single meals do not significantly alter leptin levels,[12] whereas short-term fasting[13,14] and overfeeding[15] lead to a rapid decrease and increase, respectively, of leptin that precede any weight alterations. However, it is not clear whether leptin levels are different with disturbed eating patterns in patients with eating disorder.

Since eating disorders are the paradigm of psychosomatic disorders, their endocrine disturbances have prompted many investigators to attempt to unravel the pathophysiology.[16] Besides regulating energy balance, leptin influences several neuroendocrine mechanisms in rodents.[6] In light of these findings, it is probable that leptin mediates endocrine alternations, including the abnormality of the hypothalamic-pituitary-gonadal axis, in eating disorders.

Therefore, in the present study, the plasma leptin level was measured in a large group of subjects with eating disorders with different body fat mass, abnormal eating behavior, and endocrine abnormalities, to determine the factors controlling leptin secretion and also to clarify the role of leptin in these disorders.

SUBJECTS AND METHODS

The subjects were 152 female patients with eating disorders and 24 age-matched female controls. The patients were 82 women with restricting anorexia nervosa, 19 with bulimic anorexia nervosa, and 51 with bulimia nervosa. All eating disorder diagnoses were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[8] The standard body weight was calculated from the body length according to a formula described previously.[17] At the time of study, the patients were eating-disordered, under treatment, and at different stages of therapeutic evolution. Seventy-seven patients with restricting anorexia nervosa, 15 with bulimic anorexia nervosa, and 14 with bulimia nervosa had amenorrhea. None of the patients had evidence of disease other than the stated eating disorders. They did not use any medications. Control subjects were women aged 23.9 ± 1.2 years (mean ± SE) with a body weight between 85% and 105% of the standard body weight, normal menstrual function, and no medications. They had normal eating behavior and no history of eating disorders. Their body fat mass was between 10.7 and 20.0 kg. Since 25 bulimic patients and all control subjects had a normal ovarian cycle, they were studied at the follicular period.

Informed consent for participation in the study was obtained from all subjects. A blood sample was collected from each subject while fasting, and the plasma was frozen until analysis.

Plasma immunoreactive leptin levels were measured by radioimmunoassay (RIA) using commercial kits (Human Leptin RIA kit; Linco Research, St. Charles, MO). The limit of sensitivity was 0.5 ng/mL and the intraassay and interassay coefficients of variation were 3.5% and 2.3%, respectively. Plasma luteinizing hormone (LH), follicle-stimulating hormone (FSH), triiodothyronine (T_3), free thyroxine (T_4),

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Submitted April 7, 1998; accepted July 20, 1998.

Supported by a grant from the Ministry of Health and Welfare of Japan and a Medical Research Grant from the Smoking Research Foundation (Japan).

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0026-0495/99/4802-0014$10.00/0

insulin, and cortisol levels were measured by RIA using commercial kits. Fat mass was determined by multiplying the percent body fat by the body weight. The percent body fat was determined from bioelectrical impedance analysis, a method that has been previously validated.[18] The eating behavior score was assessed by obtaining a detailed history of eating behavior within 48 hours before blood sampling using recall methods[19]: almost fasting for longer than 48 hours, 1: low calorie intake, 2; nearly normal calorie intake with different eating patterns from almost normal eating to binging and purging, 3; high calorie intake with binging and purging, 4; and extremely high calorie intake with binging, 5. Although it is difficult to estimate the exact amount of calories eliminated by vomiting, the estimated caloric intake was less than 500 kcal/d for a score of 1, 500 to 1,500 kcal/d for score 2, 1,500 to 2,500 kcal/d for score 3, 2,500 to 4,000 kcal/d for score 4, and greater than 4,000 kcal/d for score 5.

Plasma leptin concentrations were logarithmically transformed to normalize the distribution. The significance of differences was tested with one-factor ANOVA with Scheffe's F test for a post hoc group difference, with statistical significance at a P level less than .05. Linear regression and/or Spearman correlations were used to evaluate the relation among different variables. Partial parametric correlations were performed by substituting the rank of the observation for the actual value. Multiple linear regression with a backward stepwise procedure was used to define the variables most predictive of log leptin concentrations. All calculations were performed with programs from SPSS (User's Guide, SPSS 7.5 J for Windows; SPSS, Chicago, IL, 1997).

