Plasma Ghrelin Concentrations Are Lower in Binge-Eating Disorder1-3

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ABSTRACT Binge-eating disorder (BED), characterized by binge meals without purging afterward, is found in about 30% of obese individuals seeking treatment. The study objective was to ascertain abnormalities in hormones influencing appetite in BED, especially ghrelin, an appetite-stimulating peptide, which was expected to be elevated. Measurements were made of plasma insulin, leptin, glucagon, cholecystokinin, and ghrelin, as well as glucose following an overnight 12-h fast, prior to and after ingestion (from 0 to 5 min) of a nutritionally complete liquid meal (1254 kJ) at 0830 h, at −15, 0, 5, 15, 30, 60, 90, and 120 min. Appetite ratings including hunger and fullness were also obtained. An acetaminophen tracer was used to assess gastric emptying rate. Three groups of comparably obese women (BMI = 35.9 ± 5.5; % body fat = 44.9 ± 4.7) participated: 12 nonbinge eating normals (NB), 14 subthreshold BED, and 11 BED. The BED subjects, compared to NB subjects, had lower baseline ghrelin concentrations prior to the meal, a lower area under the curve (AUC), with lower levels at 5, 15, 30, 90, and 120 min, and a smaller decline in ghrelin postmeal (all P < 0.03). The other blood values did not differ among groups, and neither did gastric emptying rate nor ratings of fullness. The BED subjects were then randomly assigned to treatment with cognitive-behavior therapy and diet (n = 5) or to a wait-list control (n = 4). Baseline ghrelin (P = 0.01) and AUC increased (P = 0.02), across both conditions, in which most subjects (7 of 9) stopped binge eating. The lower fasting and postmeal plasma ghrelin levels in BED are consistent with lower ghrelin levels in obese compared to lean individuals and suggests downregulation by binge eating. J. Nutr. 135: 1326–1330, 2005.

KEY WORDS: • obesity • peptide hormones • satiety • ghrelin • binge eating • leptin • CCK

• insulin • glucagon

The prevalence of obesity, associated with chronic diseases such as diabetes and heart disease, continues to increase globally, especially in the United States (1), where it has reached epidemic proportions (2). Obesity is highly resistant to treatment, with most lost weight regained within 5 y after dieting (3,4). About 30% of obese subjects who participate in weight loss programs have binge-eating disorder (BED)5 (5). They overeat (objectively large amounts) at least twice a week for 6 mo with a sense of loss of control, but do not purge afterward, as do patients with bulimia nervosa (BN), who are usually of normal weight. BED, characterized relatively recently, is listed in the Appendix of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (6). With the rising epidemic of obesity, BED prevalence is also increasing, lending urgency to the study of its pathogenesis. There is evidence of a biological basis for BED, including moderate heritability of 0.50 (7), possible association with melanocortin 4 receptor mutation (8), and an enlarged stomach capacity (9).

Peripheral hormones that influence food intake also may play a role in BED. These hormones induce satiety signals that act directly on the brain or indirectly via the vagus nerve or by slowing gastric emptying (10). Such appetite-influencing hormones include insulin, leptin, glucagon, and cholecystokinin (CCK), the levels of which rise after meals and which suppress food intake when administered peripherally (10,11) or cen-
trally (10). In BN, slower gastric emptying has been reported (12,13), decreasing the duodenal release of the anorexigenic peptide CCK (13,14), which may contribute to the binge eating. We have proposed that slower gastric emptying following a fixed liquid meal in BN (12) and BED (9) is associated with a larger gastric capacity, which results in a smaller rise in intragastric pressure and, hence, diminished driving force for emptying (12,15). Gastric emptying of a liquid meal can be assessed with the tracer acetaminophen (paracetamol), which is rapidly absorbed from the duodenum after leaving the stomach and correlates well with radiolabeling and intragastric suction (16). Leptin, which is secreted mainly by adipose tissue, is higher in obese than in lean individuals and decreases during weight and fat loss (17). In one report, leptin was higher in BED patients compared to controls (18).

Ghrelin is a recently discovered peripheral peptide hormone that stimulates food intake (19). Ghrelin is produced mainly by the stomach and, when administered, increases food intake in animals (20) and humans, without altering human gastric emptying, as assessed by acetaminophen (21). Ghrelin rises before and falls following meals (22).

This study was undertaken to test the hypotheses that obese BED subjects have higher fasting and postprandial ghrelin levels, as well as a slower gastric emptying rate, and therefore lower postprandial CCK, than non-BED obese controls.

