Hyperghrelinemia Does Not Accelerate Gastric Emptying in Prader-Willi Syndrome Patients

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Prader-Willi syndrome (PWS) is the most common form of syndromic obesity associated with hyperphagia. Because ghrelin stimulates gastric motility in rodents, and PWS patients have 3- to 4-fold higher fasting plasma ghrelin concentrations than normal subjects, we hypothesized that hyperphagia associated with PWS may be partly explained by rapid gastric emptying due to the increased gastric motility caused by ghrelin. We determined gastric emptying times (GETs) and measured ghrelin levels in 11 PWS children and 11 age-, sex-, and body mass index-matched controls using a standard meal containing $^{99m}$Tc-diaminotriaminepentacetate. Median plasma ghrelin levels before (precibum) and after the GET study were higher in PWS patients than in controls ($P = 0.004$ and $P = 0.001$, respectively). Median percent gastric retentions at 90 min after the standard meal were 57.1% (range, 34.0–83.2%) in PWS patients and 40.2% (range, 27.2–60.2%) in controls ($P = 0.03$). In particular, precibum ghrelin concentrations were not significantly correlated with the rate of gastric emptying in PWS patients ($P = 0.153$; $r = 0.461$) or controls ($P = 0.911$; $r = 0.048$). Our results show that gastric emptying in PWS is reduced despite higher ghrelin levels, and that the voracious appetite associated with PWS is related to another mechanism. (J Clin Endocrinol Metab 90: 3367–3370, 2005)
ease, or the taking of any medication. Tissue fat percentage was measured by dual energy absorptiometry in PWS patients, but it was not measured in controls. The study design was reviewed and approved by the Samsung Medical Center institutional review board, and the parents of the participants provided informed consent.

**GETs**

After an overnight fast of 12 h, PWS patients and control subjects were imaged at the Department of Nuclear Medicine at our institute. On the morning of the test, subjects were fed a standard meal, which consisted of one egg cooked with 74 MBq $^{99m}$Tc-diaminodimethoxypentetate, a bowl of rice, soup, and 50 ml water. They were instructed to consume the total test meal within 10 min, and we ensured that the egg had been consumed by all subjects. Scintigraphic imaging began within 1–2 min after the standard meal:

**ELISA for ghrelin**

Plasma ghrelin levels were measured before (precibum ghrelin) and after (postcibum ghrelin) the GET study in all subjects. Ghrelin levels in plasma were measured using a commercially available ghrelin ELISA kit (Phoenix Pharmaceuticals, Belmont, CA). The details of the procedure have been previously described (8). All samples were measured in triplicate.

**Statistical analysis**

Data normality was tested using the Shapiro-Wilkes test. If data deviated from a normal distribution, the Wilcoxon signed-rank test was used (i.e. for postcibum ghrelin and $t_{1/2}$). The paired $t$ test was used to determine differences between percent gastric retentions at 90 min and precibum plasma ghrelin levels, which were normally distributed. Data are expressed as medians and ranges.

**Results**

Median percent gastric retentions at 90 min were 57.1% (range, 34.0–83.2%) in PWS patients and 40.2% (range, 27.2–60.2%) in controls ($P = 0.03$, by paired $t$ test); their corresponding $t_{1/2}$ values were 102.2 min (range, 52.3–254.8 min) and 62.8 min (range, 37.1–98.2 min), respectively ($P = 0.049$, by Wilcoxon signed-rank test; Fig 1).

Median plasma ghrelin levels before the GET study were 19,600 pg/ml (range, 6,490–52,060 pg/ml) in PWS patients and 6,298 pg/ml (range, 1,010–10,610 pg/ml) in controls ($P = 0.003$); after the GET study, they were 11,762 pg/ml (range, 3,770–38,160 pg/ml) in PWS patients and 3,060 pg/ml (range, 1,190–10,160 pg/ml) in controls ($P = 0.001$, by Wilcoxon signed-rank test). There was no significant correlation between BMI and the rate of gastric emptying in PWS patients (BMI vs. $t_{1/2}$: $P = 0.986$; $r = -0.527$; BMI vs. 90 min after the standard meal: $P = 0.259$; $r = -0.373$) or in control subjects (BMI vs. $t_{1/2}$: $P = 0.606$; $r = 0.217$; BMI vs. 90 min: $P = 0.967$; $r = -0.017$) or between the percentage of body fat and the rate of gastric emptying in PWS patients (fat percentage vs. $t_{1/2}$: $P = 0.272$; $r = -0.364$; fat percentage vs. 90 min after the standard meal: $P = 0.612$; $r = -0.173$).

