Note

A Comparison of Serum Leptin Concentrations in Obese and Normal Weight Japanese Women with Regular Menstrual Cycle

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Summary

Leptin is a protein that is synthesized and secreted from adipose tissue. We examined the changes in serum leptin level during the menstrual cycle in 5 normal and 5 obese Japanese women, and compared the data with those of serum estradiol (E2) and progesterone (P4) concentrations. Serum leptin levels were highly correlated with body mass index (BMI) and percent body fat, being higher in the obese group than in the normal group. In the obese group, serum leptin level increased in the luteal phase in parallel with the rise in the serum E2 level. In the normal group, however, there was no significant change in serum level during the menstrual cycle. These results suggested that the serum leptin levels were influenced by the phase of menstrual cycle, probably through the action of E2, in different ways for obese and non-obese women.

Key Words leptin, estradiol, progesterone, obese women, menstrual cycle

Leptin, a product of the ob gene, is a 16-kD protein which is produced by adipocytes (1). This protein regulates fat stores and body weight by affecting appetite and thermogenesis (2–4). It is known that a correlation exists between circulating leptin levels, body mass index (BMI) and percent body fat. It is also known that plasma leptin levels are higher in women than men, are higher in pregnant women, and rise at the onset of puberty (5, 6). Leptin has been shown in vitro to affect the hypothalamic-pituitary release of gonadotropin and ovarian steroidogenesis (7–9). These findings suggest that leptin may be associated with normal reproductive events. Thus, plasma leptin concentrations may change during the menstrual cycle. The aim of the present study was to compare the plasma leptin levels with those of sex steroid hormones such as estradiol (E2), and progesterone (P4) during the menstrual cycle both in normal and obese Japanese women.

Materials and Methods

Subjects. Ten healthy Japanese women (five obese, BMI>26 kg/m2, five normal, BMI≤26) were investigated. They were recruited for serial venous blood sampling throughout one complete menstrual cycle at the Outpatient Clinic of Nippon Medical School 2nd Hospital. All subjects had regular menstrual cycles (28–35 d between onset of menses) and biphasic basal body temperature, and they had kept their weight stable ±2.0 kg for over one year. None was taking any medications, smoking or showed any metabolic diseases. All participants provided written informed consent to participate in this study. The characteristics of subjects are as follows: (1) Normal weight women (n=5, aged 35.1±4.0 years old (means±SE), BMI 22.4±0.3), (2) Obese Women (n=5, aged 34.2±2.0, BMI 28.2±0.9).

Methods. Three blood samples were collected at different points during the menstrual cycle; one sample between the 2nd and 5th day after the onset of menses (early follicular phase), another between the 1st and 3rd day after the gonadotropin surge (ovulatory phase) and the third on the 7th day after the gonadotropin surge (luteal phase). Every subject was instructed to eat her last meal or snack before 2200 h on the days preceding outpatient visits and to have nothing to eat or drink until after the visit. They had at least 1 h rest in a sitting position before the samples were taken from a large forearm vein. Blood samples were collected between 0900 and 1100 h. Serum leptin, E2 and P4 were measured by radioimmunoassay (RIA) using previously described methods (7). Body weight was measured to the nearest 0.1 kg on a digital scale and the percent body fat was measured by bioelectrical impedance analysis (Body Composition Analyser, Tanita TBF-541, Japan). The BMI was estimated by dividing the body weight (in kilograms) by the square of the height (in meters). The subjects maintained their usual lifestyle, physical activity, and diet. Study subjects had an ad libitum diet. Their food intakes and activities were recorded on three consecutive weekdays before the three phases. Total energy intake was analyzed using nutritional as-
assessment software Exel Eiyoukun, version 2.1 (Kenpakusha, Japan) and energy expenditure was analyzed using nutritional assessment system NUT version 4.0 (Human science laboratory, Japan). The average of the three days was calculated as one day.

Statistics. The data were expressed as means±SE. Statistical analyses were performed with SPSS/Windows/Version 9.0 (SPSS, Chicago). The menstrual data were grouped into three phases: early follicular, ovulatory and luteal phase. The changes between leptin, BMI, percent body fat, E2, P4 energy intake and energy expenditure were tested by within-group comparisons using one-way analysis of variance (ANOVA) with repeated measures. When the result of the repeated measures ANOVA was statistically significant, paired t-test was used. Baseline characteristics among normal and obese subjects were analyzed using unpaired t-test. Linear regression analysis was used to test the correlation between serum leptin, BMI and the percent body fat. Statistical significance was defined as p<0.05.