SUBJECTS AND METHODS

Subjects

We recruited 38 overweight and obese women (BMI > 27) and classified them into 3 groups: 12 nonbinge eating (NB), 14 binge eating but not meeting full criteria (BE), and 11 BED (full-fledged syndrome), assessed with the Questionnaire on Eating and Weight Patterns (5) and confirmed by clinical interview. The 3 groups did not differ on level of education, race, or ethnicity. Except for their weight, the subjects were all healthy as revealed by a medical history and physical examination, including electrocardiogram and blood chemistry. They were all premenopausal, nonsmokers, and weight stable within ±3.5% in the past 3 mo. Exclusions included use of illegal drugs or any medications that could affect body weight. All subjects signed an informed consent form, which had been approved by the St. Luke’s-Roosevelt Institutional Review Board. The characteristics of the participants are shown in Table 1.

Procedures

All procedures were performed following a 12-h overnight fast after a usual dinner completed by 0830 h. They included measures of body composition on 1 day and hormones and gastric emptying on another day, at least 2 d apart.

Body composition. Air displacement plethysmography (BOD-POD; Life Measurement Instrument) was used to determine body fat. Density from air displacement correlates well with underwater weighing (23) and has a CV of 0.7%.

TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>Body weight</th>
<th>Height</th>
<th>BMI</th>
<th>% Body fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB</td>
<td>12</td>
<td>33.1 ± 8.7</td>
<td>91.4 ± 15.0</td>
<td>1.61 ± 0.08</td>
<td>35.3 ± 5.5</td>
<td>44.9 ± 4.33</td>
</tr>
<tr>
<td>BE</td>
<td>14</td>
<td>28.6 ± 6.7</td>
<td>98.6 ± 15.2</td>
<td>1.66 ± 0.06</td>
<td>35.9 ± 5.3</td>
<td>44.3 ± 5.33</td>
</tr>
<tr>
<td>BED</td>
<td>11</td>
<td>29.0 ± 8.4</td>
<td>97.8 ± 18.8</td>
<td>1.63 ± 0.07</td>
<td>36.6 ± 6.2</td>
<td>45.4 ± 4.9</td>
</tr>
</tbody>
</table>

1 None of the characteristics differed by group.
2 Based on air displacement plethysmography.
3 n = 11.
the groups and test meal–related blood concentrations for the baseline (mean of $-15$ and $0$ min), AUC (calculated by the trapezoidal method), gastric emptying rate based on the time to the peak value and the AUC for acetaminophen, and the AUC for appetite ratings. If the AUC for concentrations or ratings revealed important group differences, MANOVA followed by Tukey’s HSD post hoc tests were used to analyze specific time points. Serial blood concentrations and ratings were also analyzed by GLM repeated measures for changes over time and interactions among BED groups. Stepwise multiple regression was performed to relate AUC for hormones with AUC for fullness rating. Pearson’s $r$ correlations were determined for selected variables. Two-tailed $P \leq 0.05$ was required for significance. The statistical analyses were performed using SPSS version 11.5.

RESULTS

Weight, BMI, and percentage body fat did not differ among groups (Table 1). In relation to the test meal, fasting or AUC for glucose, insulin, leptin, glucagon, CCK, or ratings of appetite did not differ among groups (Table 2). Gastric emptying rate did not differ by time to peak value for acetaminophen, $F(2,35) = 1.22, P = 0.31$ (for NB (±SEM): 103.8 ± 5.5 min, for BE: 96.4 ± 6.4, and for BED: 109.1 ± 4.6 min) or by AUC for acetaminophen, $F(2,35) = 1.87, P = 0.17$ (Table 2). Insulin resistance did not differ between groups, $F(2,34) = 1.7, P = 0.20$, ns.

However, for BED compared to the NB group, ghrelin had a lower fasting baseline value, $F(2,34) = 3.7, P = 0.03$, and smaller AUC, $F(2,34) = 4.2, P = 0.02$ (Table 2), with lower values at 5, 15, 30, 90, and 120 min; all post hoc test $P's < 0.05$. Ghrelin also declined less after the meal in BED individuals compared to the normal group, $F(14,231) = 2.4, P = 0.004$, and Tukey’s post hoc comparison, $P = 0.03$ (Fig. 1, Top panel). Ghrelin for the BE group was intermediate and did not differ from the other 2 groups. Although there were no differences in characteristics among the groups, all ghrelin statistical analyses were rerun after controlling for body weight, body mass index, or body fat, with comparable results.