Moreover, precibum ghrelin concentrations were not significantly related to the rate of gastric emptying in PWS patients (ghrelin vs. $t_{1/2}$: $P = 0.250$; $r = 0.379$; ghrelin vs. 90 min after the standard meal: $P = 0.153$; $r = 0.048$) or in control subjects (ghrelin vs. $t_{1/2}$: $P = 0.433$; $r = -0.324$; ghrelin vs. 90 min: $P = 0.911$; $r = 0.048$; Table 2). Postcibum ghrelin concentrations were not significantly related to the rate of gastric emptying in PWS patients (ghrelin vs. $t_{1/2}$: $P = 0.340$; $r = 0.318$; ghrelin vs. 90 min after the standard meal: $P = 0.179$; $r = 0.436$) or in controls (ghrelin vs. $t_{1/2}$: $P = 0.501$; $r = -0.227$; ghrelin vs. 90 min: $P = 0.417$; $r = -0.272$).

**Discussion**

To our knowledge this is the first investigation of gastric emptying in PWS. Before commencing the study, we believed that PWS patients would show rapid gastric emptying because of their characteristic voracious appetites and tendency not to vomit, and because they have 3- to 4-fold higher plasma ghrelin concentrations than normal (8), which are known to stimulate gastric motility in rodents (6, 7). However, our results contradicted this expectation. In the event, GET in PWS patients was found to be delayed, and precibum and postcibum ghrelin concentrations were not significantly related to gastric emptying rates in PWS patients or controls.

Two recent animal studies suggested that ghrelin promotes gastric emptying (6, 7). However, only one study determined a relationship between ghrelin and gastric motility in man (12). This study showed that the iv administration of ghrelin stimulated appetite and food intake in nine healthy volunteers. However, the same study found that ghrelin had

### TABLE 1. Age, sex, height, body weight, BMI, genotype, and tissue fat percentage of the PWS patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Body weight (kg)</th>
<th>BMI</th>
<th>Genotype</th>
<th>Tissue fat (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>F</td>
<td>124</td>
<td>31.5</td>
<td>20.5</td>
<td>Deletion</td>
<td>41.7</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>M</td>
<td>116</td>
<td>36.5</td>
<td>27.1</td>
<td>Deletion</td>
<td>53.5</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>F</td>
<td>105</td>
<td>18.5</td>
<td>16.8</td>
<td>Deletion</td>
<td>49.3</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>F</td>
<td>131.5</td>
<td>33</td>
<td>19.1</td>
<td>Deletion</td>
<td>39.1</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>M</td>
<td>133.3</td>
<td>39.5</td>
<td>22.2</td>
<td>Deletion</td>
<td>49.8</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>M</td>
<td>128.5</td>
<td>27.5</td>
<td>16.7</td>
<td>UPD</td>
<td>48.3</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>M</td>
<td>138</td>
<td>60.5</td>
<td>31.5</td>
<td>Deletion</td>
<td>50.5</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>F</td>
<td>139</td>
<td>37.5</td>
<td>19.4</td>
<td>UPD</td>
<td>30.4</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>F</td>
<td>143.5</td>
<td>61.3</td>
<td>29.8</td>
<td>Deletion</td>
<td>52.2</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>M</td>
<td>152.5</td>
<td>53</td>
<td>22.8</td>
<td>Deletion</td>
<td>47.7</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>M</td>
<td>142</td>
<td>95</td>
<td>47.1</td>
<td>Deletion</td>
<td>67.9</td>
</tr>
</tbody>
</table>

Controls were matched for age, sex (F, female; M, male), and BMI. UPD, Uniparental disomy.
no effect on gastric emptying, as assessed by the paracetamol absorption test (12). Despite the small number of subjects involved, these findings suggest that human and animal ghrelin function in different ways, at least in terms of gastric emptying. Our findings confirm that although there is a large difference in ghrelin levels in PWS and normal control subjects, these elevated ghrelin levels are associated with a reduction in the rate of gastric emptying in PWS.