RESULTS

Table 1 shows Spearman correlations for log leptin, fat mass, eating behavior score, LH, FSH, T_3, free T_4, insulin, and cortisol in eating-disordered patients. Log values for plasma leptin were significantly correlated with the fat mass ($r = .828$, $P < .001$) and eating behavior score ($r = .777$, $P < .001$) (Fig 1). They were also significantly correlated with LH ($r = .465$, $P < .001$), FSH ($r = .440$, $P < .001$), T_3 ($r = .572$, $P < .001$), cortisol ($r = -.389$, $P < .001$), and insulin ($r = .410$, $P < .001$) (Figs 2 and 3). In multiple linear regression with a backward stepwise procedure, the fat mass and eating behavior score were significant determinants of log leptin concentrations.

Body fat mass was significantly correlated with LH ($r = .670$, $P < .001$), FSH ($r = .484$, $P < .001$), T_3 ($r = .513$, $P < .001$), insulin ($r = .383$, $P < .001$), cortisol ($r = -.361$, $P < .001$), and the eating behavior score ($r = .548$, $P < .001$) in patients with eating disorder.

Table 1. Spearman Correlations for Log Leptin, Fat Mass, Eating Behavior Score, LH, FSH, T_3, Free T_4, Insulin, and Cortisol in Patients With Eating Disorder

Variable	Fat Mass	EB Score	LH	FSH	T_3	Free T_4	Insulin	Cortisol
Log leptin	.828*	.777*	.465*	.440*	.572*	.196	.410*	−.389*
Fat mass		.548*	.670*	.484*	.513*	.128	.383*	−.361*
EB score			.434*	.314†	.450*	.195	.403*	−.258‡
LH				.763*	.428*	.187	.185	−.454*
FSH					.306†	.224	.146	−.419*
T_3						.262‡	.383*	−.344†
Free T_4							.121	−.082
Insulin								−.290‡
Cortisol								

Abbreviation: EB, eating behavior.
*$P < .001$.
†$P < .01$.
‡$P < .05$.

Table 2 shows partial correlations among log leptin and hormone levels after adjusting for the fat mass or eating behavior score. The correlations for log leptin with LH, FSH, insulin, and cortisol were not statistically significant, but log leptin remained correlated with T_3 ($r = .370$, $P < .01$) after adjusting for the fat mass. On the other hand, log leptin remained correlated with LH ($r = .314$, $P < .01$), FSH ($r = .305$, $P < .01$), T_3 ($r = .415$, $P < .01$), and cortisol ($r = -.306$, $P < .01$) after adjusting for the eating behavior score.

Plasma leptin concentrations were compared in the normal controls versus subjects with different eating behavior scores. Since the body fat mass in 24 normal controls was between 10.6 and 20.0 kg, eating-disordered patients with a body fat mass between 10.6 and 20.0 kg were divided into three groups: 19 with an eating behavior score of 1 or 2 (group 1), 15 with a score of 3 (group 2), and 14 with a score of 4 or 5 (group 3). A one-factor ANOVA for body fat mass was not significant ($F = 1.46$, $P = .23$). However, a one-factor ANOVA for log leptin was significant ($F = 18.8$, $P < .0001$). Log leptin concentrations were significantly lower for group 1 (0.68 ± 0.03 ng/mL) versus group 3 (1.15 ± 0.04 ng/mL) and the controls (0.85 ± 0.05 ng/mL). The concentrations were significantly higher for group 3 versus group 2 (0.84 ± 0.04 ng/mL) and the controls.

DISCUSSION

In the present study, log values for plasma leptin were significantly correlated with the fat mass in 152 eating-disordered women ($r = .828$, $P < .001$). These results are consonant with previous reports.[9-11] However, a more interesting finding in the present study is that log values for plasma leptin were also significantly correlated with the eating behavior score ($r = .777$, $P < .001$), which was assessed with a detailed history of eating behavior within 48 hours prior to blood sampling.