The plasma concentrations of CCK (Fig. 1, Top panel) increased over time after the meal ($F, 7,224 = 12.1, P < 0.001$) and peaked at 15–30 min without varying by groups. The leptin concentrations (Fig. 1, Third panel) also changed over time, $F(7,238) = 4.49, P < 0.001$, with an acute rise from 0 to 5 min across groups, $F(1,34) = 5.3, P = 0.03$, without differing between groups. This acute change in leptin did not correlate with change in fullness over the same time period, $r = 0.03, P = 0.86$, ns. There were trends for inverse correlations between fasting leptin and fasting ghrelin, $r = -0.30, P = 0.07$, as well as leptin AUC and ghrelin AUC, $r = -0.30, P = 0.07$. Ratings of hunger and fullness did not differ among groups (Fig. 1, Fourth and bottom panels). A multiple stepwise regression between AUC for the hormones and for fullness revealed that the only hormone related to fullness was ghrelin, $F (1,30) = 5.16, P = 0.03$, with $r = -0.36$, an inverse correlation.

Following the intervention in the BED subjects, when ghrelin was reexamined there was an increase ($F (1,7) = 7.8, P = 0.03$) in fasting baseline ghrelin (±SEM) from 350 ± 36 to 587 ± 67 ng/L, with no difference between treated and untreated groups, $F(1,7) = 1.8, P = 0.22$, ns. Likewise, there was an increase, $F (1,7) = 8.75, P = 0.02$, in AUC for ghrelin from 39,298 pg/mL · min ± 3693 to 68,315 pg/mL · min ± 8340, with no difference between treated and untreated groups, $F (1,7) = 1.4, P = 0.27$. The weight change in both groups combined of $-1.5$ kg ± 3.9 had no impact on the ghrelin baseline change, $F (1,6) = 0.01, P = 0.94$, ns, or on the ghrelin AUC change, $F (1,6) = 0.03, P = 0.88$, ns. Closer examination showed that all 5 treated BED subjects remitted with absence of binge eating, and 2 of the 4 wait-listed BED subjects also remitted. When remission status was entered as a covariate, the change in baseline ghrelin, $F (1,6) = 0.00, P = 1.0$, ns, and the change in AUC for ghrelin were no longer significant, $F (1,6) = 0.27, P = 0.62$, ns.

DISCUSSION

Lower fasting baseline ghrelin levels in overweight and obese BED subjects is counterintuitive because ghrelin, a peptide that stimulates hunger, was expected to be higher. The finding is buttressed by the intermediate fasting ghrelin levels in the subthreshold BE group. The fasting ghrelin values for the obese NB group fell in the range of levels reported in comparably obese subjects (22,25,26). The lower fasting ghrelin level in BED suggests that binge eating may downregulate ghrelin. Indeed, binge eating may occur in the absence of hunger (6), consistent with low ghrelin levels. These results complement the finding that fasting ghrelin is 27% lower in obese than in lean individuals (25), with the exception of Prader-Willi patients, who have elevated values (27,28). The lower ghrelin level in obesity may be a secondary response to overeating (25), possibly a conditioned response, rather than a primary causal factor (29). Even if ghrelin is not a primary factor, a ghrelin antagonist may still help to reduce food intake in obesity (30).

At the other end of the weight spectrum, in anorexia nervosa (AN), fasting ghrelin is highest (31). The elevated ghrelin in AN is consistent with ghrelin rising in animals to

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Glucose</th>
<th>Acetaminophen</th>
<th>Insulin</th>
<th>Leptin</th>
<th>Glucagon</th>
<th>CCK</th>
<th>Ghrelin</th>
<th>Fullness</th>
<th>Hunger</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB</td>
<td>12</td>
<td>12,950± 352</td>
<td>84.3± 11.3</td>
<td>8801± 911</td>
<td>4189± 404</td>
<td>10,642± 809</td>
<td>693± 2002</td>
<td>65,793± 674</td>
<td>5086± 819</td>
<td>2184± 625</td>
</tr>
<tr>
<td>BE</td>
<td>14</td>
<td>13,195± 788*</td>
<td>107.2± 14.5*</td>
<td>10,073± 1923</td>
<td>4454± 532</td>
<td>12,359± 797</td>
<td>848± 243</td>
<td>51,389± 690</td>
<td>5007± 665</td>
<td>4225± 704</td>
</tr>
<tr>
<td>BED</td>
<td>11</td>
<td>14,640± 1310</td>
<td>133.6± 25.9</td>
<td>11,796± 1256</td>
<td>4998± 536</td>
<td>10,668± 732</td>
<td>769± 212</td>
<td>39,242± 325</td>
<td>4356± 805</td>
<td>2590± 718</td>
</tr>
</tbody>
</table>

1 For glucose, to convert to mmol/L, multiply by 0.05551; for acetaminophen, to convert to mmol/L, multiply by 66.1; for insulin, to convert to pmol/L, multiply by 7.175; for leptin, to convert to pmol/L, multiply by 0.08; for glucagon, to convert to ng/L, multiply by 1; for ghrelin, to convert to pmol/L, multiply by 0.296.