Results

Serum leptin concentration, body weight, percent body fat and BMI in the obese group were significantly higher than in the normal. Throughout the menstrual cycle serum leptin concentrations were highly correlated with BMI (r=0.742, obese, r=0.796, normal; p<0.05 for each) and the percent body fat (r=0.642, obese, r=0.750, normal; p<0.05 for each). No significant differences in energy intake and energy expenditure were found in either normal or obese subjects were analyzed using unpaired t-test. Linear regression analysis was used to test the correlation between serum leptin, BMI and the percent body fat. Statistical significance was defined as p<0.05.

Discussion

Leptin, a 16-kD adipocyte-derived polypeptide hormone, regulates food intake and stimulates energy expenditure. The metabolic significance of leptin in humans is currently under intensive investigation in various laboratories. Many reports have involved the measurement of circulating leptin levels under various metabolic conditions. The changes in leptin concentrations during the menstrual cycle were detected and its correlation with E2 and P4 are in accordance with earlier reports (7–9). In general, women experienced dramatic changes of hormones, metabolism and body composition during the menstrual cycle. In addition, the level of changes in different phases varies between normal body weight women and obese women.

Our results also showed that leptin, body weight, percent body fat and BMI are higher in the obese group than that in the normal, as in previously published reports (6).

On the other hand, leptin concentrations correlated with E2 concentrations throughout the regular menstrual cycle (with minimal changes in BMI) (r=0.865, obese, r=0.420, normal). Leptin concentrations at the luteal phase increased significantly in the obese group. But in the normal group such increase was not shown. Since E2 can potentiate leptin release in vitro (10), the ovulatory rise in E2 may be the prime reason for leptin release during the ovulatory and luteal phase. It has been reported that leptin levels were not affected by a small increase in E2 but were affected by a large increase (11). In our study, E2 increased at a higher rate from the early follicular phase to the ovulatory phase in the obese group than in the normal. The transition of E2 may have affected leptin concentrations in the obese group. Thus it is conceivable that E2 may have an effect on the production of leptin by adipose tissue in humans.

In an earlier report (8), leptin concentrations were at their peak in the luteal phase, coinciding with an elevation of serum P4. In our study, serum P4 concentrations rose 10-fold and serum leptin rose about 1.3-fold during the same cycle; therefore P4 may not regulate the production of leptin.

In this study, the results did not show any differences in energy intake or expenditure between the obese

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>BMI kg/m²</th>
<th>Leptin ng/mL</th>
<th>E2 pg/mL</th>
<th>P4 ng/mL</th>
<th>Energy intake kcal/d</th>
<th>Energy expenditure kcal/d</th>
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<tbody>
<tr>
<td>Normal group</td>
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<tr>
<td>Early follicular phase</td>
<td>35.1±4.0</td>
<td>22.4±0.3</td>
<td>7.5±1.4</td>
<td>35.0±4.2</td>
<td>0.4±0.0</td>
<td>1.857±103</td>
<td>1.700±122</td>
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<td>Ovulatory phase</td>
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<td>Luteal phase</td>
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<td>Obese group</td>
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<tr>
<td>Early follicular phase</td>
<td>34.2±2.0</td>
<td>28.2±0.9</td>
<td>18.1±1.1</td>
<td>46.0±7.3</td>
<td>0.9±0.5</td>
<td>1.787±203</td>
<td>1.684±150</td>
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<td>Ovulatory phase</td>
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Values are the means±SE. *p<0.01 vs. early follicular phase, **p<0.05 vs. early follicular phase, + p<0.01 vs. early follicular and ovulatory phase; *p<0.01 vs. Normal group.
group and the normal. In general, obesity is a common finding in women with polycystic ovary syndrome (PCO). But as none of the subjects were PCO, this study may have suggested that obesity with regular menstrual cycle is related with normal energy intake.

In conclusion, serum leptin concentrations changed during the menstrual cycle. This change of leptin concentrations may have affected normal reproductive events.

REFERENCES