Short-term fasting[13,14] and overfeeding[15] lead to a rapid decrease and increase, respectively, in leptin that precede any weight alterations. These results support our present finding of a significant correlation between log leptin and the eating behavior score.

The mediator that produces this effect remains unknown. The role of insulin in regulating leptin levels is still under dispute.[5] Although a significant correlation between log leptin and insulin levels was observed in the present study, the association was dependent on the body fat mass. On the other hand, log leptin remained correlated with the eating behavior score after adjusting for the fat mass, suggesting that the association was independent of body fat mass. These results suggest that eating behavior affects the plasma leptin level through a factor(s) other than insulin. Furthermore, stepwise regression analysis showed that the fat mass and eating behavior score were significant determinants of log plasma leptin levels.

Another interesting finding of the present study is that in eating-disordered patients, log plasma leptin was correlated with plasma LH and FSH levels. This association was dependent on the body fat mass. Leptin has been linked to the control

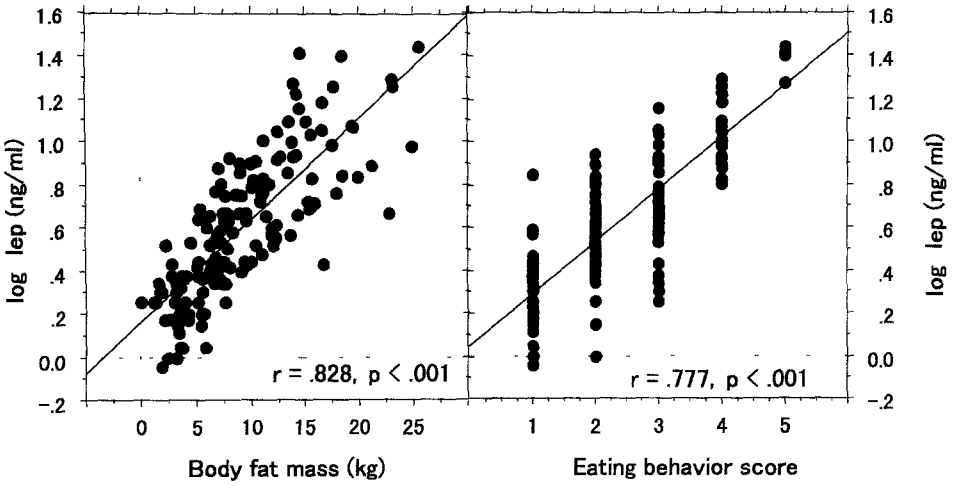

Fig 1. Individual log values for plasma leptin (log lep) plotted against the body fat mass (r = .828, P < .001) and eating behavior score (r = .777, P < .001) in 152 women with eating disorder.