2 n = 11.

3 n = 13.

* Differs between groups, $P = 0.02$. 

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**TABLE 2**

AUC for glucose, acetaminophen, appetite hormones, and appetite ratings (mean ± SEM)
The fall in ghrelin may itself be a signal for satiation, which would be weaker with a smaller decline in ghrelin, as also suggested by a recent report of blunted decline in ghrelin after a meal in BN individuals (33). The differences in ghrelin levels in the BED and NB groups were not related to differences in body fat because body composition did not differ between these groups. The ghrelin differences between the BED and the NB groups were more than twice the magnitude of the change observed in obese subjects prior to and following substantial weight loss, when ghrelin increases (22).

The low ghrelin values in the BED subjects were nevertheless much higher than the low values in severely obese patients following gastric bypass surgery (22), and in both of these patient groups, ghrelin is not very responsive to meals (22). The smaller fall in ghrelin we observed is unlikely to represent a floor effect from a lower baseline, because some of the individual values of ghrelin fell much lower than the means shown in Figure 1 to <100 pg/ml but still within the sensitivity of the assay. Following remission of BED, which occurred in all those in the treated group and in half the wait-list group, there was an increase in AUC for ghrelin toward the normal state, bolstering the findings of an association of the disorder with the ghrelin abnormality. This increase in ghrelin could help thwart the recovering BED patient. In any case, this observed increase in plasma ghrelin in a small sample needs to be confirmed in a larger group of treated BED subjects.

The results also showed that BED individuals did not have slower gastric emptying after a fixed meal, and consistent with this, CCK levels were not lower postprandially, unlike the findings in BN (13,14). Although a large gastric capacity has been associated with slower emptying, capacity was not as large in BED as in BN individuals (9) and may not be large enough to lead to substantially slower emptying and a greater delay in the release of CCK (34).

We did not observe substantially higher fasting leptin in BED as in one previous report (18), but our results are consistent with another report demonstrating no difference in leptin levels (35). We did observe an acute rise in leptin just after the meal across all subjects, which is the first report to our knowledge of such a short-term rise in leptin after a meal in humans, although it did not correlate with changes in fullness. Generally, a delay of several hours is needed before leptin increases after a meal. This acute rise may be related to leptin released by the stomach, a recently discovered additional source of leptin besides the adipose tissue (36,37). Few studies have examined leptin changes this soon after a meal. The meal was also relatively high in carbohydrate (55%), which is known to stimulate leptin more than fat (38).

Although the AUC for the appetite ratings among the groups did not differ, the pattern was in the direction expected of less fullness after the same-size meal in the BED subjects. Indeed, in previous studies, when BED subjects were requested to consume a meal until extremely full, they ingested much larger meals than non-BED subjects (39). We found an inverse substantial correlation across groups between fullness and ghrelin, the only hormone of those measured to show a significant relation. The study, however, concerned a limited number of hormones, and other hormones involved in appetite mechanisms, such as peptide YY3–36 (40) glucagon-like peptide-1 (10), and amylin (41), were not examined.

In conclusion, BED subjects had lower ghrelin levels pre-meal, which then declined only slightly postmeal. The lower fasting ghrelin may be due to down regulation by binge eating, and the smaller decline in ghrelin following the meal may then provide a weaker satiety signal. The lower fasting and post-

[Image of graphs showing plasma concentrations of ghrelin, CCK, leptin, and ratings of fullness and hunger before and after a fixed test meal.]

FIGURE 1 Plasma concentrations of ghrelin, CCK, leptin, and ratings of fullness and hunger prior to and following a fixed test meal, ingested from 0 to 5 min, in obese subjects with BED, with BE, and with NB. Top panel: Fasting plasma ghrelin and AUC for plasma ghrelin levels were smaller, and the postprandial decline in ghrelin was smaller ($P < 0.05$) in BED than in NB. Ghrelin levels for BE were intermediate and did not differ from either group. (To convert to pmol/L, multiply by 0.296.) Second panel: Fasting and AUC for plasma CCK levels did not differ among the 3 groups of obese subjects. Third panel: Fasting and AUC for leptin levels did not differ between groups and showed an acute rise from 0 to 5 min across groups, $P = 0.03$. (To convert to nmol/L, multiply by 0.08.) Fourth panel: Fasting and AUC for fullness ratings did not differ among groups. Bottom panel: Fasting and AUC for hunger ratings did not differ among groups.
prandial concentrations of ghrelin, a key hormone influencing food intake and appetite, may thus be related to the pathophysiology of BED.

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LITERATURE CITED