A possible mechanism for delayed GETs in PWS may be the obesity itself. Jackson et al. (13) found delayed gastric emptying in obese women using a noninvasive nonradioactive method, after adjusting for the effects of potential confounders, particularly for age, gender, and exercise. They concluded that this delay may be a consequence of a high fat diet, a sedentary lifestyle, or increased gastric distension associated with obesity, which also suggests that delayed gastric emptying is a contributory factor in the pathogenesis of obesity due to the inactivation of gastrointestinal satiety signals and an increase in food intake. It is known that obese persons have lower plasma ghrelin levels than healthy lean controls and delayed gastric emptying times (14). However, gastric motility in obese subjects with elevated ghrelin levels has not been previously reported.

In the present study PWS children with elevated ghrelin levels showed delayed gastric emptying. However, the present study is limited by the relatively small number of patients enrolled between 6 and 17 yr of age. Thus, a study of adult PWS patients may broaden the understanding of the relationship between ghrelin and gastric emptying. Also, it is known that young PWS patients (even underweight children) have increased levels of body fat, and that BMI has its limitations as a comparable obesity index (15). Thus, our controls may not ideally match PWS patients, and tissue fat percentage measured by dual energy absorptiometry may be a better index to match. However, we did not measure the tissue fat percentage in controls.

Taken together, the above observations support the idea that gastric emptying is independent of plasma ghrelin levels and that gastric emptying is delayed in PWS children. We conclude that the voracious appetite of PWS patients is probably related to another mechanism, such as the action of

**Table 2. Gastric emptying rates and ghrelin levels in PWS patients and controls**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>BMI (kg/m²)</th>
<th>Fat (%)</th>
<th>t₁/₂, median (min, range)</th>
<th>GET at 90 min, median (%)</th>
<th>Precibum ghrelin (ng/ml), median (range)</th>
<th>Postcibum ghrelin (ng/ml), median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWS</td>
<td>11</td>
<td>8.0</td>
<td>6/5</td>
<td>22.2</td>
<td>49.3</td>
<td>102.2</td>
<td>57.1</td>
<td>19.6</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6–17)</td>
<td></td>
<td>(16.6–47.1)</td>
<td>(30.4–67.9)</td>
<td>(52.3–254.8)⑥</td>
<td>(34.0–83.2) ⑥</td>
<td>(6.49–52.1)⑥</td>
<td>(3.77–38.1)⑥</td>
</tr>
<tr>
<td>Control</td>
<td>11</td>
<td>9.0</td>
<td>6/5</td>
<td>23.3</td>
<td>62.8</td>
<td>62.8</td>
<td>40.2</td>
<td>6.30</td>
<td>3.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6–16)</td>
<td></td>
<td>(16.7–46.0)</td>
<td>(37.1–98.2)</td>
<td>(27.2–60.2) ⑥</td>
<td>(1.01–10.6)</td>
<td>(1.19–10.16)</td>
<td></td>
</tr>
</tbody>
</table>

M, Male; F, female.

⑥ P = 0.049 vs. control.

⑦ P = 0.03 vs. control.

⑧ P = 0.003 vs. control.

⑨ P = 0.001 vs. control.
ghrelin on the central nervous system, but this speculation remains to be elucidated.

Acknowledgments

Received August 19, 2004. Accepted January 10, 2005.
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This work was supported by a grant from the Korean Health 21 R&D Project, Ministry of Health and Welfare (01-PJ10-PG6-01GN15-0001) and the In-Sung Foundation for Medical Research (C-A1-822).

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JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.