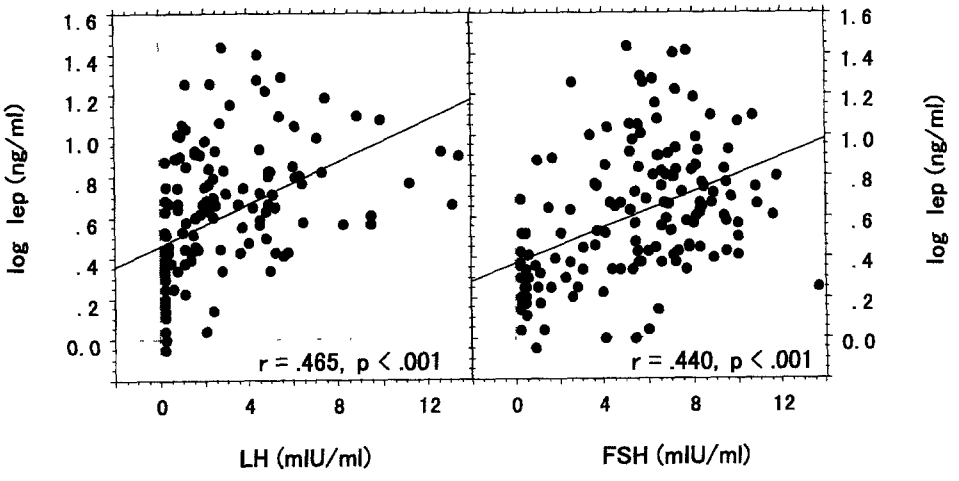

Fig 2. Individual log values for plasma leptin (log lep) plotted against plasma LH (r = .465, P < .001) and FSH (r = .440, P < .001) in 152 women with eating disorder.

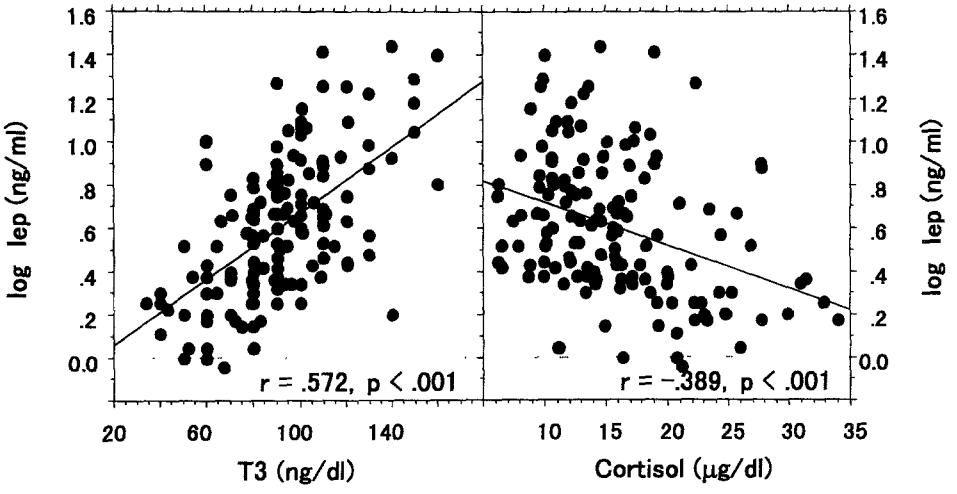

Fig 3. Individual log values for plasma leptin (log lep) plotted against plasma T_3 (r = .572, P < .001) and cortisol (r = −.389, P < .001) in 152 women with eating disorder.

Table 2. Partial Correlations Among Log Leptin and Hormone Levels After Adjusting for Fat Mass or Eating Behavior Score in Patients With Eating Disorder

Hormone	Log Leptin	
	Fat Mass	Eating Behavior Score
LH	.225	.314*
FSH	.205	.305*
T_3	.370*	.415*
Free T_4	.110	.098
Insulin	.002	.002
Cortisol	−.197	−.306*

*$P < .01$.

of reproduction.[6,20] However, the role of leptin in reproductive function in patients with eating disorders must be carefully evaluated, since plasma FSH levels were within the normal range even with extremely low plasma leptin levels in some patients of the present study.

Cheung et al[21] recently reported that leptin is not the primary signal that initiates the onset of puberty, but that it acts in a permissive fashion as a metabolic gate to allow pubertal maturation to proceed, and other metabolic factors besides leptin influence the timing of the puberty onset under conditions of more severe dietary stress. Thus, leptin may act in a permissive fashion to restore gonadotropin secretion in eating disorders.

In the present study, log leptin was correlated with T_3 levels and correlated negatively with cortisol levels. These findings are consonant with previous reports that leptin levels are decreased in hypothyroid patients[22] and the activity of the hypothalamic-pituitary-adrenal axis in humans varies inversely with serum leptin levels.[23] Whether such an association is causal or merely reflects a common determinant cannot be ascertained from our essentially correlational study. In summary, the present findings show that eating behavior, as well as the body fat mass, is the control factor for leptin secretion in eating disorders.

ACKNOWLEDGMENT

The secretarial assistance of Hitomi Kawamura is greatly appreciated.

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